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What are we changing with neurocognitive rehabilitation? Illustrations from two single cases of changes in neuropsychological performance and brain systems as measured by SPECT

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Abstract

If cognitive remediation is to be developed further, there have to be not only large-scale randomized trials but also detailed analysis of the strategies used to produce improved performance. In this study the strategies adopted by two people who took part in a remediation program are investigated, with their results on neuropsychological tasks and with concomitant brain image data gathered via SPECT while the participant was performing a Verbal Fluency task. After remediation there were improvements in many of the neuropsychological tests, and changes in the scan data. The changes in strategies and brain activation were different for both individuals. One person increased his verbal output but without close monitoring, so also increased his errors. The other participant decreased his output but monitored it more closely, and so decreased the errors. These strategies were reflected in the changes in activation between scans, i.e. increases in temporal areas for the increased output and bilateral decreases in the anterior cingulate and left pre-motor areas for the decreased output case. Together these results imply that the participants continue to use individual strategies which for many of the neuropsychological tasks produced gains. Further investigation of whether it is possible to change idiosyncratic strategy use is needed if we are to develop the efficacy of this remediation technique. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Despite the decreases in symptoms following pharmacotherapy, there are still too few instances of people with schizophrenia returning to normal life. The continuing disabilities may result from the cognitive deficits (memory, executive functioning and attention) which patients with schizophrenia experience which directly affect their ability to utilize social and occupational skills. These cognitive deficits have been labeled as the 'core of schizophrenia' (Bleuler, 1950) and may be primary to the illness and/or secondary to the symptoms which are pathognomic to schizophrenia, i.e. intrusive thoughts. The majority of published papers on cognitive deficits associated

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with schizophrenia suggest that they must be refractory. But there is now new evidence that these dysfunctions may still be open to modification using cognitive and behavioral techniques (Green, 1993, 1996). If these information processing problems are open to amelioration, then there may be further improvements in life skills subsequent to their rehabilitation as the rate limiting effect of the deficit is removed.

Although showing some promise, these neurocognitive remediation methods have not yet produced unequivocal results from randomized control trials and most have produced little evidence of generalization. One reason for this may be the sophistication of the programs themselves. For example Brenner et al. (1992) use a group format which relies on the generation and correction of responses rather using the more powerful errorless learning approaches generated from laboratory studies (e.g., Kern et al., 1996; Rossell and David, 1997). And specific test skills have been improved by simple techniques (e.g., Stratta et al., 1994; Benedict et al., 1994). Because of the lack of generalization to other skills, these authors suggested that remediation programs should concentrate on training information-processing strategy use. For this to succeed, a wide range of tasks needs to be provided in order to practice different processing elements or different aspects of a basic process. Several packages have adopted this approach with some success in improving performance on a small number of cognitive tasks (e.g., Brown et al., 1993; Delahunty et al., 1993). There is clearly a need to investigate the efficacy of these more complex remediation packages in randomized control trials, but information is also required on what processes are actually being changed by remediation and this is the focus of the current paper. We will use as our examples two patients with schizophrenia who have different symptom profiles and who may benefit in different ways from cognitive remediation.

The remediation package adopted in this study was devised by Delahunty and Morice (1993). It contains a number of different tasks which encourage the employment of different information-processing controls. These are generally known as executive processes, a term coined by Alan Baddeley (1992). Evidence of deficits in these executive processes is abundant in schizophrenia (e.g., Goldberg et al., 1987, 1990; Morice, 1990; Morris et al., 1995). The majority of neuropsychological tests, as well as normal everyday functioning, require the employment of all these processes in various proportions. Information about what patients do learn from remediation which relates to their improvement in neuropsychological tasks may allow us to develop programs further and to increase their effectiveness.

Changes in strategies can be examined by investigating the behavioral outcome from tests. Improvements may not be a result of a change in information-processing approach; it may be that the whole processing system becomes more active, enabling faster processing of information. One way to investigate such changes is to carry out brain imaging during the tasks before and after remediation.

Brain imaging studies have shown that deficits in tasks of planning and cognitive flexibility have been associated with activation problems in the dorso-lateral prefrontal cortex (DLPFC) and temporal lobe (e.g., Weinberger et al., 1986; Andreasen et al., 1992; Morris et al., 1993; Frith et al., 1995). When the stimuli and responses are equated, patients with schizophrenia seem to activate a larger area of the DLPFC, although others have reported low activation in this area. In normal people there also appears to be a functional connection between the temporal and frontal lobes such that activation in the temporal lobe decreases when the DLPFC increases its activation (Frith et al., 1991). This is not so for patients with schizophrenia (Frith et al., 1995). It is not clear whether this processing deficit is the result of a specific lesion or whether it arises from a lack of stimulation from other brain regions. For example, abnormalities in the subicular loop have been suggested as affecting the fronto-temporal connections (Hemsley, 1993). It is also not clear what the effect, if any, cognitive remediation has on the brain systems responsible for executive processing. Improvements may be correlated with increases in brain activation in the areas responsible for executive processing in normals or, alternatively, there may be compensatory mechanisms which become more active and correct for functional disconnections. Whichever outcome is found will have an effect on the further development of remediation programs. For instance, compensatory mechanisms may be limited (or slow) in their ability to change, whereas increasing activation may be less restricted.

The study reported here is a small pilot based on a case study approach suggested by Shallice et al. (1991) and incorporates a variety of neuropsychological tasks as outcomes. The neuropsychological tests employed in this study have been shown to be stable over time without intervention (e.g., Delahunty et al., 1993; Shallice et al., 1991). However, because of the measurement error on all these tests, the data from these cases will be compared with those of comparison groups of patients with schizophrenia. The design therefore relies on finding greater improvements in all neuropsychological measures.

As well as these comparisons, changes in the brain system responsible for a particular cognitive task, verbal fluency, will also be investigated. A previous study by Lewis et al. (1992) showed that patients with schizophrenia show reduced activity in the left mesial, inferior and dorso-lateral frontal regions compared to age-matched controls while performing an adapted Verbal Fluency test. The Verbal Fluency task in our study was paced as in Frith et al. (1995) to overcome the problems of interpreting brain-scan data when patients run out of words. In this study it is hypothesized that following successful neurocognitive rehabilitation, patients will show increased activation in the areas associated with carrying out the task. Previous literature (e.g., Raichle et al., 1994) suggests that practice on verbal tasks reduces activation in the anterior cingulate, left prefrontal and left posterior temporal cortices.

2. Method

2.1. Participants

2.1.1. Case 1

AB is a 25-year-old Caucasian man who was born in the UK, with a DSM-IV diagnosis of schizophrenia. He has had some skilled employment but is currently unemployed. When he entered the trial his mental state was stable. His total BPRS score was 43, indicating moderate to severe disturbance. He scored at a high level on the thinking-disturbance item (score 6) and low on social withdrawal (score 3). He was relatively socially skilled but required the support of his community team and his family to remain in the community.

2.1.2. Case 2

CD is a 55-year-old Afro-Caribbean man who was born in Jamaica and has a DSM-IV diagnosis of schizophrenia. Although in the past he has been reported as having persistent widespread delusional beliefs (e.g., he is working for the government and receives messages from other agents), when he entered the trial he showed mainly negative symptoms. His clinical state on entering the trial was stable. His total BPRS score was 37 (moderate to severe) and his social-withdrawal score was 9, much higher than his thinking-disturbance score of 3. When chosen for the trial he had been an inpatient for several months mainly because he was homeless, but just before the first therapeutic session he moved to a supervised hostel in the community.

2.2. Design

Both participants were tested on a variety of neuropsychological tests (WAIS-R and specific functioning tests) before and after rehabilitation. The word fluency test was carried out as part of the SPECT scanning procedures at baseline and after rehabilitation. Daily rehabilitation sessions were carried out during the working week over a 3-month period, with short breaks for illness and public holidays.

2.3. Procedure for the neurocognitive rehabilitation

The participants each received up to 32 sessions of intensive neurocognitive training from two modules of the course devised by Delahunty and Morice (1993), Cognitive Shift and Planning. Each module consists of a number of different sorts of tasks which are graded according to difficulty, with easier items presented first. The order of the tasks is specified by the handbook. The therapist can show patients more effective methods of dealing with information, but should not perform the tasks for them. The three steps of the process are: (a) the therapist demonstrates the information processing overtly; (b) the patient uses such methods overtly; and (c) the patient uses these methods covertly.

2.4. Procedure for brain imaging using SPECT

2.4.1. Cognitive task

A modified paced Verbal Fluency test was used (Frith et al., 1995) in which participants were given 20 opportunities to name words beginning with a specific letter at 2-s intervals.

2.4.2. Scanning procedure

The detailed procedure adopted is described in Lewis et al. (1992). After the procedure had been explained, the participant was asked to lie on the scanning couch and a heparinized cannula was inserted into the anterior fossa vein of the non-dominant arm. The task instructions were given and the participant began to name the words. After 2 min a 500 MBq bolus of ^{99m}Tc-HMPAO was injected into the cannula. The participant continued with the task for 6 min until it was completed. Then he underwent scanning. An SME-810 multidetector head-dedicated SPECT system was used to obtain measures of regional cerebral blood flow (rCBF). Eight overlapping slices were acquired in a plane parallel to the orbitomeatal line. A minimum of 10^6 counts were acquired per slice. A 128×128 matrix was used for display and analysis.

2.4.3. Image analysis

Two slices were chosen for rCBF analysis for each series of scans. The first was midventricular through the head of the caudate, lying between 40 and 55 mm above the orbitomeatal line. The second slice was 20 mm above this. Region of interest (ROI) analysis was performed by an independent rater blind to the identity of the subject. The cortex was operationally defined as a 6-pixel wide rim within the brain boundary. This was divided up as described in Lewis et al. (1992). Image boundary was defined by using 40% of the lower cut-off threshold, enabling a clear edge to be identified. On the midventricular slice the cortex was divided into four segments on each side (M1–M4). These were defined by dropping perpendiculars at a quarter, half and three-quarters of the distance between the midline and the frontal and occipital poles. A strip of mesial frontal cortex (M0) was defined either side of the midline within the first quarter segment. On the higher slice the cortex was divided into two equal sectors on each side (S1, S2). The basal ganglia and thalamus were defined using a template. All measurements were performed on an Apple-Mackintosh using dedicated software (Strichman Medical Equipment Inc., Version 2.66). Mean counts in a region were normalized to mean counts for the whole slice.

2.5. Neuropsychological assessments

2.5.1. Premorbid and current IQ

National Adult Reading tests (NART, Nelson and Willison, 1991) and all sub-tests of the WAIS-R, each of which relies on different proportions of executive processes.

2.5.2. Specific executive-functioning tests

All tests of executive functioning require elements of cognitive flexibility, attention and planning, as well as working memory. However, it is generally accepted that, of the tests below, the main components of tests (a)–(e) is the ability to be cognitively flexible, whereas for test (f) it is the ability to plan.

(a) Wisconsin Card Sort Test (*WCST*: Milner, 1963). The long form of this well-known classification test was used where the measure of success is the number of categories sorted and the number of perseverative errors.

(b) Stroop Neuropsychological Screening Test (Trenerry et al., 1989). This is a test of the ability to switch between categories. The key measure was the proportion of color words to color names correctly named in 2 min.

(c) Modified Paced Verbal Fluency (Frith et al., 1991, 1995). The key measures are the number

of correct items and the number of errors (repetitions, non-words etc.).

(d) Trail Making (Reitan, 1958). The key measures are the time taken on each condition (A and B) of the test and the excess time taken to carry out condition B (i.e., time B – time A).

(e) Hayling Sentence Completion test (Burgess and Shallice, 1996). The subject has to complete a set of sentences with a word that does not make sense. The number of errors is the key outcome variable (scoring manual provided by Burgess and Shallice, 1996).

(f) Tower of London test (Shallice, 1982). In this test the object is to move a series of discs from peg to peg in as few moves as possible in order to match a specified outcome. The key measure is the number of trials completed in the minimum number of moves, but planning time prior to beginning the first move and the total time for the task are also monitored.

Comparison data for the repeat assessment of 13 of the neuropsychological tests (eight WAIS subtests and all the specific executive-functioning tests), Self-esteem, BPRS and Social Behavior collected from a similar group of patients with schizophrenia were available courtesy of Wykes et al. (1990, 1997) and Greenwood (personal communication).

In addition to the neuropsychological assessments, mental state, disability and self-esteem were monitored using the Brief Psychiatric Rating Scale (Lukoff et al., 1986), the Social Behavior Schedule (Wykes and Sturt, 1986), and the Rosenberg Self-esteem schedule (Rosenberg, 1965).

3. Results

The performances on the baseline neuropsychological tests are shown in Table 1. The most obvious finding is the discrepancy between the predicted versus the obtained IQ results. The predicted IQ is in the normal range for all subjects, but the obtained IQ on the WAIS-R was approximately 20 points below this level.

On the tests sensitive to poor executive functioning, both cases showed a mixed pattern, but overall they showed significantly poor responding on some aspect of at least 80% of the tests for which normal data are available. On the paced Verbal Fluency test, both participants exhibited repetitions of words, non-words and omissions, and when these were taken into account performance fell below normal (see Frith et al., 1995 for normative data). These data are similar to those reported by Perret (1974), Milner (1963) and others which showed that these tests are sensitive to frontal lobe damage. But Eslinger and Grattan (1993) and Axelrod et al. (1996) suggest that although these tasks are sensitive to frontal lobe pathology, they are not necessarily a marker for it.

3.1. Changes in functioning after the rehabilitation program

Changes in performance were measured in two ways. Firstly, a reliable change index was calculated following the method suggested by Hageman and Arrindell (1993). This method used the information from the comparison samples to produce a set of z scores for each individual. The results of these analyses are shown in Table 2. Although most scores were positive (including four out of five tests of specific executive processing), only five tests achieved the 5% significance level (AB 3 scores; CD 2 scores). Secondly, when the z scores were rated as showing either improvement, same performance or decrements (irrespective of their significance) the chi-square statistics were as follows: AB 5.69, $p=0.058$; CD 3.77, $p=0.052$.

There was also an improvement in the scores on the paced Verbal Fluency task for AB and CD who completed the task in the scanner (AB 78 to 80; CD 76 to 87). There are no normative data on this task, although Frith et al. (1995) assume no change in performance over time. Both participants increased their verbal fluency level, but in two different ways. AB increased his word output (87 to 95), but also increased the number of non-words and repetitions of words (9 to 15). But because of the increase in his overall output his performance still improved. On the other hand CD decreased his word output (94 to 87), but had fewer non-words and repetitions (28 to 10). Both changes in performance led to improvements in

Table 1
Neuropsychological tests

	AB	CD
Baseline tests		
WAIS-R		
Verbal IQ	86	74
Performance IQ	80	65
Full-scale IQ	82	69
Estimated premorbid full-scale IQ (NART)	103	95
	Significantly above current levels	Significantly above current levels
Tests sensitive to executive functioning		
Paced Verbal Fluency test[a] (possible total 120)	78	76
Trails		
A[b]	Below 10th centile*	Below 10th centile*
B	Below 10th centile*	Below 10th centile*
(B−A)	Below 10th centile*	Below 10th centile*
Stroop color naming[c]	Below 1% population*	Below 1% population*
Hayling Sentence Completion test[d]		
No. of errors	Poor performance	Poor performance
Response latency (b−a)	Less than 5% population	Less than 1% population
WCST[e] categories	6–10th centile	Below 1st centile*
No. of perseverative errors	Below 10th centile ($N=30$)	Below 16th centile ($N=22$)
Tower of London[f]	Within normal range	Within normal range
% problems solved within time limit	11%	9%
Proportion of tests with poor performance	87%	100%

[a]Frith et al. (1995); [b]Lezak (1995); [c]Trenerry et al. (1989); [d]Burgess and Shallice (1996); [e]Heaton et al. (1993) and Lezak (1995); [f]Shallice (1982) and Morice and Delahunty (1996).
*Significantly lower performance than control samples matched for age.

scores, but probably via different routes. This difference in strategies is also obvious in the Tower of London task. Instead of increasing his planning time AB decreased it, even in proportion to the time spent in completing the task (from 71% to 61%). But CD increased his planning time after remediation, and even in proportion to the total time taken on the task (from 10% to 33%). In other words, the improvement or deterioration was despite any improvements in execution time for the whole task. AB seems to have increased his behavioral output but with little monitoring, whereas CD has decreased his behavioral output and monitors his responses more closely.

For both AB and CD there were improvements in community functioning and the z score was statistically significant in the case of CD ($z=1.73$, $p<0.05$). This was mostly accounted for by both patients carrying out more tasks. Both participants also decreased their BPRS total scores (z scores: AB 2.2, $p<0.01$; CD 1.5, $p<0.08$). There were no significant changes in self-esteem.

Table 2
Mean and standard deviation of reliable change indexes

	AB	CD
Mean z score	0.54	0.71
SD	0.91	0.68
Range	−60 to 2.27	0 to 2.31
Proportion indicating improvement	54%	77%

3.2. SPECT scans

Two people independently rated four slices from two scans of case AB. The mean difference in average isotope uptake in ROI was 1.7% (SD= 1.87). The reliability of the ROI analysis of the SPECT scan was therefore high. Table 3 shows all the results. Few data are available for comparison, but Wyper et al. (1991) have shown that for a single case a change of 12% can be detected across

Table 3
Differences between baseline and follow-up scans

Anatomical area	AB	CD	Putative cognitive function
Left			
Anterior cingulate (M0)	11%	−16%*	Response selection and initiation of behavior
Inferior frontal (M1)	1%	−2%	
'Rolandic' (M2)	−4%	−3%	
Superior temporal (M3)	14%*	−2%	Word representation
Occipital (M4)	0	0	
Dorso-lateral frontal (S1)	0	11%	Planning and executive processing
Parietal (S2)	4%	4%	
Right			
Anterior cingulate (M0)	5%	−37%*	Response selection and initiation of behavior
Inferior frontal (M1)	1%	5%	
'Rolandic' (M2)	1%	−15%*	Speech and secondary motor control
Superior temporal (M3)	3%	0	
Occipital (M4)	−8%	−3%	
Dorso-lateral frontal (S1)	7%	7%	Planning and executive processing
Parietal (S2)	4%	9%	STM or selective attention
Basal ganglia (left and right)	0	11%	
Thalamus (left and right)	−3	8%	

*Indicates those measures which are above the 95% confidence interval suggested by Wyper et al. (1991).

cortical regions by this repeat scan method with a confidence limit greater than 95%. A value of 15% is used for deep matter regions. These criteria are used in the assessment of significant change for each patient. These were: an increase in blood flow in the superior temporal region for AB, and for CD decreased isotope in Rolandic regions (Brodman areas, 44, 6, 1, 2, 3), and decreased bilateral anterior cingulate changes. There were also changes in other areas, but we cannot be confident that they can be accounted for by the rehabilitation program rather than the variability of the scanning procedure. However, they do all seem to be in the cortico-frontal pathway (Goldman-Rakic, 1986; Kolb and Wishaw, 1990) which was hypothesized.

4. Discussion

Both participants had a DSM-IV diagnosis of schizophrenia, were representative of the sorts of patients who are currently attached to most psychiatric services and who, in general, will require long-term support. Both participants showed a significant intellectual decline from premorbid to current levels of IQ, which has been found in many other studies (e.g., Heaton et al., 1994; Goldberg et al., 1993). They were also disabled on the majority of specific executive-functioning tests.

The majority of other studies have shown no changes in neuropsychological performance without some intervention, i.e., there are few practice effects and little generalization to tasks not in the remediation battery. Shallice et al. (1991) indicated that patients with chronic schizophrenia had stable scores on Digit Span and Verbal Fluency when they were repeated six times at 2-month intervals. Similarly Delahunty et al. (1993) showed no improvement when they repeated the Wisconsin Card Sort Test on two separate occasions with a 3-month interval. Participation in this rehabilitation program seems to have provided some improvements for patients even when stringent criteria for improvements were adopted.

The repeat SPECT scans showed differences in activation between the two time periods. The significant changes in isotope uptake, however, were different in the two cases. For AB there was an increase in the isotope uptake in the left superior temporal regions (M3)—the opposite of what would be expected by practice on this task (Raichle et al., 1994). For CD the significant changes were bilateral decreases in uptake in the anterior cingulate (M0) and a decrease in right Rolandic (M2) regions. The scan changes need to be interpreted together with the individual task performance. AB seems to be generating more words but not adequately monitoring them. His significant scan change was in the left temporal area. This is probably associated with increases in word production from semantic memory. Previous studies have suggested that patients with schizophrenia have more widely activated semantic networks, which might account for this change and for the availability of incorrect responses (Andrews et al., 1993).

CD seems to be using some memory capacity to monitor his output. The bilateral decrease in the anterior cingulate might relate to the decreased motor output (i.e., a reduction in the initiation of verbal behavior). The decrease in the mid-frontal region is also likely to reflect this decreased output. The reduction in non-words or repetitions may be because of increased monitoring in a short-term store. These results suggest a new interpretation of the results of Allen et al. (1993); perhaps the decreased output does not reflect an early search termination but a termination at the output phase which prevents too many non-words and repetitions from intruding.

These alternative routes to task completion are included in the categorization suggested by both Hemsley (1977) and Allen and Frith (1983). These include: (a) reducing their responsiveness, producing poverty of speech and other negative features or (b) allowing the intrusion of errors into performance which produces incoherence. More recently Allen et al. (1993) have suggested that people with chronic schizophrenia who show negative features terminate the selection procedure for words which protects them from selecting inappropriate items. But those patients with more positive symptoms show increased category-inappropriate words and more variable words from a larger word pool.

CD's main difficulties were negative symptoms and after rehabilitation he seemed to reduce his behavioral output further in the Verbal Fluency task, which allows him to monitor more closely to prevent the choice of category-inappropriate words. In the Tower of London test this resulted in further monitoring of the plans to carry out the task before he initiated his first response. On the other hand, AB, who had high positive symptoms at entry to the study, increased his output and did not monitor as closely and consequently produced more category-inappropriate words in the Verbal Fluency task. Likewise in the Tower of London test he initiated a response on each trial quickly, which in this test did not result in an improvement in task performance. There was also some anecdotal behavioral evidence that AB was using this as a general strategy. His father had reported that AB was doing more for himself at the end of the rehabilitation program, but that his disabilities were more obvious. This mirrors the change in AB's performance on the fluency task—he said more words but many of these were errors. This pattern may not be helpful in some tasks because the errors might have a detrimental effect on performance.

Although there were only two patients, the results of the scan changes do make sense in terms of the aims of the neurocognitive rehabilitation. But clearly a more rigorous test is required and the interpretation of such data can only be speculative. However, the changes in brain scans were seen as consequences of changes in the adoption of certain information-processing strategies. This suggests some plasticity of the neural network as a result of specific behavioral training.

Neurocognitive rehabilitation does seem to improve patients' performance on neuropsychological tasks. The improvements in test performance may be due to non-specific effects of therapist contact and this clearly needs to be further investigated. But, in addition, the limitations of such remediation packages must also be acknowledged. Neither participant seemed to be developing new skills; rather both were extending their information-processing adaptations to new tasks. The individual responses to these remediation packages need to be analyzed further in order to refine and individualize their procedures if they are to make a significant contribution to improving cognition in this group.

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