Prospective Trials to Assess Treatment Effects on Cognition in Schizophrenia: Challenges and Results

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Disclaimer

- The strategies, views, and opinions expressed in this presentation are solely those of the authors and do not necessarily reflect the policies and procedures of Janssen Pharmaceutica INC
- The purpose of this presentation is to highlight methodological challenges in the assessment of cognitive functions in schizophrenia and does not aim at making any claims related to the effect of drugs on cognition

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Categories of Issues

Design

- Patient selection, use of concomitant psychotropics
- Duration of treatment
- All cause attrition

Data collection and management

- Missing data, out of range
- Calculation of a global/composite score
- Logistic issues – global trials, conventional/computerized

Interpretation of results

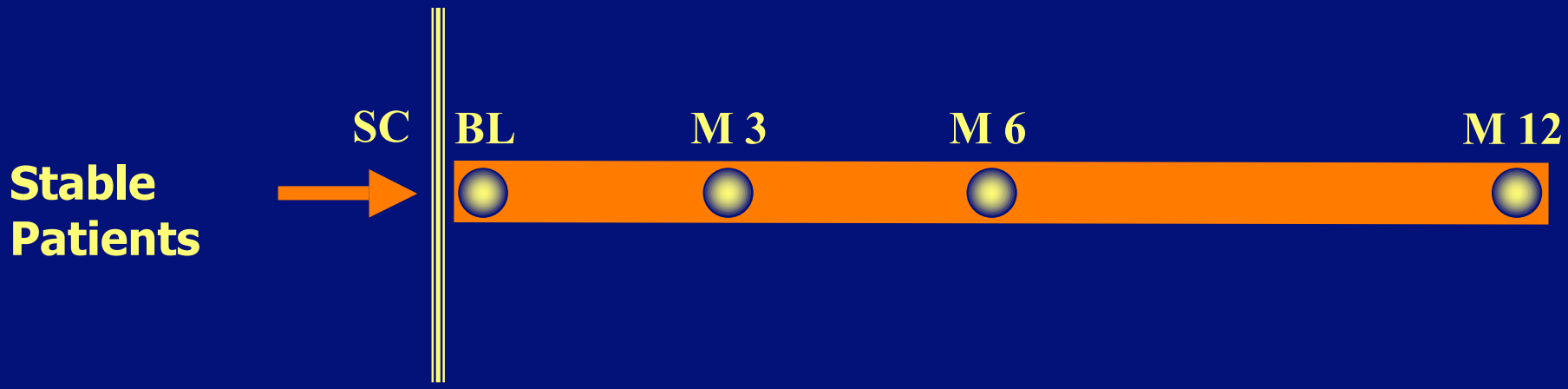
- Individual domains versus composite score
- Contribution of symptom and cognitive change
- Sensitive/validated functional outcomes

MATRICS[1]-Proposed Study Design

- DSM-IV schizophrenia (Q1)
- Symptom and treatment stability (Q2-5)
- Level of impairment (Q6-7)
- Outcome measures: primary and co-primary (8-12)
- Evaluation frequency and trial duration (Q13 & 17)
- Interactions between symptom fluctuation and cognition (Q14-15)
- Comparison groups (Q16)

[1] Buchanan et al, Schizophrenia Bulletin Jan 2005

Study SCH 401: Design



	BL	M 3	M 6	M 12
Symptoms	X	X	X	X
Cognition	X	X	X	X
Functioning	X		X	X

Sites in the USA, Canada, Argentina and Chile (English and Spanish)

Study SCH 401: Entry Criteria

- Male or female (non fecund) 18-70 years
- DSM-IV diagnosis of schizophrenia or schizoaffective disorders (≠ MATRICS)
- Exclude patients currently treated with clozapine, carbamazepine or recently treated with ECT or investigational drugs
- Exclude patients with unstable physical conditions
- Newly prescribed adjunctive therapies other than lorazepam not allowed

Study SCH 401: Stability Criteria

Criteria for stability

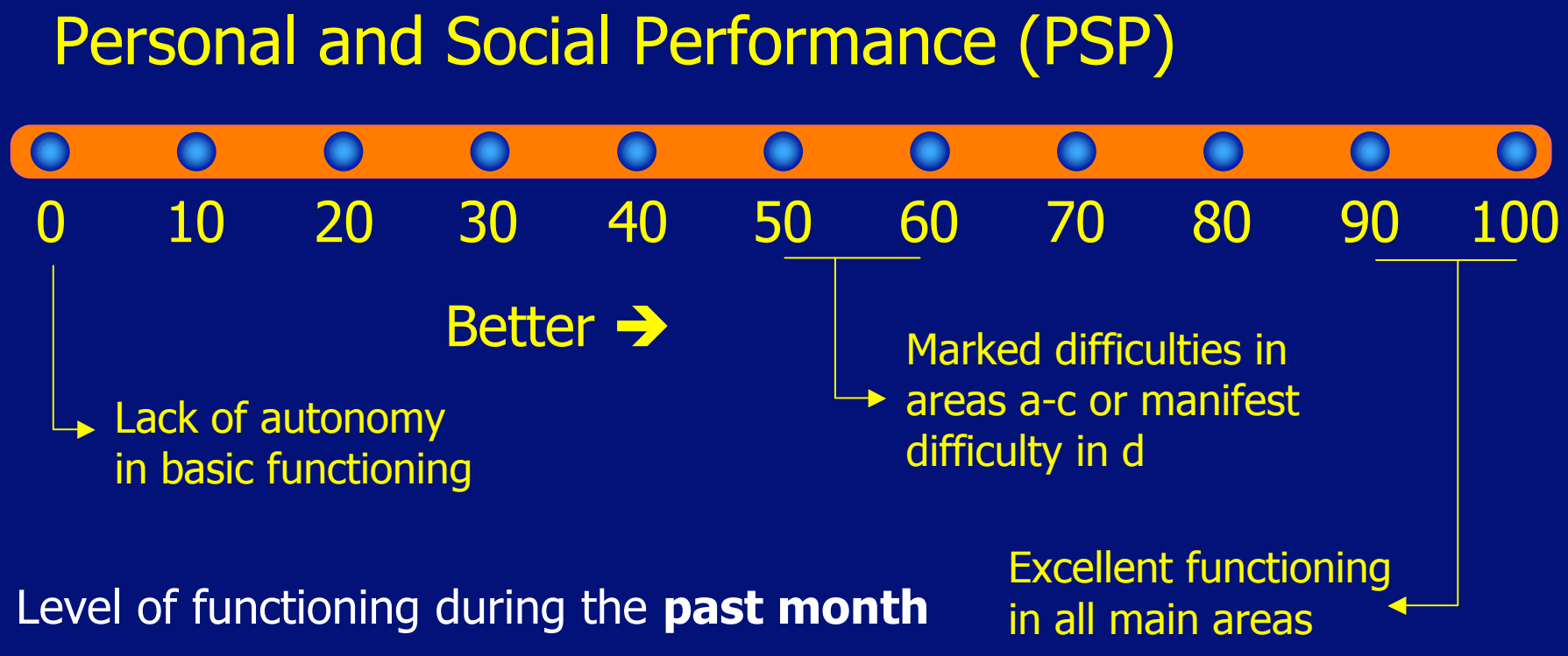
- Symptomatic stability prior to study entry
  - Lack of psychiatric hospitalization (4 months)
  - Lack of suicidal behavior (4 months)
  - No need for acute crisis intervention (4 weeks)
- Treatment stability
  - Treated with stable doses of oral APs (≥ 4 weeks; MATRICS: 6-8 weeks)

Study SCH 401 Outcome Parameters *

- Psychopathology
  - PANSS and PANSS factors (Positive, negative, disorganized, depression/anxiety)
- Functioning
  - Personal and Social Performance Scale (PSP)
  - Strauss-Carpenter Level of Functioning (LOF)

* Limited to outcomes addressed in this presentation

Personal and Social Performance Scale (PSP)



a – Socially useful activities including work and study
b – Personal and social relationship
c – Self care
d – disturbing and aggressive behavior

Strauss-Carpenter Level of Functioning (LOF)

Overall Level of Function (Consider as baseline a hypothetical "normal" person with full employment, meaningful social relationship, no symptoms etc.)

- **4** No impairment
- **3** Slight impairment most of the time. Or moderate impairment on rare occasions
- **2** Moderate impairment some of the time
- **1** Severe impairment some of the time, or moderate impairment continuously
- **0** Continuous and severe impairment

MATRICS Cognitive Battery

- Total battery time approx 60 min
- Domains assessed (total 7):
  - Speed of processing: category fluency, BACS (symbol coding), Trail making A
  - Attention/vigilance: CPT (identical pairs)
  - Working memory: Verbal, University of Maryland (letter number span), non-verbal, Wechsler Memory Scale-III (spatial span)
  - Verbal learning: Hopkins Verbal Learning Test (HVLT)
  - Visual learning: Brief visuospatial memory test (BVMT)
  - Reasoning and problem solving: Neuropsychological Assessment Battery (NAB)
  - Social cognition: MSC Emotional intelligence test

MATRICS website

Study SCH 401: Cognitive Battery

- Total battery time approx 60 min
- Domains assessed (total 7 + motor speed):
  - CPT – AX, Flanker, Identical Pairs, Strategic Target Detection test: attention/vigilance, working memory
  - Word List Memory test: verbal learning and memory
  - Face Memory test: visual learning and memory
  - Object Working Memory test: working memory
  - Strategic Target Detection test: speed of processing, reasoning and problem solving
  - Set Shifting test: reasoning and problem solving
  - Penn Emotional Acuity Test: social cognition

Study SCH 401 - Results

Study SCH 401
Baseline Demographics

	Cognition N= 282	ITT: N = 323
Gender (F/M)	110 (39%)	122 (38%)
Race		
Caucasian	133 (47.2%)	159 (49%)
Hispanic	56 (19.9%)	62 (19%)
African	77 (27.3%)	84 (26%)
Age (y mean ± SD)	41 ± 12.22	41 ± 11.9
Diagnosis: Schizophrenia	225 (79.8%)	258 (80%)
Age at Onset (y mean ± SD)	25.3 ± 9.6	25.4 ± 9.4
Tobacco use (%)	165 (58.5%)	194 (60%)

Data on file , Janssen

Study SCH 401
Symptom Severity at Baseline

	Cognition (N = 282)	ITT (N = 323)
PANSS Total	67.0 ± 16.6	66.5 ± 16.4
Positive[1]	18.4 ± 6.1 (21.7%)	18.4 ± 6.0 (21.7%)
Negative[1]	17.9 ± 5.7 (25.5%)	17.7 ± 5.7 (25.5%)
Disorganized[1]	15.6 ± 4.8 (20.0%)	15.4 ± 4.7 (20.0%)
Depression[1]	9.0 ± 3.3 (20.8%)	9.0 ± 3.3 (20.8%)
Hostility[1]	6.1 ±2.0 (8.3%)	6.0 ±2.2 (8.3%)
CGI-S	3.5 ± 0.84	3.5 ± 0.82
% with Remission[2]	98 (35%)	100 (31%)

[1] Marder et al, 1997
[2] Andreassen et al 2005

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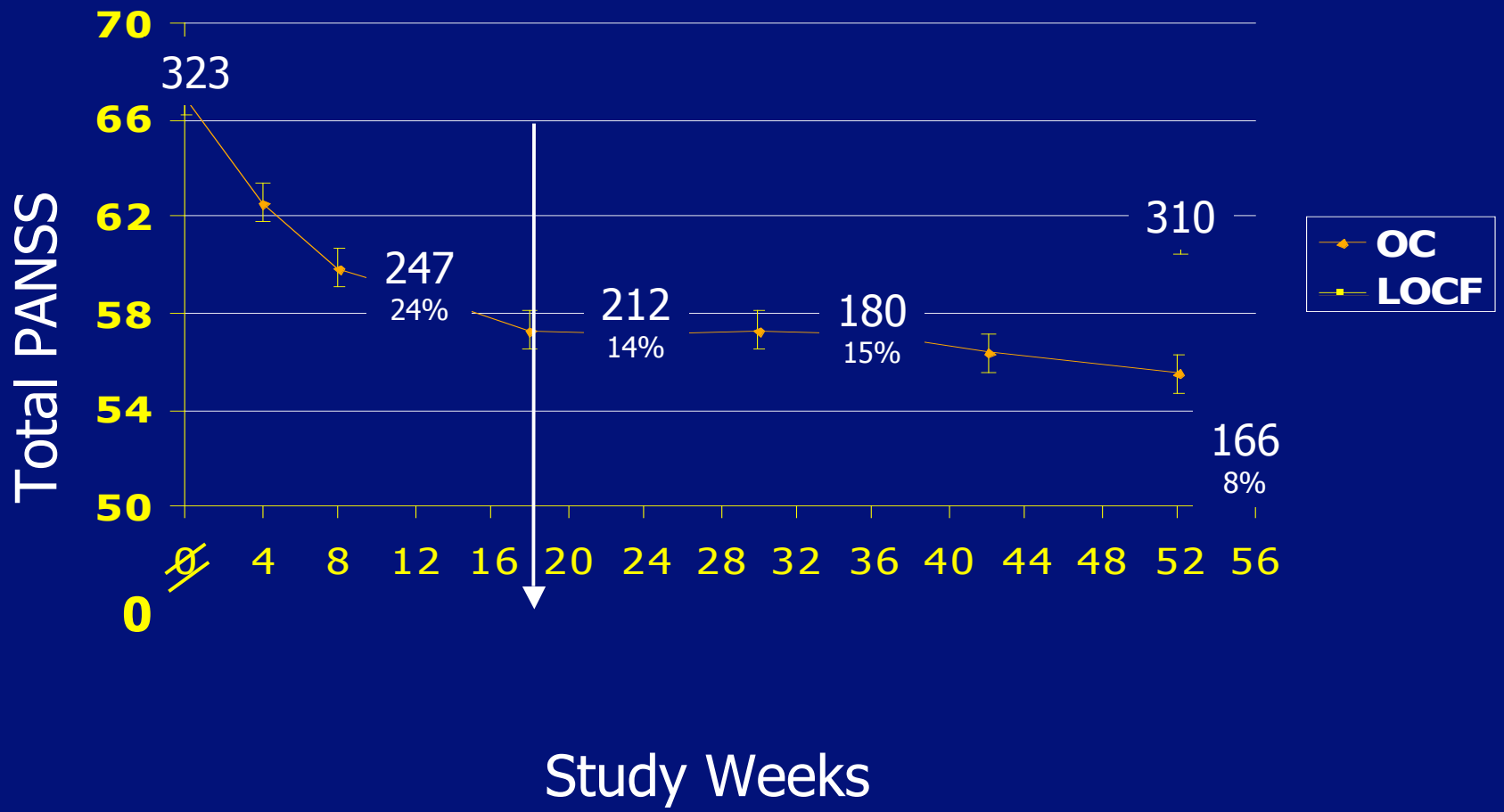
Study SCH 401:
Total PANSS - Change over time



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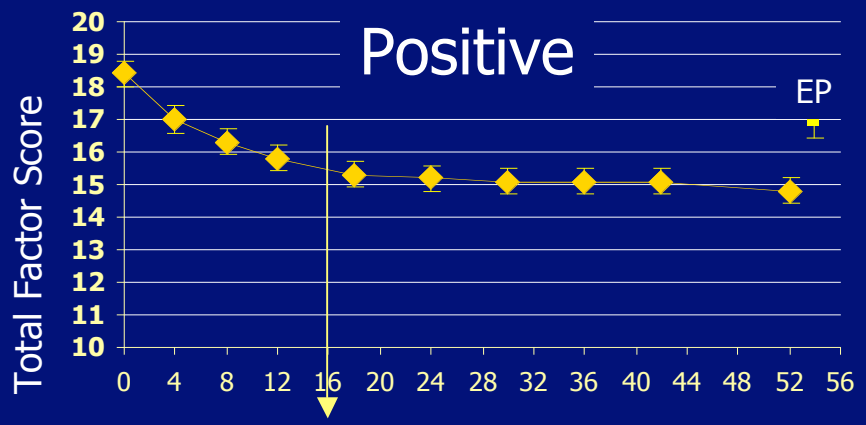
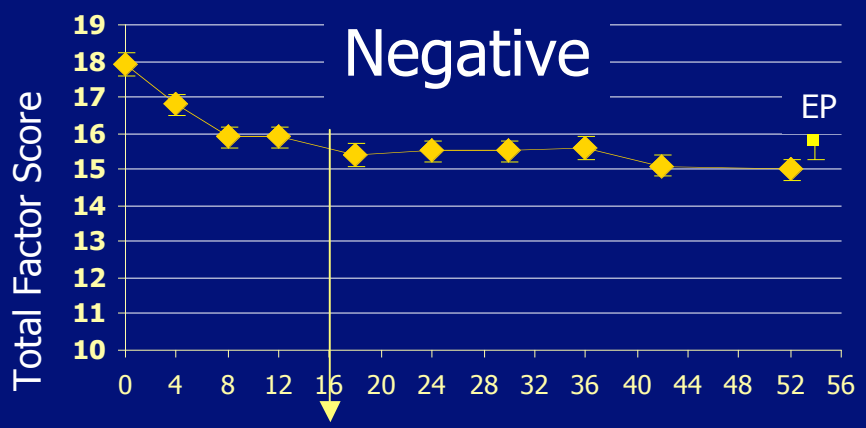
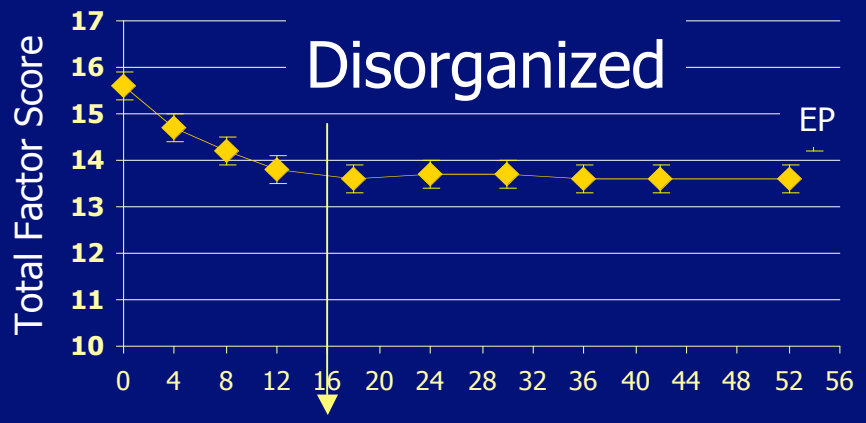
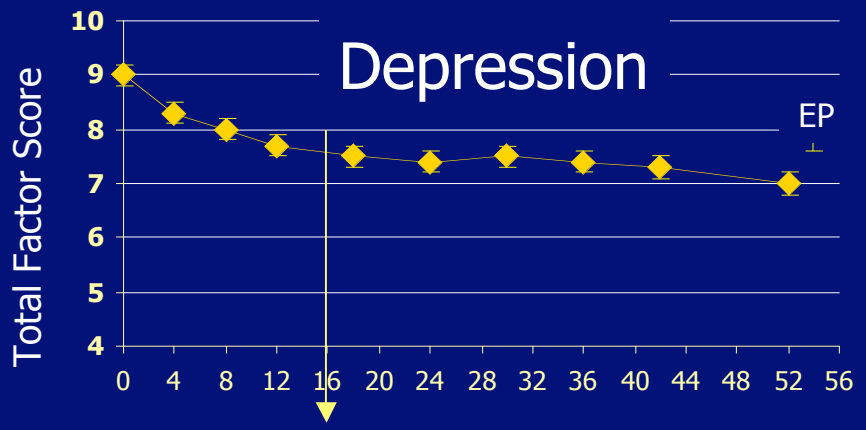
Study SCH 401 - PANSS Factors









Study Weeks

Study Weeks

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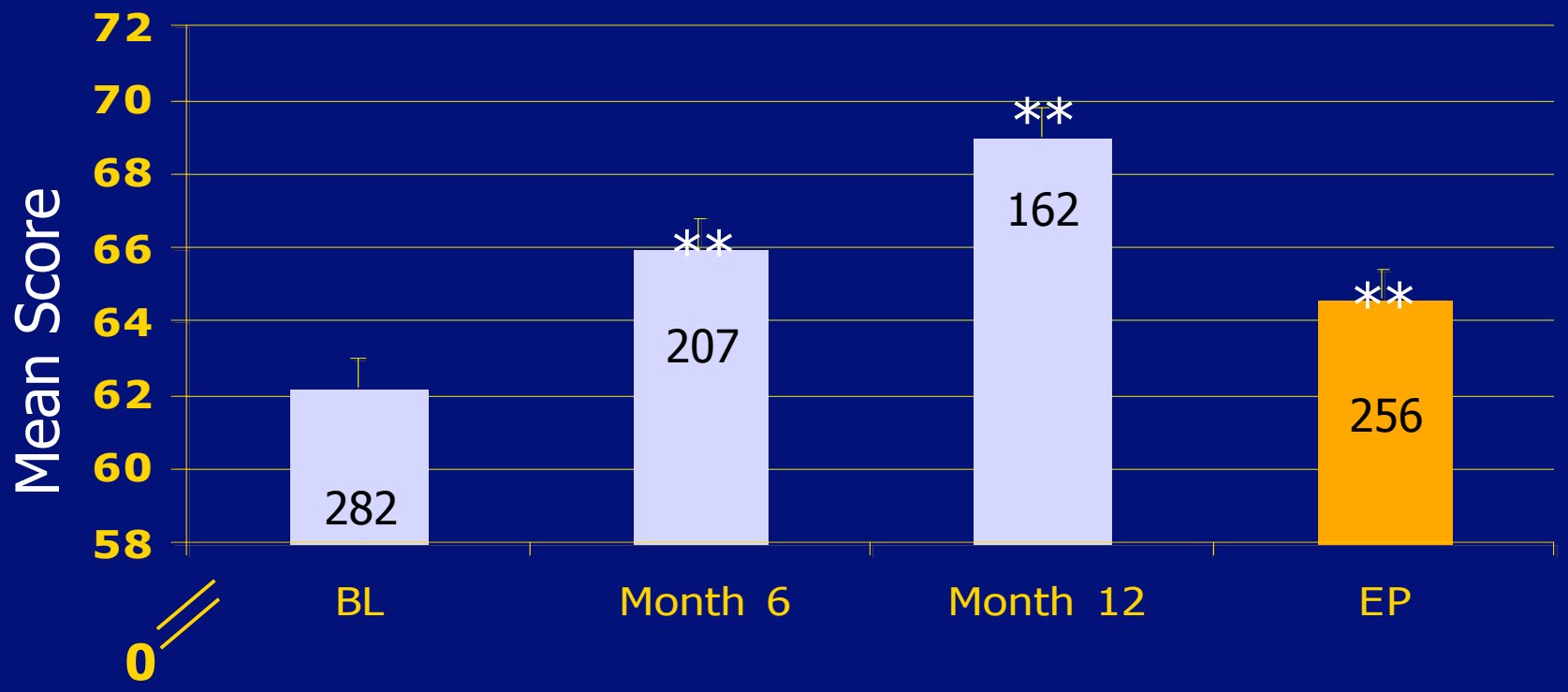
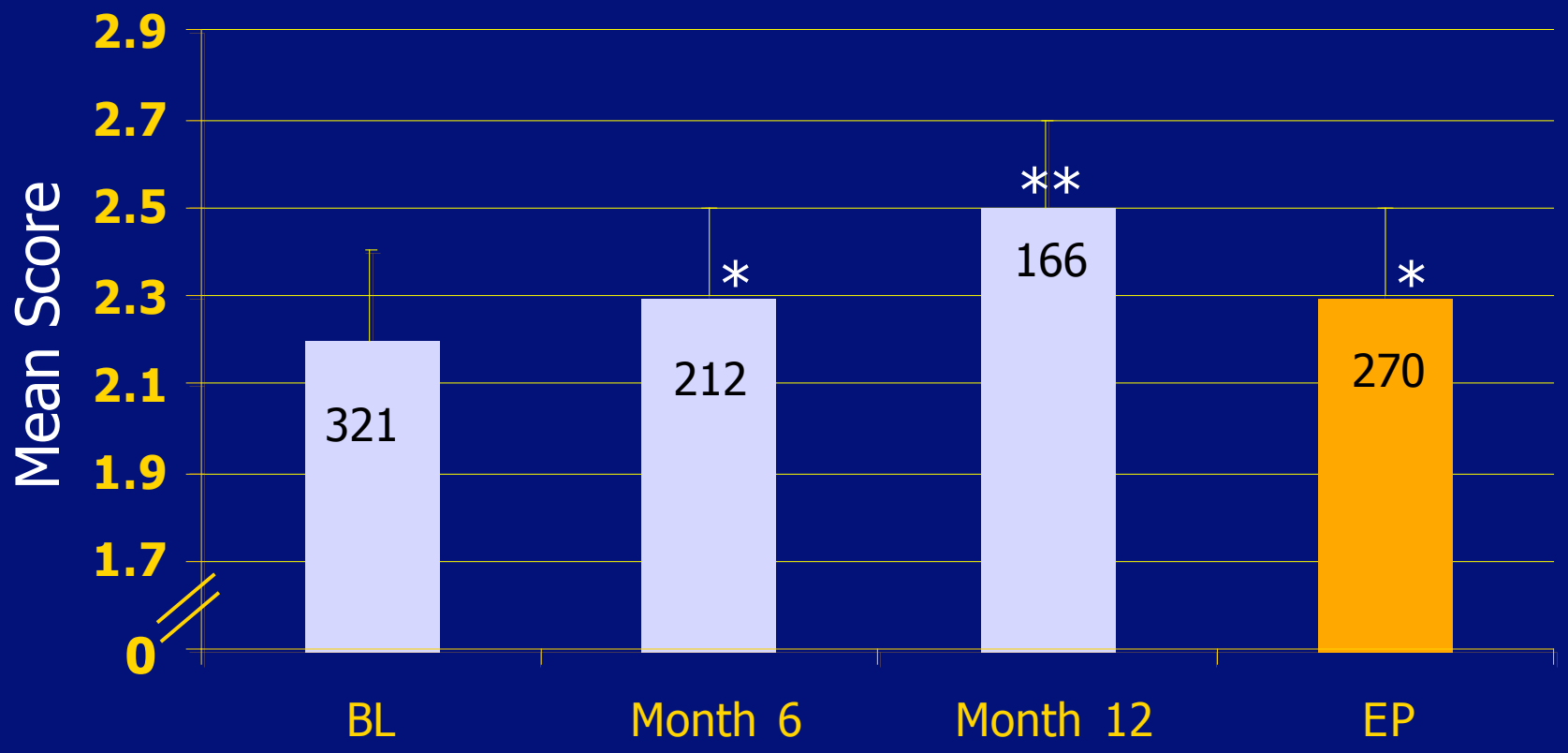
Study SCH 401
PSP - Change over time



** p<0.01

Presented at APA, 2005

Study SCH 401
Overall LOF - Change over time



* p<0.05; ** p<0.01

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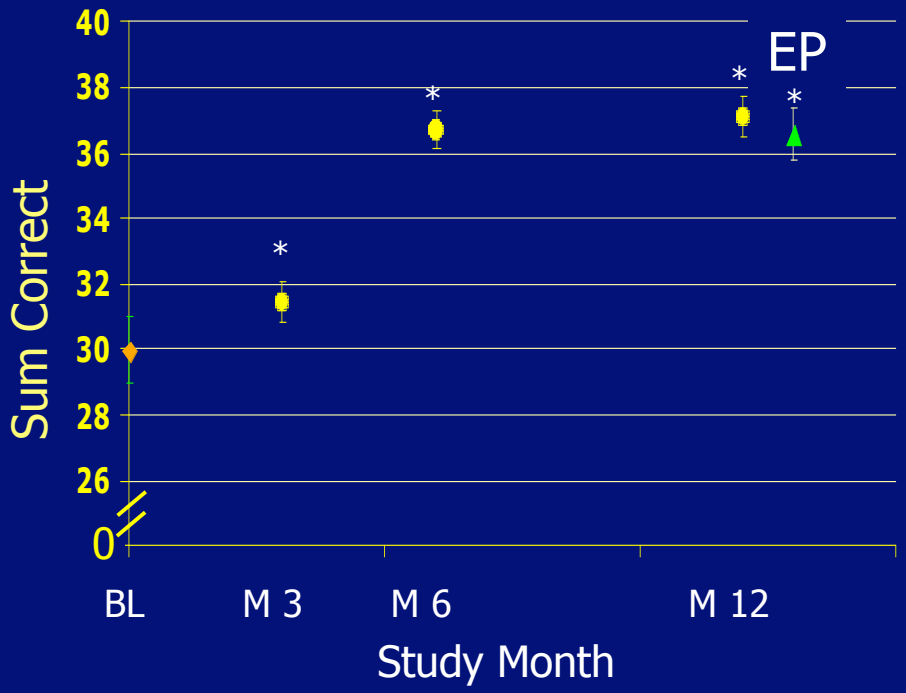
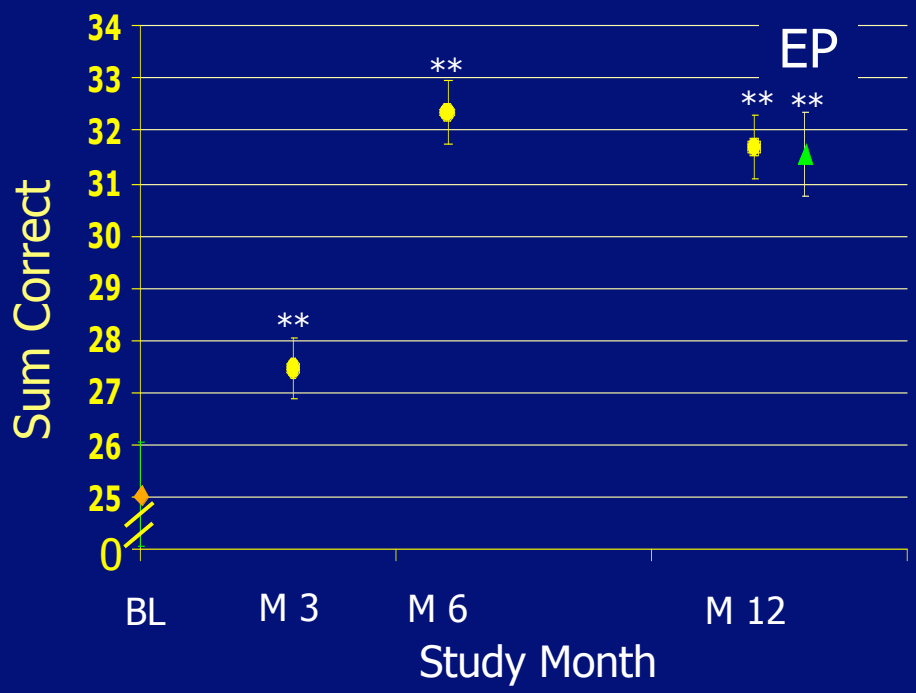
Study SCH 401
Attention and Vigilance (Flanker CPT)



Congruent

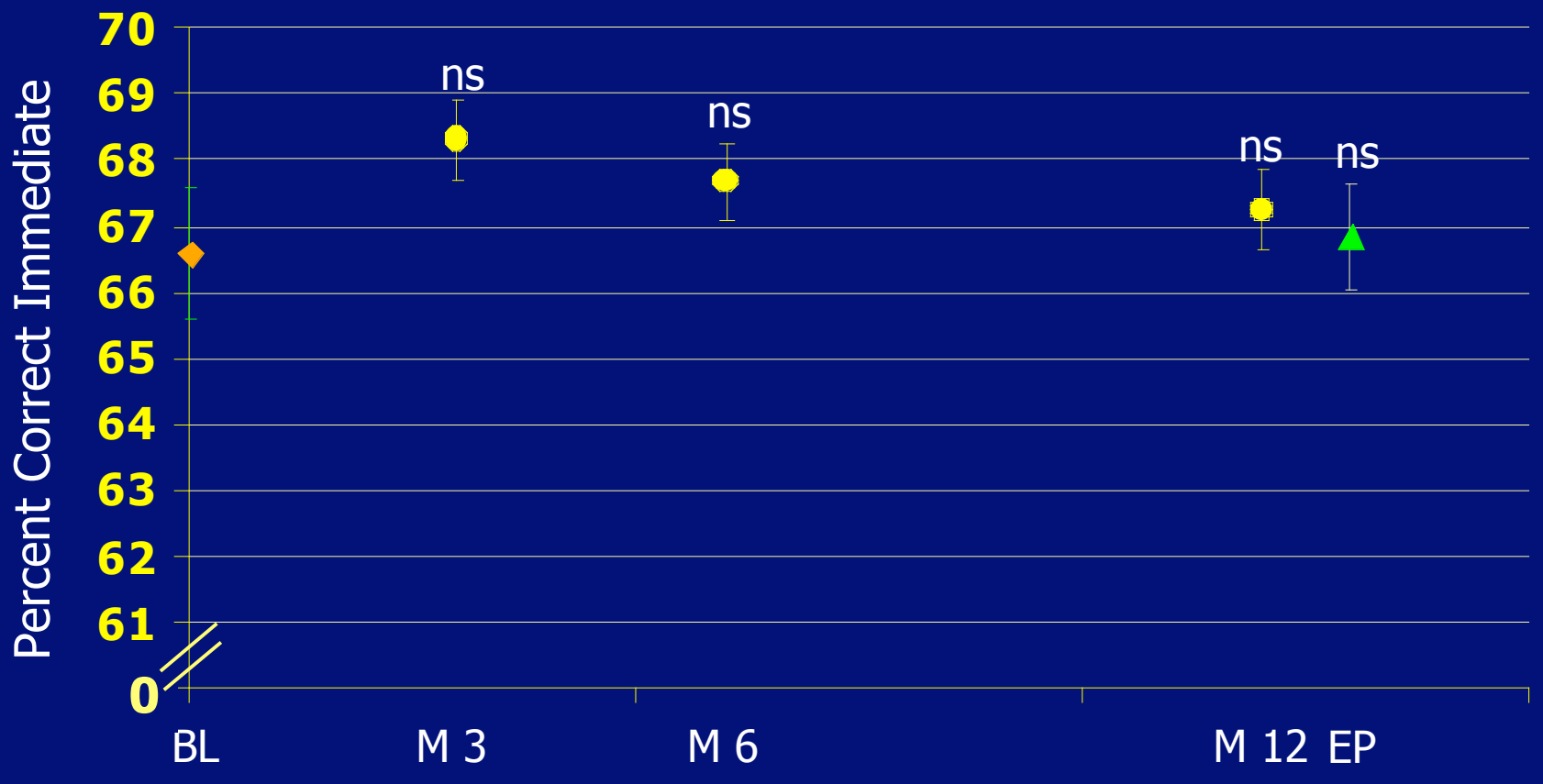


Incongruent

* p<0.05; ** p<0.01

Data on file , Janssen

Study SCH 401
Visual Memory (FMT)



ns = non significant

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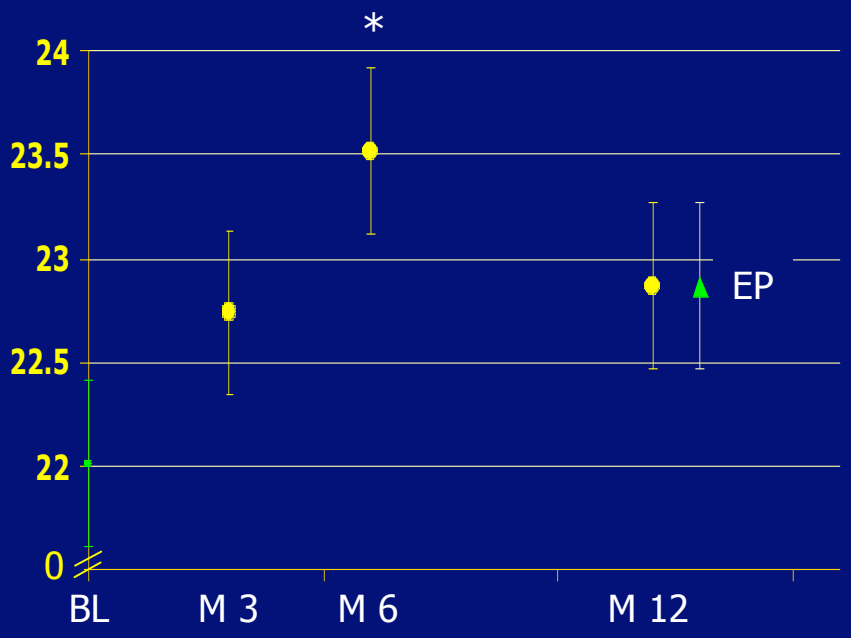
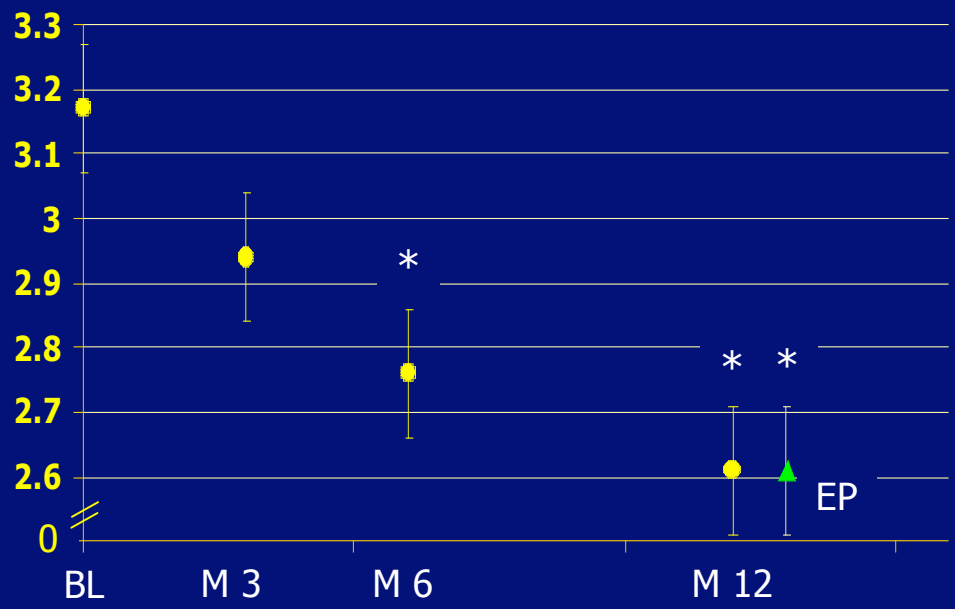
Study SCH 401
Social Functioning (PEAT)

Total Correct



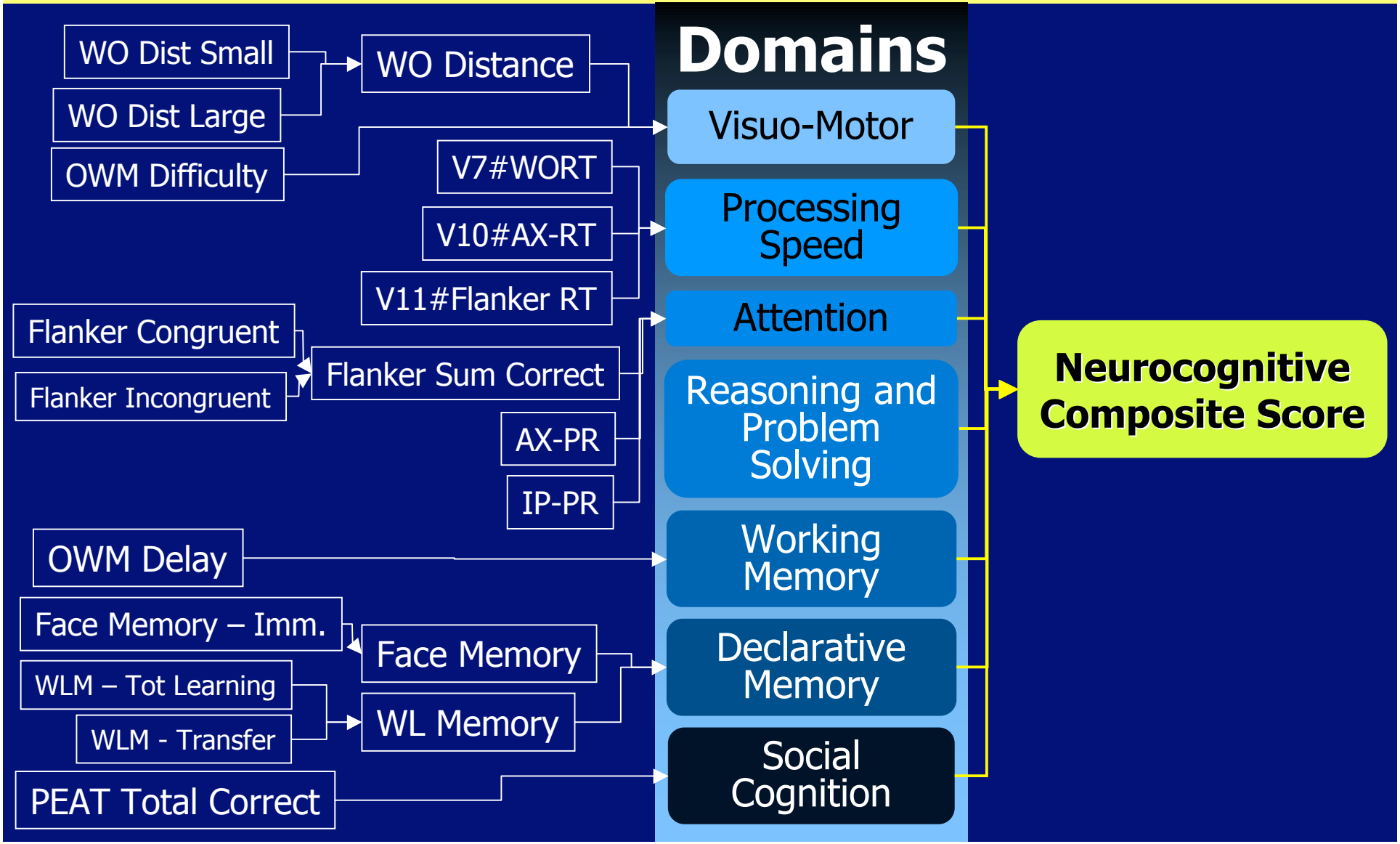
Mean RT



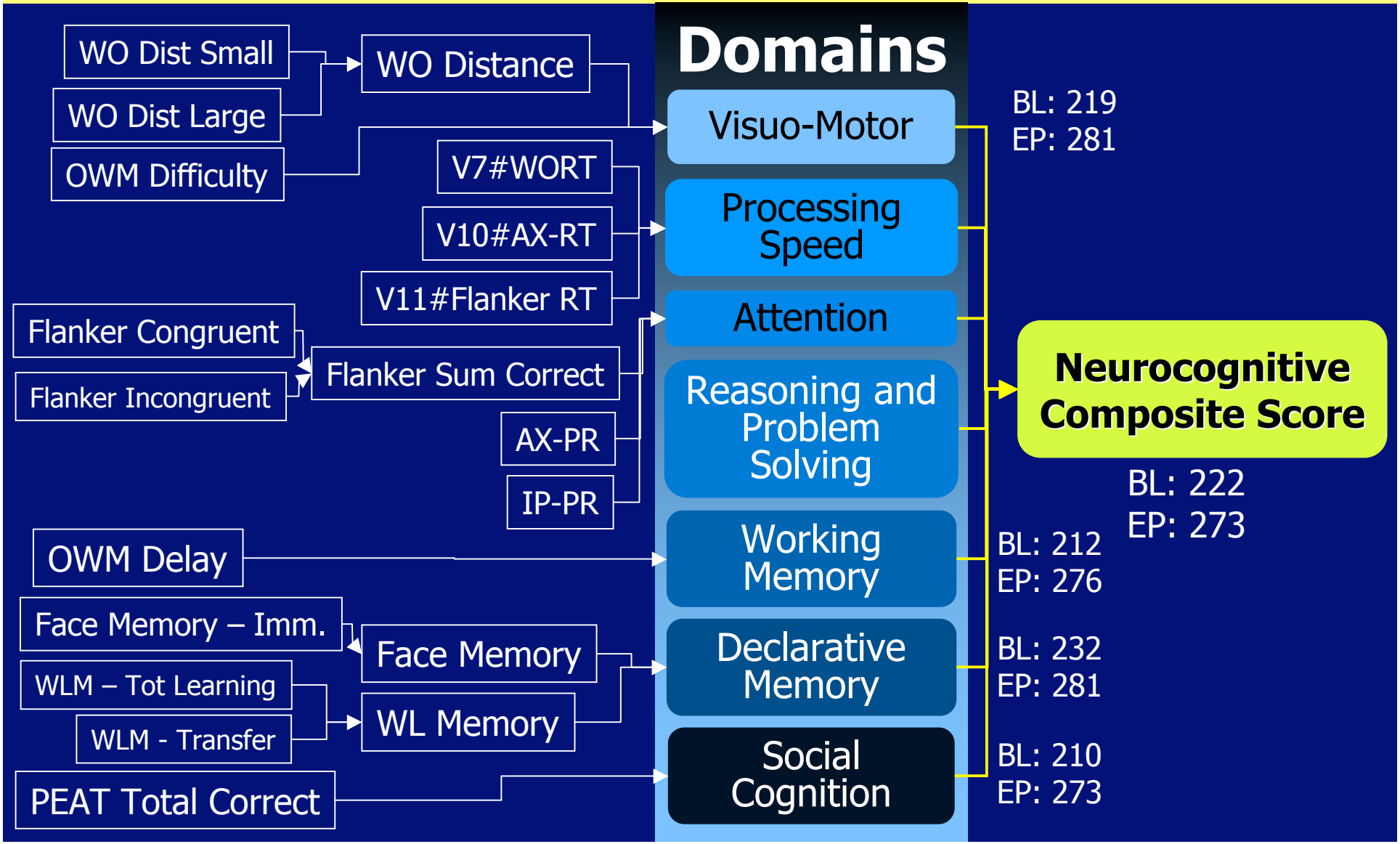
Data on file , Janssen

Data Collection

Computing a Composite Score For Cognition



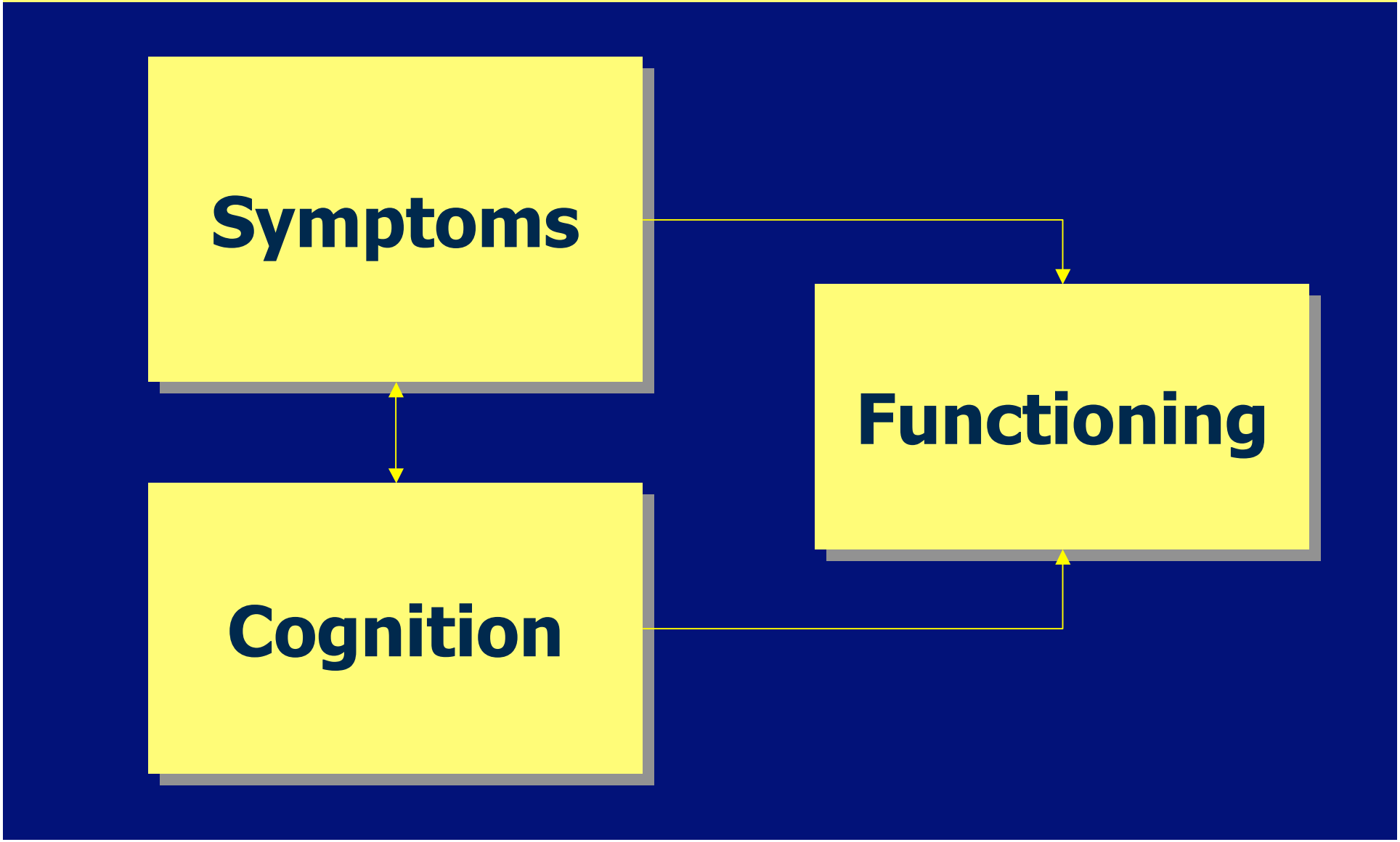
Computing a Composite Score For Cognition



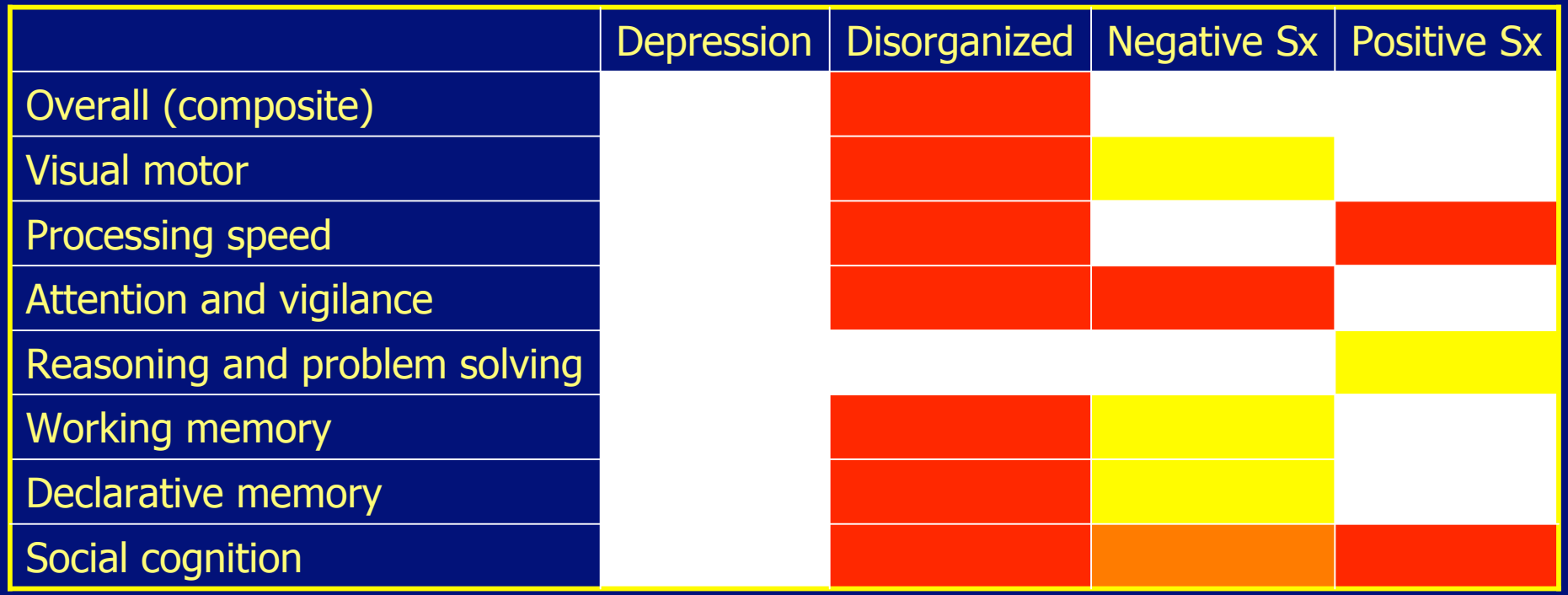
Data interpretation

Correlations Between Cognitive Domains, Symptom Severity and Social Functioning

Understanding the Relationship Between Symptoms, Cognition and Functioning



Cross-sectional Correlations* Between Cognitive Measures and Symptom Severity



* Pearson correlations at EP

ns P<0.05 P<0.01 P<0.001

Data on file , Janssen

Cross-sectional Correlations Between Cognitive Measures and Function

	PSP	LOF
Overall (composite)		
Visual motor		
Processing speed		
Attention and vigilance		
Reasoning and problem solving		
Working memory		
Declarative memory		
Social cognition		

*Pearson correlations at EP

Data on file , Janssen

Interactions between Symptom Severity, Cognition and Functioning

- Examined the contribution of change in symptom severity and cognition on social and overall functioning
- Used linear regression and included the following variables
  - Demographics: Age, gender, prior AP dose
  - PANSS factors
  - Cognitive domains

Main Contributors to Social Functioning

	PSP estimate	LOF estimate
R square	0.33	0.13
Age	ns	ns
Depression/Anxiety (change)	-0.52*	ns
Disorganized thoughts (change)	ns	ns
Negative Sx (change)	-0.49**	-0.2**
Positive Sx (change)	-0.43**	ns
Overall Cognition	ns	ns
Visual motor domain	-2.35*	ns

Linear regression used to examine change in functioning at LOCF
The following variables did not contribute to the PSP variance:
Age, gender, Prior antipsychotic dose, processing speed, attention, reasoning and problem solving, working memory, declarative memory and social cognition.

Summary of cross sectional and longitudinal correlations between cognitive measures, symptom severity and social performance/overall function

- Cognitive measures correlated
  - best with the PANSS disorganized thoughts and functioning
  - Less robust correlations are observed with positive and negative symptoms and least with depression/anxiety
- Correlations between cognitive domains and other variables
  - Social cognition, attention measures and processing speed showed the most robust correlations with majority of variables followed by memory (declarative and visual)
  - Reasoning and problem solving (executive functioning) correlated poorly with symptom severity and measures of functioning
- Change in PSP explained by change in positive, negative and depressive symptoms and visual-motor cognitive domain. LOF explained by change in negative symptoms

Conclusions

- Shortcomings of this approach
  - Large spectrum of severity: would exclusion of patients with some severe symptoms change the outcome?
  - Choice of instruments
    - Limitations of PSP
    - LOF
  - Contributions of analytical methodology used for the composite score
  - "Missingness" significantly contributes to loss of power
  - Observational design (lack of comparator)

Conclusions

- Attrition rate of 24% (month 1-3), only slightly lower (15%) over most of the remaining risk period.
- Improvement of psychiatric symptoms, specially negative symptoms contributes significantly to improvement in functioning
- Improvement in cognition was not associated with improved functioning