Comparison of Two Fully Computerized Cognitive Test Batteries to the MATRICS Consensus Cognitive Battery

M. Stewart, Ph.D.[1]; R. Goldman, Ph.D.[2], Ph.D.; M. Stolar, Ph.D.[1]; E. Watsky, M.D.[1]; M. Versavel, M.D.[3]; and W. Moritz, B.S.[1]

Pfizer Global Research & Development, New London, Groton, CT 06340[1] ; Pfizer Headquarters, New York, NY 10017[2]; Sepracor, Marlborough, MA 01752[3]

ABSTRACT

Background: Cognitive impairment in schizophrenia is now widely accepted as a therapeutic target for pharmacologic treatment. A rapid growth in the number of clinical trials conducted in this area has increased the need to find efficient ways to assess cognition as a primary endpoint. The MATRICS effort delineated seven cognitive domains to be assessed and created a consensus test battery (MCCB) to assess them. However, the mostly pencil-and-paper based MCCB has some limitations such as length of time to administer, requirement for highly trained test administrators, and limited number of parallel tests. Fully computerized test batteries are now available to assess these seven cognitive domains and purport to overcome these limitations. Yet few data exist to address how these computerized tests compare to the MCCB.

Methods: The current noninterventional, cross-sectional study compared two commercially available computerized tests to the MCCB. A secondary objective was to evaluate the relationships between the cognitive batteries and potential intermediate functional measures. Subjects were stable, outpatient schizophrenia patients aged 18-65 years under treatment with FDA-approved antipsychotics. All subjects (N = 202) completed the MCCB and were randomized to do one of the two fully computerized tests, CNS Vital Signs (N = 103) or CogState (N = 99). Clinical (PANSS, CGI) and functional measures (UPSA, SCoRS) were also administered. Subjects completed a questionnaire to assess their preferences for the cognitive batteries.

Results: The results from the computerized batteries were comparable to those obtained with the MCCB at the composite level. Correlations between the batteries at the domain level were mostly in the moderate range. The functional measures varied in their relationships with the three batteries, with the performance-based approach (UPSA) showing higher correlations. Correlations with the clinical measures were generally of expected magnitude and direction, and similar across the batteries. No differences were seen for subject preferences among the batteries.

Conclusions: In clinical trials, where efficient assessment of cognitive functioning is critical, fully computerized batteries may offer a viable alternative to the MCCB. Although the performance-based intermediate functional measure used in this study generally demonstrated a stronger relationship to cognition, the interview-based approaches were promising and merit further study.

INTRODUCTION

- Cognitive impairment associated with schizophrenia is a target for pharmacotherapy with the potential to provide meaningful functional improvements in outcome for patients with schizophrenia and has become a high priority for developing future treatments.
- The FDA has indicated that approval of a drug for this indication will require positive results on two co-primary endpoints: a neurocognitive test battery and a functional endpoint.
- The NIMH-funded initiative, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), identified 7 relevant cognitive domains and developed the MATRICS Consensus Cognitive Battery (MCCB) to assess them.
- However, the MCCB has several drawbacks: the requirement for highly skilled administrators, the need for extensive training to learn to administer it, potential difficulty with ensuring standard administration across sites, lengthy administration time, and a limited number of parallel forms for repeat administrations of some tests.
- Fully computerized batteries are now commercially available and purport to assess the 7 MATRICS domains while overcoming many of the limitations of the MCCB.
- The primary objective of the current study was to compare 2 fully computerized neurocognitive batteries (CNS Vital Signs & CogState) to the MCCB to inform the selection of instruments for future clinical trials.
- The secondary objective was to examine the relationships between various intermediate (functional) measures and the neurocognitive tests.

METHODS

Study Design: Cross-sectional, unblinded study with randomization to testing condition. All subjects completed the MCCB. Half completed the CogState battery while the other half completed the CNS Vital Signs battery. Batteries were administered in counter-balanced order.

Subjects: Participants were adult outpatients (ages 18-65) with schizophrenia or schizoaffective disorder (DSM-IV-TR) who were clinically stable (no medication changes for past 1 month and none anticipated for next month, CGI-Severity ≤ 4), taking an FDA-approved antipsychotic, and willing to provide an informant. Exclusion criteria included active substance abuse/dependence, neurological disease or head injury, and other medical conditions that might interfere with participation. Thirteen sites participated.

Assessments:

Neuropsychological tests:
MCCB – MATRICS Consensus Cognitive Battery
CogState – Fully computerized cognitive battery
CNS Vital Signs – Fully computerized cognitive battery
Clinical measures:
PANSS – Positive & Negative Syndrome Scale
CGI-Severity – 7-point item to rate illness severity
Functioning measures related to cognition:
SCoRS – Schizophrenia Outcomes Rating Scale
UPSA-2 – University of San Diego – Performance-based Skills Assessment
GACF – Global Assessment of Cognitive Function
General functioning & other measures:
GAF – 100-point scale to rate symptoms & functioning
SCLoF – Strauss-Carpenter Level of Functioning scale
MOS Cognitive Scale – 6-item self-reported measure of cognitive problems
PPA – Patient Preference Assessment – self-reported preference for tests
Clinician & Subject Global Ratings of Severity of Cognitive Impairment

Cognitive testing and clinical ratings were done by separate raters.

Statistical analyses:

- Neuropsychological tests were scored two ways: (1) corrected for norms per developer's recommendations and (2) without norm corrections (standardized on sample). Norms were based on age and gender (MCCB) or age (CNS Vital Signs & CogState).
- The calculation of the un-normed composites required data from all 7 domains. The normed composites followed the developer's usual practice.
- Correlations (Pearson's *r*) between the neuropsychological tests were calculated, as well as correlations of the 3 tests with the functioning and clinical measures. Confidence intervals for correlations were calculated using Fisher's z-transformation.
- Variability in the composite score attributable to site differences was analyzed separately for each battery using linear mixed models with a random effect for *site* and no fixed effects.
- Two analyses were done to assess test order effects on scores for each battery: (1) t-tests for the difference of two independent means for taken first versus second and (2) For CogState and CNS Vital Signs, linear mixed models with a fixed effect for *order* and a random effect for *site* and *subject within site*. For the MATRICS battery, we fit a linear mixed model with a fixed effect for *sequence group* and a random effect for *site* and *subject within site*, and then another model with a fixed effect for *order* and a random effect for *site* and *subject within site*.
- Linear mixed modeling was used to assess differences in patient preferences (PPA) for the three batteries. Four models were considered consisting of fixed main effects for *battery* and *order* with or without a *battery-by-order* interaction, and random effects for *site* with or without *subject within site.*

RESULTS

FIGURE 1. SUBJECT FLOWCHART

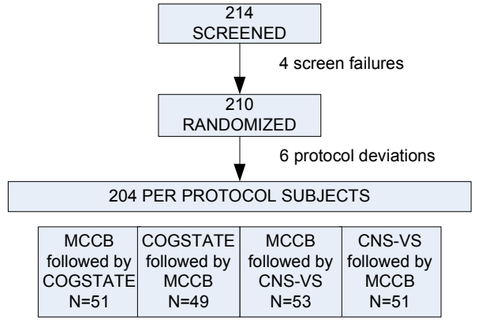

TABLE 1. DEMOGRAPHICS OF STUDY SAMPLE

	MCCB → CS	CS → MCCB	MCCB → CNS VS	CNS VS → MCCB
Age in yrs (mean & SD)	41.7 (10.6)	42.8 (10.2)	43.3 (10.2)	42.3 (10.3)
Male	62.3%	58.8%	64.8%	69.2%
White	54.7%	43.1%	38.9%	42.3%
Never married	75.5%	51%	68.5%	73.1%
Smoker	71.7%	52.9%	57.4%	59.6%
At least HS Education	39%	37%	37%	39%
Receiving SSA benefits	88.2%	73.5%	84.9%	90.2%
Employed (part/full-time)	23.5%	8.2%	20.8%	13.8%
Living in facility	31.4%	26.4%	17.0%	23.5%
Right-handed	84.9%	90.2%	90.7%	78.8%
Estimated premorbid IQ	92.4 (18.9)	82.8 (17.6)	88.3 (19.0)	86.4 (16.4)

TABLE 2. CLINICAL CHARACTERISTICS OF STUDY SAMPLE

Diagnosis	
Schizophrenia – Paranoid	71.1%
Schizoaffective disorder	19.1%
Schizophrenia - Residual Type	8.3%
Schizophrenia - Disorganized	1.5%
PANSS Total *Mean (SD)*	69.6 (13.4)
• Positive subscale	17.3 (4.96)
• Negative subscale	17.7 (4.7)
CGI-Severity *Mean (SD)*	3.58 (.62)
Atypical antipsychotics %	
Risperidone	26%
Olanzapine	16%
Quetiapine	13%
Aripiprazole	10%
Other atypical	10%
Conventionals	5%
> 1 Antipsychotic medication	20%

TABLE 3. NEUROPSYCHOLOGICAL BATTERIES: DESCRIPTIVES FOR NORMED COMPOSITE SCORES

Battery (n)	***Mean (SD)***
MCCB composite (203)	24.1 (13.4)
CNS Vital Signs composite (103)	78.7 (13.6)
CogState composite (98)	-1.6 (2.14)

For the composite scores, the percentage of the total variance attributable to between-site variability was 6.6%, 2.3%, and 8.2% for MBBC, CNS Vital Signs, and CogState, respectively.

TABLE 4. CORRELATIONS WITH MCCB: COMPOSITE SCORES

Battery	***Normed Pearson's r (p value) 90% CI Variance Explained***	***Un-normed Pearson's r (p value) 90% CI Variance Explained***
CNS Vital Signs	.76 (p < .0001) .67 - .81 N = 102 58%	.75 (p < .0001) .67-.81 N = 100 56%
CogState	.57 (p <.0001) .44 - .67 N = 97 32%	.75 (p <. 0001) .66-.82 N = 87 56%

- Subjects showed no preference for any particular battery (assessed by the PPA) after adjusting for order effects.
- There were no statistically significant order effects for any composite scores (p > .05). Among the domain scores, there was a statistically significant order effect for the Attention Domain score for the MCCB (p < .0001) for those who also took the CogState battery. Higher Attention Domain scores on the MCCB were seen on average for those who took MCCB first. There was also a significant order effect for the Reasoning Domain score on the CogState battery (p < .001). Those who took CogState before MCCB had lower Reasoning Domain scores on average than those who took CogState after MCCB.

TABLE 5. CORRELATIONS WITH MCCB: STANDARDIZED DOMAIN SCORES

Domain	**CNS Vital Signs** ***Pearson's r (90% CI)***	**CogState** ***Pearson's r (90% CI)***
Attention	**.51** (.38 - .62)	.41 (.25 - .55)
Reasoning	.39 (.24 - .52)	.45 (.29 - .58)
Social cognition	.40 (.25 - .53)	.36 (.19 - .50)
Speed of processing	.30 (.15 - .45)	.23 (.06 - .39)
Verbal learning	.40 (.26 - .53)	.61 (.49 - .71)
Visual learning	.42 (.28 - .55)	.39 (.23 - .53)
Working memory	.51 (.37 - .62)	.37 (.21 - .51)

All correlations are significantly different from zero (p < .05). None are different from one another.

TABLE 6. CORRELATIONS FOR THE 3 STANDARDIZED COMPOSITES WITH OTHER MEASURES

Scale	**MCCB** ***Pearson's r (90% CI)***	**CNS Vital Signs** ***Pearson's r (90% CI)***	**CogState** ***Pearson's r (90% CI)***
PANSS Total	**-.24**	-.18	**-.31**
Negative subscale	**-.26**	-.09	**-.26**
Positive subscale	**-.17**	-.16	**-.28**
CGI-S	**-.16**	-.08	**-.26**
GAF	**.15**	.09	**.23**
SCLoF	**.20**	.13	**.29**
SCoRS (global item)	**-.29**	-.19	**-.23**
UPSA-2	**.63**	**.56**	**.48**
MOS Cognitive Scale	.05	-.06	.08
GACF	**.42**	**.40**	**.38**
Clinician Global rating	**-.37**	**-.26**	**-.38**
Subject Global rating	-.10	.07	-.15

BOLD are statistically significant (p < .05).

CONCLUSIONS

- Overall, the 2 computerized batteries correlated at a comparable level with the MCCB at the composite level, explaining > 50% of the variance for 3 of the comparisons. The correlation between the normed CogState and MCCB batteries is lower than other correlations and may be due to differences in the norming procedures used.
- At the domain level most of the correlations were in the moderate range between .30 - .50, explaining 9-25% of the variance. There were numerical differences in how well the 2 fully computerized batteries correlated with the MCCB at the domain level but none reached statistical significance.
- Correlations between the 3 batteries and the other clinical and functioning measures were in the range observed for the MATRICS psychometric study[3] (PASS) and were generally consistent among the 3 batteries.
- Subjects cannot reliably self-report their level of cognitive impairment. Newly developed single item clinician ratings (Clinician Global & GACF) performed nearly as well as the more established measures the UPSA-2 and SCoRS.

REFERENCES

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