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INVITED REVIEW

# Defining the cognitive impairment in schizophrenia

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## INTRODUCTION

Cognitive psychology became an important discipline in schizophrenia research when information processing deficits were implicated as the basis from which psychotic symptoms emerged (Broen & Storms, 1967; Hemsley, 1977; Frith, 1979). The study of cognition as an independent construct began in earnest when the detection of brain morphological abnormalities on computed tomography (CT) in patients with schizophrenia (Johnstone *et al*. 1976; Weinberger *et al*. 1979) prompted the search for behavioural correlates. It became apparent that impairments typical of damage to frontal or medial temporal lobes could be seen in patients with schizophrenia, irrespective of symptom type or severity (Goldberg *et al*. 1988; McKenna *et al*. 1990). Since then a number of findings have been replicated sufficiently to make certain conclusions about the nature and extent of cognitive dysfunction in this disorder.

## EVIDENCE FROM NEUROPSYCHOLOGY

Deficits are widely present at the onset of psychosis (Bilder *et al*. 1992; Hoff *et al*. 1992) and have been found in large-scale studies irrespective of whether patients are medication naive, recently medicated or well stabilized on medication (Mohamed *et al*. 1999; Bilder *et al*. 2000; Joyce *et al*. 2002). Individuals destined to develop schizophrenia as an adult are more likely than their peers to under-perform scholastically as an adolescent or even as an infant (Jones *et al*. 1994; Kremen *et al*. 1998; Erlenmeyer-Kimling *et al*. 2000; Fuller *et al*. 2002). A proportion of patients appear to undergo a decline in general intellectual function at some point either prior to, or around the time of onset of psychosis (Kremen *et al*. 1998; Wieckert *et al*. 2000; Fuller *et al*. 2002; Joyce *et al*. unpublished observations). During the years immediately following onset these impairments do not generally deteriorate further (e.g. Sweeney *et al*. 1991; Censits *et al*. 1997; Gold *et al*. 1999; Hoff *et al*. 1999). These findings are evidence that cognitive impairment is present at an early stage of the illness, is independent of symptom and drug effects and, therefore, is an outward manifestation of the neural abnormality subserving schizophrenia which should be thought of as central to the concept of the disorder.

What is less clear is whether specific cognitive impairments, like symptoms, can be regarded as a *defining* feature of schizophrenia. For example, several studies have found that patients can be characterized as 'neuropsychologically normal' (Goldstein, 1990; Heinrichs & Awad, 1993; Palmer *et al*. 1997). In other words, when clinical neuropsychology criteria are applied, approximately 25% of patients perform in the normal range across many tasks. Two studies have looked at this phenomenon more closely and have concluded that when such patients are directly compared to healthy controls, impairments can be discerned. These indicate that either they have previously performed at a higher level and have thus deteriorated to a normal level (Kremen *et al*. 2000) or they have isolated subtle impairments in executive and 'sensorimotor' function against a background of normal performance on a wide range of other tasks (Allen *et al*. 2003). Our own studies show that

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patients with first-episode schizophrenia and relatively high pre-morbid and current IQ (>100) performed similarly to a tightly matched normal control group on a range of tests but were specifically impaired on a test of spatial working memory (Joyce *et al.* unpublished observations).

On balance, it appears that cognitive impairment is a ubiquitous feature of schizophrenia but that this can vary from patient to patient. What is this variability? Is it characterized by impairments across many cognitive domains that vary between patients only in severity, or do patients differ in their profile of impairments, with some being general and others being specific? Large-scale studies which have employed major batteries of neuropsychological tests assessing general intelligence (Wechsler Adult Intelligence Scale; WAIS), executive function, perception and motor skill (Halstead–Reitan Battery; HRB) or memory (Wechsler Memory Scale; WMS) all find that their patient group is significantly worse than their healthy control group on most subtests (Mohamed *et al.* 1999; Bilder *et al.* 2000; Townsend *et al.* 2001; Addington *et al.* 2003). Dickinson and colleagues (2004) explored the putative distinction between generalized and specific impairments in a large dataset of subtest variables from the WAIS-III and WMS-III. They applied common factor analysis, a form of structural equation modelling, which identifies those aspects of performance which differentiate two groups. They found that two-thirds of the difference in cognitive performance between schizophrenia and healthy control groups was mediated by a common cognitive factor. In other words, performance on subtests tended to co-vary, with performance on one subtest predicting performance on the remainder. Only performance on a subset of visual memory tests and a measure of psychomotor speed contributed to the difference independently, and even then to a minor degree. Thus, in this study, cognitive impairment was global and indicated that any variation from patient to patient was a matter of degree.

Although the subtests employed in this study measured a broad range of cognitive functions, they fell short on the assessment of executive function. Other studies, including some with large numbers of patients, have looked for variations in performance profile and have included measures of executive function. These have found evidence for a subgroup with executive dysfunction only and a subgroup with impairments on all measures (Heinrichs & Awad, 1993; Goldstein & Shemansky, 1995; Weickert *et al.* 2000; Joyce *et al.* unpublished observations). One conclusion is that there are two cognitive subtypes of schizophrenia, one with a generalized impairment and another with specific executive deficits and preserved general intellectual function.

## FINDING SPECIFIC COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

Many of the studies described above have examined cognitive function in schizophrenia with tasks commonly used in clinical practice such as the HRB, WAIS and WMS. Together these assess general domains of function often described as memory, perception, intelligence, cognitive flexibility and abstraction. Such studies have practical significance because they describe performance problems relevant to real life. However these types of task are blunt instruments when it comes to the detection of more fundamental cognitive impairments. For example, in the logical memory subtest of the WMS, subjects are required to recount a short story. Although the story consists of only a few sentences, these are long and contain several information-dense clauses. To perform well, subjects need to attend and process the sentences strategically, as well as hold the information in mind over the time-course of the task. Thus this 'memory' task requires the operation of a number of different cognitive processes, any of which might cause performance decrements if impaired. Furthermore, the propensity to be overwhelmed and 'give up' on this task is greater for individuals who are generally unwell, sedated or have poor motivation. This implies that a finding of a generalized decrement on neuropsychological batteries may reflect, at least in part, factors other than cognitive impairment (see also MacDonald & Carter, 2002 for a full discussion of this point).

To be able to fully appreciate the neural abnormalities underlying schizophrenia it is necessary to use experimental approaches which allow task performance to be decomposed into more basic psychological processes or which

have within-task control procedures that allow measures other than global accuracy or reaction time to be taken. As suggested by Knight & Silverstein (2001), this approach switches the emphasis from between-group differences to the pattern of within-group differences, and they term this the *disconfirmation strategy*. The pattern of performance across the conditions of a given experimental task reflects processing biases indicative of fundamental cognitive functions. Through the pattern of effects in controls and patients it is possible to determine if a certain process is impaired. However, if the pattern of effects is the same between groups but overall patients are slower or less accurate then the specific cognitive process may be intact but a global deficit, secondary to illness factors, may be present.

An example of this approach is provided by study of spatial working memory (SWM) by Gold and colleagues (2003). Spatial working memory impairment is a core feature of schizophrenia in that similar abnormalities are found in patients across all phases of the illness – chronic, first episode and prodromal, and in patients who are high functioning in other cognitive domains (Pantelis *et al*. 1997, 2004; Hutton *et al*. 1998; Wood *et al*. 2003; Joyce *et al*. unpublished observations). Models of working memory normally implicate several cognitive subprocesses (Baddeley, 1986) and, depending on the nature of the paradigm, a range of different processing deficits could give rise to impairments on SWM tasks. The study by Gold and colleagues (2003), distinguishes between storage capacity, i.e. the amount of information that can be held in mind at any one time, and processing capacity, which refers to the ability to manipulate this information. In a visual change detection paradigm designed to investigate storage capacity, arrays of bars were presented so that bars could vary on colour and orientation, while set size varied from two bars to six. A single item would change and the subject's task was simply to indicate whether a change had occurred. Although the patients were inferior to controls overall, the authors were able to detect specific areas of preserved and impaired performance. Thus poor performance could not be explained by a generalized non-specific factor or the inability to encode and maintain both colour and orientation features of the stimuli simultaneously. Rather the pattern of performance of the patients compared to controls indicated problems with sustained and selective attention in working memory. Patients seemed unable to maintain task-set from trial to trial across all set sizes, a concept defined as 'context maintenance' elsewhere (Cohen & Servan-Schreiber, 1992). A second deficit became evident when the number of items to be encoded exceeded storage capacity. Patients seemed less able to select and focus on a subset of stimuli for encoding and this gave rise to a collapse in performance not witnessed in controls.

## THE IMPORTANCE OF SPECIFICITY

There are a number of reasons why it is important to define impairments as precisely as this. First, working memory is a fundamental cognitive operation essential for the successful conduct of a wide range of behaviours (Gold *et al*. 2003). Thus, impairment in a single facet of working memory might be responsible for many of the cognitive failures seen when batteries of neuropsychological tests are administered, as well as explaining some of the problems of everyday life encountered by patients with schizophrenia. If this proves to be the case, it will help focus strategies for remediation both in the clinic and laboratory. Second, it will benefit scientific strategies for a better understanding of the neural abnormalities underlying schizophrenia. Neuroimaging techniques are more powerful when activation paradigms are derived from cognitive psychology. The growing trend for using endophenotypes, i.e. behavioural or biological markers, rather than clinical features to identify the genetic basis of schizophrenia will also be more successful if these can be precisely defined. For example, in a series of twin studies, the same group have shown that the degree of impairment in SWM is proportional to the degree of genetic loading for the disorder, and that allelic variation of a region on chromosome 1 is associated uniquely with variations in SWM performance (Cannon *et al*. 2000; Gasperoni *et al*. 2003; Glahn *et al*. 2003). The working memory impairment in these studies was measured using a spatial span task and it is conceivable that more precise measures may yield stronger genetic associations. Precision in this type of research is

already beginning to yield results. A measure of context maintenance, mentioned above, has been identified as a possibly specific endophenotype and has also been used to identify a specific abnormal neural system in the dorsolateral prefrontal cortex in patients with schizophrenia (Barch *et al*. 2001; MacDonald & Carter, 2003). Furthermore, a genetic mechanism possibly linking the two observations has been proposed which implicates allelic variation in the gene coding for the enzyme catechol-*O*-methyl transferase (COMT) which regulates the amount of dopamine available in the synapse for cell signalling (Egan *et al*. 2001; Goldberg *et al*. 2003).

## CONCLUSION

Developing methodology that enables areas of intact and abnormal function to be established in patients with schizophrenia will allow several related questions to be addressed with greater conviction. It is suggested that poor motivation, engagement with testing procedures and related factors might be responsible, in part, for findings of generalized impairment across a range of cognitive domains. This may be remedied by the use of tests derived from experimental psychology that contain sufficient internal control conditions. Targeting cognitive functions in this way allows the question of within-group heterogeneity of cognitive abnormalities in schizophrenia to be better addressed. This improved isolation of cognitive abnormalities should enable stronger links between specific cognitive dysfunctions and biological correlates of schizophrenia such as neuroimaging or genetic abnormalities.

## DECLARATION OF INTEREST

None.

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