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Computer-Assisted Cognitive Remediation for Schizophrenia: A Randomized Single-Blind Pilot Study

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Abstract

Cognitive impairment is a core symptom in schizophrenia that has a significant impact on psychosocial function, but shows a weak response to pharmacological treatment. Consequently, a variety of cognitive remediation strategies have been evaluated to improve cognitive function in schizophrenia. The efficacy of computer-based cognitive remediation as a stand-alone intervention on general measures of neuropsychological function remains unclear. We tested the effectiveness of biweekly training using computerized cognitive remediation programs on neuropsychological and event-related potential outcome measures. Schizophrenia patients were randomly assigned to cognitive remediation training (N=17), active control (TV-watching; N=17), or treatment as usual (N=10) groups for ten weeks and run in parallel. Functional, cognitive, and ERP measures revealed no differential improvement over time in the cognitive remediation group. Practice

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effects might explain change over time on several cognitive measures for all groups, consistent with studies indicating task-specific improvement. Computer-assisted cognitive remediation alone may not be sufficient for robust or generalized effects on cognitive and electrophysiological measures in schizophrenia patients.

Keywords

schizophrenia; cognitive remediation; cognitive training; event-related potentials; auditory steady state potentials; intervention

1. Introduction

Schizophrenia (SZ) is a psychotic disorder characterized by cognitive deficits that occur across many domains, including attention, learning and memory, sensory processing, and executive function (Kurtz et al., 2007; Ranganath et al., 2008; Twamley et al., 2003). Cognitive deficits precede psychosis onset, are resistant to treatment with antipsychotic medication, and persist after symptoms have remitted (Medalia and Choi, 2009). Importantly, neurocognitive deficits are good predictors of psychosocial, occupational, and functional outcomes (Kurtz et al., 2007; McGurk et al., 2007; Medalia and Choi, 2009; Twamley et al., 2003). The pressing need for new therapeutic interventions is evident in SZ, where cognitive symptoms are major contributors to poor functional status and are better predictors than clinical symptoms in this regard, accounting for 20–60% of outcome variance (Green et al., 2000). Therefore, a cognitive intervention could serve as a beneficial adjunctive treatment for SZ patients.

A variety of cognitive remediation (CR) interventions has been used to improve cognitive function in SZ. Patients show improvement with practice on specific training tests, including measures of executive function and learning (Kurtz et al., 2001). Some, but not all studies have suggested that CR can improve performance on neuropsychological measures that were not part of the training set, indicative of transfer across tasks or cognitive domains. Due to variation in intervention study design, type, duration, outcome measures, and sample characteristics, metaanalytic approaches have been utilized to test for efficacy and attempt to estimate the effects of modulating factors. Recent meta-analyses have supported a small-to-moderate effect on global cognition in SZ (e.g., Grynszpan et al., 2011; McGurk et al., 2007; Wykes et al., 2011). In their recent and comprehensive meta-analysis, Wykes et al. (2011) reviewed forty studies that included outcome measures distinct from the trained tasks and tested potential moderators that might influence CR efficacy. A significant effect of CR was found for global cognition and functioning. Notably, the effect size was larger when CR was combined with other psychiatric rehabilitation and utilized a strategic training approach. Surprisingly, there was little effect of specific treatment approach or duration. McGurk et al. (2007) reviewed twenty-six randomized, controlled studies and similarly found a moderate effect size for cognitive performance (0.41).

Among CR interventions, computer-assisted CR has many attractive features, including standardized training that can adapt to performance level, immediate feedback and patient engagement by virtue of a game-like design, and cost-effectiveness. A basic question in the field, therefore, is whether computerized CR intervention has generalized effects on cognition as a stand-alone intervention. Grynszpan et al. (2011) specifically examined computer-assisted CR and found a modest effect size (0.38) on cognitive outcome measures. Grynszpan also identified methodological issues in many of these initial studies. One important interpretative issue in previous studies is whether an active control group is used. Traveling to a clinic, interacting with staff, and using a computer provide behavioral

activation that may be unrelated to the computer-based remediation. Other important aspects of design have been variable as well. For example, in the Grynszpan (2011) meta-analysis of computer CR, ten of sixteen studies used a treatment-as-usual (TAU) comparison group, ten of sixteen explicitly ensured blind evaluations, and five of sixteen studies employed functional outcomes, rather than cognitive tests. Finally, attrition is another important analytic issue. Wykes et al. (2011) point out that the statistical validity of studies with a dropout rate greater than 15% is questionable, although they make up twelve of the studies they evaluated.

The present study tested outpatient computerized CR as a stand-alone intervention for outpatients with a diagnosis of SZ or schizoaffective disorder using randomized assignment to treatment, an active control arm, and later inclusion of a passive, treatment-as-usual control arm. We investigated the efficacy of a restorative, bottom-up cognitive training intervention using commercially available software developed by the PositScience Corporation (http://www.positscience.com/). Patients complete adaptive, high-intensity training exercises that target processing, attention, memory, and cognitive control to promote neural efficiency. This program incorporates errorless learning and motivating instructions that target cognitive domains as well as real-world application. Previous studies have found that SZ patients who trained for 50 or 100 hours using the PositScience auditory modules showed improved cognitive function and increased serum brain-derived neurotrophic factor (Fisher et al., 2009b, 2010; Vinogradov et al., 2009a). In contrast, two recent studies found improvement on the auditory modules but no transfer to outcome measures (Keefe et al., 2012; Murthy et al., 2012). We sought to replicate and expand previous CR findings by including a follow-up assessment, using both the auditory and visual exercises, and incorporating neurobiological outcome measures, which are rarely included in CR studies. We used a blind, multi-dimensional outcome assessment consisting of neuropsychological testing and event-related potentials (ERP) to evaluate functional, cognitive, and auditory processing outcomes. Based on the study by Fisher et al (2009a) which also used PositScience training software, we chose the primary outcome measures of global cognition (effect size (d) = 0.86 and verbal learning (d = .86). In the study design, the target N for each group was 20, yielding power of .85 to detect a treatment effect (Cohen, 1988).

2. Methods and Materials

2.1. Participants

The outpatient sample was recruited through psychiatrists affiliated with the Larue Carter Hospital and the Indiana University School of Medicine. Axis-I diagnosis of schizophrenia or schizoaffective disorder (SZ) was obtained by Structured Clinical Interview for DSM-IV (SCID-I: First et al., 2001), clinical observations, and chart review. Inclusion criteria for all participants were: 1) age between 18 and 50 years; 2) no history of electroconvulsive therapy; 3) no history of neurological illness; 4) no current alcohol or drug dependence (DSM-IV criteria) as ascertained by administration of the SCID sections on substance use disorders; 5) no hearing impairments on audiometry; 6) verbal I.Q. above 70; 7) visual acuity (with correction) of 20/30 or better; 8) no alcohol use in the 24 hours prior to testing. All participants received detailed information about the study protocol and gave written and oral informed consent. The protocol was approved by the Indiana University–Purdue University Indianapolis Human Subjects Review Committee. Participants were paid for participation.

Forty-four individuals with SZ participated in the study and are described in Table 1. All but three participants were taking medications at entry (Table 2). Figure 1 is a flow diagram of

progress through the phases of the trial. The attrition rate of the present study (6%) was similar to the rate found in the Wykes et al. (2011) meta-analysis (*M*=11%).

2.2. Design

Participants were randomly assigned using a random number table to cognitive remediation treatment (CR) or an active control study arm. After preliminary analyses of ten participants in each group showed no systematic differences on outcome measures between the CR or active control groups, a treatment-as-usual (TAU) arm was added to the randomization procedure to evaluate potential effects of practice and social interaction. The groups were run in parallel at the Larue Carter Hospital, Indianapolis, IN. Assessments were completed at baseline, five weeks, ten-weeks, and twenty weeks follow-up by staff blind to treatment condition. TAU participants were not assessed at follow-up because no differences had been found after 10 weeks in the treatment and active control groups.

2.3. Treatment

The CR and active control participants completed assigned tasks for two hours, including breaks, two days per week for ten weeks, a treatment schedule consistent with other studies that showed positive outcomes (McGurk et al., 2007; Twamley et al., 2003; Wykes et al., 2011). The active control group watched films, cartoons, or television shows using the same schedule as the treatment arm: two-hour biweekly sessions. The TAU participants came in only for assessments. A comparison of all groups showed no differences of age, estimated I.Q., or gender (χ^2=2.96, *p*=.23), however, the active control group was older than the CR group (Table 1).

The CR group completed a cognitive training regimen using software that applies adaptive algorithms to continuously adjust the demands of each task according to performance (Mahncke et al., 2006). Participants completed auditory exercises described previously by Fisher et al. (2009a) and visual exercises. The visual module aims to improve the speed and accuracy of visual processing to facilitate perception, improve visual memory, and reduce response time. Exercise 1 has participants locate specific birds appearing briefly on the screen and exercise 4 has participants track details of cars and road signs to enhance visual perception and field of view. Exercise 2 is designed to improve divided attention by having participants track multiple moving items. Exercise 3 aims to speed visual processing and reaction time by having participants respond to visual sweeps. Exercise 5 targets visual working memory using a task where participants must remember and match similar pictures.

2.4. Clinical and Cognitive Assessment

The Positive and Negative Syndrome Scale measured current symptom levels (PANSS; Kay et al., 1987). Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) estimated premorbid intelligence (Wechsler, 1999). Verbal memory function was assessed using the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) and the Hopkins Verbal Learning Test (HVLT; Brandt and Benedict, 2001). WAIS-III Spatial Span forward and backward assessed visual working memory (Wechsler, 1997). The Brief Visuospatial Memory Test assessed non-verbal learning and memory (BVMT; Benedict, 1997). WAIS-III Digit Symbol Coding assessed information processing speed. The Trail Making Tests assessed psychomotor speed and set-shifting in working memory (Reitan and Wolfson, 1993). Letter and category fluency were assessed using a one-minute interval using the letter F and animals, respectively. The Multiple Ability Self-Report Questionnaire assessed language, visual-perceptual function, verbal memory, visual memory, and attention (MASQ; Seidenberg et al., 1994).

2.5. Electrophysiological Assessment

The Auditory Steady State Response (ASSR) is an evoked potential generated by the synchronous activity of auditory cortical neurons in response to periodic auditory stimuli (Pastor et al., 2002; Simpson et al., 2005). The ASSR is thought to reflect auditory neural circuit function (Gratton et al., 1983) and is often attenuated in SZ at the 40 Hz stimulation frequency (Brenner et al., 2009; Kwon et al., 1999; Light et al., 2006; Spencer et al., 2008; Teale et al., 2008; Vierling-Claassen et al., 2008). The P300 event-related potential (ERP) response is usually elicited by infrequent target stimuli in the background of frequent standard stimuli and elicits a large positive-going potential with a latency of approximately 300 ms after stimulus onset (Polich and Criado, 2006). P300 amplitude is usually reduced and latency is increased in SZ (Ford, 1999; O'Donnell et al., 2004).

The EEG was continuously recorded (band pass 0.1–200 Hz, sampling rate 1000 Hz) and digitized (NeuroScan SynAmps) from the scalp, using a 29-channel electrode cap with a nose reference. Electrode impedances were maintained at <10 kOhm. Epochs were corrected for ocular artifacts by algorithm (Gratton et al., 1983). Epochs with voltage exceeding ±150 μV (ASSR) and ±100 μV (P300) at any site were automatically excluded from further analyses.

2.5.1. ASSR—Eighty click trains at 80 dB were presented at the 40 Hz frequency, resulting in a stimulus duration of 475 ms and included 700-ms inter-train intervals. Time-frequency analyses were used to obtain measures of change in power from baseline (mean trial power, MTP) and phase consistency or coherence (phase locking factor, PLF) as described in previous papers (Delorme et al., 2002; Makeig et al., 2004; Rass et al., 2010; TallonBaudry et al., 1997; Vohs et al., 2010; Vohs et al., 2009). Mean values were obtained for the 100 to 500 ms interval after stimulus onset for 5 Hz below and above the 40 Hz stimulation frequency for the FCz electrode.

2.5.2. P300—ERPs were elicited by 40 ms tone-pips (10 ms rise/fall time) presented at 1.2-second inter-stimulus intervals. Participants responded to infrequent (15%) high-pitched tones (1500 Hz), randomly interspersed among frequent distractor tones (1000 Hz). A 30 Hz (24 dB/octave roll-off) low-pass filter was applied to the waveform of each epoch. After averaging target epochs (−200 to 800 ms) for each participant, P300 peak latency and amplitude were obtained in the 280 to 600 ms window at the Pz channel.

2.6. Statistical Analysis

Separate mixed model Analysis of Covariance (ANCOVA) are reported for comparisons of 1) CR vs. active control and 2) CR vs. TAU to determine treatment effects on clinical, neuropsychological, and EEG measures. Baseline WASI I.Q. scores served as the covariate. The first analysis used a between-subjects factor of Group (2: CR, control) and within-subject factor of Time (3: baseline, end, follow-up). The second analysis used a between-subjects factor of Group (2: CR, TAU) and within-subject factor of Time (2: baseline, end). For all analyses, post-hoc *t*-tests clarified interactions revealed by ANOVA. Greenhouse-Geisser epsilon adjustments were included when appropriate. A composite score of global cognition (computed as the average across letter fluency, category fluency, spatial span, letter-number sequencing, digit symbol, HVLT total and BVMT total) was used as a primary outcome variable for comparison with studies using a similar approach (Vinogradov et al., 2009a; Vinogradov et al., 2009b). Participants with missing outcome scores at one assessment were not included in the average that time point (e.g., baseline).

3. Results

3.1. Baseline Measures

Groups did not differ by gender, illness duration, education level, IQ score, or PANSS symptom score. There were marginally fewer patients with schizoaffective disorder diagnosis in the TAU group than the other groups. The CR group was younger than the Active control (*LSD* p=.030).

3.2. CR vs. Active Control

Outcome measures for the CR and control groups are reported in Table 3. A 2 (Group) × 3 (Time) mixed model ANCOVA with IQ as the covariate was used to analyze treatment effects on outcome measures. Table 4 displays significant and trend results. Since the groups differed at baseline on most cognitive tests, a Group × Time interaction would indicate a treatment effect. A trend for a Group × Time interaction for BVMT Total significant revealed increases for both groups between baseline and ten weeks. From end of treatment to follow-up, the CR group continued improving, whereas the active control group decreased in perfomrnace. Active control participants had marginally greater scores at 10 weeks (t(32)=1.96-, p=.059). A main effect of Group indicated that active control participants scored higher on Letter Fluency, Letter-Number Sequencing, HVLT Total Recall, BVMT Total and Delayed Recall, and reported better visual perceptual ability and verbal memory than the CR group. No effect on P3 or ASSR was found. In summary, there was no Group × Time interactions on the primary outcome measure (global cognition) or exploratory measures to suggest a differential effect of treatment arm.

3.3. CR vs. TAU

Outcome measures for the TAU group are reported in Table 5. A 2 (Group) × 2 (Time) mixed model ANCOVA with IQ as the covariate was used to analyze treatment effects on outcome measures. Table 4 displays significant and trend results. A Group × Time interaction for letter fluency and marginal interaction HVLT recognition discrimination did not reach significance in post-hoc comparisons. Performance on category fluency improved over time for both groups. A main effect of Group indicated significantly greater BVMT total and delay scores and marginally greater letter fluency, global cognition, MASQ visual perceptual ability, and MASQ verbal memory in the TAU group compared to the CR group at baseline and retest. A main effect of Time for revealed a decrease in P3 peak over time for both groups. No effect on ASSR was found. Again, there was no Group × Time interaction for the primary outcome measure or exploratory measures indicative of a treatment effect.

4. Discussion

Schizophrenia patients were randomly assigned to forty hours of cognitive remediation (CR), an active control group of TV/Movie watching, or Treatment-as-Usual (TAU). Neuropsychological and electrophysiological outcome measures evaluated the efficacy of treatment on cognitive performance outside of trained tasks. Patients in all groups improved on measures of information processing, verbal memory, and visuospatial memory during the ten-week intervention. It is important to note that baseline performance differences, which occurred despite randomized assignment, might limit possible treatment effect size. For example, the active and TAU control groups had generally better baseline scores on cognitive measures. Change over time on some tests likely reflected practice effects or behavioral activation across groups. While meta-analyses (Grynszpan et al., 2011) indicate a range of effect sizes for computer CR in the moderate range, study design has been quite variable. The present results are similar to studies finding that improvement on training tasks did not generalize to cognitive or functional outcome measures (Dickinson et al, 2012;

Keefe et al., 2012; Murthy et al., 2012). Similarly, Field and colleagues (1997) attributed any performance improvement to practice effects. Although a recent study found a trend toward normalization of the M100 auditory cortex response in SZ patients following 50 hours of PositScience auditory training, we were unable to find improved auditory cortical function using EEG measures (Adcock et al., 2009). The present controlled trial of computer-assisted CR suggests that cognitive training alone may not be sufficient to produce effects that generalize to functional, cognitive, and electrophysiological outcomes.

Several factors may contribute to the absence of differential improvement in the CR group compared to either control group. Large effects ($d = .86$) were predicted for the primary outcome measures based on the Fisher et al (2009b) study. The small sample size may not have produced sufficient power to find the small-to-moderate effect sizes of training found in previous studies (Wykes et al., 2011). However, since change scores for measures of interest showed little systematic direction between treatment and comparison groups, it is questionable whether increasing the sample size would detect a significant or clinically meaningful treatment effect. Incorporating complementary rehabilitation strategies, like vocational and social training, may produce a larger effect size by promoting transfer of cognitive training effects as suggested by the Wykes et al. (2011) meta-analysis. Other factors might play a role in our null findings, including an anticholinergic burden from medications, a training regimen lacking the necessary intensity, and illness severity and chronicity (Vinogradov et al., 2009b). These factors might account for the absence of expected practice-related changes in neural activation (Holcomb, 2004; Kelly et al., 2006; Wexler et al., 2000). Future studies are necessary to determine the most effective framework for computer CR while incorporating individual differences, such as disorder length and onset.

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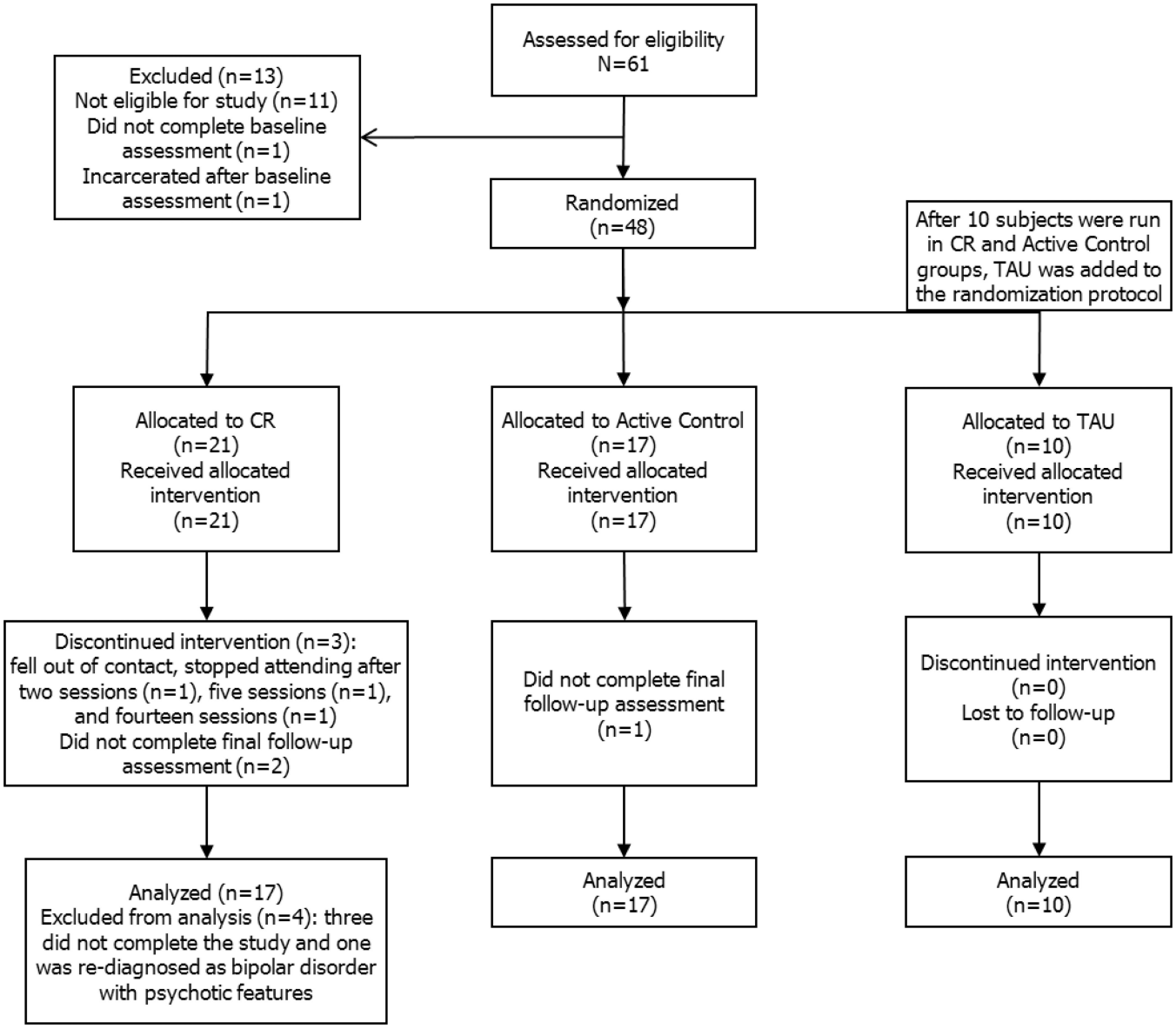

Figure 1.
Flow diagram describing the phases of a parallel randomized trial of the cognitive remediation (CR), active control, and treatment-as-usual (TAU) groups.

Table 1

Baseline Characteristics of Participants with Schizophrenia or Schizoaffective Disorder Who Received Treatment with Computer-Assisted Cognitive Remediation or a Control Group

	CR	Active Control	CR vs. Active Control		TAU	All Groups	
Variable	***N*=17**	***N*=17**	***X*²(1)**	***p***	***N*=10**	***X*²(2)**	***p***
Male (*n*)	10	11	0.13	0.72	9	2.98	0.23
Schizoaffective Disorder (*n*)	9	11	0.49	0.49	2	5.13	0.08
	Mean (SD)	***Mean***	***F*(1,32)**	***P***	***Mean***	***F*(2,41)**	***p***
Age (years)	37.2 (12.5)	45.4 (9.0)	4.72	0.04	43.9 (8.9)	2.78	0.07
Illness Duration	17.9 (11.6)	22.6 (12.1)	1.13	0.30	19.9 (9.3)	0.62	0.55
Education level	3.2 (0.8)	3.1 (0.8)	0.05	0.83	3.3 (1.0)	0.03	0.97
WASI I.Q.	94.8 (11.2)	97.8 (10.0)	0.71	0.41	91.2 (13.3)	1.10	0.34
PANSS Positive	15.2 (5.6)	16.5 (6.2)	0.41	0.53	13.6 (3.8)	0.90	0.41
PANSS Negative	12.4 (5.5)	13.2 (5.4)	0.17	0.69	15.0 (3.9)	0.80	0.46
PANSS General	27.3 (7.9)	30.6 (8.2)	1.43	0.24	26.0 (3.8)	1.49	0.24

Note. CR=cognitive remediation; TAU=treatment-as-usual. WASI=Wechsler Abbreviated Scale of Intelligence; PANSS=Positive and Negative Syndrome Scale. Four CR and three TAU participants were unable to report age of illness onset. Three CR participants had a recent (< 4 years) onset of the illness, whereas all other participants had the illness for more than 5 years (*M*=22, *SD*=11). Education level included self-report data on completion of grade school (1), junior high school (2), high school (3), some college (4), bachelor's degree (5), master's degree (6), and doctoral degree (7). The degrees of freedom differ for Illness Duration: *F*(1,28) and F(2,34).

Table 2

	Group		
Medication Type	**CR**	**Active Control**	**TAU**
No Medications	3	-	-
Atypical Antipsychotic	11	15	9
Conventional Antipsychotic	2	3	2
Antidepressant	6	9	6
Anticonvulsant	4	3	-
Possible anticholinergic	1	3	1
Definite anticholinergic	11	11	2
Other brain medication	2	2	4

Note. Medications are reported for baseline assessment. CR=cognitive remediation; TAU=treatment-as-usual. Patients taking psychotropic medications typically used multiple medications. Other brain medications included benzodiazepine, muscle relaxant, opioid analgesic, and anxiolytic prescriptions.

Table 3

Scores on cognitive domains before intervention, after intervention, and following a 10-week break from intervention for the treatment and active control groups.

	PositScience Training			TV/Movie Control		
Cognitive Domain *M* (*SD*)	**Baseline**	**After Training**	**Follow-up**	**Baseline**	**After Training**	**Follow-up**
Letter Fluency	13.8 (3.7)	14.8 (3.3)	13.5 (5.0)	16.0 (5.6)	17.2 (5.8)	16.6 (4.7)
Category Fluency	16.4 (3.7)	17.1 (5.4)	18.5 (5.4)	16.6 (4.0)	16.1 (4.1)	17.1 (4.0)
Spatial Span	7.4 (2.8)	7.8 (3.1)	7.5 (3.0)	8.5 (3.3)	9.1 (3.3)	8.9 (3.5)
Letter Number Sequencing	8.5 (2.8)	8.7 (2.3)	9.0 (2.0)	8.9 (2.3)	8.8 (2.0)	8.9 (3.0)
Digit Symbol	6.5 (2.3)	7.2 (2.4)	7.1 (2.0)	6.4 (1.3)	7.4 (1.9)	7.8 (1.4)
HVLT Total Recall	34.1 (12.2)	33.5 (10.2)	39.6 (11.4)	35.5 (8.7)	33.2 (9.9)	38.8 (10.8)
HVLT Delayed Recall	34.8 (11.2)	29.9 (13.5)	36.2 (11.1)	34.9 (10.1)	30.7 (9.9)	37.3 (10.4)
HVLT % Retention	39.8 (14.1)	35.9 (14.6)	41.3 (10.7)	38.8 (15.2)	37.1 (14.0)	45.0 (10.2)
HVLT Recognition Discrimination	43.4 (11.4)	39.9 (12.0)	38.8 (11.4)	43.3 (12.8)	41.2 (12.5)	44.9 (11.1)
BVMT Total	31.4 (14.7)	34.4 (12.8)	37.5 (11.6)	37.1 (12.5)	43.0 (12.8)	41.7 (11.0)
BVMT Learning	52.5 (14.5)	46.2 (8.3)	50.8 (8.2)	50.5 (11.0)	49.0 (10.6)	53.3 (6.8)
BVMT Delayed Recall	32.4 (15.6)	36.0 (16.7)	39.4 (14.0)	39.7 (11.5)	46.1 (12.1)	43.1 (11.5)
Global Cognition	16.8 (4.8)	17.6 (4.2)	18.6 (4.2)	18.4 (3.7)	19.3 (4.2)	20.0 (3.7)
Self-Report						
MASQ						
Language	18.5 (3.8)	19.0 (5.7)	17.9 (6.2)	19.5 (4.1)	20.2 (3.2)	19.2 (2.6)
Visual Perceptual Ability	12.8 (3.6)	12.2 (3.7)	13.3 (4.0)	16.2 (4.4)	16.4 (4.1)	16.7 (3.9)
Verbal Memory	19.0 (5.4)	18.4 (5.5)	19.7 (5.6)	23.4 (4.7)	22.1 (3.8)	22.2 (4.7)
Visual Spatial Memory	16.9 (5.2)	17.2 (6.0)	14.9 (5.6)	20.2 (4.8)	20.6 (3.5)	18.8 (6.0)
Attention Concentration	19.5 (5.2)	19.3 (6.1)	17.8 (6.1)	22.1 (3.9)	20.9 (4.2)	21.1 (5.1)

Note. HVLT=Hopkins Verbal Learning Test; BVMT=Brief Visuospatial Memory Test; MASQ=Multiple Ability Self-Report Questionnaire.

Table 4

Outcome analysis for Cognitive Remediation (CR), Active Control, and Treatment-As-Usual (TAU) groups across time.

	CR vs. Active Control			CR vs. TAU		
Cognitive Domain	**Group × Time**	**Time**	**Group**	**Group × Time**	**Time**	**Group**
Letter Fluency	-	-	-	$F(1,24)=4.30^{*}$	-	$F(1,24)=9.69^{**}$
Category Fluency	-	-	-	-	$F(1,24)=12.68^{**}$	-
Letter-Number Sequencing	-	-	-	-	-	$F(1,23)=3.60^{\dagger}$
HVLT Total Recall	-	-	-	-	-	$F(1,24)=3.05^{\dagger}$
HVLT Recognition Discrimination	-	-	-	$F(1,23)=3.13^{\dagger}$	$F(1,23)=4.43^{*}$	-
BVMT Total	$F(2,54)=2.51^{\dagger}$	-	-	-	-	$F(1,24)=11.05^{**}$
BVMT Delayed Recall	-	-	-	-	-	$F(1,24)=10.06^{**}$
Global Cognition	-	-	-	-	-	$F(1,23)=10.69^{**}$
MASQ						
Visual Perceptual Ability	-	-	$F(1,29)=9.12^{**}$	-	-	$F(1,23)=3.03^{\dagger}$
Verbal Memory	-	-	$F(1,29)=5.21^{*}$	-	-	$F(1,23)=3.68^{\dagger}$
Visual Spatial Memory	-	-	$F(1,29)=5.63^{*}$	-	-	-
EEG						
P300 Peak	-	-	-	-	$F(1,22)=5.07^{*}$	-

Note. Time for CR vs. Active control included baseline, ten weeks, and follow-up assessment; time for CR vs. TAU included baseline and ten weeks assessment. For CR vs. Active Control and vs. TAU ANCOVA analyses, IQ was a significant covariate ($p<.05$) for the following measures: Letter Fluency, Category Fluency, Digit Symbol, Spatial Span, Letter Number sequencing, HVLT Total Recall, Delayed Recall, and Recognition Discrimination, BVMT Total Recall and Delayed Recall, and Global Cognition.

$^{\dagger}p\leq.10$,

Note. HVLT=Hopkins Verbal Learning Test; BVMT=Brief Visuospatial Memory Test; MASQ=Multiple Ability Self-Report Questionnaire.

* $p < .05$,

** $p < .01$,

*** $p < .001$.

Table 5

Scores on cognitive domains at baseline and after ten weeks for the Treatment as Usual Group.

Cognitive Domain *M* (*SD*)	Baseline	After 10 Weeks
Letter Fluency	18.1 (4.9)	15.6 (5.5)
Category Fluency	17.9 (3.8)	18.3 (4.7)
Spatial Span	8.7 (2.5)	8.7 (3.7)
Letter Number Sequencing	9.1 (1.5)	10.0 (1.8)
Digit Symbol	7.1 (2.2)	8.1 (3.0)
HVLT		
Total Recall	39.0 (13.5)	39.5 (15.1)
Delayed Recall	34.8 (13.6)	37.1 (15.1)
% Retention	34.8 (13.3)	38.7 (15.4)
Recognition Discrimination	37.1 (15.1)	43.1 (14.7)
BVMT		
Total	40.3 (12.2)	48.8 (16.1)
Learning	51.2 (10.6)	48.0 (9.8)
Delayed Recall	46.0 (16.7)	45.7 (15.0)
Global Cognition	20.1 (4.3)	21.3 (5.7)
MASQ		
Language	21.0 (4.3)	19.6 (4.7)
Visual Perceptual Ability	15.3 (3.4)	14.6 (4.9)
Verbal Memory	22.6 (4.6)	22.2 (5.0)
Visual Spatial Memory	18.9 (5.7)	18.9 (5.7)
Attention Concentration	20.7 (3.6)	21.6 (6.7)

Note. HVLT=Hopkins Verbal Learning Test; BVMT=Brief Visuospatial Memory Test; MASQ=Multiple Ability Self-Report Questionnaire.