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A Broad Cortical Reserve Accelerates Response to Cognitive Enhancement Therapy in Early Course Schizophrenia

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Introduction

Neuroimaging studies have provided compelling evidence for structural (Shenton et al., 2001) and functional (Gur et al., 2007, Minzenberg et al., 2009) brain abnormalities in schizophrenia. An understanding of the relation between brain abnormalities and functional outcome in schizophrenia is of considerable clinical importance. Nearly a half century ago, Cazzullo (Cazzullo, 1963) observed that patients with schizophrenia who had cerebral atrophy and/or enlarged ventricles as evaluated with pneumoencephalography had poorer response to antipsychotic treatment than patients without this abnormality. More recent studies using Magnetic Resonance Imaging (MRI) have shown that poor short term outcome following antipsychotic drug treatment in schizophrenia may be predicted by pre-treatment brain structural alterations, particularly in the prefrontal (Prasad et al., 2005, Kasperek et al., 2009) and the temporal cortex (Gur et al., 2007).

Increasing data suggest that psychological treatments such as cognitive remediation in schizophrenia lead to improvements not only in cognition but also in functional outcome in schizophrenia. Over the past twenty years, our group had developed the rationale, principles and approaches to cognitive remediation (Keshavan and Hogarty, 1999, Hogarty and Flesher, 1992, Hogarty, 2002), and tested a comprehensive approach to cognitive remediation, Cognitive Enhancement Therapy (CET), which has demonstrated efficacy (Hogarty et al., 2004, Hogarty and Greenwald, 2006, Eack et al., 2009, Eack et al., 2010b). CET is an integrated approach to the remediation of social and non-social cognitive impairments in schizophrenia. Several correlational studies show that executive functioning and memory may significantly predict social functioning in general (Green et al., 2004a) and following cognitive remediation (Kurtz et al., 2009). However, little is known about neurobiological predictors of treatment response in schizophrenia following psychosocial interventions.

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It has been known that the clinical manifestations of brain dysfunction in neuropsychiatric disorders often are not strongly associated with degree of brain pathology (Stern, 2002). For example, about a third of individuals who show characteristic post-mortem neuropathological markers of Alzheimer's disease (AD), such as plaques and tangles, show no cognitive impairment (Mortimer et al., 1981). Brains in these non-demented subjects are larger and have a greater number of neurons than elderly control subjects without histopathological markers of AD. Such observations have led to the view that a pre-illness neuronal "reserve", may moderate the relationship between pathology and clinical symptoms (Satz, 1993, Mortimer et al., 1981, Katzman et al., 1988). In this model, high brain reserve is seen as a protective factor against the development and/or expression of neurological conditions, and low reserve is a risk factor for the illness. The concept of cortical reserve has been investigated primarily in dementia and acute brain injury, but less so in schizophrenia, and may help address the question of outcome and treatment response prediction in the disorder.

In this study, we investigated the relationship between pre-treatment cortical reserve as measured by cortical gray matter volumes and surface areas (GM/CS) and cognitive/social cognitive outcome following intervention with cognitive remediation or a supportive control intervention over a two year period in early course schizophrenia patients. Specifically, we hypothesized that pre-treatment cortical volumetric measures would predict the previously documented robust effects of CET on neurocognition and social cognition (Eack et al., 2009). We sought to examine the one and two year outcome measures to investigate the relation between pre-treatment GM/CS and the speed of therapeutic response. We also investigated the degree to which any specific brain regions of interest were responsible for these moderating effects, with the hypothesis that structures strongly implicated in schizophrenia such as the prefrontal and temporal cortices might have a stronger predictive value on outcome, based on prior literature (Prasad et al., 2005, Gur et al., 1998).

Method

Participants

Participants consisted of 50 individuals in the early course of schizophrenia ($n = 33$) or schizoaffective disorder ($n = 17$) verified by the Structured Clinical Interview for DSM-IV (First et al., 2002). All individuals participated in a two-year randomized-controlled trial of CET reported on previously (Eack et al., 2009, Eack et al., 2010b). Eligibility criteria for entering the trial included a diagnosis of schizophrenia or schizoaffective disorder, stabilization on antipsychotic medications, time since first psychotic symptom of no greater than 8 years, $IQ \geq 80$, the absence of significant substance abuse for at least 2 months prior to study enrollment, and the presence of significant social and cognitive disability on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). Participants enrolled were young, with an average age of 25.72 ($SD = 5.94$) years, had been ill for an average of 3.26 ($SD = 2.21$) years, and the majority were male ($n = 32$). The sample was predominantly White ($n = 34$), with 9 African Americans, 6 Asians, and 1 patient describing his/her race as other. The majority of participants had attended some college ($n = 36$), although most were not employed ($n = 36$).

Treatments

Participants were randomly assigned to two years of either CET or an active Enriched Supportive Therapy (EST) control condition, both of which have been described in previous reports (Hogarty et al., 2004, Eack et al., 2009). During the course of CET individuals complete approximately 60 hours of weekly computer-based neurocognitive training in attention, memory, and problem-solving, along with 45 weekly social-cognitive group

sessions focusing on improving broad domains of social cognition. Neurocognitive training is conducted in patient pairs with the aid of CET therapist/coach and makes use of the attention training exercises developed by Ben-Yishay (Ben-Yishay et al., 1985), as well as the memory and problem-solving exercises of Bracy (Bracy, 1994). After approximately 3 months of computer-based training in attention, 3 to 4 patient pairs form a small social-cognitive group. These groups focus on providing the secondary socialization and experiential learning opportunities needed to develop broad social-cognitive abilities, including perspective-taking, gistfulness, social context appraisal, emotion perception and management, and foresightfulness. Social-cognitive groups are provided for 1.5 hours per week, and proceed concurrently with the 1-hour weekly neurocognitive training sessions throughout the remaining two years of treatment. A complete description of the treatment can be found in the CET training manual (Hogarty and Greenwald, 2006).

EST is an individual illness management and psychoeducation approach based on components of the basic and intermediate phases of Personal Therapy (Hogarty, 2002). In this approach, patients meet individually with a therapist to learn more about schizophrenia and the role of stress in exacerbating the illness, how to identify and detect their own personal cues of distress, and how to develop and apply healthy coping strategies for managing stressors that pose particular challenges to social and role adjustment. EST is tailored to the phase of recovery of each individual. In the first phase of the treatment, individuals meet weekly with a therapist for 30 to 60 minutes to learn basic information about schizophrenia and ways to minimize or avoid stress. In the second phase, the sessions are biweekly and the therapy focuses on a personalized approach to the identification of an individual's early cues of stress and the application of specific healthy coping strategies. Individuals are encouraged to pace themselves and gradually work towards their goals while managing life stressors that typically challenge social and role functioning. No attempt was made to artificially match the number of hours of treatment provided in CET and EST, and EST was chosen to control specifically for the effects of illness management and psychoeducation on outcome.

Finally, all patients were maintained by a study psychiatrist on antipsychotic medications approved by the Food and Drug Administration for the treatment of schizophrenia or schizoaffective disorder. Medication changes were allowed during the course of the study, although every effort was made to stabilize patients on an effective and acceptable medication regime prior to starting psychosocial treatment. There were no significant differences between CET and EST patients at any study time point with regard to antipsychotic dose, type, or clinician-estimated compliance (Eack et al., 2009).

Image Acquisition and Processing

Structural magnetic resonance imaging (MRI) data were acquired at study baseline prior to the initiation of psychosocial treatment using a 3-T Signa whole body scanner and head coil (GE Medical Systems, Milwaukee, WI). Whole-brain volume was acquired in 124 1.5mm-thick contiguous coronal slices with spoiled gradient recalled acquisition in steady state pulse sequence (TE = 5ms, TR = 25ms, acquisition matrix = 256×192 , FOV = 24cm). Images were checked manually for quality by a master's-level research assistant, and then normalized to standard Montreal Neurological Institute (MNI) space. Cortical surface area parameters were extracted using FreeSurfer version 4.3 (<http://surfer.nmr.mgh.harvard.edu>). FreeSurfer has three automated stages, each followed by manual image editing by an experienced rater; the first stage performs skull stripping, motion correction and gray-white segmentation. This is followed by an automated parcellation of the cortex based on an MNI template, gyral anatomical landmarks and gray matter volume measurements of the parcellated regions, a method shown to be valid and reliable with manual tracing (Fischl et al., 2002) (Desikan et al 2006) and is robust to anatomical alterations noted in schizophrenia

(Boos et al., 2007). To obtain cortical lobar surface area measures, the gyral and sulcal surface measurements across cortical regions within each lobe were averaged. Freesurfer provides cortical surface area measures which tell us about trait- related variations in brain structure (while cortical thickness more closely reflects the state related brain structural changes that may be influenced by illness and developmental changes; these measures may be differentially affected in schizophrenia (Voets et al 2008; Prasad et al 2010)). Cortical volume measures, by contrast, are derived from a composite of area and thickness measures.

Volumetric data were first processed by segmenting normalized images into gray matter, white matter, and cerebrospinal fluid compartments using the unified voxel based morphometry (VBM) segmentation algorithm based on a MNI adult brain template in Statistical Parametric Mapping software, version 5 (Ashburner and Friston, 2005) (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Cortical and sub-cortical gray matter volumes were then extracted from segmented images modulated by their Jacobian determinants obtained during spatial normalization based upon whole-brain and regional masks outlined by Tzourio-Mazoyer and colleagues (Tzourio-Mazoyer et al., 2002) and implemented using the Brodmann area- based Wake Forest University PickAtlas toolbox for SPM5 (Maldjian et al., 2003).

Measures

Neurocognitive and social-cognitive assessments were conducted to examine the effects of CET on broad cognitive domains, and the degree to which a pre-treatment brain structural measures might moderate these effects. Neurocognitive measures represented the domains of verbal and working memory, executive function, language, psychomotor speed, and soft neurological signs, all of which have been commonly implicated in cognitive impairment in schizophrenia (Heinrichs and Zakzanis, 1998). Given the number of items included across neurocognitive tests, a composite index of neurocognition was constructed from immediate and delayed recall items from stories A and B of the Revised Wechsler Memory Scale (Wechsler, 1987); vocabulary, digit span, digit symbol, and picture arrangement items from the Revised Wechsler Adult Intelligence Scale (Wechsler, 1981); List A total recall, short-term free recall, and long-term free recall from the California Verbal Learning Test (Delis et al., 1987); categories completed, perseverative and non-perseverative errors, and percentage of conceptual responses from the Wisconsin Card Sorting Test (Heaton et al., 1993); Trails B time to completion (Reitan and Waltson, 1985); total move score and ratio of initiation to execution (planning) time from the Tower of London (Culbertson and Zillmer, 1996); and cognitive-perceptual and repetition-motor subscales from the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989; Sanders et al 2005). These items were scaled to a z-metric and averaged to form the neurocognitive composite, which displayed good internal consistency (Cronbach's $\alpha = .88$).

Social cognition was assessed using the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer et al., 2003). The MSCEIT is a performance-based measure of emotion processing designed to assess the four domains of emotional intelligence theorized by Salovey and Mayer (Salovey and Mayer, 1990). These domains or "branches" consist of the perception, facilitation, understanding, and management of emotions. The MSCEIT contains 141 multiple choice items spanned across 8 different tasks. Two tasks form a single branch in Salovey and Mayer's 4-branch model of emotional intelligence. For example, a task asking participants to judge emotions in faces and another task asking participants to judge emotions in scenery form the Emotion Perception subscale of the instrument. The MSCEIT was completed using the computerized method recommended by the test developers, and scored based on unadjusted consensus norms. The Emotion Management subscale of this measure has been recommended by the NIMH-MATRICES committee for the assessment of social cognition in schizophrenia (Green et al., 2004b), and we and others have previously

demonstrated the reliability and validity of the MSCEIT among schizophrenia patients (Eack et al., 2010a, Nuechterlein et al., 2008). The complete MSCEIT was used in this research, and the total MSCEIT score was used to assess social cognition, which demonstrated excellent internal consistency (Cronbach's $\alpha = .95$).

Procedures

Patients were recruited from Western Psychiatric Institute and Clinic, Pittsburgh, PA and nearby community clinics for a two-year trial of CET. Upon recruitment, participants were assessed for study eligibility and then randomized to two years of either CET or EST. Neurocognitive and social-cognitive assessments were completed prior to treatment, and at one and two years of treatment. Computer-based neurocognitive and social-cognitive measures were completed by patients on the computer with the supervision of a research associate, and the remaining measures were collected by trained neuropsychologists and raters who were not blind to treatment assignment. In total, 58 patients were randomized to CET or EST and received any exposure to treatment. However, complete cognitive and pre-treatment MRI data were only available on 50 individuals (29 in CET, 21 in EST), who are included in this study. There were no significant differences with regard to demographics, IQ, treatment assignment, baseline symptomatology or baseline cognition (social or non-social cognition) between the 50 individuals included in this study and the total sample. In addition, there were no significant differences between treatment groups with regard to any of these characteristics or attrition (Eack et al., 2009). All 50 individuals received some exposure to their respective treatment condition, with 44 (88%) and 41 (82%) completing one and the full two years of treatment, respectively. There were no significant differences between treatment groups with regard to attrition, all $\chi^2(1, N = 50) < .06$, all $p > .835$. In addition, there were no significant differences between treatment groups with regard to whole brain cortical surface area or gray matter volume, all $|t(48)| < .60$, all $p > .585$.

Data Analysis

Moderator models based on the clinical trials framework for moderator analyses outlined by Kraemer, Wilson, Fairburn, and Agras (Kraemer et al., 2002) were constructed to assess the impact of pre-treatment cortical surface area and gray matter (GM/CS) volume on social and non-social cognitive response to CET. To establish that these baseline brain structural measures are a specific predictor of CET treatment response, moderator analyses were conducted with the total sample of patients assigned to CET or EST, which allowed for the examination of GM/CS effects on differential treatment response to CET versus EST. In such models, the Treatment $\times$ Time $\times$ GM/CS interaction is the effect of interest and represents the impact of a neurobiologic reserve on improvement (Time) that is specific to one of the study treatments (CET or EST), also known as a moderator of differential treatment effects. A Time $\times$ GM/CS interaction in the absence of a Treatment $\times$ Time $\times$ GM/CS interaction represents a predictor of treatment improvement, but one that is not specific to any of the study treatments and thus is not a moderator of treatment effectiveness. Reserve predictors (cortical surface area and gray matter volume) and their interactions were analyzed as untransformed continuous variables. Visualization of interactions for high vs. low reserve patients are based upon model estimates at .50 *SD* above and below, respectively (Aiken and West, 2001). Moderator analyses utilized intent-to-treat linear mixed-effects models with all 50 patients who received any exposure to their respective treatment condition. Missing data were handled during maximum-likelihood estimation using the expectation-maximization approach (Dempster et al., 1977). All moderator models adjusted for the potential confounding effects of age, gender, IQ, illness duration, medication dose, and baseline social cognition; and made use of an auto-regressive error structure most suitable for longitudinal data when appropriate (Raudenbush and Bryk, 2002). Type I error rates were maintained at acceptable ($p = .05$) levels within primary

analyses of the effects of whole brain and lobar cortical surface area and gray matter volume measures on neurocognitive and social-cognitive treatment response at each follow-up period using Benjamini and Hochberg's (Benjamini and Hochberg, 1995) correction for multiple inference testing. Corrections to control Type I error were not applied to post-hoc region of interest analyses.

Results

Effects of a Cortical and Brain Volumes on Response to Cognitive Enhancement Therapy

We began our analysis of the association between baseline GM/CS and cognitive response to CET by first conducting a series of moderator analyses examining the effects of both total and lobar pre-treatment surface area and gray matter volume on differential neurocognitive and social-cognitive improvement during CET. As can be seen in Table 1, neither pre-treatment cortical surface area nor gray matter volume was predictive of a differential neurocognitive response to CET, indicating that CET patients demonstrated similar levels of neurocognitive improvement regardless of baseline GM/CS measures. However, increased pre-treatment cortical surface area and gray matter volume were both broadly predictive of social-cognitive response to CET. Effects ranged from small ($d = .19$) to medium ($d = .58$) in magnitude, and the benefits of a larger GM/CS were apparent in all lobar measurements of surface area and gray matter volume, with the exception of occipital lobe volume, which did not reach conventional significance levels after correction for multiple inference testing. Interestingly, a greater GM/CS was only predictive of social-cognitive response to CET during the first year of treatment, but not at the end of the full two years of CET.

To inspect the nature of the moderating effect of a pre-treatment brain structural measures on social-cognitive response to CET, effect sizes of social-cognitive improvement were examined among those with higher versus lower surface area and gray matter volume at study baseline (see Figure 1). Results revealed that CET patients with greater baseline GM volumes showed a rapid improvement in social cognition during the first year of treatment. In contrast, patients with reduced cortical surface and gray matter demonstrated an attenuated 1-year social-cognitive treatment response, which only approached the level of improvement of high GM/CS patients after completing the full two years of treatment. This effect was particularly marked for pre-treatment gray matter volume, where little social-cognitive improvement ($d = .09$) was observed among low GM volume CET patients during the first year of treatment, compared to the strong improvement ($d = .64$) demonstrated by CET patients with high GM volume. However, by the end of the full two years of CET, effect sizes of social-cognitive improvement for low ($d = .45$) and high GM volume ($d = .60$) patients were of similar magnitude. Together, these findings suggest that baseline GM/CS may predict an accelerated treatment social-cognitive treatment response to CET.

Regional Neurobiologic Predictors of Social-Cognitive Response to Cognitive Enhancement Therapy

Having observed that baseline cortical GM/CS was significantly predictive of a more rapid social-cognitive response to CET across whole-brain and the majority of lobar measurements, we proceeded to examine the degree to which any specific brain regions of interest were responsible for these moderating effects. When first examining the relative contribution of cortical surface area lobar measurements simultaneously, none of the individual lobes significantly contributed to differential 1-year CET response on social cognition, after adjusting for other lobar surface areas, all $|t(24)| < .76$, all $p > .457$. This suggested a global cortical “reserve” effect on social-cognitive response to CET, and thus surface areas of individual regions of interest were not further investigated. With regard to brain volume, only temporal lobe gray matter volume significantly contributed to an

accelerated CET response on social cognition after adjusting for other lobar measurements, $t(24) = 4.71, p = .033$, potentially indicating a specific effect of temporal lobe volumetric measures on social-cognitive improvement during CET.

We then examined the moderating impact of GM volumes in individual temporal regions of interest commonly implicated in social-cognitive impairment in schizophrenia (Pinkham et al., 2003), on 1-year CET effects on social cognition. As can be seen in Table 2, all region of interest measurements of temporal gray matter volume demonstrated a significant bilateral moderating effect, with the exception of a non-significant trend in right amygdala. The direction of these effects was consistent, and indicated that a broad range of regions, the amygdala, fusiform gyrus, hippocampus, insula, parahippocampal gyrus, and superior temporal gyrus predicted an accelerated 1-year social-cognitive response to CET. Bilateral superior temporal gyri volumes were the strongest predictors of social-cognitive treatment response. However, when examining these regional effects while adjusting for the effect of a global gray matter volumes, none of the individual regions continued to be predictive of social-cognitive improvement during CET, although right superior temporal gyrus gray matter volume continued to display a large and trend-level effect. Regions of interest in other lobes (e.g., dorsolateral prefrontal cortex, anterior cingulate) were also explored, which showed the same pattern of results and did not remain significant predictors of CET response after adjusting for a global gray matter effect. Such results largely point to the impact of a global cortical surface and gray matter volumes on early social-cognitive response to CET, with regional-specific effects in the temporal lobe, particularly the superior temporal gyrus.

Discussion

Our main findings indicate that higher baseline cortical surface area and gray matter volume both broadly predicted social-cognitive response to CET. The effects of a greater GM/CS “reserve” were apparent in all lobar measurements of surface area and gray matter volume, except for occipital lobe volume, which did show a trend-worthy relationship to social-cognitive response that did not survive correction for multiple inference testing. This observation is of interest, since occipital lobe reduction is relatively less common across individuals in schizophrenia (Shenton et al., 2001, Goldstein et al., 1999, Quarantelli et al., 2002, Okugawa et al., 2007). Interestingly, poor outcome in schizophrenia has been reported to be related to lower fronto-occipital metabolic ratios (Buchsbaum et al., 2002). However, some studies do suggest morphometric alterations in this brain region as well as assessed in MRI (Davatzikos et al., 2005) and neuropathological studies (Selemon et al., 1995).

While the relationship between cortical structure and social cognition response was broadly present across diverse lobar regions, it appeared that the temporal cortex had a stronger effect, in particular the superior temporal cortex. This may be related to the observations that superior temporal gyrus (STG) gray matter reduction is among the most frequently reported MRI finding in patients with schizophrenia (Shenton et al., 2001); additionally, this brain region is a critical part of the neural network subserving key aspects of social cognition that may be impacted by CET (Bertrand et al., 2008, Yu et al., 2010, Hooker et al., 2010). A broad predictive effect was observed, however, in many different brain regions using two different methodologies covering cortical surface area (FreeSurfer) and gray matter volume (modulated volumes from VBM). The widespread nature of these effects across the brain may represent the importance of a global brain “reserve”, or point to the cumulative impact of the many different brain regions involved in social cognition (Pinkham et al., 2003). Further, gray matter measurements clearly implicated sub-cortical regions as predictors of accelerated social-cognitive response to CET, highlighting the importance of both cortical and sub-cortical reserves to treatment.

An interesting observation is that baseline GM/CS was predictive of social-cognitive response to CET during the first, but not second year of treatment. Those patients with greater brain pre-treatment reserve maintained their social-cognitive response and continued to improve in other dimensions (e.g. social adjustment, $p = .006$) during the second year of treatment (Eack et al., 2009). Additionally, the patients with less GM/CS at the beginning of the study were able to demonstrate significant improvements in social cognition, as well as other important areas given the full two years of treatment exposure. It is likely that the two-year neuroprotective effects of CET against gray matter loss and the benefits of continued treatment exposure had important roles in the improvements for both of these groups (Eack et al., 2010b).

It is worth considering possible mechanisms underlying the earlier therapeutic benefits seen in patients with greater cortical GM/CS. It is possible that initial improvements in social cognition are related to compensatory adaptations in neural networks engaged in cognitive and social cognition processes by engagement of surplus neural capacity thereby revealing stronger relationships between baseline neuronal capacity and early outcome; whereas subsequent improvements may depend more on the expansion (or strengthened connectivity) of these networks involved in these functions which may not necessarily depend on surplus capacity. If this is true, neural network connectivity may show more prominent reorganization in those with larger cortical reserve, a hypothesis that may be tested by fMRI studies examining effective connectivity. That CET patients with a low GM/CS prior to treatment continued to show strong social-cognitive benefits, but after longer periods of training compared to their high-GM/CS counterparts, lends support to this possibility.

A number of limitations must be acknowledged regarding this study that point to the need for future investigations to confirm and expand upon the relevance of a cortical reserve to response to cognitive remediation. This study was characterized by a relatively modest sample size, which may have precluded detecting smaller moderating effects on neurocognition or within individual regions of interest. Lack of blinding of assessors is a limitation, but the key cognitive measures such as the performance based MSCEIT is unlikely to have been impacted by assessor bias. The impact of pre-treatment brain structural measures may also have been present on individual neuropsychological tests, which could not be realized at the composite level. However, the large number of cognitive tests employed precluded individual analyses that would have resulted in excessive inference testing. In addition, pre-treatment data were limited to cortical structure and brain volume, and it is likely that pre-treatment reserves in brain function and connectivity will also contribute to treatment response. Third, we do not have a healthy control group which would have determined whether more brain is actually better in regard to cognitive and social cognitive abilities. However, the extant literature supports a relationship, albeit modest, between brain size and general cognitive abilities (Rushton and Ankney 2009). Finally, although we were able to reliably detect the effects of greater brain reserves on response to cognitive remediation in this study, it is important to remember that baseline brain structural measures were relative to the schizophrenia sample. Currently, it is not known whether high-GM/CS patients demonstrated *preserved* brain resources comparable to unaffected individuals, or whether the magnitude of the impact of schizophrenia on cortical surface area and volume was merely reduced among these individuals. It will be important for future studies to employ larger samples that include healthy control participants to clarify this issue, which may also lead to further understanding of the contribution of preserved individual brain regions on response to cognitive remediation.

Despite these limitations, our observations have several important clinical implications. Imaging studies of cortical structural and functional reserve may help prediction of outcome with cognitive remediation, thereby facilitating personalized interventions for patients with

schizophrenia. It is important to remember, however, that patients with less neurobiologic reserves also improved substantially after the complete two years of CET (and in fact nearly matched their high-GM/CS counterparts). In addition, a cortical reserve was not predictive of neurocognitive (i.e. non-social) improvement. It may be that structural brain reserves are more likely to be called upon for neuroplastic change during cognitive remediation, while executing complex cognitive processes, such as social cognitive functions, by comparison to non-social cognitive functions. It is also possible that the larger effect of pretreatment brain structure in social cognitive change resulted simply from the fact that therapeutic change with CET was larger in magnitude for social cognition (Eack et al 2009). Our findings also point to the importance of investigating therapeutic interventions that may increase cortical plasticity, such as Transcranial Magnetic Stimulation (rTMS) (Ziemann 2005) and pharmacological agents such as SSRIs (Peng et al 2008) and atypical antipsychotics (González-Pinto et al 2010) that may enhance release of neurotrophic factors, including Brain Derived Neurotrophic Factor (BDNF). Nevertheless, these observations need to be confirmed by larger studies, and their functional implications need to be further investigated using neuroimaging techniques such as functional MRI and diffusion tensor imaging.

References

- Aiken, LS.; West, SG. Multiple regression: Testing and interpreting interactions. Thousand Oaks, CA: Sage; 2001.
- Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005; 26:839–851. [PubMed: 15955494]
- Ben-Yishay, Y.; Piasetsky, EB.; Rattok, J., editors. A systematic method for ameliorating disorders in basic attention. New York: Guilford Press; 1985.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)*. 1995; 57:289–300.
- Bertrand MC, Achim AM, Harvey PO, Sutton H, Malla AK, Lepage M. Structural neural correlates of impairments in social cognition in first episode psychosis. *Soc Neurosci*. 2008; 3:79–88. [PubMed: 18633849]
- Bracy, OL. PSSCogRehab [computer software]. Indianapolis, IN: Psychological Software Services Inc; 1994.
- Buchanan RW, Heinrichs DW. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res*. 1989; 27:335–350. [PubMed: 2710870]
- Buchsbaum MS, Shihabuddin L, Hazlett EA, Schroder J, Haznedar MM, Powchik P, Spiegel-Cohen J, Wei T, Singer MB, Davis KL. Kraepelinian and non-Kraepelinian schizophrenia subgroup differences in cerebral metabolic rate. *Schizophr Res*. 2002; 55:25–40. [PubMed: 11955961]
- Cazzullo CL. Biological and clinical studies on schizophrenia related to pharmacological treatment. *Rec Adv Biol Psychiatry*. 1963; 5:114–143.
- Culbertson WC, Zillmer EA. Tower of London-DX manual. 1996
- Davatzikos C, Shen D, Gur RC, Wu X, Liu D, Fan Y, Hughett P, Turetsky BI, Gur RE. Whole-brain morphometric study of schizophrenia revealing a spatially complex set of focal abnormalities. *Arch Gen Psychiatry*. 2005; 62:1218–1227. [PubMed: 16275809]
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test Manual. San Antonio, TX: Psychological Corp; 1987.
- Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data using the EM algorithm. *Journal of the Royal Statistical Society. Series B (Methodological)*. 1977; 39:1–38.
- Desikan RSF, Segonne, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006; 31(3):968–980. [PubMed: 16530430]

- 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. *Schizophr Bull.* 2010a; 36:370–380. [PubMed: 18648021]
- 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; 60:1468–1476. [PubMed: 19880464]
- Eack SM, Hogarty GE, Cho RY, Prasad KM, Greenwald DP, Hogarty SS, Keshavan MS. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. *Arch Gen Psychiatry.* 2010b; 67:674–682. [PubMed: 20439824]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview For DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
- Goldstein JM, Goodman JM, Seidman LJ, Kennedy DN, Makris N, Lee H, Tourville J, Caviness VS Jr, Faraone SV, Tsuang MT. Cortical abnormalities in schizophrenia identified by structural magnetic resonance imaging. *Arch Gen Psychiatry.* 1999; 56:537–547. [PubMed: 10359468]
- Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res.* 2004a; 72:41–51. [PubMed: 15531406]
- 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-MATRICES conference to select cognitive domains and test criteria. *Biol Psychiatry.* 2004b; 56:301–307. [PubMed: 15336511]
- Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry.* 1998; 55:145–152. [PubMed: 9477928]
- Gur RE, Keshavan MS, Lawrie SM. Deconstructing psychosis with human brain imaging. *Schizophr Bull.* 2007; 33:921–931. [PubMed: 17548845]
- 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.
- Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology.* 1998; 12:426–445. [PubMed: 9673998]
- Hogarty, GE. Personal Therapy for schizophrenia and related disorders: A guide to individualized treatment. New York: Guilford; 2002.
- Hogarty GE, Flesher S. Cognitive remediation in schizophrenia: proceed ... with caution! *Schizophr Bull.* 1992; 18:51–57. [PubMed: 1553500]
- Hogarty GE, Flesher S, Ulrich R, Carter M, Greenwald D, Pogue-Geile M, Keshavan 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; 61:866–876. [PubMed: 15351765]
- Hogarty, GE.; Greenwald, DP. Cognitive Enhancement Therapy: The Training Manual. In: AUTHORS, U. O. P. M. C. (ed.). 2006.
- Hooker CI, Verosky SC, Germine LT, Knight RT, D'esposito M. Neural activity during social signal perception correlates with self-reported empathy. *Brain Res.* 2010; 1308:100–113. [PubMed: 19836364]
- Kasperek T, Prikryl R, Schwarz D, Kucerova H, Marecek R, Mikl M, Vanicek J, Ceskova E. Gray matter morphology and the level of functioning in one-year follow-up of first-episode schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009; 33:1438–1446. [PubMed: 19647777]
- Katzman R, Terry R, Deteresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol.* 1988; 23:138–144. [PubMed: 2897823]

- Keshavan MS, Hogarty GE. Brain maturational processes and delayed onset in schizophrenia. *Dev Psychopathol.* 1999; 11:525–543. [PubMed: 10532623]
- Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry.* 2002; 59:877–883. [PubMed: 12365874]
- Kurtz MM, Seltzer JC, Fujimoto M, Shagan DS, Wexler BE. Predictors of change in life skills in schizophrenia after cognitive remediation. *Schizophr Res.* 2009; 107:267–274. [PubMed: 19006657]
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage.* 2003; 19:1233–1239. [PubMed: 12880848]
- Mayer JD, Salovey P, Caruso DR, Sitarenios G. Measuring emotional intelligence with the MSCEIT V2.0. *Emotion.* 2003; 3:97–105. [PubMed: 12899321]
- Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry.* 2009; 66:811–822. [PubMed: 19652121]
- Mortimer, JA.; Schuman, L.; French, L., editors. *Epidemiology of dementing illness.* New York: Oxford University Press; 1981.
- Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ 3rd, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Meshulam-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; 165:203–213. [PubMed: 18172019]
- Okugawa G, Tamagaki C, Agartz I. Frontal and temporal volume size of grey and white matter in patients with schizophrenia: an MRI parcellation study. *Eur Arch Psychiatry Clin Neurosci.* 2007; 257:304–307. [PubMed: 17464546]
- 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; 160:815–824. [PubMed: 12727681]
- Prasad KM, Sahni SD, Rohm BR, Keshavan MS. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. *Psychiatry Res.* 2005; 140:147–155. [PubMed: 16256315]
- Prasad KM, Goradia D, Eack S, Rajagopalan M, Nutche J, Magge T, Rajarethinam R, Keshavan MS. Cortical surface characteristics among offspring of schizophrenia subjects. *Schizophr Res.* 2010 Feb; 116(2–3):143–151. [PubMed: 19962858]
- Quarantelli M, Larobina M, Volpe U, Amati G, Tedeschi E, Ciarmiello A, Brunetti A, Galderisi S, Alfano B. Stereotaxy-based regional brain volumetry applied to segmented MRI: validation and results in deficit and nondeficit schizophrenia. *Neuroimage.* 2002; 17:373–384. [PubMed: 12482090]
- Raudenbush, DSW.; Bryk, DAS. *Hierarchical Linear Models: Applications and data analysis methods.* Thousand Oaks, CA: Sage; 2002.
- Reitan, RM.; Waltson, D. *The Halstead-Reitan Neuropsychological Test Battery.* Tucson, AZ: Neuropsychology Press; 1985.
- Rushton JP, Ankney CD. Whole brain size and general mental ability: a review. *Int J Neurosci.* 2009; 119(5):691–731. [PubMed: 19283594]
- Salovey P, Mayer JD. *Emotional Intelligence. Imagination, Cognition, and Personality.* 1990; 9:185–221.
- Sanders RD, Allen DN, D Forman S, Tarpey T, Keshavan MS, Goldstein G. Confirmatory factor analysis of the Neurological Evaluation Scale in unmedicated schizophrenia. *Psychiatry Res.* 2005 Jan 30; 133(1):65–71. [PubMed: 15698678]
- Satz P. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. *Neuropsychology.* 1993; 7:273–295.
- Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry.* 1995; 52:805–818. discussion 819–20. [PubMed: 7575100]

- Shenton ME, Dickey CC, Frumin M, Mccarley RW. A review of MRI findings in schizophrenia. *Schizophr Res.* 2001; 49:1–52. [PubMed: 11343862]
- Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc.* 2002; 8:448–460. [PubMed: 11939702]
- 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; 15:273–289. [PubMed: 11771995]
- Voets NL, Hough MG, Douaud G, Matthews PM, James A, Winmill L, Webster P, Smith S. Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. *Neuroimage.* 2008 Dec; 43(4):665–675. [PubMed: 18793730]
- Wechsler, D. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp; 1981.
- Wechsler, D. Manual for the Wechsler Memory Scale-Revised. San Antonio, TX: Psychological Corp; 1987.
- Yu C, Tu S, Wang T, Qiu J. The neural basis of self-evaluation processing in social judgment. *Neuroreport.* 2010; 21:497–501. [PubMed: 20375707]

Figure 1. Social-Cognitive Improvement during Cognitive Enhancement Therapy versus Enriched Supportive Therapy among Early Course Schizophrenia Patients with High and Low Neurobiologic Reserve

Effects of Pre-Treatment Cortical Surface Area and Gray Matter Volume on Response to Cognitive Enhancement Therapy in Early Course Schizophrenia (N = 50).

Table 1

Variable	Treatment Response					
	Year 1			Year 2		
	B	SE	p ^a	B	SE	p ^a
Neurocognition						
Surface Area	.83	1.57	.916	.08	1.17	2.15
Frontal	1.17	1.61	.916	.12	.69	2.22
Temporal	.83	1.57	.916	.08	1.43	2.13
Parietal	.78	1.60	.916	.08	1.09	2.16
Occipital	.48	1.57	.916	.05	.96	2.20
Gray Matter Volume	-.18	1.73	.916	-.02	1.20	2.30
Frontal	.18	.85	.916	.02	.80	1.13
Temporal	.24	.87	.916	.02	.80	1.15
Parietal	-.29	.86	.916	-.03	.73	1.15
Occipital	-.32	.88	.916	-.03	.40	1.18
Social Cognition						
Surface Area	7.27	3.09	.031	.44	4.03	3.66
Frontal	7.48	3.14	.031	.46	3.11	3.82
Temporal	7.29	3.07	.031	.44	4.90	3.63
Parietal	6.42	3.11	.048	.39	3.35	3.69
Occipital	7.10	3.16	.036	.43	4.33	3.67
Gray Matter Volume	9.54	2.92	.007	.58	3.36	4.05
Frontal	4.66	1.45	.007	.28	1.46	2.00
Temporal	5.16	1.45	.007	.31	1.59	2.06
Parietal	4.50	1.46	.008	.27	1.84	2.00
Occipital	3.05	1.58	.058	.19	.81	2.09

Note. Effects are the results of moderator analyses examining the effect of pre-treatment cortical surface area and brain volume on the differential treatment response of patients receiving Cognitive Enhancement Therapy versus Enriched Supportive Therapy. Individual cortical surface area and brain volume predictors are examined separately in all models.

^a *p*-values are adjusted using Benjamini & Hochberg's (1995) correction for multiple inference testing

^b Effect sizes are computed by dividing the mean effect of a neurobiologic reserve (*B*) by the baseline standard deviation of the outcome (neurocognition or social cognition)

Effects of Gray Matter Volumes in Temporal Regions of Interest on First-Year Social-Cognitive Response to Cognitive Enhancement Therapy in Early Course Schizophrenia (N = 50).

Table 2

Region	Not Adjusting for Global Gray Matter Effect				Adjusting for Global Gray Matter Effect ^a			
	B	SE	p	d	B	SE	p	d
Amygdala	3.50	1.67	.041	.21	-.77	2.74	.779	-.05
L	6.93	3.24	.037	.42	-.75	4.95	.879	-.05
R	5.43	3.24	.099	.33	-1.74	4.91	.724	-.11
Fusiform Gyrus	4.63	1.52	.004	.28	2.14	5.47	.697	.13
L	9.50	2.98	.002	.58	7.89	9.11	.390	.48
R	8.24	3.04	.009	.50	-3.20	9.46	.736	-.20
Hippocampus	5.20	1.68	.003	.32	4.05	2.71	.141	.25
L	10.27	3.33	.003	.63	6.59	5.68	.251	.40
R	9.47	3.22	.005	.58	6.95	4.59	.135	.42
Insula	4.17	1.53	.009	.25	.53	3.66	.886	.03
L	7.95	2.98	.010	.48	-.55	6.43	.932	-.03
R	8.10	3.05	.010	.49	2.11	7.35	.775	.13
ParaHippocampal Gyrus	4.87	1.64	.004	.30	2.41	3.03	.431	.15
L	9.48	3.32	.006	.58	4.94	5.74	.394	.30
R	8.90	3.14	.006	.54	3.57	5.66	.530	.22
Superior Temporal Gyrus	5.49	1.48	.000	.33	8.14	5.08	.115	.50
L	10.21	2.92	.001	.62	9.07	7.94	.258	.55
R	10.77	2.94	.001	.66	14.20	8.54	.102	.86

Note. Effects are the results of moderator analyses examining the effect of pre-treatment regional temporal gray matter volume on the differential treatment response of patients receiving Cognitive Enhancement Therapy versus Enriched Supportive Therapy. Individual brain volume predictors are examined separately in all models.

^a Analyses adjusting for the moderating effect of global pre-treatment gray matter volume