Durability and Mechanism of Effects of Cognitive Enhancement Therapy

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Objectives: **This study sought to determine whether previously reported effects of cognitive enhancement therapy (CET) are maintained one year after treatment. CET is a developmental, small-group approach to the remediation of neurocognitive and social-cognitive deficits among persons with schizophrenia. A mechanism of action that might explain the effects of CET was also sought.** _Methods:_ **After a study in which 121 participants with schizophrenia or schizoaffective disorder were randomly assigned to CET (N=67) or an enriched supportive therapy (EST) (N=54) for a two-year period, 106 patients who completed treatment underwent behavioral and neuropsychological assessments one year later. Data were analyzed by linear trend analysis. Mechanisms of action were explored with a mediator analytic strategy.** _Results:_ **Significant improvement favoring CET continued through the follow-up year on composite measures of processing speed, cognitive style, social cognition, and social adjustment. The difference between CET and EST on the neurocognition composite measure was not maintained because the stress-regulating effects of treatment appeared to lead to improved neurocognitive performance in both groups. Early improvement in processing speed was a strong (partial) mediator of long-term CET effects on social cognition and social adjustment. To a lesser extent, early improvement in neurocognition partially mediated changes in cognitive style (impoverished, disorganized, or rigid) in the CET group but had little influence on social adjustment or social cognition in the CET group.** _Conclusions:_ **Most effects of the highly efficacious CET were sustained one year after treatment. Early improvement in processing speed (and perhaps other unassessed aspects of attention) seems to be the principal mediator of CET effects.** (_Psychiatric Services_ **57:1751–1757, 2006)**

C ognitive deficits are widely believed to limit recovery in schizophrenia (1). Attempts at remediation have focused on attention, memory, and problem solving, with little or no emphasis on social-cognitive difficulties (2). Although modest neurocognitive training effects have been found, little evidence exists regarding their durability. How neuropsychological change is "linked" to changes in behavior, beyond simple correlations, is even less understood (3).

Cognitive enhancement therapy (CET) is a holistic, small-group approach (six to eight patients) to the remediation of neurocognitive and social-cognitive deficits among patients with schizophrenia and schizoaffective disorder in the post-acute, recovery phase of illness. In a randomized trial, CET was compared with a state-of-the-art enriched supportive therapy (EST) (4). Over two years of treatment, CET demonstrated significant differential effects on composite indices of processing speed, neurocognition, cognitive style, social cognition, and social adjustment. (There was no difference on a residual-symptom composite measure because most patients were clinically stable at baseline and all were provided EST illness-management strategies.)

For this follow-up study, we hypothesized that the effects of two years of CET would be sustained for at least one year posttreatment. Further, we investigated whether a possible mechanism or "mediator" for these effects could be identified. Historically, there has been an unfortunate tendency for many psychosocial treatment effects in schizophrenia to end once the active treatment ends (5). Among cognitive rehabilitation approaches, the maintenance of effects appears more encouraging, but the evidence is limited. Of the 17 cognitive rehabilitation studies recently reviewed by Twamley and colleagues (2), only three follow-up reports were identified. A three-week posttreatment assessment of an eight-session approach (6) and a 48-hour follow-up of a single training session (7) indicated that earlier improve-

ment was sustained. A four-week follow-up of a problem-solving approach also showed that a differential effect persisted on an independent measure of problem solving (8). Since this review, other investigators have described the maintenance of a cognitive rehabilitation effect on a test of working memory at six months post-training (9); however, no information was offered on the durability of other neuropsychological test effects that had been reported earlier (10). Additionally, a recent study of early-onset psychosis that controlled for IQ found an isolated effect of cognitive remediation on visual information processing among 14 participants one year after hospital discharge (11). However, no differential effects were reported during the controlled phase of treatment. Otherwise, the "delta" question raised by Green and

Neuchterlein (3) remains a challenge: "whether changes in neurocognitive functioning are directly linked to changes in functional outcome." Reports have primarily described correlations between neurocognitive measures and behavior (1).

Methods
Participants and procedures
A description of the study design and two-year results (4), together with the theory (12), practice principles (13), and CET manual (14), are available elsewhere. Briefly, 121 patients with schizophrenia or schizoaffective disorder were randomly assigned to either CET (N=67) or EST (N=54) and treated for two years, between January 1995 and February 2002. Patients' mean±SD age was 37.3±8.9 years. They had been ill for a mean of 15.7±9.3 years and had 5.96±5.97

previous hospitalizations. Most (99 patients, or 82 percent) had never been married. Seventy-one patients (59 percent) were male, 108 (89 percent) were white, and 13 (11 percent) were African American.

Patients were clinically stable at baseline and thus were at reduced risk of relapse (15). Eligibility required an IQ of at least 80, and the mean IQ of the patient group was 97.2±11.5. Although nearly one-third had completed college (38 patients, or 31 percent), most patients were not working (83 patients, or 69 percent). Participants had not worked for a median of four years, and 30 (25 percent) had not worked in more than ten years. All met criteria for social-cognitive and neurocognitive disability (4). [A Methods supplement to this article that describes the eligibility criteria related to cognitive style and social cognition is available on the journal's Web site at http://ps.psychiatryonline.org.]

Upon recruitment (baseline) participants were assessed with the measures described below. They were readministered at one and two years during treatment and again one year after treatment ended. Between months 4 and 6, four CET and four EST participants left the study, as did another four EST and two CET participants at 12 months (4). Of the 107 participants eligible for follow-up, data were collected for 106. (Because of missing data for some composite measures, the range of participants was 100 to 104.) On the key characteristics examined, these 106 participants did not differ from the original 121 participants at baseline. (It was deemed inappropriate to carry forward to 36 months the assessments of the 14 patients who left the study during the first year.)

All patients provided informed consent, and the study was reviewed annually by the University of Pittsburgh Institutional Review Board.

Treatment
CET is a multidimensional, developmental approach to the remediation of social-cognitive and neurocognitive deficits that was influenced by Brenner and colleagues' work (16) with patients with schizophrenia and

by the work of Ben-Yishay and colleagues (17) among patients with traumatic brain injury. CET attempts to increase mental stamina, active rather than passive information processing, and spontaneous and appropriate negotiation of unrehearsed social challenges. Specifically, CET provides experiential exercises designed to facilitate the ability to take the perspective of other people (that is, to determine their thoughts, feelings, and likely behavior) by utilizing verbal and nonverbal cues. Perspective taking is the linchpin around which key aspects of social cognition are addressed: appraising the social context (beyond first impressions), judging affect in others, regulating one's own affect, reevaluating previous interpersonal encounters, using reciprocity, and forming shared understandings.

Through the course of approximately 56 social-cognitive group sessions of 90 minutes each (14), patients are challenged to think abstractly about one or more of these concepts. CET attempts to shift a reliance on concrete cognitive processing to a "gistful" abstraction of relationship themes (18). Unlike cognitive-behavioral therapy that seeks to correct faulty self-schemas (particularly regarding the nature of persistent hallucinations or delusions), CET addresses incorrect or incomplete cognitive schemas about other people. CET approaches neurocognitive deficits through approximately 75 one-hour sessions using computer exercises from the attention software of Ben-Yishay and colleagues (19) and the memory and problem-solving software of Bracy (20). All CET participants began neurocognitive remediation before entering the social-cognitive group (usually within six months of beginning neurocognitive training).

EST relied on most practice principles of the basic and intermediate phases of the demonstrably effective personal therapy approach, which fosters illness management through psychoeducation and control of stress (21). All participants received stress reduction strategies and education, either individually (EST) or through the social-cognitive group (CET), and all were maintained on antipsychotic medication approved by the U.S. Food and Drug Administration. Both treatments were supervised for fidelity. No differences were found between treatment groups in the type or dosage of medication or clinician-rated compliance. Three posttreatment social-cognitive group follow-up sessions were offered to CET participants in the year after the active phase of treatment, primarily for staff to learn about CET successes or implementation difficulties.

Measures

Highly reliable, multivariate composite measures were constructed from new and existing scales (4). [A Methods supplement to this article that describes the construction of the composite measures and specific scales is available on the journal's Web site at http://ps.psychiatryonline.org.] Four behavioral composite measures were derived from clinicians who were not blind to patients' treatment group and from patient ratings. Cognitive style was assessed using our newly developed Cognitive Style Inventory and clinical ratings on our cognitive style eligibility criteria (14); these instruments assess aspects of impoverished, disorganized, and rigid patterns of thinking. The assessment of social cognition included factor score measures of self-confidence, social perception, supportiveness, and tolerance from our newly developed Social Cognition Profile (14) as well as global measures of vocational and interpersonal effectiveness, foresight, and adjustment to disability taken from our social-cognitive eligibility criteria (14).

Social adjustment represented broad assessments of employment, major role performance, and overall adjustment as assessed by the Major Role Adjustment Inventory (22), Global Assessment Scale (23), and selected measures from the Social Security Administration's functional disability criteria (24). Symptom measures included patients' ratings of mood and self-esteem, as well as selected factors from the Brief Psychiatric Rating Scale (25) and total scores from the Raskin Depression (26) and Wing Negative Symptom (27) scales. All measures for these behavioral composite indices were completed by clinicians trained in their use who were not blind to patients' treatment group.

Two neuropsychological composite measures were derived from standard tests on which patients had not been trained. Processing speed relied on measures of visual scanning ability (19) and on simple reaction time (19) and choice reaction time (28). The neurocognition composite index included measures from the Wechsler Memory Scale (29), California Verbal Learning Test (30), Wechsler Adult Intelligence Scale–Revised (31), Trails B (32), and Wisconsin Card Sorting Test (33). Neuropsychological tests were administered systematically by a psychometrician who was uninvolved in treatment. Clinicians were blind to the annual test results.

Data analysis

Maintenance of effects was tested by a stringent linear trend analysis that compared the amount and rate of improvement between the treatment groups over all three years. This trend analysis also tested for four potential moderators at baseline—sex, length of illness (greater or less than 15 years), psychosis level (greater or less than mild), and IQ (greater or less than 98)—to determine whether certain individuals benefited from treatment more than others. A moderator can indicate for whom a treatment works best. A mediator, on the other hand, might suggest a mechanism by which a treatment produces a favorable outcome (34). Such mechanisms of change were explored by the mediator analytic strategy of Kraemer and colleagues (34). This strategy is useful for identifying how improvements that occur during a treatment influence its later outcomes and points to the mechanisms by which a treatment achieves its effects.

In Kraemer and colleagues' framework, a mediator must occur before the observed changes in the outcome that is mediated; the mediator must be affected by treatment and must directly affect or interact with treatment to influence the mediated outcome. Full mediation is said to exist if the effects of treatment are completely reduced after changes in the medi-

Table 1

Maintenance of treatment effects among 67 patients with schizophrenia assigned to cognitive enhancement therapy (CET) or 54 assigned to enriched supportive therapy (EST)

| | Baseline | | Controlled phase | | | | Year 3 (follow-up) | | Trend analysis across 3 years | | |
| | | | Year 1 | | Year 2 | | | | | | |
Measure	M	SD	M	SD	M	SD	M	SD	F	df	p
Processing speed									6.55	1, 99	.012
CET	49.3	10.3	56.5	8.6	57.4	7.9	56.5	7.8			
EST	50.2	9.1	50.6	9.3	49.8	12.6	51.0	11.7			
Neurocognition									1.71	1, 99	.195
CET	51.3	10.5	57.3	9.9	60.1	11.1	60.7	11.2			
EST	48.1	9.6	50.8	10.3	54.0	10.5	55.0	9.7			
Social cognition									9.87	1, 99	.002
CET	48.5	9.6	58.4	10.2	66.9	10.7	70.8	9.1			
EST	50.9	10.1	57.0	10.9	60.6	13.0	64.7	11.9			
Cognitive style									7.6	1, 100	.007
CET	50.6	9.9	59.4	9.5	67.7	11.2	70.9	10.6			
EST	49.0	9.6	53.9	11.5	57.6	12.5	61.7	11.6			
Social adjustment									7.99	1, 103	.006
CET	48.5	9.6	58.4	11.9	64.0	12.1	67.6	11.2			
EST	50.8	10.3	55.6	11.9	59.2	13.5	61.6	14.2			

[a] Scores from various measures were standardized to reflect a baseline mean±SD of 50±10. Means have been transformed such that a score above 50 indicates improvement.

ator are accounted for. In turn, partial mediation exists if the effects of treatment are only partially reduced after accounting for the mediator, indicating that other changes that occur during treatment also influence outcome in addition to changes in the mediator (35). It is important to remember that not all mediators represent causal mechanisms of change (34). They do, however, provide the basis for future tests of a treatment that capitalize on the enhancement of efficacy of a possible mediator.

Results

Maintenance of effects

As shown in Table 1, except for the neurocognition composite index, the four remaining composite measures that demonstrated a significant CET effect at two years (4) continued to be significant at 36 months. (Analyses of covariance of the 36-month data, which used baseline measures as the covariates, were also highly significant, except for differential improvement in neurocognition.) Visual inspection of the 36-month means shown in Table 1 also reaffirms the maintenance of these effects, with two-year CET effects on cognition and behavior enduring but not significantly improving after the end of treatment, compared with the group receiving EST. In terms of the nonsignificant neurocognition composite, CET participants did not deteriorate between years 2 and 3; rather, neurocognitive functioning of EST participants continued to improve over time despite the absence of cognitive training. As was true at one and two years, no differential treatment effect on the symptom composite was evident at three years.

Other "real-world" main and moderator effects

When attendance in the three CET follow-up sessions during the year after treatment was adjusted for, the between-group difference in engagement in a social, recreational, or therapeutic group activity during year 3 was significant. Eighteen CET participants (30 percent) but only four EST participants (9 percent) engaged in these activities (χ^2=6.92, df=1, p= .009). The difference in engagement in some type of vocational rehabilitation experience was also significant— 24 CET participants (40 percent) compared with seven EST participants (16 percent) (χ^2=7.38, df=1, p= .007). Although no significant group differences were found in the proportion of patients who had paid employ-

ment, 16 CET participants (27 percent) but only two EST recipients (4 percent) performed in a volunteer role during year 3, (χ^2=10.25, df=2, p=.006). Because patients were at reduced risk of relapse, differences in relapse rates were not expected or observed over the three years; nine EST and five CET patients relapsed. Receipt of clozapine (N=47), a second-generation antipsychotic (N= 41), or a first-generation antipsychotic (N=12) was nearly identical for the EST and CET samples during year 3. The groups did not differ in the number of medication visits, clinician-rated medication compliance, or the number of individual psychotherapy sessions or family sessions.

We found evidence for moderator effects of IQ, length of illness, and psychosis level, but not sex, across several cognitive and behavioral outcomes. Although no significant main effect was found for neurocognition at three years, a significant interaction was noted between treatment and IQ (F=4.27, df=1 and 99, p= .042), indicating that the neurocognitive deficits of participants with higher IQs (≥98) improved more with CET than with EST.

Among patients who had been ill for less than 15 years, CET had a

Table 2

Outcome effects of cognitive enhancement therapy (CET) at 36 months, with and without neuropsychological mediators

| | CET effects without mediators | | | CET effects with mediators | | | | | |
| | | | | Processing speed | | | Neurocognition | | |
Behavioral outcome	F[†]	p	Effect size	F[††]	p	Effect size	F[†††]	p	Effect size
Social cognition	18.5	<.001	.86	6.5	.013	.51	9.8	.002	.63
Social adjustment	14.3	<.001	.75	4.2	.043	.41	8.1	.006	.57
Cognitive style	13.4	<.001	.73	4.1	.047	.41	5.9	.017	.49

[a] The significance (F, p, and effect size) of CET will decrease as the influence of a mediator increases.
[†] df=1 and 101
[††] df=1 and 98
[†††] df=1 and 97

greater effect than EST on ability to shop for basic necessities (F=5.34, df=1 and 87, p=.023) and a marginally greater effect in regard to household cleaning (F=3.79, df=1 and 87, p=.055), as assessed by the Social Security Administration's standards for functional disability (24), as well as significantly greater effects on patients' adjustment to their disability (F=8.43, df=1 and 89, p=.005) and on impoverished thinking (F=12.91, df=1 and 89, p=.001). Among patients who were less psychotic at baseline, those who received CET also were better at managing finances than those who received EST (F=4.37, df=1 and 87, p=.039).

Mechanism of action
Using the criteria of Kraemer and colleagues (34), we first sought to identify potential mediator variables that improved early with CET and thus preceded significant changes in other long-term outcome measures. The neuropsychological composites—processing speed and neurocognition—were the only measures to improve with CET at a highly significant level (p<.01) during year 1 (4), before the highly significant (p<.01) CET effects on social cognition, cognitive style, and social adjustment that occurred during years 2 and 3 (4) (Table 1). (We did not consider the symptom composite because it showed no treatment effect at any rating period.) Improvement in processing speed immediately followed attention training at six months and persisted for the next 2.5 years.

EST participants did not improve on processing speed (Table 1). Nearly all improvement in processing speed among CET patients occurred by 12 months. This regressed change score in processing speed became the first "mediator" candidate. To a lesser extent, the same pattern was true for the neurocognition composite measure (memory, problem solving, and executive functions), because although neurocognitive training did not begin until six months after intake, the most significant CET improvement in neurocognition (p< .003) also occurred at 12 months (4). This first-year regressed change score in neurocognition became the second potential mediator of long-term treatment outcome.

Next, we needed to show that these potential mediators had a significant effect on the behavioral composite indices at three years while accounting for the effects of CET. We accomplished this by examining the main effects of the mediators on three-year behavioral outcomes, after controlling for treatment effects. Early improvement in processing speed (year 1) had a significant effect on year 3 social cognition (F=4.25, df=1 and 98, p=.042) and social adjustment (F=4.16, df=1 and 98; p=.044) but not on cognitive style. Early improvement in neurocognition had no effect on long-term social adjustment and only a marginal effect on social cognition (F=3.89; df=1 and 97, p=.051). Its primary main effect occurred, as one might expect, on cognitive style (F=5.62, df=1 and 97, p=.020).

After finding that early changes in processing speed and neurocognition indeed mediated the long-term behavioral effects of CET, we next evaluated the extent of this mediation. Data presented in Table 2 indicate that changes in processing speed and neurocognition partially mediated the effect of CET on social cognition, social adjustment, and cognitive style. However, processing speed was the stronger "partial mediator" because the effect sizes of CET (Cohen's d) were reduced substantially when the analysis controlled for improvement in early processing speed. (However, CET continued to have its own statistically significant effect on outcome beyond that accounted for by processing speed.) Early improvement in neurocognition was also a partial mediator, but it did not lessen or mediate the long-term CET effect on outcome nearly as much as processing speed.

Discussion
This study found that the effects of CET were broadly maintained. With the exception of the improvement in processing speed that was evident early and exclusively among CET recipients, both treatment groups continued to improve on other composite measures during the follow-up year, which provides continuing support for the effects of personal therapy on adjustment (21). In terms of the improvement in neurocognition observed for EST participants, Spaulding and colleagues (36) suggested that control of stress and arousal might

lower state-related neurocognitive deficits. Recent evidence shows that stress-related hormone levels are indeed associated with neurocognitive performance (37). Although one cannot rule out practice effects on the neuropsychological tests as a cause of improvement among participants in the EST group, such effects are unlikely when evaluations are conducted annually.

That psychological techniques to help individuals manage stress and regulate affect might independently improve their neurocognitive functioning provides a challenge to cognitive rehabilitation interventions that rely exclusively on training in memory, problem solving, or executive functions or that exclusively use novel medications to target cognitive deficits. CET effects on "real-world" behaviors (for example, employment and social group participation) continued to be modest during follow-up, largely because patients had found their adjustment niche before treatment and were not inclined to vocational pursuits that might jeopardize disability benefits. Rather, most sought CET as a way to improve their quality of life.

In terms of possible mediators, improvement in processing speed (or attention) might be the necessary condition for a maximum behavioral response to future cognitive rehabilitation interventions. Other investigators have demonstrated the importance of addressing attention deficits (38–40). As previously noted in the initial CET study (4), CET effect sizes on cognition and behavior appear to exceed the average effect sizes reported for other cognitive rehabilitation approaches (2) and medication approaches (41).

Although there has been informative discussion about possible cognitive mediators (3,42,43), we know of no formal mediator analysis of psychosocial treatment outcomes that used neuropsychological variables. Overall, it appears that maximum behavioral change lags behind neuropsychological change, as suggested elsewhere (3). Given that improvement in processing speed was a strong partial mediator of both social cognition and social adjustment, we

can now propose that early improvement in processing speed might be the condition upon which greater-than-expected treatment improvement in these areas depends.

Some models have indicated that changes in basic neurocognition mediate functional outcomes (3). We feel that processing speed (and the associated components of attention) could profitably be separated from memory, problem solving, perception, and executive functions. It is increasingly recognized that attention is a mental state upon which other cognitive operations depend (44). Unfortunately, our attention measure proved to be unreliable (4), and we were reduced to four measures of simple reaction time and choice reaction time as proxy measures of vigilance and selective attention. Processing speed, however, has long been viewed as a precursor to learning (45), and its unequivocal improvement among CET participants is encouraging.

Neurocognitive improvement had some mediating influence on outcome but not nearly as much as we anticipated. Neurocognitive training might well improve impoverished, disorganized, or inflexible thinking, but we found that the ability of neurocognitive change to independently influence social adjustment longitudinally was modest. It could be argued that early improvement in processing speed accounts for later changes in neurocognition. Because the CET effect on the neurocognition composite at year 3 was not significant, this mediator analysis would be inappropriate because there was essentially no clear effect to be mediated (35). The issue is further complicated because neurocognitive improvement likely arises from two distinct sources: computer training (remediation) among CET participants and stress reduction strategies (compensation) among all participants. A different study that separates remediation and compensation strategies is needed to answer this question.

Finally, CET was developed for clinically stable but functionally disabled patients in the postacute, recovery phase of illness. Among these patients, neuropsychological and be-

havioral changes appear to follow a longitudinal course that is largely independent of symptom improvement. The same might not be true for acutely symptomatic patients who receive cognitive training.

A replication of these observations in an ongoing study of CET among patients in the early course of schizophrenia (46) is eagerly awaited. Whether CET is effective for other mental disorders that implicate social-cognitive deficits in recovery remains an important question for clinicians and researchers.

Conclusions

In this study of the long-term, posttreatment effects of CET, results indicate that most of the effects of the highly efficacious CET on cognition and behavior were maintained one year after treatment ended. Early improvements in processing speed were found to be a partial mediator of these effects, which provides a putative mechanism of action for the effects of CET on long-term behavioral outcomes to guide future clinical trials.

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