One-year durability of the effects of cognitive enhancement therapy on functional outcome in early schizophrenia

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Abstract

Cognitive rehabilitation is an effective intervention for addressing cognitive impairments in patients with schizophrenia. Previous research has shown that the early application of Cognitive Enhancement Therapy (CET) can improve neurocognitive and social-cognitive deficits in the early course of the disorder, and ultimately reduce the substantial functional disability that these patients experience. However, the lasting effects of CET on functional outcome in early course schizophrenia patients remain unknown. In this study, 58 patients in the early course of schizophrenia or schizoaffective disorder treated with 2 years of either CET or an Enriched Supportive Therapy (EST) control were followed-up 1 year after the completion of treatment to examine the durability of CET effects on functional outcome. At one-year post-treatment, a high (72%) retention rate was observed in both treatments. Results from intent-to-treat analyses employing linear mixed-effects models indicated that CET effects on functional outcome were broadly maintained one-year post-treatment, and that patients receiving CET continued to demonstrate highly significant differential functional benefits compared to patients treated with EST. These findings support the durability of CET effects on functional outcome in the early course of schizophrenia, and point to the potential of cognitive rehabilitation to have a lasting impact on the early trajectory of the disorder.

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1. Introduction

Schizophrenia is characterized by marked impairments in neurocognition and social cognition (Heinrichs and Zakzanis, 1998; Penn et al., 1997), which have been consistently linked to poor functional outcomes in the disorder (Couture et al., 2006; Green et al., 2000). Cognitive rehabilitation has emerged as an effective strategy for addressing these cognitive impairments, and has produced meaningful gains in social adjustment, vocational functioning, and other functional domains in many studies (Hogarty et al., 2004; McGurk et al., 2007a,b). The early emergence of cognitive impairments in the course of schizophrenia (Saykin et al., 1994), their persistence after the remission of psychosis (Hoff et al., 1999), and the benefits of cognitive rehabilitation approaches for chronic patients (e.g., Hogarty et al., 2004), have generated enthusiasm that the early application of these approaches might significantly alter the frequently deleterious functional course of the disorder (Keshavan and Hogarty, 1999).

To date, while numerous studies have been conducted on cognitive rehabilitation for schizophrenia (McGurk et al., 2007b), few have examined the effectiveness of these approaches when applied to early course patients, who may experience less cognitive impairment in some domains (e.g., Braw et al., 2008). Recently, we completed a two-year randomized-controlled trial of Cognitive Enhancement Therapy (CET; Hogarty and Greenwald, 2006), an integrated approach to the remediation of social and non-social-cognitive impairments, with 58 individuals in the early course of schizophrenia or schizoaffective disorder. Results indicated that not
only was CET effective at improving both social cognition and neurocognition in early schizophrenia, but that the treatment was also effective at improving broad domains of functional outcome, including social functioning, major role adjustment, and competitive employment (Eack et al., 2009; Eack et al., 2010, in press).

While CET has shown promise in early schizophrenia, the degree to which the beneficial effects of cognitive rehabilitation, particularly with regard to functional outcomes, are maintained after the completion of treatment remains unclear. In general, few studies have examined the durability of the effects of cognitive rehabilitation. We previously observed that the effects of CET on both cognition and social adjustment were durable one-year post-treatment in a two-year trial with chronic schizophrenia patients (Hogarty et al., 2006). Wykes et al. (2007) also found that 3 months of neurocognitive remediation produced durable effects on memory functioning in a sample of chronic patients at a 6-month follow-up; however, effects on symptoms and self-esteem in this study were not maintained. In the only durability study of the effects of cognitive rehabilitation in early schizophrenia, Ueland and Rund (2005) observed favorable post-treatment effects on early visual information processing at 1 year following neurocognitive training, which were not present at treatment completion, in a sample of early-onset patients with schizophrenia. To date, no studies have examined the most critical question: whether the effects of cognitive rehabilitation on functional outcome in early course patients can be maintained after the completion of treatment.

In this investigation, we conducted a one-year follow-up study of functional outcome in early course schizophrenia patients treated with either CET or an Enriched Supportive Therapy (EST) control to examine the degree to which the previously reported significant effects of CET on functional outcome in this sample were maintained post-treatment (Eack et al., 2009). In addition, we examined the effects of baseline cognitive functioning and cognitive improvement during the trial on the probability that treatment gains in functional outcome would be durable in the year following treatment completion.

2. Methods

2.1. Participants

Participants consisted of 58 patients in the early course of schizophrenia (n = 38) or schizoaffective disorder (n = 20), confirmed by the Structured Clinical Interview for DSM-IV (First et al., 2002). Eligibility criteria for participation included a diagnosis of schizophrenia, schizoaffective, or schizoaffective disorder; stabilization on antipsychotic medications; a time-span of no greater than 8 years since the onset of first psychotic symptoms; IQ ≥ 80; the absence of significant substance use problems for at least 2 months prior to study enrollment; and the presence of significant social and cognitive disability, as assessed using the Cognitive Style and Social Cognition Eligibility Interview (Hogarty et al., 2004). On average, participants included in this trial were young, with an age of 25.92 (SD = 6.31) years, and had been ill for 3.19 (SD = 2.24) years. The majority of participants were male (n = 40), Caucasian (n = 40), and not employed at study baseline (n = 43). Most participants had completed at least some college education (n = 39).

2.2. Measures

2.2.1. Functional outcome

Functional outcome was measured using the Social Adjustment Scale-II (SAS-II; Schooler et al., 1979) and the Major Role Adjustment Inventory (MRAI; Hogarty et al., 1974b), two standard measures of social adjustment in patients with schizophrenia. The SAS-II is an interview-based measure of social adjustment that consists of 44 items rated on a scale of 0 (good adjustment) to 4 or 5 (poor adjustment), depending on the item, that cover the domains of work affinity (e.g., work performance, time lost at work due to illness), primary/family relations in the household (e.g., friction with parents/spouse), social functioning outside the home (e.g., friction with extended relatives or parents not living with the patient), interpersonal anguish (e.g., distress at work, loneliness, satisfaction with social adjustment), sexual relations (e.g., frequency, interest in sexual relations), social leisure (e.g., frequency of social contacts, participation in social leisure activities, interpersonal effectiveness), and self-care (e.g., personal hygiene). The MRAI is a 32-item measure of major role adjustment that assesses vocational, social, and household role functioning. To complement data gathered from the SAS-II and maintain consistency with previous reports of CET (Hogarty et al., 2004; Eack et al., 2009), MRAI global functioning ratings concerning employment status (e.g., working, involved in volunteer work, involved in vocational rehabilitation), role functioning (e.g., meeting social and occupational obligations), functioning outside the home (e.g., interpersonal relations with friends), and overall functioning were included in this research. Previous studies have found the SAS-II and MRAI to have good interrater and test–retest reliability, to converge with other measures of functional outcome, and to be sensitive to treatment effects on functional outcome in schizophrenia (Hogarty et al., 2004; Hogarty et al., 1997; Eack et al., 2009; Schooler et al., 1979). To summarize effects on overall functional outcome, SAS-II and MRAI items were scaled to a common metric and averaged to form a social adjustment composite index, which displayed adequate internal consistency (α = .73).

2.2.2. Cognition

Neurocognitive and social-cognitive data were collected during the active phases of this treatment trial to examine CET effects on these cognitive domains. These data are included in this durability study to examine the degree to which cognitive functioning at baseline, as well as cognitive improvement during treatment was associated with greater maintenance of effects on functional outcomes. Neurocognitive data reflected the relevant domains outlined by the NIMH MATRICS committee, and included measures from the Revised Wechsler Memory Scale (Wechsler, 1987), California Verbal Learning Test (Delis et al., 1987), Revised Wechsler Adult Intelligence Scale (Wechsler, 1981), Trails B (Reitan and Walton, 1985), Wisconsin Card Sorting Test (Heaton et al., 1993), Tower of London (Culbertson and Zillmer, 1996), and Neurological Evaluation Scale (Buchanan and Heinrichs, 1993).
social-cognitive impairments in schizophrenia. The treatment consists of 60 h of computer-based training in attention, memory, and problem-solving; integrated with 45 1.5-hour social-cognitive group therapy sessions designed to facilitate the development of higher-order social-cognitive abilities, such as perspective-taking, social context appraisal, and foresightfulness. CET begins with approximately 3 months of computer-based training in attention in patient pairs, after which 3 to 4 pairs join together to form a social-cognitive group. Subsequently, neurocognitive and social-cognitive training continues concurrently throughout the remaining 2 years of treatment.

EST is a personalized, individual approach involving illness management and psychoeducation based on the demonstrably effective Personal Therapy (Hogarty, 2002). In this treatment, participants meet individually with a study clinician to learn more about schizophrenia, the effects of stress on the disorder, and how to develop and apply healthy coping strategies to prevent relapse and enhance adjustment. EST consists of two phases, the first of which is provided on a weekly basis and focuses on basic psychoeducation about schizophrenia and stress, and basic methods for avoiding/minimizing stress. The second phase is provided biweekly, and involves the personal identification of early warning signs of distress and application of coping strategies (e.g., diaphragmatic breathing, passive and active relaxation strategies) to manage stressors that pose particular challenges to each individual's social and role adjustment.

Finally, all participants were maintained by a study psychiatrist on antipsychotic medication approved by the Food and Drug Administration for the treatment of schizophrenia or schizoaffective disorder. Medication changes throughout the study were allowed, although every effort was made to stabilize patients on an acceptable medication regimen prior to the initiation of psychosocial treatment. No significant differences in medication dose, type, or clinician estimated compliance were observed between CET and EST patients during treatment (Eack et al., 2009).

### 2.4. Procedures

Participants were recruited from inpatient and outpatient clinics at the Western Psychiatric Institute and Clinic, Pittsburgh, PA and several nearby community clinics and hospitals. Upon recruitment, participants were screened for eligibility in consensus conferences utilizing videotaped interviews and then randomized to 2 years of CET or EST treatment by a project statistician. Participants were then assessed using the aforementioned measures of functional outcome by highly trained clinical raters not blind to treatment assignment. Functional outcome assessments were conducted annually during the 2 years of CET or EST treatment, and 1 year after treatment completion to assess the durability of functional gains. Cognitive assessments were administered via computer-based tests or by trained neuropsychologists not involved in the patient's treatment, and were conducted annually during the 2 years of active CET or EST treatment. In total, 58 patients were randomized and treated with either CET (n = 31) or EST (n = 27) in this trial. Of those randomized and treated, 49 (85%) and 46 (79%) patients completed the full 2 years of treatment, and 42 (72%) of
patients were available for follow-up at one-year post-treatment. There were no significant demographic or symptom differences between treatment groups at baseline (Eack et al., 2009), and no differences emerged between treatment groups with regard to attrition at one-year post-treatment follow-up, \( \chi^2(1, N = 58) = .001, p = .976 \).

2.5. Data analysis

Analysis of the durability of functional outcome effects of CET was conducted using an intent-to-treat approach with all 58 patients who were randomized and received any treatment in the trial. The primary test of treatment durability relied upon linear mixed-effects trend models to examine the degree to which CET maintained its functional advantage over EST at one-year post-treatment on the composite index of social adjustment. These analyses were followed by within-group trend models that characterized the degree of post-treatment gain or loss in social adjustment for each treatment group. Primary analyses on the social adjustment composite were followed by exploratory analyses of within-composite components of adjustment. Finally, post-hoc moderator analyses using piecewise linear mixed-effects models (separating the active and maintenance treatment phases of the trial) were employed to examine the degree to which demographic, illness, and cognitive characteristics at baseline, as well as degree of neurocognitive and social-cognitive improvement during treatment, predicted differential rates in the maintenance of functional gains. All mixed-effects models used random intercept and slope parameters, were estimated using restricted maximum-likelihood, employed autoregressive error structures where appropriate, and controlled for the confounding effects of age, gender, IQ, and illness duration at baseline. Missing data were estimated using the maximum-likelihood expectation maximization approach (Dempster et al., 1977).

3. Results

3.1. One-year durability of social adjustment effects

We began our analysis of the durability of CET effects on functional outcome by examining the persistence of differential effects between CET and EST on the overall multivariate composite of social adjustment, as well as its individual components, 1 year after treatment completion. Highly significant differential effects favoring CET on overall social adjustment continued to persist at one-year follow-up (see Table 2). In addition, no significant decreases in adjustment were observed in CET patients during the follow-up period (see Fig. 1). Interestingly, patients treated with EST showed a slight, but significant \( (p = .035) \) level of continued improvement in overall adjustment at one-year post-treatment.

With regard to effects on individual components of the social adjustment composite, differential improvement favoring CET continued to be observed at one-year post-treatment on 4 of the 5 measures of social adjustment that demonstrated significant effects during the active phases of treatment (see Table 2). In particular, significant maintenance of active CET treatment effects was found on social functioning in relationships outside the household and participation in social leisure activities, as well as on major role adjustment and overall ratings of global functioning. Previously observed differential positive effects on SAS-II interpersonal anguish scores were not maintained, primarily due to increased improvement on these scores in EST patients during post-treatment follow-up. In addition, trend-level employment effects were not significant at follow-up. In our previous report on competitive employment among patients treated in this trial, we observed a greater proportion of CET patients (54%) competitively employed compared to EST (18%) upon treatment completion (Eack et al., 2009; Eack et al., 2010, in press). At one-year follow-up, employment rates for CET patients were similar to those observed during active treatment (48%), whereas EST patients demonstrated a two-fold increase in competitive employment at follow-up (37%). Taken together, these findings indicate that CET effects on functional outcome among patients with early course schizophrenia are broadly maintained over the course of 1 year following the completion of treatment, and that EST may continue to promote some gains on social functioning and employment domains after treatment ends.

3.2. Predictors of one-year treatment durability

Having found that the effects of CET on functional outcomes were broadly maintained at one-year post-treatment, we proceeded to conduct a series of post-hoc analyses to examine the degree to which demographic and illness-related factors at baseline were predictive of treatment durability. In addition, we examined whether the magnitude of neurocognitive and social-cognitive improvement during the active phase of the trial was associated with a greater maintenance of treatment gains in social adjustment. Overall, no significant effects were observed for baseline age, gender, IQ, or illness duration on the durability of CET or EST effects on the social adjustment composite, all \( F(1, 121) < 1.33, \) all \( p > .252 \), and no interactions pointing to differential prediction of these factors between treatment groups was observed, \( F(1, 121) < .25, \) all \( p > .619 \).

When examining the effects of cognitive factors on treatment durability, neither neurocognitive, \( F(1, 123) = .12, \) \( p = .730 \), nor social-cognitive, \( F(1, 123) = .12, \) \( p = .730 \) functioning at baseline was predictive of who would maintain treatment gains on the social adjustment composite. However, two-year improvement in neurocognitive ability was significantly predictive of CET effects on social adjustment at one-year follow-up, such that individuals who demonstrated greater neurocognitive improvement during the active phases of treatment were significantly more likely to maintain gains in social adjustment during post-treatment follow-up, \( F(1, 123) = 7.56, \) \( p = .007 \). Concerning social cognition, people maintained their adjustment gains regardless of their degree of social-cognitive improvement during the active phases of treatment, \( F(1, 123) = 1.56, \) \( p = .214 \).

4. Discussion

Cognitive rehabilitation is emerging as an effective treatment for addressing cognitive impairments in patients with schizophrenia (McGurk et al., 2007a,b). Targeting cognitive impairments early in the course of the disorder
<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td>One-year durability effects of cognitive enhancement therapy on social adjustment in early schizophrenia.</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>CET</th>
<th>EST</th>
<th>Between-group effect</th>
<th>Within-group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 31)</td>
<td>(N = 27)</td>
<td>Active phase</td>
<td>Overall trend</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 3</td>
</tr>
<tr>
<td>Overall social adjustment</td>
<td>50.73 (9.58)</td>
<td>60.89 (11.22)</td>
<td>70.53 (13.50)</td>
<td>69.44 (14.19)</td>
</tr>
<tr>
<td>Employment</td>
<td>2.95 (1.30)</td>
<td>2.32 (1.26)</td>
<td>1.92 (1.21)</td>
<td>2.86 (1.36)</td>
</tr>
<tr>
<td>Work affinity</td>
<td>2.95 (1.30)</td>
<td>2.32 (1.26)</td>
<td>1.92 (1.21)</td>
<td>2.86 (1.36)</td>
</tr>
<tr>
<td>Social functioning</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Relationships outside the home</td>
<td>2.71 (0.89)</td>
<td>2.00 (0.91)</td>
<td>1.50 (0.66)</td>
<td>1.78 (0.85)</td>
</tr>
<tr>
<td>Interpersonal anguish</td>
<td>1.09 (0.64)</td>
<td>.79 (0.50)</td>
<td>.64 (0.49)</td>
<td>.68 (0.54)</td>
</tr>
<tr>
<td>Sexual relations</td>
<td>3.29 (1.31)</td>
<td>3.19 (1.51)</td>
<td>2.69 (1.65)</td>
<td>2.25 (1.71)</td>
</tr>
<tr>
<td>Primary relations</td>
<td>.98 (.74)</td>
<td>.72 (.65)</td>
<td>.50 (.60)</td>
<td>.65 (8.2)</td>
</tr>
<tr>
<td>Social leisure</td>
<td>1.51 (.84)</td>
<td>.98 (.87)</td>
<td>.66 (.70)</td>
<td>.94 (.73)</td>
</tr>
<tr>
<td>Global functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Major role adjustment</td>
<td>6.06 (.97)</td>
<td>5.26 (1.57)</td>
<td>3.83 (1.91)</td>
<td>3.81 (1.85)</td>
</tr>
<tr>
<td>Overall functioning</td>
<td>4.83 (.35)</td>
<td>4.38 (.71)</td>
<td>3.78 (1.18)</td>
<td>3.84 (1.14)</td>
</tr>
<tr>
<td>Self care</td>
<td>1.05 (.65)</td>
<td>.64 (.44)</td>
<td>.57 (.43)</td>
<td>.54 (.41)</td>
</tr>
</tbody>
</table>

Note. CET = Cognitive Enhancement Therapy, EST = Enriched Supportive Therapy.

* Composite indexes were scaled with a baseline mean (SD) of 50 (10), with higher scores indicating better adjustment.

* Possible scores range from 1 to 4, with higher scores indicating worse adjustment.

* Possible scores range from 0 to 5, with higher scores indicating worse adjustment.

* Possible scores range from 1 to 7, with higher scores indicating worse adjustment.
can result in significant functional benefits in such critical domains as employment, social functioning, and major role functioning (Eack et al., 2009). As with many studies of cognitive rehabilitation with chronic patients with schizophrenia, important questions remain about the lasting effects of these interventions, particularly their continued generalizability to broad functional improvements. In this study, we examined the effects of CET 1 year after treatment completion on functional outcomes in early course schizophrenia patients. Findings indicated that the benefits of CET on functional outcome were maintained in the year following treatment completion, particularly among those demonstrating earlier neurocognitive improvement, suggesting a lasting positive effect in the reduction of functional disability typically associated with the early course of the illness.

It is important to note that functional improvement was observed in both CET and EST. Improvements in EST likely reflect the benefits of psychoeducation and relapse prevention strategies, including stress reduction techniques, based on the effective Personal Therapy (Hogarty et al., 1997), which are also provided in CET. Although there is evidence of functional improvement with antipsychotic medication alone in the early course of schizophrenia (Robinson et al., 2004), that patients treated with CET continued to demonstrate large and significant improvements in social adjustment compared to EST suggests that CET confers greater benefits than those that can be achieved with combined antipsychotic treatment and effective psychoeducation and relapse prevention strategies. The social functioning domains that demonstrated the largest differential improvements favoring CET are to be expected, given the central focus of social cognition in the intervention. Other studies employing neurocognitive remediation strategies alone have had difficulty yielding broader functional benefits (Dickinson et al., 2010), which is consistent with the findings of a recent meta-analysis indicating that the effects of cognitive remediation programs on functional outcome are greater when combined with broader psychosocial interventions (McGurk et al., 2007a,b). CET accomplishes this by integrating neurocognitive and social-cognitive rehabilitation, which appears to confer significant functional benefits to both early course and chronic schizophrenia patients (Hogarty et al., 2004; Eack et al., 2009).

It is also interesting to note that the previously observed significant differential benefits of CET on competitive employment at the end of treatment were not maintained at one-year post-treatment. The absence of differential employment effects for CET was not due to a loss of employment gains among CET patients, who continued to demonstrate relatively high rates of employment (48%), but rather was a result of improved post-treatment employment outcomes among EST patients. The continued improvement of EST patients at one-year follow-up is likely reflective of the lasting benefits of stress regulation on functioning, which we have observed previously (Hogarty et al., 2006). Such findings also suggest that CET may produce more rapid effects on work outcomes, which are eventually possible for patients treated with a disorder-relevant, enriched supportive intervention. CET did, however, continue to maintain a large advantage over EST in other domains of functional outcome. The necessity of providing the full 2 years of CET is supported by previous reports indicating that the strongest effects from the intervention accrued only after 2 years of treatment (Hogarty et al., 2004; Eack et al., 2009). It will be important, however, for future studies to examine the durability of these effects over longer time periods, as well as whether they result in significant cost savings for society.

Although the results of this research point to the durability of CET effects on functional outcome in early schizophrenia, they should be interpreted in the context of a number of limitations. Raters were not blind to treatment assignment, and although structured interviews and highly trained clinical raters were used to avoid substantial rater bias, the absence of blind raters remains a limitation in this follow-up study. In addition, due to budget constraints, we were not able to collect data on neurocognitive and social-cognitive measures post-treatment, and thus the durability of previously reported effects on these domains is not known (Eack et al., 2009). Further, CET patients did receive more hours of treatment compared to those treated with EST. However, evidence from mediator analyses currently underway points to cognitive improvements as active mechanisms of functional gains in CET, as was found with chronic schizophrenia patients (Hogarty et al., 2006), supporting the presence of specific treatment effects on functional outcome. Finally, the modest sample size may have precluded the detection of smaller effects on functioning, particularly in the context of moderator analyses.

In summary, the results of this study indicate that the beneficial effects of CET on functional outcome in early schizophrenia can be maintained a year after the completion of treatment. While this investigation is limited by the absence of durability data on cognition and the use of non-blind raters, these findings highlight the potential lasting benefits of early cognitive rehabilitation in schizophrenia for reducing functional disability in the disorder. Given its potential lasting impact on the early trajectory of the illness, cognitive rehabilitation should be a key component of early intervention programs seeking to produce durable functional changes in the lives of early course schizophrenia patients.

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Contributors

This durability study was designed by the late Prof. Hogarty, and Drs. Keshavan and Eack. Dr. Eack conducted the analyses. Dr. Eack wrote the
initial draft of the manuscript, and Drs. Keshavan, Greenwald, and Mrs. Hogarty provided critical revisions and feedback on both the manuscript and analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest
The authors report no conflicts of interest.

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References


