Neuroplasticity-Based Cognitive Training in Schizophrenia: An Interim Report on the Effects 6 Months Later

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\textbf{Background:} New cognitive treatments for schizophrenia are needed that drive persistent gains in cognition and functioning. Using an innovative neuroplasticity-based cognitive training approach, we report our interim findings on the effects on cognition and functional outcome at 6 months after treatment. \textit{Methods:} Thirty-two clinically stable schizophrenia subjects were randomly assigned to either targeted cognitive training (TCT, $N = 22$) or a computer games (CGs) control condition ($N = 10$). Twelve TCT subjects completed 50 hours of auditory based training; 10 TCT subjects completed an additional 50 hours of training targeting visual and cognitive control processes. Subjects were assessed on neurocognition and functional outcome after training and at 6-month follow-up. \textit{Results:} Both TCT subject groups showed significant durable gains at 6 months on measures of verbal learning/memory and cognitive control. Only TCT subjects who completed 100 hours of training showed durable gains on processing speed and global cognition, with nonsignificant improvement in functional outcome. Improved cognition was significantly associated with improved functional outcome at 6 months for TCT subjects. \textit{Conclusions:} A total of 50 hours of neuroplasticity-based computerized cognitive training appears sufficient to drive improvements in verbal learning/memory and cognitive control that endure 6 months beyond the intervention, but a higher “dose” and more “broad-spectrum” training may be necessary to drive enduring gains in processing speed and global cognition. Training-induced cognitive improvement is related to enhanced functioning at 6 months. These data suggest that (1) higher and “broader” doses of cognitive training may confer the most benefits for schizophrenia patients; (2) the posttraining period opens a critical window for aggressive adjunctive psychosocial rehabilitation.

\textit{Key words:} schizophrenia/cognitive remediation/neuroplasticity/durability

\textbf{Introduction}

Our field now recognizes the urgent need to develop treatments for the cognitive deficits of schizophrenia. In order to be clinically useful, such treatments must have reasonably robust effects, result in meaningful functional gains, and be of enduring benefit. Randomized controlled trials have demonstrated that various remediation methods improve cognitive performance,\textsuperscript{1,2} but effect sizes are modest, and only a small handful of studies have explored whether the gains are durable and result in long-term positive functional outcomes. A recent meta-analysis\textsuperscript{3} found significantly stronger effects on functional measures when cognitive remediation was combined with psychiatric rehabilitation rather than provided as a stand-alone intervention, but most of the studies in this analysis reported on the effects immediately after treatment rather than at follow-up.

Six studies of cognitive remediation in adult schizophrenia have conducted a follow-up assessment at a minimum of 6 months after treatment. In two, a therapist-guided cognitive therapy program\textsuperscript{4} was provided as a stand-alone treatment.\textsuperscript{4,5} Improvements in several cognitive domains endured at 6 months after treatment, along with some gains in social functioning. The remaining studies have combined computerized cognitive remediation with other forms of psychiatric rehabilitation. Vauth et al\textsuperscript{6} found a higher rate of job placement at 12 months after treatment in subjects who completed computer-assisted cognitive training, strategy coaching, and vocational rehabilitation compared with subjects who received therapy for the reduction of negative symptoms plus vocational training. Hogarty et al\textsuperscript{7} found significant improvements on measures of processing speed, social cognition, and social adjustment that endured 1 year after treatment when cognitive training was provided with social skills group treatment. Wexler,
ory processes, with the fundamental goal of "forcibly" restore and enhance early perceptual and working memory into a suite of exercises that are designed to cascade of basic research in learning-induced cortical plasticity as a target. Our approach translates the past developmental and that was in part designed with the schizophrenia population as a target. The primary goal for all exercises is to train the individual to become more efficient in the early processing of auditory, verbal, and visuospatial information, to increase working memory capacity, and to improve cognitive control and response efficiency to salient targets. The exercises are theoretically grounded on basic principles of neuroplasticity-based learning, which were translated into the following core features of the program: (1) intensive—many thousands of learning trials are performed for each specific exercise; (2) neuroadaptive—the dimensions of each exercise (eg, speed, working memory load) are parametrically and continuously modified on a trial-by-trial basis for each individual user during the course of each exercise in order to maintain performance at ~80% accuracy; (3) attentionally engaging—each trial is gated by a "ready" signal from the user to indicate and require directed attention, and task difficulty is continuously adjusted to a level that is neither too easy nor too difficult in order to maximize attention; (4) rewarding—correct responses are continuously rewarded by amusing auditory and visual stimuli. This delivery of frequent predictable and anticipated rewards is designed to drive high levels of training compliance and to reengage dopaminergic reward systems and noradrenergic novelty detection systems that are crucial neurobiological components for successful learning.

The program used in the current study consisted of 100 hours of training exercises developed by PositScience, Inc (50 auditory, 30 visual, and 20 cognitive control). An earlier version of the auditory training module was originally developed for the treatment of children with learning disabilities but has been subsequently heavily modified and adapted for adults, with an emphasis on both individuals with schizophrenia and the cognitive decline associated with aging. The visual module was more recently developed to target both the needs of the aging adult population as well as individuals with schizophrenia. The cognitive control module was specifically developed for individuals with schizophrenia.

We previously reported the robust positive neurocognitive effects of the first training module in this program in 55 schizophrenia subjects: after 50 hours of treatment focused on auditory processing, schizophrenia subjects (N = 29) showed significant improvements on measures of verbal working memory, verbal learning, verbal memory, and problem solving, relative to an active computer games (CGs) control condition (N = 26), with an effect
size of 0.86 (Cohen’s $d$ of $z$ score change) on the global cognition composite score (average $z$ score across all primary outcome measures of cognition).27 Given the large effect size we obtained immediately after treatment, we sought to determine whether this form of neuroplasticity-based targeted cognitive training (TCT), provided as a stand-alone treatment, would result in durable effects on cognition as well as positive functional outcomes, when subjects were reexamined 6 months after the intervention. We also investigated the effect of dosing, predicting that subjects who completed 100 hours of treatment would show greater benefits than those who completed 50 hours. Finally, we posited that improved cognition 6 months after treatment would show positive associations to improvement in functional outcome in the cognitive training group. In this report, we describe our findings from the first cohorts of 32 subjects, in this ongoing study, who have completed training plus the follow-up assessment at 6 months after training.

Materials and Methods

Participants

We describe below our first 2 cohorts of subjects who have completed 50 hours or 100 hours of training, respectively, plus the 6-month follow-up and who received behavioral assessments only. We note that a final cohort of subjects are undergoing sequential imaging as well as behavioral assessments and have not yet reached the 6-month follow-up assessment period. Our first 2 cohorts consisted of a total of 51 clinically stable (see table 1), chronically ill, volunteer schizophrenia subjects who were recruited from mental health treatment settings in the community. All participants gave written informed consent and underwent a series of baseline clinical and cognitive assessments. Subjects were stratified by age, education, gender, and symptom severity and randomly assigned to either the neuroplasticity-based TCT condition or a control condition of engaging commercial computer games (CG). Subjects were receiving case management in the community but were not enrolled in any psychiatric rehabilitation program, and no subjects received prior cognitive remediation treatment. Subjects remained on stable doses of medications during the study, defined as no change in dosage greater than 10%. All subjects received nominal payment for each successful day and week of participation that was contingent on attendance only and not performance.

Seven subjects declined participation or dropped out of the study during the assessment period. Forty-four subjects were randomized. Four subjects (9%) left the study during the first 2 weeks of training (2 TCT, 2 CG). The 40 remaining subjects participated in either TCT or CG for 1 hour per day, 5 days per week. Four subjects did not return for the 6-month follow-up; 2 were excluded from data analyses due to IQ < 70; and 2 due to being symptomatic/intoxicated during testing. The final sample size was 32 (TCT = 22, CG = 10).

When this project was initiated, only the auditory training module was fully developed, providing 50 hours of training. A first cohort of 14 subjects were randomly assigned to receive either this module ($N = 7$) or the CG condition ($N = 7$); shortly thereafter, 2 subjects were assigned to TCT in order to obtain pilot imaging data. Nine months later, 2 additional training modules were developed, one that focuses on visual processing (30 h) and another that focuses on cognitive control (20 h). A new cohort of 16 schizophrenia subjects was recruited and randomly assigned in a ratio of 2:1 to either 100 hours of TCT or 100 hours of CG. Three of these TCT subjects completed the first 50 hours and then withdrew from training. Thus, 6-month follow-up data were available on the following groups of subjects: 12 TCT subjects who received 50 hours of training (first module), 10 TCT subjects who received 100 hours of training (second module) and another that focuses on cognitive control (20 h). A new cohort of 16 schizophrenia subjects was recruited and randomly assigned in a ratio of 2:1 to either 100 hours of TCT or 100 hours of CG. Three of these TCT subjects completed the first 50 hours and then withdrew from training. Thus, 6-month follow-up data were available on the following groups of subjects: 12 TCT subjects who received 50 hours of training (first module), 10 TCT subjects who received 100 hours of training (second module) and another that focuses on visual processing (30 h) and another that focuses on cognitive control (20 h).

### Table 1. Demographics of the Computer Games (CGs) Control Group and the Targeted Cognitive Training (TCT) Groups Who Completed 50 h and 100 h of Training

<table>
<thead>
<tr>
<th></th>
<th>CG ($N = 10$), Mean (SD)</th>
<th>TCT-50 ($N = 12$), Mean (SD)</th>
<th>TCT-100 ($N = 10$), Mean (SD)</th>
<th>ANOVA, $F$ ($P$-Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>8/2</td>
<td>10/2</td>
<td>7/3</td>
<td>NA</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.90 (9.17)</td>
<td>48.50 (6.94)</td>
<td>42.90 (8.06)</td>
<td>1.37 (0.27)</td>
</tr>
<tr>
<td>Education</td>
<td>12.50 (1.43)</td>
<td>13.25 (1.66)</td>
<td>13.40 (1.58)</td>
<td>0.96 (0.39)</td>
</tr>
<tr>
<td>Chlorpromazine equivalent</td>
<td>492.50 (470.23)</td>
<td>458.79 (344.96)</td>
<td>542.50 (507.99)</td>
<td>0.09 (0.91)</td>
</tr>
<tr>
<td><strong>PANSS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total average rating</td>
<td>2.22 (0.34)</td>
<td>2.35 (0.69)</td>
<td>2.54 (0.40)</td>
<td>0.90 (0.42)</td>
</tr>
<tr>
<td>Positive subscale</td>
<td>2.43 (0.54)</td>
<td>2.49 (0.84)</td>
<td>2.90 (0.68)</td>
<td>1.29 (0.29)</td>
</tr>
<tr>
<td>Negative subscale</td>
<td>2.62 (0.67)</td>
<td>2.63 (1.01)</td>
<td>2.51 (0.93)</td>
<td>0.05 (0.95)</td>
</tr>
<tr>
<td>General psychopathology</td>
<td>2.02 (0.47)</td>
<td>2.10 (0.73)</td>
<td>2.43 (0.55)</td>
<td>1.30 (0.29)</td>
</tr>
</tbody>
</table>

aPositive and Negative Syndrome Scale (Kay et al 1987).
(3 modules), and 10 CG subjects who performed either 50 (N = 7) or 100 (N = 3) hours of the control intervention. Demographic characteristics of the subject groups are presented in table 1.

**TCT Exercises**

TCT was provided by software developed by Posit-Science, Inc. In the auditory exercises, subjects were driven to make progressively more accurate distinctions about the spectrototemporal fine structure of auditory stimuli and speech under conditions of increasing working memory load. The exercises were continuously adaptive in that 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. These same principles were applied in the second training module, focused on the visual system. In the third module, exercises were designed to improve categorization, prediction, and the association of information from auditory and visual stimuli while under appropriate cognitive control (eg, novelty detection and task switching).

**CG Control Condition**

The CG condition was designed to control for the effects of computer exposure, contact with research personnel, and monetary payments. Subjects in the CG condition came to the laboratory 5 days a week, 1 hour per day, and were monitored by staff in the same manner as TCT subjects. CG subjects rotated through a series of 16 different enjoyable commercially available computerized games (eg, visuospatial puzzle games, clue-gathering mystery games) playing 4 to 5 games on any given day. Subjects rated both conditions as equally enjoyable on the 7-item subscale of Interest/Enjoyment from the Intrinsic Motivation Inventory (CI) (TCT M = 4.78, SD thinsp;= 0.99; CG M = 5.44, SD = 1.01; 1–7 Likert Scale, with higher scores corresponding to greater interest/enjoyment).

**Assessments**

The Positive and Negative Syndrome Scale (PANSS) (N = 22) to the CG group (N = 10) on (1) change from baseline to after training and (2) change from baseline to the 6-month follow-up. Effect sizes were calculated using change scores from baseline to after training and from baseline to the 6-month follow-up. Both Cohen’s $d$ and Lipsey’s and Wilson’s recommended method for pre-post gain scores were computed. Taking a conservative approach, we reported the smaller of these values (Cohen’s $d$).
In order to test our secondary hypothesis, that subjects who completed more hours of training would show greater cognitive benefits, the 3 subject groups (CG, 50 h; TCT, 50 h; TCT, 100 h) were compared on change from baseline to the 6-month follow-up using repeated-measures ANCOVA (controlling for baseline global cognition). We did not include the posttraining time point in this analysis given the small sample sizes and number of variables entered in the analysis. Post hoc analyses tested for significant differences between the 3 subject groups.

Planned analyses focused on the following domains of interest: speed of processing (symbol coding, category fluency, trails A), verbal working memory (letter-number span), verbal learning and memory (HVLT trials 1–3, HVLT delayed recall), cognitive control (BACS Tower of London, Trails B), and global cognition (composite score of all measures). Composite and domain scores were computed as the average z score across all measures defining the composite or cognitive domain score.

On the QLS and PANSS, mean item scores were computed as described in Cramer et al. Mean item scores are an average of the response items (eg, a 7-point range of possible responses might average 4.0 at baseline, declining to 3.5 at follow-up). Repeated-measures ANOVA was used to compare the 3 subject groups on the change in PANSS and QLS total and subscale mean item score measures. Post hoc analyses tested for differences between the groups on (1) the change from baseline to after training and (2) the change from baseline to the 6-month follow-up. Pearson correlations were conducted to determine the association between change in cognition and change in functional outcome. Given our current sample size, and to reduce the risk of a type I error, correlations were conducted between cognitive measures and the QLS total item mean score only (ie, not QLS subscale measures).

**Results**

**Durability**

Baseline, posttraining, and 6-month z scores for the CG (N = 10) and TCT (N = 22) groups are shown in figure 1. The CG and TCT groups differed significantly, or at trend level significance, in the change from baseline to after training to the 6-month follow up, across all measures with the exception of verbal working memory (.02 < P < .09). Post hoc contrasts revealed that (1) from baseline to after training, the CG and TCT groups differed significantly on measures of global cognition, speed of processing, verbal learning and memory, and cognitive control and (2) from baseline to the 6-month follow-up, the CG and TCT groups differed significantly on the measures of verbal learning and memory and cognitive control, indicating durability (table 2). Effect sizes are listed in table 3. With the exception of verbal working memory, large positive effects of this intervention are shown on change scores from baseline to after training (0.83 < d < 1.11), and medium to large effects are shown on change scores from baseline to the 6-month follow-up (0.58 < d < 1.54).

**Dosing**

Subject performance at the 6-month follow-up is presented in table 3, along with the results of the ANCOVA comparing the 3 subjects groups on total change from baseline to the 6-month follow-up. The significance values (P) of the omnibus F tests ranged from .03 to .09 across all measures, with the exception of verbal working memory. Post hoc analyses revealed that both the TCT subjects who received 100 hours of training (TCT-100) and TCT subjects who received 50 hours of training (TCT-50) made significantly greater gains from baseline to the 6-month follow-up on measures of verbal learning and memory and cognitive control relative to the CG group (P < .05 for all post hoc comparisons with the exception of cognitive control, P = .08 for TCT-50 vs CG). In contrast, only the TCT-100 subjects showed significant cognitive gains from baseline to the 6-month follow-up on measures of global cognition and speed of processing, relative to the CG group (table 4).
Table 2. A Comparison of Cognitive Performance at Baseline, After Training, and at 6-mo Follow-up in 10 Schizophrenia Subjects in the Computer Games (CG) Control Condition Vs 22 Schizophrenia Subjects in the Targeted Cognitive Training Condition (TCT)

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>CG Group</th>
<th>TCT Group</th>
<th>ANCOVA F (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>Post Mean (SD)</td>
<td>6 mo Mean (SD)</td>
</tr>
<tr>
<td>Global cognition</td>
<td>-0.83 (0.55)</td>
<td>-0.76 (0.66)</td>
<td>-0.66 (0.68)</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>-0.74 (0.83)</td>
<td>-0.92 (0.72)</td>
<td>-0.84 (0.64)</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>-0.72 (1.55)</td>
<td>-0.51 (1.41)</td>
<td>-0.49 (1.34)</td>
</tr>
<tr>
<td>Verbal learning + memory</td>
<td>-1.86 (1.07)</td>
<td>-2.08 (1.08)</td>
<td>-2.24 (0.83)</td>
</tr>
<tr>
<td>Cognitive control</td>
<td>-0.34 (0.65)</td>
<td>-0.44 (0.79)</td>
<td>-0.37 (0.65)</td>
</tr>
</tbody>
</table>

Note: Mean age-adjusted z scores are presented, with the results of repeated-measures analysis of covariance, adjusting for baseline global cognitive performance. Both groups show negligible non-significant changes in cognition in the 6-month period following treatment, indicating that the posttreatment gains in cognition achieved by TCT subjects are durable.

Change from Baseline to Post-Training significant group contrasts:
- Global cognition: CG vs TCT P = .03
- Speed of processing: CG vs TCT P = .03
- Verbal learning + memory: CG vs TCT P = .04
- Cognitive control: CG vs TCT P = .01

Change from baseline to 6-mo follow-up significant group contrasts:
- Verbal learning + memory: CG vs TCT P = .01
- Cognitive control: CG vs TCT P = .02

Symptoms and Functional Outcome
The difference between groups on the PANSS subscales and total score, change in ratings from baseline to after training, and from baseline to the 6-month follow-up were nonsignificant. CG subjects showed a PANSS total average rating change from baseline to 6 months of -0.83 (SD = 0.43), TCT-50 subjects showed a change of -0.06 (SD = 0.43), and TCT-100 showed a change of -0.01 (SD = 0.59), F2,28 = 0.07, P = .93.

The difference between groups on the QLS subscales and total score, change in ratings from baseline to after training, and from baseline to the 6-month follow-up were also nonsignificant. However, TCT-100 subjects showed larger nonsignificant gains in QLS ratings from baseline to after 6 months compared with the TCT-50 and CG subjects: on the QLS total mean item score, CG subjects showed a change of 0.12 (SD = 0.51), TCT-50 subjects showed a change of -0.06 (SD = 1.33), and TCT-100 showed a change of 0.45 (SD = 0.83), F2,28 = 0.74, P = .48 (figure 2). The distribution of change scores were carefully checked for normalcy and outlying values. The Pearson correlations between change in cognition and change in QLS total revealed strong associations, as displayed in figure 3.

Discussion
Our results demonstrate that schizophrenia patients are able to make significant, enduring cognitive gains as a result of the specific effects of stand-alone restorative neuroplasticity-based computerized cognitive training compared with schizophrenia patients in a control

Table 3. Effect Size (Cohen’s d) of Change in Cognition From Baseline to After Training and Baseline to 6-mo Follow-up

<table>
<thead>
<tr>
<th>Measures</th>
<th>Global Cognition</th>
<th>Speed of Processing</th>
<th>Verbal Working Memory</th>
<th>Verbal Learning and Memory</th>
<th>Cognitive Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to after training</td>
<td>0.86</td>
<td>0.94*</td>
<td>0.20</td>
<td>1.11*</td>
<td>1.01</td>
</tr>
<tr>
<td>Baseline to 6-mo follow-up</td>
<td>0.59</td>
<td>0.58</td>
<td>0.23</td>
<td>1.54*</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Note: Cohen’s d was recalculated adjusting the change in the computer games (CG) group to zero on measures where CG subjects showed a decrement greater than -0.1 between pre and post scores:
- *Speed of processing (baseline to after training) = 0.69.
- *Verbal learning and memory (baseline to after training) = 0.83.
- *Verbal learning and memory (baseline to 6-mo follow-up) = 0.97.
Cognitive control: CG vs TCT-100

Verbal learning

\[ r = 0.34 \text{ (SD 0.12) } 0.55 \ (t < 0.01) \]

Speed of processing: CG vs TCT-100

Global cognition: CG vs TCT-100

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Computer Games</th>
<th>TCT-50</th>
<th>TCT-100</th>
<th>ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, Mean (SD)</td>
<td>6 mo, Mean (SD)</td>
<td>Baseline, Mean (SD)</td>
<td>6 mo, Mean (SD)</td>
</tr>
<tr>
<td>Global cognition(a)</td>
<td>-0.83 (0.55)</td>
<td>-0.66 (0.68)</td>
<td>-1.02 (0.66)</td>
<td>-0.73 (0.46)</td>
</tr>
<tr>
<td>Speed of processing(a)</td>
<td>-0.74 (0.83)</td>
<td>-0.84 (0.64)</td>
<td>-0.79 (0.90)</td>
<td>-0.69 (0.55)</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>-0.72 (1.55)</td>
<td>-0.49 (1.35)</td>
<td>-0.73 (1.23)</td>
<td>-0.46 (1.16)</td>
</tr>
<tr>
<td>Verbal learning + memory(a)</td>
<td>-1.86 (1.07)</td>
<td>-2.24 (0.83)</td>
<td>-2.54 (0.66)</td>
<td>-1.97 (0.89)</td>
</tr>
<tr>
<td>Cognitive control(a)</td>
<td>-0.34 (0.65)</td>
<td>-0.37 (0.64)</td>
<td>-0.95 (0.98)</td>
<td>-0.39 (0.82)</td>
</tr>
<tr>
<td>QLS Total, Mean Item Score</td>
<td>2.81 (1.01)</td>
<td>2.93 (1.02)</td>
<td>3.02 (1.22)</td>
<td>2.97 (0.93)</td>
</tr>
</tbody>
</table>

\(a\)Change from baseline to after 6 months significant post hoc tests:
Global cognition: CG vs TCT-100 \(P = .02\)
Speed of processing: CG vs TCT-100 \(P = .04\)
Verbal learning + memory: CG vs TCT-100 \(P = .01\); CG vs TCT-50 \(P = .03\)
Cognitive control: CG vs TCT-100 \(P = .01\); CG vs TCT-50 \(P = .08\)

In this study, large effect sizes were shown immediately following treatment on measures of global cognition, speed of processing, verbal learning and memory, and cognitive control. At the 6-month follow-up, the effects showed durability and remained large on measures of verbal learning and memory and cognitive control and medium on measures of speed of processing and global cognition. As discussed in Fisher et al,\textsuperscript{27} we suspect that several factors may be contributing to the enhanced response we obtained using this approach as compared with conventional methods. First, prior cognitive remediation approaches have not specifically targeted the restoration of degraded perceptual processes, although a growing body of research has identified early sensory deficits in schizophrenia and has related them to higher order cognitive impairments.\textsuperscript{18–26} Second, the exercises are theoretically grounded in basic principles of learning-induced neuroplasticity, which were assiduously...
translated into core features of the program. Finally, the exercises aggressively harness the mechanisms of implicit learning and repetitive practice (which are relatively intact in schizophrenia). At this point, we do not know whether similar effect sizes could also be obtained from more “traditional” computer-assisted cognitive remediation programs, delivered as a stand-alone treatment, if they were administered for a sufficient number of hours.

We note that the current findings differ from our previous report in 2 respects. In our previous report, TCT and CG subject groups showed significant differences in verbal working memory after treatment. In the current report, these differences did not reach statistical significance that we suspect is due to the smaller sample size analyzed in the current study (a final cohort of subjects included in the previous report have not yet reached the 6-month posttraining assessment). We anticipate that in our final analyses on a larger sample, the effects on verbal working memory will reach statistical significance. Second, in our previous report, subject groups did not differ after treatment on the measure of speed of processing, while the current findings show significant group differences. We note that these differences are only evident among the subjects who completed the additional training modules (100 h of training). Schizophrenia subjects who have only completed 50 hours of training in our prior report, and in this report, do not show evidence of improved speed of processing. Thus, it appears that a longer training period, or additional training of visual and cognitive control processes, may be required to drive improvements in speed of processing.

The present findings also suggest that a longer training period results in more durable gains in functional outcome: Subjects who completed 100 hours of training showed larger gains on the QLS total mean item score at the 6-month follow-up compared with CG and TCT-50 subject groups, although this difference did not reach statistical significance. As displayed in figure 2, all 3 subject groups show gains on the QLS from baseline to after training, but only TCT subjects who completed 100 hours of training show continued gains at the 6-month follow-up, for a total change from baseline of 0.45. The clinical significance of gains on the QLS was tested by Cramer et al in a sample of 423 patients evaluated at 6 weeks, 3, 6, and 12 months. Patients judged as “improved” by clinicians showed an average QLS mean item score change of 0.23, while patients judged as “much better” showed an average change of 0.92. Our preliminary finding of a 0.45 gain suggests that clinically, the TCT-100 subjects would be judged as somewhere between “improved” and “much better.”

In the total sample of TCT subjects, significant positive associations were shown between change in cognition (speed of processing and cognitive control) and change in functional outcome (QLS Total, Mean Item Score) in 22 Targeted Cognitive Training (TCT) Subjects.
studies have directly tested the temporal relationship between change in cognition and change in functioning.\textsuperscript{43} Most prior studies have relied on single time-point assessments of either variable (eg, baseline cognitive performance is used to predict change in functional outcome). Green and colleagues note that a critical question is the degree to which changes in cognition are linked to changes in functional outcome.\textsuperscript{44,45} This is especially germane to the study of cognitive remediation and other behavioral treatments because the cognitive functions that at baseline show associations to functioning may not be the same as those cognitive functions that, through their improvement, have the capacity to drive change in functional outcomes.

Interestingly, the small number of studies that has tested the relationship between change in cognition and change in functional outcome suggest that this may indeed be the case. For example, Reeder et al\textsuperscript{46} found that at baseline, social functioning was significantly associated with a number of cognitive measures; however, only change in schema generation predicted change in social functioning. Wykes et al\textsuperscript{5} also found that the variance in social functioning and symptoms at 6-month after treatment were partially accounted for by change on a measure of executive functioning (cognitive flexibility). In contrast, Fiszdon et al\textsuperscript{43} recently reported a negative association between change on the QLS interpersonal factor (social functioning) and change in executive functioning (Wisconsin Card Sorting Test), while positive associations were found between change in verbal memory and change in the QLS instrumental factor (occupational functioning).

Our results are consistent with Reeder et al\textsuperscript{46} and Wykes et al\textsuperscript{5} and indicate that change in cognitive control is significantly associated with change in functional outcome. Further, our results suggest that change in speed of processing may also be critically related to change in functional outcome. While replication of these results is required, our preliminary findings suggest that training of both “bottom-up” (speed of processing) and “top-down” (cognitive control) processes are important for driving changes in functional outcome and may provide a parsimonious explanation for the positive effects found for distinctly different cognitive treatment approaches (eg, drill-and-practice vs compensatory approaches). We note that our findings are preliminary and that research on the relationship between change in cognition and change in functional outcome is at a very early stage.

The main limitation of the present study is our small sample size due to the complexity of recruiting and retaining subjects through an intensive 8-month protocol that requires daily participation, followed by a 6-month follow-up. Such complexity also begs the question as to how transportable this intensive cognitive training approach will be to real-world treatment settings. Our data thus far suggest that the broadest enduring benefit for individuals with schizophrenia will accrue when 100 hours of training is delivered using modules that target auditory, visual, and cognitive control processes. However, our data also indicate that, if a primary goal of treatment is improved response to a psychosocial program, 50 hours (8–10 wks) of the auditory training module alone is sufficient to induce large beneficial effects, both immediately after training\textsuperscript{27} and at 6 months after treatment, on verbal declarative memory and cognitive control—domains especially relevant to successful vocational and social outcomes. This dosing schedule is well within the range employed by successful psychiatric rehabilitation programs that include computerized cognitive remediation.\textsuperscript{7–10} Optimal training appears to be achieved when a specific exercise (and each module consists of ~6 specific exercises) is practiced a total of 8–10 hours, for shorter periods of time (~15 min), on a more frequent basis. However, at this point, we do not know if similar cognitive gains could be achieved in schizophrenia patients with longer sessions delivered less frequently.

A second limitation is that subjects in the first cohort were randomly assigned on a 1:1 basis to either the auditory module or control condition; subjects in the following cohort were assigned on a 2:1 basis to all 3 training modules or control condition. Although this allows us to investigate the effects of “dosing” at the 6-month no-contact follow-up, it does attenuate our ability to draw firm conclusions about the overall 6-month follow-up results. Third, we cannot say whether the enhanced durability of cognitive gains across a wider range of measures in the subjects who received 100 hours of training is the result solely of the longer treatment period or whether it is due to the effects of a “broader” form of dosing, ie, to the use of an additional 2 modules that target different neural systems. Fourth, there were no statistically significant differences between groups on the change in functional outcome, and it is unknown whether this is the result of (1) an underpowered study, (2) insufficient sensitivity of the QLS as a measure of functioning, (3) true lack of direct effect of the training on functional status, and (4) the need to combine cognitive training with evidence-based psycho-social rehabilitation in order to maximally improve functioning in patients with schizophrenia. Such limitations must be addressed in future research.

The converging evidence over the last several years strongly indicates that the successful treatment of schizophrenia will require an empirically derived multimodal and sequential series of targeted therapies. Our data provide tantalizing early evidence that a highly specific form of computerized neuroplasticity-based cognitive training markedly improves key cognitive functions in a robust manner that endures 6 months beyond treatment. Further, our preliminary results show a strong and significant relationship between change in cognition and change in functional outcome 6 months after the cessa-
ments in both “top-down” and “bottom-up” processes are necessary to drive enduring changes in functional outcome in schizophrenia. In total, these findings suggest that—as part of the treatment armamentarium—neuroplasticity-based cognitive training may prepare the patient to make optimal use of ecologically meaningful learning events and may create a critical window for successful psychosocial rehabilitation.

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