Cognition as an outcome measure in schizophrenia

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Background Cognitive deficits are a core feature of schizophrenia. These deficits are not caused by medication or symptoms, and have a dramatic negative effect on real-world functioning.

Aims To critically examine a selection of the most common batteries used to assess cognition in schizophrenia.

Method Literature review of cognitive assessment batteries for use in schizophrenia.

Results A wide variety of neurocognitive test batteries have been developed or adapted to assess cognition in schizophrenia. These differ in time requirements, repeatability, ease of administration, degree of face validity, availability of co-normative data and degree to which results can be parsed into separate domains of cognitive functioning. The most appropriate depends on the setting and the question being addressed.

Conclusions Cognitive outcome measures have reshaped our understanding of schizophrenia and will be essential tools for unravelling the aetiology of the disease and designing more effective interventions.

Declaration of interest R.S.E.K. receives royalties from sales of the Brief Assessment of Cognition in Schizophrenia (BACS) battery and the MATRICS Consensus Battery (MCCB). He is a member of the MATRICS Neurocognition Committee and Director of the TURNS Chief Neuropsychologists Group. He receives consultancy fees from several pharmaceutical companies.

In an attempt to classify the multitude of mental disorders he encountered in his work, Emil Kraepelin adopted the term 'dementia praecox' to label a condition characterised by early psychosis and cognitive deterioration (Hoenig, 1983). Although Bleuler renamed the disease schizophrenia in 1911, emphasising his view of the disease as a lack of connection between a person's affect, thought and perception, he still viewed cognitive deficits as integral to the disorder (Gabriele, 2000). The perceived importance of cognition in schizophrenia has since waxed and waned. Cognitive and negative symptoms, which were regarded as integral by both Kraepelin and Bleuler, were later overshadowed by the more easily observable and identifiable positive symptoms. The Research Diagnostic Criteria (RDC), which were designed to formalise the diagnosis of mental disorders, emphasised the Schneiderian symptoms, and this tradition has continued into DSM–III and IV (Andreasen, 1997). Although negative symptoms were added as criteria in DSM–IV, cognition is still not included in the formal criteria.

Although the move away from cognitive impairment as a focus in schizophrenia was initially motivated by enhancement of diagnostic reliability, it came to shape how the disease was viewed and investigated. However, a renewed interest in cognition has been evident recently, spurred in part by the strong empirical relationship between cognition and real-world functioning (Green, 1996). Several studies have failed to demonstrate a significant correlation between positive symptoms and functional outcome (Green, 1996), suggesting that a diagnostic and treatment focus on Schneiderian first-rank symptoms has sidelined key aspects of the disease.

IMPAIRED COGNITION AS A CORE FEATURE

A mounting body of evidence indicates that diminished cognitive ability is a core feature of schizophrenia. Severely impaired performance on cognitive tests (two standard deviations below the mean of healthy controls) in several cognitive domains is strong evidence for the importance of cognitive impairment in the disease (Saykin *et al*, 1991; Harvey & Keefe, 1997) Broad cognitive deficits, of moderate to severe magnitude, have been found in meta-analysis (Heinrichs & Zakzanis, 1998), large clinical trials (Harvey *et al*, 2003, 2004; Keefe *et al*, 2006*a*) and research studies (Bilder *et al*, 2000; Heaton *et al*, 2001; Keefe *et al*, 2004). Cognitive deficits have been shown to lack correlation with severity of positive symptoms and to be only mildly correlated with severity of negative symptoms (Addington *et al*, 1991; Gold *et al*, 1999; Keefe *et al*, 2006*a*), indicating that impaired cognition is not an epiphenomenon of clinical symptoms.

Although some studies have indicated that a significant portion of people with schizophrenia test in the normal cognitive range (Palmer *et al*, 1997), strong evidence suggests that even these exhibit cognitive abilities below those expected if they did not have the disease. A study of monozygotic twins found that 80–95% of twins with schizophrenia scored below their unaffected twin (Goldberg *et al*, 1993). Another study found that 98% of people with schizophrenia performed below the level predicted by estimates of their premorbid functioning based on level of parental education, compared with 42% of controls (Keefe *et al*, 2005).

Many early studies of the cognitive deficit in schizophrenia were of people who were either taking antipsychotics at the time of the study or had taken them in the past. However, several studies have since demonstrated cognitive deficits in people with first-episode schizophrenia who have never taken antipsychotics (Saykin *et al*, 1994; Mohamed *et al*, 1999; Bilder *et al*, 2000; Torrey, 2002).

Unlike Schneiderian first-rank symptoms, cognitive deficits correlate highly with measures of functional outcome (Velligan *et al*, 1997; Addington & Addington, 1999; Green *et al*, 2000). In addition, the literature overwhelmingly supports a longitudinal correlation between cognitive ability at baseline and later assessments of functional outcome (Green *et al*, 2004; Carlsson *et al*, 2006), suggesting that cognitive deficits are a key and perhaps limiting factor in rehabilitation of people with schizophrenia. The overwhelming evidence

supporting neurocognitive deficits as a core feature of schizophrenia and predictive of functional outcome has spurred the United States National Institute of Mental Health (NIMH) to target such deficits for pharmacological intervention (Marder & Fenton, 2004).

SEPARATE DOMAINS OF DEFICIT *V.* GENERAL DEFICIT

A crucial consideration for practical assessment of cognition in schizophrenia centres around whether the cognitive deficit is best described as broad or is more pronounced in specific domains. A large factor-analytical study involving the Wechsler Adult Intelligence Scale (WAIS–III) and Wechsler Memory Scale (WMS–III) batteries found that the performance of 1250 healthy controls was best described by a model composed of six separable domains of cognition: verbal comprehension, perceptual organisation, auditory memory, visual memory, working memory and processing speed (Tulsky & Price, 2003). Although a meta-analysis of 22 studies of cognitive performance in populations with schizophrenia reported a strikingly broad deficit spanning all domains (Heinrichs & Zakzanis, 1998), some theories have focused on specific domains of impairment, such as working memory (Goldman-Rakic, 1994), verbal memory (Saykin *et al*, 1994), and executive functions (Goldberg *et al*, 1987). However, these results may reflect differences in test sensitivity as opposed to true differential ability across domains.

Although some studies have emphasised differential impairment across domains, others indicate that cognitive performance (Keefe *et al*, 2006*a*) and cognitive deficits (Dickinson *et al*, 2004) exhibited by people with schizophrenia are largely mediated through a single common factor, suggesting a generalised cognitive impairment. This ongoing debate has implications for the aetiology of the disease (whether underlying brain abnormalities are local or global) as well as intervention strategies.

TOOLS FOR MEASURING COGNITION

A great many tasks have been developed to assess cognition and various batteries comprised of these tasks have been employed in research with populations with schizophrenia (Table 1). The most appropriate battery for a given study will depend upon the questions being addressed, study settings and available resources. A long battery comprised of many different tests has the disadvantage that missing data will be increased (Keefe *et al*, 2004). In addition, attrition rates and missing data may be higher in those with the most impairment, thus skewing results. Also, in many settings extensive batteries are impractical because of the time requirements placed on staff members administering the tests. However, a longer test battery usually will increase the ability of the data to measure multiple domains of cognition. Thus if the research question involves the efficacy of a treatment intervention for improving cognition, a composite score from a small battery might be sufficient and allow for a larger number of participants to complete the study while requiring fewer staff resources. If, however, the research question involves relative strengths and weaknesses of various cognitive domains, a thorough battery composed of multiple tasks in each domain may be required. If the research question is primarily focused on one cognitive domain, a brief general battery in combination with

Table 1 Advantages and disadvantages of selected cognitive batteries

Battery	Advantages	Disadvantages
WAIS–III and WMS–III	Long history of use allows comparison with previous studies, norms available	Lengthy, not designed specifically for research in schizophrenia
MCCB	Designed by panel of experts for research in schizophrenia, allows for domain scores with minimal testing, norms available	Many domain scores based on performance on one test
SCoRS	High face validity, easily administered by clinicians, minimal time requirements, demonstrated correlation with other measures of cognitive and functional outcomes	High subjectivity
UPSA	High face validity, proxy test of real-world functioning, minimal time requirements	Domain-level analysis not possible
RBANS	Minimal time requirements, small practice effects, performance correlated with that on WAIS–III and WMS–III.	Lacks measures of important cognitive domains in schizophrenia, significant ceiling effects
BACS	Minimal time requirements, designed for use in schizophrenia research, high correlation with composite scores from more extensive batteries, minimal practice effects, available in nine languages, norms available	Domain-level analysis is minimal
BCA	Extreme brevity of administration, high correlation with extensive cognitive battery and functional outcome measures	Domain-level analysis minimal
Computerised batteries	Automatic administration reduces rater error	Validity of many tests has not been examined
Psychophysiological tasks	Much of underlying neurobiological circuitry is known, afford quick assessment of schizophrenia-related endophenotypes	Relationship between improvement in these tasks and functional outcome unknown

WAIS–III, Wechsler Adult Intelligence Scale – III; WMS–III, Wechsler Memory Scale – III; MCCB, MATRICS Consensus Cognitive Battery; SCoRS, Schizophrenia Cognition Rating Scale; UPSA, UCSD Performance-Based Skills Assessment; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; BACS, Brief Assessment of Cognition in Schizophrenia; BCA, Brief Cognitive Assessment.

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multiple tests of the domain of primary interest might be most appropriate.

Wechsler Adult Intelligence and Memory Scales

The Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997*a*) and Wechsler Memory Scale (WMS; Wechsler, 1997*b*) have long been the most widely employed batteries of assessment for IQ and memory in healthy populations. However, the WAIS–III alone requires approximately 100 min for completion in a mixed clinical population (Ryan *et al*, 1998). For studies of populations with schizophrenia, researchers using these batteries have tended to reduce the number of sub-tests administered to reduce demands on the patients and staff. Blyler *et al* (2000) used regression analysis to determine the four tests covering all four domains of functioning assessed by the WAIS–III that would best account for the variance in full-scale IQ in a sample of 41 out-patients with schizophrenia. They found that a shortened version of the WAIS–III, consisting of the sub-tests information, block design, arithmetic and digit symbol took only 30 min to administer and accounted for 90% of the variance in the full-scale IQ of the schizophrenia patients. Because of its brevity, the shortened version of the WAIS may have utility as a routine measure of cognition in clinical practice.

MATRICS Consensus Cognitive Battery

As part of the NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), the MATRICS Consensus Cognitive Battery (MCCB) was constructed to provide a standard battery for the assessment of cognition-enhancing drugs (Nuechterlein & Green, 2006). From more than 90 tests nominated for inclusion, a final battery of ten tests covering seven domains of cognitive functioning was chosen with a view to practicality of administration, high test–retest reliability, small practice effects, small ceiling effects and demonstrated relationship to functional outcome. The domains and relevant tests which comprise the final battery are: speed of processing (Brief Assessment of Cognition in Schizophrenia – Symbol Coding; Category Fluency; Animal Naming; Trail Making Test Part A), attention/vigilance (Continuous Performance Test – Identical Pairs), working memory (WMS–III Spatial Span; University of Maryland Letter-Number Span), verbal learning (Hopkins Verbal Learning Test – Revised), visual learning (Brief Visuospatial Memory Test – Revised) reasoning and problem-solving (Neuropsychological Assessment Battery – Mazes) and social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test – Managing Emotions). The MCCB is a relatively concise battery (taking just 65 min to administer) that none the less allows for measurement of cognition at a domain-specific level. Because the final battery was co-normed with 300 community controls across five academic sites, an individual's results can be normalised against this same control group for all seven domain scores as well as a composite score. The MCCB has a computerised scoring system that produces *t*-scores and percentiles corrected for age and gender. Although the MCCB was designed to assess effects of pharmaceutical interventions on cognition in schizophrenia, the battery is suitable for use in cognitive remediation and non-intervention studies of people with schizophrenia. Although the MCCB requires more time to administer than the shortened WAIS–III, it has the potential to provide a more detailed assessment of a patient's cognitive performance.

Schizophrenia Cognition Rating Scale

The Schizophrenia Cognition Rating Scale (SCoRS; Keefe *et al*, 2006*b*) is an 18-item interview-based assessment which covers all the cognitive domains tested in the MCCB, except social cognition, and takes approximately 12 min to complete. It is administered separately to the patient and to an informant (family member, friend, social worker, etc.) The interviewee is asked to rate the patient's level of difficulty in performing various cognitive functions on a 4-point scale, with 4 being the most difficulty and 1 being the least. Upon completion of the 18 items, the interviewee is asked to give a global rating of the patient's cognitive functioning on a scale of 1–10. After the interview has been administered to both the patient and the informant, the interviewer ranks the patient on all 18 items, and gives a global score based on the responses of both the patient and informant as well as the interviewer's observations of the patient.

Initial assessments of SCoRS results have demonstrated high interrater reliability (Keefe *et al*, 2006*b*). The administrator's global rating was shown to be the single SCoRS measure that correlated most significantly with measures of cognition (BACS; Brief Assessment of Cognition in Schizophrenia; Keefe *et al*, 2004), performance-based assessment of function (UPSA; Patterson *et al*, 2001) and real-world assessment of function (Independent Living Skills Inventory (ILSI); Menditto *et al*, 1999). Step-wise regression analysis demonstrated that the interviewer's global rating accounted for significant variance in real-world functioning as measured by the ILSI beyond that explained by results from the BACS and the UPSA (Keefe *et al*, 2006*b*). Because the SCoRS assessment is based on patient and informant reports, it has high face validity.

In addition to its utility as a coping measure with the MCCB in drug trials, the SCoRS is ideally suited for use in the clinic and may thus increase awareness of cognitive deficits in the diagnosis and treatment of people with schizophrenia. Because patient scores have been found to account for little variance in cognitive performance, functional capacity or real-world functioning scores beyond that accounted for by informant ratings (Keefe *et al*, 2006*b*), it is possible that informant ratings alone could be collected when an informant has sufficient contact with the patient. The assessment time could then be limited to 15 min. In addition, the SCoRS should be a familiar procedure for clinicians, who should require significantly less training than for batteries involving less familiar cognitive testing procedures. Interrater reliability of the SCoRS should be established before it is used for clinical or research purposes.

UCSD Performance-Based Skills Assessment

The University of California San Diego Performance-Based Skills Assessment (UPSA) was developed as a proxy of real-world functioning that is implemented in role-play. The UPSA measures daily living skills by recreating, in a clinical environment, situations a patient is likely to encounter in the real world. The tasks fall into five categories of functional skills: household chores; communication; finance; transportation; and planning recreational activities. The assessment is relatively brief,

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requiring an average of 30 min to administer and has demonstrated high interrater reliability (Patterson *et al*, 2001). Initial assessment found that UPSA scores for people with schizophrenia and schizoaffective disorders correlated significantly with both negative symptom severity and cognitive impairment, but not positive symptom severity (Patterson *et al*, 2001). Owing to the high face validity imparted by the 'real-world' nature of the assessment, the MATRICS committee adopted the UPSA as a second co-primary measure for studies of cognition in schizophrenia. The high degree of face validity might increase the cooperation of patients when it is used as a routine clinical assessment.

Repeatable Battery for the Assessment of Neuropsychological Status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) is a brief (45 min) assessment originally designed to test cognitive performance in older patients which has shown utility in providing reliable assessment of cognitive performance in populations with schizophrenia (Wilk *et al*, 2002; Weber, 2003). The performance of people with schizophrenia on the RBANS is highly correlated with performance on the much longer WAIS–III and WMS–III batteries (Gold *et al*, 1999; Hobart *et al*, 1999). Because it was designed to be administered repeatedly, the RBANS does not suffer from large practice effects. However, because the battery was developed to test for dementia, it is comprised largely of tests of memory, language and visual perception, and may suffer from ceiling effects on some sub-tests when used in people with schizophrenia. The battery also lacks measures of motor, executive and working memory performance, cognitive domains thought to be important in the cognitive impairment observed in schizophrenia. Despite these omissions, the RBANS is an appealing tool for the assessment of cognition in routine clinical practice owing to its relative brevity.

Brief Assessment of Cognition in Schizophrenia

The Brief Assessment of Cognition in Schizophrenia (BACS; Keefe *et al*, 2004) retains the positive attributes of the RBANS (brevity of administration and scoring, repeatability and portability) and more completely assesses the extent of cognitive impairment over multiple domains thought to be affected by schizophrenia (Table 2). The BACS, available in nine languages, requires approximately 30 min to complete and is devised for easy administration and scoring. The battery is specifically designed to measure treatment-related changes in cognition, and has alternate forms, thus minimising practice effects. The battery includes brief assessments of executive functions, verbal fluency, attention, verbal memory, working memory and motor speed, and generates a composite score that is calculated by summing *z*-scores derived by comparisons with a normative sample of 400 healthy controls. Its reliability, validity and comparability of forms has been established empirically (Keefe *et al*, 2004). The composite score has high test–retest reliability in people with schizophrenia and healthy controls (intraclass correlation coefficients >0.80). The BACS composite score has been shown to be as sensitive to the cognitive deficits of schizophrenia as a standard 2.5-hour battery (Keefe *et al*, 2004) and is highly correlated ($r=0.84$, $P<0.001$) with the composite score derived from the CATIE neurocognitive test battery (Keefe *et al*, 2007). The BACS also has clear functional relevance, as the composite score is strongly related to functional measures such as independent living skills ($r=0.45$), performance-based assessment of functioning ($r=0.56$) and interview-based assessments of cognition in people with schizophrenia ($r=0.48$) (Keefe *et al*, 2006*c*). The BACS is well suited to routine clinical administration when a quick assessment of overall cognitive functioning is required.

Brief Cognitive Assessment

An even shorter battery is the Brief Cognitive Assessment (BCA; Velligan *et al*, 2004), which was designed to assess cognition in people with schizophrenia in 15 min. Initial assessment of the battery has indicated good test–retest reliability and strong correlation ($r=0.72$; $P<0.0001$) with an extensive 2-hour battery (Velligan *et al*, 2004). The two batteries showed similar correlations with measures of functional ability. Normative data are available allowing adjustments for practice effects when performing repeated assessments. The extreme brevity of the BCA makes it a strong candidate for routine clinical administration.

Computerised batteries

A recent development in cognitive assessment for clinical trials is the availability of computerised test batteries that allow direct data transfer to study databases. These methods minimise rater error and reduce the costs for human quality assurance. However, many of these methods have not been fully validated and therefore results must be evaluated carefully.

PSYCHOPHYSIOLOGICAL TASKS

Assessment of psychophysiological tasks is appealing because much of the underlying neurobiological circuitry has been uncovered in animal and human studies. However, care must be taken when inferring an aetiological basis or treatment strategy for schizophrenia from the performance of patients on these tasks. The outstanding

Table 2 Classification of BACS tests according to MATRICS neurocognitive domain[1]

MATRICS neurocognitive domain	BACS tests
Processing speed	Verbal fluency
	Category instances (supermarket items)
	Letter fluency (F and S words)
Processing speed	Token Motor Task
	Symbol coding
Reasoning and problem-solving	Tower of London Test
Verbal memory	List learning
Working memory	Digit sequencing

BACS, Brief Assessment of Cognition in Schizophrenia; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia.
1. Keefe *et al* (2007).

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question remains whether interventions that improve the performance of patients on these tasks would have any effect on the whole of cognition or on functional outcomes. Regardless of their utility in uncovering neurobiological underpinnings of the disease, psychophysiological tasks are particularly appealing for use in genetic studies as tools to quickly assess an endophenotype that might reflect a specific genotypic vulnerability to schizophrenia. Some of the most utilised psychophysiological tasks are briefly described below.

Eye movements

Several eye movement abnormalities have been associated with schizophrenia. Two of the most prominent are abnormalities in smooth-pursuit eye movements, in which the patient is instructed to maintain foveation of a smoothly moving target, and antisaccade performance, in which the patient is instructed to make a mirror image saccade away from a suddenly appearing visual cue.

Antisaccade

Lesion studies in non-human primates have demonstrated the importance of the dorsolateral prefrontal cortex for inhibiting reflexive prosaccades in the antisaccade paradigm (Fukushima *et al*, 1994). Likewise, converging evidence has suggested that the dorsolateral prefrontal cortex is compromised in people with schizophrenia (Bunney & Bunney, 2000). A review of patients' performance on the antisaccade task strongly indicates a significant elevation in erroneous prosaccades that is stable over time (Everling & Fischer, 1998). This was recently replicated in a seven site study by the Consortium on the Genetics of Schizophrenia in which the antisaccade performance of 143 people with schizophrenia was compared with that of 195 controls (Radant *et al*, 2007). All sites found a significant difference in the number of errors (reflexive prosaccades) made by the two groups. In addition, first-degree relatives of people with schizophrenia have demonstrated higher reflexive saccade rates than unrelated controls (Clementz *et al*, 1994), suggesting that the endophenotype reflects a genetic vulnerability to schizophrenia.

Smooth-pursuit eye tracking

Decreased pursuit gain has long been viewed as a characteristic impairment in people with schizophrenia. However, it was recently shown that people with affective disorder displayed an indistinguishable smooth-pursuit gain (Kathmann *et al*, 2003). Likewise, unaffected relatives of the two groups did not differ in their pursuit gain deficiencies. These results argue against the utility of smooth-pursuit gain as a phenotypic marker reflecting a genotype specific to schizophrenia. However, high rates of catch-up saccades (Sweeney *et al*, 1994) and anticipatory saccades (Rosenberg *et al*, 1997) in the smooth-pursuit paradigm appear to be specific to schizophrenia and may offer phenotypic measures for genetic studies.

Prepulse inhibition and P50

Prepulse inhibition and P50 are both measures of pre-attentive processing that display impairment in people with schizophrenia and have been thoroughly researched in animal models. However, impairment in both of these paradigms is fairly widespread over various psychiatric populations, thus decreasing the utility of these measures as an endophenotype for schizophrenia (Bart, 2004)

CONCLUSIONS

Cognitive impairment is returning to prominence in the conceptualisation and practical assessment of schizophrenia, and is being considered for inclusion in the ICD and DSM diagnostic criteria. A wide variety of batteries currently exist for assessing cognitive impairment in relation to the disease, and cognitive outcome measures are essential as the field moves forward. However, current options are lacking in several regards. Notably, most cognitive outcome measures tend to suffer from low face validity: it is not obvious to patients or caregivers that improvements in performance on these batteries would make a difference to the patient's quality of life. Therefore, it is essential in many circumstances that an appropriate test of functional outcome is co-administered with a cognitive battery. Interview-based measures and functional proxy measures are based upon measures of intuitive value to patients and clinicians, and are amenable to use in the clinic, where cognitive assessments are far from routine because of the onerous nature of administering most batteries. Also, although modern cognitive batteries strive to include tasks with low practice effects, this confound is substantial. Thus, trials involving repeated assessments of patients require comparison with comparable control groups that have experienced the same testing procedure. Another consideration in the choice of cognitive testing batteries is that differential sensitivity to between-group or over-time differences across individual tasks can cause spurious findings of differential impairment across domains of cognitive functioning. The parsing of cognitive functioning into various domains is weakened by the lack of domain specificity for many cognitive tests (Keefe, 1995). Despite these shortcomings, cognitive outcome measures have reshaped our view of schizophrenia and will be essential for identifying its aetiology as well as designing more effective interventions.

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