

Real-world Application of the MATRICS Consensus Cognitive Battery (MCCB) in Multisite Clinical Trials

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Outline

- ◆ Negative studies
 - Is the cognitive outcome the culprit?
- ◆ Characteristics of cognitive test batteries for schizophrenia cognition trials
 - Potential differences between phase 2 and 3 trials
 - Implementation difficulties
 - Too long to complete?
 - Much missing data?
 - Sensitivity to cognitive impairment
 - Ceiling and floor effects – are they real risks
 - Test-retest reliability
 - Number one in MATRICS survey
 - Practice effects
 - Mis- and Disinformation
 - Relation to other co-primary measures
 - Most important: Sensitivity to treatment effects
 - Absence of 'active comparator'
 - D-serine data
 - Cognitive remediation

Evaluation Criteria

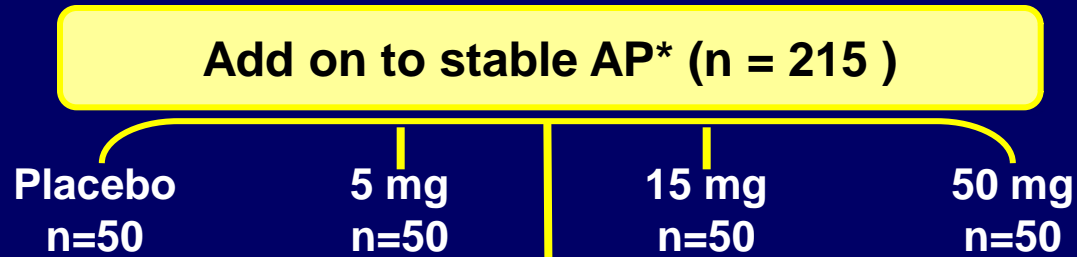
1. Implementation
2. Sensitivity
3. Reliability
4. Practice
5. Relation to co-primaries
6. Sensitivity to treatment effects

Overview of Trials with Available Psychometric Data

- ◆ **R3487/MEM3454; N=215**
 - *alpha7 partial agonist 8-week study*
 - MCCB at screening, baseline, weeks 4, 8, 10
- ◆ **DSP lurasidone versus risperidone; N=323**
 - MCCB at screening, baseline,
- ◆ **2 TURNS trials**
 - **MK-0777; N=60**
 - MCCB at baseline and week 4
 - Cognitive Neuroscience measures of specific domains
 - **AL-108; N=59**
 - MCCB at baseline, week 6, week 12
- ◆ **Sanofi-Aventis AVE 1625 CONNECT trial; N=477**
 - MCCB at baseline, weeks 12, 26, 52

CIAS POC Study Overview:

R3487/MEM3454 alpha7 partial agonist 8-week study



**Primary Efficacy variable:
Cognition (MATRICS Composite Score)**

**Secondary Efficacy variables:
Negative Symptoms (PANSS, NSA); Depressive Symptoms (MADRS)
Function (UPSA, PSP); Cognitive Domains (MATRICS Domain Scores)**

	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 8	Wk 10
MATRICS	X	X			X	X	X
WMS III Paired Associates (Immediate & Delayed Recall)		X			X	X	X
UPSA-2		X				X	X
PSP		X			X	X	X
PANSS	X	X	X	X	X	X	X
NSA		X	X	X	X	X	X
MADRS		X	X	X	X	X	X

*Antipsychotics included: risperidone, paliperidone, aripiprazole
Umbricht, et al, 2009.

Smokers: Non Smokers 3:1

MCCB in Schizophrenia Clinical Trials: *Baseline Characteristics*

Characteristic	Lurasidone v. Risperidone (N=323)	R3487/MEM34 54 (N=215)
Age, mean (SD)	43.1 years (10.4)	39.6 years (9.0)
Men	72%	72%
Race		
White	31%	32%
African American	64%	54%
Other	5%	13%
PANSS Total Score Mean (SD)	67.5 (11.7)	57.0 (10.3)
UPSA-B Total Score Mean (SD), N=308	70 (16.2)	85 (15)
MCCB Composite T-Score, Mean (SD), N=321	26.9 (12.4)	27.6 (12.1)

TURN S MK-0777 Trial

	Placebo N=21	MK-0777, 3 mg. B.I.D. (N=18)	MK-0777, 8 mg B.I.D. (N=21)
	Mean \pm S.D.	Mean \pm S.D.	Mean \pm S.D.
Age, yrs.	40.0 (10.9)	43.3 (9.3)	44.9 (8.7)
Education, yrs.	12.2 (2.5)	13.3 (3.0)	14.2 (2.4)
Gender (male)	77.3%	61.1%	61.9%
Race (white)	45.4%	50.0%	42.9%
WTAR reading score	29.2 (10.3)	27.1 (12.0)	29.7 (14.0)
MCCB composite score	30.1 (13.1)	31.0 (12.6)	27.8 (12.2)
BPRS total score	26.8 (6.4)	28.9 (5.2)	29.8 (6.2)
BPRS positive symptom score	7.0 (3.5)	7.6 (2.8)	6.8 (2.1)
SANS total score	18.6 (11.5)	17.8 (10.5)	20.6 (14.7)
Calgary total score	1.6 (11.5)	2.1 (2.4)	2.0 (2.1)
Simpson-Angus total score	1.1 (1.5)	0.8 (1.2)	1.4 (1.6)

TURNNS Allon-108 trial

	Placebo (N=20)		AL-108 5 mg (N=19)		AL-108 30 mg (N=19)	
	Mean	SD	Mean	SD	Mean	SD
Age, years	41.4	10.4	43.2	10.5	45.2	8.2
Education, years	12.1	2.7	12.6	2.2	12.4	2.7
Wechsler test of adult reading (WTAR) score	26.1	13.1	32.0	13.7	28.6	11.4

Evaluation Criteria

1. Implementation
2. Sensitivity
3. Reliability
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5. Relation to co-primaries
6. Sensitivity to treatment effects

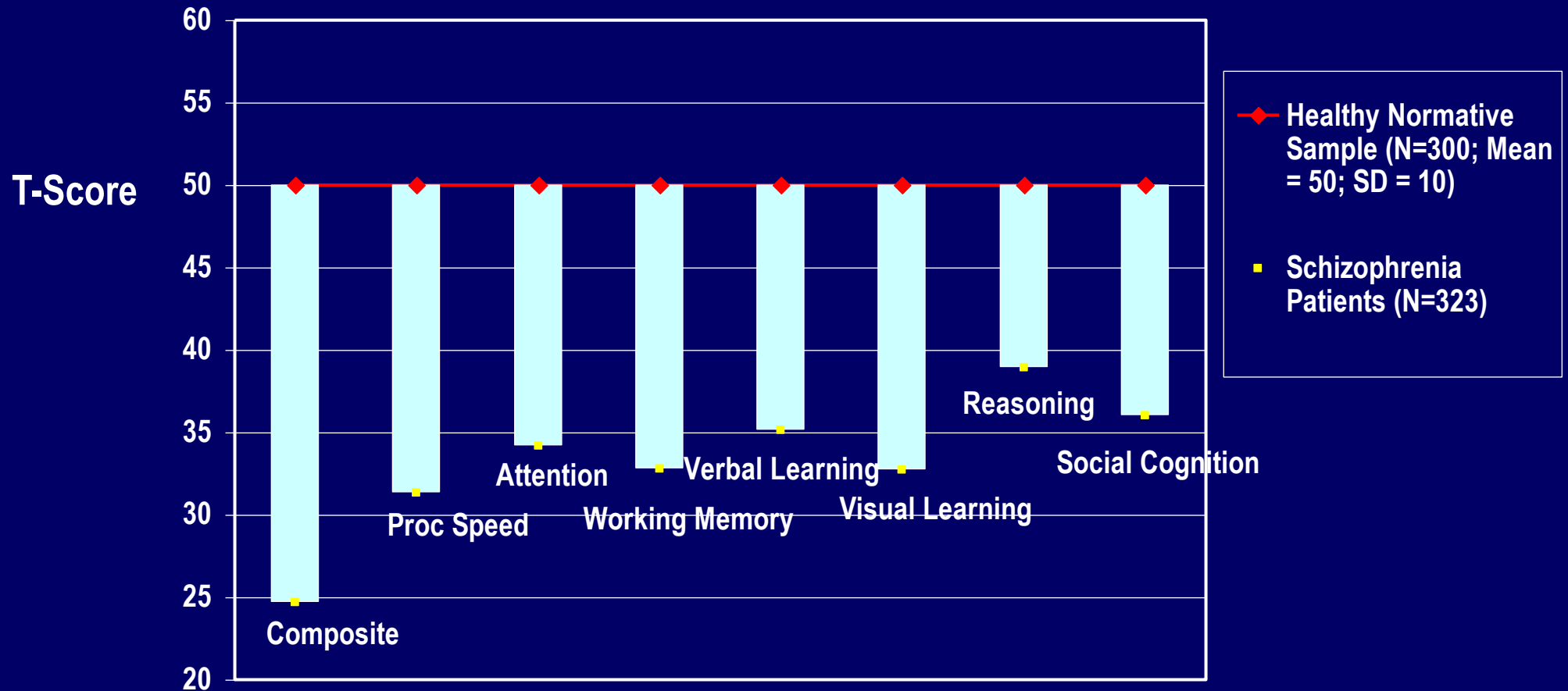
MCCB Test Scores: Missing Data Rate

<u>Variable</u>	<u>Memory/Roche</u> <u>N=215</u>	<u>DSP</u> <u>N=323</u>
Total number of invalid MCCB tests at screening and baseline	14/4300 (0.03%) N=4300 (=215X10x2)	16/6460 (0.02%) N=6460 (=323x10x2)
Subjects with complete MCCB tests (excluding invalid or missing tests)		
Screening	210/215 (98%)	320/323 (99.1%)
Baseline	213/215 (99%)	321/323 (99.4%)
Screening & Baseline Scores	208/215 (97%)	318/323 (98.5%)
Subjects missing > 2 domains		
Screening	0 (0%)	1 (0.3%)
Baseline	0 (0%)	0 (0%)
Median duration between screening and baseline tests	10 days	15 days

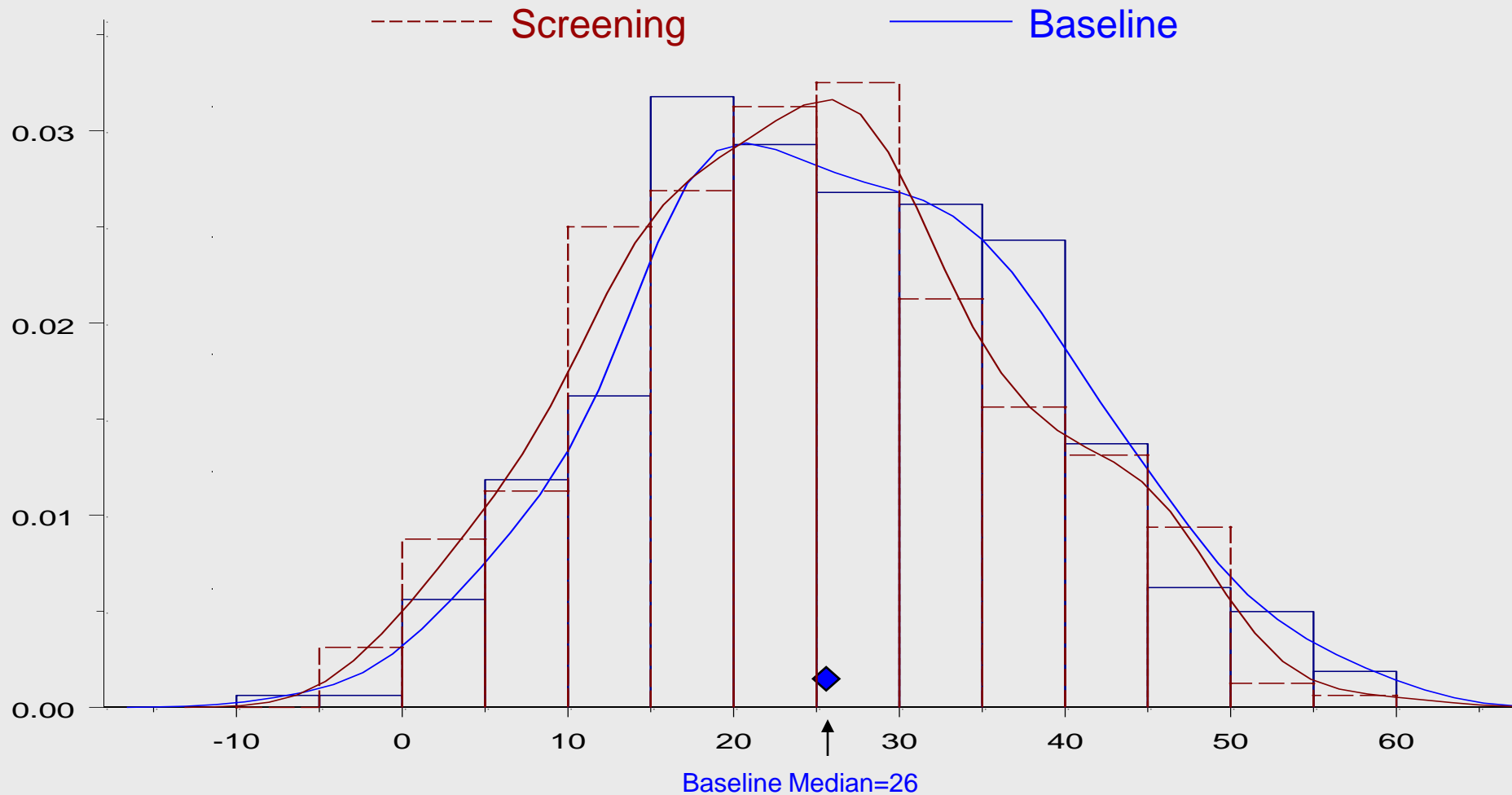
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Severity and Profile of Cognitive Impairment in Schizophrenia at Baseline of Clinical Trial

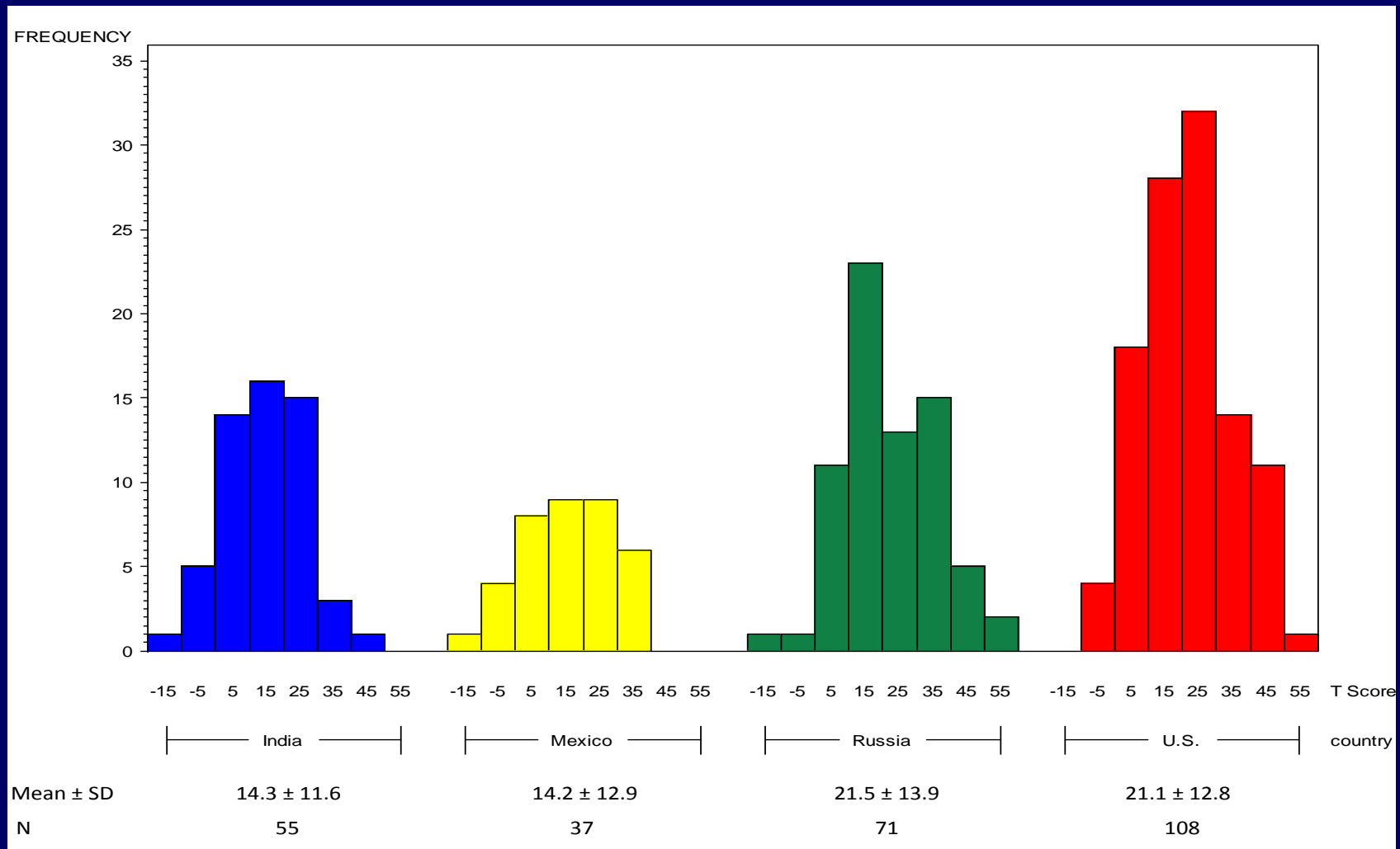


Screening and Baseline MCCB Composite T-score: Normal Density Estimate and Histogram (N=323)



Mean T-score at baseline =26.9 (SD=12.4); skewness =0.13; normality test $p>0.05$
Mean T-score at Screening =24.7 (SD=12.1). Area under the curve (histogram)=1.

Baseline MCCB Standardized Composite T Score by Country

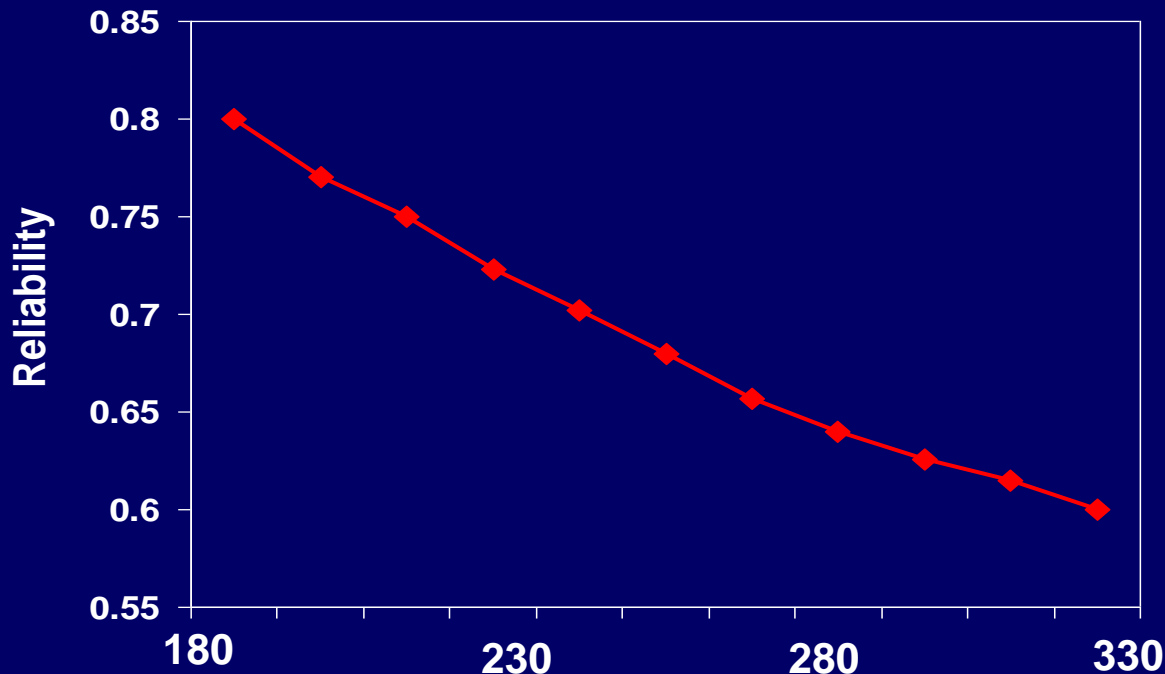


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Implications of Reduced Reliability

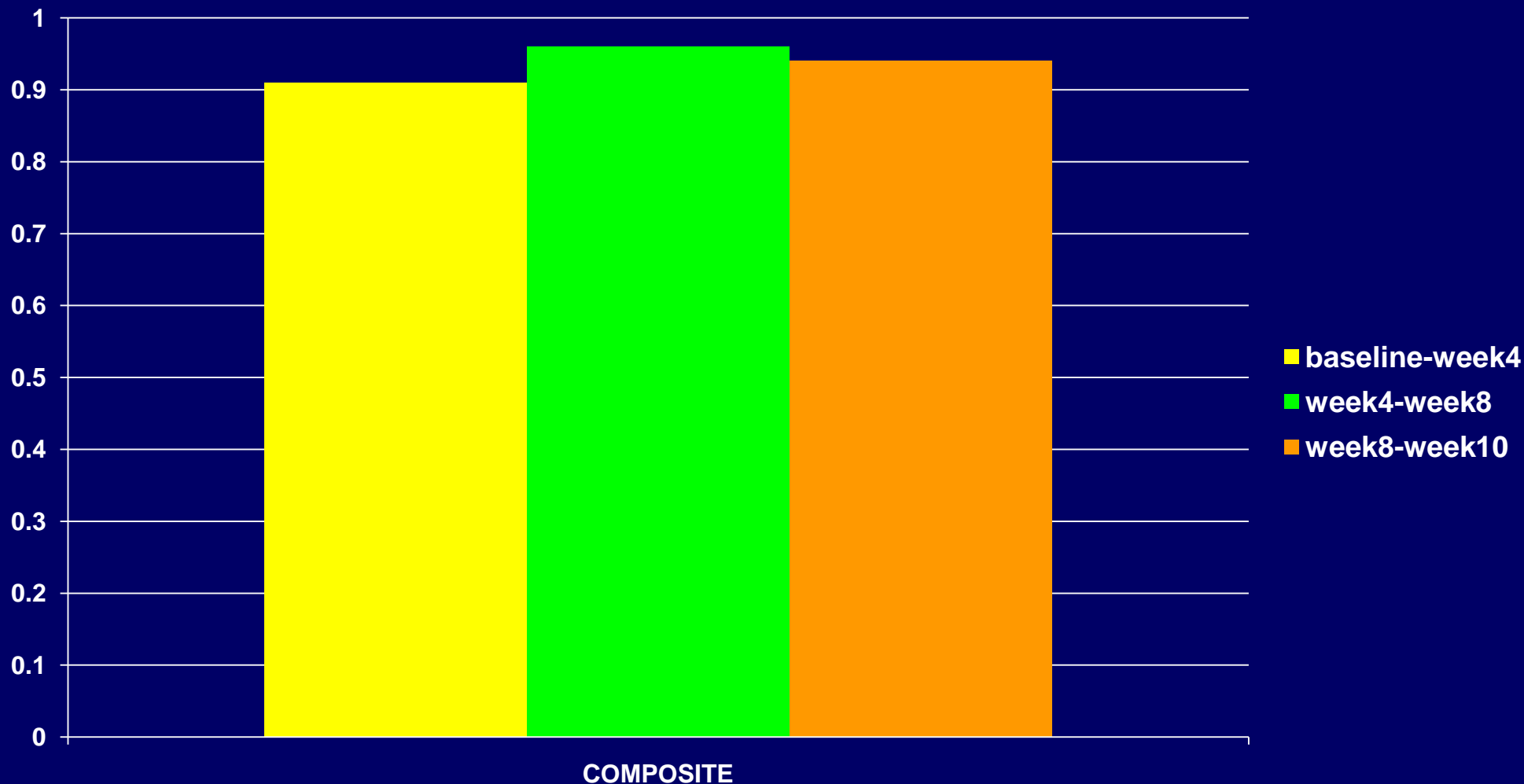
- ◆ A very simple hypothetical:
 - Effect size of $d = .5$ exists in reality between 2 groups
 - Total sample size needed to achieve power = .80, alpha = .05, 2-tailed at different levels of reliability



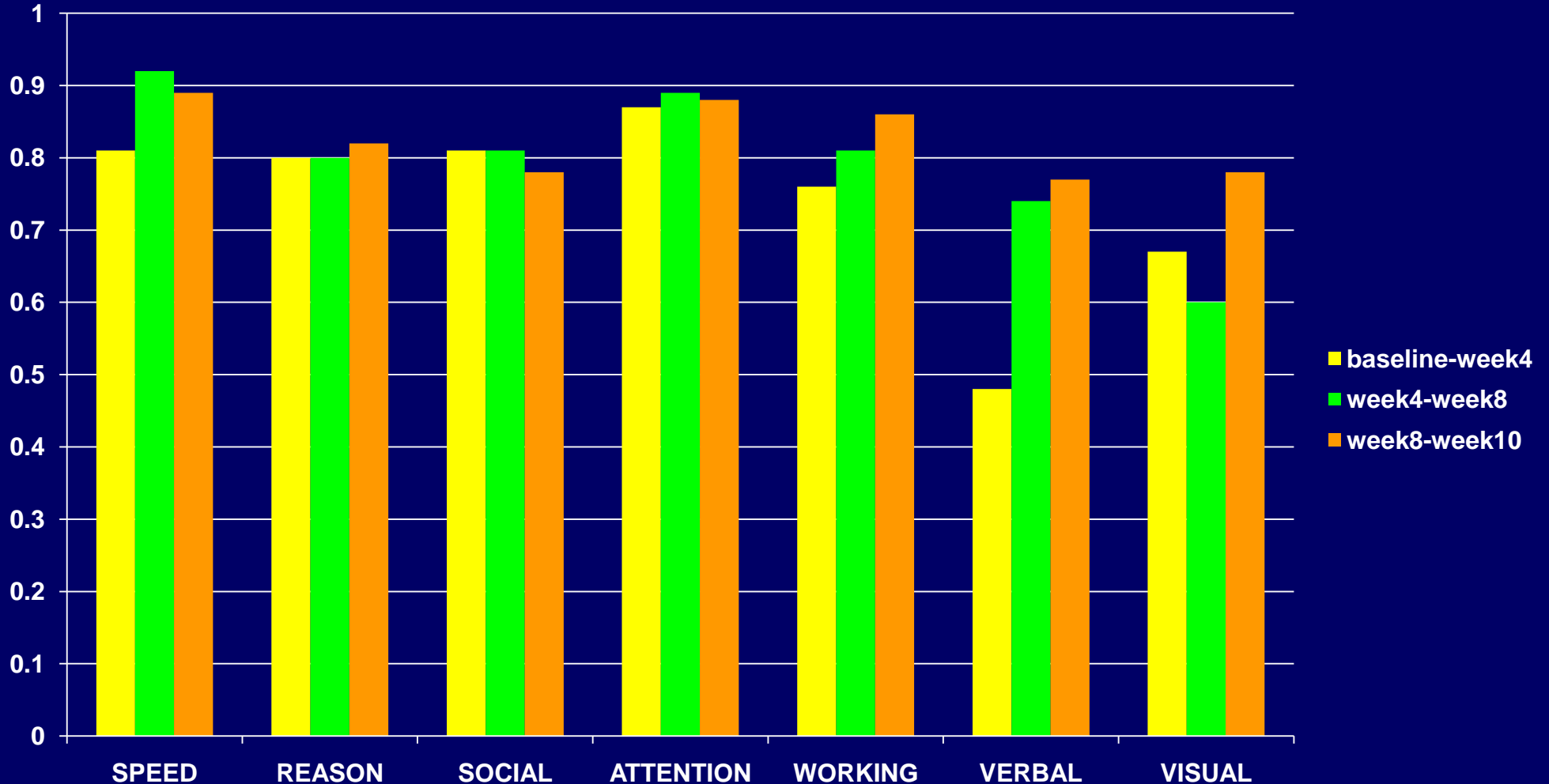
MCCB Composite T-Score Test-retest Reliability

Domain	Memory/ Roche (ICC)	Lurasidone (ICC)	MK-0777 (Pearson r)	AL-108 (ICC)
Composite T-score	0.88	0.88	0.95	0.93
Speed of processing	0.81	0.79	0.89	0.88
Attention/Vigilance	0.82	0.79	0.80	0.84
Working memory	0.81	0.79	0.90	0.85
Verbal learning	0.65	0.58	0.72	0.77
Visual learning	0.70	0.65	0.84	0.73
Reasoning/Problem solving	0.77	0.77	0.84	0.72
Social cognition	0.75	0.75	0.78	0.80

Composite ICC across Sessions in Placebo Group (N=42)



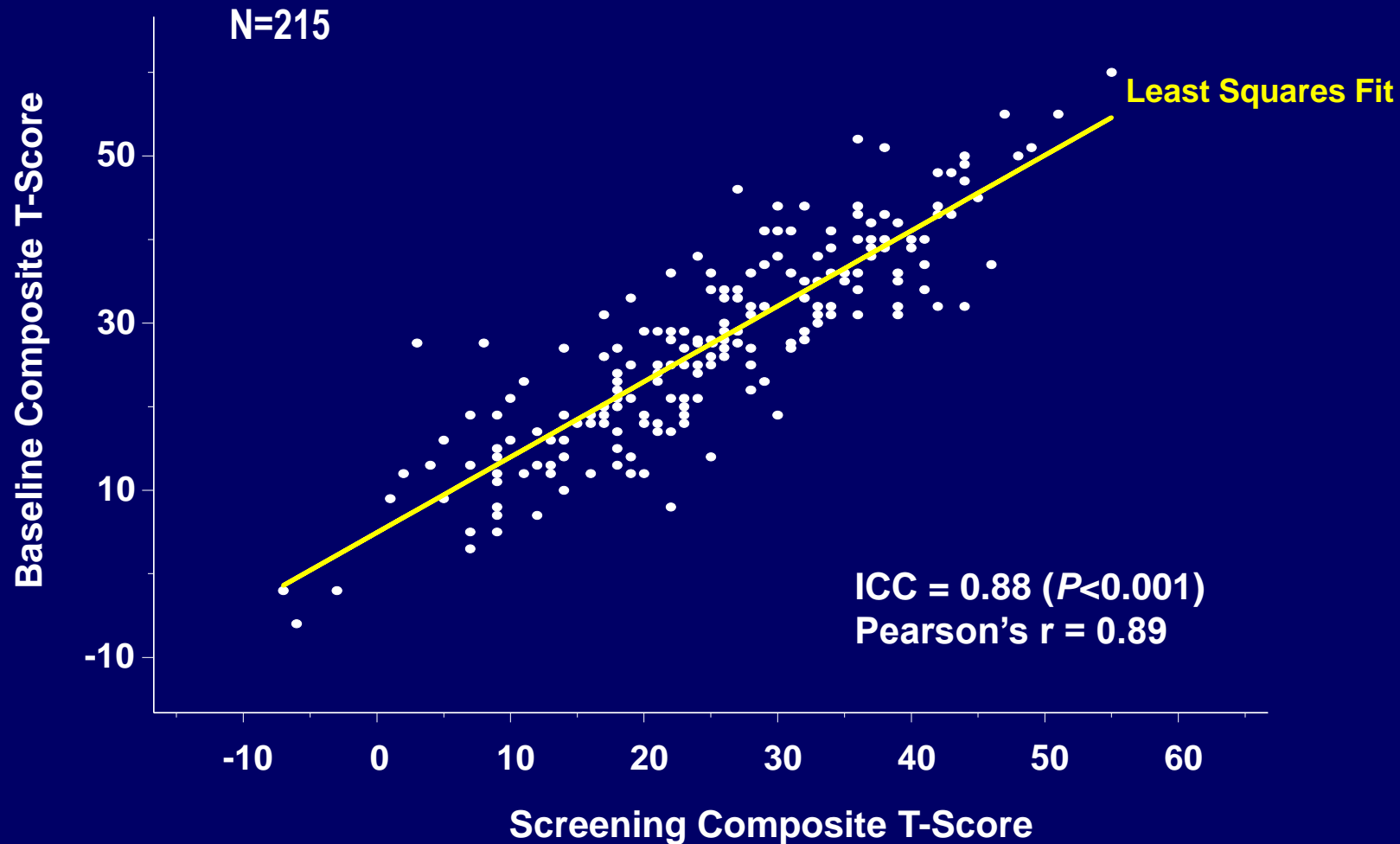
Domain ICC across Sessions in Placebo Group (N=42)



AX-CPT and N-back Reliability in TURNS MK-0777 Trial (All Patients)

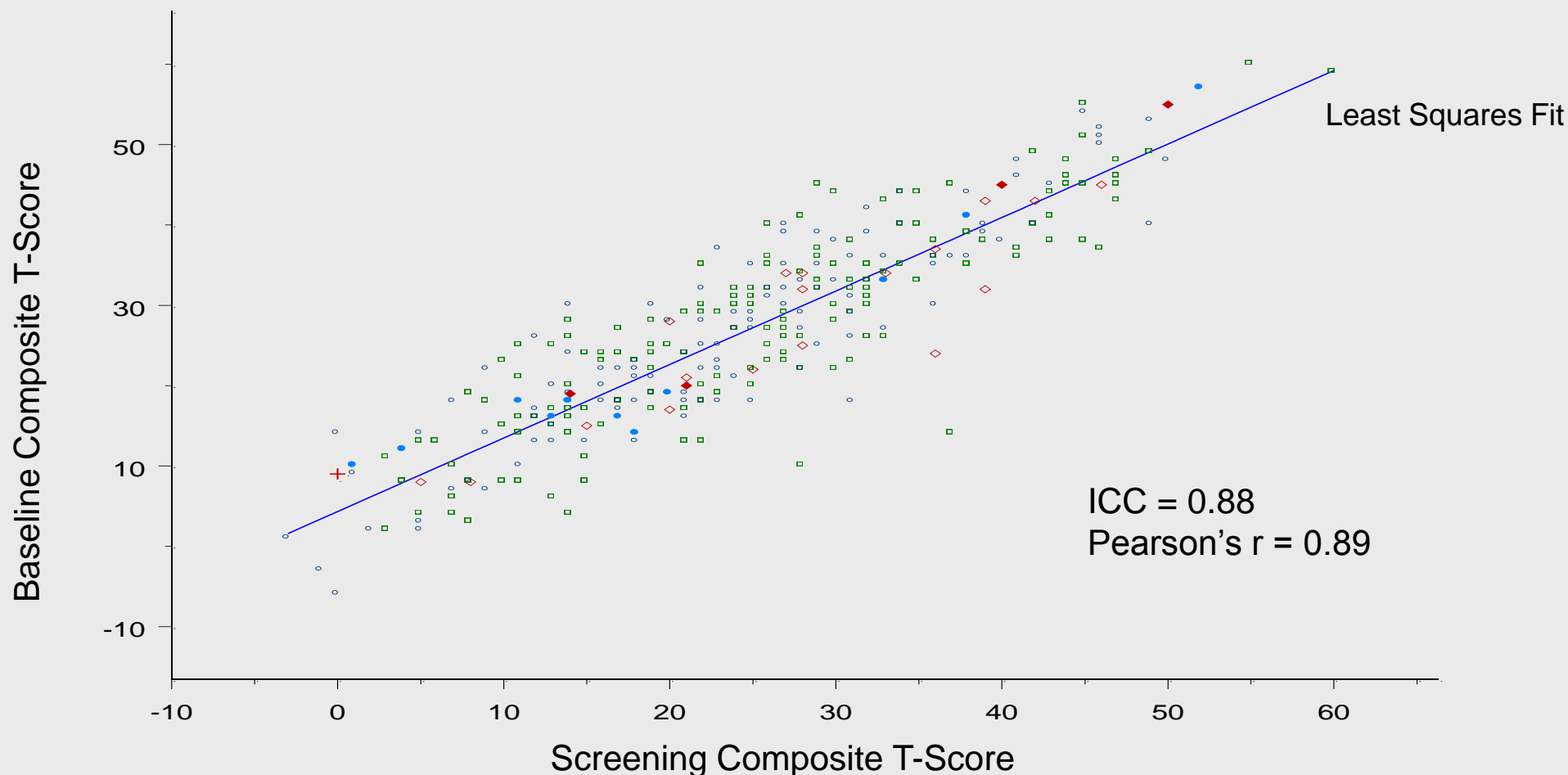
Domain (measure)	Test-Retest Reliability
AX-CPT d-prime	0.67
N-Back d-prime	
0-back (all non-targets)	0.68
1-back (all non-targets)	0.84
2-back (all non-targets)	0.82
2-Back response times	
Target hit	0.78
Novel correct rejection	0.54
Repeated correct rejection	0.78

Test-Retest MCCB Composite T-Score in R3487/MEM3454 Trial



Testing-Retest MCCB Composite T-Score (N=318)

Between screening and baseline visit (days): ● 2-5, ○ 6-14, □ 15-25, ◇ 26-32, ◆ 33-37 + 117



Effect of time elapsed between screening and baseline visits: nonsignificant ($p > 0.4$, interaction test for slope in least squares regression).

Evaluation Criteria

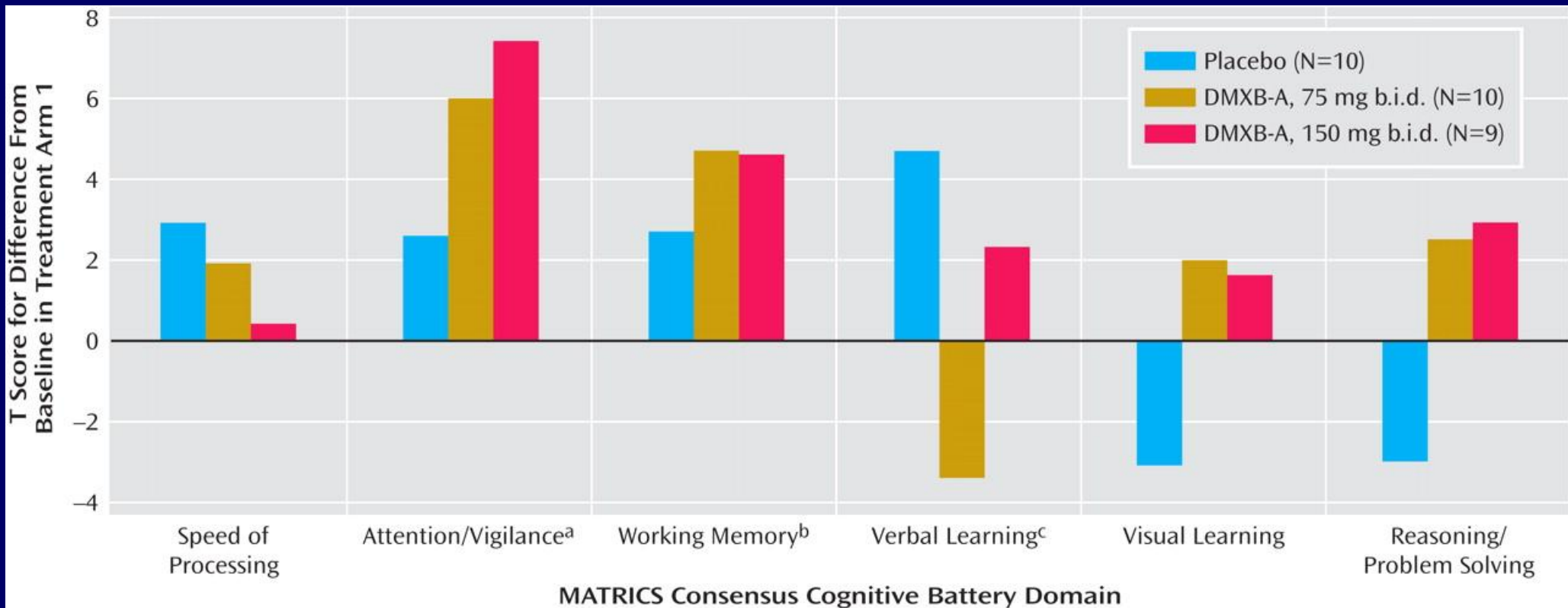
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Practice Effects in MATRICS PASS Validation Study

TABLE 3. Utility of the 20 Tests in the MATRICS Beta Battery as Repeated Measures: Performance Levels at Baseline and 4-Week Follow-Up

Domain and Tests	T ₁		T ₂		T ₂ -T ₁ Difference		Number of Scores at Floor/ Ceiling	t	p	Effect Size (Cohen's d)
	Mean	SD	Mean	SD	Mean	SD				
Speed of processing										
Category fluency test, animal naming	18.6	5.7	18.6	5.6	0.0	4.0	0/0	-0.04	0.96	0.00
Trail Making Test, Part A	42.7	15.6	39.5	14.4	-3.2	10.4	0/0	-4.09	<0.0001	0.22
Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III), digit symbol-coding subtest	52.3	13.4	55.5	15.0	3.2	7.8	0/0	5.24	<0.0001	0.22
Brief Assessment of Cognition in Schizophrenia (BACS), symbol coding subtest	41.2	12.1	41.6	11.3	0.4	6.4	0/0	0.74	0.46	0.03
Attention/vigilance										
3-7 Continuous Performance Test, shortened version	3.94	0.97	3.96	1.02	0.02	0.92	0/19	-0.65	0.52	0.04
Continuous Performance Test—Identical Pairs version	2.21	0.81	2.28	0.84	0.07	0.46	1/1	2.01	0.04	0.09
Working memory										
BACS, digit sequencing subtest	17.1	4.7	17.7	4.4	0.6	3.1	0/3	2.40	0.02	0.13
WAIS-III, letter-number sequencing subtest	8.7	2.9	8.9	2.6	0.2	1.9	0/0	1.32	0.19	0.07
Letter-Number Span test	11.6	4.1	12.3	3.7	0.7	2.4	0/0	3.28	0.001	0.16
Wechsler Memory Scale, 3rd ed., spatial span subtest	13.2	3.4	13.3	3.2	0.1	2.4	0/0	0.23	0.82	0.01
Spatial delayed response task	24.1	11.8	22.3	11.8	-1.8	8.2	0/0	-2.69	0.008	0.15
Verbal learning										
Neuropsychological Assessment Battery, daily living memory subtest	38.4	7.1	38.4	6.9	0.0	4.9	0/1	0.01	0.99	0.00
Hopkins Verbal Learning Test—Revised, immediate recall	21.3	5.4	21.8	5.7	0.5	4.3	0/0	1.51	0.13	0.09
Visual learning										
Neuropsychological Assessment Battery, shape learning subtest	14.3	4.6	14.0	4.7	-0.3	4.1	0/0	-1.00	0.32	0.07
Brief Visuospatial Memory Test—Revised	17.6	8.2	17.8	7.9	0.2	6.1	0/0	0.36	0.72	0.02
Reasoning and problem solving										
WAIS-III, block design subtest	29.4	13.3	32.5	13.7	3.1	7.0	1/0	5.62	<0.0001	0.22
BACS, Tower of London subtest	12.7	5.1	13.6	5.2	0.9	4.6	4/9	2.46	0.01	0.17
Neuropsychological Assessment Battery, mazes subtest	11.8	6.9	12.4	7.1	0.6	4.0	11/8	1.85	0.07	0.08
Social cognition										
Mayer-Salovey-Caruso Emotional Intelligence Test, perceiving emotions branch	94.7	16.6	93.9	18.3	-0.8	11.0	5/0	0.97	0.33	0.04
Mayer-Salovey-Caruso Emotional Intelligence Test, managing emotions branch	85.6	11.0	85.0	10.6	-0.6	8.0	0/0	0.95	0.34	0.06

Initial Phase 2 Trial of Nicotinic Agonist in Schizophrenia



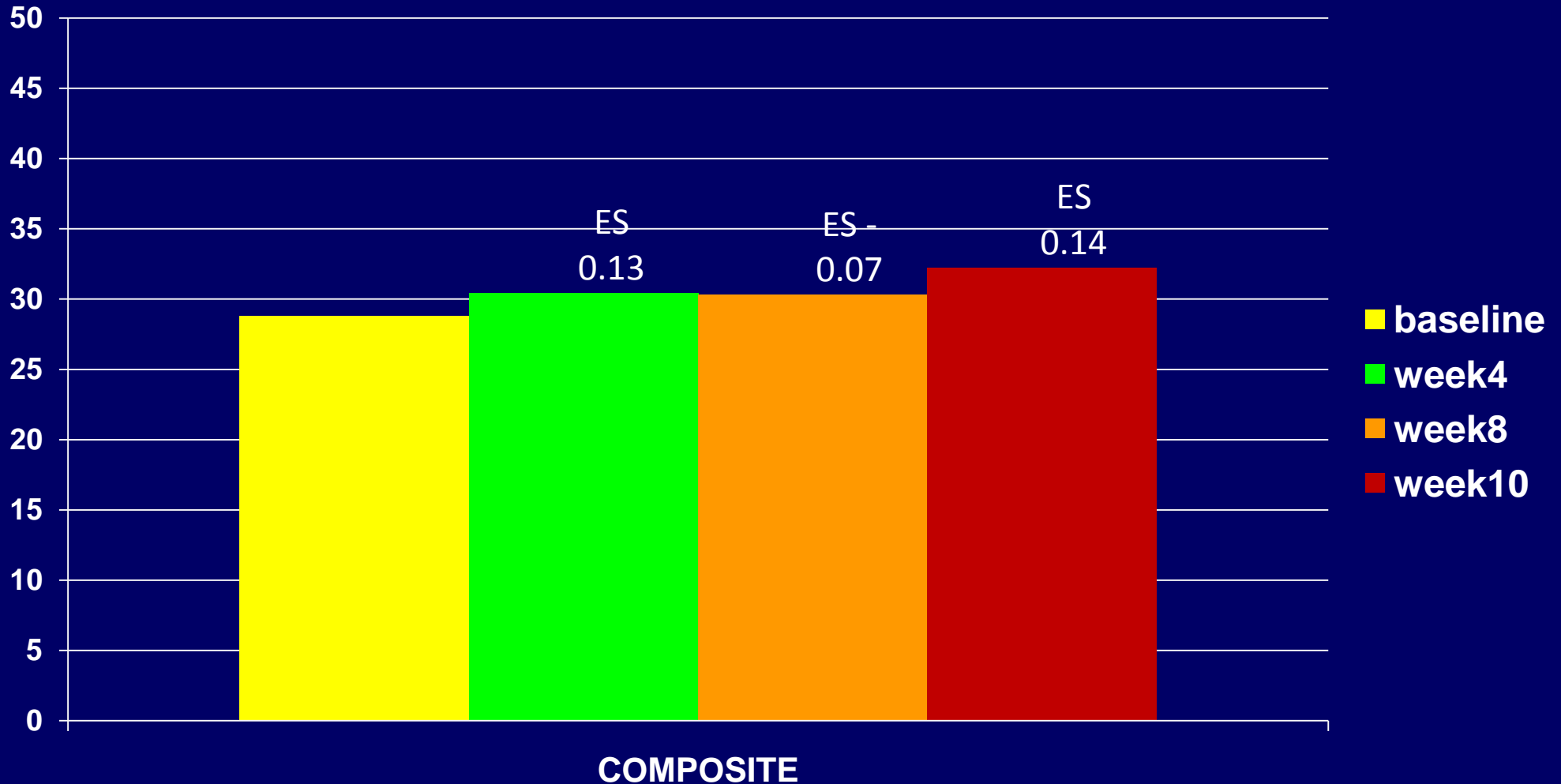
MCCB Practice Effects

Domain	Memory/ Roche (d)	DSP Lurasidone v. Risperidone (d)	TURNS MK-0777 (T)
Composite T-score	0.21	0.18	2.47
Speed of processing	0.22	0.20	1.12
Attention/Vigilance	0.27	0.17	-0.71
Working memory	0.18	0.16	1.00
Verbal learning	0.02	0.09	3.47
Visual learning	0.08	0.13	3.24
Reasoning/Problem solving	0.16	0.14	3.94
Social cognition	0.01	0.03	-1.24

d = (Baseline – Screening)/SD_{screening}

T = number of Normative SDs/10

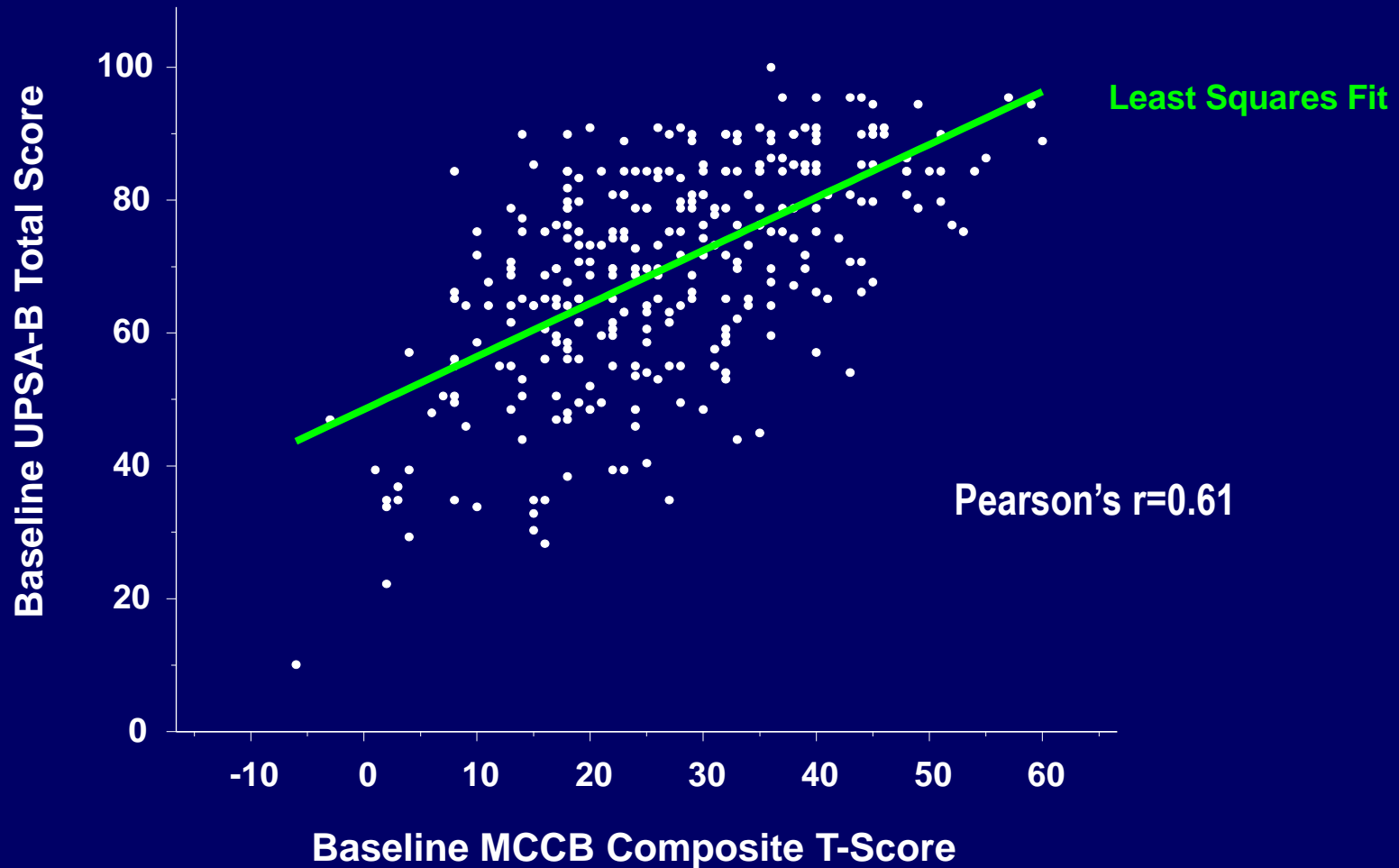
Composite T-scores across Sessions In Placebo Patients (N=42)



Evaluation Criteria

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MCCB in Antipsychotic Clinical Trial in Schizophrenia: *Cross-Sectional Relationship between Composite T-Score and UPSA-B at Baseline*

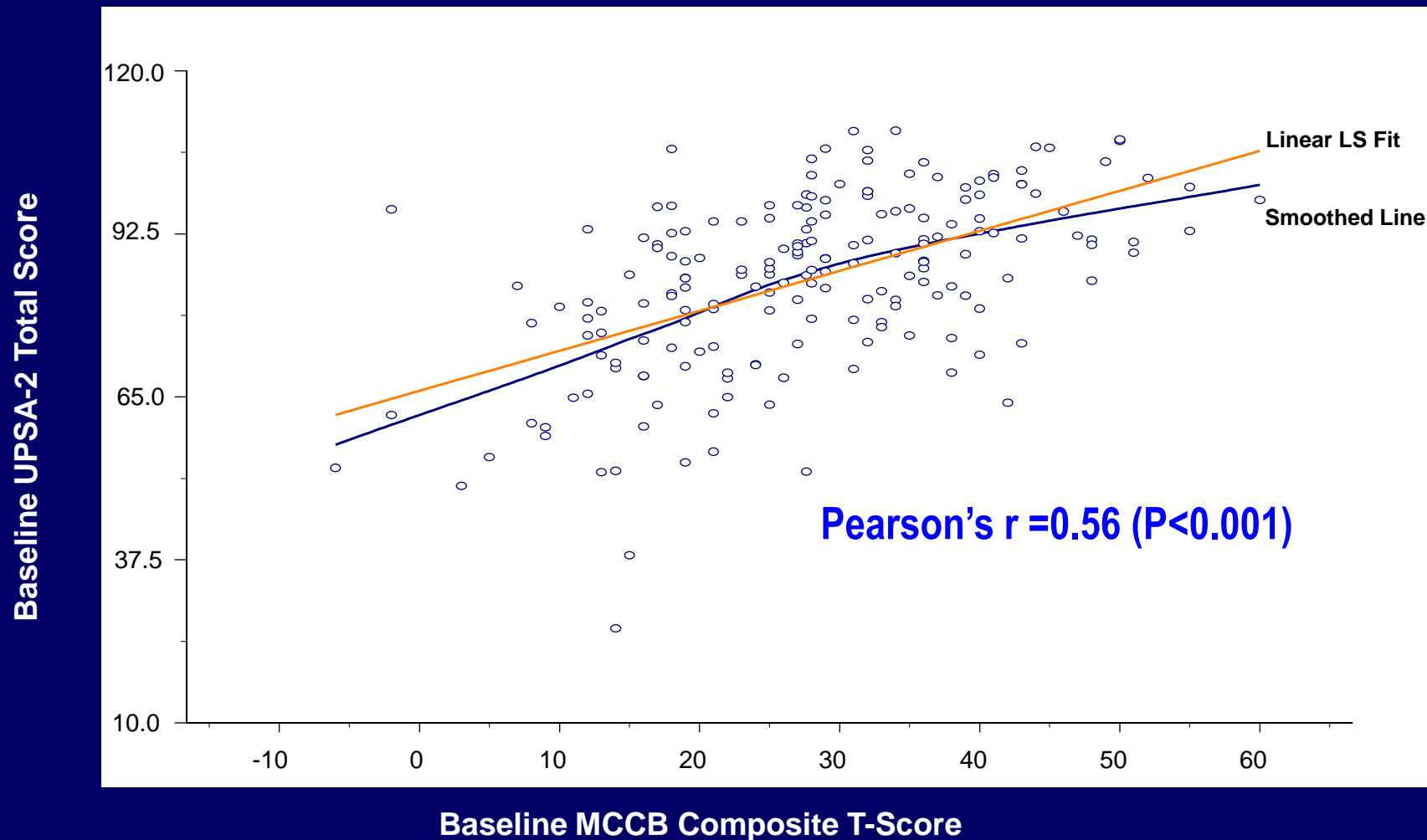


29 Sites, N=308

Lurasidone vs. Risperidone 6-month study

Keefe et al, *Schiz Res*, in press

Cross-Sectional Relationship Between Composite T-Score and UPSA-2 at Baseline (N=189)



Smoothed line by robust LOESS method.

Keefe RSE, et al. International Congress on Schizophrenia Research; March 28-April 1, 2009; San Diego, CA.

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MCCB composite score treatment data in TURNS MK-0777 Study

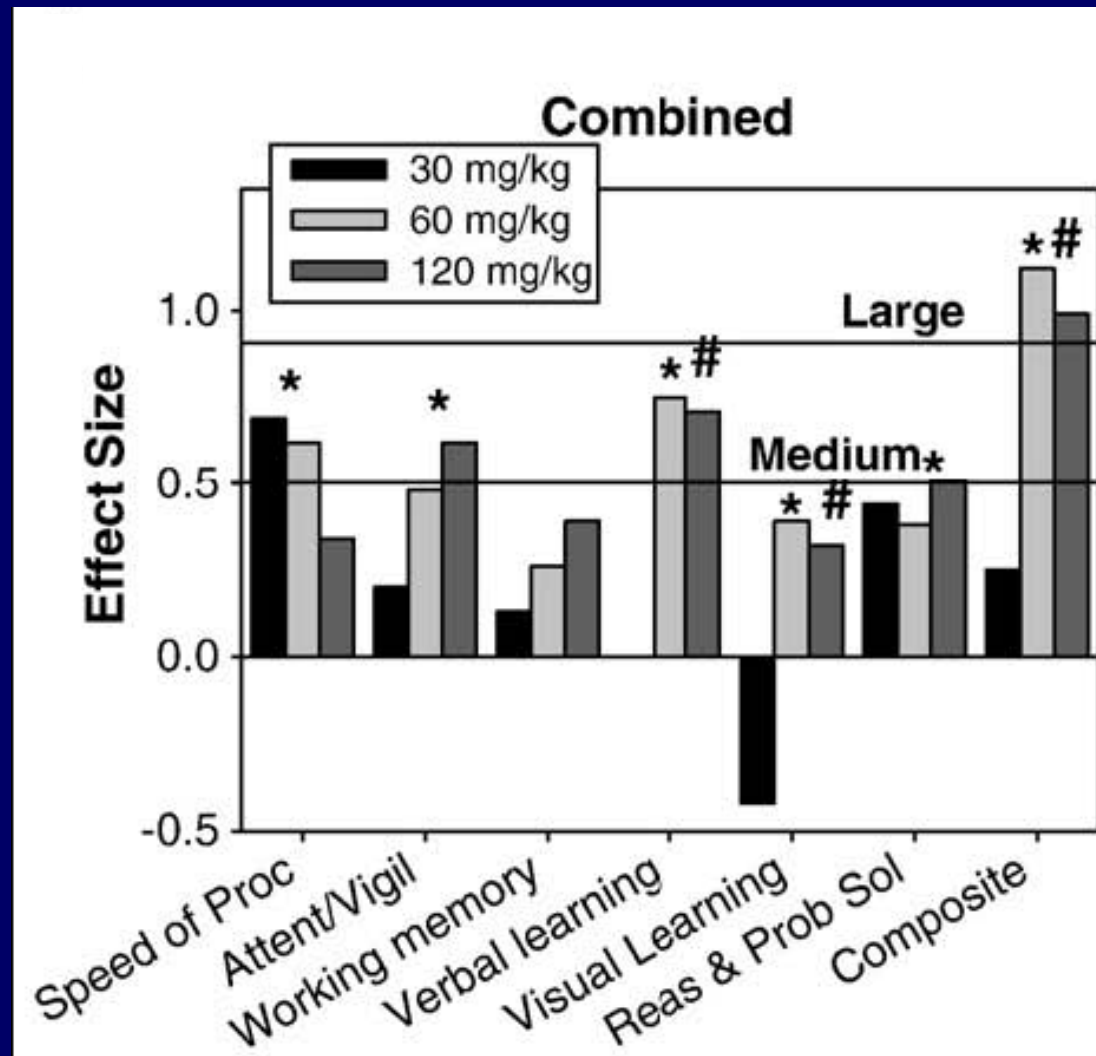
Measure	Placebo (N=17)		MK-0777, 3 mg BID (N=15)		MK-0777, 8 mg BID (N=18)		ANCOVA		
	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4	F	df	p
MCCB Composite	30.1 (13.1)	32.5 (14.0)	31.0 (12.6)	31.3 (13.9)	27.8 (12.2)	27.9 (12.7)	1.61	2,49.0	0.210
N-Back									
0-Back	3.7 (0.5)	3.7 (0.6)	3.7 (0.6)	3.7 (0.6)	3.4 (0.5)	3.6 (0.6)	0.01	2,46	0.98
1-Back	2.7 (0.8)	2.8 (0.8)	3.0 (0.6)	3.0 (0.7)	2.7 (0.8)	2.6 (0.6)	0.35	2,46	0.71
2-Back	1.4 (0.8)	1.6 (0.6)	1.4 (0.6)	1.4 (0.6)	1.5 (0.8)	1.4 (0.6)	0.97	2,46	0.39
AX-CPT									
d-prime	(N=16) 2.4 (1.1)	(N=16) 2.2 (1.4)	(N=16) 2.5 (1.1)	(N=16) 2.5 (1.2)	(N=15) 2.0 (1.2)	(N=15) 2.0 (1.1)	0.25	2,43	0.78

High Dose D-serine in the Treatment of Schizophrenia

Demographics for Study Completers

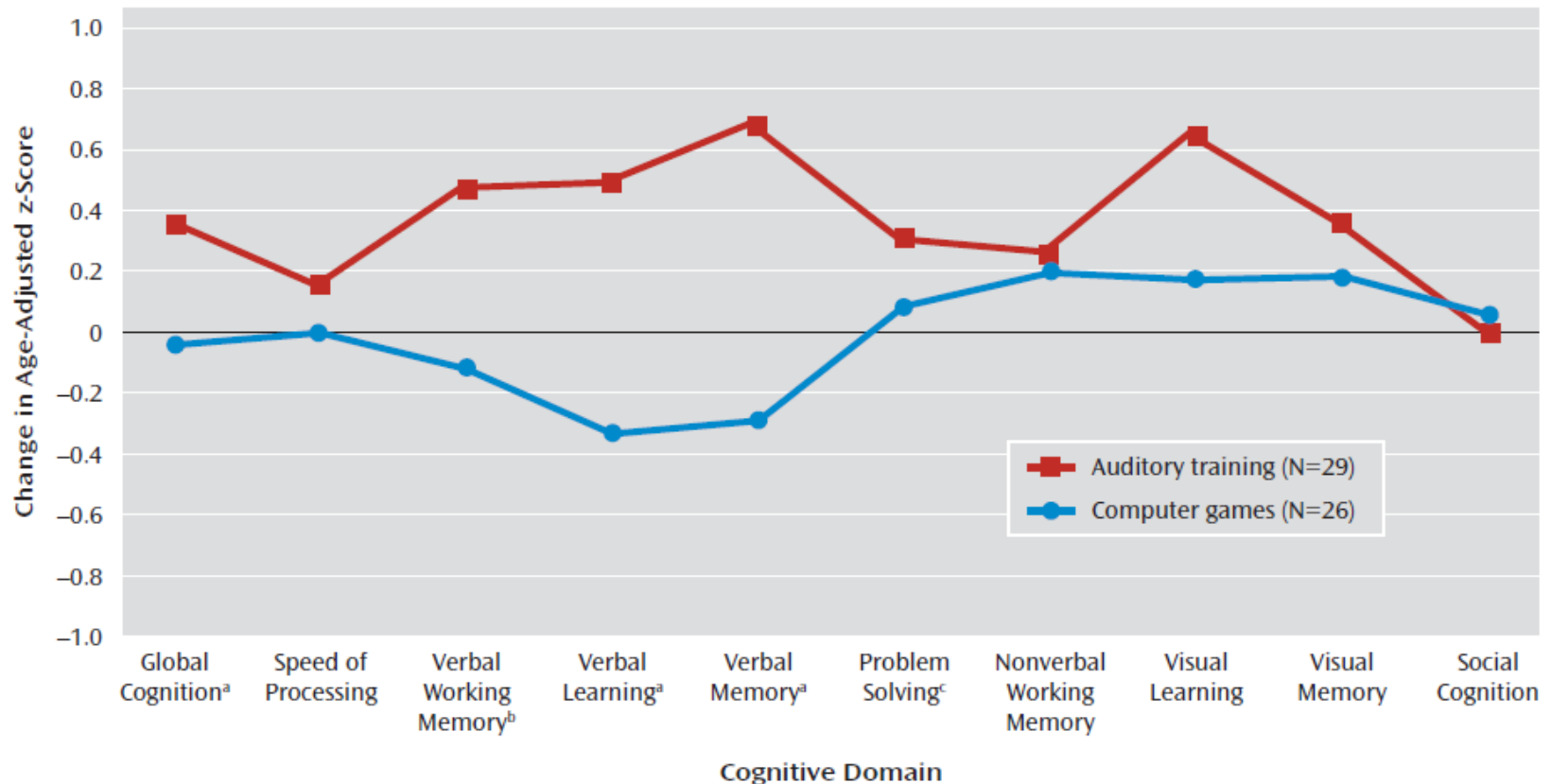
Nominal relative D-serine dose (mg/kg/d)	30 mg/kg (n=12)	60 mg/kg (n=19)	120 mg/kg (n=16)
Age	41.7 _± 11.4	43.5 _± 9.4	43.2 _± 9.6
Male (%)	75%	95%	88%
Schizophrenia (n)	9	16	13
Schizoaffective (n)	3	3	3
Inpatient (n)	5	8	6
Highest Education	12.1 _± 2.3	11.7 _± 1.9	11.9 _± 2.8
Age of 1 st Treatment	21.9 _± 5.4	21.1 _± 6.4	20.8 _± 8.9
Age of 1 st Hospitalization ¹	22.3 _± 4.5	22.6 _± 5.1	24.0 _± 8.6
Antipsychotic dose (CPZ Equivalent/d)	468.8 _± 252	602.6 _± 295	493.7 _± 319
Atypical (%)	67%	68%	75%
Achieved absolute D-serine dose (g/d)	2.58 _± 0.31	5.58 _± 0.45	11.1 _± 1.1

MATRICES Outcomes in d-serine Treatment



Using Neuroplasticity-Based Auditory Training to Improve Verbal Memory in Schizophrenia

FIGURE 2. Change in Cognitive Performance in Patients With Schizophrenia After 50 Hours of Computerized Auditory Training or 50 Hours of Computer Games



^a Significant difference between groups ($p < 0.01$, repeated-measures ANOVA).

^b Significant difference between groups ($p < 0.05$, repeated-measures ANOVA).

^c Nonsignificant difference between groups ($p = 0.10$, repeated-measures ANOVA).

MCCB Conclusions

1. Minimal missing data
2. Sensitive to cognitive impairments overall and in on individual tests and “domains”
 - Plenty of room for improvement
3. Reliability is high for composite, and variable for domains
4. Practice effects are small
 - May continue through multiple assessments in attenuated form
5. Strong correlation to UPSA co-primary scales
6. Sensitivity to treatment effects appears possible, but there have been many negative studies

Collaborators

Duke

Trina Walker
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NeuroCog Trials, Inc.

Kolleen Fox
Nicole Turcotte
Jessica Farber
Rebecca Lakey
Vicki Davis

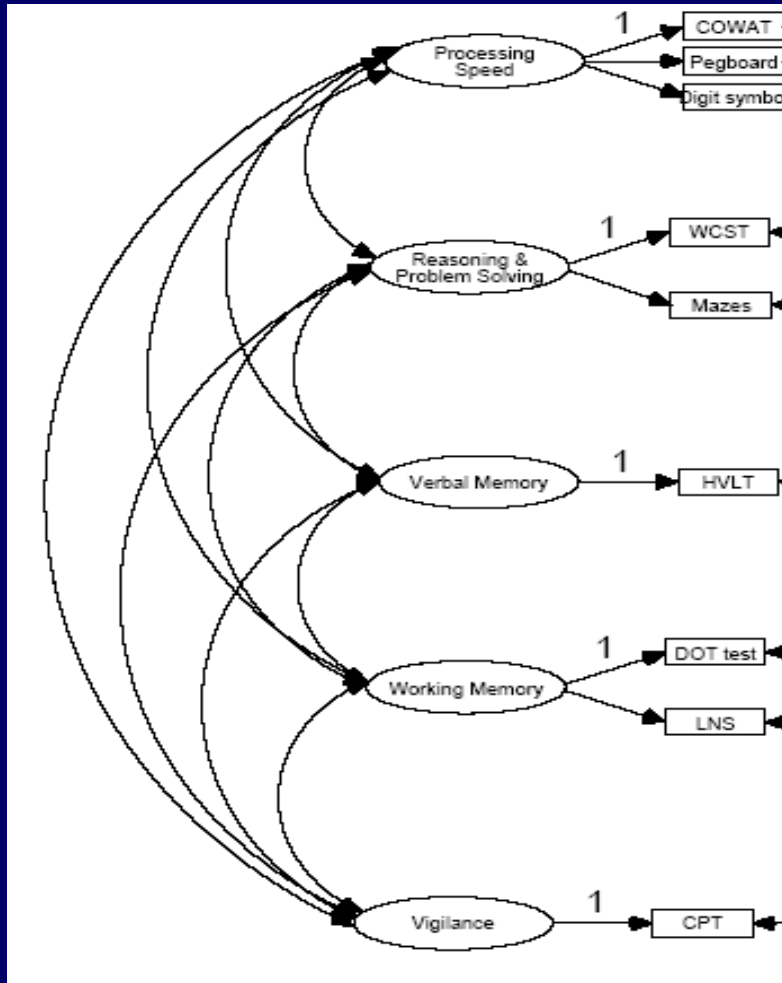
Industry Clinical Trial Data

Josephine Cucchiaro
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URNS/TENETS Network

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Michael Green
Don Goff
Jim Gold
Dan Javitt
Bob Kern
David Kimhy
Jeff Lieberman
Steve Marder
Joe McEvoy
Bob McMahon
Karen Nolan
Larry Seidman

Structural Equation Modeling Analyses on CATIE Baseline Data (N=1331)



- ◆ Null model failed to fit the data
- ◆ A uni-factorial model based on the nine tests was an improvement in fit; $\chi^2(27)=192.18$, $p<0.001$; CFI=.94, GFI=.97, RMSEA=.077
- ◆ A uni-factorial model including the five pre-defined domain scores was a considerable improvement in fit over the uni-factorial model from the nine tests ($\chi^2(22)=152.27$, $p<0.001$; CFI=.98, GFI=.97; RMSEA=.080 .
- ◆ A five-factor model that included the tests from each of the five cognitive domains as separate factors was a significantly poorer fit compared to the uni-factorial model from the five pre-defined domain scores $\chi^2(14)=78.04$, $p<0.001$.

Power Table (from Cohen)

Effect size (Cohen's d)	N required (power = 0.80; $\alpha = .05$) for each of two groups
.50	62
.35	128