Operationalizing Cognitive Impairment Associated with Schizophrenia: MATRICS Consensus Cognitive Battery & Alternatives

M. Stewart, Ph.D.[1]; M. Stolar, Ph.D.[1]; Sally Olderbak, M.A.[2]; R. Goldman, Ph.D.[3]; and E. Watsky, M.D.[2]

Pfizer Global Research & Development, New London, Groton, CT 06340[1] ; University of Arizona, Tucson, AZ 85721[2] ; Pfizer Headquarters, New York, NY 10017[3]

ABSTRACT

Background: The NIMH-funded academic-FDA-industry partnership known as MATRICS delineated seven cognitive domains to assess cognitive impairment associated with schizophrenia (CIAS) and created a consensus test battery (MCCB), which represents one operationalization of the concept of CIAS. Fully computerized batteries now commercially available offer alternative ways to operationalize CIAS. Whether these alternatives assess the same constructs as MCCB remains to be fully explored.

Methods: As part of a noninterventional, cross-sectional study all subjects were tested on the MCCB (N=202) while half were randomized to do one of two fully computerized tests, CNS Vital Signs (N = 103) or Cogstate (N = 99). Subjects were stable, outpatient schizophrenia patients aged 18-65 years under treatment with FDA-approved antipsychotics. Clinical (PANSS, CGI) and functioning (UPSA-2, SCoRS) measures were administered. Two global clinician-rated functioning items were also included. The correlational structure of the computerized batteries and MCCB were examined using linear regression and factor analytic methods. The influence of symptom measures on functional endpoints was explored.

Results: Correlations between composites for the two fully computerized batteries and the MCCB were fairly high (r=.75); at the domain level they were in the moderate range (.30-.50). Fit for a one-factor model was good for MCCB, marginal for CNS Vital Signs, and poor for Cogstate. Across all three, the domains of working memory and attention domains were among the highest loadings. The comparability of these different operationalizations of CIAS is analyzed in terms of domain structure and associations with the clinical severity and functioning measures.

INTRODUCTION

- Cognitive impairment associated with schizophrenia (CIAS) is a target for future pharmacotherapy with the potential to provide meaningful functional improvements in outcomes for patients with schizophrenia.
- The NIMH-funded initiative the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) brought together the FDA, academic and pharmaceutical partners to develop a cognitive test battery to assess the 7 domains most relevant to CIAS.
- The result was the MATRICS Consensus Cognitive Battery (MCCB) which is now widely accepted as satisfying one of the two FDA requirements to show improvement on a neurocognitive battery and a functional endpoint.
- The MCCB has drawbacks including the requirement for highly skilled administrators, the need for extensive training to learn how to administer it, lengthy administration time, and few available translations for use outside the U.S.
- Alternatives to the MCCB exist, including fully computerized batteries that are now commercially available. Many of these purport to assess the 7 MATRICS domains while overcoming many of the limitations of the MCCB.
- This objective of these post hoc analyses was to extend previous work comparing 2 fully computerized neurocognitive batteries (CNS Vital Signs & CogState) to the MCCB to inform the selection of instruments for future clinical trials.
- These analyses explore whether the two alternative batteries offer comparable ways to operationalize the CIAS domains.

METHODS

Study Design: Post hoc analyses of data from a cross-sectional, unblinded study with randomization to testing condition. All participants completed the MCCB; half completed the CogState battery while the other half completed the CNS Vital Signs (CNS VS) battery. Batteries were administered in counter-balanced order.

Subjects: Participants were 204 adult outpatients (ages 18-65) with schizophrenia or schizoaffective disorder (DSM-IV-TR). Inclusion Criteria:

- Clinically stable - no medication changes for past 1 month & none anticipated for next month
- CGI-Severity ≤ 4
- Currently taking an FDA-approved antipsychotic
- 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 in the U.S. participated.

Assessments:

Neuropsychological tests:

MCCB – MATRICS Consensus Cognitive Battery
Cogstate – Fully computerized cognitive battery
CNS Vital Signs – Fully computerized cognitive battery

Other measures used in these analyses:

PANSS – Positive & Negative Syndrome Scale
GACF – Global Assessment of Cognitive Function – 100-point item
SCoRS – Schizophrenia Outcomes Rating Scale
UPSA-2 – Univ of SD – Performance-based Skills Assessment

Cognitive testing & clinical ratings were done by separate raters.

ABBREVIATIONS: SOP = Speed of processing; ATTN = Attention; WKMEM = Working memory; VERL = Verbal learning; VISL = Visual learning; REAS = Reasoning; SOC = Social cognition

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). Analyses reported here were done on the un-normed data.
- Correlations (Pearson's *r*) among the domains of the 3 batteries were calculated, as well as correlations of the tests with other selected measures. Confidence intervals for correlations were calculated using Fisher's z-transformation.
- Confirmatory factor analysis (CFA) using SAS Proc Calis was used to fit a one-factor model for the 3 batteries. Exploratory factor analyses (EFAs) were conducted using SAS Proc Factor (ML extraction) for those batteries where the CFA indicated a poor fit for one factor. Oblique rotation (Promax) was used to look at factor structure.
- Regression models were fit using least-squares with each domain regressed on the other 6 domains.

RESULTS

- Participants were predominantly male (64%), white (45%), smokers (61%), right-handed (86%), with an average age of 42.3 years (SD=10.3). The majority were never married (67%), received Social Security benefits (84%), and were unemployed (81%). Majority was living with other family members (29%) or alone (27%). Most frequent diagnosis was schizophrenia, paranoid type (71%) and estimated premorbid IQ was 88 (SD=18).

TABLE 1. CORRELATIONS WITH MCCB: COMPOSITE SCORES

Battery	*Normed Pearson's r (90% CI)*	*Un-normed Pearson's r (90% CI)*
CNS Vital Signs	.76 (.67 - .81) N = 102	.75 (.67-.81) N = 100
CogState	.57 (.44 - .67) N = 97	.75 (.66-.82) N = 87

All correlations are significantly different from zero (p<.0001).

- Correlations between the two computerized batteries at the domain level and the corresponding MCCB domains varied from .30-.51 for CNS Vital Signs and .23-.61 for CogState. Most correlations were in the .30-.50 range. All were statistically significant from zero but the correlations were not significantly different for the 2 fully computerized batteries.

TABLE 2. CORRELATIONS BETWEEN GACF ITEM AND THE 3 COMPOSITES

Battery composite	GACF with composite	GACF with PANSS Total partialled out
MCCB	.42	.34
CNS Vital Signs	.40	.36
CogState	.38	.27

- The GACF is a single global clinician-rated item to assess functioning related to cognition on a 1-100 scale.

FIGURE 1. MCCB DOMAIN CORRELATIONS

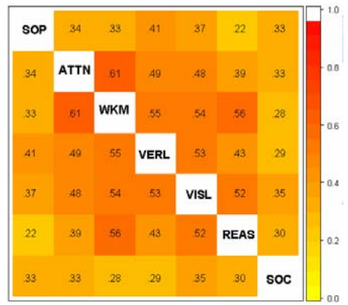


FIGURE 2. CNS VS DOMAIN CORRELATIONS

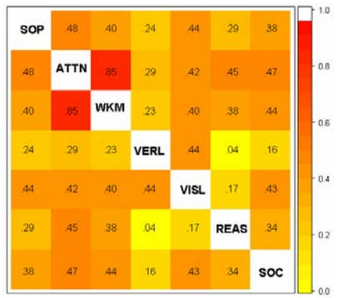


FIGURE 3. COGSTATE DOMAIN CORRELATIONS

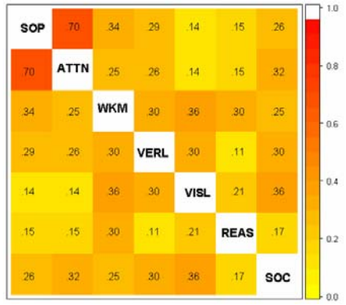


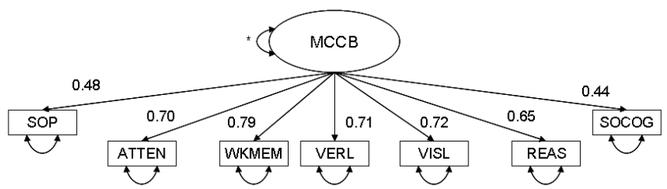
TABLE 3. TESTS FOR EQUIVALENCE OF MATRICES

Comparison	*Tests of Equality*
CogState – MCCB N = 87	GFI = .93 X^2 = 51.77, p = .0002 Tucker-Lewis coefficient = .70 Measure of Centrality = .84
CNS VS – MCCB N = 100	GFI = .93 X^2 = 56.31, p < .0001 Tucker-Lewis coefficient = .72 Measure of Centrality = .84

- Tests for the equivalence of correlation matrices[1] comparing each of the computerized batteries to the MCCB showed that they are not equivalent.
- Regressing each domain onto the other 6 domains showed that for the MCCB the R-squared values for the 7 domains ranged from .20-.52; for CNS VS from .22-.74; and for CogState from .15-.39.

- Follow up EFAs revealed two factors best fit CogState – speed of processing and attention comprised the first factor while second factor was dominated by visual learning, verbal learning, social cognition, and working memory. CNS VS showed one strong factor with high loadings for attention, working memory and weak evidence for a second factor with higher loadings for verbal learning and visual learning.
- CFA tests for measurement invariance and weak factorial invariance for each of the fully computerized batteries with MCCB did not show a good fit.

FIGURE 4. ONE-FACTOR CFA MODEL FOR MCCB



** Indicates that variance was set to 1. All loadings are statistically significant.*

TABLE 4. FIT FOR ONE-FACTOR CFA MODELS

Battery	Model Fit
MCCB	$X^2_{(14,\ n=196)}$ = 28.41, p = .013 RMSEA = 0.073 (0.033- 0.111). CFI = 0.967, NFI = .937, NNFI = .950
CNS Vital Signs	$X^2_{(14,\ n=100)}$ = 38.13, p < .01 RMSEA = 0.132 (0.083- 0.183). CFI= 0.903, NFI = .858, NNFI = .854
CogState	$X^2_{(14,\ n=87)}$ = 41.02, p < .01 RMSEA = 0.150 (0.098- 0.204) CFI = 0.765, NFI = .698, NNFI = .647

TABLE 5. CORRELATIONS OF THE 7 DOMAINS FROM THE BATTERIES WITH 3 MEASURES OF FUNCTIONING RELATED TO COGNITION

MCCB / CNS VS / CogState	SOP	ATTEN	WKMEM	VERL	VISL	REAS	SOCOG
UPSA-2 total score	.39 / .46 / .23	.51 / .49 / .27	.48 / .40 / .32	.52 / .34 / .40	.40 / .24 / .26	.38 / .31 / .05	.41 / .41 / .49
SCoRS Global rating	-.23 / -.24 / -.03	-.14 / -.15 / .03	-.19 / -.08 / -.17	-.25 / -.11 / -.35	-.31 / -.10 / -.08	-.18 / -.08 / -.12	-.12 / -.08 / -.19
GACF item	.25 / .39 / .14	.25 / .20 / .20	.25 / .17 / .22	.34 / .29 / .39	.39 / .36 / .18	.31 / .17 / .26	.32 / .30 / .25

CONCLUSIONS

- The correlations between the computerized batteries and the MCCB at the composite level were fairly high and the correlations observed at the domain level were more modest. The correlations among the 7 domains on the 3 batteries varied greatly. Formal testing of the equivalence of the matrices demonstrated they are not strictly equal.
- The domains from each of the batteries varied in how well they correlated with measures of functioning related to cognition. Most of these correlations were in the modest range and there was variability in the magnitude of the correlations across the 3 batteries. Finally, the severity of clinical symptomatology did not appear to strongly influence the clinician's global rating of functioning related to cognition.
- A single underlying construct appears to explain most of the variance observed on the MCCB domains whereas it does not appear to do so for the fully computerized batteries. Further analyses are needed to fully explore these differences.
- Overall, the fully computerized batteries tested show promise in assessing the 7 MATRICS domains but appear to operationalize them differently than the MCCB.

REFERENCES

[1] Green JA. Dev Psychology 1992; 28: 215-224.

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