Assessment of Cognitive and Functional outcomes in Depression Treatment Studies

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Disclosures

- In the past 12 months Dr. Harvey has served as a consultant for:

Boehringer-Ingelheim, Forum Pharma, Genentech, Lundbeck, Otsuka-America, Roche Pharma, Sanofi Pharma, Sunovion Pharma, and Takeda

How Do You Assess Cognition and Everyday Functioning?

- Performance-based tests

- Observation

- Self-report

- Informant report

Requirements for Cognitive and Functional Assessment

– Correct Content
  - i.e., validity
– Adequate psychometrics
  - Reliability, sensitivity, range of scores, usefulness as a repeated measure
– Practicality and tolerability

Tailoring the Cognitive Assessment for Mood Disorders

- There are several highly salient domains in mood disorders

- These include attention, executive functioning, and, importantly, processing bias

- Processing bias as a "hot" cognition domain is not covered by many NP assessment strategies

- Setting aside the issue of hot cognition, are there truly different domains of cognitive impairment in mood disorders vs. other conditions with well validated cognitive assessments?

The MCCB

- MATRICS battery (Measurement and Treatment Research to Improve Cognition in Schizophrenia)[1]
    - Speed of processing
        - Category fluency
        - Trail making test, part A
        - Symbol-coding
    - Attention/vigilance
        - Continuous performance test - identical pairs (CPT-IP)
    - Working memory
        - Letter-number span
        - Spatial span
    - Verbal learning
        - Hopkins verbal learning test – revised (HVLT-R)
    - Visual learning
        - Brief visuospatial memory test – revised (BVMT-R)
    - Reasoning and problem solving
        - Mazes
    - Uses mean of t-scores for an estimate of global neuropsychological performance

Recommended Changes for use in Bipolar Disorder

- Consensus statement regarding modifications of MCCB for use in bipolar treatment studies (Yatham et al., 2010)

- Suggests two alterations:
    - More complex episodic memory tests
    - More complex executive functioning assessments

Performance of First Episode
Patients Compared to Normative Standards
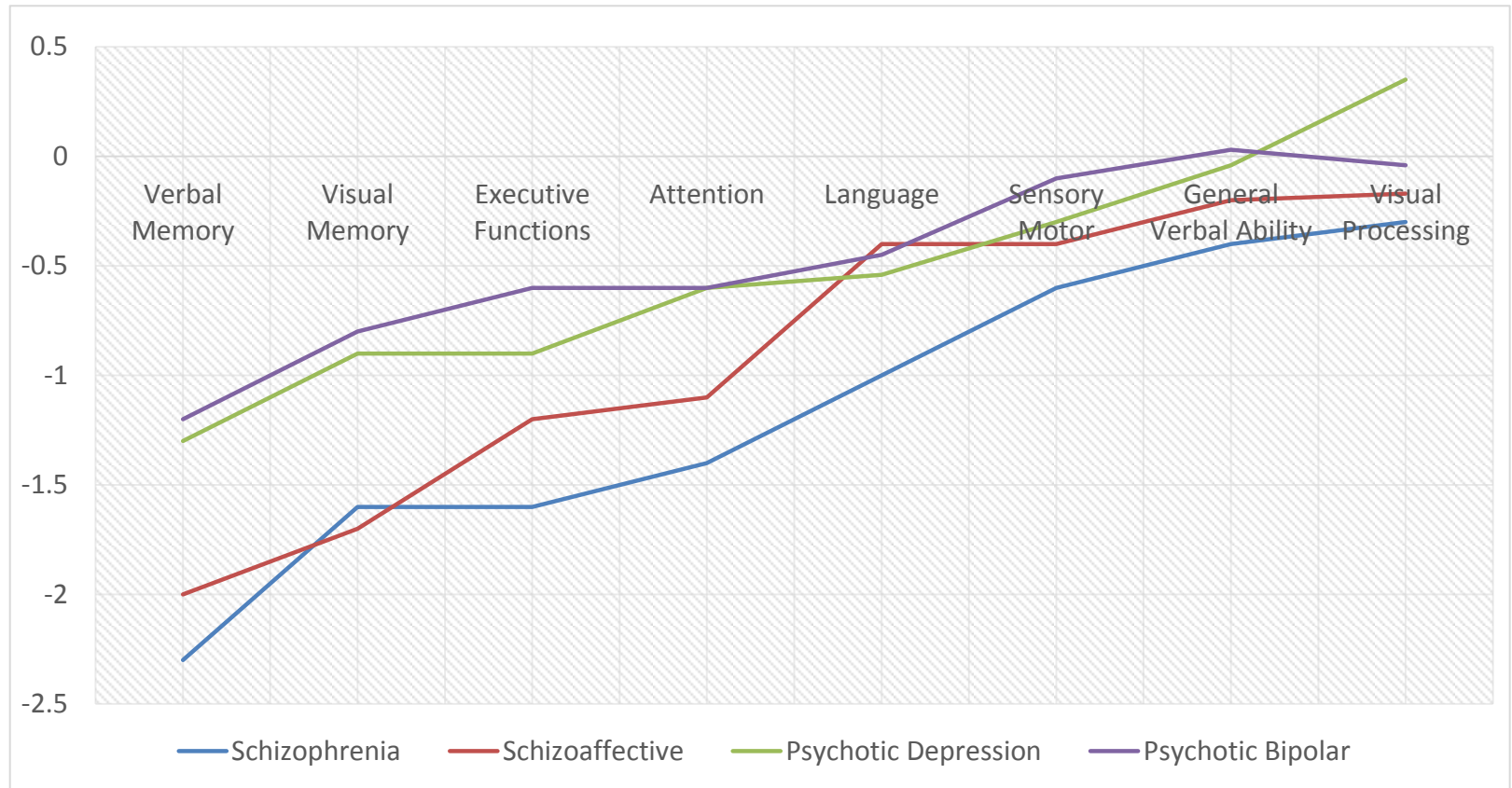
From Reichenberg et al., 2009

Functional Differences Between MDD and Schizophrenia

- Greater lifetime achievement in several critical areas:
  - Employment
  - Social Outcomes
  - Everyday activities
  - Educational Attainment
- These may have implications for selection of outcomes measures

Interview-Based Strategies

- Several structured inventories are developed

- Some are aimed at mood disorders in specific

- Others are aimed at schizophrenia and have been partially validated in mood disordered populations

- Interview-based measures offer greater ease of alteration of difficulty

Potential Biases in Self reports in Mood disorder

- Self-reported mood symptoms, particularly in the residual state when augmentation therapy would be considered, are poorly correlated with performance-based measures

- Sometimes the correlation is 0

- The open question, however, is whether informant/observer ratings would be better

Self reports of Functioning and Cognition in Bipolar Depression are Driven by Mood Symptoms

Pearson Correlations Between Self-reported vs Clinician Rated Functioning

Clinician Rated	Patient Reported
SLOF Interpersonal Functions	.17
SLOF Activities Subscale	.01
SLOF Vocational Subscale	.30[a]
Cognitive Assessment Inventory	.07

Correlations Between Self-reported vs Clinician Rated Functioning and Performance and Symptom Measures

	MCCB Total Score	UPSA-B	WCST Performance	BDI Total
Clinician Rated				
SLOF Interpersonal Functions	.16	.07	.10	-.20
SLOF Activities Subscale	.31*	.39*	.29[a]	.21
SLOF Vocational Subscale	.23	.37*	.28	-.20
Cognitive Assessment Inventory	.41*	-.30[a]	.54*	.20
Self-Reported				
SLOF Interpersonal Functions	.24	-.13	-.06	-.58*
SLOF Activities Subscale	.11	.14	-.06	-.40*
SLOF Vocational Subscale	.08	.00	.22	-.59*
Cognitive Assessment Inventory	.22	-.29	.06	.60*

Need for Co-Primary Measures

- Regulatory agencies have asked for co-primary measures in AD and SCZ trials

- Both Performance-based and Interview based measures have been used

- The Performance-Based measures are typically functional capacity measures

- The FDA has allowed the use of interview-based measured aimed at functional cognition in previous studies

VIM Study Results

	Pearson r	r²
TABS	.57	.32
UPSA	.67	.45
ILS	.51	.26
CAI	.23	.05
CGI-cog.	.38	.14

Shared variance (r squared) with cognitive performance
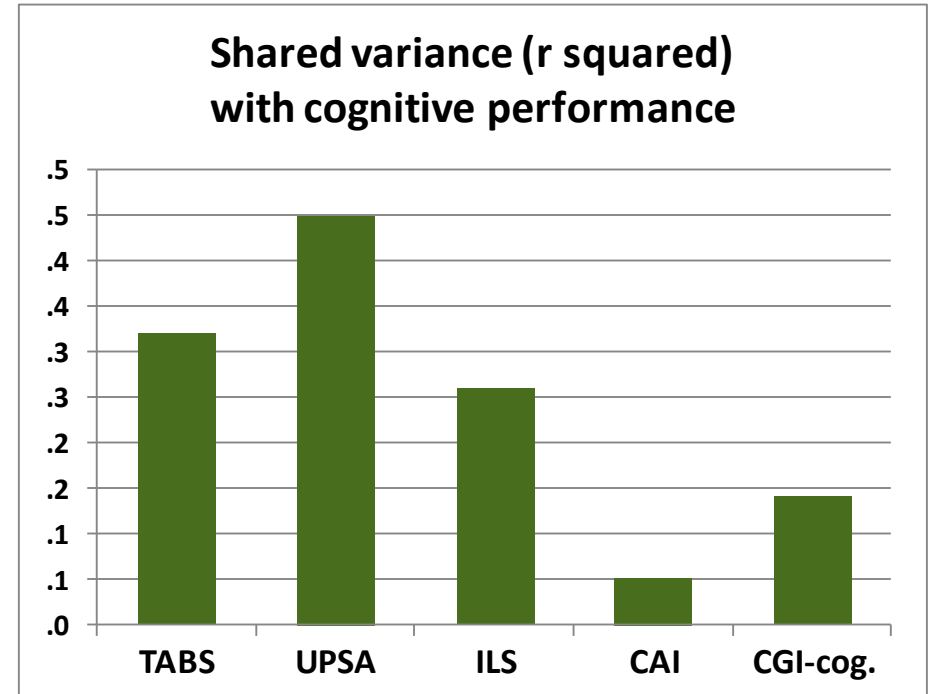
UPSA > ILS > CGI-cog. CAI

TABS > CGI-cog, CAI

Note. VIM: Validation of Intermediate Measures

UCSD Performance-Based Skills Assessment (UPSA)

- Developed as a performance-based measure of everyday living skills

- Five domains
  - Comprehension/Planning
  - Finance
  - Communication
  - Mobility
  - Household Chores

- Scaled to 100-point score

- Several previous versions

Interviews vs. Performance based Co-Primaries

- Most studies use either performance-based or interview based co-primary measure
- In this study a performance-based cognitive assessment was correlated with
  - Self report
  - Informant Report
  - Interviewer impression based on two reports
  - UPSA

Correlation Between Cognition Scores, Functional Capacity, and Ratings of Impaired Cognition in Schizophrenia


Pearson r
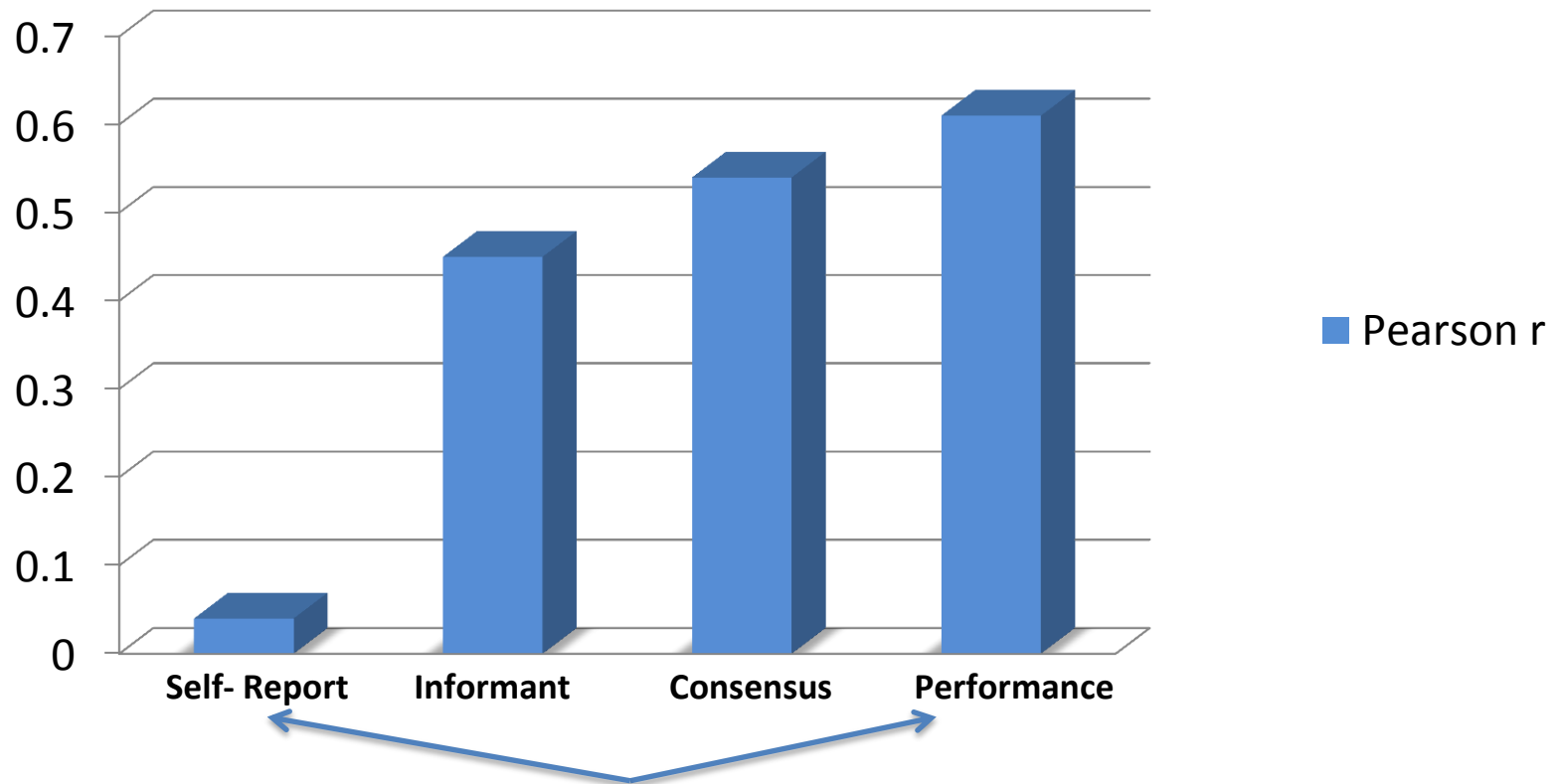
Performance More Closely Related to Cognitive Functioning than Self-Report

Keefe et al., 2006

Validity in Other conditions

- The UPSA has been widely used in other conditions, including bipolar disorder and bipolar depression

- There is considerable evidence of evidence of validity in Bipolar disorder with predominant depression

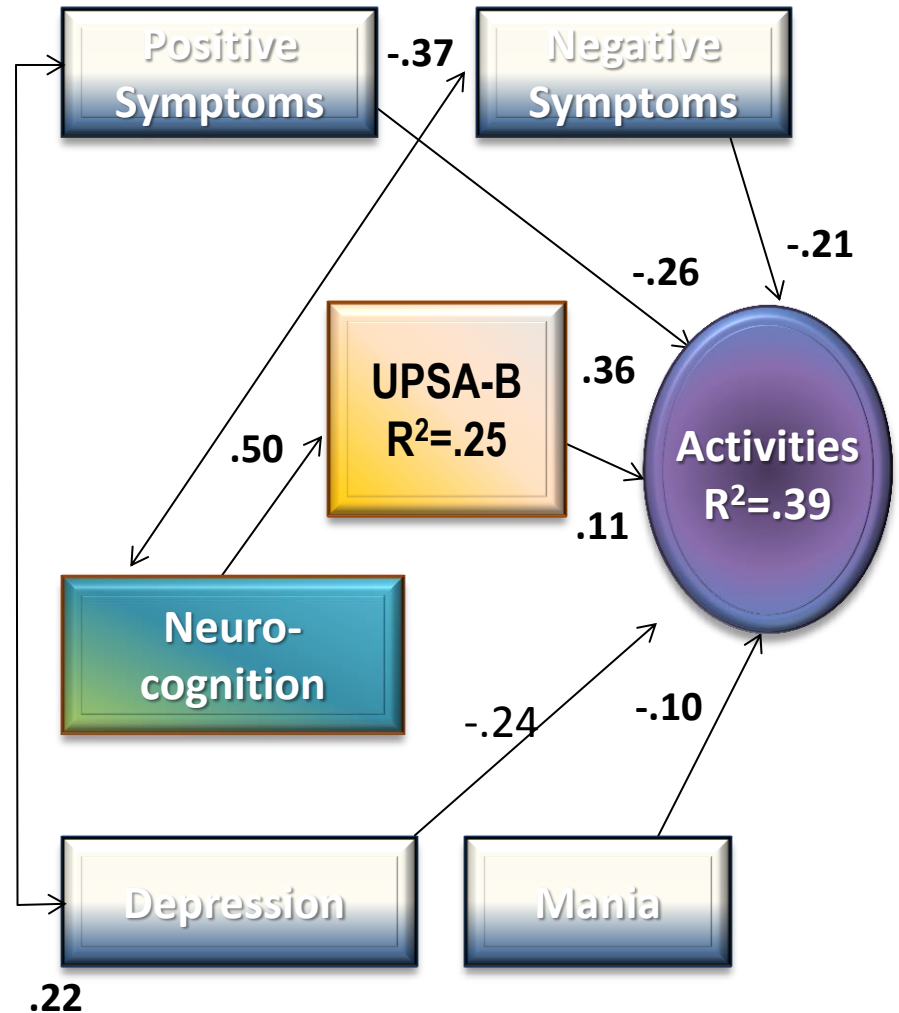# UPSA B Scores as a Function of Residential Status
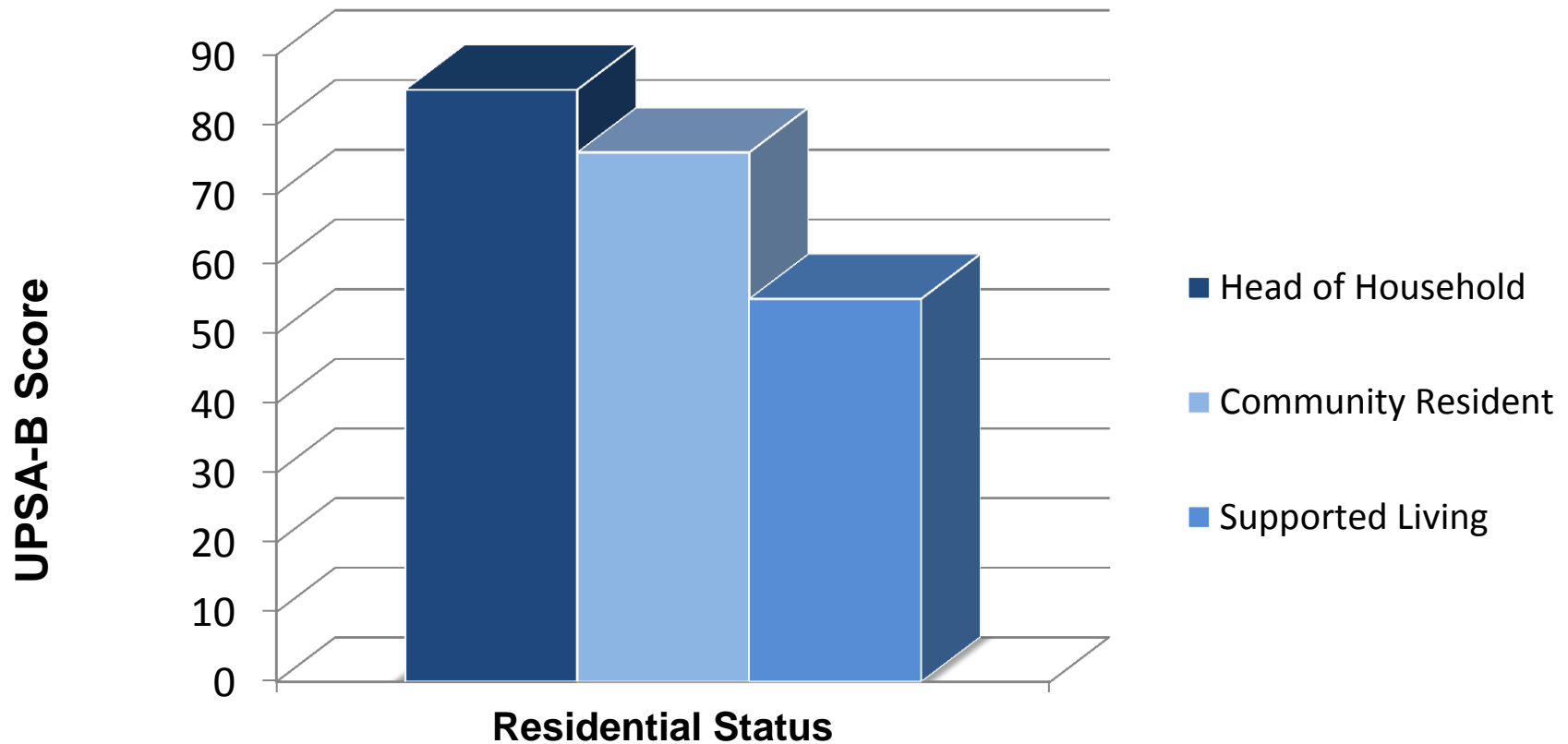
Note: Diagnostic effect: F = 0.66, p = .417;

Mausbach et al., in 2010

Schizophrenia
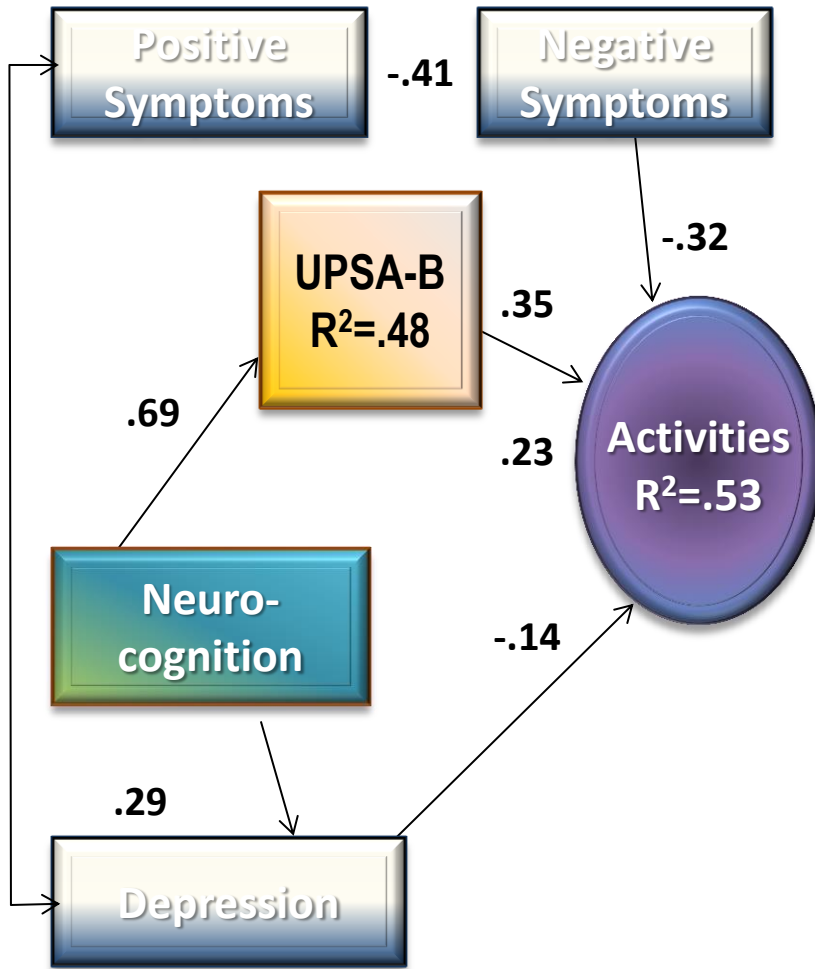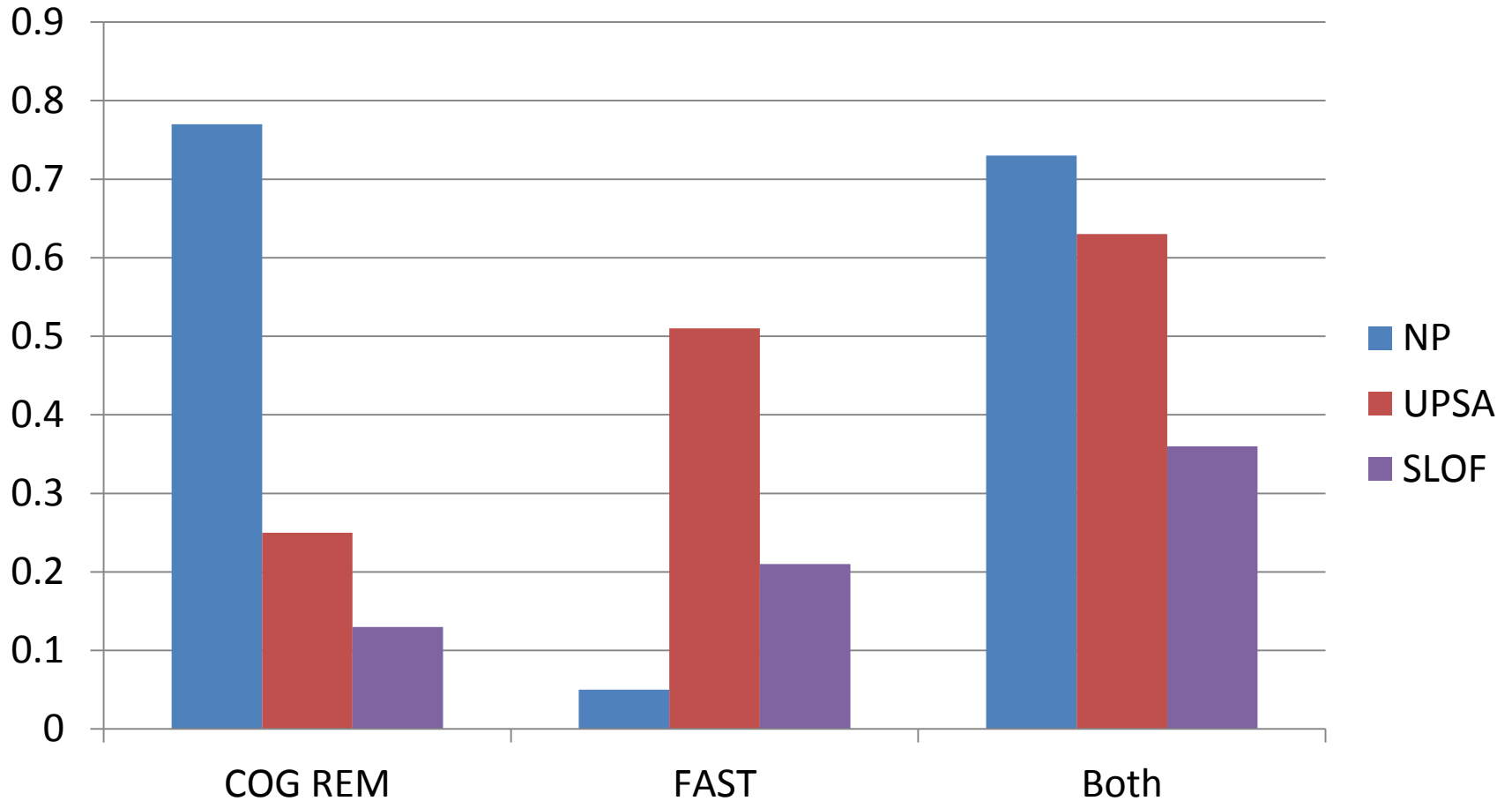
Bipolar

Bowie et al., 2010

Sensitivity to Treatment for co-primary measures

- Several studies have found the UPSA to be sensitive to treatment in pharmacological studies of schizophrenia
  - Davunitide
  - Pregnenolone
- Similarly, interview based measures have shown sensitivity as well

Outcomes of the Study:
# End of Treatment

Effect Size (Cohen's d)

FAST: Functional Adaptation Skills Training

Uses of the UPSA Outside SCZ and BD

1. UPSA scores correlate with NP performance in healthy older controls
2. UPSA scores separate MCI from AD and HC
3. UPSA scores correlate with MCCB scores and lifetime functional outcomes in PTSD
4. UPSA scores correlate with NP test scores and current residential and vocational outcomes in schizotypal PD
5. UPSA scores correlate with WCST performance in abstinent methamphetamine abusers
6. Lower UPSA Scores predict poorer response to diabetes management programs in non psychiatric patients

SCoRS (Visits with Informant Present)

SCoRS Interviewer Total (Subjects with Informants)
(Adjusted Mean Change from Baseline)

1 mg vs. placebo:
P = 0.003
ES = 0.51

EVP-6124 0.3 mg
EVP-6124 1.0 mg
Placebo
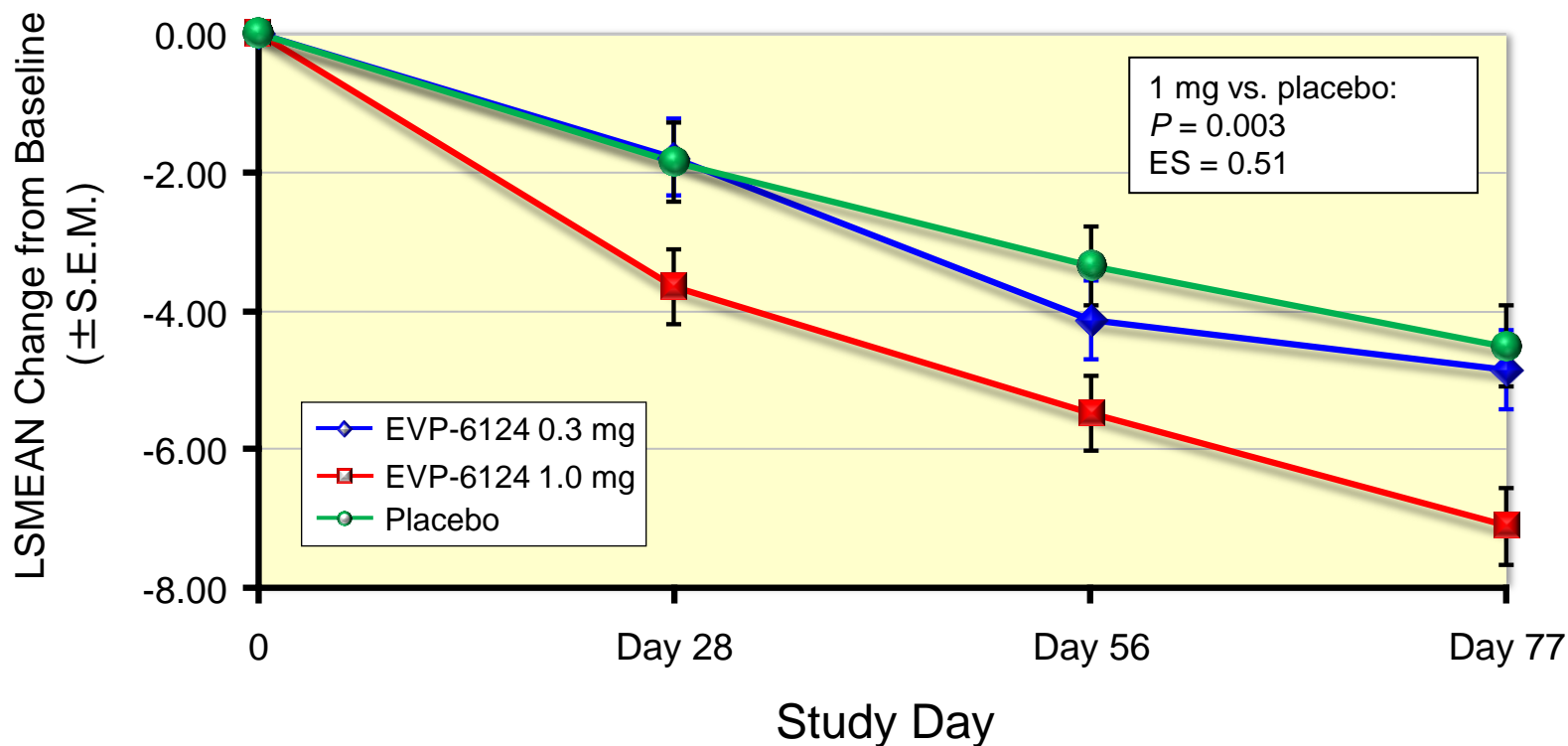
SCORS: Schizophrenia Cognition Rating Scale