

# **Assessment of Cognition in Schizophrenia: A Multi-Pronged Challenge**

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# Questions

- ◆ How to assess cognition in schizophrenia?
  - (What is the question?)
- ◆ Why is it difficult?
  - (How to make it easier)

# What is the Question? Schizophrenia Research Neurocognitive Battery

Edinburgh Inventory  
Complete WAIS-R  
Mesulam-Weintraub Cancellation (4 forms)  
Hand Grip Strength  
Finger Tapping Test  
Motor Performance Battery (from Rudel-Denckla)  
Purdue Pegboard  
COWAT  
Wepman Auditory Discrimination Test  
Menyuk Syntactic Comprehension Test  
Oldfield-Wingfield Picture Naming Test  
Semantic Fluency (3 tests)  
Word Reading Test  
Sentence Reading Test  
Sentence Repetition Test (Spreen-Benton)  
BDAE Complex Ideational Material  
BDAE Responsive Naming Test

Popplereuter Figure Analysis  
Corsi Spatial Span/Memory  
Benton Facial Recognition Test  
Prosopoaffective Agnosia Test  
Wasserstein Closure Test  
Beery-Buktenica Test of Visuomotor Integration  
Buschke Selective Reminding Test  
Graphesthesia (Reitan-Klove)  
Finger Gnosis (Kinsbourne Warrington)  
Right Left Discrimination (Benton)  
Trails A,B  
Competing Programs  
WCST  
Wechsler Memory Scale (complete)  
Kimura's Recurring Figures Test  
Temporal Lobe Personality Inventory  
Mini-Mental State Exam  
Raven Standard Progressive Matrices

**Duration:**  
**8-24 hours**

**Courtesy of Robert Bilder**

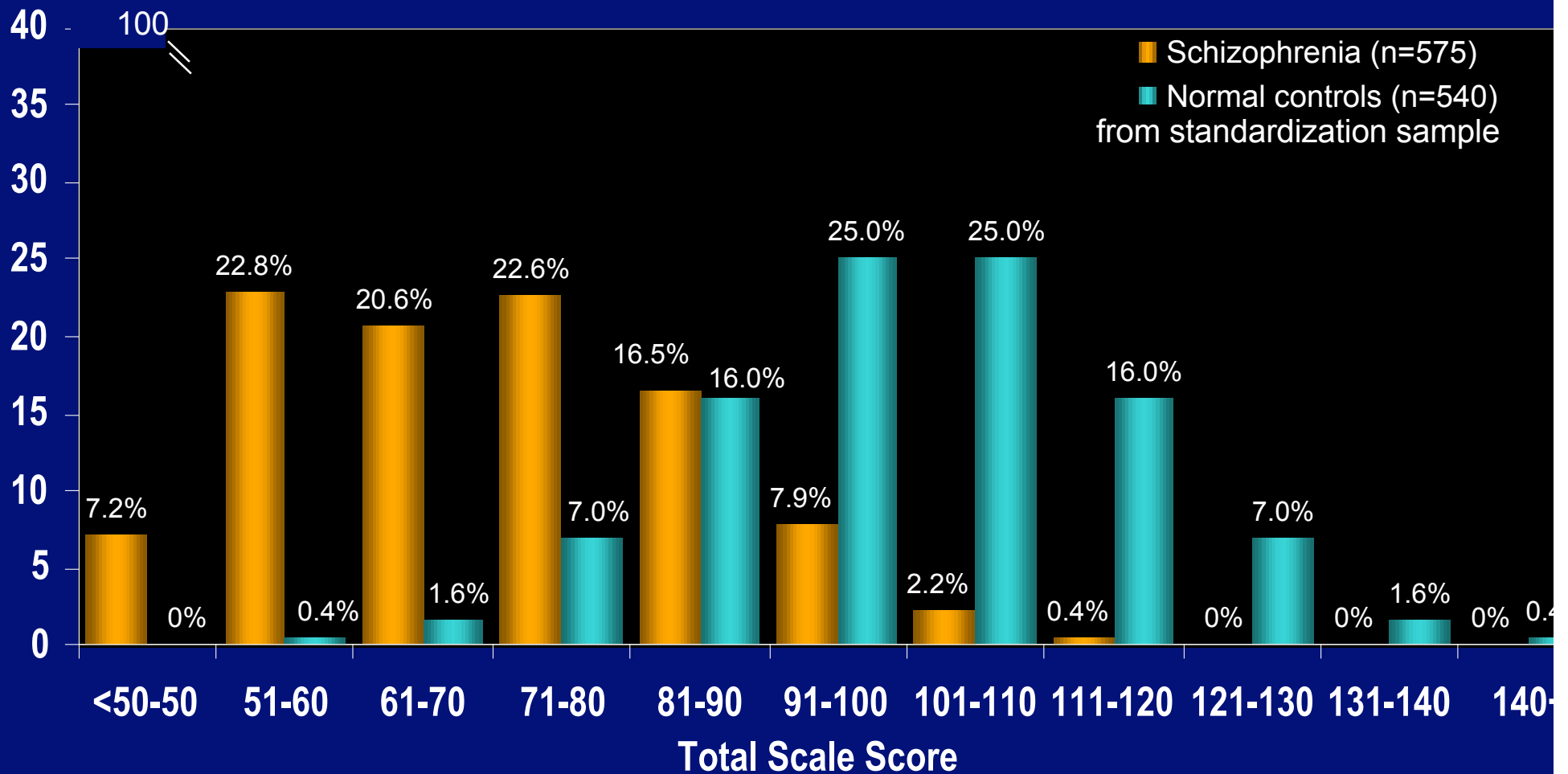
# What is the Question? Patient Population

- ◆ Diagnosis: schizophrenia
- ◆ Age group
  - Upper range limit?
    - Deterioration of function in upper middle age
- ◆ Phase of Illness
  - First Episode
  - Chronic
    - Stable
    - Exacerbated
  - Antipsychotic Treatment-resistant

# What is the Question? Inclusion Criteria

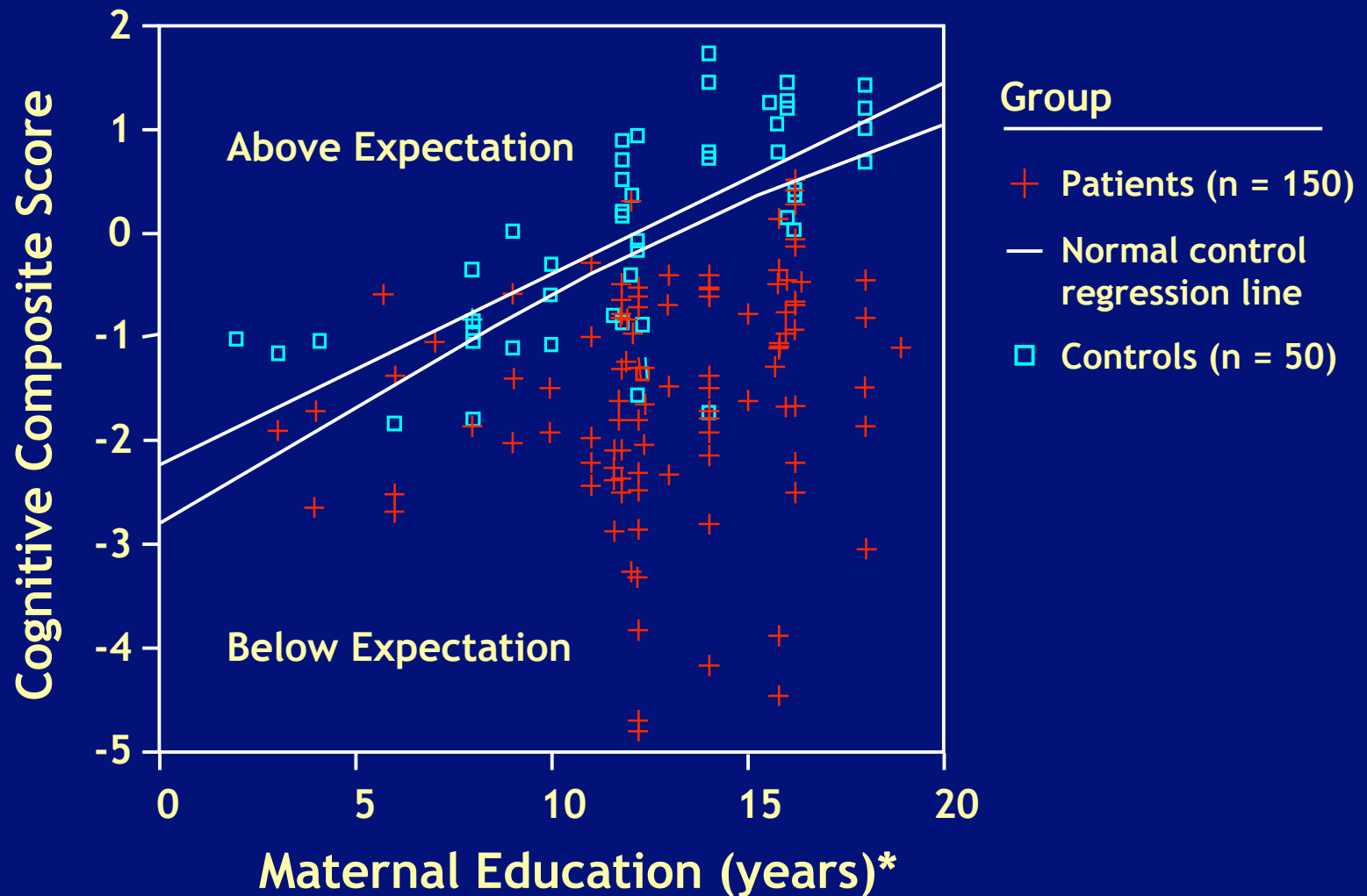
- ◆ All patients with schizophrenia versus only those with “cognitive impairment?”
- ◆ Symptom severity
  - Problems with using symptom exclusion criteria to avoid pseudospecificity
  - Why should negative symptom patients be excluded if the validity of the testing can be maintained?
- ◆ What level of uncooperativeness is acceptable?
  - TURNS uses Seidman Uncooperativeness Scale and assesses threats to test validity
- ◆ What level of disengagement is acceptable?
  - When we exclude patients who are disengaged during testing are we excluding the part of schizophrenia we want to treat?

# Normative Data Compared to a Schizophrenia Sample: RBANS Total Scale Score Distribution



Randolph C. *RBANS Manual-Repeatable Battery for the Assessment of Neuropsychological Status*; 1998.  
 Wilk CM, et al. *Schizophr Res.* 2004;70(2-3):175-186.  
 RBANS: Repeatable Battery for Assessment of Neuropsychological Status

# Expected Performance Based on Maternal Education of Healthy Sample



\*Maternal education values jittered for clarity.

Keefe RSE et al. *Biol Psychiatr.* 2005;57:688-691.

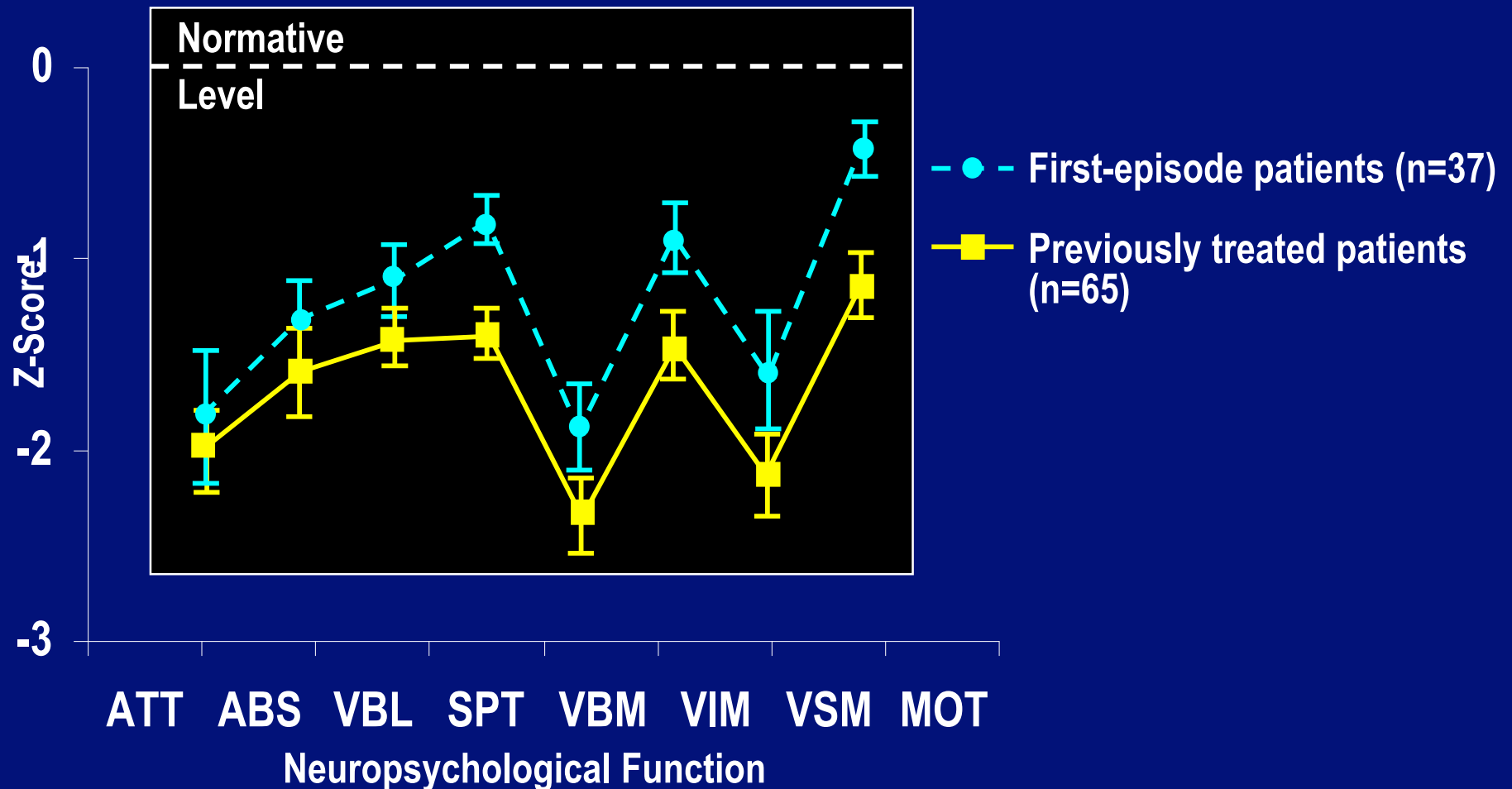
# Properties of Assessment Batteries for Clinical Trials

- ◆ Reliability
- ◆ Validity
- ◆ Measures of relevant constructs or domains
- ◆ Standardized with available norms or control data
- ◆ Experience in previous schizophrenia samples
  - Reasonable distribution of scores
  - Avoidance of ceiling and floor effects
- ◆ Use in previous treatment studies
- ◆ Combination of standard and experimental assessment tools
- ◆ Derivation of outcome measures

# Relevant Constructs

- ◆ Substantial impairments in patients with schizophrenia
- ◆ Related to functional outcome
- ◆ Sensitivity to change?
  - Logical exclusion
    - Example: crystallized intelligence unlikely to change with treatment
  - Outcome measure distribution properties

# Neuropsychological Profile for Drug-Naïve First-Episode and Previously Treated Patients



ATT=attention vigilance. ABS=abstraction-flexibility. VBL=verbal intelligence and language function. SPT=spatial organisation. VBM=verbal memory and learning. VIM=visual memory. VSM=speeded visual-motor processing and attention. MOT=fine manual motor functions.  
Saykin AJ, et al. *Arch Gen Psychiatry*. 1994;51(2):124-131.

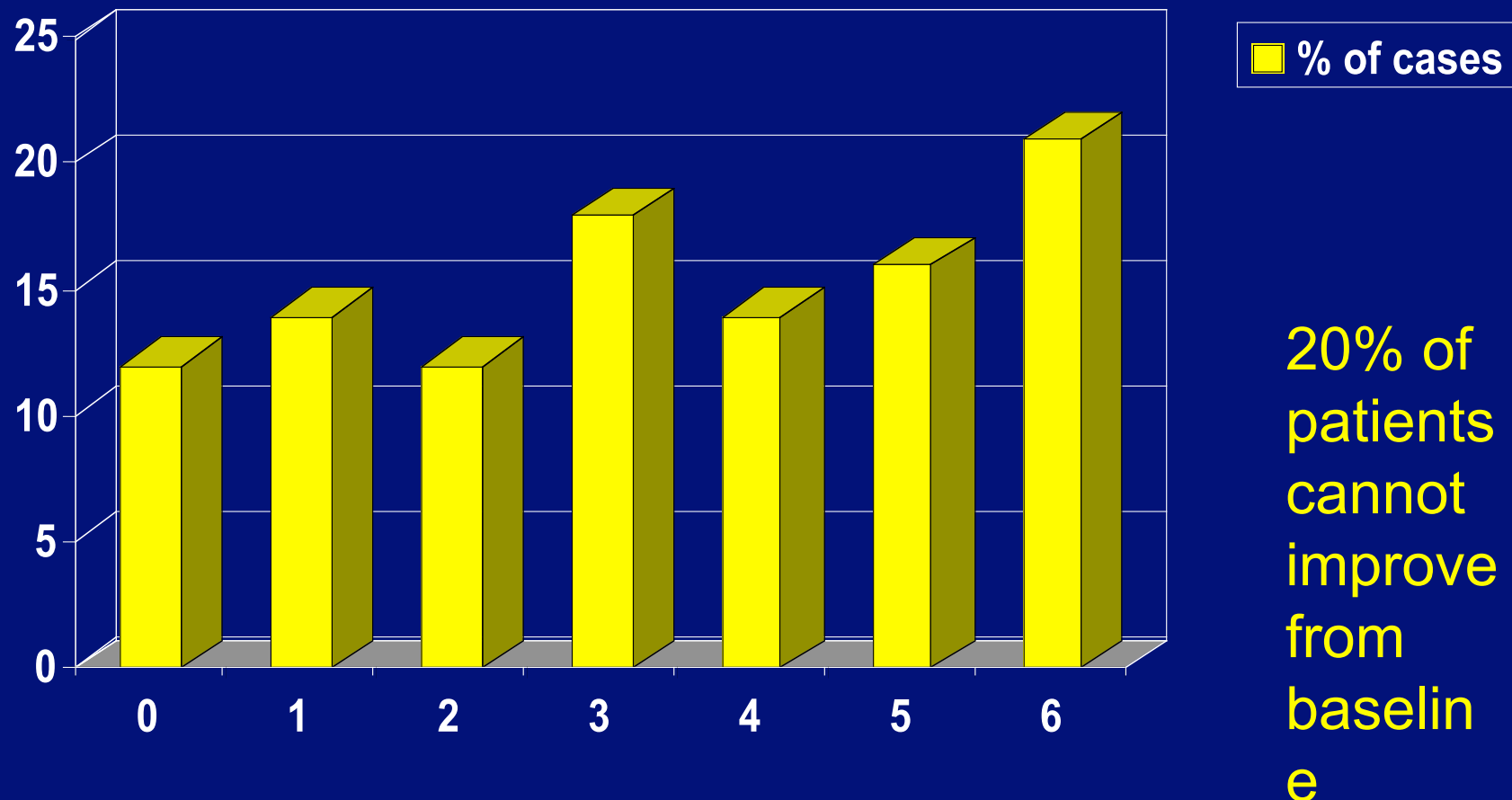
# Cognitive Domains in Schizophrenia

## Which are related to Functional Status?

1. Verbal learning and memory **yes**
2. Speed of processing (verbal fluency) **yes**
3. Auditory working memory **yes**
4. Reasoning and problem solving **yes**
5. Vigilance (Continuous Performance Test) **yes**
6. Visual memory **??**
7. Social cognition **??**

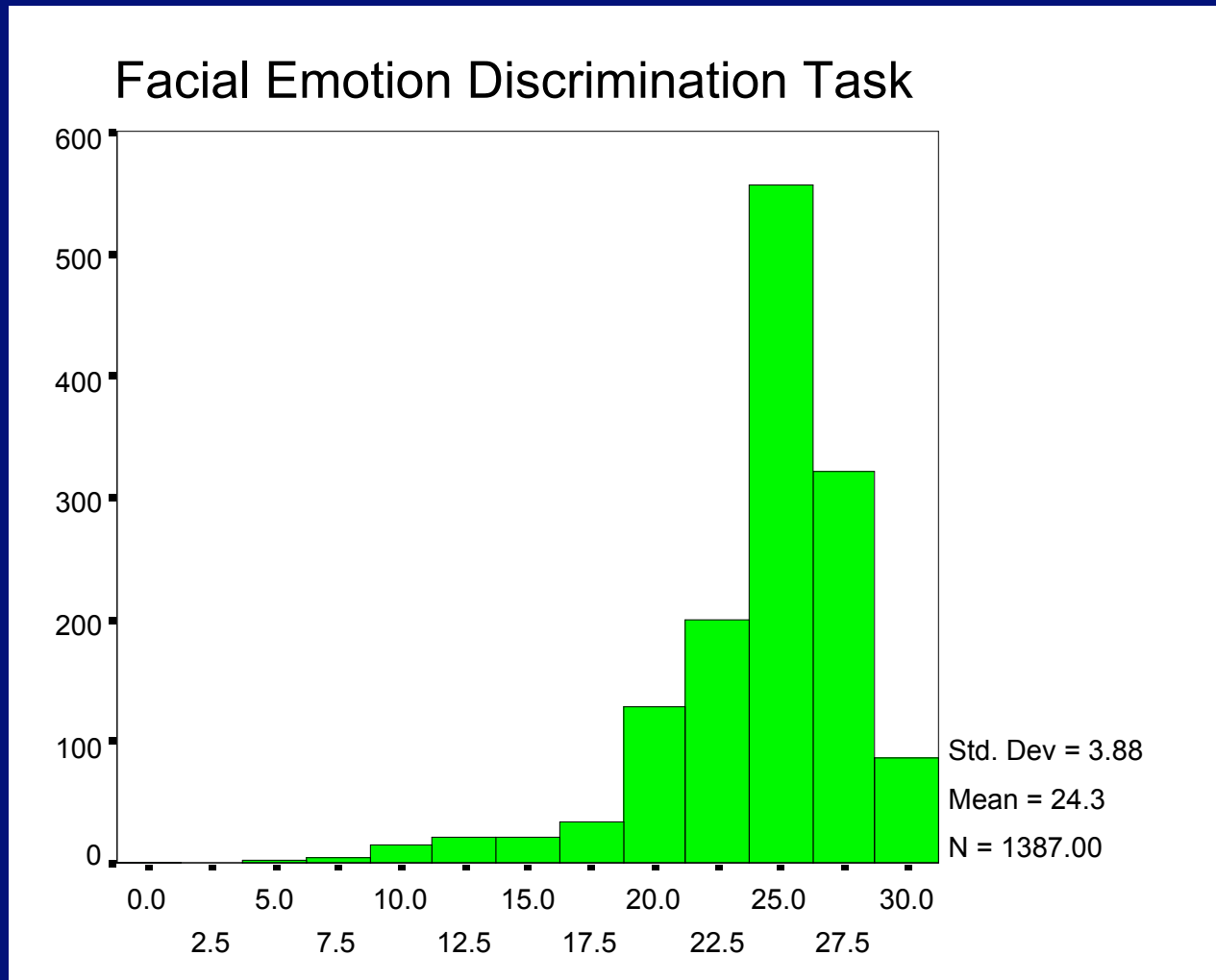
**Green, MATRICS Neurocognition Meeting, April, 2003**

# WCST-128 Categories Completed at Baseline: First Episode Patients



Harvey et al., 2003

# Ceiling Effect



CATIE Schizophrenia Trial data

# Use in Previous Treatment Studies

- ◆ Experience in multi-site studies is helpful to determine distribution properties and implementation challenges
- ◆ Balance of utilizing new technologies and latest scientific findings with history of serving the needed purpose
- ◆ One possible resolution of this balance is to combine standard instruments with experimental methods specifically tailored for the trial

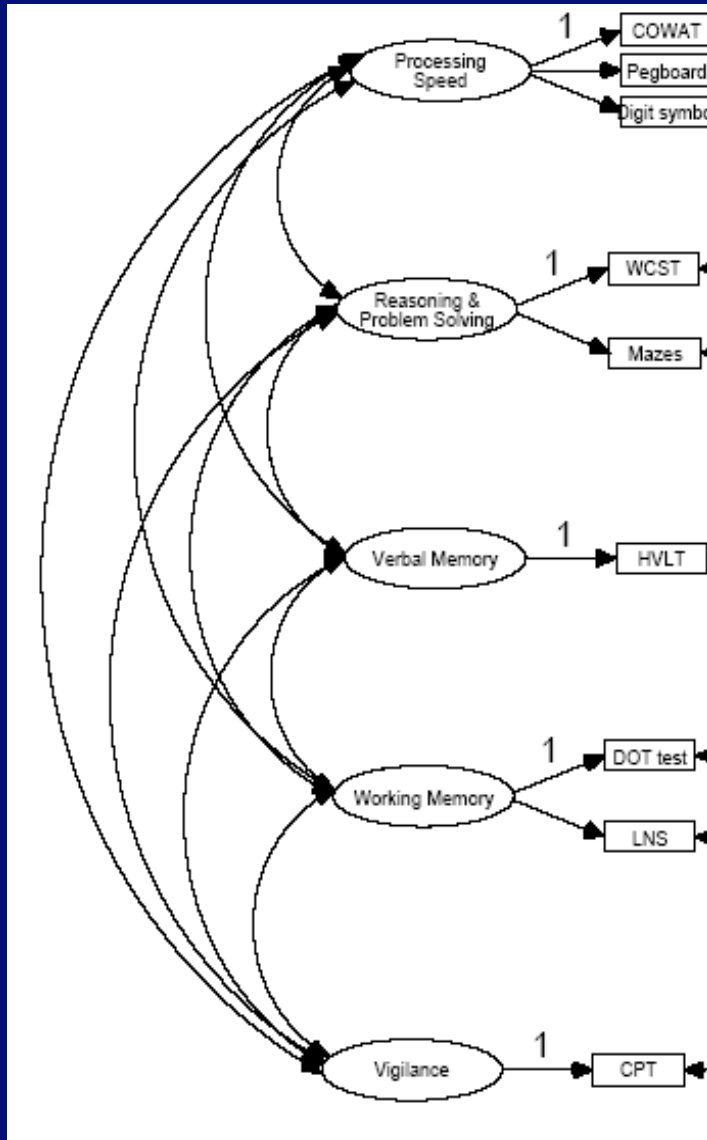
# Outcome Measures

- ◆ General
- ◆ Specific

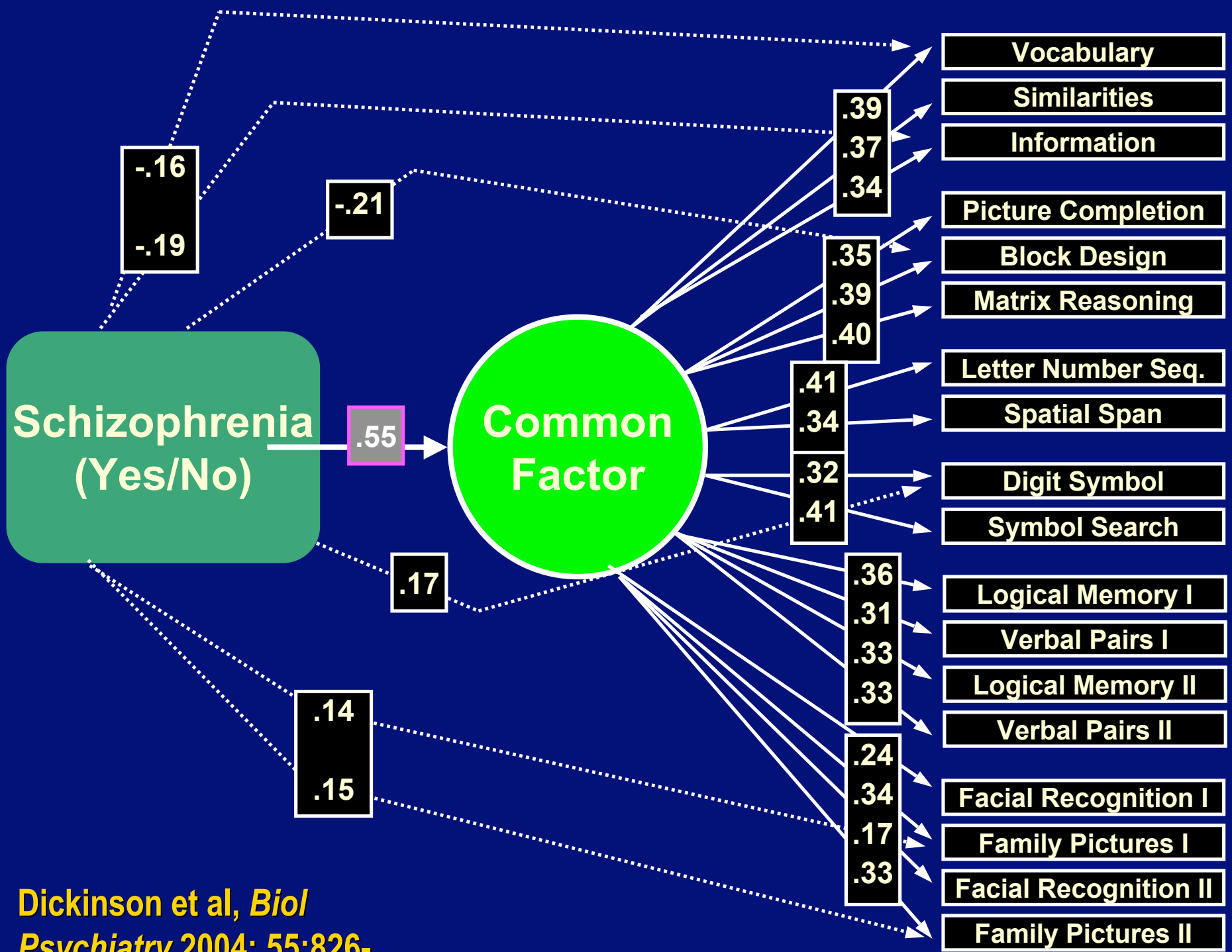
# Principal Component Analysis (PCA) of CATIE Baseline Neurocognitive Data

- ◆ A single component best described the data (eigenvalue = 4.07), accounting for 45.2% of the overall variance in test scores.
- ◆ No other principal component greater than 1.0.
- ◆ Since the first component accounted for a relatively low percentage of the overall variance, 2, 3, and 4-component solutions were examined, but did not adequately explain the data structure.

# Structural Equation Modeling Analyses

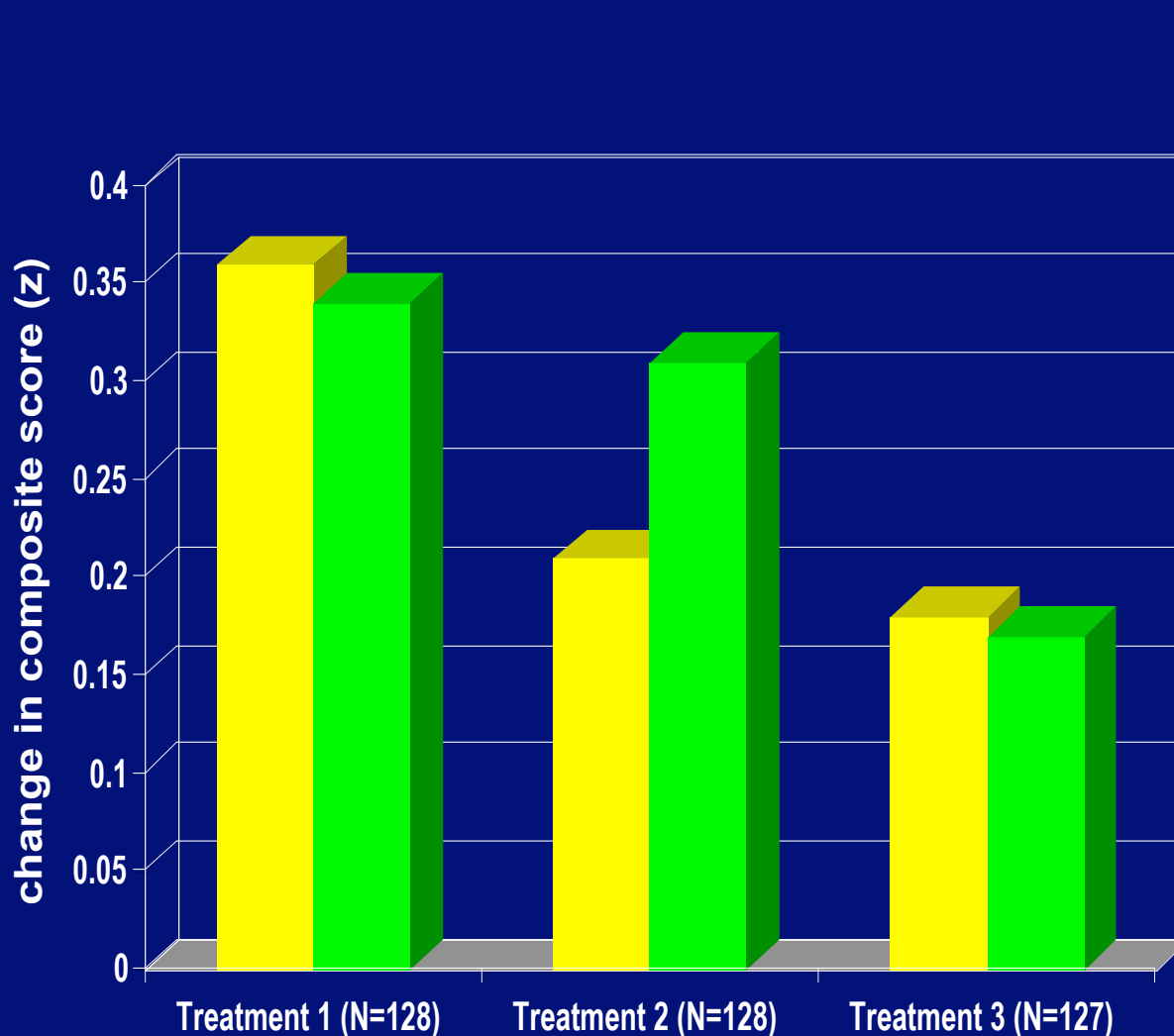


- ◆ Null model failed to fit the data
- ◆ The unifactorial model was a considerable improvement in fit;  $\chi^2(27)=192.18$ ,  $p<0.001$ . Fit statistics: CFI=.94, GFI=.97, RMSEA=.077
- ◆ A domain-based, five-factor model also fit the data well,  $\chi^2(19)=117.95$ ,  $p<.001$ , CFI=.96, GFI=.97, RMSEA=.071, and was also a significantly better fit than the unifactorial model:  $\chi^2(8)=74.0$ ,  $p<.001$



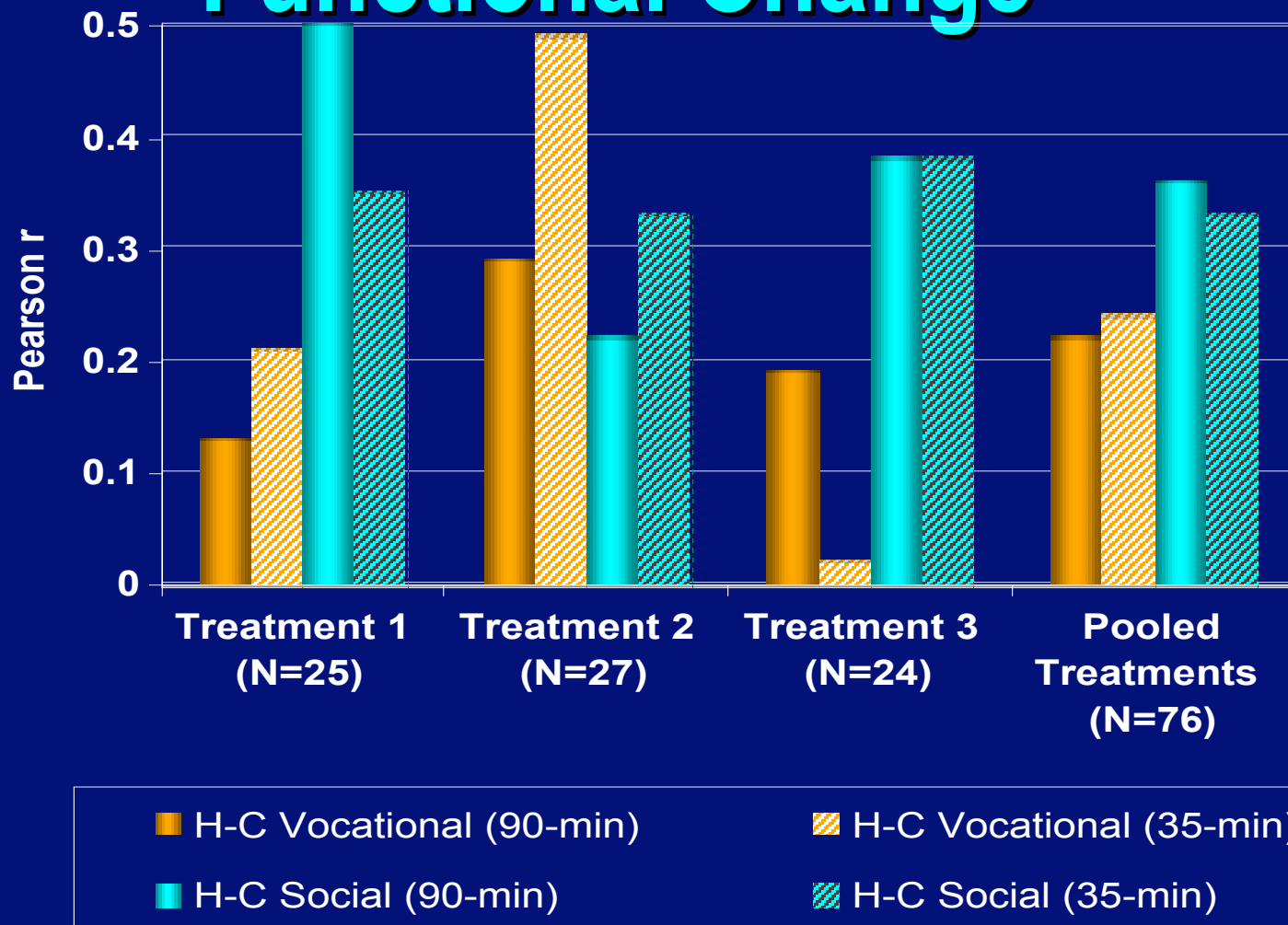
Dickinson et al, *Biol Psychiatry* 2004; 55:826-833

# Atypical Antipsychotic Treatment in First Episode Psychosis



Composite scores did not differ significantly between groups. Four of the nine tests (44%) in the 90-minute battery demonstrated significant differences among the treatments. Two of six tests (33%) in the 35-minute battery were sensitive to between-group differences

# One Year of Atypical Antipsychotic Treatment in First Episode Psychosis: Correlation of Cognitive Change and Functional Change



# Symbol Coding

—	—	γ	X	—	=	—	—	∞
1	2	3	4	5	6	7	8	9

—	—	—	—	γ	=	—	X	—	=		—	—	=	—
X	=	—	—	—	=	γ	X	—	—	=	∞	X	γ	—
X	—	—	—	—	γ	—	X	—	—	—	∞	γ	X	—

# Limitations of a Measure of Processing Speed

- ◆ Symbol coding (as measure of processing speed) performance depends on several processes, among them:
  - Motor speed – writing numbers
  - Attention – staying on task without distraction
  - Working memory – keeping number/symbol associations in mind facilitates performance
  - Executive functions – thinking to remember the associations
- ◆ Possible to parse these components with refined tasks
- ◆ Neuroimaging measures give traction to the measurement of these components
- ◆ Localizing specific deficits may yield more specific drug interventions

Modified from Jonides, J. at MATRICS Biomarkers Meeting, 9/9/04

# TURNS Cognitive Neuroscience Measures

- ◆ Psychometric characteristics such as test-retest reliability and practice effects were key criteria in choosing tasks for the MATRICS battery.
- ◆ One of the reasons cognitive neuroscience measures were not included in the MATRICS battery was that we currently have less information about the psychometric characteristics of these types of tasks.
- ◆ The TURNS studies may offer opportunities for one or more of the sites to incorporate measures of cognitive function derived from human and animal cognitive neuroscience that could supplement the measures to be included in the MATRICS battery.

# Outcome Measures: Specific Effects

- ◆ Cognitive neuroscience tasks assess specific cognitive functions not measurable with standard neuropsychological tests
- ◆ Criteria for TURNS studies
  - Linked to relevant neurotransmitter systems?
  - Measures more specific cognitive construct?
  - Known to be responsive to specific pharmacologic manipulations?
  - Measures a process known to be supported by specific neural system?
  - Cross-species applicability?
  - Parametric characteristics?
- ◆ Do these tasks enable an enhanced sensitivity to a cognitive signal? Are the effect sizes larger? Are treatment effects earlier allowing shorter early-phase trials?
- ◆ Difficulties of implementing these tasks at multiple sites

# TURN'S Cognitive Neuroscience Measures Considerations

- ◆ Linked to relevant neurotransmitter systems?
- ◆ Measures more specific cognitive construct?
- ◆ Known to be responsive to specific pharmacologic manipulations?
- ◆ Measures a process known to be supported by specific neural system?
- ◆ Cross-species applicability?
- ◆ Parametric characteristics?

# Outcome Measures: Biomarkers

- ◆ Enable understanding of neurophysiological responses to new compounds
  - Are the results consistent with the expected pharmacologic effect and with what is believed to be needed in patients with schizophrenia?
  - P50
  - fMRI
  - Anti-saccade paradigms

# Measuring Drug Effects Using Non-Invasive Imaging

- ◆ Has the promise of providing direct measurement of drug effects on brain circuits underlying impaired cognition in



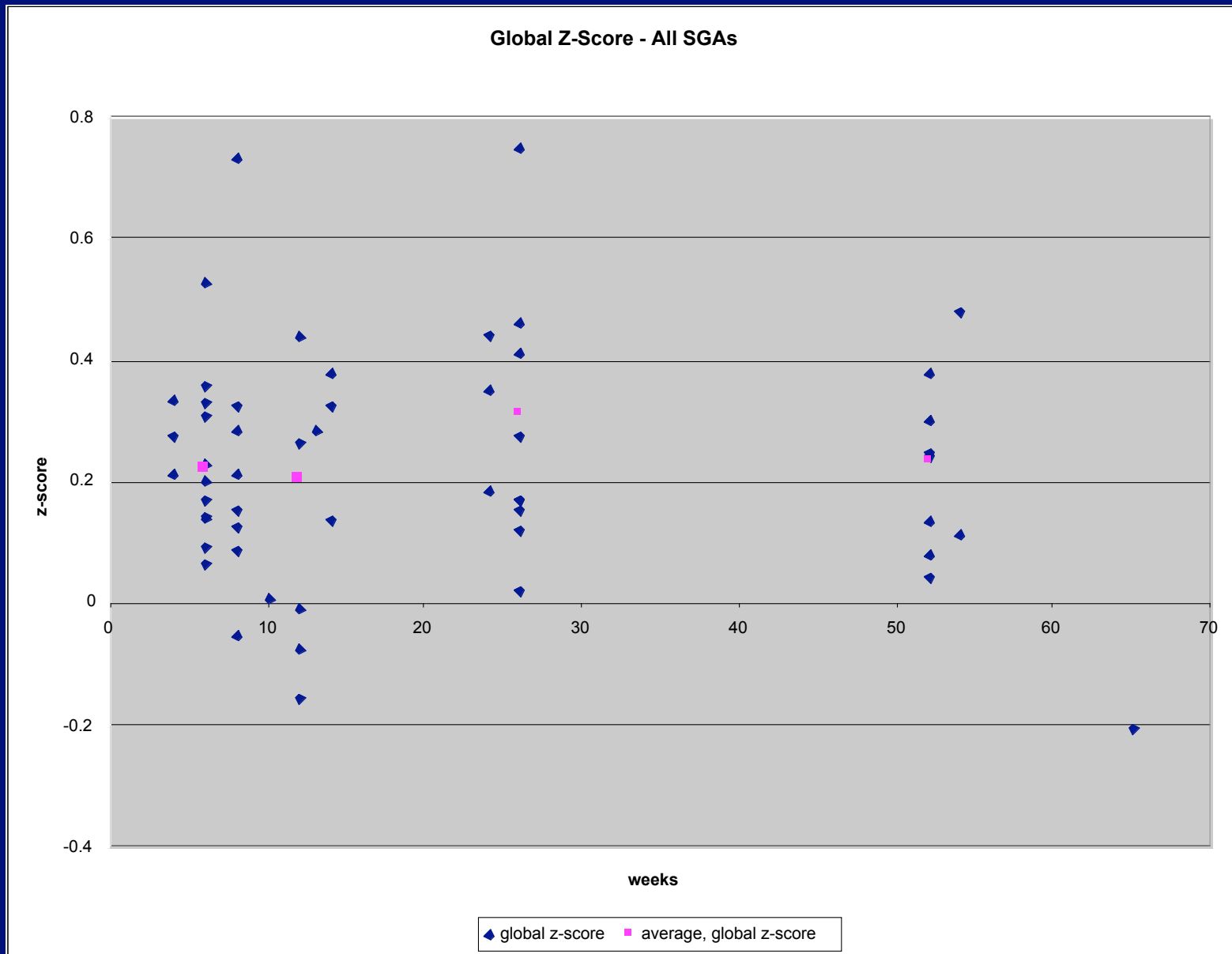
BUT Many conceptual and technical challenges need to be overcome!

Carter, C. MATRICS Biomarkers Meeting, 9/9/04

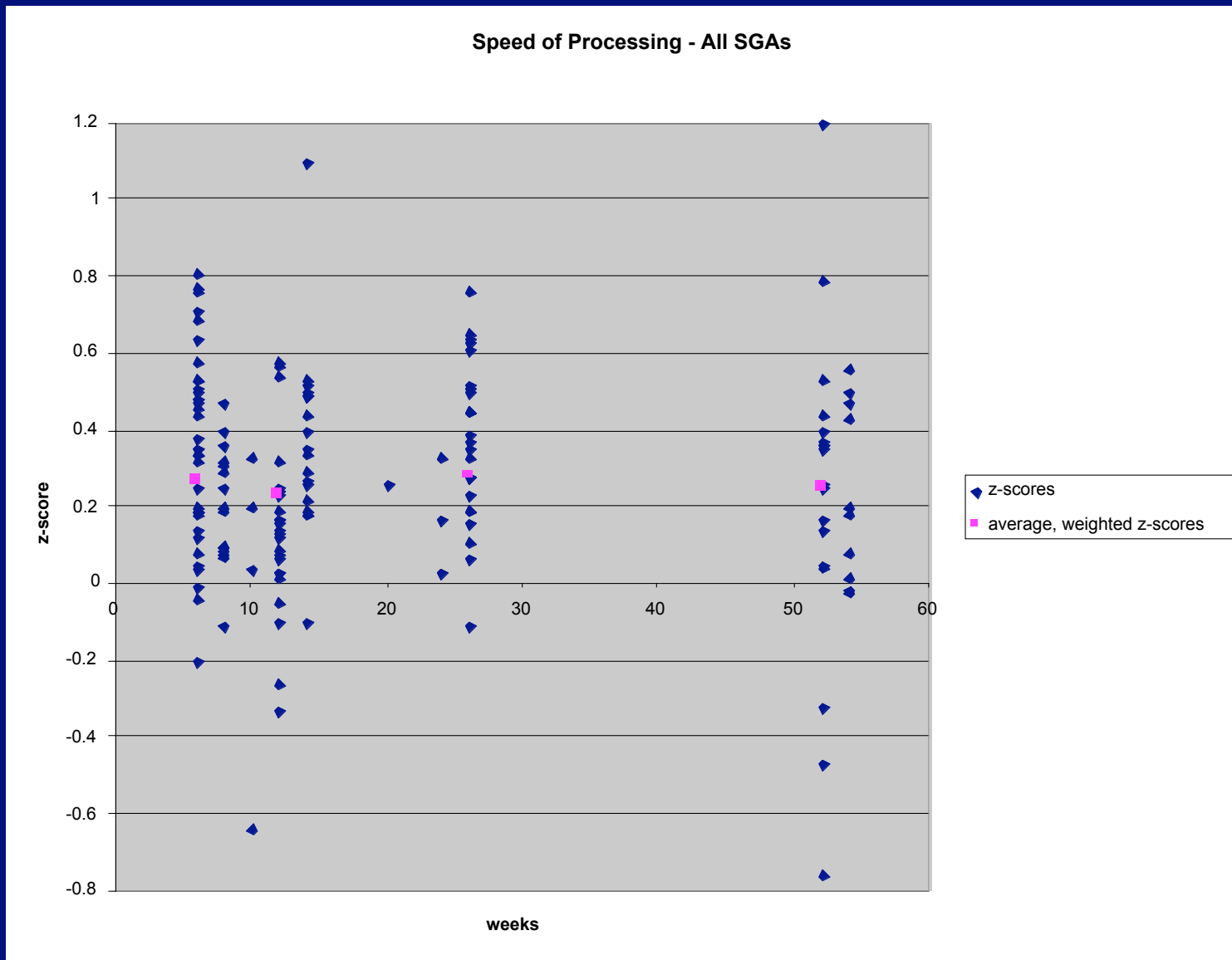
# What is the Question? Study Duration

- ◆ How quick might effects occur?
- ◆ Will effects be sustained?
- ◆ Will effects increase over time?
- ◆ Will effects persist after treatment discontinuation?

# Time Course of Cognitive Improvement with SGAs: Global Scores



# Time Course of Cognitive Improvement with SGAs: Processing Speed



# Neurocognitive Assessment in Clinical Trials: Primary or Secondary?

- ◆ Neurocognitive assessment in antipsychotic trials has almost always been a secondary outcome measure
  - Reflected in time and resource allotment
- ◆ Neurocognitive assessment in cognitive enhancement trials (“co-treatments”) requires more attention to quality and completeness of data
  - Reflected by equivalent increases in time and resource allotments? The bizarre perseverative error in current cognitive enhancement trials

# TURNNS Cognitive Measures

- ◆ Primary outcome measure: Composite score developed from an unweighted mean of the 7 domain scores from the MATRICS battery.
- ◆ Secondary cognitive outcome measures
  - Ancillary MATRICS measures
    - Organon 24448 trial
      - HVLT Delayed recall
      - NAB Daily Living Memory test
    - Ispronidine trial
      - CDR “power of attention” – simple RT, choice RT, digit vigilance

# Cognitive Battery: Registration Trials

- ◆ The MATRICS battery is specifically designed for clinical trials of compounds that may improve cognition in schizophrenia
- ◆ Is it the only option? Should it be?

# Cognitive Battery: Proof-of-Concept Studies

- ◆ What is the concept you are trying to prove?
- ◆ Do the early data encourage a specific cognitive hypothesis?
- ◆ Should the MATRICS battery be used for proof-of-concept studies?
  - FDA view?
  - Resource considerations
    - Is reduced company funding for POC trials a limiting factor?

# Cognitive Battery: Post Marketing Studies

- ◆ The majority of schizophrenia clinical trials that have assessed cognition have been phase IV studies of antipsychotic medication
- ◆ Assessment approaches for when cognition is a secondary outcome
  - Reduced resource allocation
    - Impact on patient assessment time
    - Impact on tester training and certification

# Why Is Cognitive Assessment in Schizophrenia Difficult?

- ◆ It is not THAT difficult.
  - Little differences between patients who do and do not complete testing
  - The *tests* that can be completed may differ in an “all-comer” population

# Implementation Challenges: Testers

- ◆ Education level is far less important than testing experience, clinical experience and being a reasonable person, which usually can not be determined without face-to-face certification procedures.
- ◆ What level of testing experience is ideal?
  - Too little - fundamental testing procedures are key
    - “Do the practice trials? That’s ridiculous!!”
  - Too much experience can be bad too - like rowing.
  - Previous experience with schizophrenia patients is key since psychotic people can respond to the testing environment in odd ways.
    - In training raters, we challenge them by doing a lot of the things that patients may do. Ex: verbal memory pattern 7-9-5-5-2

# Training: What is Necessary and Optimal?

- ◆ Pre-certification training CD, experience questionnaire, and CD questionnaire
- ◆ Investigator Meeting: two testers preferred
- ◆ Follow up: at least first two source docs and CRFs sent to us for immediate review, with random immediate review required during trial
- ◆ Procedures necessary for testers who do not attend meeting or for sites whose testers leave prematurely, which happens often

# Collaborators

## Duke

- Joe McEvoy
- William Wilson
- Meg Poe
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- Kirsten Hawkins
- Jon Cone
- Chuck Eesley
- Susan Schiffman

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- Barton Palmer
- Sonia Davis
- Richard Mohs
- James Gold
- Michael Green
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- *CATIE Neurocognitive Working Group*

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- Scott Stroup
- Robert Rosenheck
- Marvin Swartz
- Diana Perkins