

Computer-assisted cognitive remediation in schizophrenia: What is the active ingredient?

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Abstract

An emerging body of research has shown that computer-assisted cognitive remediation, consisting of training in attention, memory, language and/or problem-solving, produces improvement in neurocognitive function that generalizes to untrained neurocognitive tests and may also impact symptoms and work functioning in patients with schizophrenia. The active ingredient of these interventions, however, remains unknown as control groups in these studies have typically included few, if any, of the elements of these complex behavioral treatments. This study compared the effects of an extended (12-month), standardized, computer-assisted cognitive remediation intervention with those of a computer-skills training control condition that consisted of many of the elements of the experimental intervention, including hours spent on a computer, interaction with a clinician and non-specific cognitive stimulation. Forty-two patients with schizophrenia were randomly assigned to one of two conditions and were assessed with a comprehensive neuropsychological test battery before and after treatment. Results revealed that cognitive-remediation training produced a significant improvement in working memory, relative to the computers-skills training control condition, but that there was overall improvement in both groups on measures of working memory, reasoning/executive-function, verbal and spatial episodic memory, and processing speed. Taken together, these findings suggest that specific practice in neurocognitive exercises targeted at attention, memory and language, produce improvements in neurocognitive function that are not solely attributable to non-specific stimulation associated with working with a computer, interacting with a clinician or cognitive challenge, but that non-specific stimulation has a salutary effect on neurocognition as well.

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1. Introduction

Schizophrenia is a chronic and profoundly disabling psychiatric disorder. Current estimates suggest that 70–80% of patients with schizophrenia are unemployed at any one time, and only 1/2 of 1% of patients with schizophrenia who receive Social Security Insurance (SSI/SSDI) ever remove themselves from

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entitlements (Rupp and Keith, 1993; Torrey, 1999). A growing body of data suggests that deficits in neurocognition are linked to social disability. Evidence over the past 15 years has revealed that as many as 70% of patients with schizophrenia (Palmer et al., 1997) exhibit neurocognitive deficits on measures of attention, learning and memory, problem-solving, language and/or sensory-motor skill (Heinrichs and Zakzanis, 1998; Saykin et al., 1991, 1994). These neurocognitive deficits are present at disease onset, are resistant to the effects of typical and atypical antipsychotic medication, persist into senescence and are closely linked to poor outcome in this disorder, explaining 20–60% of the variance in measures of clinician-rated community function, social problem-solving, and progress in rehabilitation programs (Green et al., 2000; Kurtz et al., 2005; Revheim et al., 2006). Other studies have linked neurocognitive deficits to competitive work status or tenure (e.g., Gold et al., 2002; McGurk and Meltzer, 2000; McGurk and Mueser, 2003, 2004) and ability to participate in supported employment programs (McGurk et al., 2003).

In light of these links, a growing number of studies have investigated behavioral methods for improving neurocognitive deficits as a possible mechanism for helping attenuate the profound disability evident in this disorder. These behavioral approaches, while heterogeneous in terms of the degree to which they consist of rote rehearsal or are strategy-based, whether they are individualized or administered in groups, and whether they are paper-and-pencil or computer-assisted, are all focused on the improvement of neuropsychological impairment in schizophrenia and are labeled collectively, cognitive remediation, rehabilitation or training.

While results from one of the first controlled studies of cognitive rehabilitation in schizophrenia failed to show generalization of an attention training program to other neurocognitive measures (Benedict et al., 1994), results of more recent randomized treatment trials have been promising, with selected studies demonstrating effect sizes of over 1.0 for measures of sustained auditory attention, speed visual sequencing, reaction time, susceptibility to distraction, memory and visuospatial function in selected studies (see Twamley et al., 2003). While there have been some exceptions (e.g., Medalia et al., 2000), the majority of studies in this domain have reported rehabilitation-related improvement on neurocognitive instruments that are distinct from those instruments used for rehabilitation training, despite wide differences in sample characteristics, methodological approach and outcome measures selected (see Krabbendam and Aleman, 2003; Twamley et al., 2003, Wykes and van der Gaag, 2001; for reviews).

For example, Bellucci et al. (2002) in a study of 34 patients with schizophrenia, investigated the effects of a 16-session program of computer-assisted cognitive remediation program that targeted attention, visuo-motor skills and memory relative to a wait-list control condition. The results of this study revealed remediation-linked improvement in delayed, but not immediate, prose recall and speeded set-shifting at the termination of treatment, along with an improvement in negative symptoms.

Bell et al. (2001) investigated the effects of a comprehensive and extended 5-month program of computer-assisted cognitive remediation consisting of drill-and-practice exercises in attention, memory, language and problem-solving on performance on a comprehensive neurocognitive test battery in sixty-five patients with schizophrenia. Patients were randomly assigned to a work therapy plus cognitive remediation condition or work therapy alone. Results revealed improvements in executive-function, working memory and affect recognition in the cognitive remediation condition. Follow-up studies have shown that these improvements in cognitive function are durable and accompanied by improved work outcomes (Bell et al., 2003, 2005).

Despite these promising results, the mechanism of treatment effects in these studies remains unclear. An underlying assumption of studies to date is that the “active” ingredient of cognitive remediation interventions is repeated practice on neurocognitive tasks that either directly strengthens the requisite neurocognitive skills to perform these tasks, or enables patients to acquire compensatory strategies to circumvent areas of persistent cognitive difficulties (e.g., semantic grouping for memory deficiencies). This improved neurocognitive skill in turn generalizes to unpracticed neuropsychological tests that make similar neurocognitive demands. An alternative and equally plausible (albeit not mutually exclusive) explanation of these results is that exposure to a computer, consistent interaction with a supervising clinician, and the non-specific cognitive challenge associated with completing demanding computer exercises produces “non-specific” change in neurocognitive function unrelated to specific task practice in attention, memory and problem-solving.

One well-accepted method for understanding the mechanisms of behavioral treatment effects is the “dismantling” or “component-control” design (e.g., Kirsch, 2005) in which elements of a complete therapy are first identified and then contrasted with a therapy that contains a subset of most, but not all of the elements of the complete therapy. This approach has been used effectively for understanding the elements of behavioral

therapy crucial for improvement in anxiety disorders (Butler et al., 1991) and allows for specific causal inferences regarding a unique component of treatment that are not possible in the wait-list, or comparative control designs that have characterized many studies in this research domain to date (but see Medalia et al., 2000, 2001 for an exception). In the absence of such studies, the mechanisms of neurocognitive improvement evident in studies of cognitive remediation remain elusive.

We report the results of a single-blind, randomized study that contrasted the effects of a treatment with computer-assisted cognitive remediation that included explicit training in attention, verbal and non-verbal working and episodic memory, and language processing exercises, with a comparison condition that included an equivalent duration of exposure to and operation of a computer, equivalent interaction with a clinician and non-specific cognitive challenge (acquiring skills in basic computer literacy through multi-modal, computer-based lessons and completion of content exams on an ongoing basis) but without repetitive practice in specific neurocognitive functions. We hypothesized that patients in both conditions would show enhanced performance on non-trained neurocognitive tests at the conclusion of training, but that the cognitive remediation condition would produce a greater improvement in neuropsychological function.

2. Methods

2.1. Design

All study procedures met with institutional ethical approval. Patients who agreed to take part in the study completed written, informed consent and were randomly assigned to one of the two treatment groups (cognitive remediation or computer-skills training). The therapies were provided in addition to other day program activities. Patients were assessed before and after treatment on a comprehensive neuropsychological test battery conducted by trained research assistants who were blind to the intervention condition of the participants. Neurocognitive testing and scoring was supervised by a doctoral-level neuropsychologist.

2.2. Participants

Forty-two outpatients meeting DSM-IV (APA, 1994) criteria for schizophrenia or schizoaffective disorder as determined by the Structured Clinical Interview for DSM-IV (First et al., 1995) participated. Exclusion criteria for patients included auditory or visual impairment, evidence of mental retardation, traumatic brain

injury with a sustained loss of consciousness, presence or history of any neurologic illness other than schizophrenia, lack of proficiency in English, and/or criteria met for concurrent substance abuse or dependence. Recruitment for the study was continuous, over a period of 5 years (2001–2005) and occurred at two sites. The majority of patients in the study (91%) were recruited from and enrolled in an intensive outpatient program for patients with schizophrenia at The Institute of Living in Hartford, CT. and a smaller cohort (9%) was recruited from a community mental health center in Meriden, CT. See Table 1 for a summary of demographic, clinical and treatment characteristics of the two experimental groups.

2.2.1. Neurocognitive measures

In order to reduce the number of statistical comparisons and associated elevation of Type I error, individual measures were grouped into general neurocognitive domains based on results of maximum likelihood confirmatory factor-analysis of neurocognitive test results in patients with schizophrenia from a previous published report (Gladsjoe et al., 2004). Where individual measures selected for the current study were different from those of Gladsjoe et al. (2004), measures were grouped according to the theoretical neurocognitive construct they were presumed to measure. For each measure, raw scores were

Table 1
Demographic, clinical and treatment characteristics of schizophrenia patients randomly assigned to either the cognitive remediation ($n=23$) or computer-skills training group ($n=19$)

Variable	CR	CS	Test-statistic	<i>p</i> -value
			<i>T</i> -test	
Age	36.7 (12.2)	32.9 (9.3)	1.1	NS
			<i>Chi-square</i>	
Percent male	60	74	.77	NS
			<i>T</i> -test	
Education	13.1 (1.9)	13.2 (1.9)	-.1	NS
Duration of illness (years)	11.0 (10.4)	9.8 (6.3)	.4	NS
Number of hospitalizations	4.0 (2.5)	3.9 (2.9)	.1	NS
Vocabulary Scaled Score (WAIS-III)	10.0 (3.6)	11.0 (3.2)	-.9	NS
Number of training hours	67.4 (28.7)	70.7 (28.2)	-.4	NS
			<i>Chi-square</i>	
Percent treated with atypical antipsychotic medication	91	95	.22	NS

Note: CR=cognitive remediation training; CS=computer skills training; NS=non-significant; WAIS-III=Wechsler Adult Intelligence Scale.

transformed into *z*-scores using relevant published normative data and *z*-scores for each measure were then averaged to create each domain score. (1) *Working memory*: The Digit Span, Arithmetic and Letter–Number Sequencing subtests from the Wechsler Scale of Adult Intelligence – III (WAIS-III; Wechsler, 1997a); (2) *Verbal episodic memory*: the Logical Memory I and II subtests from the Wechsler Memory Scale-III (WMS-III; Wechsler, 1997) and California Verbal Learning Test – II, Total and Long-delay Free Recall (CVLT-II; Delis et al., 2000); (3) *Speed of information processing*: the Digit Symbol and Symbol Search subtests from the WAIS-III (Wechsler, 1997a,b), Trailmaking Test (Spreen and Strauss, 1991), Grooved Pegboard (Matthews and Klove, 1964), and Letter Fluency (Benton and Hamsher, 1989); (4) *Visual episodic memory*: Rey Complex Figure Test (Myers and Meyers, 1995); and (5) *Reasoning and problem-solving*: the Block Design subtest from the WAIS-III (Wechsler, 1997a,b), The Penn Conditional Exclusion Test (Kurtz et al., 2004a,b), and The Booklet Category Test (DeFilippis and McCampbell, 1985).

If even a single neuropsychological measure that comprised part of the composite neuropsychological function was missing for a specific participant, data for that composite function was not calculated. Individual measures were missing from 2 patients for the spatial episodic memory and processing speed function domains, and individual measures for 9 patients were missing from the executive-function/ reasoning domain. In two cases this reflected refusal of a participant to complete the battery, in three cases these missing measures reflected addition of a test to the battery after the onset of the study, in six cases these missing data represented technical loss and in two cases a measure was not administered by the tester.

2.3. Procedures

2.3.1. Cognitive remediation

The intervention was a 12-month, standardized course of cognitive remediation (100 h of training was the target) consisting of a sequence of computerized cognitive exercises designed to improve attention, verbal and non-verbal memory and language processing through repeated drill-and-practice (Bracy, 1995; Seltzer et al., 1997; Bell et al., 2001). Neuropsychological deficits were directly targeted by these exercises. Exercises and goals were started at a level of difficulty at which all patients were successful. Goals were modified as performance improved. Components of the intervention have produced performance gains on practiced tasks (e.g., Wexler et al., 1997), generalization of improve-

ment to other tasks (Seltzer et al., 1997; Bell et al., 2001), and normalization of task-related frontal lobe activation in fMRI studies (Wexler et al., 2000). The intervention included the following tasks:

2.3.1.1. Simple visual reaction time (Bracy, 1995). In this exercise the participant was asked to respond as quickly as possible by single-clicking a computer mouse whenever a yellow-square was presented on the computer screen. The task was made more difficult by varying the size of the square (large or small) and its location (fixed or random). This exercise was targeted at sustained attention and response time.

2.3.1.2. Simple auditory reaction time (Bracy, 1995). The participant was asked to single-click on the computer mouse as quickly as possible whenever a tone was presented. This exercise was targeted at sustained attention and response time as well.

2.3.1.3. Simple choice reaction time visual (Bracy, 1995). In this exercise the participant was asked to respond as quickly as possible by single-clicking a computer mouse whenever a yellow-square was presented. The participant had to inhibit responding whenever a blue square was presented. This exercise was targeted at sustained attention, response time and response inhibition.

2.3.1.4. Simple choice reaction time auditory (Bracy, 1995). In this exercise the participant was asked to respond as quickly as possible by single-clicking a computer mouse whenever a high-pitched tone was administered. The participant must inhibit responding whenever a low-pitched tone was played. This exercise was targeted at sustained attention, response time and response inhibition.

2.3.1.5. Progressive attention training-respond to a selected color (Loong, 1988). In this exercise a participant was presented a series of playing cards and asked to press the space whenever a red card was shown. Level of difficulty was modified by varying the duration of stimulus exposure. This exercise targeted sustained visual attention and response inhibition.

2.3.1.6. Progressive attention training-alternate black and red by a signal (Loong, 1988). In this task the participant was presented with a series of playing cards and asked to respond whenever the color of the card was black. Every 10–15 cards the word “change” was presented at the top of the screen and the participant was

asked to shift the response rule from one color to the other. Level of difficulty was modified by varying stimulus-exposure time. This exercise targeted sustained visual attention, response inhibition and set-shifting.

2.3.1.7. Simultaneous multiple attention (Bracy, 1995). In this task the participant was asked to monitor several rows of moving colored squares simultaneously on a computer screen, single-clicking the mouse on a designated square when the color of the moving squares matched a target square. Shifting attention was trained in this exercise.

2.3.1.8. Sequenced recall digits auditory – Forward and backward (Bracy, 1995). In this task the participant was orally presented with a series of 2 to 10 digits. The participant was asked to then select the numbers, either in the order they were presented, or in reverse order, from a list of numbers located at the bottom of the computer screen. This exercise was targeted at auditory attention and memory.

2.3.1.9. Sequenced recall digits visual – Forward and backwards (Bracy, 1995). In this task the participant was presented with a series of 2 to 10 digits displayed serially on the computer screen. The participant was then asked select the numbers either in the order they were presented, or in reverse order from a list of numbers at the bottom of the computer screen. This exercise was targeted at sustained visual attention and memory.

2.3.1.10. Sequenced recall words visual (Bracy, 1995). In this exercise the participant was presented with 2 to 10 words on a computer screen. After a study period the participant was asked to select the studied words from a list of 16 words in the same order the studied words were presented. This exercise was targeted at memory for verbal material and serial position.

2.3.1.11. Graphics visual – Forward and backwards (Bracy, 1995). In this exercise the participant was presented 2 to 10 novel shapes on a computer screen. After a study period the participant was asked to select the studied items, either in order or in reverse, from a list of shapes located at the bottom of the computer screen. This exercise was targeted at attention and spatial memory.

2.3.1.12. Verbal memory categorizing (Bracy, 1995). The participant was asked to sort a series of 20 words into four semantic categories. After sorting, the words were removed from the screen and the participant was asked to select the 20 studied words out of a list containing both

the 20 target words and distractor items. Task difficulty was manipulated by increasing the delay period between study and recall. This exercise was targeted at semantic processing and verbal memory.

2.3.1.13. Speed reader. In this task the participant was asked to read and remember a narrative presented on the computer monitor, typically several paragraphs in length. Reading comprehension questions were then administered immediately after presentation of the passage. Task difficulty was modified by speed of presentation of the passages (in words-per-minute). This exercise trained speed of language processing.

2.3.2. Computer-skills training

The computer-skills component control intervention consisted of a 12-month course of computerized tutorials in general computer literacy and specific skills in using Microsoft Office. Participants in this group received a similar duration of treatment (target of 100 h) and equivalent interaction with a clinician. Treatment in this group consisted of a sequence of training on general word processing skills, spread-sheet management, internet use and other skills directly applicable to an entry-level office position in the community. Participants in this condition did *not* receive practice on exercises expressly designed to strengthen basic neurocognitive skills, e.g., attention, memory and problem-solving. Participants took periodic content tests to assess their acquisition of computer skills and to increase the cognitive challenge associated with this condition. Participants in both groups trained on computers side-by-side in rooms of 3–4 computers each, supervised and coached by both pre-doctoral, and doctoral level clinicians trained in these procedures who offered positive reinforcement for progress on the respective training sequences. Participants in the non-remediation trained control group received neuropsychological assessments at similar time intervals as the cognitive remediation group. In both conditions, while 100 h of training was the target, outcome data from all patients randomly assigned to a condition were included, regardless of degree of participation, with the exception of patients who achieved less than 15 total hours of computer training in either of the two conditions. Sixteen patients completed the initial assessment and began computer training but were excluded for not meeting a minimum of 15 computer-training hours.

2.3.3. Statistical analysis

The distribution of scores for each variable in each group was inspected for normality and compared to

relevant comparison groups for homogeneity of variance. In no case was there evidence that variables violated the assumptions underlying the use of parametric statistical procedures. To ensure that the two experimental groups were similar on baseline neurocognitive domain scores, we compared these scores via independent sample *T*-tests for each of the five domains. We then used a series of five 2×2 mixed-design analyses of variance (ANOVAs) with time (pre- vs. post-training assessment) as a within-subjects variable and group (cognitive remediation vs. computer skills training) as the between-subjects variable for the five neurocognitive domains studied. In this design, the critical test for a significant non-specific change is the *F*-value of the repeated measures effect (time), while the test of a differential treatment effect is the *F*-value of the groups-by-repeated measure interaction term.

In a second set of analyses, change in the individual tests that comprised neuropsychological domains for which cognitive remediation showed a greater advantage was evaluated. To ensure that baseline neurocognitive test performance was similar across groups, scores were compared for each measure via independent sample *T*-tests. Pre- and post-training neuropsychological test scores were then analyzed in a 2×2 mixed design ANOVAs with time (pre- vs. post-training assessment) as a within-subjects variable and group (cognitive remediation vs. computer-skills training) as the between-subjects variable. Lastly, in those neurocognitive domains in which greater improvement was evident in the cognitive remediation condition, we evaluated individual participant performance and classified the number of participants showing none, small to medium ($\geq .2$ SD) or large ($\geq .8$ SD) *z*-score improvement to help understand the magnitude of change for

individual participants in each of the two conditions. We compared the frequency of large *z*-score improvement to the frequency of no or small-to-medium size *z*-score improvement in participants in the cognitive remediation vs. computer skills training conditions via chi-square. All statistical tests were two-tailed and alpha was set at .05.

3. Results

No significant differences were evident between the cognitive remediation or computer-skills training groups for demographic, clinical or treatment variables (see Table 1). There were also no significant between-group differences on pre-training *z*-scores for any of the five neurocognitive domains (all *ps* > .18). The mixed design (time \times group) ANOVA for each of the five neurocognitive domains revealed main effects of time for working memory ($F[1, 40]=19.2, p<.001$), verbal episodic memory ($F[1, 40]=23.4, p<.001$), spatial episodic memory ($F[1, 38]=11.0, p=.002$), processing speed ($F[1, 38]=14.6, p<.001$) and reasoning/executive-function ($F[1, 31]=16.2, p<.001$) suggesting that participants in both groups improved in these neurocognitive domains. A significant time \times group interaction was evident for working memory ($F[1, 40]=5.3, p=.027$), suggesting an advantage for cognitive remediation training in this specific neurocognitive domain (see Table 2).

Analysis of change in scores for the individual tests comprising the neurocognitive domain that showed greater change in the cognitive remediation condition (working memory) showed several interesting findings (Table 3). First, there were no significant between-group differences on pre-training *z*-scores for any of the three

Table 2

Mean neuropsychological domain *z*-scores (\pm SD) for patients with schizophrenia treated with cognitive remediation or computer-skills lessons before and after training

Variable	Group	<i>n</i>	Pre-training	Post-training	<i>F</i> -statistic time time \times group	<i>p</i> -value
Working memory	CR	23	-.6 (1.1)	-.1 (1.2)	19.2	<.001
	CS	19	-.2 (1.0)	0.0 (1.2)	5.3	.027
Verbal episodic memory	CR	23	-1.3 (1.0)	-.9 (1.1)	23.4	<.001
	CS	19	-.9 (.9)	-.3 (.7)	1.9	NS
Spatial episodic memory	CR	22	-2.6 (1.1)	-2.2 (1.3)	11.0	.002
	CS	18	-2.1 (1.1)	-1.4 (1.5)	.4	NS
Processing speed	CR	21	-1.2 (.8)	-1.0 (.9)	14.6	<.001
	CS	19	-1.2 (.7)	-.9 (.7)	.4	NS
Reasoning/executive Function	CR	17	-.8 (1.1)	-.2 (1.2)	16.2	<.001
	CS	16	-.6 (1.2)	-.2 (1.2)	.4	NS

Note: SD=standard deviation; CR=cognitive remediation, CS=computer skills, NS=non-significant.

Table 3
Mean *z*-scores (\pm SD) for individual neuropsychological tests that comprised the working memory domain before and after training

Variable	Group	<i>n</i>	Pre-training	Post-training	<i>F</i> -statistic time \times group	<i>p</i> -value
<i>Working memory</i>						
Digit Span	CR	23	-.2 (1.3)	.4 (1.2)	19.1	<.001
	CS	19	.2 (1.2)	.4 (1.3)	6.0	.019
LNS	CR	23	-.8 (1.3)	-.3 (1.5)	2.8	NS
	CS	19	-.4 (1.1)	-.3 (1.0)	1.4	NS
Arithmetic	CR	23	-.8 (1.2)	-.4 (1.4)	12.6	.001
	CS	19	-.3 (1.2)	-.1 (1.1)	1.2	NS

Note: SD=standard deviation; CR=cognitive remediation training; CS=computer skills training; LNS=Letter–Number Sequencing from the WAIS-III.

neurocognitive tests that comprised the working memory domain (all *ps* > .22). Second, significant main effects of time were evident for Digit Span ($F[1, 40]=19.1$, $p<.001$) and Arithmetic ($F[1, 40]=12.6$, $p=.001$) from the WAIS-III, suggesting that participants in both computer treatments improved on these attention/working memory measures. Second, a significant time \times group interaction was evident for Digit Span ($F[1, 40]=6.0$, $p=.019$) suggesting an advantage of cognitive remediation for improvement of this measure of attention/working memory.

In terms of individual participant response in each of the two experimental groups for the working memory domain, 61% of the participants in the cognitive remediation condition showed evidence of at least a small ($\geq .2$ SD) *z*-score improvement in this study, and 22% showed a large ($\geq .8$ SD or greater) *z*-score improvement from pre- to post-treatment assessment. In contrast, no patients in the computer skills sample showed large *z*-score improvements in this cognitive domain, and only 42% of the sample showed even small-to-medium sized *z*-score improvements. The difference in frequency of large *z*-score improvement vs. no or small-to-medium size *z*-score improvement between the two groups was significant ($\chi^2=4.9$, $p<.05$).

4. Discussion

This is the among the first studies, to our knowledge, to use a “dismantling” design in which the effects of a standardized, extended program of computer-assisted cognitive remediation targeted directly at neurocognitive deficits were contrasted with those of a control condition consisting of many of the elements of the treatment condition, including duration of exposure to a computer, interaction with a clinician and non-specific

cognitive challenge, in order to begin to decompose the potential mechanism of actions of positive effects of computer-assisted cognitive remediation on neurocognitive function that have been reported in the literature (Bell et al., 2001; Bellucci et al., 2002; Medalia et al., 2001; Seltzer et al., 1997). The results from this study suggest that training in cognitive exercises targeted at specific neurocognitive deficits provides incremental benefit for specific aspects of neurocognition, but that exposure to a computer, interaction with a clinician and non-specific cognitive challenge produce non-specific improvement in neurocognitive function as well. More specifically, patients randomly assigned to the cognitive remediation treatment condition showed improvement in working memory that was greater than that produced by training in computer literacy alone. Non-specific effects were evident in both groups for working memory, reasoning/problem-solving, verbal and non-verbal episodic memory and processing speed. These latter findings are important as a growing number of studies have shown that neuropsychological test findings are highly stable in young-adult to middle-age patients with schizophrenia over a one to as many as 10-year longitudinal follow-up (e.g., Censits et al., 1997; Stirling et al., 2003; Kurtz et al., 2005), suggesting that these non-specific effects are most likely not simply the effect of practice, task familiarity or extended pharmacologic intervention.

The remediation-linked improvements in working memory in this study are highly consistent with those reported in a previous study using a similar cognitive training protocol (Bell et al., 2001), and suggest that neurocognitive training in skills related to holding information in mind and manipulating that information can be improved in patients with schizophrenia, even when these skills are assessed with instruments different from those used for training. The current study extends previous findings by showing that these effects can be linked to training on neurocognitive tasks per se.

Patients were administered the cognitive remediation intervention over a lengthy period of time and many patients failed to reach their goal of 100 treatment hours due to a variety of factors including greater time devoted to competitive employment or volunteer work, return to school, changes in location of home and discharge to other community care providers. Exploratory analyses investigating the relationship of hours of cognitive remediation training to *z*-score improvement in the working memory factor failed to show a relationship between these variables ($p=.10$).

The finding of a selective advantage of cognitive remediation on working memory in patients with

schizophrenia, but not accompanying evidence of a commensurate advantage in the reasoning/executive-function domain in this treatment group is paradoxical as a variety of studies have shown a close link between more elementary working-memory functions and higher-level reasoning and problem-solving skills (e.g., Gold et al., 1997). One potential hypothesis is that given the non-specific effect of treatment on working memory in the sample as a whole, some improvement in working memory may improve more complex executive-functions but only up to a threshold (perhaps to the level of average functioning), after which improved working memory does not produce accompanying improvements in executive-function. The finding that both experimental groups scored within $-.5$ SD of healthy control performance in the reasoning/executive-function domain after intervention supports this view.

Given that both treatment groups showed improvement in working memory function across this trial, it remains unclear exactly how much more effective cognitive remediation was for treating this domain of neurocognitive functioning. Analysis of the pattern of treatment response in individual patients indicated that large z -score improvements ($\geq .8$ SD) were evident in 22% of patient of the cognitive remediation condition, and in no patients in the computer skills intervention, suggesting a clear advantage for cognitive remediation treatment for working memory deficits in a subgroup of patients with schizophrenia. This analysis also suggested large inter-participant variability in response to cognitive remediation.

In light of the large individual differences in response to the remediation intervention on working memory measures evident in our study, an important area of future study will be determining which patient characteristics predict these variable treatment responses. An exploratory analysis of the current data failed to show a relationship of age, age of illness onset, duration of illness or number of hospitalizations to z -score improvement in working memory for patients treated with cognitive remediation (all $ps \geq .36$). The small sample size ($n=23$), however, most likely precluded detection of even moderate-size effects.

The current sample consisted of stable outpatients who typically were chronically ill (mean duration of illness = 11.0 years), in early middle-age (mean age = 36.7 years), and were of average estimated premorbid intelligence (mean vocabulary scaled score = 10.0). It remains unclear to what degree these findings would generalize to patients earlier or later in the course of their illness, in long-term inpatient or nursing home care, or of poorer estimated premorbid intelligence. Age, outpatient status and

duration of illness of our sample are similar to some positive reports of cognitive training in the literature (e.g., Bell et al., 2001; Bellucci et al., 2002) but not others (e.g., Medalia et al., 2001).

The finding that both experimental groups showed significant improvement in a variety of neurocognitive domains suggests that the cognitive stimulation linked to repeated exposure to a computer, interaction with a clinician and the non-specific stimulation of learning and remembering information for periodic exams produces stimulation well beyond that provided in most patients' natural environment. One potential implication of these findings is that the neurocognitive deficits and negative symptoms of the disorder place such large restrictions on patients social and occupational life, that any type of sustained, goal-directed cognitive activity in the presence of supportive clinicians, regardless of its content, has the potential to elevate neuropsychological function significantly in this patient population. Consistent with this viewpoint, a small but growing number of studies suggest that structured behavioral rehabilitation improves neurocognitive skills in patients with schizophrenia in the absence of any specific cognitive training (e.g., Spaulding et al., 1999; Silverstein and Wilkness, 2004). This possibility also emphasizes the significance of reports showing an advantage of cognitive remediation for a variety of outcome measures, even when cognitive remediation interventions are compared with control interventions that involve considerable non-specific stimulation such as work therapy or supported employment programs (Bell et al., 2001; McGurk et al., 2005).

The advantage of cognitive remediation for working memory function in the present study suggests however that at least some additional neurocognitive benefit may accrue from the careful titration of task difficulty of cognitive exercises to ensure appropriate cognitive challenge, the rapid repetition of demanding exercises, and the frequency of reinforcement associated with achievement of intermediate and overall task goals characteristic of this condition. The hierarchical nature of the training program, starting with training in elementary attention skills and then graduating to considerably more complex episodic and verbal memory tasks may also play a role in the advantage of this condition.

It is important to note that while the majority of randomized controlled studies of cognitive remediation in schizophrenia have not employed control conditions that were matched with the intervention for time spent on a computer, clinician interaction and "non-specific" cognitive challenge, there are several exceptions. For example, Medalia et al. (2000, 2001) in a study of 54 chronic inpatients with schizophrenia, compared the

effects of computerized programs of problem-solving and memory training against one another, and a non-computer-trained control condition, on measures of problem-solving skill for independent living, verbal comprehension, immediate paragraph recall and verbal list learning. Results revealed that the problem-solving training produced improvements in problem-solving skills, but not comprehension or memory measures, relative to the memory-trained group that also had exposure to a computer, interaction with the same clinician and “non-specific” challenge. There was no evidence of “non-specific” effects of the control computer training on cognition in this study, however. This difference in findings from the current study may relate to differences in duration of the control interventions and the differences in patient populations studied (in- vs. outpatient).

Several limitations to the current study should be mentioned. First, sample size was small and effects of small to medium size may have been obscured secondary to limited power. Nonetheless, this observation highlights the robustness of the effects of cognitive remediation on working memory and the non-specific effects of both interventions on a variety of neurocognitive measures. Second, the relationship of cognitive-remediation-linked improvements in working memory, or non-specific improvements in working memory, reasoning/problem-solving, verbal and non-verbal episodic memory, and processing speed observed in this study, to performance-based, proxy measures of daily-life functioning and actual measures of community-function, remains unclear. We note that integration of cognitive remediation interventions similar to the type employed in the current study with work therapy or supported employment programs have produced improvements in measured work function (Bell et al., 2005; McGurk et al., 2005). We are currently conducting studies to investigate the relationship of the improved cognitive skills evident in the current study to proxy and actual measures of community function. Third, the design of the study would have been improved by an independent measurement of the level of “cognitive challenge” produced by each intervention. While we assume that the processing of novel verbal information and the periodic content exams characteristic of the computer-training control would produce non-specific cognitive challenge that would be similar to that of drill-and-practice cognitive exercises, it remains unclear whether patients may have perceived one condition as more difficult than another. Fourth, the current remediation intervention selected for this study employed a “bottom-up” approach in which training was hierarchical-

ly organized such that elementary neurocognitive functions (e.g., simple sustained attention) were trained before more complex functions (e.g., verbal memory). It remains unclear as to what degree our findings relate to “top-down” remediation approaches that emphasize training of multiple cognitive domains simultaneously, with procedures that are selected for their ability to promote task engagement (e.g., Medalia et al., 2001). Future studies will be aimed at understanding what demographic, neurocognitive or symptom characteristics predict treatment responses to cognitive remediation interventions, how training-related improvements in neurocognition may be enhanced through pharmacologic manipulation, and the durability of observed specific and non-specific treatment effects after termination of these interventions.

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