Test-Retest Characteristics of the MATRICS Consensus Cognitive Battery in A 29-Site Schizophrenia Clinical Trial of Lurasidone Versus Risperidone

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Background

- The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Project produced a battery of tests designed to assess cognitive treatment effects in clinical trials of patients with schizophrenia.
- This battery of tests, the MATRICS Consensus Cognitive Battery (MCCB), was vetted through a detailed process involving leaders from academia, industry and NIMH, validated through a 5-site academic consortium, and approved by FDA.
- In the validation process, the MCCB demonstrated excellent reliability, minimal practice effects and large correlations with measures of functional capacity.
- It has been an empirical question whether the MCCB would demonstrate these favorable characteristics when administered in the context of the type of large multi-site industry trial for which it was designed.
- The current study design provides an opportunity to assess the sensitivity, test-retest reliability and construct validity of the MCCB in a 29-site study and to assess practice effects without the confounding effects of placebo.

Methods

- 323 clinically-stable outpatients with schizophrenia in the United States were randomized 2:1 to flexibly-dosed lurasidone and flexibly-dosed risperidone, respectively. (see Table 1).
- Testers from 29 sites were trained and certified, and all MCCB data were reviewed and re-scored centrally. The MCCB was administered at screening.
- At baseline, which occurred 7-21 days after screening, the MCCB was administered again along with a measure of functional capacity, the UCSD Performance-based Skills Assessment - Brief Version (UPSA-B).
- Patients were aged 18-65 and were required to have a CGI-S total score of 4 or less at both screening and baseline. No more than a "moderate" severity rating on the PANSS positive scale items. No hospitalization for psychiatric illness for at least 8 weeks prior to screening.
- This cognition sub-study, part of a larger trial, was 6 months in duration. In that time, patients received the MCCB, the UPSA-B, and the Cognitive Assessment Interview (CAI) multiple times.

Results

- Utilizing rigorous data quality assurance procedures, only 16 test scores were missing out of a total of 6460 test assessments for the 10 MCCB tests performed in 323 subjects at 2 occasions (99.8% complete) (see Table 3).
- The mean MCCB composite score was 24.7 at screening and 26.9 at baseline. Mean cognitive domain T-scores at screening and baseline are described in Table 4.
- Test-retest reliability for the MCCB composite score was very high (ICC=0.88), with ICC=0.75 for social cognition, 0.79 for speed of processing, 0.79 for working memory, 0.79 for attention/vigilance, 0.58 for verbal learning, 0.77 for reasoning/problem solving, and 0.65 for visual learning (see Table 4).
- The practice effect on the composite score was small (z=0.18). The practice effects for the individual cognitive domains were also small, with all 7 domains less than or equal to z=0.20 (see Table 4).
- Although the UPSA-B composite score was negatively skewed with a ceiling effect (see Figure 4), construct validity was also strong, as the MCCB composite score demonstrated a large correlation with the UPSA-B composite score (r=.61, df=304, P<.001) (see Figure 5).

Table 1. Demographics and Baseline Characteristics

	All Subjects (N=323)
Age	43.1 (SD=10.4)
Gender	Male 231 (72%); Female 92 (28%)
Race	White 99 (31%) African American 206 (64%) Other 18 (5%)
PANSS Total Score	67.5 (SD=11.7)
UPSA-B Total Score	70 (SD=16.2) N=308
MCCB Composite T-Score	Mean 26.9 (SD=12.4) N=321

Table 2. MATRICS Consensus Cognitive Battery

Speed of Processing
- Category Fluency
- BACS Symbol Coding
- Trail making A

Attention / Vigilance
- Continuous Performance Test - Identical Pairs version

Working Memory
- University of Maryland 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

Table 3. MCCB Test Scores: Quality Assurance

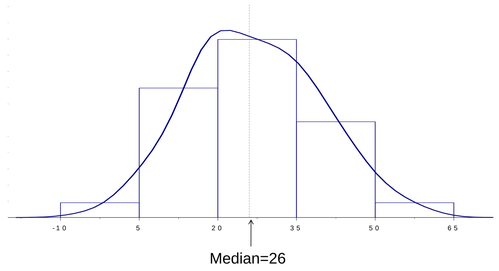
	All Subjects (N=323)
Total number of invalid or missing MCCB tests	16 N=4300 (=215x10x2)
Subjects with complete MCCB tests (excluding invalid or missing tests):	
Screening	320/323 (99.1%)
Baseline	321/323 (99.4%)
Screening and Baseline scores	318/323 (98.5%)
Subjects with missing >=3 tests:	
Screening	1 (0.3%)
Baseline	0 (0%)
Duration between screening and baseline tests	15 days (median) (2, 117)

Table 4. MCCB Composite T-Score: Screening versus Baseline (N=323)

	Screening Mean (SD)	Baseline Mean (SD)	ICC	Test-Retest Effect Size†	P-value ($SD_{screening}$ = $SD_{Baseline}$)
Composite T-Score	24.7 (12.1)	26.9 (12.4)	0.88	0.18	0.32
Speed of Processing	31.3 (12.0)	33.7 (12.1)	0.79	0.20	0.77
Attention/Vigilance	34.2 (11.8)	36.2 (12.5)	0.79	0.17	0.06
Working Memory	32.8 (11.1)	34.5 (11.2)	0.79	0.16	0.73
Verbal Learning	35.1 (7.0)	35.7 (7.5)	0.58	0.09	0.13
Visual Learning	32.7 (11.8)	34.2 (11.7)	0.65	0.13	073
Reason/Problem Solving	38.9 (8.1)	39.9 (9.3)	0.77	0.14	<0.001
Social Cognition	36.` (13.0)	36.4 (12.6)	0.75	0.03	0.44

† Effect Size for paired sample=(Baseline – Screening)/$SD_{Screening}$

Figure 1. MCCB Composite T-score Distribution at Baseline Visit (N=321)



Mean T-score at baseline =26.9 (SD=12.4), missing data imputed by average score

Figure 2. MCCB Composite T-Score Practice Effect: Baseline Minus Screening T-Scores

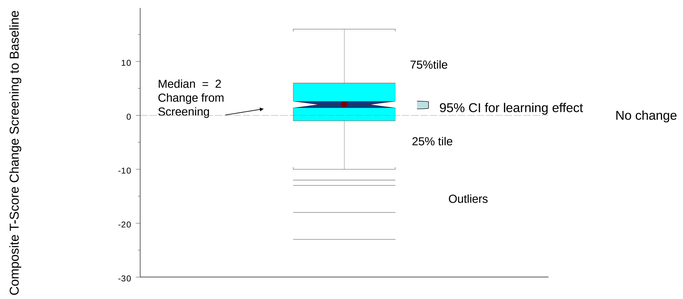
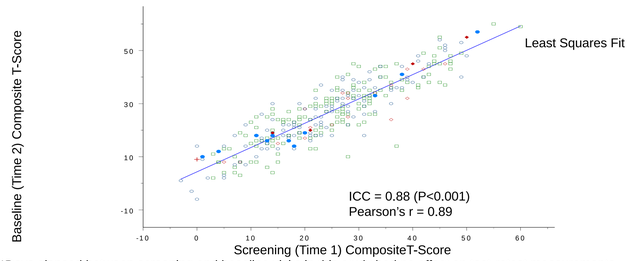
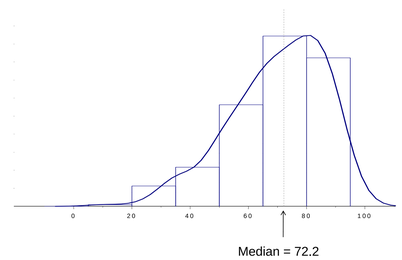


Figure 3. Test-Retest MCCB Composite T-Score (N=318)*



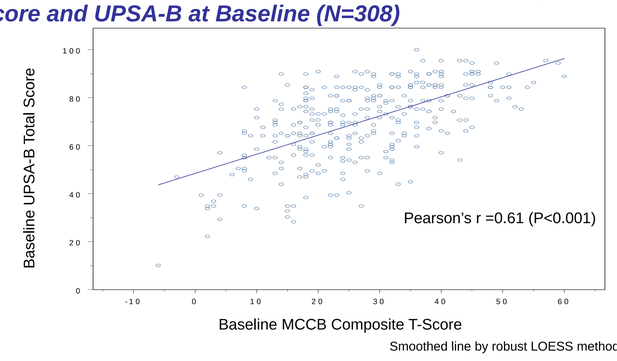
*Days elapsed between screening and baseline visits in this study had no effect on test-retest measurements.

Figure 4. UPSA-B Score Distribution at Baseline Visit (N=308)



Mean UPSA-B score at baseline = 69.97 (SD=16.23); Skewness = -0.70; normality test p<0.05

Figure 5. Cross-Sectional Relationship between Composite T-Score and UPSA-B at Baseline (N=308)



Smoothed line by robust LOESS method.

Discussion

- In the context of a 29-site clinical trial in stable patients with schizophrenia, the MCCB is sensitive to cognitive deficits in all domains, demonstrates excellent test-retest reliability and construct validity, and small practice effects.

Author Disclosures

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