Cognitive Assessment in Schizophrenia Clinical Trials: MATRICS and Beyond

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MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

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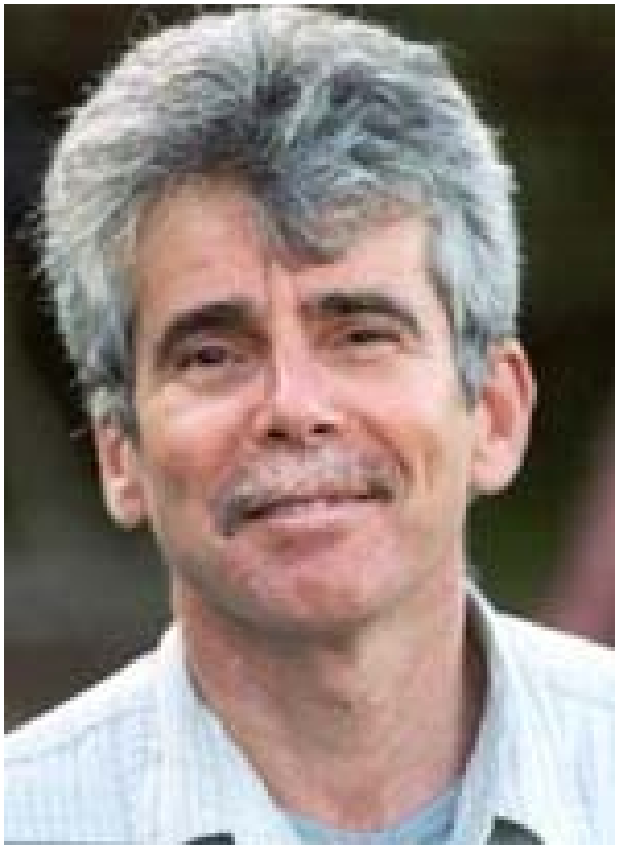

Wayne Fenton

1953-2006

Science That Matters

MATRICS:
Background and Rationale

- Increasing evidence that cognitive deficits are core features of schizophrenia

- Increasing support for relationships between cognition and functional outcome in schizophrenia

- Increasing research focus on the basic studies of neuropharmacology of cognition

MATRICS

Targeting Cognition in Schizophrenia: Why the Bottleneck?

- Lack of consensus regarding cognitive targets.
- No widely accepted endpoint.
- Ambiguity regarding optimal clinical trial design.
- No path to FDA approval and labeling (not a DSM entity).

FDA Processes Focus Industry Efforts

- FDA registration targets DSM disorders
- "No fundamental objection to syndrome-based clinical targets (fever, pain, agitation)"
- "We will not accept a new clinical endpoint for the convenience of any drug company"
- NIMH can use its convening authority as independent scientific entity to define new and valid clinical endpoints

NIMH
National Institute of Mental Health

NIMH – MATRICS
Goals and Products

- Create Standardized Measure for use in Clinical Trials
- Define Optimal Experimental Designs
- Establish path to FDA Approval
- Attract large pharmaceutical companies to focus efforts on this important clinical target

- Success required involvement of: NIMH, FDA, pharmaceutical industry, and academia

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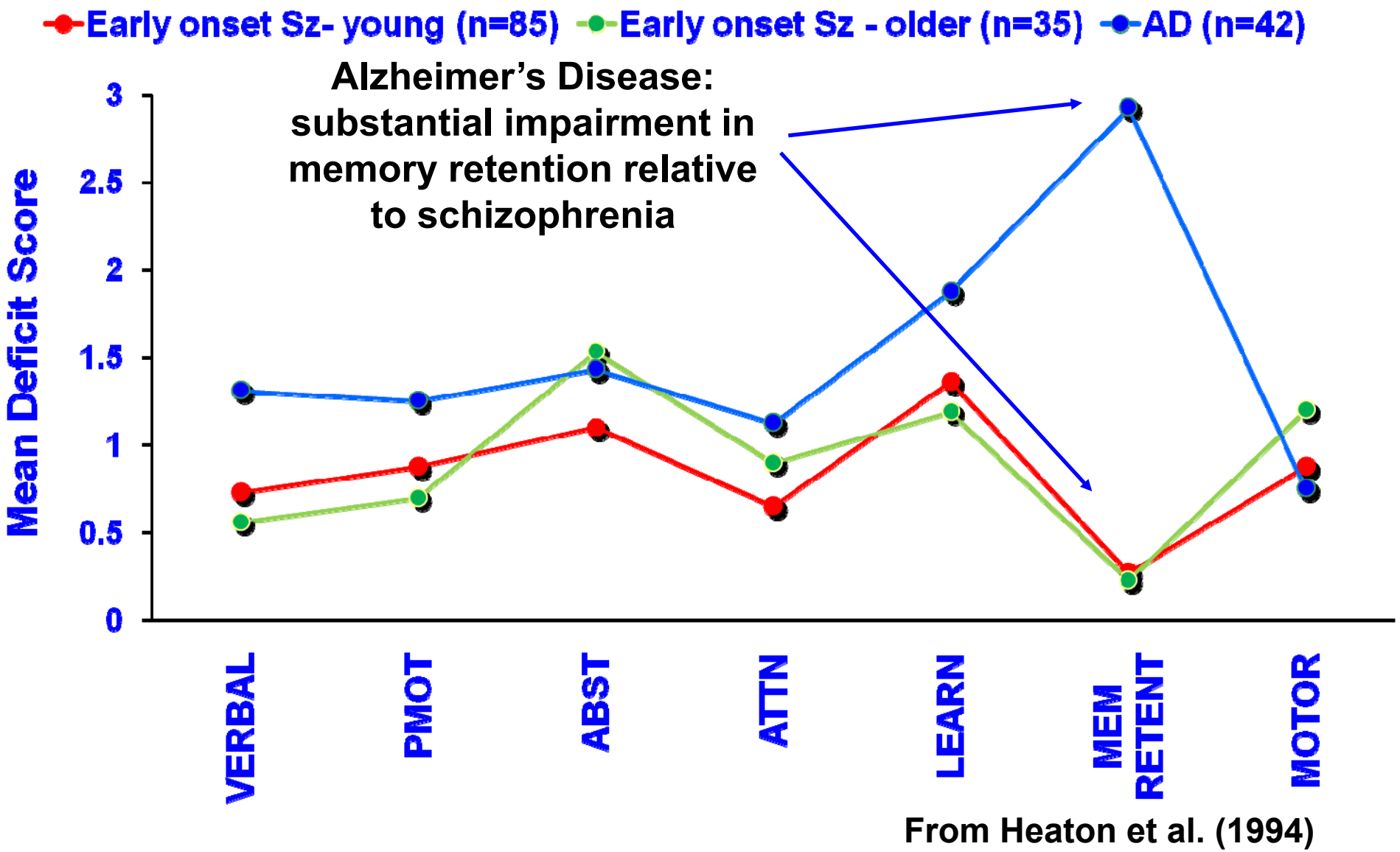
MATRICS

Alzheimer's Dementia compared with Schizophrenia Neuropsychological Deficit Scores

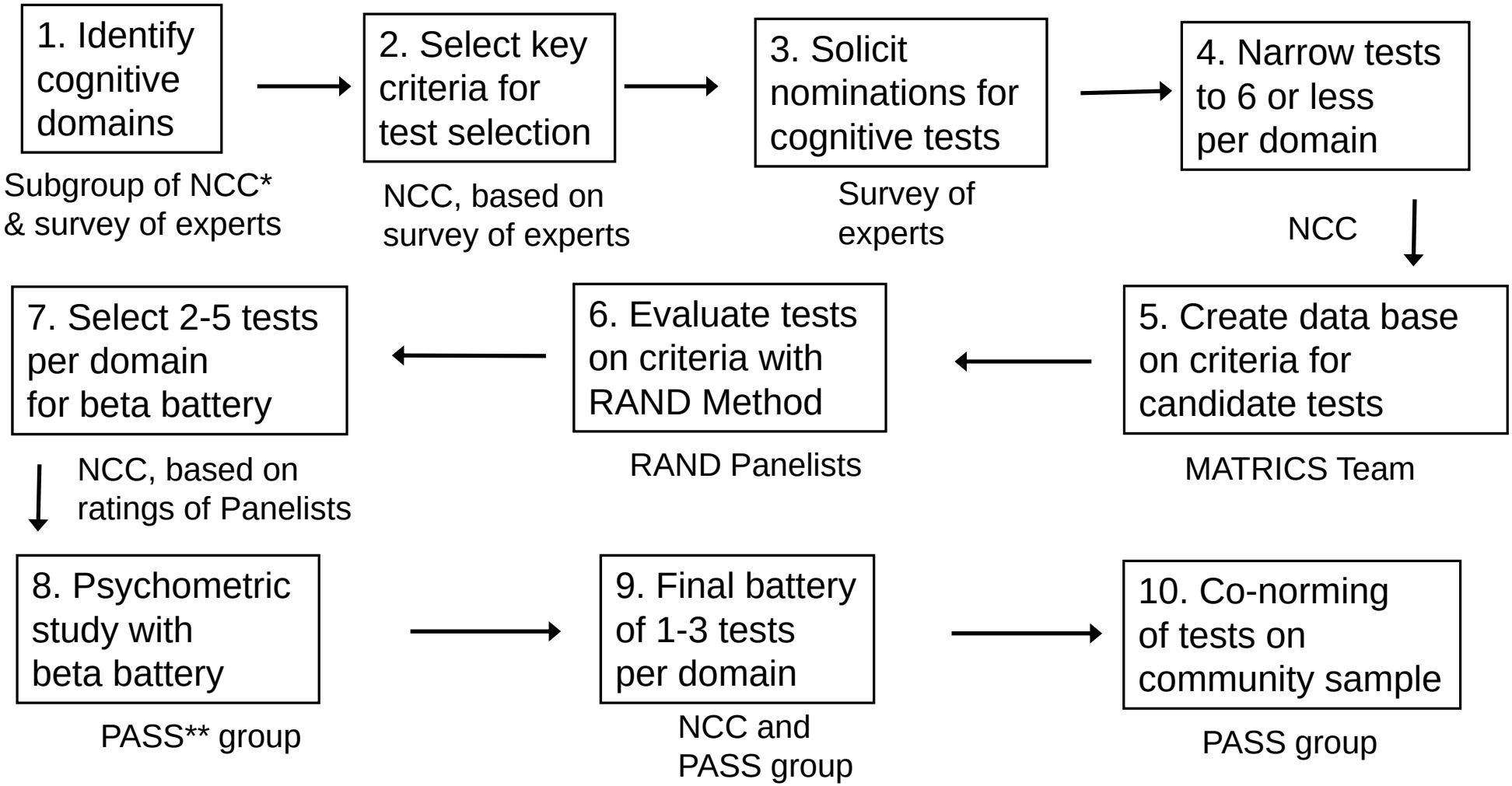


From Heaton et al. (1994)

MATRICS
Principles for Developing Consensus

- Consensus should be as broad as possible
- Transparency of process
- Inclusion of academia, NIMH, industry, FDA, consumer representatives
- *A priori* development of a path to consensus (e.g., RAND Panel, a modified Delphi process)
- Management of conflicts of interest

Steps to MATRICS Consensus Cognitive Battery



*NCC: MATRICS Neurocognition Committee
**PASS: MATRICS Psychometric and Standardization Study

MATRICS Consensus Cognitive Battery

Estimated administration time – 63.5 min

Speed of Processing
- Category Fluency
- BACS Symbol Coding
- Trial Making A

Attention / Vigilance
- Continuous Performance Test
- Identical Pairs version

Working Memory
- Maryland Letter Number Span
- WMS Spatial Span

Verbal Learning
- Hopkins Verbal Learning Test

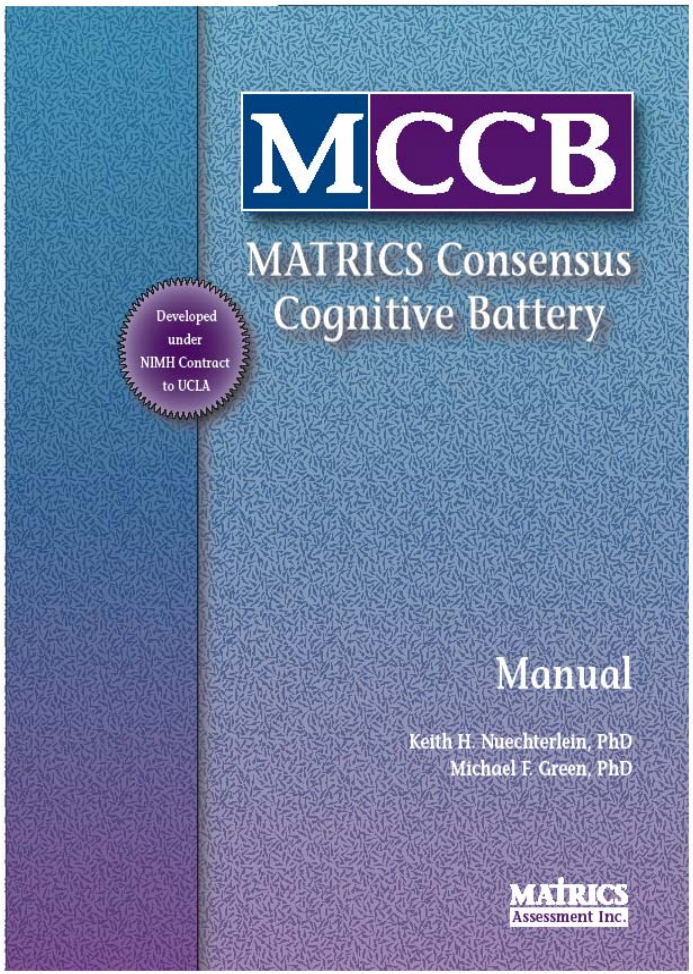
Visual Learning
- Brief Visuospatial Memory Test

Reasoning and Problem Solving
- NAB Mazes

Social Cognition
- MSCEIT Managing Emotions

MATRICS

MATRICS Consensus Cognitive Battery (MCCB)

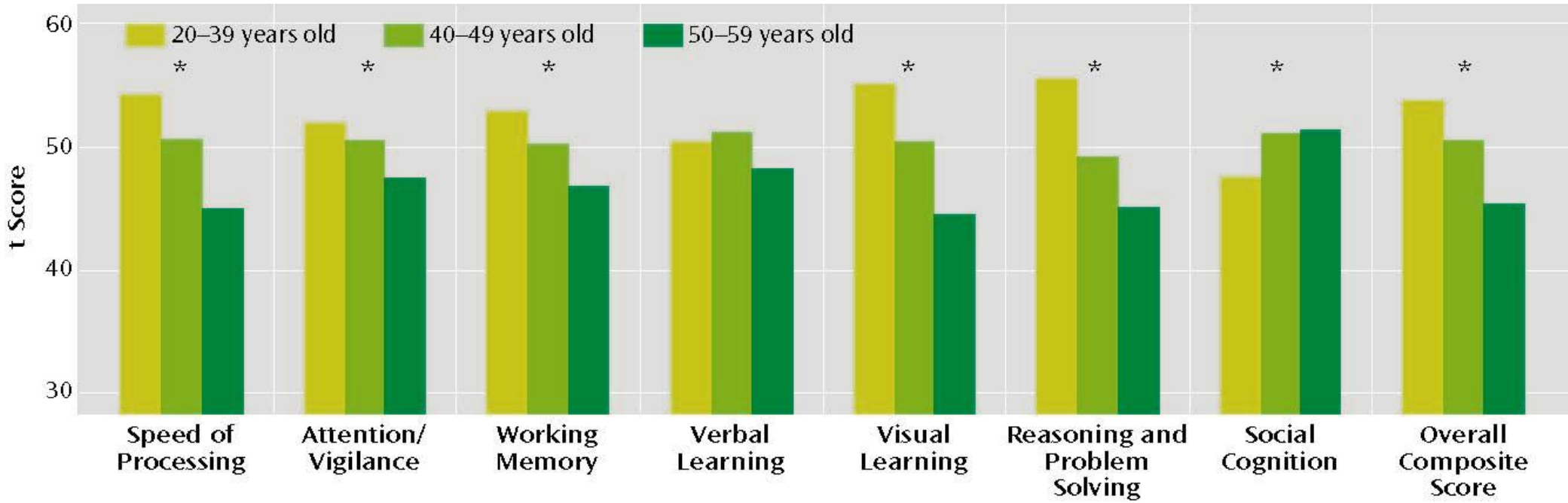


Distributed by:

- Pearson - Harcourt Assessment, Inc
- Multi-Health Systems (MHS)
- Psychological Assessment Resources (PAR)

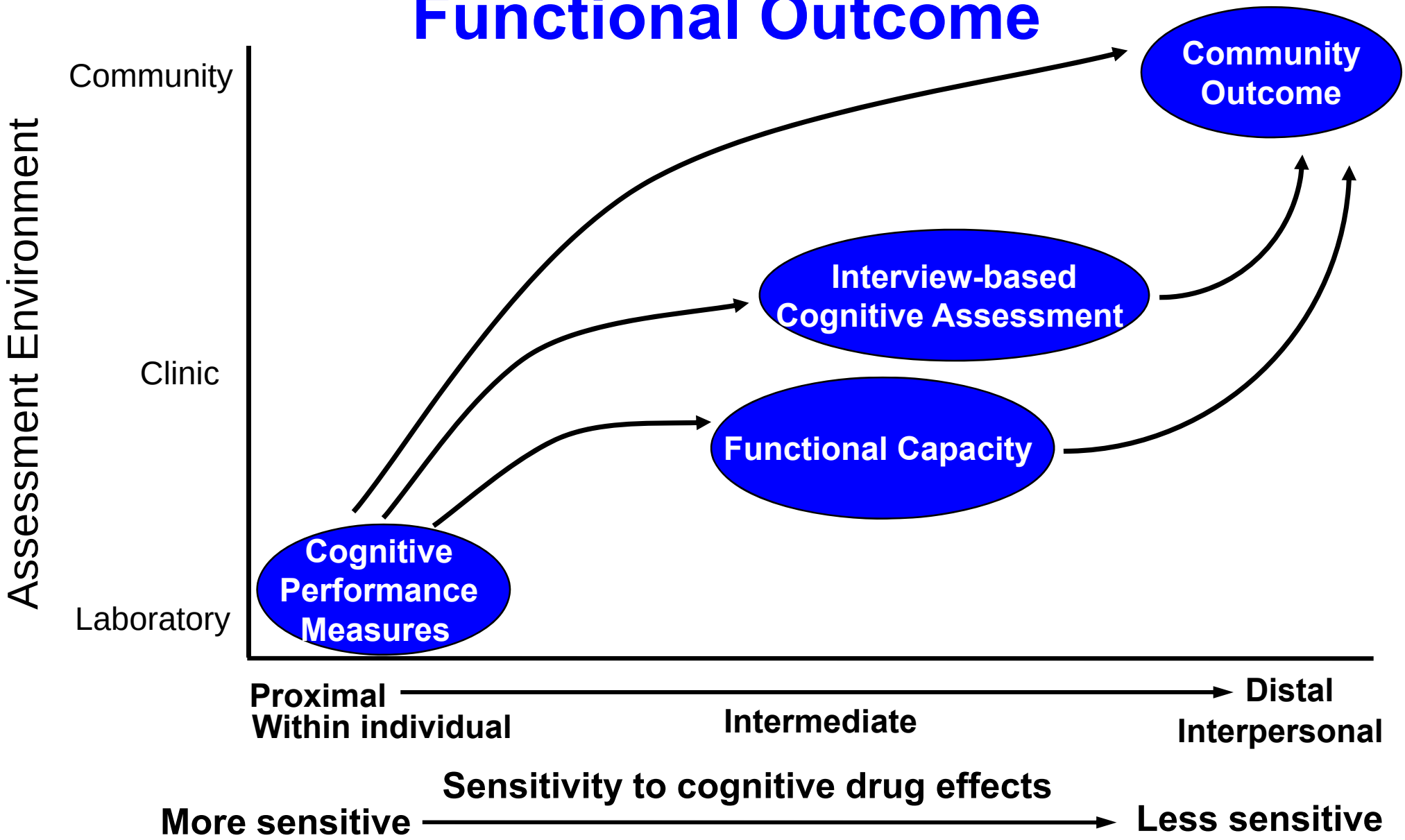
MATRICS Assessment Inc.

Norms from MATRICS-Psychometric and Standardization Study (PASS)



Kern et al. *Am J. Psychiat*. 2008

Key Linkages for Cognition and Functional Outcome



Follow up Activities to MATRICS

1) TURNS: NIMH Sponsored: Clinical trials network for cognition enhancing drugs;

- TENETS Network (Treatment and Evaluation Network for Trials in Schizophrenia)

2) Negative Symptoms Initiative

- New negative symptom scale

3) CNTRICS: NIMH Initiative for cognitive neuroscience measures in clinical trials

4) MATRICS-CT: Translation and Co-primary: Industry / Academic Consortium

- Translation and co-norming of MCCB into other languages for international trials
- Evaluation of co-primary measures

NIMH-TURNS / TENETS
Ongoing Clinical Trials

1. Merck (MK-0777)
- 4-week trial
- $GABA_A$ (α2, α3) partial agonist

2. Allon (AL-108)
- 8-week trial
- 8 amino acid peptide fragment
- promotes assembly of microtubles
- potentially neuroprotective

3. Novartis (AQW051)
- single dose cross-over study
- 2-week parallel group study
- α7 nicotinic agonist

TURNS
Treatment Units for Research on Neurocognition in Schizophrenia

- Identify set of cognitive systems and component processes as targets for treatment development in schizophrenia.
- Delineate psychometric and pragmatic issues relevant to the development of tasks that measure these cognitive systems.
- Develop specific measures of target cognitive processes that can be implemented as behavioral tasks, as well as non-invasive functional neuroimaging studies.

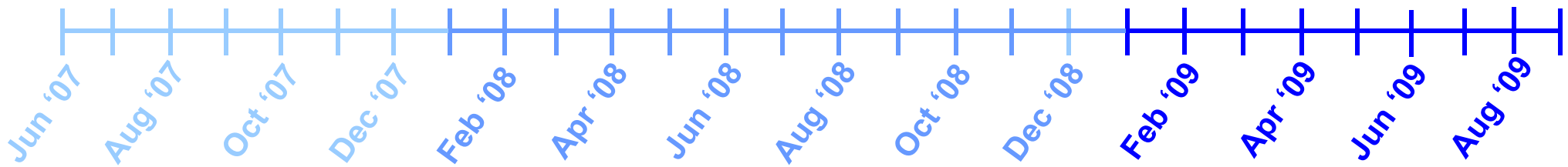
MATRICS-CT Scientific Board

Representation by:

- **NIMH**
- **NIH Foundation**
- **Academia**
- **Consumer Perspective**
- **Pharmaceutical Industry**

  AstraZeneca
  Bristol-Myers Squibb
  Eli Lilly
  GlaxoSmithKline
  Lundbeck
  Johnson & Johnson
  Pfizer
  Merck
  Roche,
  Sanofi-Aventis
  Wyeth

MATRICS – CT
Translation of the MCCB



- Obtain Legal Permission, Licensing
- Establish Procedures for MCCB Academic Translations
- Forward / Backward Translations for MATRICS-CT Languages
- Test Owner Review and Approval
- Final Reconciliation, Cultural Adaptation
- Page composition, Printing of MCCB Translated Components
- Collection of Norms

1st Tier Languages: Chinese, German, Hindi, Russian, Spanish (plus dialects for South and Central America)

Validation of Intermediate Measures (VIM) Study: Key Dependent Measures

Performance-based measures

1. Test of Adaptive Behavior in Schizophrenia (TABS)
2. UCSD Performance-based Skills Assessment (UPSA)
3. Independent Living Scales (ILS)

Each of these performance-based assessments will be administered so that short forms can be compared with long forms.

Interview-based measures

1. Semi-structured: Cognitive Assessment Interview (CAI)
2. Global assessment (1-100 pt scale): Global Assessment of Function from CAI
3. Clinical impression (1-7 pt scale): CGI for Cognitive Impairment

What we did not anticipate in MATRICS

- Role of co-primary (intermediate) measures
- Importance of norms
- Intellectual property issues for tests selected for MCCB
- Challenges for inclusion of tests from cognitive neuroscience
- Limits of an English-only battery