Neuroprotective Effects of Cognitive Enhancement Therapy Against Gray Matter Loss in Early Schizophrenia

Results From a 2-Year Randomized Controlled Trial

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Context: Cognitive rehabilitation has shown efficacy in improving cognition in patients with schizophrenia but the underlying neurobiologic changes that occur during these treatments and support cognitive improvement are not well known.

Objective: To examine differential changes in brain morphology in early course schizophrenia during cognitive rehabilitation vs supportive therapy.

Design: Randomized controlled trial.

Setting: An outpatient research clinic at a university-based medical center that provides comprehensive care services for patients with severe mental illness.

Patients: A total of 53 symptomatically stable but cognitively disabled outpatients in the early course of schizophrenia or schizoaffective disorder.

Interventions: A 2-year trial with annual structural magnetic resonance imaging and cognitive assessments. Cognitive enhancement therapy is an integrated approach to the remediation of cognitive impairment in schizophrenia that uses computer-assisted neurocognitive training and group-based social-cognitive exercises. Enriched supportive therapy is an illness management approach that provides psychoeducation and teaches applied coping strategies.

Main Outcome Measures: Broad areas of frontal and temporal gray matter change were analyzed with longitudinal, voxel-based morphometry methods using mixed-effects models followed by volumetric analyses of regions that demonstrated significant differential changes between treatment groups.

Results: Patients who received cognitive enhancement therapy demonstrated significantly greater preservation of gray matter volume over 2 years in the left hippocampus, parahippocampal gyrus, and fusiform gyrus, and significantly greater gray matter increases in the left amygdala (all corrected P < .04) compared with those who received enriched supportive therapy. Less gray matter loss in the left parahippocampal and fusiform gyrus and greater gray matter increases in the left amygdala were significantly related to improved cognition and mediated the beneficial cognitive effects of cognitive enhancement therapy.

Conclusion: Cognitive enhancement therapy may offer neurobiologic protective and enhancing effects in early schizophrenia that are associated with improved long-term cognitive outcomes.

Trial Registration: clinicaltrials.gov Identifier: NCT00167362

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Schizophrenia is characterized by marked impairments in cognition that place profound limitations on functional recovery. Evidence increasingly suggests that a variety of neurobiologic abnormalities contribute to cognitive impairment in schizophrenia. Progressive loss of gray matter, frontal hypofunction, and decreased white matter integrity have been consistently observed in patients with schizophrenia. Frontotemporal dysfunction and gray matter loss in the prefrontal cortex, anterior cingulate, hippocampus, and superior temporal gyrus have all been linked to neurocognitive impairments in memory and executive function processes. Likewise, abnormalities in medial temporal and medial frontal brain networks including the amygdala, fusiform gyrus, and orbitofrontal cortex have been implicated in social-cognitive impairments in perspective taking, emotion perception, and foresight. Given the growing appreciation of the central importance of cognitive impairments and their underlying neurobiologic mechanisms in schizophrenia, there is great interest in developing novel therapeutics that preserve or restore cognitive and brain function in the disorder.
To date, the neurobiologically based impairments in cognition observed in schizophrenia have had limited response to pharmacotherapy\textsuperscript{19,20} at the cost of continued disability.\textsuperscript{21} In contrast, psychosocial cognitive rehabilitation programs have emerged as effective methods for remediating the cognitive impairments in schizophrenia that limit functional recovery.\textsuperscript{22,23} A recent meta-analytic review of all randomized controlled trials of cognitive remediation for individuals with schizophrenia found that, on average, patients who participate in these programs experience a nearly four-tenths standard deviation improvement in neurocognitive function, with modest improvements also seen in functioning and psychopathology.\textsuperscript{24} Programs that provide more comprehensive integration with other psychosocial components beyond neurocognitive rehabilitation also showed greater effects on functioning. We have previously demonstrated that an integrated neurocognitive and social-cognitive rehabilitation program known as Cognitive Enhancement Therapy\textsuperscript{25} (CET) can produce strong (Cohen $d > 1.00$) and lasting improvements in cognition and functioning for patients who have had chronic schizophrenia for many years.\textsuperscript{22,26,27} Very recently we provided evidence indicating that the cognitive and functional benefits of CET can be extended to individuals in the early course of the disorder, possibly capitalizing on a greater neurobiologic reserve in the first several years of the illness.\textsuperscript{28} After 2 years of treatment, young individuals with early course schizophrenia who received CET demonstrated substantial improvements in social and nonsocial cognition that ultimately translated into significant functional gains in employment, social functioning, major role adjustment, and activities of daily living.\textsuperscript{28}

Although the methods used in CET and other cognitive rehabilitation programs are psychosocial in nature, improvements in cognition presumably produce associated neurobiological changes\textsuperscript{29}, thus, the gains in neurocognitive and social-cognitive functioning in schizophrenia observed during cognitive rehabilitation could result in measurable changes in the brain. Furthermore, given that progressive neurobiologic deterioration has been observed in schizophrenia,\textsuperscript{6} cognitive rehabilitation might be best applied in the earliest phases of the illness to capitalize on a presumed neurobiologic and neuroplasticity reserve and protect against future neurobiological decline.\textsuperscript{29} Animal studies have repeatedly shown the ability of the brain to reorganize itself in response to environmental experiences,\textsuperscript{30} and previous studies conducted in children with dyslexia support the notion that cognitive training can induce a positive neurobiologic response.\textsuperscript{31} To date, only 2 published studies have examined the neurobiological effects of cognitive rehabilitation in schizophrenia. Wykes and colleagues\textsuperscript{32} studied the 3-month effects of cognitive rehabilitation in 12 patients with chronic schizophrenia using functional magnetic resonance imaging (MRI) and found significant increases in frontocortical activation in patients who received the treatment. However, potential associations of these functional changes with cognitive improvement were not examined. In addition, Wexler and colleagues\textsuperscript{33} found increased activation in the inferior frontal cortex after 10 weeks of verbal memory training in 8 patients with chronic schizophrenia, which was associated with verbal memory improvement. No studies have examined the long-term neurobiological effects of cognitive rehabilitation in early schizophrenia or the association of these effects with cognitive changes that occur during early course treatment.

In this study, we sought to characterize changes in brain morphology in a sample of patients with early course schizophrenia previously described in a 2-year randomized controlled trial of CET or an Enriched Supportive Therapy (EST) control,\textsuperscript{28} and examine the associations between brain structural and cognitive changes in an effort to identify the potential neurobiological effects of cognitive rehabilitation in early schizophrenia. It was hypothesized that CET would exert a neuroprotective effect against gray matter loss in regions implicated in neurocognitive and social-cognitive impairment and that these effects would be associated with better cognitive outcomes and mediate the previously demonstrated effects of CET on cognition.\textsuperscript{34}

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**METHOD**

**PARTICIPANTS**

Participants included 53 individuals in the early course of schizophrenia (n=35) or schizoaffective disorder (n=18) who participated in a 2-year randomized controlled trial of CET. Patients were included if they were stabilized with antipsychotic medication and had a diagnosis of schizophrenia or schizoaffective or schizophreniform disorder, as assessed using the Structured Clinical Interview for DSM-IV.\textsuperscript{35} Experienced their first psychotic symptom (including duration of untreated psychosis) within the past 8 years, had an intelligence quotient of 80 or higher, were not abusing substances for at least 2 months prior to study enrollment, and exhibited significant social and cognitive disability on the Cognitive Style and Social Cognition Eligibility Interview.\textsuperscript{28} Enrolled participants had a mean (SD) age of 26.17 (6.51) years, two-thirds (n=35) were male, and most were white (n=36) or African American (n=10). Most patients (77%) had experienced their first psychotic symptom within the past 5 years and, on average, individuals had been ill for a mean (SD) duration of 3.22 (2.2) years since their first psychotic symptom. Most patients had completed some college education (n=39), although most were not employed at study baseline (n=38).

**TREATMENT**

**Medications**

All participants were treated with antipsychotic medication for schizophrenia or schizoaffective disorder as prescribed by a study psychiatrist. Most participants received atypical antipsychotic medications (n=52) and were seen at least biweekly by a psychiatric clinical nurse specialist to evaluate efficacy, tolerability, and compliance. There were no significant differences in medication dose or clinician-estimated medication compliance between treatment groups at any point during the course of the study (eTable 1; http://www.archgenpsychiatry.com).

**Cognitive Enhancement Therapy**

Cognitive enhancement therapy\textsuperscript{25} is an integrated, developmental approach to the remediation of social and nonsocial cognitive deficits in schizophrenia. The treatment consists of 60 hours of weekly computer-based neurocognitive training in attention,
en can be found in the CET training manual.25

deficits in schizophrenia. A complete description of the treat-

ment is conducted in patient pairs with the assistance of a CET

of the basic and intermediate phases of the demonstrably effective

and EST and, while individuals treated with CET did, by design,

were also made available to patients who received CET through

a biweekly basis, although more frequent sessions were available

at their own pace. In the basic phase, patients meet weekly

with a therapist, and in the intermediate, treatment is provided on

a biweekly basis, although more frequent sessions were available

if needed. Components of EST on illness and stress management

were also made available to patients who received CET through

as 2 interview-based measures of social cognition, the Social Cog-

nition were included to assess the relationship between neuro-

ological and cognitive change during the 2 years of treatment.

Individual measures used to construct these composites have been

described in detail elsewhere.26 Briefly, a comprehensive neuro-

psychological testing battery was used to construct the general

neurocognitive composite, which included immediate and de-

layed recall of stories A and B from the Revised Wechsler Memory

Scale44; List A total recall, as well as short- and long-term free

recall scores from the California Verbal Learning Test42; digit-

span, vocabulary, picture arrangement, and digit symbol scores from

the Revised Wechsler Adult Intelligence Scale43; Trails B
time to completion45; categories achieved, perseverative and non-

perseverative errors, and percentage of conceptual-level

responses from the Wisconsin Card Sorting Test46; total move score

and ratio of initiation to execution time from the Tower of Lon-

don47; and cognitive-perceptual and repetition-motor neurologi-

cal soft sign scores from the Neurological Evaluation Scale.25 These

domains are reflective of those outlined by the National Insti-

tute of Mental Health Measurement and Treatment Research to

Improve Cognition in Schizophrenia (NIMH-MATRICS) com-

mittee as critical targets for cognitive enhancing treatments in

schizophrenia.28 We found the internal consistency of this neu-

rocognitive composite containing 18 variables from the afore-

mentioned measures to be excellent (α = .88).

The social cognition composite included a purposively broad

array of social-cognitive measures. These included the Mayer-

Salovey-Caruso Emotional Intelligence Test,48 which has sub-

sequently been recommended by the NIMH-MATRICS committee

for the assessment of social cognition in schizophrenia,29 as well

as 2 interview-based measures of social cognition, the Social Cog-

MEASURES

Enriched Supportive Therapy

Enriched supportive therapy is an individual psychotherapy ap-

proach that fosters illness management through psychoeducation

and applied coping skills. The approach is based on components

of the basic and intermediate phases of the demonstrably effective

personal therapy.37 In EST, patients meet individually with a thera-

pist to learn and practice a variety of stress-reduction and illness-

management techniques designed to forestall relapse and enhance

adjustment to the illness. The EST approach is designed to be sen-

sitive to the patient’s stage of recovery and divided into 2 phases.

The first, basic phase focuses on psychoeducation about schizo-

phrenia, the role of stress in the disorder, and symptom exacer-

bation, and introduces basic coping strategies to minimize and/or

avoid stress in one’s life. The second, intermediate phase advances

to a personalized approach to the identification of early cues of dis-
	ress and the application of healthy coping strategies to enhance

adjustment. By tailoring the treatment to the patient’s stage of re-

cover, EST allows individuals to move through the phases of treat-

ment at their own pace. In the basic phase, patients meet weekly

with a therapist, and in the intermediate, treatment is provided on

a biweekly basis, although more frequent sessions were available

if needed. Components of EST on illness and stress management

were also made available to patients who received CET through

the social-cognitive group curriculum. No attempt was made to

match the number of sessions or hours of treatment between CET

and EST and, while individuals treated with CET did, by design,

receive more hours of treatment, adherence, as defined by the per-

centage of scheduled sessions missed, was similar for both inter-

ventions (eTable 1).

IMAGE ACQUISITION AND PROCESSING

Structural MRIs were acquired from most patients using a 3-T

Signa whole-body scanner and head coil (GE Medical Systems,

Milwaukee, Wisconsin), although a small proportion of pa-

tients (n = 7) received 2-year scans on a 3-T Siemens whole body

scanner and head coil (Siemens, Erlangen, Germany). Struc-

tural MRI acquisition was identical between scanners, and whole-

brain volume was acquired in 124 1.3-mm–thick contiguous coro-

nal slices with spoiled gradient recalled acquisition in steady state

pulse sequence (echo time, 5 milliseconds; time to repetition, 25

milliseconds; acquisition matrix, 256 × 192; field of view, 24 cm).

After acquisition and initial quality control, images were nor-

malized to standard Montreal Neurological Institute space and

segmented into gray matter, white matter, and cerebrospinal fluid

compartment using the unified segmentation algorithm based

on a Montreal Neurological Institute template of adult brains in

the Statistical Parametric Mapping software, version 5 (Well-

come Department of Cognitive Neurology, Institute of Neuro-

logy, London, England).38 Segmented images were then smoothed

using a 12-mm gaussian kernel, and radio frequency inhomoge-

neity artifacts were corrected during image postprocessing using

a bias correction algorithm built into the segmentation proce-

dure. As this is the first study to examine the neuroanatomical

effects of cognitive rehabilitation in schizophrenia, broad re-

gions of interest were specified a priori based on previous liter-

ature on the neurobiologic correlates of cognitive dysfunction

in schizophrenia13,17 and included amygdala, caudate, cingulate

gyrus, dorsolateral prefrontal cortex, fusiform gyrus, hippocam-

pus, parahippocampal gyrus, putamen, and superior temporal

gyrus gray matter. Regions of interest were defined using the Wake

Forest University PickAtlas toolbox for SPM5,28 with regional
definitions outlined by Tzourio-Mazoyer and colleagues.30

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nition Profile and the Cognitive Style and Social Cognition Eligibility Interview, which were developed in previous studies of CET.23 The Mayer-Salovey-Caruso Emotional Intelligence Test is a 141-item, computer-administered, performance-based measure of emotion processing and management that has shown good psychometric properties in patients with schizophrenia.30,31 The Social Cognition Profile is a 50-item clinician-rated measure of social-cognitive behaviors gleaned from the literature on social cognition.32-35 The measure is based on Selman’s33 hierarchical stages of social-cognitive development and includes the domains of perceptive, supportive, tolerant, and self-confident behaviors indicative of adequate social cognition. The Cognitive Style and Social Cognition Eligibility Interview is a semistructured interview designed, in part, to capture functional disability relevant to impaired social cognition and covers 5 broad domains that include lack of foresight, social gist extraction deficits, interpersonal ineffectiveness, vocational ineffectiveness, and difficulty adjusting to disability. Previous psychometric studies have indicated good interrater, test-retest, and internal reliability for both of these measures.23 We found the internal consistency of this social cognition composite, which consisted of 12 variables from the aforementioned measures, to be acceptable (α = .71).

PROCEDURES

On recruitment, participants were randomly assigned by a project statistician to either CET or EST using computer-generated random numbers and treated for 2 years in their respective treatment condition. Individuals were then assessed using structural MRI and the aforementioned neurocognitive and social-cognitive measures prior to the initiation of treatment, and then annually for the 2 years of treatment. Initially, 67 patients were randomized to a treatment condition; however, only 38 received treatment because 9 patients moved, withdrew, or were found ineligible on further review prior to beginning psychosocial treatment (Figure 1). Although 38 patients were treated and had cognitive and behavioral data available for analysis, structural imaging data were only collected on 53 individuals, as 2 participants were too large to fit into the scanner, 1 had a metal object embedded in his thigh, 1 could not complete the scanning procedure owing to anxiety, and 1 withdrew consent before imaging. While there were no significant differences between those who had imaging data and those who did not with regard to age, illness duration, sex, race, employment status, diagnosis, symptomatology, treatment assignment, or cognitive performance on the neurocognitive and social-cognitive composites; individuals who completed the MRI procedures were significantly more likely to have some college education (χ2 = 8.14, P = .004). However, there were no significant differences between treatment conditions among individuals with MRI data with regard to demographics, attrition, or symptomatology at baseline (eTable 1). Of those with available imaging data, 8 had only an MRI at baseline, and 8 individuals had only 2 MRIs (6 with only baseline and year 1 scans and 2 with only baseline and year 2 scans). Reanalysis, excluding individuals with only baseline imaging data, did not change the results (eTable 2 and eTable 3). This research was reviewed annually by the University of Pittsburgh Institutional Review Board, and all patients provided written informed consent prior to participation.

STATISTICAL ANALYSIS

Intent-to-treat analyses were conducted with all 53 patients who had structural MRI data for at least 1 study time point and received any exposure to their psychosocial treatment condition. Differential rates of gray matter change between CET and EST were first investigated with voxel-based morphometry using linear mixed-effects models restricted to the anatomical regions of interest outlined above. Significant treatment × time interactions showing differences in linear rates of change in gray matter density were the effects of interest in these models. When testing the significance of more than 50 000 voxels in our region-of-interest mask across both brain hemispheres, we used AlphaSim to conduct a Monte Carlo simulation based on our imaging parameters and regions of interests to estimate a combined voxel-extent and α threshold that would maintain the corrected experimentwise error rate at acceptable levels (P < .05). This approach is more powerful than α thresholds alone, as random field theory indicates that effects are less likely to be false positives when they cluster together. Taking this into account allows more information than just P values to judge the veracity of an effect and, consequently, larger clusters of effects can be detected at greater α levels without sacrificing the overall experimentwise error rate. The results of 10 000 different simulations indicated that a combined voxel-extent threshold of 220 voxels and an uncorrected α threshold of P < .005 was sufficient to keep the corrected experimentwise rate at P < .05.

After identifying clusters of differential gray matter change between patients who received CET and EST during the 2 years of treatment using voxel-based morphometry, follow-up volumetric analyses were conducted by extracting gray matter volumes from SPM5 segmented images modulated by the Jacobian determinants of the images obtained during normalization to examine the differential effects of CET on gray matter volumes of specific anatomical regions. These volumetric data were then subjected to a series of linear mixed-effects trend models, using an

Figure 1. Flowchart of 2-year randomized trial of cognitive enhancement therapy for early-course schizophrenia. MRI indicates magnetic resonance imaging.
autoregressive error structure most appropriate to longitudinal data and allowing model intercepts and longitudinal trajectories to vary across subjects. All mixed-effects models, whether using voxel-based morphometry or extracted volumetric data, adjusted for potential demographic and medication confounds by including age, sex, intelligence quotient, illness duration, and medication dose as model covariates. In addition, although most (93%) data were collected on the same scanner, potential between-scanner differences were also controlled for by entering the scanner into the linear models as a covariate. Further, while only a small minority (2%) of structural scans demonstrated significant motion, sensitivity analyses were also conducted without these scans and revealed no significant differences in the results. All volumetric analyses also adjusted for intracranial volume, and $P$ values were corrected, when appropriate, for repeated inference testing of multiple volumetric regions within each cluster of results using Hochberg's correction.

Finally, mixed-effects growth curve models were used to explore the associations between longitudinal changes in gray matter volume and cognition, after adjusting for age, sex, intelligence quotient, illness duration, medication dose, scanner, and intracranial volume. Significant associations between gray matter and cognitive change prompted the initiation of mediator analyses using Kraemer and colleagues’ mediator-analytic framework developed for clinical trials. In this framework, the mediating effect is examined by regressing changes in brain volume on the previously documented differential rates of gray matter change and the beneficial cognitive effects of CET reported previously. Results from a series of mixed-effects growth models indicated that less loss of gray matter volume in the left parahippocampal gyrus, hippocampus, and fusiform gyrus; a cluster covering the left amygdala; and a cluster in right insula.

Follow-up tests of volumetric differences between treatment groups for specific regions identified in voxel-based morphometry analyses were consistent with a neuroprotective effect of CET against gray matter loss only for medial temporal regions. As can be seen in Figure 2, patients who received EST demonstrated significantly greater gray matter loss during 2 years in the left fusiform gyrus, hippocampus, and parahippocampal gyrus compared with patients who received CET. This trend was also apparent, although not statistically significant, at the nominal $\alpha$ level in the right insula. In addition, patients who received CET demonstrated significantly greater gray matter increases in the left amygdala than patients who received EST, who demonstrated no substantive increase in left amygdala volume during the 2 years of study. Significant differential effects observed in the anterior cingulate using voxel-based morphometry were not maintained in volumetric analyses.

RELATIONS BETWEEN CHANGES IN GRAY MATTER VOLUME AND COGNITION

Having found that patients who received CET demonstrated a decelerated loss of and, in some cases, increase in gray matter volume during 2 years of treatment compared with their EST-receiving counterparts, we proceeded to examine the relations between these differential rates of gray matter change and the beneficial cognitive effects of CET reported previously. Results from a series of mixed-effects growth models indicated that less loss of gray matter volume in the left parahippocampal and fusiform gyrus and greater growth in left amygdala volume were all significantly related to greater 2-year improvement in social cognition (Figure 3). In addition, less loss of left parahippocampal and fusiform gyrus volume was also significantly related to more improve-

Table 1. Voxel-Based Morphometric Analyses of Gray Matter Density Change in a 2-Year Trial of Cognitive Enhancement Therapy or Enriched Supportive Therapy (n=53)

<table>
<thead>
<tr>
<th>MNI Coordinates</th>
<th>Location</th>
<th>BA</th>
<th>$P$ Value</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x$</td>
<td>$y$</td>
<td>$z$</td>
<td>Cluster Size</td>
<td></td>
</tr>
<tr>
<td>-4</td>
<td>-66</td>
<td>-12</td>
<td>2925</td>
<td>Bilateral cerebellum, left culmen</td>
</tr>
<tr>
<td>-2</td>
<td>-32</td>
<td>34</td>
<td>553</td>
<td>Left medial and posterior cingulate</td>
</tr>
<tr>
<td>-26</td>
<td>-42</td>
<td>-6</td>
<td>803</td>
<td>Left parahippocampal gyrus, left fusiform gyrus, left hippocampus</td>
</tr>
<tr>
<td>-14</td>
<td>-2</td>
<td>-24</td>
<td>466</td>
<td>Left parahippocampal gyrus, left amygdala</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>16</td>
<td>346</td>
<td>Bilateral anterior cingulate</td>
</tr>
<tr>
<td>46</td>
<td>0</td>
<td>-6</td>
<td>268</td>
<td>Right insula</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; CET, cognitive enhancement therapy; EST, enriched supportive therapy; MNI, Montreal Neurological Institute; NA, not applicable.
ment in neurocognitive function. No significant relationships were observed between changes in anterior cingulate, left hippocampal, or right insula volume and change in cognition.

Subsequent mediator analyses indicated that the neuroprotective effects of CET against gray matter loss in the left parahippocampal ($z' = 1.56; P = .04$) and fusiform gyrus ($z' = 1.60; P = .03$) as well as CET effects on left amygdala increases ($z' = 1.64; P = .03$) all mediated the robust 2-year effects of CET on social cognition previously reported from this trial. $^{28}$ Further, CET effects protecting against gray matter loss in the left parahippocampal ($z' = 1.75; P = .03$) and fusiform gyrus ($z' = 1.78; P = .02$) also mediated the effects of CET on neurocognition.

Cognitive rehabilitation approaches have emerged as effective methods for ameliorating cognitive impairment in schizophrenia. $^{23}$ While the effects on cognition that these approaches produce have a presumed neurobiologic basis and, when applied in early schizophrenia, may exhibit a neuroprotective effect against loss of gray matter and brain function, $^{29}$ no study has examined the long-term neurobiologic effects of cognitive rehabilitation in schizophrenia. We assessed brain morphology in a sample of patients with early course schizophrenia who were treated for 2 years with CET or an active EST control.

**COMMENT**

Cognitive rehabilitation approaches have emerged as effective methods for ameliorating cognitive impairment in schizophrenia. $^{23}$ While the effects on cognition that these approaches produce have a presumed neurobiologic basis and, when applied in early schizophrenia, may exhibit a neuroprotective effect against loss of gray matter and brain function, $^{29}$ no study has examined the long-term neurobiologic effects of cognitive rehabilitation in schizophrenia. We assessed brain morphology in a sample of patients with early course schizophrenia who were treated for 2 years with CET or an active EST control.

**Table 2. Changes in Gray Matter Volume During 2 Years of Cognitive Enhancement Therapy or Enriched Supportive Therapy**

<table>
<thead>
<tr>
<th>Site/Cluster</th>
<th>CET (n=30)</th>
<th>EST (n=23)</th>
<th>Between-Group Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
<td>Year 2</td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior cingulate</td>
<td>5.85 (0.83)</td>
<td>5.88 (0.82)</td>
<td>5.90 (0.88)</td>
</tr>
<tr>
<td>Right anterior cingulate</td>
<td>5.08 (0.72)</td>
<td>5.04 (0.71)</td>
<td>5.00 (0.74)</td>
</tr>
<tr>
<td>Medial temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left amygdala</td>
<td>1.06 (0.13)</td>
<td>1.08 (0.11)</td>
<td>1.09 (0.12)</td>
</tr>
<tr>
<td>Left fusiform gyrus</td>
<td>9.84 (1.11)</td>
<td>9.92 (1.00)</td>
<td>10.00 (1.08)</td>
</tr>
<tr>
<td>Left hippocampus</td>
<td>3.96 (0.35)</td>
<td>3.97 (0.33)</td>
<td>3.97 (0.35)</td>
</tr>
<tr>
<td>Left parahippocampal</td>
<td>3.80 (0.46)</td>
<td>3.82 (0.38)</td>
<td>3.83 (0.43)</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right insula</td>
<td>7.76 (1.03)</td>
<td>7.84 (0.93)</td>
<td>7.91 (0.99)</td>
</tr>
</tbody>
</table>

Abbreviations: CET, cognitive enhancement therapy; EST, enriched supportive therapy; NA, not applicable.

$^a$ P Values are adjusted for multiple inference testing within each cluster of results using Hochberg’s correction.
The results support our hypothesis that cognitive rehabilitation provides a neuroprotective effect against gray matter loss in key regions implicated in social and non-social cognitive impairment in schizophrenia. In particular, while patients who received EST demonstrated loss of gray matter volume in the fusiform and parahippocampal gyrus, patients who received CET demonstrated gray matter preservation in these areas, and even a significant differential increase in left amygdala gray matter volume. Consistent with previous reports on the effects of CET on cognitive and functional outcome, these neuroprotective effects were the greatest after the full 2 years of treatment, suggesting the benefits of long-term exposure to cognitive rehabilitation. Importantly, these differential effects of CET on gray matter change were significantly related to improved cognitive outcome, with patients who experienced less gray matter decline and greater gray matter increases also demonstrating significantly greater cognitive improvements over the 2 years of study. Further, these neurobiologic changes were found to be significant mediators of CET effects on cognition. These findings persisted after adjusting for a variety of potential demographic, illness, and medication confounders and suggest that CET can have direct benefits to the brains of patients with schizophrenia.

Despite the beneficial effects of CET on brain morphology demonstrated in this study, these findings need to be interpreted in the context of a number of important limitations. Although morphometric findings support a neuroprotective effect of CET against the gray matter loss seen during the early course of schizophrenia (and in the case of the amygdala, even increase in gray matter), in the absence of functional neuroimaging data, the pathophysiological significance of these results for brain function is not clear. Overall structural changes in regional brain volumes were not large but were reliably detectable and may reflect functional changes. The fact that we observed significant relations between increased gray matter and cognitive improvement, and that the effects of CET on gray matter change were significant mediators of CET effects on cognition, suggests that brain functions that subserve neurocognition and social cognition have been improved. Nonetheless, functional neuroimaging data are needed to better understand the effects of CET on brain function. An integration of morphometric and functional MRI studies could be particularly informative in this regard.

It is also interesting to note that CET effects on brain regions commonly implicated in neurocognitive dysfunction in schizophrenia were quite modest. For example, no effects were seen in the dorsolateral prefrontal cortex, and only modest effects were observed in the anterior cingulate and hippocampus, which were not associated with neurocognitive change. Although gray matter change in the anterior cingulate and hippocampus might be more strongly related to individual neuropsychological tests, this pattern of findings parallels, to some degree, the cognitive effects observed in this trial of patients with early course schizophrenia. In this population, we have observed much stronger effects on social cognition and noted relative preservation of some general cognitive functions (particularly processing speed) in this sample. The absence of morphometric findings could reflect the better-preserved neurocognitive capacity of patients with early course schizophrenia. It is also possible that the effects of CET on brain regions impli-
18. Carter CS, Barch DM. Cognitive neuroscience-based approaches to measuring

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