



Negative symptom improvement during cognitive rehabilitation: Results from a 2-year trial of Cognitive Enhancement Therapy



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ABSTRACT

Cognitive rehabilitation has shown beneficial effects on cognition in patients with schizophrenia, which may also help to improve negative symptoms due to overlapping pathophysiology between these two domains. To better understand the possible relationship between these areas, we conducted an exploratory analysis of the effects of Cognitive Enhancement Therapy (CET) on negative symptoms. Early course schizophrenia outpatients ($n=58$) were randomized to 2 years of CET or an Enriched Supportive Therapy (EST) control condition. Results revealed significant and medium-sized ($d=0.61$) differential improvements favoring CET in overall negative symptoms, particularly social withdrawal, affective flattening, and motor retardation. Neurocognitive improvement was associated with reduced negative symptoms in CET, but not EST patients. No relationships were observed between improvements in emotion processing aspects of social cognition, as measured by the Mayer–Salovey–Caruso Emotional Intelligence Test, and negative symptoms. CET represents an effective cognitive rehabilitation intervention for schizophrenia that may also have benefits to negative symptoms. Future studies specifically designed to examine negative symptoms during the course of cognitive rehabilitation are needed.

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1. Introduction

Schizophrenia is a severe psychiatric disability that is characterized by significant impairments in social and non-social cognition at all phases of the illness (Penn et al., 1997; Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009), which significantly limit the ability of individuals to recover from the disorder (Green et al., 2000; Couture et al., 2006). While the benefits of pharmacologic treatment for these pervasive cognitive deficits are currently limited (Buchanan et al., 2011; Keefe et al., 2013), cognitive rehabilitation approaches have emerged as effective intervention strategies for improving cognition in schizophrenia (McGurk et al., 2007; Wykes et al., 2011). The increasing evidence for the efficacy of cognitive rehabilitation in people with schizophrenia has raised important questions regarding the secondary benefits of enhancing cognition on other core aspects of the disorder. A growing body of research indicates significant effects on positive symptomatology and patient functioning (e.g., Eack et al., 2011; Subramaniam et al., 2012), highlighting the potential

benefits of these rehabilitation strategies beyond the core cognitive domains that are the primary focus of treatment.

One critical area of impairment in schizophrenia that might also be positively affected by cognitive rehabilitation interventions is negative symptoms, which, like cognitive impairments, have proven to be particularly resistant to current treatment approaches (Erhart et al., 2006). Previous studies have concluded that while negative symptoms and cognition are separable in the disorder, considerable overlap does exist (Harvey et al., 2006). Some of this overlap likely stems from conceptual blurring between these two constructs (e.g., when poor attention is included in operational definitions of negative symptoms), yet evidence from animal models also suggests that similar neural pathways may underlie the processes involved in components of both negative symptoms and cognitive impairments in schizophrenia (Karlsson et al., 2008; Labrie et al., 2008). Indeed, the potential shared pathophysiology of these areas of impairment in the disorder has led some to consider pharmacologic initiatives targeting both negative symptom and cognitive domains with the same agent (e.g., Buchanan et al., 2007; Marx et al., 2009).

To date, few studies have specifically examined the effects of cognitive rehabilitation interventions on negative symptoms in schizophrenia, as most studies have understandably been focused on isolating potential benefits to cognition. Bellucci et al. (2003)

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and Bark et al. (2003) both reported improvements in negative symptoms following short-term cognitive rehabilitation in patients with schizophrenia. Recently, we published the results of a 2-year randomized-controlled trial of Cognitive Enhancement Therapy (CET; Hogarty and Greenwald, 2006), a comprehensive cognitive rehabilitation approach targeting both social and non-social cognition, in early course patients with schizophrenia. We observed medium-to-large effect sizes in this trial on neurocognition ($d=0.46$), social cognition ($d=1.55$), and functional outcome ($d=1.53$) (Eack et al., 2009). In addition to benefits on these important outcomes favoring CET, significant ($d=0.77$) improvements were observed on a broad symptomatology composite (e.g., positive, negative, and affective symptoms). These differential benefits of CET on symptomatology were not expected; given that entry criteria for the trial included symptom stabilization and that the treatment is not focused on symptomatology. Further inspection suggested that composite symptom effects were not due to reductions in positive symptoms, but reflect, in large part, improvements in negative symptom domains.

The pattern of psychopathological improvement observed in this trial of CET in early course schizophrenia provided a unique opportunity to explore the effects of cognitive rehabilitation on negative symptom improvement in the disorder. This study investigates the differential effects of CET on individual negative symptom domains, as well as the relationship between cognitive improvement and changes in negative symptoms during the course of this trial, in an effort to elucidate the potential benefits of cognitive enhancement during cognitive rehabilitation on negative symptoms in schizophrenia.

2. Method

2.1. Participants

Participants included all 58 individuals in the early course of schizophrenia ($n=38$) or schizoaffective disorder ($n=20$) participating in a randomized trial of CET for early course schizophrenia; the study design, sample characteristics, and primary effects of which have been reported elsewhere (Eack et al., 2009). Individuals were included in this study if they had a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder verified by the Structured Clinical Interview for DSM-IV (First et al., 2002), had experienced their first psychotic symptom within the past 8 years, had an IQ ≥ 80 , as estimated by Ammon's Quick Test (Ammons and Ammons, 1962), did not have a recent (within past 2 months) history of substance abuse, and demonstrated significant social and cognitive disability, using pre-defined cut-off scores on the Cognitive Styles and Social Cognition Eligibility Interview (Hogarty et al., 2004). Enrolled participants were young, with an average age of 25.92 (S.D.=6.31) years, had been ill on average 3.19 (S.D.=2.24) years since the emergence of their first psychotic symptom, and the majority were male ($n=40$) and Caucasian ($n=40$). Many of the participants had received some college education ($n=39$), but most were not employed at study baseline ($n=43$).

2.2. Treatments

Eligible participants were randomized to 2 years of either CET or an Enriched Supportive Therapy (EST) control. Both of these intervention approaches have been described in detail elsewhere (Hogarty et al., 2004; Eack et al., 2009). Briefly, CET is a comprehensive cognitive rehabilitation approach that integrates approximately 60 h of computer-based training in attention, memory, and problem-solving with 45 social-cognitive small group sessions focused on enhancing the ability of patients to take the perspective of others, accurately appraise spontaneous social contexts, be foresightful, and understand the social "gist" from novel interpersonal encounters, in addition to teaching psychoeducation, illness management and coping skills for stress management. Together, these rehabilitation activities are designed to address the core social and non-social cognitive deficits that limit functional recovery from schizophrenia. The contrasting psychosocial treatment condition was EST, which is based on Personal Therapy (Hogarty, 2002), and is an individual therapy focusing on illness management and psychoeducation designed to help patients learn about their disorder, identify early cues of stress, and implement coping strategies to minimize the impact of stress on their lives and promote psychiatric stability. In EST, strategies for managing stress are tailored to

the level of recovery of the patient. For example, for patients in the earlier phases of recovery, stress management approaches rely upon simple behavioral techniques, including passive distraction and avoiding stressful situations. As individuals proceed, more advanced stress management techniques are learned, such as diaphragmatic breathing and criticism management. Individual sessions lasting approximately 30–60 min are held weekly in the early phase of the treatment, and then progress to biweekly sessions in the later phases of the intervention. No attempt was made to artificially match the number of hours of treatment exposure between CET and EST, and those receiving CET by design received a greater number of hours of treatment, due to the increased frequency and length of treatment sessions in that condition (Eack et al., 2009). All individuals were maintained on antipsychotic medications approved by the U.S. Food and Drug Administration for the treatment of schizophrenia or schizoaffective disorder by a study psychiatrist.

2.3. Measures

2.3.1. Negative symptoms

Negative symptoms were assessed using the Wing Negative Symptom Scale (Wing, 1961) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). The Wing Negative Symptom Scale consists of six items rated on a 5-point Likert scale from 1 ("no evidence") to 5 (highly present, e.g., "Almost always disinterested and unmotivated, no spontaneous interest in work, play, reading, conversations, etc.") that cover core negative symptom domains in schizophrenia including affective flattening, poverty of speech, slowness of movement, under-activity, social withdrawal, and amotivation. This scale has been used in previous psychiatric research (McEvoy et al., 1991; Hogarty et al., 1997), and demonstrated good internal consistency reliability in this sample ($\alpha=0.80$). The BPRS is a widely used measure of psychopathology that assesses positive, negative, and affective symptoms, as well as thought disturbance and hostility on a 1 (not observed) to 7 (very severe) scale. Previous factor-analytic studies have identified a clear negative symptom factor for the BPRS consisting of the items covering emotional withdrawal, motor retardation, and blunted affect (Shafer, 2005). For primary analyses, items from the Wing Negative Symptom Scale and BPRS were scaled to a common (z) metric based on baseline scores for the entire sample and averaged to form an overall negative symptom composite index, which demonstrated excellent internal consistency ($\alpha=0.86$).

2.3.2. Cognition

Assessments of neurocognitive and social-cognitive domains were included in this study to examine the degree to which the previously reported benefits of CET on these domains (Eack et al., 2009) were associated with any improvements in negative symptoms. Neurocognition was assessed using a standardized neuropsychological testing battery mostly reflective of the domains later outlined by the NIMH MATRICS committee (Green et al., 2004). This included assessments of verbal memory (immediate and delayed recall items from stories A and B of the Revised Wechsler Memory Scale (Wechsler, 1987); List A total recall, short-term free recall, and long-term free recall from the California Verbal Learning Test (Delis et al., 1987)), working memory (digit span from the Revised Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981)), language (vocabulary items from the WAIS-R), executive functioning (Trails B time to completion, Reitan and Walston, 1985); perseverative and non-perseverative errors, categories completed, and percentage of conceptual responses from the Wisconsin Card Sorting Test (Heaton et al., 1993); total move score and ratio of initiation to execution time from the Tower of London (Culbertson and Zillmer, 1996); and picture arrangement score from the WAIS-R), and neurological soft signs (cognitive-perceptual and repetition-motor subscales from the Neurological Evaluation Scale, Buchanan and Heinrichs, 1989). All items were scaled to a common (z) metric and averaged to form an overall neurocognitive composite, which demonstrated excellent internal consistency ($\alpha=0.87$). Full details on the construction of this composite index have been reported elsewhere (Eack et al., 2009).

Social cognition was assessed using the MATRICS-recommended Managing Emotions branch of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer et al., 2003). The MSCEIT is a computerized 141-item performance-based measure of emotion processing that covers the four domains of emotional intelligence proposed by Salovey and Mayer (1990), which include emotion perception, facilitation, understanding, and management. Each domain is assessed using two performance-based tasks that come together to form a branch in one of the four domains of emotional intelligence. The measure has demonstrated excellent psychometric properties in previous studies (Mayer et al., 2003), and been shown to be a reliable and valid measure of social cognition in patients with schizophrenia (Nuechterlein et al., 2008; Eack et al., 2010a). For the purposes of this research, the fourth branch of the instrument (Managing Emotions) that was recommended by the NIMH MATRICS committee (Nuechterlein et al., 2008) for assessing social cognition in schizophrenia was used. Analyses were also conducted with total MSCEIT scores, which did not change the results, and thus are not presented here.

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