

First-episode schizophrenia: review of cognitive deficits and cognitive remediation

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Abstract The presence of cognitive deficits in schizophrenic illness has been extensively documented, and deficits in memory and executive functioning may be related to poor prognosis. Targeting these deficits during the early phase has potential benefits. The neural basis for cognitive deficits in schizophrenia is not well understood, and hence pharmacological interventions alone are insufficient. Future strategies should focus on pharmacological interventions combined with psychological techniques such as cognitive remediation. This review summarises recent findings relating to first-episode schizophrenia.

This article is one of two in this issue of APT (see also Singh & Fisher, 2005) continuing a series introduced by Robin McCreadie's editorial 'Schizophrenia revisited' (McCreadie, 2004). Previous contributions have discussed environmental influences in schizophrenia (Leask, 2004) and implementation of the NICE schizophrenia guidelines (Rowlands, 2004). Future articles are planned on neuroimaging and lifestyle issues.

The occurrence of cognitive impairment in schizophrenia has been well documented since Kraepelin's description of the illness as dementia praecox. Research has shown that subtle but definite cognitive deficits are identified during the first episode that persist with the progress of the illness, even after the more dramatic symptoms have improved.

The exact timing of onset of cognitive impairment during the early phase of schizophrenic illness and its progress and course after the first episode are unclear. Furthermore, the clinical significance of cognitive impairment in first-episode psychosis is not well understood, and there is evidence to suggest that it pre-dates the onset of illness (O'Carroll, 2000). Numerous studies (e.g. Bilder *et al*, 1996; Heinrichs & Zakzanis, 1998) have reported deficits in attention, memory and executive functioning that are now thought to be strongly related to clinical outcome, perhaps more than are positive and negative symptoms (Hoff & Kremen, 2003). Cognitive deficits can manifest as an inability accurately to recognise social cues or to retrieve appropriate responses. Consequently, patients have difficulty acquiring social and interpersonal skills. It is understandable that,

during periods of increased arousal such as psychosocial crisis or relapse, this capacity becomes limited and cognitive functions can worsen.

Some studies suggest that the cognitive impairment in first-episode psychosis differs from that in chronic schizophrenia only in terms of degree of severity (Saykin *et al*, 1994). In the West London study, Joyce *et al* (2002) identified a profile of executive impairment in first-episode psychosis that they suggested differs from previous findings in chronic schizophrenia. They suggested that this difference might imply that rehabilitation strategies directed at deficits early in the illness are relevant.

Understanding the aetiology and interrelationship with other symptoms, and developing appropriate treatment models for this clinically significant but poorly understood symptom cluster, are hampered by the fact that schizophrenia is a heterogeneous syndrome.

Nature and type of cognitive deficits

Current understanding does not allow a simple listing of cognitive deficits in schizophrenia. A lack of clear understanding of neural and neuropsychological substrates makes it difficult to know whether the cognitive problems that occur are isolated deficits or whether they reflect a more global impairment (Bilder *et al*, 2000).

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Deficits in the following areas have been consistently highlighted against a background of diffuse impairment:

- memory: immediate and delayed recall, verbal and spatial memory
- attention processes: slowed cognitive speed
- executive functioning: sequencing, organisation and flexibility.

Language, motor and visuospatial functions are less consistently impaired.

It is clear that none of the above is a unitary construct. Attempts have been made to look for a particular dimension of these functions which is maximally impaired in first-episode psychosis.

Memory

In a group of 94 patients with first-episode schizophrenia, Mohamed *et al* (1999) found that patients were as impaired on immediate recall as on delayed recall. They suggested that, since their patients were tested during an acute, unmedicated phase of psychosis, their performance may have been worse than if they were assessed soon after stabilisation of their psychosis. However, Bilder *et al* (2000), in another group of 94 patients with first-episode psychosis that had just been stabilised, found that memory was more impaired than in 36 healthy controls. Finally, when Hoff *et al* (1992), to rule out the effects of acute psychosis, retested their sample of 32 first-episode patients during remission, they found no changes in the originally identified deficits in verbal and spatial memory. This suggests that memory deficits are present irrespective of the illness status.

Deficits in verbal memory appear to be an essential component of schizophrenic pathology. Saykin *et al* (1994) identified 37 neuroleptic-naïve patients with first-episode schizophrenia and compared them with 65 previously treated patients and 131 healthy controls. They concluded that verbal memory and learning is selectively compromised relative to other functions and that memory impairment is not secondary to anticholinergic medication. When attention and executive functioning were controlled for, deficits in verbal memory were still present. This finding suggests that deficits in verbal memory are not secondary to lack of attention or deficits in sequential executive functioning.

It could be argued that memory deficits reflect underlying intellectual impairment. Joyce *et al* (2002) found significant deficits in spatial working memory, short-term spatial memory and long-term episodic memory in 136 patients with schizophreniform disorder (with less than 12 weeks' medication)

compared with 81 healthy controls. Although IQ correlated with memory deficits, the difference between patients and controls remained highly significant.

Attention processes

In a study of 37 patients with first-episode psychosis, Saykin *et al* (1994) found that attention/vigilance and speeded visuomotor processing were selectively impaired, but to a lesser extent than memory.

Mohamed *et al* (1999) demonstrated that there was impairment in certain cognitive tasks with and without a motor component. When they compared timed motor tasks and timed cognitive tasks, patients were found to be better at the motor tasks, suggesting bradyphrenia rather than bradykinesia. Patients' better performance on tasks with a motor component than without suggested a decrease in information-processing speed.

Executive functioning

It is common knowledge that people with schizophrenia have difficulties with problem-solving and planning. Patients in their first episode also appear to have severe impairments in sequencing, organisational flexibility (Mohamed *et al*, 1999), planning ability and strategy use (Hutton *et al*, 1998). Findings indicating that first-episode patients perform less well on free recall than on verbal memory tests have led to the suggestion that difficulty with free recall is possibly secondary to impaired executive functioning (Hutton *et al*, 1998).

Mohamed *et al* (1999) found that aspects of executive functioning such as sequencing, organisation and flexibility were highly impaired in first-episode psychosis compared with controls. A slightly later study (Bilder *et al*, 2000) reports that executive and motor dysfunctions were relatively less impaired than memory and attention in first-episode patients.

The possibility that first-episode schizophrenia has a different profile of executive functioning compared with the chronic state has been raised by Joyce *et al* (2002). They found that patients with first-episode psychosis were quicker to initiate responses than were controls, but took the same time to complete each task. In contrast, people with chronic schizophrenia have normal initial thinking times but are slower in thinking about subsequent moves than are controls (Pantelis *et al*, 1999). Joyce *et al* suggest that pre-existing pathophysiological processes in the prefrontal cortex that underlie executive impairment further deteriorate at the onset of psychosis and continue to worsen with time.

Aetiology

Are cognitive deficits a trait or a state marker? If they are a trait marker one would expect that they remain stable in spite of treatment. Various studies have shown that cognitive dysfunction does remain stable from the acute phase to follow-up after clinical stabilisation, suggesting that these deficits are indeed trait markers. This trait deficiency may exist in addition to state-related cognitive impairments (Saykin *et al*, 1994).

Association with other symptoms

The interrelationship between cognitive deficits and other symptoms of schizophrenia is not well understood. Mohamed *et al* (1999) investigated the effects of positive, negative and disorganised symptoms on specific cognitive deficits and found that only negative symptoms were correlated with impaired performance and that the correlation was weak.

Hoff *et al* (1999), in a longitudinal follow-up study of 42 patients with first-episode schizophrenia, found that improvement in cognitive performance was associated with improvement in positive symptoms, but was not associated with improvement in negative symptoms or commencement of medication. Changes in cognitive functioning were not correlated with changes in brain morphology revealed by magnetic resonance imaging (MRI).

Small correlations between neuropsychological profile and symptoms of first-episode schizophrenia at the time of study entry, and stronger correlations after clinical stabilisation, were found in a study by Bilder *et al* (2000). They generally found stronger correlations in the neuropsychological scales with negative than with positive symptoms.

The current evidence suggests that the specific memory deficits that occur are not related to generalised intellectual impairment. In a meta-analysis, Aleman *et al* (1999) concluded that schizophrenia and memory deficits are significantly associated, and that the memory deficits are not secondary to attentional deficits. Researchers have suggested that memory difficulties are primarily caused by deficits in encoding and retrieval rather than in storage (Paulsen *et al*, 1995).

Organic correlates

Initial computer tomography findings showing an association between cortical atrophy, increased ventricular volumes and poor cognitive function led to the postulation that cognitive impairment is directly related to cerebral damage. Structural brain

abnormalities are now known to be present during the first episode of schizophrenia, and some believe them to pre-date its onset (Lim *et al*, 1996; Zipursky *et al*, 1998). Zipursky *et al* demonstrated significant deficits in grey matter volume in patients experiencing first-episode non-affective psychosis compared with normal controls. Their sample, however, included patients with schizoaffective disorder, delusional disorder or psychotic disorder not otherwise specified. A few studies have shown that schizophrenia patients with poor outcome exhibit an increase in ventricular volumes over time. The observed worsening of structural defects in the brain of patients with chronic schizophrenia might be caused by an unidentified pathological process that affects brain structure over time. It could also be argued that these differences are a methodological artefact arising because different studies used different assessment tools on different patient groups.

In a comparison of 25 healthy controls and 37 patients with first-episode psychosis, Fannon *et al* (2000) found in the latter significant deficits of cortical and temporal lobe grey matter and abnormalities in cerebrospinal fluid. These deficits were not attributable to the effects of chronicity of illness or medication. No relationships were found between any brain matter volumes and positive and negative symptoms.

Selective dysfunction in the dorsolateral prefrontal cortex on functional MRI has been shown to be associated with deficits in working memory in 14 neuroleptic-naïve first-episode schizophrenia patients compared with 12 healthy controls (Barch *et al*, 2001). Such findings add further evidence to the hypothesis that cognitive deficits are present before illness onset.

Szesko *et al* (2002) studied 43 males and 32 females experiencing first-episode schizophrenia and found significant correlation between hippocampal volume and executive and motor functioning in the male patients. They did not, however, find significant correlation between hippocampal volume and memory functioning. There were severe limitations in the techniques they used to measure anterior hippocampal volumes and the fact that the correlations were significant only for the male patients indicates possible selection bias.

In a sample of 156 patients with first-episode schizophrenia, Ho *et al* (2003) found no correlation between neurocognitive functioning, MRI brain volumes, brain surface anatomy and duration of untreated illness. However, patients with longer than median duration of untreated illness showed significantly greater verbal memory impairment and thinner cortical sulcal depth than the patients in the shorter-duration group.

Difficulties arise when attempting to understand the relationship between clinical symptoms that are highly variable over short periods of time and brain-matter changes that are relatively fixed over the same time span. We were unable to find a prospective cohort study that looked directly at the relationship between cognition and progression in brain morphology from the first episode of illness through to the chronic-deficit state.

Course

In 1992 Bilder *et al* published the results of their prospective longitudinal study on the course of deterioration in cognition in patients with first-episode schizophrenia. They suggest that patients' intellectual functioning suffers both developmental and deteriorative effects due to schizophrenia. They also reported that men showed more evidence of deterioration than women, which supports the hypothesis that men are more vulnerable to a more severe form of the illness and that they have more focal/lateralised abnormalities (revealed in neuropsychological and neurological examinations, cerebral blood-flow studies and MRI scans).

Hoff *et al* (1999), in their longitudinal follow-up study conducted over 2 to 5 years (mean time to follow-up 3.6 years for the 42 patients, 3.8 years for the 16 healthy controls), found that verbal memory showed less improvement in people with schizophrenia than in healthy controls. However, a major limitation of this study was the size of the control group, which may have led to a finding of greater improvements in executive and spatial memory in patients than in controls.

Several researchers assert that early treatment of first-episode psychosis leads to better outcome. But Norman *et al* (2001) and Hoff *et al* (2000) found no relationship between duration of untreated psychosis and performance on any component of neuropsychological functioning, suggesting that there is no support for the toxic effect of duration of psychosis on cognitive functioning. However, these findings cannot be generalised because they have not included results from long-term follow-up.

Assessment

We were unable to find in the literature a clinical assessment tool that could be used in day-to-day practice. Simple bedside assessments for attention, recent and remote memory, and praxis can be used, although it must be borne in mind that underlying psychosis might affect performance. A review by Heinrichs & Zakzanis (1998) lists the neurocognitive categories and tests that have been used.

Box 1 Effects of clozapine on cognitive function (McGurk, 1999)

- Significant improvement in attention and verbal fluency
- Limited improvement in verbal learning, memory and some measures of executive function
- Minimal or no effect on visual learning and memory and verbal working memory

Treatment options

Medication

Research findings suggest that typical antipsychotics such as haloperidol have minimal influence on cognitive functioning compared with atypical antipsychotics. A review of 12 published studies of the effects of clozapine on cognitive function (McGurk, 1999) revealed the range of its influence (Box 1). Other atypicals, such as olanzapine (Purdon *et al*, 2000), quetiapine (Good *et al*, 2002) and risperidone (Green *et al*, 1997), are also reported to have positive effects on cognitive function. It remains unclear whether these benefits are due to the drugs' effects on neurotransmitters and subsequent symptom improvement or to the absence of the bradykinetic side-effects common with conventional antipsychotics.

Psychological interventions

Cognitive remediation therapy

Cognitive remediation therapy in schizophrenia is an interventional programme for improving cognitive function by focusing on the specific cognitive deficits of the illness such as poor memory and difficulties in planning and decision-making. Some authors prefer to call it 'cognitive habilitation' or 'cognitive rehabilitation', to imply that remediation is not just about improvements on tests found in some studies using the Wisconsin Card Sorting Test.

In 1990, Flescher conceptualised cognitive habilitation as consisting of three main treatment components:

- assessing the cognitive impairment and the functionally related disabilities
- engineering treatment experiences designed to remediate impairments
- cognitive mediation – helping the patients to integrate the treatment experience.

Improvements in attention and concentration are the first step in remediation of other cognitive deficits. Verbal learning and memory are critical components for the acquisition of new skills.

Box 2 Errorless learning

The approach aims to eliminate error during learning by:

- providing easy discrimination of the different parts of the information being learned
- ensuring that the individual does not experience failure during learning
- extremely gradual increase of the difficulty of the task to be learned

The mechanism of cognitive improvement resulting from cognitive remediation therapy is not well understood. However, one randomised controlled study has shown dorsolateral prefrontal cortical activity changes following cognitive remediation therapy in patients with schizophrenic illness of at least 2 years duration (Wykes *et al*, 2002a).

A computer-assisted cognitive remediation package is available (Sandford & Browne, 1998) that involves four modules: attention skills; visuomotor skills; conceptual skills; and numeric concepts/memory skills.

Bellucci *et al* (2003) used computer-assisted cognitive rehabilitation to treat 16 patients with schizophrenia and 18 patients with schizoaffective disorder (for each disorder, the mean duration since first hospitalisation was 16 years). They recorded significant improvement on several measures of cognitive functioning, most noticeable being in verbal/conceptual learning and memory, and concentration.

Errorless learning

Errorless learning (Box 2) is another approach that has been used in cognitive remediation of memory deficits in schizophrenia. It is based on the simple concept that memory-impaired people implicitly remember the errors they make during learning, and these errors interfere with retrieval of target items. O'Carroll (2000) has warned that further study is needed before the benefits reported from a trial of the errorless learning approach in a group of patients with schizophrenia (O'Carroll *et al*, 1999) can be generalised beyond the research environment.

Integrated psychological therapy

This is a group-based cognitive remediation technique developed by Brenner *et al* (1994). This therapy focuses on a hierarchy of different skills, beginning with executive functioning through conceptual differentiation then social perception, verbal communication, social skills and problem-solving.

Efficacy

In a meta-analysis of randomised controlled trials of psychological techniques used in schizophrenia, Pilling *et al* (2002) found that cognitive remediation had no benefits for attention, verbal memory, visual memory, planning, cognitive flexibility or mental state. All the trials reviewed in their analysis had used patients with chronic schizophrenia.

Failure to generalise results has been the major criticism of trials of cognitive remediation in schizophrenic illness. Most of the studies involved patients with severe, chronic schizophrenia, neglecting those with less-severe or first-episode illness; and none considered the use of remediation techniques in clinical practice, where patients might not receive the intensive guidance and encouragement likely to have been given in research trials.

We found no studies on cognitive remediation techniques in first-episode schizophrenia. However, in theory, cognitive remediation should have a particular role in first-episode presentations, by improving premorbid cognitive deficits and preventing the development of further enduring deficits. Evidence that the effects of cognitive remediation therapy are durable is encouraging and merits further investigation (Wykes *et al*, 2002b).

Conclusions

The significance of cognitive deficits and the importance of remedial interventions for them in schizophrenia, particularly in first-episode presentations, might be neglected primarily because of the belief that antipsychotic medication offers an adequate treatment. It might also be assumed that lingering cognitive deficits are epiphenomenal, lacking functional clinical significance. However, the belief that cognitive deficits are nuclear and irremediable is being shaken by the evidence provided by functional MRI of changes following medication and cognitive remediation therapy.

The process by which cognitive function deteriorates remains unclear. If we were able accurately to predict the course of illness, cognitive remediation techniques could be used to avoid deterioration. We also do not know whether certain cognitive functions are more amenable than others to remediation. In the current state of knowledge, treatment efforts might be wasted on patients who would remain cognitively stable without remediation therapy.

Residual cognitive impairments remain a barrier to complete recovery from schizophrenic illness. Interest in cognitive remediation therapy in schizophrenia declined during the 1980s, as it became widely believed that antipsychotic medications offered adequate treatment. But the persistence of

negative symptoms and cognitive deficits in spite of medication led to renewed research interest in the 1990s. More recently, it appears that there is again a trend towards projecting drugs, in this case the newer atypical antipsychotics, as being complete in their ability to reduce even the cognitive deficits associated with schizophrenia. None the less, evidence remains indicating the limited effect of medication and the clear benefits of cognitive remediation therapy in treating the cognitive impairment of the disorder. This should encourage psychiatrists and service commissioners to consider the potential of cognitive remediation techniques in routine community care of patients with first-episode psychosis. The most effective strategy would be to use a combination of psychopharmacological and cognitive remediation approaches.

Cognitive remediation in schizophrenia should be aimed at improving not just specific cognitive deficits, but the functional deficits that arise from them. Focus on functional deficits is a much neglected area in which further research is urgently needed.

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MCQs

1 Cognitive dysfunction in schizophrenia:

- a has no relationship to psychological stress
- b is exactly the same during the first episode and in chronic illness
- c spares immediate memory
- d disappears after stabilisation of psychotic symptoms
- e significantly impairs executive functioning.

2 Current evidence suggests that:

- a memory deficits are a direct result of intellectual impairment after the first episode of schizophrenia
- b memory deficits are not secondary to deficits in attention
- c neuropsychological deficits are related to negative symptoms but not positive symptoms

- d structural brain abnormalities are clearly evident at the onset of the first episode of schizophrenia
- e structural brain defects are worse in patients with chronic illness than in the first episode.

3 The following are associated with cognitive dysfunction:

- a dysfunction in the dorsolateral prefrontal cortex
- b anterior hippocampal volume
- c lateral ventricular volume
- d temporal sulcal depth
- e CSF abnormalities.

4 Cognitive remediation in schizophrenia:

- a offers benefits that extend to meaningful daily activities
- b begins with improvements in attention and concentration
- c involves verbal learning and memory as critical components
- d produces no improvements in the domain of memory
- e can produce changes in activity in the dorsolateral prefrontal cortex.

5 As regards cognitive deficits during first-episode schizophrenia:

- a memory function is not related to illness status
- b verbal memory dysfunction is secondary to attentional deficits
- c spatial working memory and episodic long-term memory are impaired
- d verbal memory has been shown to be more impaired than other cognitive functions
- e pathophysiology in the prefrontal cortex underlies executive dysfunction.

MCQ answers

1	2	3	4	5
a F	a F	a T	a T	a T
b F	b T	b T	b T	b F
c F	c F	c T	c T	c T
d F	d T	d T	d F	d T
e T	e T	e T	e T	e T