Schizophrenia and Cognition **Robert Bilder**

This talk included an overview of cognitive deficits in schizophrenia, focusing on the overall severity of impairment, the domains affected, the longitudinal course of impairment, and some of the mechanisms implicated. While meta-analysis has suggested that deficits range from .46 to 1.41 SD relative to healthy comparison groups, well-conducted individual studies suggest an overall deficit of ~1.5 SD, with a likely range from 1.0 to 2.0 SD. The generalized deficit is relatively large, with more subtle variation of individual domain deficits.

There remains debate about the structure of cognitive domains, but it is agreed that patients have less deficit in "crystallized" intellectual abilities (i.e., vocabulary and general information), while more "fluid" abilities are impaired (i.e., learning/memory, executive functions, and attention). The MATRICS consensus process that led to identification of seven "domains" important for research on enhancing cognition in schizophrenia was reviewed.

While achieving expert consensus was seen as an important step, the presentation highlighted that these domains are theoretical constructs for which there is no uniform empirical basis. Different investigators use similar terms with different meanings, different terms with similar meanings, and the assignment of tests to domains is necessarily somewhat arbitrary. Tests vary considerably in specificity to a given domain, and most tests tap multiple constructs. Also, tests selected for good psychometric properties or ease of administration in humans may fail to measure constructs validated using basic neuroscience methods (e.g., MATRICS measures of 'working memory' are sequencing tasks probably involving different neural substrates than the delayed response measures associated with prefrontal cortex function in monkeys). The proposed MATRICS measure for "reasoning and problem solving" (solving maze problems) is not clearly related to the concepts of "executive function", "abstract problem solving", or "response inhibition" that have been widely studied in schizophrenia. The social cognition domain is widely agreed to deserve further attention and study. The implications of these issues for clinical trials is that while the MATRICS battery reflects an excellent consensus approach to measuring cognitive impairment in schizophrenia, it may be limited in measuring more discrete cognitive constructs that have clearer neuroscientific bases.

Evidence regarding the course of cognitive impairment in schizophrenia suggests impairment as early as measurements can be made, likely reflecting neurodevelopmental pathology, perhaps in the 2nd trimester of gestation. On average, there appears to be at most subtle decline until the onset of prodromal symptoms and the onset of the initial episode of illness, when there is a clear decline. Following onset of the initial episode, effective treatment and stabilization appears to be associated with in general stable or even slightly improved cognitive functioning. These group findings, however, disguise a myriad of unique courses experienced by individual patients, with some showing

relatively full recovery to pre-onset levels, while others show marked deterioration.

The impact of treatments was reviewed, suggesting that older antipsychotics led to at best limited normalization of certain attentional and language functions, while newer antipsychotics appear to be associated with a modest enhancement of cognition relative to the older agents (with an effect size estimated as d=.24; Woodward et al., 2005).

Several mechanisms possibly associated with cognitive impairment were summarized, including regional, neural systems, dysconnectivity, and widespread "panmodal" processing deficits. The talk mentioned possible roles of DA systems, NMDA receptor function, and several candidate genes including CHRNA7, DISC1, DTNBP1, BDNF, and COMT (e.g., there were 201 'hits' for 'schizophrenia' in NCBI's Gene database as of 8/21/05). It was concluded that cognitive deficits in schizophrenia: (1) are severe, pervasive and limit function; (2) have neurodevelopmental origins, with subsequent modulation; and (3) are unlikely to be explained by unitary models of pathology. It was suggested that advances in therapeutics for this complex syndrome will require convergence of approaches from molecular through syndromal, with improved definitions of the target phenotypes.

Assessment of cognition in schizophrenia: a multi-pronged challenge

Richard Keefe

This talk discussed practical issues in assessing cognition in clinical trials of patients with schizophrenia. The methodology for cognitive assessment depends heavily upon the questions being addressed in the trial. Different methods were considered for early phase trials, especially phase II trials, phase III trials, and post-marketing phase IV trials. Most of the previous clinical trials investigating the effects of pharmacological treatment on cognitive deficits in schizophrenia have been phase IV trials of atypical antipsychotics. These studies have suggested a mild cognitive benefit of the atypical medications, with significant effects occurring early (6-8 weeks) in the course of treatment. Other studies looking specifically at adjunctive or 'co-treatments' have been less successful.

One frequent question that arises in the design of cognitive enhancement trials is which patients should be included. While the assumption is often made that patients with the most severe cognitive deficits are the best candidates for treatment, there is no evidence to support this assumption. In fact, some studies have suggested that patients with the best cognitive performance at baseline may demonstrate the most cognitive benefit from treatment. Also, while some patients with schizophrenia may be considered by neuropsychologists to be 'unimpaired,' if their performance is within one standard deviation below the healthy control mean, almost all patients with schizophrenia have some degree

of cognitive impairment as defined by a decline from premorbid expectations. These data argue strongly that all patients with schizophrenia have the potential to benefit from cognitive enhancement therapy, and that studies designed to test the efficacy of a potential cognitive enhancing compound should include all patients who can perform the test battery validly.

The characteristics of a useful test battery for clinical trials were reviewed, including: reliability; validity; relevance of constructs; availability of normative data; experience in previous schizophrenia studies, including determination of expected distributions in schizophrenia samples and absence of ceiling and floor effects; use in previous clinical trials; and the desirability of the resulting outcome measures. Data from several studies, including the NIMH CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) Schizophrenia Trial, with a sample of 1331 patients, suggest that a small number of tests can provide a reliable single composite score for assessing whether a new treatment can improve cognition in general. However, more specific hypotheses, such as the impact of a new treatment on single domains of cognition, will require more extensive testing. The TURNS Neuropsychology Group has provided a set of criteria for the optimal characteristics of cognitive neuroscience tests that may be added to standard batteries such as the MATRICS Battery. In addition, biomarkers such as fMRI, P50, and eye-movement studies may provide important information about the potential for a new compound to improve relevant neural circuitry function in schizophrenia.

The implementation of these cognitive methods was also discussed. It was strenuously emphasized that for clinical trials in patients with schizophrenia to measure cognitive enhancement adequately, a significant paradigm shift must occur. While the training and certification procedures in schizophrenia trials normally focus on the reliability of symptom assessment, when cognition measures are the primary outcomes, it is essential that time and resources are devoted to screening, training, and certifying cognitive testers. Testers do not require a specific educational background, however experience with psychotic patients is crucial. In addition, testers should understand the importance of general testing standards, such as consistency of testing procedures, engaging patient cooperation, and maintaining a distraction-free testing environment. Almost all testers should undergo face-to-face certification procedures by trained professionals following intensive education and practice with the relevant test materials.