ORIGINAL ARTICLE

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[1,2] that place profound limitations on functional recovery.[3-5] Evidence increasingly suggests that a variety of neurobiologic abnormalities contribute to cognitive impairment in schizophrenia. Progressive loss of gray matter,[6] frontal hypofunction,[7,8] and decreased white matter integrity[9,10] 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.[11-15] 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.[16,17] 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.[18]

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To date, the neurobiologically based impairments in cognition observed in schizophrenia have had limited response to pharmacotherapy[19,20] at the cost of continued disability.[21] In contrast, psychosocial cognitive rehabilitation programs have emerged as effective methods for remediating the cognitive impairments in schizophrenia that limit functional recovery.[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.[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[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.[22,26] 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.[27] 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.[28]

Although the methods used in CET and other cognitive rehabilitation programs are psychosocial in nature, improvements in cognition presumably produce associated neurobiological changes[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,[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.[29] Animal studies have repeatedly shown the ability of the brain to reorganize itself in response to environmental experiences,[30] and previous studies conducted in children with dyslexia support the notion that cognitive training can induce a positive neurobiologic response.[31] To date, only 2 published studies have examined the neurobiological effects of cognitive rehabilitation in schizophrenia. Wykes and colleagues[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[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,[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.[8]

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*,[34] 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.[22] 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[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, memory, and problem-solving using software developed by Ben-Yishay[35] and Bracy,[36] coupled with 45 weekly social-cognitive group sessions designed to address the key social-cognitive deficits that limit functional recovery from schizophrenia. Patients begin CET by first receiving a comprehensive neuropsychological assessment and then meeting individually with a CET coach to develop a therapeutic alliance, review results of neuropsychological testing, and develop an initial treatment plan reflective of each patient's goals. Neurocognitive training then proceeds in a hierarchical fashion, beginning with Ben-Yishay's Orientation Remediation Module to improve aspects of attention and speed of processing, followed by addressing higher-order neurocognitive abilities in the domains of memory and executive functioning with Bracy's PSSCogReHab software.[36] To promote socialization and reinforce the social-cognitive abilities that are the focus of the group curriculum, neurocognitive training is conducted in patient pairs with the assistance of a CET therapist/coach. After approximately 3 months of neurocognitive training in attention, 3 to 4 patient pairs come together to form a social-cognitive group. These groups provide patients with the necessary secondary socialization and experiential learning opportunities to develop a variety of social-cognitive abilities. Critical components of social cognition are addressed including perspective-taking, social gist abstraction, nonverbal communication, emotion management, and foresight. The group curriculum includes both innovative cognitive exercises and psychoeducation that foster the development of social-cognitive abilities and effective social interaction. Generalization to real-world settings is an explicit goal of CET, and is promoted through weekly homework assignments and individual coaching sessions tailored to the unique needs of the patient. Cognitive enhancement therapy integrates neurocognitive computer-based training with the social-cognitive group sessions to provide patients with a comprehensive approach to the remediation of cognitive deficits in schizophrenia. A complete description of the treatment can be found in the CET training manual.[25]

Enriched Supportive Therapy

Enriched supportive therapy is an individual psychotherapy approach 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 therapist 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 sensitive to the patient's stage of recovery and divided into 2 phases. The first, basic phase focuses on psychoeducation about schizophrenia, the role of stress in the disorder, and symptom exacerbation, 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 distress and the application of healthy coping strategies to enhance adjustment. By tailoring the treatment to the patient's stage of recovery, EST allows individuals to move through the phases of treatment 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 percentage of scheduled sessions missed, was similar for both interventions (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 patients ($n=7$) received 2-year scans on a 3-T Siemens whole body scanner and head coil (Siemens, Erhlangen, Germany). Structural MRI acquisition was identical between scanners, and whole-brain volume was acquired in 124 1.5-mm–thick contiguous coronal 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 normalized to standard Montreal Neurological Institute space and segmented into gray matter, white matter, and cerebrospinal fluid compartments using the unified segmentation algorithm based on a Montreal Neurological Institute template of adult brains in the Statistical Parametric Mapping software, version 5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England).[38] Segmented images were then smoothed using a 12-mm Gaussian kernel, and radio frequency inhomogeneity artifacts were corrected during image postprocessing using a bias correction algorithm built into the segmentation procedure. As this is the first study to examine the neuroanatomical effects of cognitive rehabilitation in schizophrenia, broad regions of interest were specified a priori based on previous literature on the neurobiologic correlates of cognitive dysfunction in schizophrenia[11,17] and included amygdala, caudate, cingulate gyrus, dorsolateral prefrontal cortex, fusiform gyrus, hippocampus, parahippocampal gyrus, putamen, and superior temporal gyrus gray matter. Regions of interest were defined using the Wake Forest University PickAtlas toolbox for SPM5,[39] with regional definitions outlined by Tzourio-Mazoyer and colleagues.[40]

MEASURES

Composite measures of general neurocognition and social cognition were included to assess the relationship between neurobiological and cognitive change during the 2 years of treatment. Individual measures used to construct these composites have been described in detail elsewhere.[28] Briefly, a comprehensive neuropsychological testing battery was used to construct the general neurocognitive composite, which included immediate and delayed recall of stories A and B from the Revised Wechsler Memory Scale[41]; List A total recall, as well as short- and long-term free recall scores from the California Verbal Learning Test[42]; digit-span, vocabulary, picture arrangement, and digit symbol scores from the Revised Wechsler Adult Intelligence Scale[43]; Trails B time to completion[44]; categories achieved, perseverative and nonperseverative errors, and percentage of conceptual-level responses from the Wisconsin Card Sorting Test[45]; total move score and ratio of initiation to execution time from the Tower of London[46]; and cognitive-perceptual and repetition-motor neurological soft sign scores from the Neurological Evaluation Scale.[47] These domains are reflective of those outlined by the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) committee as critical targets for cognitive enhancing treatments in schizophrenia.[48] We found the internal consistency of this neurocognitive composite containing 18 variables from the aforementioned measures to be excellent ($\alpha = .88$).

The social cognition composite included a purposively broad array of social-cognitive measures. These included the Mayer-Salovey-Caruso Emotional Intelligence Test,[49] which has subsequently been recommended by the NIMH-MATRICS committee for the assessment of social cognition in schizophrenia,[48] as well as 2 interview-based measures of social cognition, the Social Cognition Profile and the Cognitive Style and Social Cognition Eligibility Interview, which were developed in previous studies of CET.[22] 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.[50,51] The Social Cognition Profile is a 50-item clinician-rated measure of social-cognitive behaviors gleaned from the literature on social cognition.[52-55] The measure is based on Selman's[53] 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.[22] We found the internal consistency of this social cognition composite, which consisted of 12 variables from the aforementioned measures, to be acceptable ($\alpha = .71$).

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 58 received treatment because 9 patients moved, withdrew, or were found ineligible on further review prior to beginning psychosocial treatment (**Figure 1**). Although 58 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 ($\chi^2_1 = 8.14$, $P = .004$). 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.

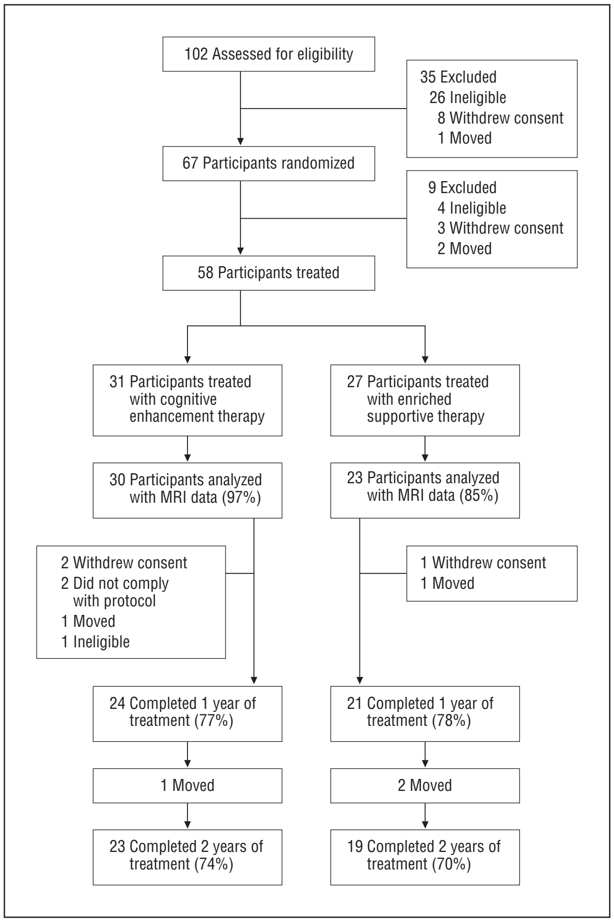

Figure 1. Flowchart of 2-year randomized trial of cognitive enhancement therapy for early-course schizophrenia. MRI indicates magnetic resonance imaging.

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[56] 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.[56] 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

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)

MNI Coordinates x	y	z	Cluster Size	Location	BA	z	*P* Value	Direction
				Main Effect of Time				
−4	−66	−12	2925	Bilateral cerebellum, left culmen	NA	5.67	<.001	Loss
−2	−32	34	553	Left medial and posterior cingulate	23, 31	3.83	<.001	Loss
				Treatment × Time Interaction				
−26	−42	−6	803	Left parahippocampal gyrus, left fusiform gyrus, left hippocampus	35, 36, 37	4.90	<.001	EST loss > CET loss
−14	−2	−24	466	Left parahippocampal gyrus, left amygdala	28, 34, 38	3.49	<.001	EST loss > CET loss
8	40	16	346	Bilateral anterior cingulate	9, 10, 32	3.46	<.001	EST loss > CET loss
46	0	−6	268	Right insula	22, 38	3.56	<.001	EST loss > CET loss

Abbreviations: BA, Brodmann area; CET, cognitive enhancement therapy; EST, enriched supportive therapy; MNI, Montreal Neurological Institute; NA, not applicable.

autoregressive error structure most appropriate to longitudinal data and allowing model intercepts and longitudinal trajectories to vary across subjects.[57] 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 (95%) 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.[58]

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'[59] mediator-analytic framework for clinical trials. In this framework, the mediating effect of changes in brain volume on the previously documented differential effects of CET on cognition[28] is examined. If mediation is present, the indirect effect of CET on cognition through neurobiologic change will achieve statistical significance and reduce the direct effect of CET on cognition.[60] The significance of the indirect effect of CET on cognition through neurobiologic change was calculated using estimates of the asymptotic distribution of indirect effects provided by MacKinnon and colleagues.[61] No correction for multiple inference testing was used in these exploratory analyses. Missing data for all analyses were handled using maximum-likelihood estimation.[62-64]

RESULTS

EFFECTS OF COGNITIVE ENHANCEMENT THERAPY ON 2-YEAR CHANGES IN GRAY MATTER MORPHOLOGY

Voxel-based morphometric analyses using mixed-effects models showed 3 primary areas of differential gray matter change between patients who received CET and those who received EST during 2 years of treatment (**Table 1** and **Figure 2**). Significant areas of differential effects included a cluster in the left medial temporal lobe, centering around the amygdala, parahippocampal gyrus, hippocampus, and fusiform gyrus; a cluster covering the bilateral anterior cingulate; 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 (**Table 2**). 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 α 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.[27,28] 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-

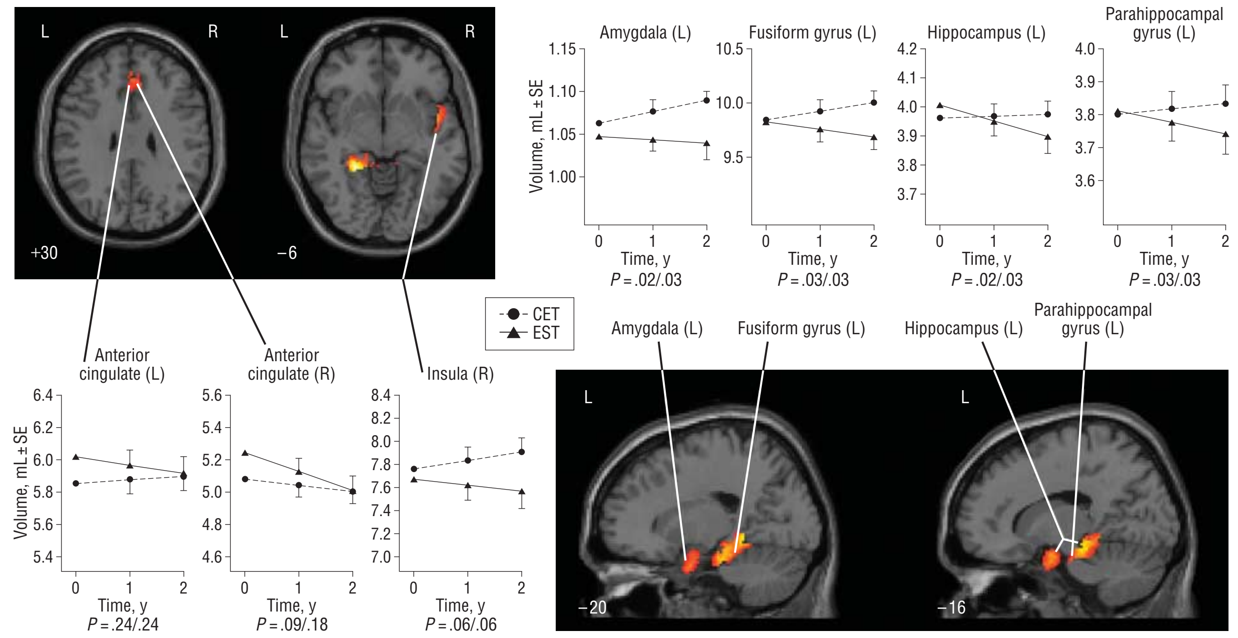

Figure 2. Regions of differential gray matter change among participants who received cognitive enhancement therapy vs enriched supportive therapy. *P* values to the right of the slash reflect Hochberg's correction. L indicates left; R, right; SE, standard error.

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

	Mean (SD) Gray Matter Volume, cm³								
	CET (n=30)			EST (n=23)			Between-Group Effect		
Site/Cluster	**Baseline**	**Year 1**	**Year 2**	**Baseline**	**Year 1**	**Year 2**	***t***	***P* Value**	***P* Value**[a]
Frontal									
Left anterior cingulate	5.85 (0.83)	5.88 (0.82)	5.90 (0.88)	6.02 (0.99)	5.97 (1.17)	5.92 (0.89)	1.17	.24	.24
Right anterior cingulate	5.08 (0.72)	5.04 (0.71)	5.00 (0.74)	5.25 (0.85)	5.13 (1.00)	5.01 (0.74)	1.72	.09	.18
Medial temporal									
Left amygdala	1.06 (0.13)	1.08 (0.11)	1.09 (0.12)	1.05 (0.13)	1.04 (0.15)	1.04 (0.12)	2.35	.02	.03
Left fusiform gyrus	9.84 (1.11)	9.92 (1.00)	10.00 (1.08)	9.83 (1.36)	9.76 (1.37)	9.69 (1.18)	2.23	.03	.03
Left hippocampus	3.96 (0.35)	3.97 (0.33)	3.97 (0.35)	4.01 (0.46)	3.95 (0.50)	3.90 (0.46)	2.28	.02	.03
Left parahippocampal gyrus	3.80 (0.46)	3.82 (0.38)	3.83 (0.43)	3.81 (0.49)	3.78 (0.49)	3.74 (0.36)	2.16	.03	.03
Temporal									
Right insula	7.76 (1.03)	7.84 (0.93)	7.91 (0.99)	7.67 (1.10)	7.62 (1.30)	7.57 (0.94)	1.91	.06	NA

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.

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.

COMMENT

Cognitive rehabilitation approaches have emerged as effective methods for ameliorating cognitive impairment in schizophrenia.[24] 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.

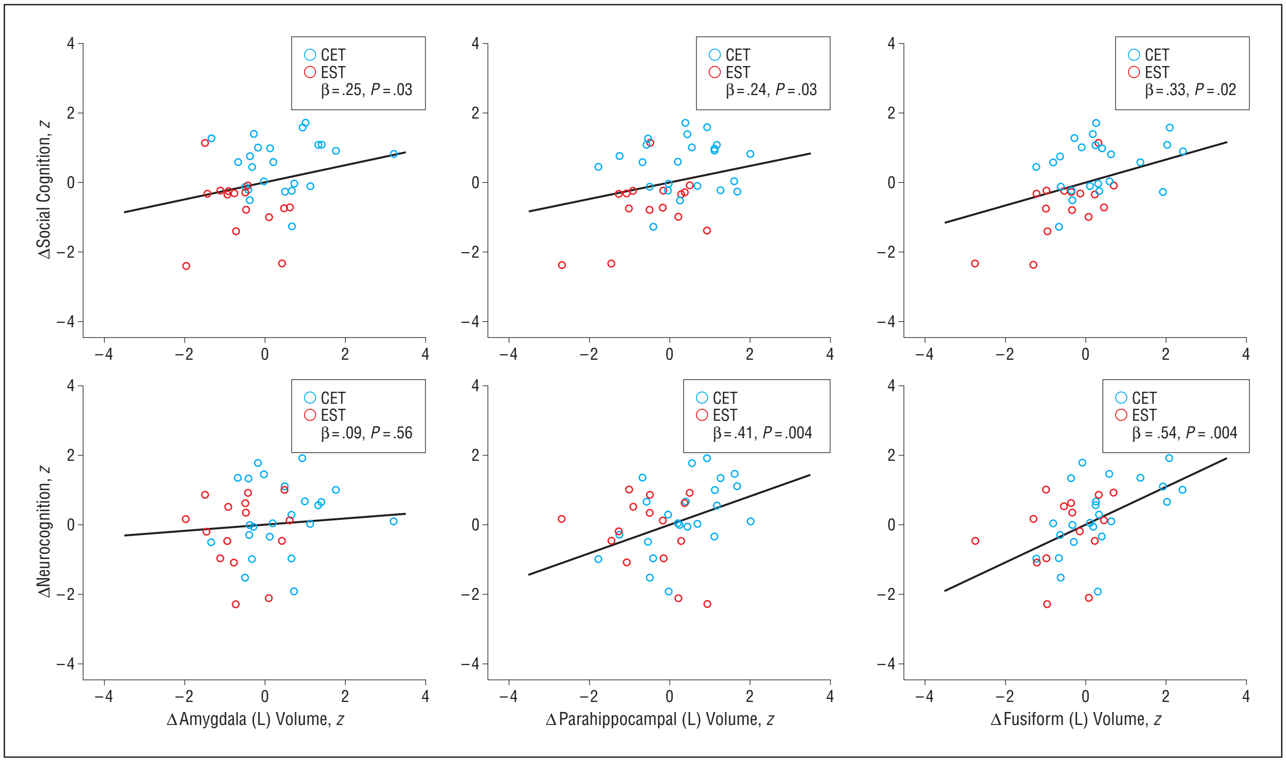

Figure 3. Relations between neurobiologic and cognitive change during 2 years of cognitive enhancement therapy (CET) or enriched supported therapy (EST).

The results support our hypothesis that cognitive rehabilitation provides a neuroprotective effect against gray matter loss in key regions implicated in social and nonsocial 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,[28] 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[6] (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.[28] The absence of morphometric findings could reflect the better-preserved neurocognitive capacity of patients with early course schzophrenia.[65] It is also possible that the effects of CET on brain regions implicated in neurocognitive impairment cannot be detected at a morphometric level but that the primary effects of this approach on frontal brain regions is toward a normalization of functioning. To date, many studies have documented frontal hypofunction in schizophrenia[8] and, if cognitive improvement occurs in the disorder, it is also likely to be the result of improved brain function.[32] As a consequence, while this study provides important information on the potential neuroanatomical effects of cognitive rehabilitation in early schizophrenia, future studies are clearly needed to continue to characterize the effects of CET on a variety of other neurobiologic parameters. It is important to remember, however, that significant relations were observed between changes in medial temporal regions and neurocognition as well as social cognition, suggesting the relevance of gray matter change in these regions to cognitive functioning. However, associations between gray matter and cognitive change were exploratory and not corrected for multiple inference testing; as such, these results need to be interpreted with caution until confirmatory replications are available.

This study is also limited by the absence of an appropriately matched group of healthy individuals who could provide data on normative brain development in early adulthood. Although a large body of evidence has accumulated in schizophrenia research indicating a progressive loss of gray matter from the earliest phases of the disorder,[6] healthy individuals also demonstrate some gray matter loss in early adulthood. However, loss appears to be greatest in the frontal cortex, not the subcortical regions demonstrating the most cognitive change in this study, which remain relatively stable or continue to grow after childhood.[66]

In summary, this investigation suggests that CET, a comprehensive cognitive rehabilitation approach, can protect against gray matter loss and may even support gray matter growth in medial temporal areas of the brain in service of cognitive enhancement among patients with early course schizophrenia. Although replication and further neurobiologic characterization is needed, these findings support the potential for cognitive rehabilitative approaches to positively affect the brain in schizophrenia. Further studies are needed to examine the durability of these effects on the brain, as Hogarty and colleagues[26] and Wexler and Bell[67] have both shown that cognitive rehabilitation can continue to confer benefits to patients with schizophrenia even after completion of treatment. Studies of neuronal mechanisms underlying brain change such as possible effects of cognitive remediation on dopaminergic function,[68] brain derived neurotrophic factor,[69] and the genomic underpinnings of response to cognitive remediation are also needed.[70]

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REFERENCES

1. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12(3):426-445.
2. Penn DL, Corrigan PW, Bentall RP, Racenstein J, Newman L. Social cognition in schizophrenia. *Psychol Bull*. 1997;121(1):114-132.
3. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. 2000;26(1):119-136.
4. Couture SM, Penn DL, Roberts DL. The functional significance of social cognition in schizophrenia: a review. *Schizophr Bull*. 2006;32(suppl 1):S44-S63.
5. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res*. 2004;72(1):41-51.
6. DeLisi LE. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. *Schizophr Bull*. 2008;34(2):312-321.
7. Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia I: regional cerebral blood flow evidence. *Arch Gen Psychiatry*. 1986;43(2):114-124.
8. Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, Berman KF, Goldberg TE. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry*. 2001;50(11):825-844.
9. Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum A. Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry*. 1999;56(4):367-374.
10. Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE, Niznikiewicz M, Connor EE, Levitt JJ, Frumin M, Kikinis R, Jolesz FA, McCarley RW, Shenton ME. DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. *Neuroimage*. 2005;26(4):1109-1118.
11. Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res*. 2004;70(2-3):117-145.
12. Perlstein WM, Carter CS, Noll DC, Cohen JD. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *Am J Psychiatry*. 2001;158(7):1105-1113.
13. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, Rotrosen J, Wolkin A. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. *Psychiatry Res*. 2002;116(1-2):1-23.
14. Kerns JG, Cohen JD, MacDonald AW III, Johnson MK, Stenger VA, Aizenstein H, Carter CS. Decreased conflict-and error-related activity in the anterior cingulate cortex in subjects with schizophrenia. *Am J Psychiatry*. 2005;162(10):1833-1839.
15. Rüsch N, Spoletini I, Wilke M, Bria P, Di Paola M, Di Iulio F, Martinotti G, Caltagirone C, Spalletta G. Prefrontal–thalamic–cerebellar gray matter networks and executive functioning in schizophrenia. *Schizophr Res*. 2007;93(1-3):79-89.
16. Eack SM, George MM, Prasad KMR, Keshavan MS. Neuroanatomical substrates of foresight in schizophrenia. *Schizophr Res*. 2008;103(1-3):62-70.
17. Pinkham AE, Penn DL, Perkins DO, Lieberman J. Implications for the neural basis of social cognition for the study of schizophrenia. *Am J Psychiatry*. 2003;160(5):815-824.
18. Carter CS, Barch DM. Cognitive neuroscience-based approaches to measuring

and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. *Schizophr Bull.* 2007;33(5):1131-1137.

19. Keefe RSE, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA; CATIE Investigators; Neurocognitive Working Group. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Arch Gen Psychiatry*. 2007;64(6):633-647.
20. Sergi MJ, Green MF, Widmark C, Reist C, Erhart S, Braff DL, Kee KS, Marder SR, Mintz J. Social cognition [corrected] and neurocognition: effects of risperidone, olanzapine, and haloperidol. *Am J Psychiatry*. 2007;164(10):1585-1592.
21. Swartz MS, Perkins DO, Stroup TS, Davis SM, Capuano G, Rosenheck RA, Reimherr F, McGee MF, Keefe RSE, McEvoy JP, Hsiao JK, Lieberman JA; CATIE Investigators. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *Am J Psychiatry*. 2007;164(3):428-436.
22. Hogarty GE, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, Kechavan M, Cooley S, DiBarry AL, Garrett A, Parepally H, Zoretich R. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. *Arch Gen Psychiatry*. 2004;61(9):866-876.
23. Bell M, Bryson G, Greig T, Corcoran C, Wexler BE. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. *Arch Gen Psychiatry*. 2001;58(8):763-768.
24. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KTA. Meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry*. 2007;164(12):1791-1802.
25. Hogarty GE, Greenwald DP. *Cognitive Enhancement Therapy: the Training Manual.* Cognitive Enhancement Therapy Web site. www.CognitiveEnhancementTherapy.com. Accessed March 1, 2010.
26. Hogarty GE, Greenwald DP, Eack SM. Durability and mechanism of effects of cognitive enhancement therapy. *Psychiatr Serv*. 2006;57(12):1751-1757.
27. Eack SM, Hogarty GE, Greenwald DP, Hogarty SS, Keshavan MS. Cognitive enhancement therapy improves emotional intelligence in early course schizophrenia: preliminary effects. *Schizophr Res*. 2007;89(1-3):308-311.
28. Eack SM, Greenwald DP, Hogarty SS, Cooley SJ, DiBarry AL, Montrose DM, Keshavan MS. Cognitive enhancement therapy for early course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatr Serv*. 2009;60(11):1468-1476.
29. Keshavan MS, Hogarty GE. Brain maturational processes and delayed onset in schizophrenia. *Dev Psychopathol*. 1999;11(3):525-543.
30. Buonomano DV, Merzenich MM. Cortical plasticity: from synapses to maps. *Annu Rev Neurosci*. 1998;21(1):149-186.
31. Temple E, Deutsch GK, Poldrack RA, Miller SL, Tallal P, Merzenich MM, Gabrieli JDE. Neural deficits in children with dyslexia ameliorated by behavioral remediation: evidence from functional MRI. *Proc Natl Acad Sci U S A*. 2003;100(5):2860-2865.
32. Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, Corner J. Effects on the brain of a psychological treatment: cognitive remediation therapy functional magnetic resonance imaging in schizophrenia. *Br J Psychiatry*. 2002;181(2):144-152.
33. Wexler BE, Anderson M, Fulbright RK, Gore JC. Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. *Am J Psychiatry*. 2000;157(10):1694-1697.
34. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview For DSM-IV-TR Axis I Disorders, Research Version, Patient Edition.* New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002.
35. Ben-Yishay Y, Piasetsky EB, Rattok J. A systematic method for ameliorating disorders in basic attention. In: Meir MJ, Benton AL, Diller L, eds. *Neuropsychological Rehabilitation.* New York, NY: Guilford; 1985:165-181.
36. Bracy OL. *PSSCogRehab.* Indianapolis, IN: Psychological Software Services Inc; 1994.
37. Hogarty GE. *Personal Therapy for Schizophrenia and Related Disorders: a Guide to Individualized Treatment.* New York, NY: Guilford; 2002.
38. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839-851.
39. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003;19(3):1233-1239.
40. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273-289.
41. Wechsler D. *Manual for the Wechsler Memory Scale-Revised.* San Antonio, TX: Psychological Corp; 1987.
42. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test Manual.* San Antonio, TX: Psychological Corp; 1987.
43. Wechsler D. *Wechsler Adult Intelligence Scale-Revised.* New York, NY: Psychological Corp; 1981.
44. Reitan RM, Waltson D. *The Halstead-Reitan Neuropsychological Test Battery.* Tucson, AZ: Neuropsychology Press; 1985.
45. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. *Wisconsin Card Sorting Test Manual: Revised and Expanded.* Odessa, FL: Psychological Assessment Resources Inc; 1993.
46. Culbertson WC, Zillmer EA. *Tower of London-DX Manual.* Dinas Powys, Wales: Cognitive Centre Foundation; 1996.
47. Buchanan RW, Heinrichs DW. The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res*. 1989;27(3):335-350.
48. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Fenton WS, Frese F, Goldberg TE, Heaton RK, Keefe RS, Kern RS, Kraemer H, Stover E, Weinberger DR, Zalcman S, Marder SR. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56(5):301-307.
49. Mayer JD, Salovey P, Caruso DR, Sitarenios G. Measuring emotional intelligence with the MSCEIT V2.0. *Emotion*. 2003;3(1):97-105.
50. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ III, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203-213.
51. Eack SM, Greeno CG, Pogue-Geile MF, Newhill CE, Hogarty GE, Keshavan MS. Assessing social-cognitive deficits in schizophrenia with the Mayer-Salovey-Caruso Emotional Intelligence Test [published online ahead of print July 22, 2008]. *Schizophr Bull*. 2010;36(2):370-380.
52. Baldwin MW. Relational schemas and the processing of social information. *Psychol Bull*. 1992;112(3):461-484.
53. Selman RL, Schultz LH. *Making a Friend in Youth.* Chicago, IL: University of Chicago Press; 1990.
54. Wyer RS, Srull TK, eds. *Handbook of Social Cognition: Basic Processes.* Vol 1. Hillside, NJ: Lawrence Earlbaum Association; 1994.
55. Brothers L. The social brain: a project for integrating primate behavior and neurophysiology in a new domain. *Concepts Neurosci*. 1990;1:27-51.
56. Ward DB. *Simultaneous Inference for fMRI Data.* Milwaukee, WI: Medical College of Wisconsin; 2000.
57. Raudenbush DSW, Bryk DAS. *Hierarchical Linear Models: Applications and Data Analysis Methods.* Thousand Oaks, CA: Sage; 2002.
58. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75(4):800-802.
59. Kraemer HC, Wilson G, Fairburn CG, Agras W. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002;59(10):877-883.
60. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173-1182.
61. MacKinnon DP, Fritz MS, Williams J, Lockwood CM. Distribution of the product confidence limits for the indirect effect: program PRODCLIN. *Behav Res Methods*. 2007;39(3):384-389.
62. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data using the EM algorithm. *J Royal Stat Soc B*. 1977;39(1):1-38.
63. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry*. 2004;61(3):310-317.
64. Hamer RM, Simpson PM. Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials. *Am J Psychiatry*. 2009;166(6):639-641.
65. Braw Y, Bloch Y, Mendelovich S, Ratzoni G, Gal G, Harari H, Tripto A, Levkovitz Y. Cognition in young schizophrenia outpatients: comparison of first-episode with multiepisode patients. *Schizophr Bull*. 2008;34(3):544-554.
66. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999;2(10):861-863.
67. Wexler BE, Bell MD. Cognitive remediation and vocational rehabilitation for schizophrenia. *Schizophr Bull*. 2005;31(4):931-941.
68. McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H, Klingberg T. Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science*. 2009;323(5915):800-802.
69. Vinogradov S, Fisher M, Holland C, Shelly W, Wolkowitz O, Mellon SH. Is serum brain-derived neurotrophic factor a biomarker for cognitive enhancement in schizophrenia? *Biol Psychiatry*. 2009;66(6):549-553.
70. Bosia M, Bechi M, Marino E, Anselmetti S, Poletti S, Cocchi F, Smeraldi E, Cavallaro R. Influence of catechol-O-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. *Neurosci Lett*. 2007;417(3):271-274.