Experience from Multi-Site Clinical Trials on Neurocognition Versus Global Cognition Endpoints

Keith H. Nuechterlein, Ph.D.
Professor, UCLA Departments of Psychiatry and Psychology
Semel Institute for Neuroscience and Human Behavior

Disclosures

Research grant support:

- Janssen Scientific Affairs
- Genentech
- Brain Plasticity, Inc.

Consultant:

- Genentech

Officer in Nonprofit:

- MATRICS Assessment, Inc. (but no financial compensation)

Acknowledgement

- Thanks to Lilly, BioLineRx, and EnVivo for allowing data from their multi-site clinical trials to be used in examples for this presentation.
- Thanks to Vicki Davis and Richard Keefe at NeuroCog Trials, Inc., for their essential aid in data analyses

Outline of Presentation

1. Development of a Neurocognitive Composite Score for the MATRICS Consensus Cognitive Battery (MCCB)
2. Psychometric characteristics of the new Neurocognitive Composite Score
3. Initial experience with pharmacological effects on Neurocognitive Composite vs. Overall Cognitive Composite
4. Example of effects on MCCB Social Cognition vs. MCCB Neurocognitive Composite

MATRICS Consensus Cognitive Battery (MCCB)

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

Attention / Vigilance
- Continuous Performance Test
  - Identical Pairs version

Working Memory
- Letter-Number Span
- WMS-III Spatial Span

Verbal Learning
- Hopkins Verbal Learning Test-R

Visual Learning
- Brief Visuospatial Memory Test-R

Reasoning and Problem Solving
- NAB Mazes

Social Cognition
- MSCEIT Managing Emotions

Nuechterlein & Green, 2006; Nuechterlein et al., 2008

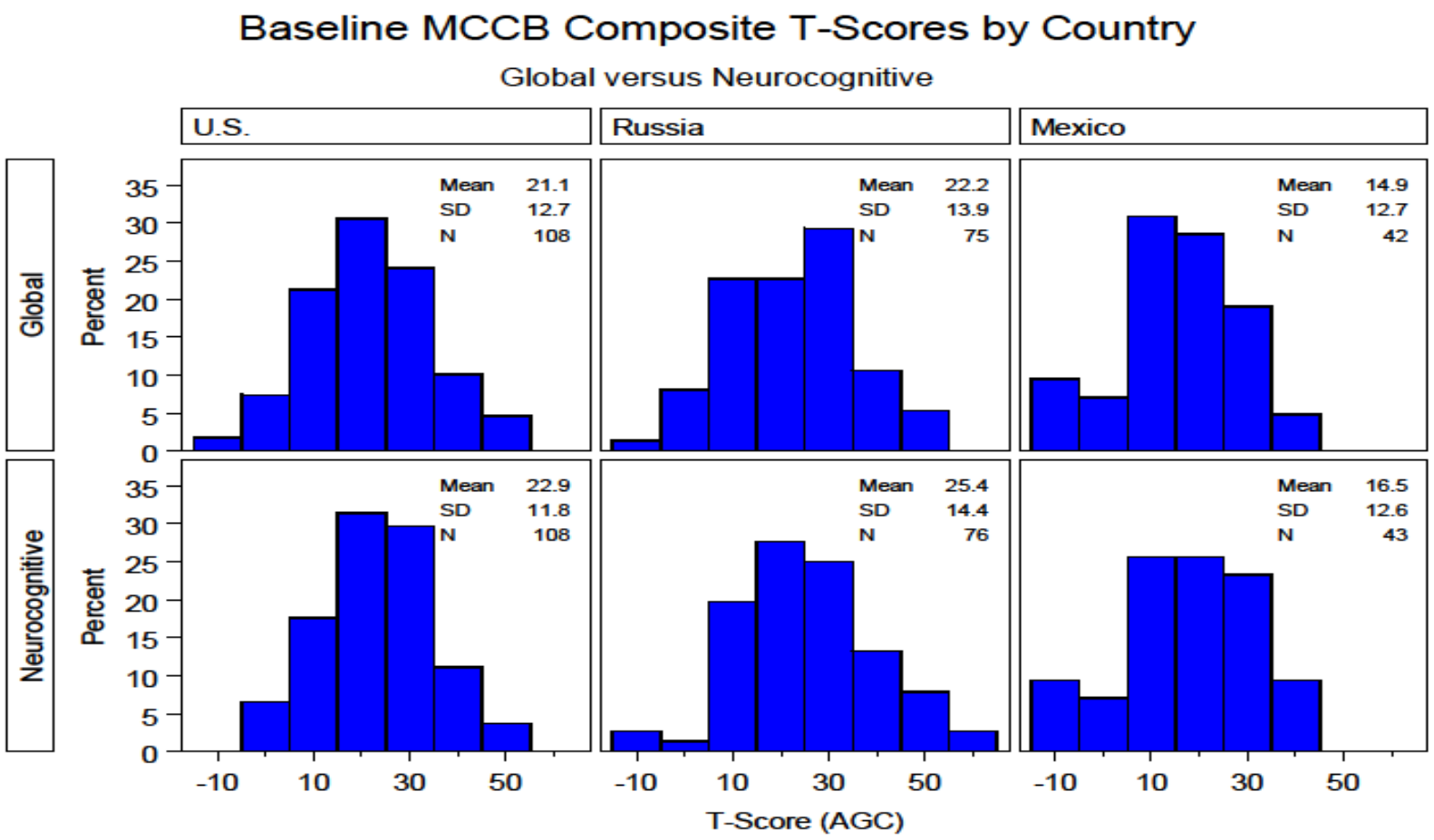
Development of a Neurocognitive Composite Score

- Increasing evidence that social cognition and neurocognition (non-social cognition) are related but separable aspects of cognitive functioning
- Therefore, desirable to consider a Neurocognitive Composite Score as an alternative to an Overall Cognitive Composite Score as an endpoint
- A MCCB Neurocognitive Composite Score was developed to reflect performance across the 6 neurocognitive domains

The derivation of a new Neurocognitive Composite Score was endorsed by the MATRICS Neurocognition Committee

- Keith Nuechterlein (UCLA) - Co-Chair
- Michael Green (UCLA) - Co-Chair
- Deanna Barch (Washington University)
- Jonathan Cohen (Princeton University)
- Susan Essock (Mt. Sinai School of Medicine)
- Wayne Fenton (NIMH)
- Fred Frese (Summit County Recovery Project)
- Jim Gold (Maryland Psychiatric Research Center)
- Terry Goldberg (NIMH)
- Robert Heaton (UCSD)
- Richard Keefe (Duke University)
- Helena Kraemer (Stanford University)
- Daniel Weinberger (NIMH)
- Steve Zalcman (NIMH)

Normality of Distributions for Overall Global Composite vs. Neurocognitive Composite



Test-Retest Stability: Baseline to 6 weeks

Composite Measure	n	ICC
US -- Neurocognitive Composite	69	.74
US – Overall Composite	69	.77
Russia – Neurocognitive Composite	51	.80
Russia – Overall Composite	51	.80
Mexico – Neurocognitive Composite	32	.68
Mexico – Overall Composite	31	.75

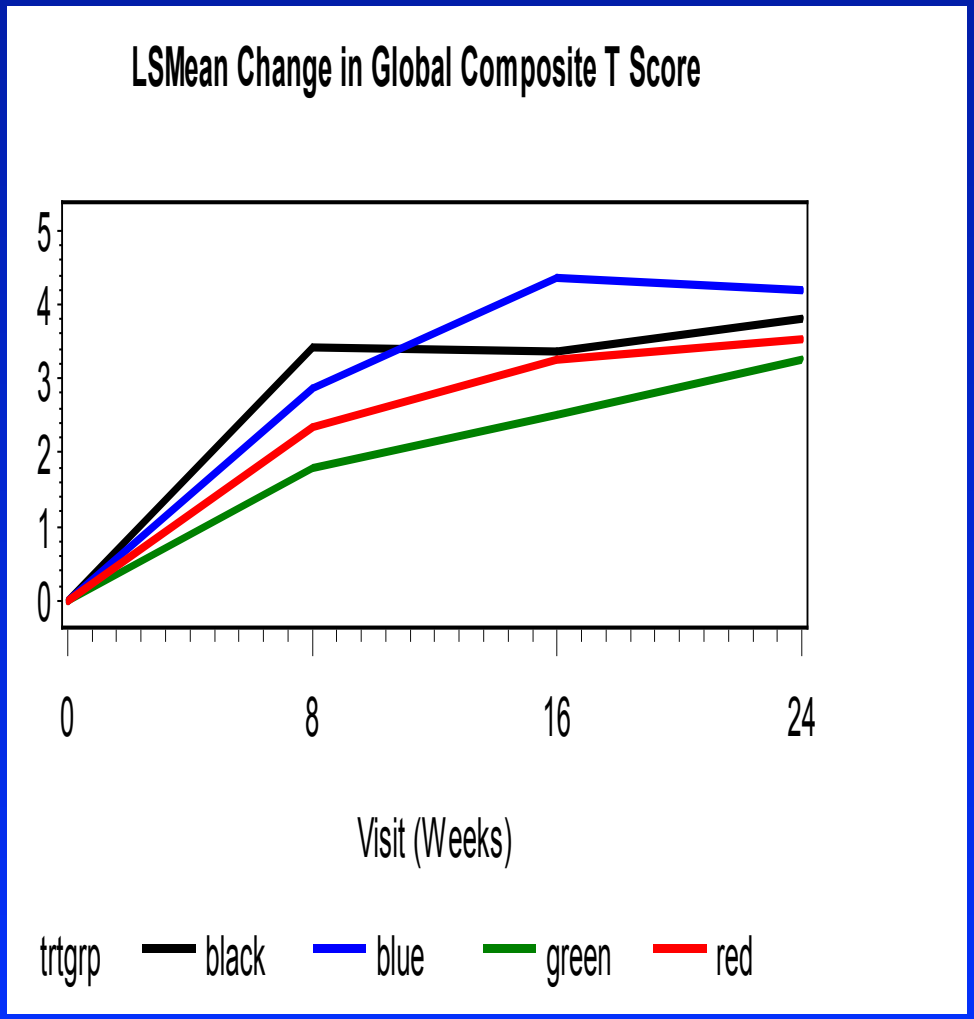
Test-Retest Reliability over Repeated Assessments in a Placebo Group

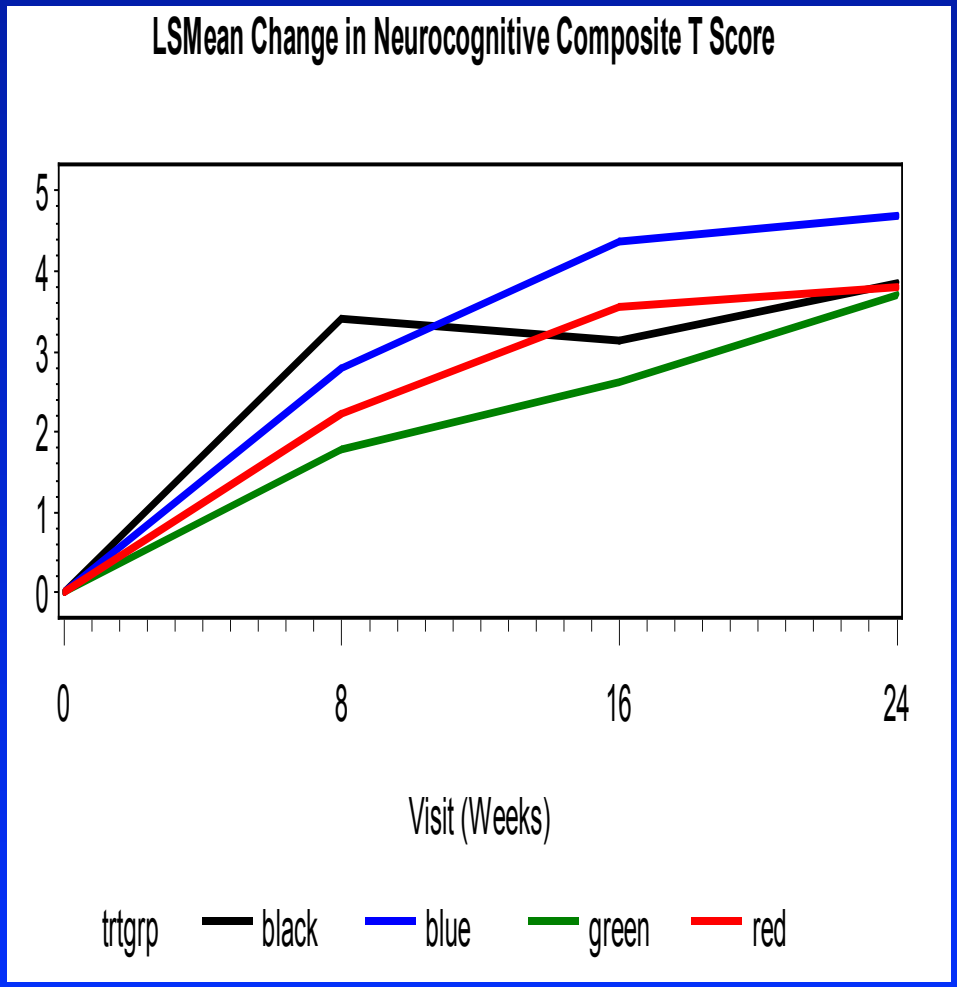
MCCB Domains and Composites	ICC Between Baseline and Follow-up		
	Week 8 (N=111)	**Week 16 (N=93)**	**Week 24 (N=86)**
Speed of Processing	0.81	0.73	0.69
Attention Vigilance	0.79	0.78	0.70
Working Memory	0.80	0.77	0.76
Verbal Learning	0.57	0.53	0.61
Visual Learning	0.63	0.55	0.56
Reasoning / Problem Solving	0.68	0.57	0.46
Social Cognition	0.82	0.72	0.76
Overall Composite	**0.90**	**0.86**	**0.86**
Neurocognitive Composite	**0.89**	**0.84**	**0.82**

Correlations of 8-week Social Cognition (MSCEIT ME) Change with Change in Neurocognitive Composite Score: Example of Separable Changes

MCCB Composite Score	Treatment = Black (N=112)	Treatment = Blue (N=112)	Treatment = Green (N=112)	Treatment = Red (N=111)
Overall Composite	0.36*	0.50*	0.45*	0.41*
Neurocogni-tive Composite	-0.05	0.10	0.09	0.04

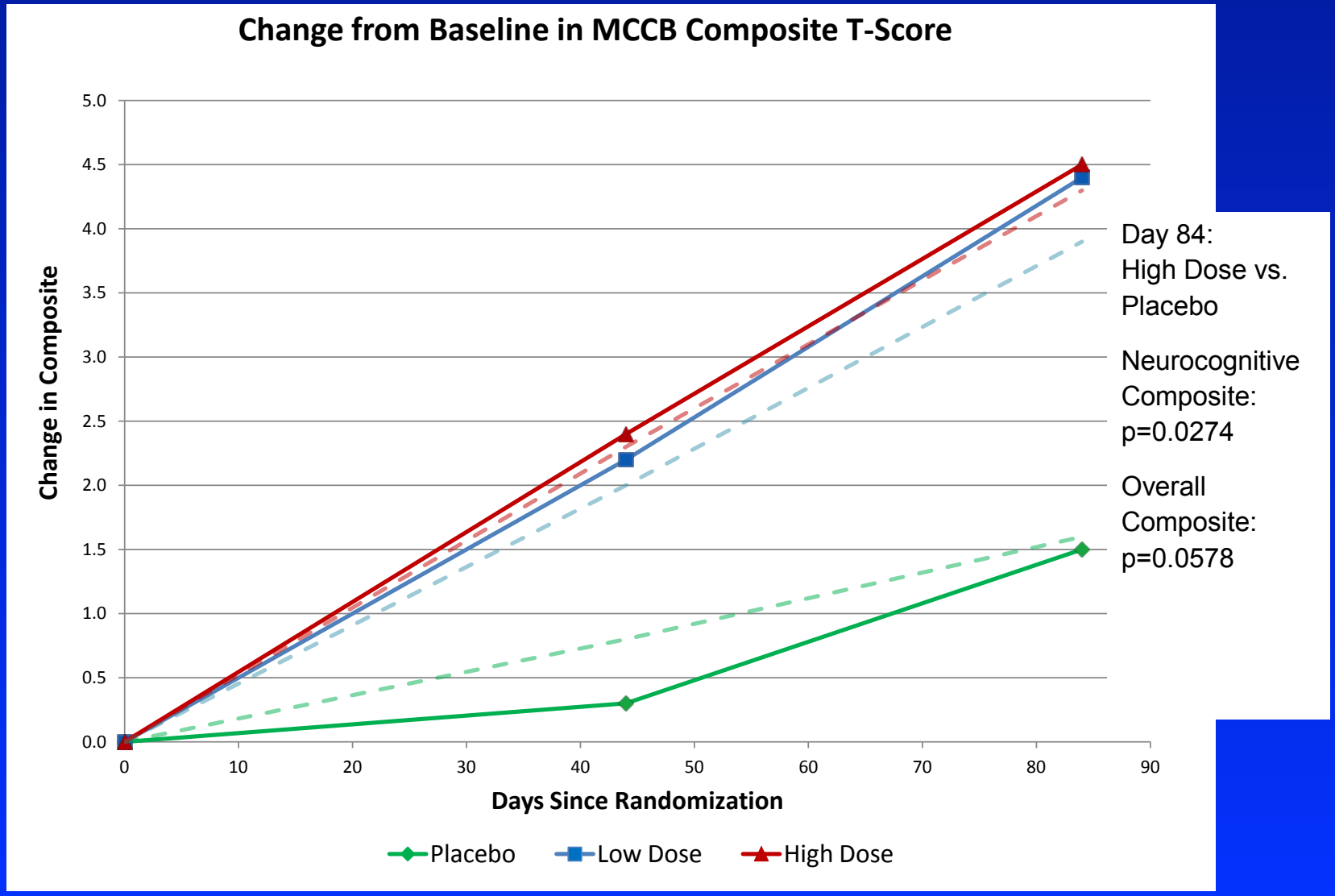
Example of Similar Treatment Group Effects for Overall Global Composite and Neurocognitive Composite Scores



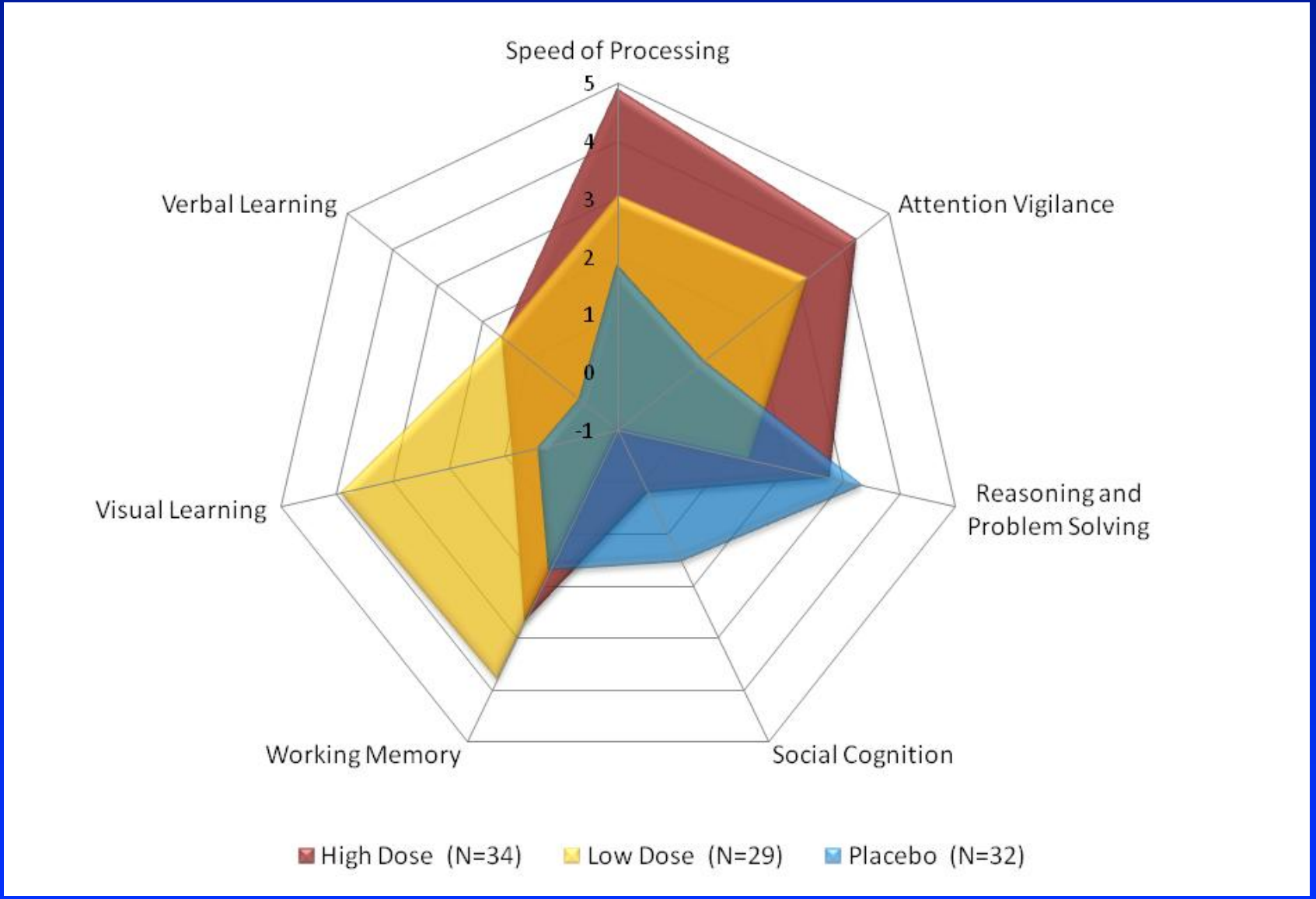


Example of Improved Sensitivity to Signal Using Neurocognitive Composite Score

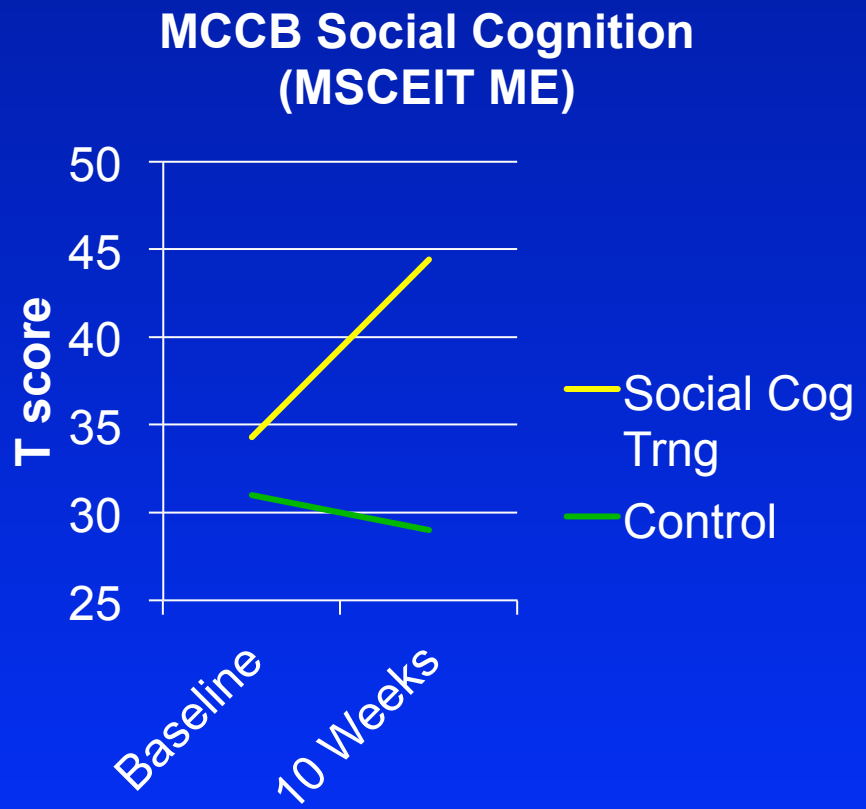
Solid lines = Neurocognitive Composite; Dashed lines = Overall Composite

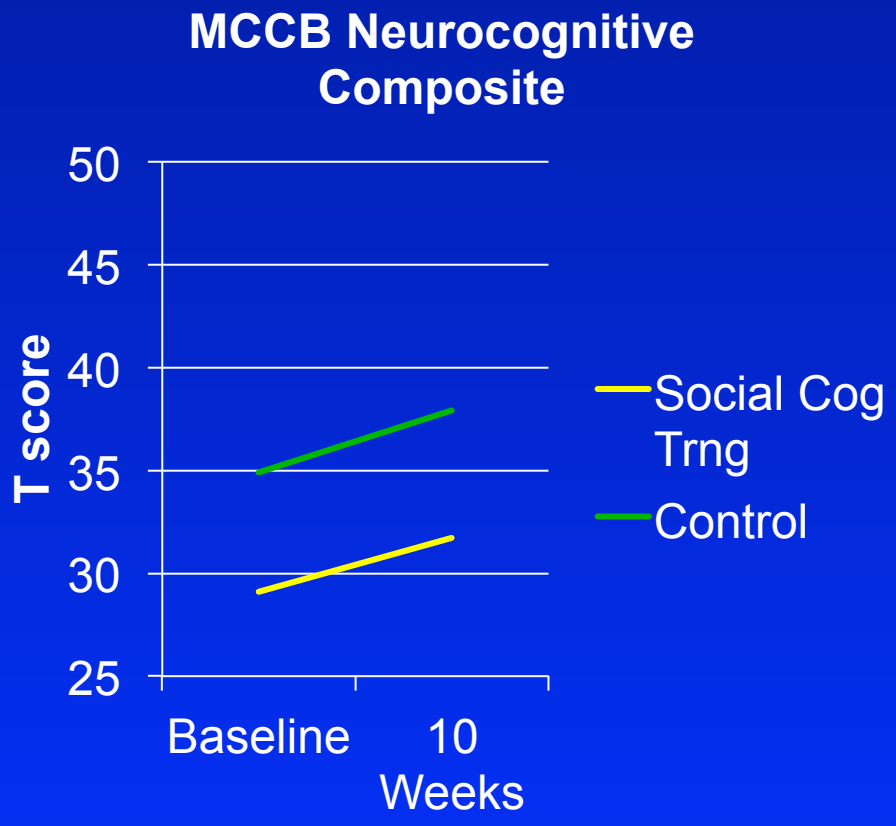


MCCB Domain Changes at Day 84 Show Why Neurocognitive Composite Has Improved Sensitivity to Signal



Example of Differential MCCB Social Cognition Change Relative to MCCB Neurocognitive Composite Change





Pilot study of computerized social cognitive training, n = 15

Summary

1. In response to evidence that neurocognition and social cognition are separable constructs, a new Neurocognitive Composite Score was developed for the MATRICS Consensus Cognitive Battery.

2. The Neurocognitive Composite Score is normally distributed, has high test-retest reliability, and shows changes over time that are separable from MCCB Social Cognition changes.

Summary

3. Initial pharmacological applications indicate that the Neurocognitive Composite may for some drugs be more sensitive to signal than the Overall Composite.

4. An example from a social cognitive training pilot study suggests that some interventions can improve MCCB Social Cognition without impacting the MCCB Neurocognitive Composite.

5. Cognitive endpoint selection should include consideration of whether an intervention targets overall cognition, neurocognition, or social cognition.