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Effects of neurocognitive enhancement therapy in schizophrenia: Normalisation of memory performance

Morris D. Bell, Joanna Fiszdon, Gary Bryson, and Bruce E. Wexler

VA Connecticut Healthcare System, West Haven, USA

Introduction. A preponderance of research indicates that cognitive function in schizophrenia can be improved through cognitive remediation. However, few studies have attempted to characterise the extent of improvement relative to nonpsychiatric controls.

Method. Cognitive performance on reaction time, digit recall, and word recall of 58 schizophrenia patients at baseline and after 6 months of cognitive remediation was compared to the performance on these tasks of 39 community controls. Schizophrenia patients participated in Neurocognitive Enhancement Therapy (NET) and received hierarchical training on the memory tasks, but not on the reaction time task, which was only administered at intake and follow-up.

Results. The schizophrenia sample showed significantly poorer performances than the community control sample on all three tasks at baseline. NET led to significant improvements in performance on trained memory tasks, but not the untrained reaction time task. There was a significant increase in the proportion of schizophrenia patients who achieved normal range performance on the memory tasks.

Conclusions. 52% of schizophrenia patients who were impaired on at least one of the memory tasks normalised their performance on at least one of those tasks as a result of cognitive training. Results suggest that clinically meaningful improvement may be possible using cognitive remediation.

Cognitive impairments in schizophrenia are well documented (Green, 1996; Heaton et al., 1994; Hoff et al., 1999; Saykin et al., 1991). Impairments in schizophrenia range from deficits in vigilance and attention to deficits in memory and problem solving, and are correlated with interpersonal, occupational, and social problem-solving skills (Green, 1996; Green, Kern, Braff, & Mintz, 2000). Verbal memory impairment, in particular, has been noted as one

Correspondence should be addressed to Dr Morris Bell, Psychology Service (116B), VA Connecticut Healthcare System, 950 Campbell Ave, West Haven, CT 06516, USA;
e-mail: Morris.Bell@Yale.edu

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of the strongest predictors of rehabilitative treatment outcome and overall level of functioning (Green, 1996; Smith, Hull, Romanelli, Fertuck, & Weiss, 1999). Moreover, without intervention, such cognitive impairments have been shown to be relatively stable over time (Hoff et al., 1999; Wykes et al., 2002).

Studies of cognitive retraining in schizophrenia indicate that cognitive function can be improved (see Kurtz, Moberg, Gur, & Gur, 2001, for a review). For example, several studies indicate that with proper instruction and feedback, performance on the Wisconsin Card Sorting Test can improve (Kern, Wallace, Hellman, Womack, & Green 1996; Stratta, Mancinia, Mattei, Casacchi, & Rossi 1994). Similarly, studies indicate that repeated practice results in increased attention span (Medalia, Aluma, Tryon, & Merriam, 1998; Silverstein et al., 1998), and that social cognition, problem solving, and memory can be enhanced through training (Medalia, Revheim & Casey, 2000, 2001; O'Carroll, Russell, Lawrie, & Johnstone, 1999; van der Gaag, Kern, van den Bosch & Liberman, 2002). Results from more comprehensive cognitive remediation programmes, which aim at remediating multiple cognitive functions, are also encouraging. In our own rehabilitation studies, we have shown that Neurocognitive Enhancement Therapy (NET), which includes specific training in memory, attention, and executive function, along with extensive feedback and a social information-processing group, is associated with improved performance on executive function and working memory domains (Bell, Bryson, Greig, Corcoran, & Wexler, 2001). Other researchers have shown that a comprehensive, milieu-based rehabilitation programme, including Integrated Psychological Therapy (IPT), results in increased social competence, attentional processing, memory, attention, and executive function (Spaulding, Reed, Sullivan, Richardson, & Weiler, 1999). Similarly, Wykes and colleagues (Wykes, Reeder, Corner, Williams, & Everitt, 1999) found that training in their neurocognitive remediation programme, which includes specific, hierarchical instruction in both simple and more complex aspects of cognition involved in planning, working memory, and frontal/executive function, results in improvement on cognitive flexibility and memory tests. In a related case study, Wykes (1998) also reported that intensive neurocognitive training not only led to improved performance on both trained and untrained tasks, but also resulted in changes in brain activation.

As summarised above, a preponderance of research indicates that cognitive function in schizophrenia can be improved through cognitive remediation. Traditionally, researchers examine pretraining and posttraining performance within the schizophrenia samples, sometimes adding an alternate treatment condition. Nearly absent are comparisons of posttraining performance to performance by nonpsychiatric controls. This largely neglected type of analysis is important, as it provides information on whether cognitive remediation training normalises performance to levels observed in nonpsychiatric samples. We are aware of only one study that examines improvement in relation to normal control performance. Wexler and colleagues (Wexler, Anderson, Fulbright, &

Gore, 2000), reported that following 10 weeks of training on auditory verbal serial position memory tasks, two of their eight patients obtained scores higher than the average scores for their normal controls. Performance improvements were associated with increased task-related activation of the left inferior frontal cortex. Additionally, for one participant who received an additional 5 weeks of training, task-related activation, as shown by functional magnetic resonance imaging (fMRI), normalised to resemble that of normal controls.

In the current paper, baseline and follow-up performances of schizophrenia patients on two trained memory tasks and an untrained reaction time task are compared with the performances on these tasks by a nonpsychiatric community sample. It was hypothesised that: (1) the schizophrenia sample would perform more poorly than the community sample on all three tasks at baseline; (2) following NET training, cognitive performance of the schizophrenia sample would significantly improve on the trained memory tasks but not on the untrained reaction time task; and (3) the proportion of patients performing within the normal range would significantly increase after training.

METHOD

Participants

Schizophrenia sample. The schizophrenia sample included 58 outpatients enrolled in the NET + WT portion of Neurocognitive Enhancement Therapy (see Bell et al., 2001, for a full description of the programme). Informed written consent was obtained for all participants. All participants completed a baseline assessment of performance on digit and word recall tasks on which they would later receive training, as well as on a simple reaction time task on which they would not receive training. Their performance on these tasks was reassessed following NET. There were 40 participants with DSM-IV (American Psychiatric Association, 1994) diagnoses of schizophrenia (7 disorganised, 26 paranoid, 6 residual, 1 undifferentiated), and 18 participants with diagnoses of schizoaffective disorder. All diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1996), administered by a PhD-level psychologist. The Mean Positive and Negative Syndrome Scale (PANSS; Kay, Opler, & Fiszbein, 1987) score was 77.34 (SD = 15.97), indicating moderate levels of symptom severity. Relevant demographic information is presented in Table 1. In order to enter into the study, schizophrenia patients met the following inclusion criteria: outpatient status, no change in psychiatric medications in past 30 days, no change in housing in past 30 days, no alcohol or drug abuse in past 30 days, no documented developmental disability, no known neurological disorder, Global Assessment of Functioning Scale score over 30. All schizophrenia participants were referred by their clinicians, and were receiving treatment either at the VA Connecticut Healthcare System or at the Connecticut Mental Health Center.

TABLE 1
Sample characteristics for schizophrenia and community participants

	Community sample (*n* = 39)	Schizophrenia sample (*n* = 58)	Significance		
Variable	*Mean* (*SD*)	*Mean* (*SD*)	*t* or χ^2	*df*	*p-value*
Age	29.6 (10.0)	41.4 (9.7)	5.84	95	< .0001
Education (yrs)	13.9 (1.9)	13.2 (2.1)	−1.73	95	.09
WAIS-III Digit Span[a]	9.3 (2.4)	7.5 (2.0)	−4.13	94[b]	< .001
WAIS-III Information[a]	9.2 (2.5)	10.2 (3.5)	1.57	95	.12
Male gender	4 (10%)	44 (76%)	40.2	1	< .0001
Right-handed	35 (90%)	53 (91%)	0.1	1	.8

[a] Scaled score.
[b] Digit span data was not available for one of the community control participants.

Community sample. A total of 39 adult students were recruited from a local technical college. Participation in the study was an optional component of an extra-credit assignment. After providing informed written consent, potential participants were asked a series of screening questions to assess eligibility for the study. In order to be eligible, participants must have denied: significant memory/attention problems; active substance abuse, current use of prescription medication that could affect cognitive function; history of traumatic brain injury; and presence of visual or motor impairments that would influence ability to complete the computer tasks.

Relevant demographic information is presented in Table 1 for all participants. It should be noted that there were no significant differences between the community and the schizophrenia sample on education levels or on the Information subtest of the WAIS-III, indicating similar levels of premorbid IQ. There were significant differences on gender and age variables. There was also a significant difference on the Digit Span subtest of the WAIS-III, supporting the need for remediation of verbal memory in the schizophrenia sample.

Computerised cognitive remediation tasks

All computerised cognitive remediation tasks were modifications of the Psychological Software Services CogReHab software (Bracy, 1995), a multimedia, windows-based software designed for use with traumatic brain injury and other neurological impairments resulting in compromised cognitive function. The following tasks were administered to both schizophrenia and community samples.

Simple reaction time. Examinees focus their eyes on the centre of a computer monitor, and are instructed to press a mouse button as soon as a yellow square appears anywhere on the monitor. A total of 15 squares is presented, with the interstimulus interval ranging from 1 second to 4 seconds. The task is administered four times, and on average reaction time is computed.

Digits sequenced recall. Examinees are presented with digits, flashed one at a time on a computer screen (list length starts with two digits and increases with success). Exposure to each digit is 1.5 seconds, and there is a built-in wait time of 5 seconds before recall can commence. Following list presentation, examinees are instructed to press corresponding numbered tabs, replicating the sequence of digits. A total of 12 trials is administered. The longest string of digits successfully recalled is recorded. Scores from longest digit list length were converted into performance level scores using a continuous scale length (*M* = 26.2; *SD* = 8.86; range = 1–41) that combines the parameters of exposure time to digit, latency prior to response, and list length.

Words sequenced recall. Examinees are presented with a list of words (list length starts with two words and increases with success). Exposure to the word list is 3 seconds per word, and there is a wait time of 5 seconds before recall can commence. Following list exposure, examinees are shown one of the word lists and asked to indicate its serial order by pressing the corresponding numbered tab. A total of 12 trials is administered. The longest word list with successful recall is recorded. As with the digits scores, the longest word list variable was converted into performance levels (*M* = 33.44; *SD* = 9.34; range = 13–49) based on list exposure time, latency prior to response, and list length.

Procedure

The community participants were administered the computerised cognitive remediation tasks and the Digit Span and Information tests from the WAIS-III (Wechsler, 1997) during individual sessions at the technical college. They were given an opportunity to become familiar with the computerised tasks to ensure that data would reflect actual task performance and not be influenced by task novelty. Next, they were given single administrations of each task. Schizophrenia patients were administered the tasks at baseline and at the conclusions of the six month course of Neurocognitive Enhancement Therapy. As part of NET, schizophrenia patients trained on the digits sequenced recall and the words sequenced recall tasks, but not the simple reaction time task. Schizophrenia patients also trained on other computerised CogReHab tasks involving memory, attention, and executive function. Task difficulty was increased based on performance, according to prespecified criteria for each task. All schizophrenia patients were encouraged to attend five computerised cognitive training sessions (45 minutes each) per week, and received monetary incentives for doing so. On average, schizophrenia participants completed 43 cognitive training sessions

(*SD* = 33.00, range = 0–114): 32 (55%) participants continued to receive cognitive training up until their follow-up assessments, while 26 (45%) had stopped cognitive training prior to follow-up. The mean latency between last cognitive training session and follow-up assessment was 35 days (*SD* = 57.76; range = 0–208 days). Despite this variability in extent and duration of training, we examined data from the sample as a whole, since we felt that this was a conservative test of our hypotheses. By following an ''intent to treat'' approach that included all participants assigned to NET, self-selection would not confound results. In addition to cognitive training, all schizophrenia patients attended a weekly social information-processing group, and participated in a paid work programme with job sites throughout the medical centre (see Bell et al., 2001 for additional information on the work and cognitive training components of the NET programme).

Data analysis

t-Tests were performed to test for differences in task performance between the community and schizophrenia samples at intake. Paired *t*-tests were used to determine differences between intake and follow-up performance within the schizophrenia sample. A cut-off score of 1 *SD* below community sample mean was set as minimal performance to categorise performance as ''normal''.

McNemar's *Q* was used to test change in proportion of patients scoring within the normal range from baseline to follow-up. Several *post-hoc* analyses were also conducted. In order to determine the relationship between performance improvements on the two memory tasks, a Pearson correlation was computed between the pre-post training change scores for the two memory tasks. In order to explore the potential relationship between symptom level and memory task improvement, Pearson correlations were also computed between intake PANSS score and pre-post training change scores for the two memory tasks. Finally, we also wished to determine the extent to which the latency between testing and last training session contributed to the variance in post-training performance. We performed two zero-order correlations partialling out number of training sessions (since length of training was correlated $r = -.53$ with the length of time until retest) with digit task difference score and word task difference score as dependent variables. The Alpha-level was set at .05 for all tests. All tests were 2-tailed.

RESULTS

Independent samples *t*-tests comparing simple reaction time, sequenced digits recall, and sequenced words recall task performance between schizophrenia patients' baseline scores and scores of the community participants are shown in Table 2. This table also contains results of paired samples *t*-tests comparing intake and posttraining performance of the schizophrenia sample on all three

TABLE 2
Comparison of healthy control and patient reaction time and memory data

	Healthy controls	*Patient intake*	*Patient follow-up*	*Healthy controls vs. Patient intake*		*Patient intake vs. Follow-up*	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*t*	*p-value*	*t*	*p-value*
Reaction time	0.3076 (0.06)	0.4208 (0.06)	0.4239 (0.21)	4.67	<.0001	0.16	.8735
Digits recall	32.26 (6.1)	22.16 (8.1)	28 (9.9)	6.54	<.001	−4.8	<.001
Words recall	40.09 (6.7)	29.66 (8.5)	32.76 (10.3)	6.06	<.001	−2.3	.022

tasks. The number of participants included in analyses varied slightly from task to task, due to procedural difficulties.

For digits sequenced recall, at intake 25% of the schizophrenia sample scored within the normal range. At follow-up, 53% of the schizophrenia sample scored within the normal range (Q_m = 9.85, $p < .005$). For words sequenced recall, at intake 28% of the schizophrenia sample scored within the normal range. At follow-up, the proportion had increased to 48% (Q_m = 7.2, $p < .01$). For simple reaction time, at intake, 40% of the schizophrenia sample scored within the normal range, while at follow-up the proportion was 47.5% (Q_m = 0.69, $p = .41$).

Figures 1 and 2 show individual performances on digits and words sequenced recall tasks at baseline and follow-up. The figures include the cut-off value for normal performance and the overall mean improvement for the schizophrenia sample. As illustrated, many patients improved their performances to within the average range of normal performance.

For the digits sequenced recall task, there were 23 patients (39.66%) who were performing below the community sample average at both intake and follow-up. For the words sequenced recall tasks there were 25 patients (43.10%) who were performing below the community sample average at both intake and follow-up. Of those patients, 19 (32.76%) were performing poorly on both tasks, at both intake and follow-up.

For the digits sequenced recall task, there were 9 patients (15.52%) whose performance was above the community sample cut-off score at both intake and follow-up. For the words sequenced recall task, there were 12 patients (20.69%) whose performance was above the community sample average cut-off score at both intake and follow-up. Of those patients, 7 (12.07%) were performing within the normal range on both tasks, at both intake and follow-up.

For the digits sequenced recall task, there were 21 (36.21%) patients who were performing below the community sample average cut-off score at intake, but whose performance improved to above the cut-off score at follow-up. For the words sequenced recall task, there were 16 (27.59%) patients who were performing below the community sample average cut-off score at intake, but whose

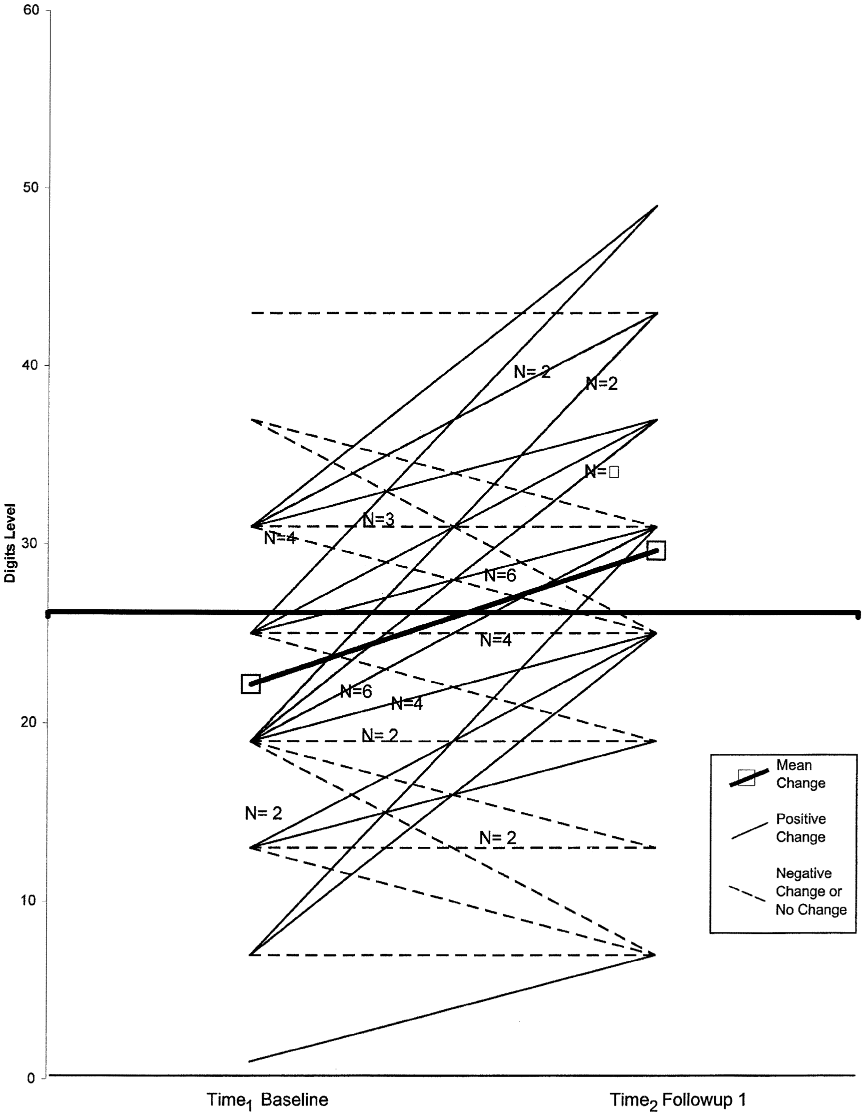

Figure 1. Individual performance changes between intake and follow-up testing on the digits sequenced recall variable. *Note*: Bold horizontal line indicates minimal cut-off for ''normalized'' performance.

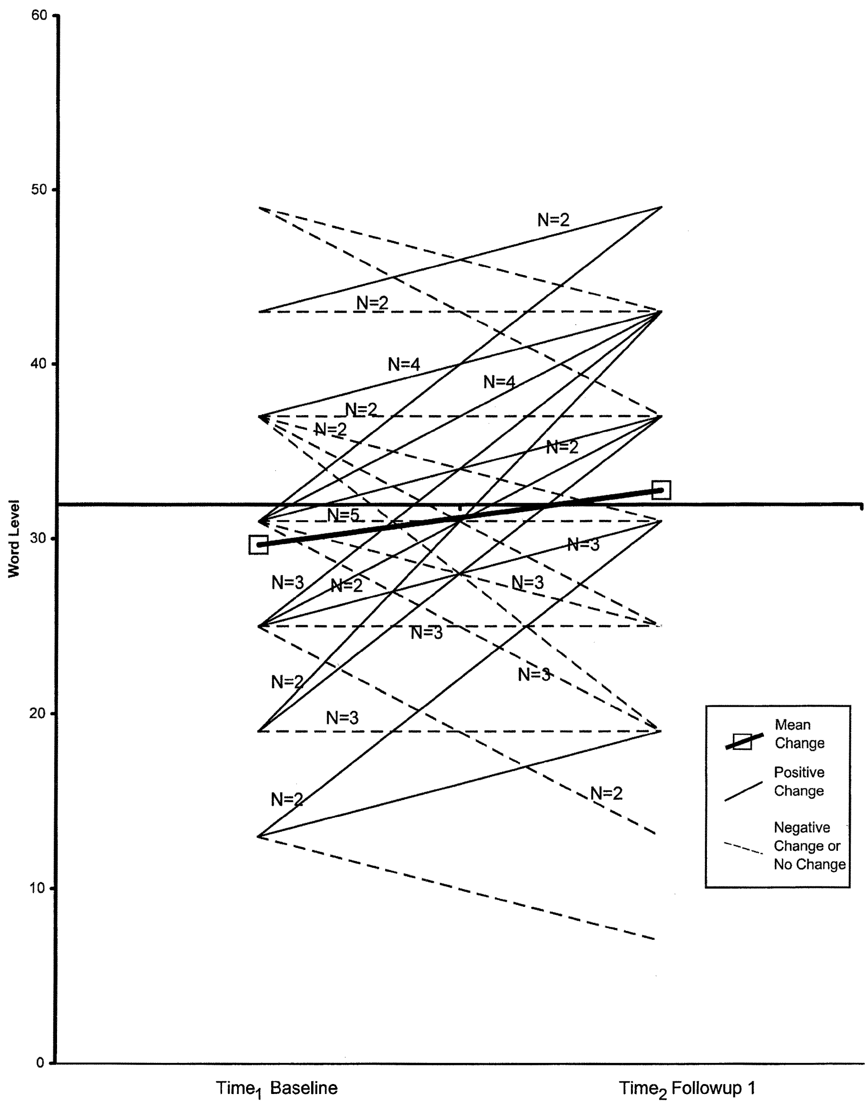

Figure 2. Individual performance changes between intake and follow-up testing on the words sequenced recall variable. *Note*: Bold horizontal line indicates minimal cut-off for ''normalized'' performance.

performance improved to above the cut-off score at follow-up. There were 9 patients (15.51%) who performed below the community sample average cut-off score on both tasks at intake, but whose performance improved to above the cut-off score at follow-up, on both tasks.

There were 28 patients (48.28%), whose performance on at least one of the memory tasks normalised (i.e., was below the community sample cut-off score at intake, and improved to above the cut-off score at follow-up). Excluded from the above analysis were 4 patients with normal range performance on both tasks at intake and follow-up (i.e., participants without cognitive impairment on these tasks), 51.85% of the remaining patients exhibited normalisation of performance on at least one of the tasks.

Post-hoc analyses were as follows. The correlation between performance improvements on the digit and word tasks was not significant (r = .087, p = .519). PANSS total score was not significantly correlated with digit task difference score (r = −.245, p = .066) nor with the word task difference score (r = .040, p = .767). Higher improvement on the digits task was significantly correlated with shorter latency (r = −.27, p = .05) but explained only 7% of variance. Latency was not significantly correlated with word task difference score (r = .11, p = .44).

DISCUSSION

Results demonstrate that people with schizophrenia can learn to improve on memory tasks through repetitive, hierarchical training and that many can reach normal levels of performance. Of schizophrenia patients who were impaired on at least one of the memory tasks, 52% normalised their performance on at least one of those tasks as a result of cognitive training. In addition, the entire sample showed significant improvement, suggesting that many who did not reach normal levels of performance on the memory tasks nevertheless benefited from the cognitive training intervention. There were no significant changes in performance on the untrained simple reaction time task, which indicates that improvements on the memory task were not because of reaction time changes. It also suggests the specificity of training: Improvements only occurred on tasks where training was provided.

In an attempt to better understand variables associated with treatment success, we examined the relationship between symptomatology (measured by PANSS) and level of improvement on the memory tasks. The correlations were not significant, suggesting that level of psychiatric symptoms does not limit the efficacy of cognitive remediation. We also examined the relationship between improvement on one memory task with improvement on the other. Somewhat unexpectedly, this correlation was not significant. This finding could be interpreted to mean that the two memory tasks require somewhat different cognitive functions for successful performance. Although both tasks engage memory systems, there are several differences between them. For example, the digit task is a sequenced recall, symbol encoding task, whereas the word task is really a serial position, lexical task. The words task may also be more difficult than the digits task because the digit task consists of a limited number of stimuli (numbers 0 through 9), which can be ''chunked'' into smaller pieces of information, while the word task consists of many more stimuli (4-letter animal words) and is less amenable to data-reduction strategies.

Although the current study did not specifically address the durability of training effects, we explored the relationship between performance improvement and amount of time since last training session, taking into account the effect of total number of sessions attended. Our analyses indicated that latency contributed significantly to predicting performance improvement on the digit span task, but not on the word task. As suggested above, these differences might be due to the differences in difficulty levels of the two tasks. A more systematic evaluation of these two tasks might shed further light on this discrepancy.

In determining the effectiveness of treatment, an important consideration is whether clinically meaningful change can occur for a substantial portion of those receiving the intervention. To attain normal range performance is generally regarded as clinically meaningful (Kendall, Marrs-Garcia, Nath, & Sheldrick, 1999). A response rate of 52% is encouraging, indicating that cognitive remediation may benefit the majority of those who receive it. These findings set a firm foundation on which to explore the clinical effectiveness of this intervention by showing that it achieves its most proximal goal, that of task improvement. From this foundation can be built future studies to investigate how long training effects endure, their generalisability to related neuropsychological tasks, and their impact on community function. It will also be worthwhile to explore predictors of response in order to learn whether there are specific neurocognitive or illness characteristics that are associated with response to training.

Cognitive remediation for schizophrenia must still be regarded as an experimental method of rehabilitation, whose benefits are undetermined. These results support its potential. Attention and memory are cognitive requirements for much of the skills training, psychoeducation, and case management that comprise most rehabilitation programmes. Adding cognitive remediation training might make it possible for those patients who are currently most impaired to benefit from other interventions dependent on adequate neurocognition.

There are several limitations to the current study. The schizophrenia patients, in addition to training on computerised cognitive tasks, also participated in a weekly social information-processing group, were placed in paid work settings, and received feedback regarding their work performance. It is possible that any one of these factors, or their combination, might have resulted in increased performance on the memory tasks. The lack of improvement on the untrained simple reaction time task suggests that improvements on the memory tasks were specific to cognitive remediation training. However, one could also speculate that the simple reaction time task is qualitatively different from the memory tasks, and not amenable to training, even if such were offered. The addition of more training tasks, as well as the addition of a separate patient control group that would receive all but the NET component of the intervention, would more definitively address the specificity of training effects question. Finally, there are several sample differences that might affect the generalisability of our findings. Our community control sample had a significantly higher proportion of women, and was significantly younger. Also, although there were no statistical differences between the samples on current educational level, the community control sample was recruited from a school setting, and was therefore much more likely to obtain further education than the patient sample. If these variables had been better matched between the patient and community samples, our cut-offs for normalised performance might have been lower.

Although our findings have a number of limitations and will require replication, they are encouraging. They indicate that with proper training, complex cognitive functions, such as memory, can be improved to normative levels. It still remains to be seen whether these improvements are sustained over time, generalise to other tasks, and lead to improvements in functional outcome.

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