Combining Computerized Social Cognitive Training with Neuroplasticity-Based Auditory Training in Schizophrenia

Stephanie Sacks [1], Melissa Fisher [2], Coleman Garrett [2], Phillip Alexander [2], Christine Holland [2], Demian Rose [2], Christine Hooker [3], Sophia Vinogradov [2]

Abstract

Objective: Social cognitive deficits are an important treatment target in schizophrenia, but it is unclear to what degree they require specialized interventions and which specific components of behavioral interventions are effective. In this pilot study, we explored the effects of a novel computerized neuroplasticity-based auditory training delivered in conjunction with computerized social cognition training (SCT) in patients with schizophrenia. **Methods:** Nineteen clinically stable schizophrenia subjects performed 50 hours of computerized exercises that place implicit, increasing demands on auditory perception, plus 12 hours of computerized training in emotion identification, social perception, and theory of mind tasks. All subjects were assessed with MATRICS-recommended measures of neurocognition and social cognition, plus a measure of self-referential source memory before and after the computerized training. **Results:** Subjects showed significant improvements on multiple measures of neurocognition. Additionally, subjects showed significant gains on measures of social cognition, including the MSCEIT Perceiving Emotions, MSCEIT Managing Emotions, and self-referential source memory, plus a significant decrease in positive symptoms. **Conclusions:** Computerized training of auditory processing/verbal learning in schizophrenia results in significant basic neurocognitive gains. Further, addition of computerized social cognition training results in significant gains in several social cognitive outcome measures. Computerized cognitive training that directly targets social cognitive processes can drive improvements in these crucial functions.

Key Words: Schizophrenia, Cognitive Remediation, Social Cognition Remediation, Social Cognition, Computerized Cognitive Training

Introduction

Impaired social cognition is a core feature of schizophrenia strongly associated with functional outcomes such as social and community functioning, and independent living skills (1-3). The relationship between social cognition and functioning underscores the need to develop effective treatments that target improved performance in this domain. Patients exhibit deficits in a number of social cognitive processes, including emotion perception (the ability to perceive, understand, anticipate and react to social cues during interactions), theory of mind (the ability to consider one's own mental state as different from the mental states of others), and attributional style (explanations people generate regarding the causes of events in their lives) (1). Deficits in social cognition are also associated with impairments in basic neurocognition in schizophrenia (4, 5). We speculate that in order to drive significant, long-term change in social cognition, bottom-up treatment approaches are required to target both social cognition and basic neurocognitive impairments. In this pilot study, we assess the effectiveness of

[1] Washington D.C. Veterans Affairs Medical Center, Washington, DC
[2] San Francisco Department of Veterans Affairs Medical Center, San Francisco, CA; and, Department of Psychiatry, University of California, San Francisco
[3] Department of Psychology, Harvard University, Cambridge, MA

Address for correspondence: Sophia Vinogradov, MD, Department of Psychiatry, UCSF/SFVAMC, Mail Code 116C, 4150 Clement Street, San Francisco, CA 94121
Phone: 415-221-4810, x. 3106; Fax: 415-379-5574;
E-mail: Sophia.Vinogradov@ucsf.edu

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Clinical Implications

The successful treatment of schizophrenia will require the development of longitudinal multimodal treatment strategies that target a number of areas of impaired cognition and functioning. The preliminary data presented here suggest that: 1) basic aspects of social cognition are very responsive to computerized cognitive training strategies, even in the absence of other resource-intensive therapeutic interventions; and, 2) this form of training provides "added value" for subject outcomes in addition to remediation of general cognitive deficits (7, 9, 39, 41). If replicated, these findings open an exciting opportunity for the development of successful cost-effective, efficient, and highly scalable cognitive remediation treatments that can become an important part of the treatment armamentarium for schizophrenia.

a novel program which combines computerized neuroplasticity-based auditory training with social cognitive training (AT+SCT) for patients with schizophrenia.

Over the past decade, researchers have focused on two general social cognition rehabilitation treatment approaches: those that focus only on the training of one or more social cognitive skills, and those that incorporate simultaneous training of social cognitive skills with training of basic neurocognition. Focused training of specific social cognitive abilities such as affect recognition or theory of mind has been achieved using computerized emotion training programs (6-8), manualized programs including computer tasks and desk work (9), and group-based social skills training interventions (10). These interventions, which train only specific social cognitive abilities, have shown positive results in the trained social cognitive functions, with no generalization to untrained functions.

A second approach is to integrate social cognition or social skills training with general cognitive remediation (11-18). For example, Cognitive Enhancement Therapy (CET, 11-15) combines computerized cognitive training exercises with social cognitive group therapy. In these studies of multimodal approaches, while strong improvements in social skills and competence are observed, neurocognitive improvements are variable, their relationship to treatment outcome is unclear and the generalization of gains in untrained social cognitive skills appears to be limited.

In the present study, we sought to answer several of the open questions in the field. Using a quasi-experimental design, we wished to establish whether social cognitive performance can be improved in schizophrenia through computerized training of very basic general cognitive and social cognitive operations (a specific "minimal ingredient"), in the absence of group therapy, social skills training, coaching in metacognitive or compensatory strategies, or other complex interpersonal therapeutic interactions. Second, we wished to see if such training would show generalization beyond the trained tasks and would drive improvements in other (untrained) social cognitive abilities and symptom severity. Third, we tested whether gains in general cognition are associated with gains in social cognition.

Methods

Subject Recruitment and Characteristics

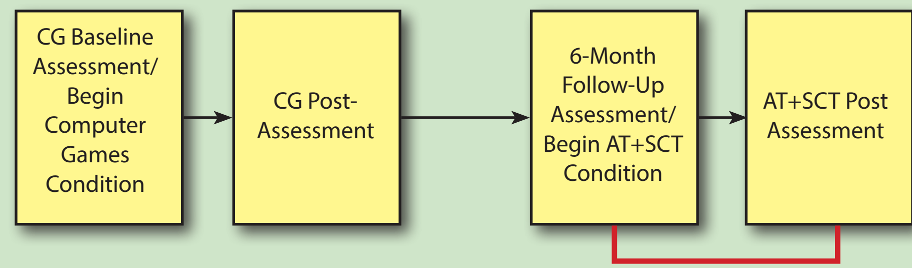
Subjects in this pilot study were drawn from our randomized controlled trial on the effects of neuroplasticity-based auditory training (AT) versus a "computer games" control condition (CG) in schizophrenia, registered at Clinicaltrials.gov (NCT00312962). In the parent study, a total of 112 clinically stable, chronically ill schizophrenia outpatients were recruited from community mental health centers. Interim behavioral data from the first 55 completed subjects have been reported previously (19). Inclusion criteria were: Axis I diagnosis of schizophrenia (determined by the DSM-IV SCID [20]); no substance dependence or current substance abuse; no major medical or neurological disorder; age between 18 and 60 years; English as first language. In order to be included in the study, schizophrenia subjects had to have outpatient status for 3 months prior to study entry and no significant medication changes (dosage change >10%) during the study.

Subjects were stratified by age, education, gender, and symptom severity, and randomly assigned to either the AT or CG condition. Twenty-nine subjects withdrew during baseline assessments, 5 subjects (2 training, 3 control) withdrew from the study during the first 4 weeks of training declining further participation, and 4 subjects (2 training, 2 control) who showed a deterioration in clinical status with concomitant protocol violations were excluded from the study. A total of 40 subjects completed the AT condition and 34 subjects completed the CG condition in the parent study. After a 6-month follow-up assessment, subjects from the first two recruitment cohorts who had originally participated in the CG control condition were invited to return to participate in this pilot study of auditory training plus social cognition training exercises (AT+SCT) (n=19), see Figure 1. Demographic characteristics of the subject group are presented in Table 1.

Study Procedures

This study was conducted in compliance with the UCSF

Figure 1 Training and Assessment Time Points of the Subject Group



Computer games (CG) control subjects from our original randomized controlled trial: the first 2 cohorts of CG subjects (n=19) were recruited at their 6-month follow-up to participate in a pilot study of auditory training plus social cognition training (AT+SCT). Findings reported here are based on the AT+SCT post-assessment compared to the 6-month follow-up assessment.

Table 1 Demographic Characteristics, Average Symptom Ratings from the PANSS, and Chlorpromazine Equivalents of the AT+SCT Subject Group (n=19)

	Mean	SD
Gender (% Male)	15 (78.9%)	—
Age	46.37	10.33
Education	13.79	2.42
WASI IQ	99.95	13.60
SES*	59.05	8.15
Ethnicity		
Caucasian	10 (52.6%)	—
African-American	5 (26.3%)	—
Latino	2 (10.5%)	—
Asian-American	2 (10.5%)	—
PANSS Mean Item Scores		
Positive Symptoms	2.83	0.80
Negative Symptoms	2.74	0.74
General Psychopathology	2.33	0.43
QLS Mean Item Score	3.35	0.87
Chlorpromazine Equivalent	480.26	479.19

*Hollingshead Two Factor Index

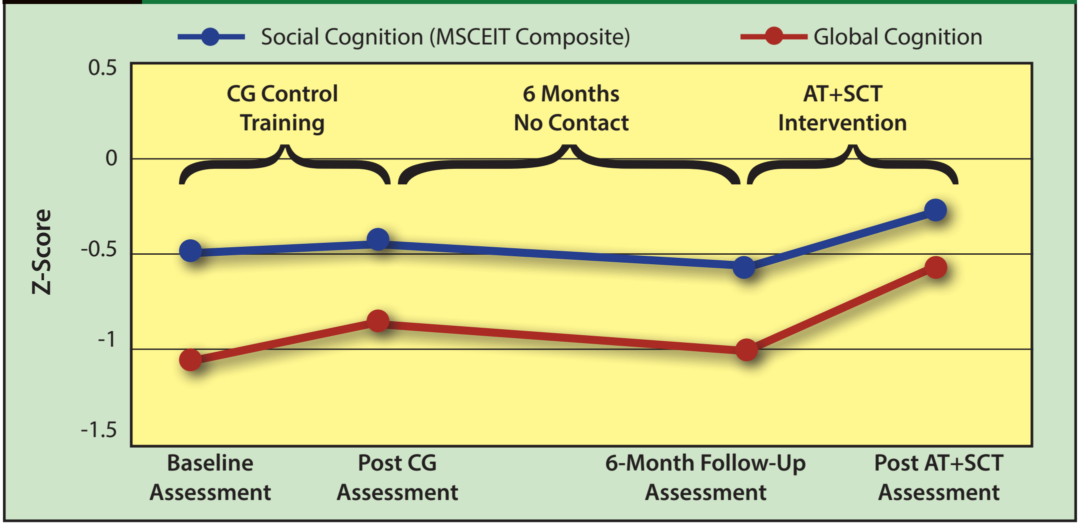
Committee on Human Research. After having procedures explained, participants provided written informed consent and underwent baseline assessments. All subjects received nominal payment for each successful day and week of participation that was contingent on attendance only and not performance.

The 19 CG control subjects underwent 50 hours of a computer games control condition, received post-intervention assessments (Assessment 2), returned for 6-month follow-up assessments (Assessment 3), and then began the pilot study of the AT+SCT condition: 75 minutes per day (60 minutes of AT plus 15 minutes of SCT), 5 days per week, over an average of 10 weeks. Thus, subjects received a total of 50 hours of training of computerized AT and 12 hours of training of computerized SCT. This was then followed by a post-training assessment (Assessment 4). Data from the 6-month follow-up assessment (Assessment 3) served as the baseline performance for the AT+SCT condition (see Figure 1). We thus note that the AT+SCT data are based on change scores from Assessments 3 and 4. We also note that we have previously shown no change in neurocognitive or social cognitive performance in computer games control subjects from Assessment 1 to 2, and from Assessment 1 to 3 (21) (see Figure 2).

Neuroplasticity-Based Computerized Auditory Training (AT)

Training of auditory/verbal processing was provided by software developed by Posit Science Corporation. In these computerized exercises (described in detail in [19]), subjects were driven to make progressively more accurate distinctions about the spectro-temporal fine-structure of auditory stimuli and speech under conditions of increasing working memory load, and to incorporate and generalize their improvements in auditory signal salience into working memory rehearsal and verbal learning. The exercises were continuously adaptive: they first established the precise parameters within each stimulus set required for an individual subject to maintain 80% correct performance; once that threshold was determined, task difficulty increased systematically and parametrically as performance improved. In all exercises, correct performance was heavily rewarded in a game-like fashion through novel and amusing visual and auditory embellishments, as well as the accumulation of points.

Figure 2 Neurocognitive and Social Cognition Performance of AT+SCT Subjects before and after the Computer Games Control Condition (CG) and after the AT+SCT Intervention



Social Cognition Training (SCT)

We developed a computerized program for training in facial emotion identification, social discrimination, simple social perception and theory of mind tasks using components drawn from three commercially available software packages: the MicroExpressions Training Tool and the Subtle Expressions Training Tool (METT and SETT), created by Dr. Paul Ekman, University of California, San Francisco (22), plus the MindReading program, created by Simon Baron-Cohen, Cambridge University (23). SCT training consisted of emotion lessons (40%), emotion quizzes (40%) and emotion games (20%). During emotion lessons, subjects viewed still pictures and videos of individuals expressing a variety of emotions. Subjects were provided with descriptions of emotions, audio of voices displaying the emotions, and sentences putting the emotion into context. During emotion quizzes, subjects were asked to match videos and sound clips of people interacting or expressing emotion with text describing/defining the situations, the emotions of the people in them, or the subtext of the situation. During emotion games, subjects viewed video clips of people in busy, real-world situations, and were asked to guess what people were thinking or feeling. Subjects engaged in the SCT for 15 minutes per day, after they had performed one hour of AT. Exercises began with easy, instructive trials, and became increasingly difficult. Difficulty level was monitored and set each day.

SCT engaged both perceptual and executive control processes which are critical for emotion recognition. Specifically, exercises steered subjects' attention to particular elements of an emotional expression (e.g., eyes, mouth, brow) and provided clear instructions about the distinguishing characteristics of each emotion (e.g., the furrowed brow is characteristic of anger). Subjects were instructed to practice identifying the intense and subtle displays of that expression. Subjects also heard the emotion label in a descriptive context, and were asked to identify that "target" expression amongst other emotional expressions, which were "distracters." More complex understanding of emotion (e.g., social perception, theory of mind) was trained through exercises that required subjects to identify emotional states of others and accompanying emotion-congruent dialogue in "real-world" social scenes. Subjects practiced what they learned using brief interactive quizzes which provided positive feedback for correct responses in the form of verbal feedback, pleasant sounds, and visual animations. Basic emotions, including happiness, sadness, anger, fear, disgust, surprise, as well as complex emotions, such as jealousy and guilt, were included in the program.

Assessment Materials

All subjects received a standardized diagnostic and clinical evaluation performed by research personnel trained in research diagnostic techniques. Evaluations included the SCID (20), the Positive and Negative Syndrome Scale (PANSS) (24), an abbreviated version of the Quality of Life Scale (QLS) (25), as well as review of clinical records and interview with patient informants (e.g., psychiatrists, therapists, and social workers). Socioeconomic status was assessed by the Hollingshead Two Factor Index (24).

Research staff who conducted neurocognitive testing or PANSS and QLS interviews first completed extensive training on testing/interviewing and scoring criteria of individual items (e.g., scoring videotaped sessions, observation of sessions conducted by experienced staff, and participating in mock sessions). In our current studies, intraclass correlation coefficients (ICCs) are greater than 0.85 for the PANSS and QLS total and subscale scores.

The following domains of neurocognition and social cognition were assessed using the measures recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Committee: Speed of Processing (Symbol Coding from the Brief Assessment of Cognition in Schizophrenia, BACS; Category Fluency Animal Naming; Trail Making Test Part A); Verbal Working Memory (University of Maryland Letter-Number Span); Non-Verbal Working Memory (Spatial Span from the Wechsler Memory Scale III); Verbal Learning and Memory (Hopkins Verbal Learning Test—Revised Trials 1–3 and Delayed Recall); Visual Learning and Memory (Brief Visuospatial Memory Test—Revised Trials 1–3 and Delayed Recall); and, Problem Solving (BACS Tower of London). Due to software difficulties, data from the Continuous Performance Test—Identical Pairs (CPT-IP) were not interpretable (the CPT-IP is the MATRICS-recommended measure of attention/vigilance). At the time this study was initiated, the MATRICS Consensus Cognitive Battery (MCCB) was not yet available, but the MATRICS-recommended measures were available. We obtained the recommended measures from test publishers, and converted raw scores to z-scores using normative data, stratified by age, published by the test authors. All measures were distinct and independent from tasks practiced during training, and assessment personnel were blind to group assignment. Alternate forms of tests were administered and counterbalanced at each assessment for tests sensitive to practice effects. The MCCB consists of 10 tests selected from over 90 candidate tests by the MATRICS Committee on the basis of psychometric properties, including test-retest reliability and practice effects (25, 26).

The following MATRICS-recommended measures of social cognition from the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (27) were used: Faces Task; Pictures Task; Emotion Management Task; Emotional Relations Task; Perceiving Emotions Total; and, Managing Emotions Total.

The MSCEIT was supplemented with an additional social cognition measure developed in our laboratory to assess self-referential source memory: the Information Source Memory Task (28-31). This test assesses source memory for three word item types: self-generated ("Self"), experimenter-presented ("Other"), and new ("New"), with alternate forms used at each assessment (described in detail in [30]). Subjects are tested on the ability to recognize the source of words generated during an earlier sentence completion task and to perform self-referential source memory (a form of reality monitoring [32]), which we have shown in a previous study to be strongly related to social cognition abilities in healthy subjects (28). In a prior study of schizophrenia subjects, self-referential source memory showed strong internal reliability (Cronbach's alpha=.95) and excellent test-retest reliability (intraclass correlation=.91) (30).

Data Analysis

All neurocognitive and MSCEIT measures were converted to age-adjusted standardized z-scores. Percent correct recognition was used for the Information Source Memory Task. All variables were screened and normally distributed after winsorising of outlying values.

Paired samples t-test was used to test for change from baseline to post-training in the measures of neurocognition, social cognition, and self-referential processing. For domains that were assessed with more than one measure, the average z-score from the measures constituting the domain was computed. A Global Cognition score was calculated as the average z-score across all cognitive measures, and a composite score of social cognition was calculated as the average z-score across MATRICS-recommended MSCEIT Subscales A, D, E, and H. Effect sizes (Cohen's d) were computed as the standardized mean difference between dependent means.

Paired samples t-test assessed change in symptom severity (Positive, Negative and General Psychopathology subscales of the PANSS) and change in QLS subscale ratings of functional outcome (Interpersonal Relations, Occupational Role Functioning, Intrapsychic Foundations, and Environmental Engagement).

Pearson correlations (two-tailed) were conducted to determine the association between baseline measures of neurocognition and baseline measures of social cognition, and between *change* in neurocognition and *change* in social cognition. Change scores were computed as post-training minus baseline performance (age-adjusted z-scores). We selected the following two measures of neurocognition that we predicted would show the greatest change in response to the AT module based on our previous findings (19): Global Cognition and Verbal Learning and Memory. For social cognition, we used the two summary scores from the MSCEIT (Perceiving Emotions Total and Managing Emotions Total) and the composite score of MSCEIT Subscales A, D, E, and H.

Results

General Neurocognition

Paired samples t-test showed significant gains from baseline to post-training on measures of Speed of Process-

Table 2 Measures of Neurocognition: Results of Paired Samples t-Test Obtained From 19 Schizophrenia Subjects Undergoing Computerized Auditory and Social Cognition Training (AT+SCT)

Outcome Measure	Baseline Mean	Baseline SD	Post Mean	Post SD	t	p-value	Effect Size
Global Cognition	-1.01	0.49	-0.59	0.55	4.01	0.001	0.80
Speed of Processing	-0.69	0.73	-0.34	0.57	2.79	0.01	0.52
Verbal Working Memory	-0.84	1.26	-0.38	1.16	2.09	0.05	0.38
Non-Verbal Working Memory	-0.37	0.78	-0.42	0.74	0.23	0.82	0.07
Verbal Learning and Memory	-2.34	1.03	-1.79	1.04	2.20	0.04	0.54
Visual Learning and Memory	-0.98	1.19	-0.38	1.10	2.60	0.02	0.51
Problem Solving	0.10	0.65	0.44	0.81	2.27	0.04	0.42

Table 3 Measures of Social Cognition: Results of Paired Samples t-Test Obtained From 19 Schizophrenia Subjects Undergoing Computerized Auditory and Social Cognition Training (AT+SCT)

Outcome Measure	Baseline Mean	Baseline SD	Post Mean	Post SD	t	p-value	Effect Size
MSCEIT							
MSC-A Faces	0.45	1.49	0.93	1.47	1.48	0.16	0.33
MSC-E Pictures	-0.70	0.79	-0.44	1.47	2.00	0.06	0.36
MSC-D Managing Emotions	-1.01	0.80	-0.75	0.80	2.10	**0.05**	0.33
MSC-H Emotional Relations	-0.99	0.85	-0.92	1.00	0.37	0.72	0.08
MSC-AE Perceiving Emotions Total	-0.49	0.81	-0.09	0.73	3.18	**0.01**	0.53
MSC-DH Managing Emotions Total	-1.15	0.85	-0.97	0.93	1.13	0.28	0.21
MSCEIT Composite Score (ADEH)	-0.56	0.59	-0.30	0.61	2.32	**0.03**	0.45
Source Memory Task							
Self Source Memory	74.71	17.47	88.43	8.99	2.84	**0.01**	0.98
External Source Memory	45.57	27.65	54.29	23.78	1.62	0.13	0.35
New Source Memory	80.91	18.41	80.45	22.63	0.09	0.93	-0.02

ing, Verbal Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Problem Solving, and Global Cognition (see Table 2). The medium to large effect sizes in Global Cognition, Verbal Learning and Memory, and Problem Solving are consistent with our previous report on the beneficial effects of AT on measures of neurocognition (19).

Social Cognition

Paired samples t-test showed significant gains from baseline to post-training on the following measures of the MSCEIT, with small to medium effect sizes: Managing Emotions Task, Perceiving Emotions Total, the MSCEIT Composite Score (Subscales A, D, E, H) (see Table 3 and Figure 3), and gains at trend level on the MSCEIT Pictures Task (p=.06). On the Information Source Memory Task, subjects showed significant improvement in self-referential processing from baseline to post-training with a large effect size, and no significant change on measures of external source memory or recognition of new items (Other and New Source Memory) (see Table 3 and Figure 4).

Symptoms and Quality of Life

The subject group showed a significant decrease on the PANSS Positive Symptom subscale, t(18)=2.22, p=0.04, with a small to medium effect size (Cohen's d=0.41). The mean change from baseline to post-training was -0.35 (standard

Figure 3 Effect Size (Cohen's d) of AT+SCT Training on the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), MATRICS-Recommended Subscales (A, D, E, H)

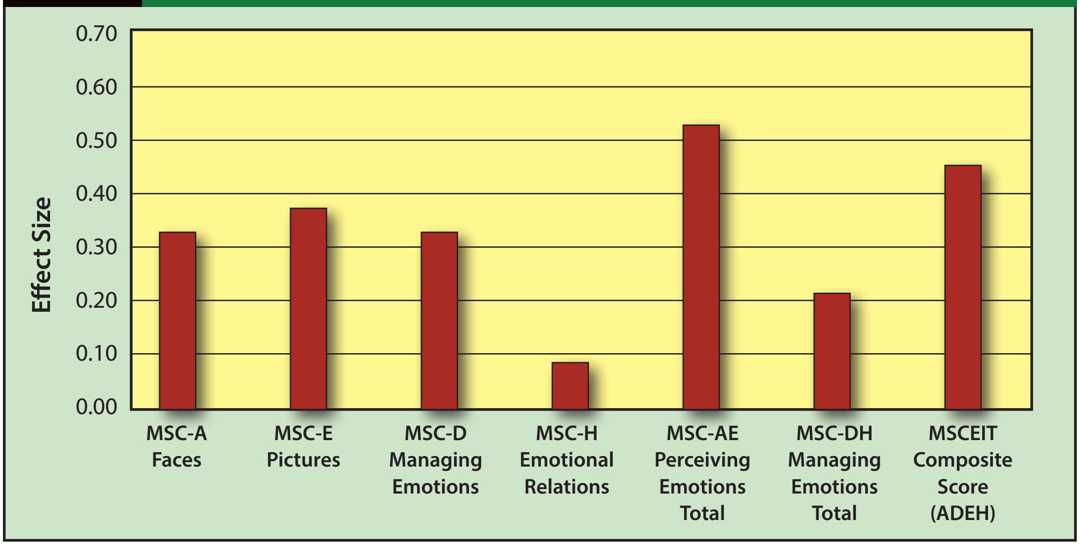
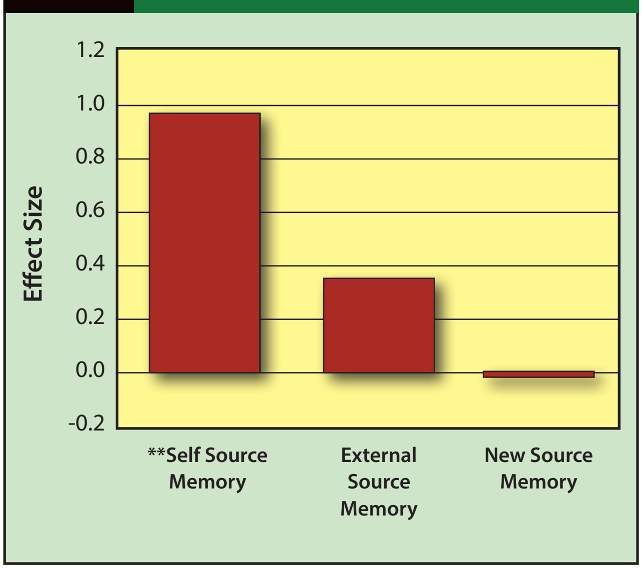


Figure 4 Effect Size (Cohen's d) of AT+SCT Training on the Self-Referential Source Memory Test



deviation=0.68). No significant changes were shown on the PANSS Negative Symptoms and General Psychopathology ratings, or on the QLS.

Associations between Neurocognition and Social Cognition

The Pearson correlation coefficients of baseline measures of neurocognition and baseline measures of social cognition ranged from -0.07<r<0.15 and were non-significant (0.56<p<0.99). The association between *change* in neurocognition and *change* in social cognition were likewise non-significant (0.15<r<0.19, 0.46<p<0.99).

Discussion

In this preliminary trial of clinically stable outpatients with schizophrenia, we found that a combination of 50 hours of computerized auditory training plus 12 hours of computerized social cognition training resulted in significant gains in neurocognition. Additionally, this training resulted in significant gains in emotion identification, social perception, and self-referential source memory, and a significant decrease in positive symptoms, compared to subjects' baseline performance. As expected, we found improvements on abilities that were explicitly trained by our AT+SCT program, such as the MSCEIT Perceiving Emotions branch. Further, we found that the benefits of AT+SCT generalized to other social cognitive abilities that were not explicitly trained, including the MSCEIT Managing Emotions subscale and self-referential source memory. Improvements in the latter skills represent a generalization of training effects to untrained tasks. While these findings suggest that the social cognition training was effective, it is important to note that our study utilized a quasi-experimental design; thus, our results must be interpreted with caution.

Our findings are consistent with prior studies that have shown improvement in basic social cognitive abilities using computerized exercises, such as Russell et al. (7) who also used the METT software and SCIT, which combines group-based therapies with computerized exercises (33). It is important to note that, while these two studies yielded significant improvements in social cognitive abilities, improvements were found only on abilities targeted during training, and did not generalize to untrained social cognitive abilities, as did the current study. Our findings suggest that at least some aspects of basic social cognition are responsive to computerized training and show generalization to more complex social cognitive abilities. Notably, although we only provided 12 hours of training in facial emotion identification and discrimination, and in simple social perception, we found that subjects made significant improvements in the MSCEIT Managing Emotions subscale, which assesses subjects' ability to judge the actions that are most effective in obtaining a specified emotional outcome for an individual in a story (27).

Subjects in the AT+SCT condition also showed improvements in self-referential source memory which was not directly targeted during training. In prior studies, we have demonstrated a strong association between social cognition and self-referential memory (but not external source memory or recognition memory) in healthy adult subjects, with attenuation of this relationship in schizophrenia subjects (28). The medial prefrontal cortex (mPFC), which plays a role in key aspects of social cognition (1, 34-36), is also implicated in self-referential processing (29, 30), indicating that common neural systems may subserve these two cognitive domains. Indeed, we find a "normalization" of hypoactive mPFC brain activation patterns on fMRI during this self-referential source memory task in subjects who have received the AT+SCT training (37). We speculate that the improvement in self-referential source memory performance we observe in the AT+SCT subjects is the direct result of the social cognitive training they have received.

Our finding of a decrease in positive symptoms in AT+SCT subjects is consistent with studies that have shown symptom improvement following social cognition training (17, 38, 39), although unanswered questions remain in this area (6, 9, 33, 40-43). We found no significant change in negative symptoms or quality of life ratings in subjects, which likely reflects the resistant nature of negative symptoms and poor community functioning to change immediately following treatment. Indeed, as Green et al. (2004) note, cognitive training may not have an immediate direct effect on real-world functioning, but rather, may enhance one's capacity to benefit from ecologically meaningful learning opportunities (44). Thus, the clinical significance of improved social cognition is difficult to determine immediately following treatment and will likely require study designs which include long-term follow-up assessment.

Finally, despite the well-established cross-sectional relationship between general cognitive abilities and social cognitive performance in schizophrenia (45), we did not find an association between gains in general cognition and gains in social cognitive processes. Interestingly, the small number of studies that have tested the relationship between cognitive *change* and change in social cognition or functional outcome suggest that these may, in fact, differ from cognitive variables that show an association at a single time point (46, 47). Neurocognitive domains that are associated cross-sectionally with accurate social cognition and higher community functioning may not be the same as those that, through intensive and targeted training, have the capacity to drive meaningful *change* in social cognition outcomes (46).

Limitations of this pilot study include our small sample size and the relatively high education level of subjects, which limits the generalizability of the results. Our low attrition rate, which may have been due in part to our subject payment schedule, may have had a differential effect on outcome as compared to previous studies. Further, despite our low attrition rate in the original study, 15 of the 34 CG subjects declined to participate in the pilot condition of AT+SCT. Interestingly, the subjects who declined to continue did not show any differences in demographic characteristics or cognitive measures from those who participated in AT+SCT, but did show significantly lower PANSS symptom ratings, and better ratings on the Quality of Life Scale (approaching trend level). Perhaps these subjects did not feel that they needed the training or that it would be of benefit to them. We have seen a similar pattern in a separate study of the effects of cognitive training in recent-onset schizophrenia: higher functioning, less symptomatic subjects drop out of training more often than lower functioning subjects (unpublished data).

Another limitation is that we did not include a control group in this pilot study; thus, the amount of variance in the gains in social cognition due to practice effects are unknown. While we cannot rule out that our findings are the result of practice effects, this seems unlikely. We have shown previously that there are no significant changes in cognitive outcome measures in the computer games control subjects when comparing baseline to post-training, or baseline to 6-month follow-up, consistent with other studies showing that practice effects tend to be low in schizophrenia (48, 49). Further, the MSCEIT showed no evidence of practice effects in a study of 167 schizophrenia subjects retested at 4 weeks (25). Finally, we did not control for multiple comparisons in our analysis, and we used a quasi-experimental design. It is possible that other known or unknown variables could explain our results. Thus, replication is needed to confirm our findings.

The successful treatment of schizophrenia will require the development of longitudinal multimodal treatment strategies that target a number of areas of impaired cognition and functioning. The preliminary data presented here suggest that: (1) basic aspects of social cognition are very responsive to computerized cognitive training strategies, even in the absence of other resource-intensive therapeutic interventions; and, 2) this form of training provides "added value" for subject outcomes in addition to remediation of general cognitive deficits (7, 9, 39, 41). If replicated, these findings open an exciting opportunity for the development of successful cost-effective, efficient, and highly scalable cognitive remediation treatments that can become an important part of the treatment armamentarium for schizophrenia.

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