Assessing Cognitive Function in Bipolar Disorder: Challenges and Recommendations for Cognitive Trial Design

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Disclosures

- Advisory Boards -- Dainippon Sumito Pharma; Takeda and Lundbeck
- Off-label data included for Mirapex© (pramipexole)
- Funding from NIMH; Stanley Medical Research Institute; NARSAD

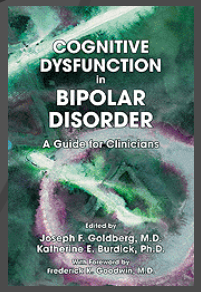
A Brief History of Neurocognition in BPD

- **1898**: Kraepelinian's Dichotomy

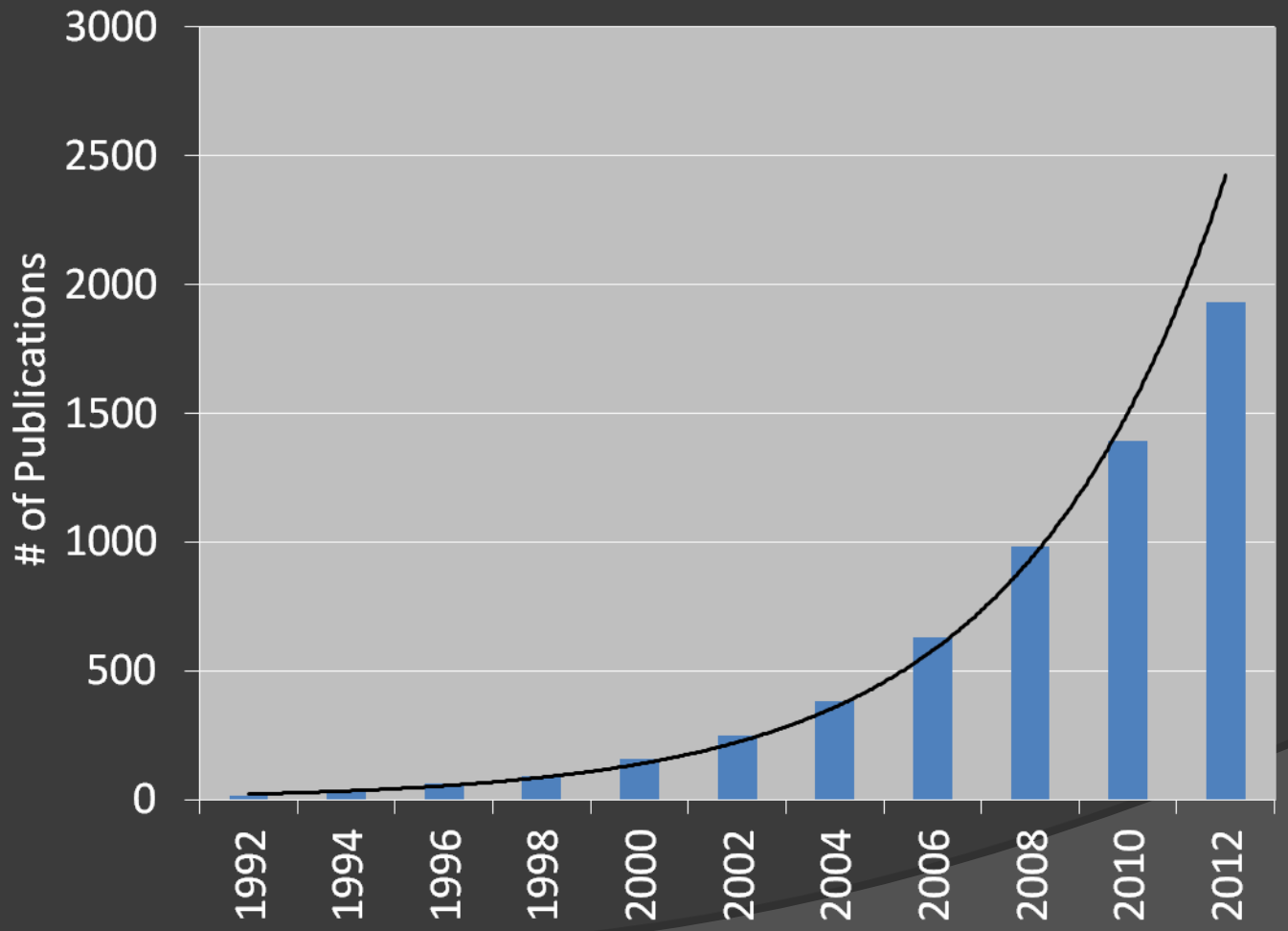
- **1978**: The first paper on BP and cognition

Cognitive functions in manic-depressives: effects of lithium and physostigmine.
R Telford and E P Worrall
BJP 1978, 133:424-428.
The British Journal of Psychiatry

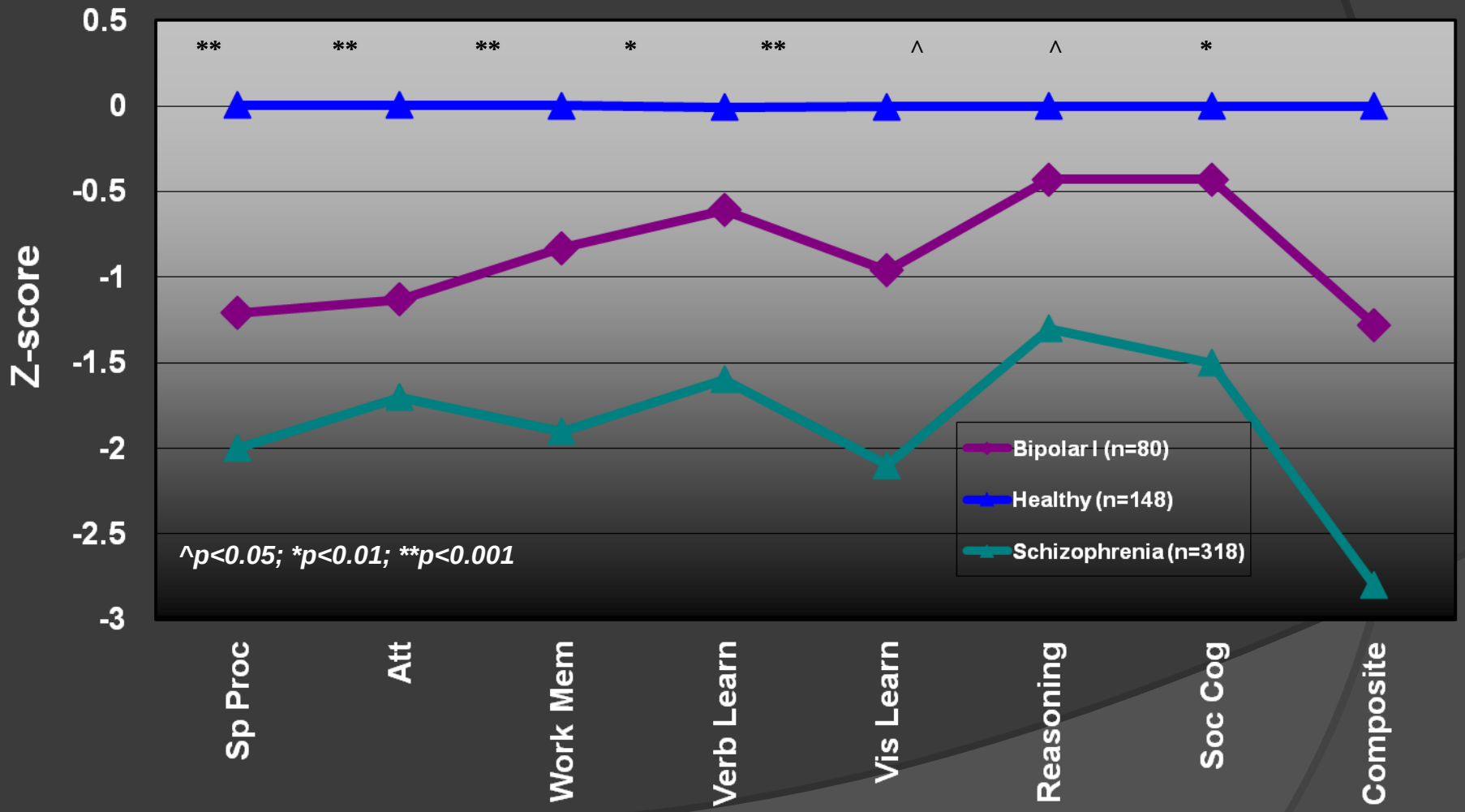
- **1998**: Less than 10 papers published on BP and cognition
  - More than 200 published in SZ
- **2008**: Over 500 papers published on BP and cognition



2013: Nearly 2000 Papers Published

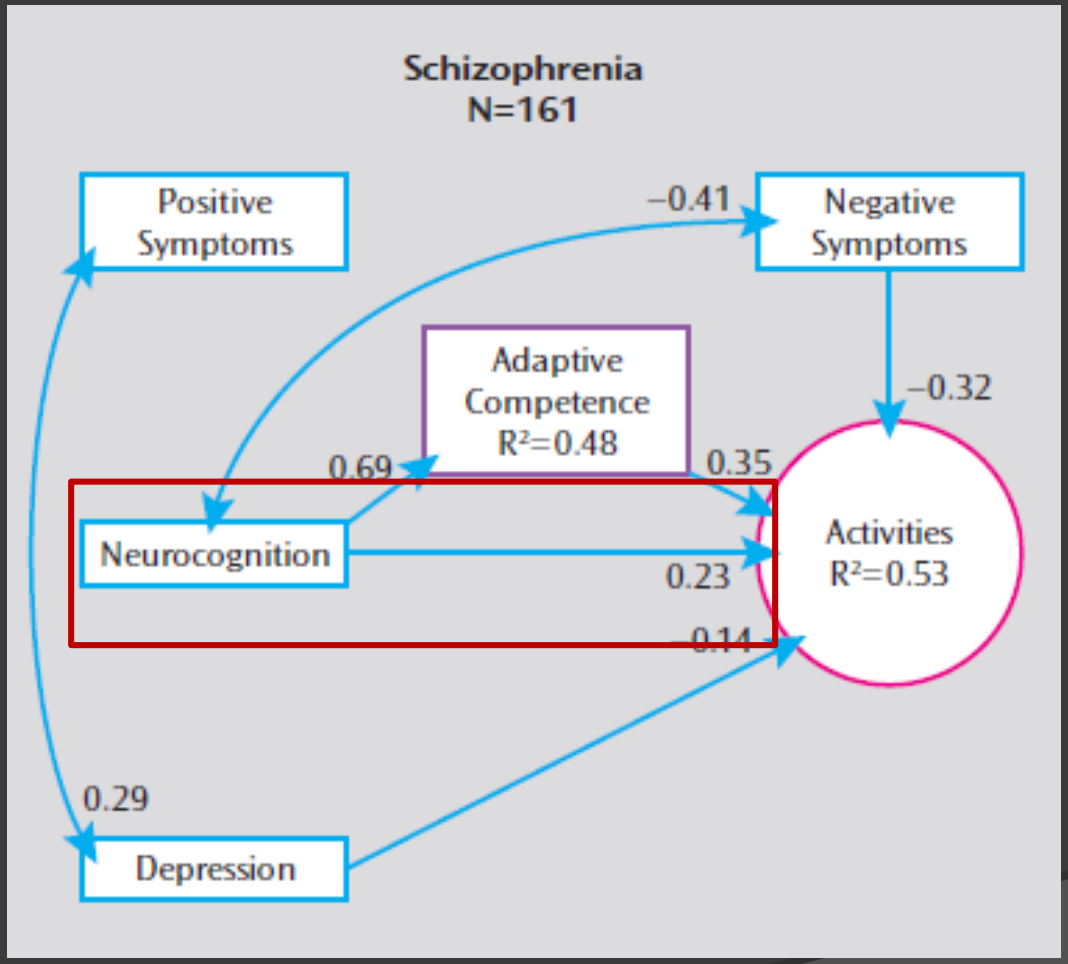


Cognition in SZ and BPD



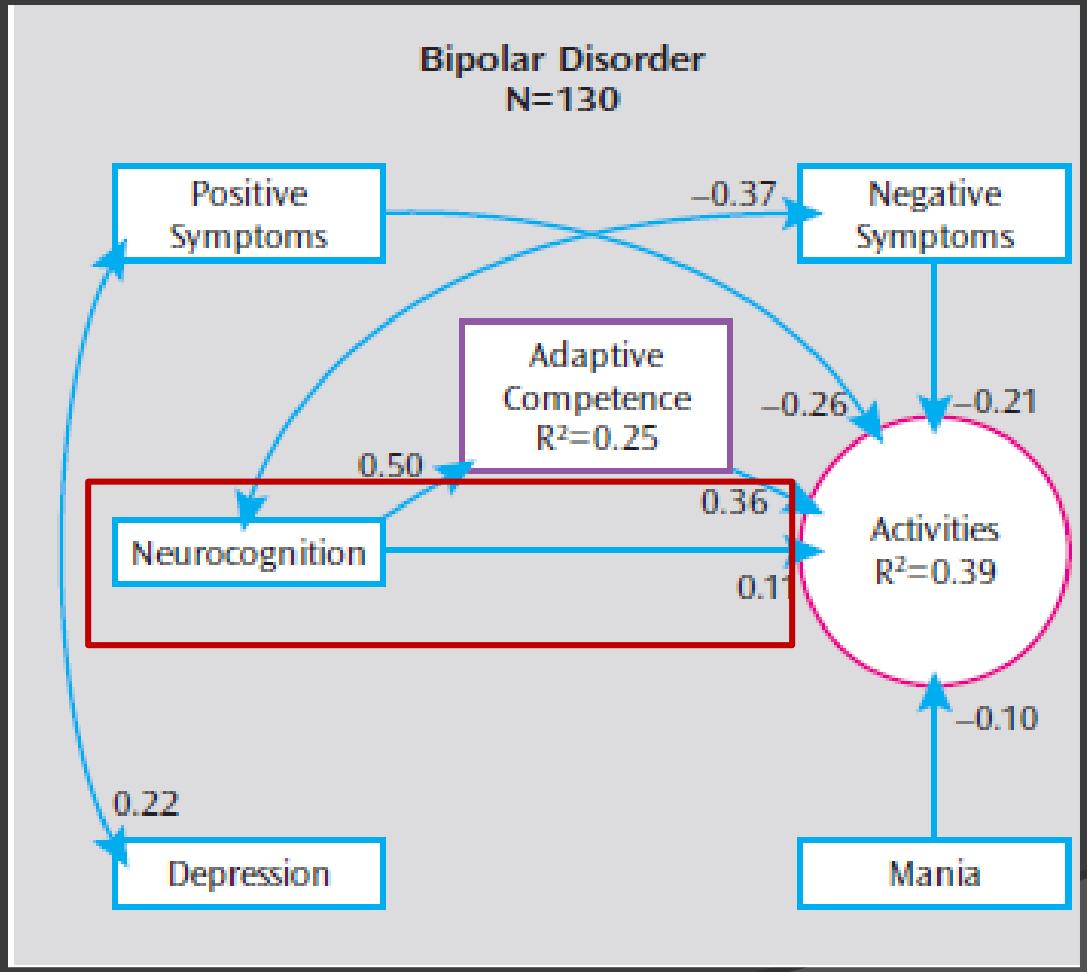
Burdick et al. 2011

Cognition-Function Relationship in SZ



(Am J Psychiatry Bowie et al.; AiA:1–9)

Cognition-Function Relationship in BPD



(Am J Psychiatry Bowie et al.; AiA:1–9)

Cognitive Dysfunction in Bipolar Disorder

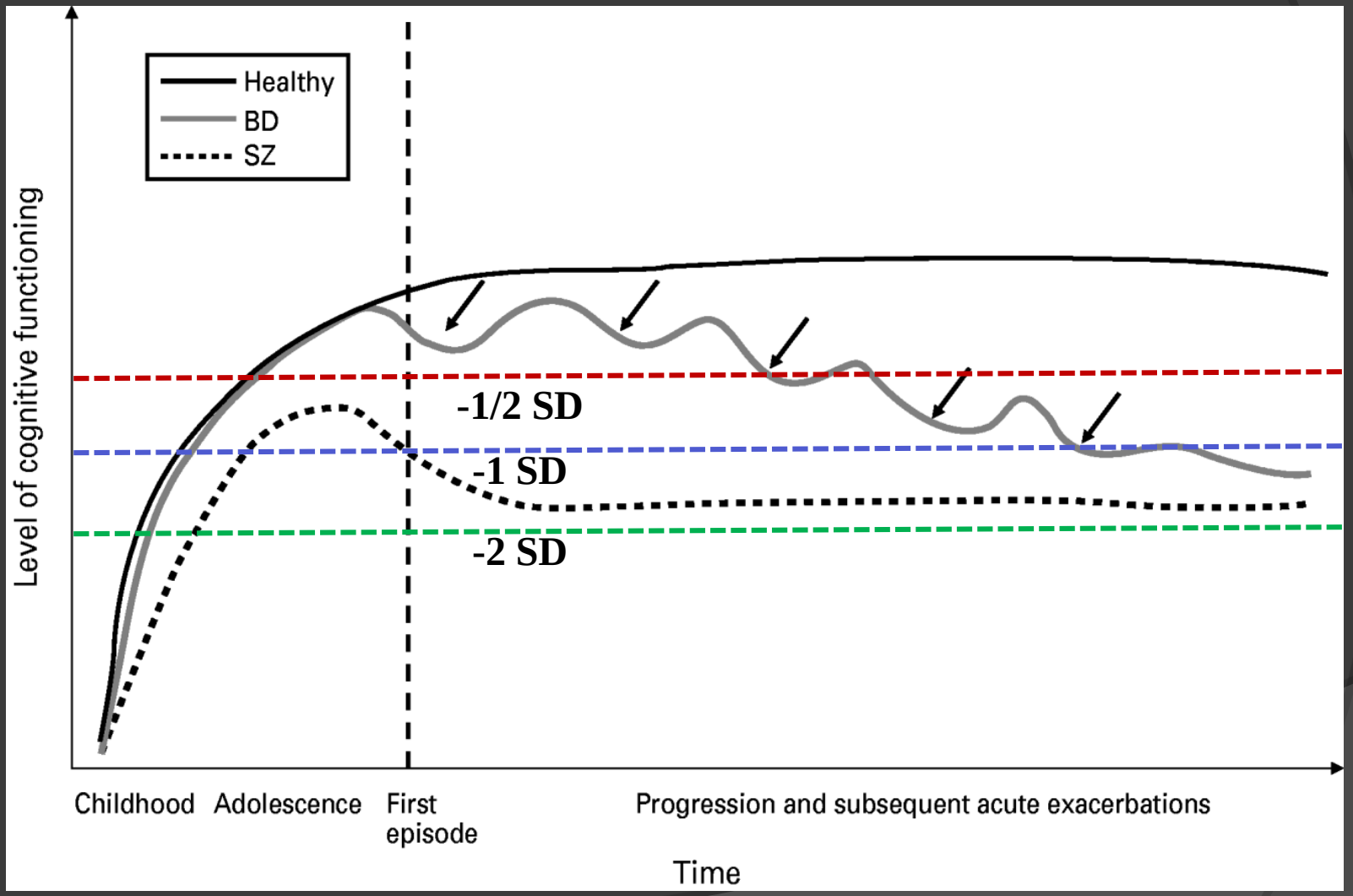
Future Place of Pharmacotherapy

Katherine E. Burdick,[1,2,3] *Raphael J. Braga,*[1] *Joseph F. Goldberg*[4] and *Anil K. Malhotra*[1,2,3]

CNS Drugs 2007; 21 (12): 971-981
1172-7047/07/0012-0971/$44.95/0

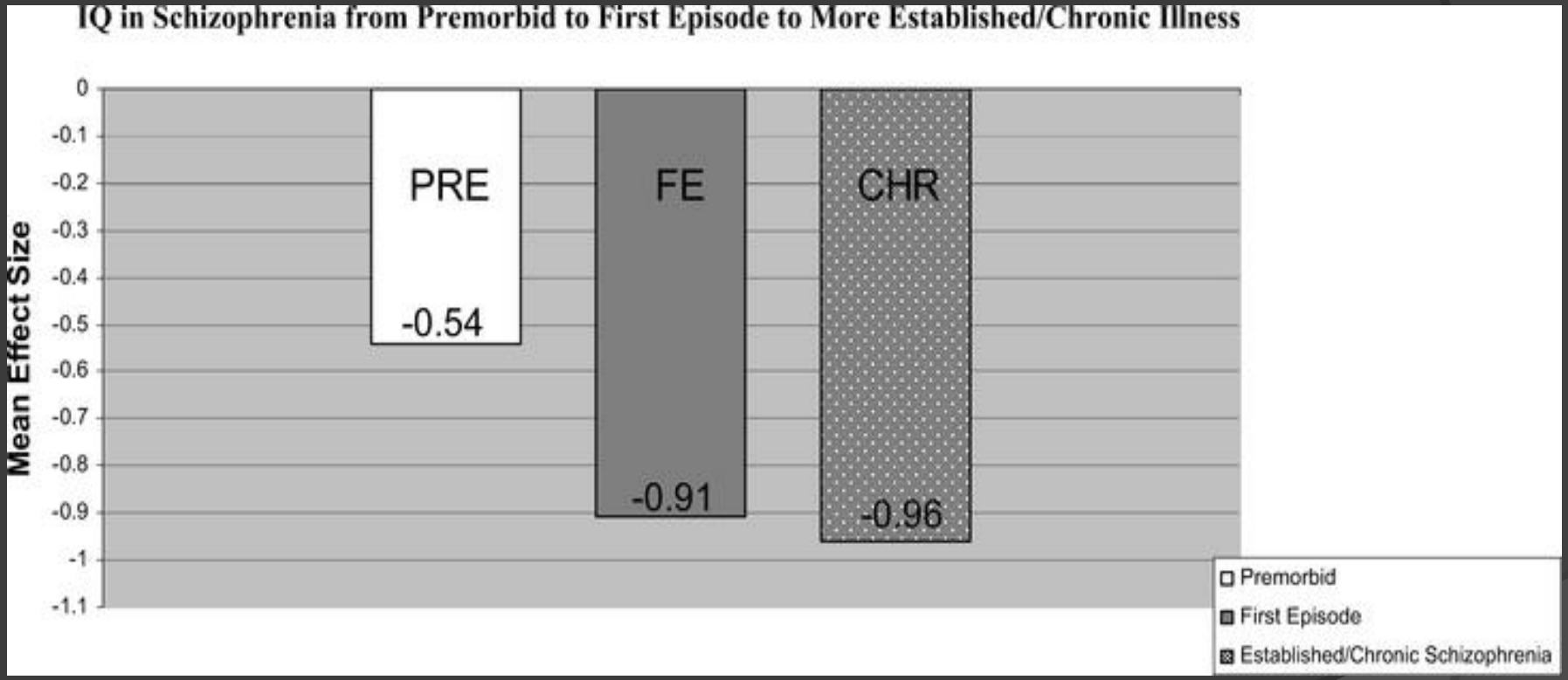
- Cognitive deficits are among the strongest predictors of functional disability in SZ and BPD.
- These deficits do not appear to respond to standard treatment.
- It is necessary to consider directly targeting them with pharmacological and non-pharmacological approaches.
  - Many trials underway in SZ
  - Very few in BPD

Optimism: The BPD Advantages



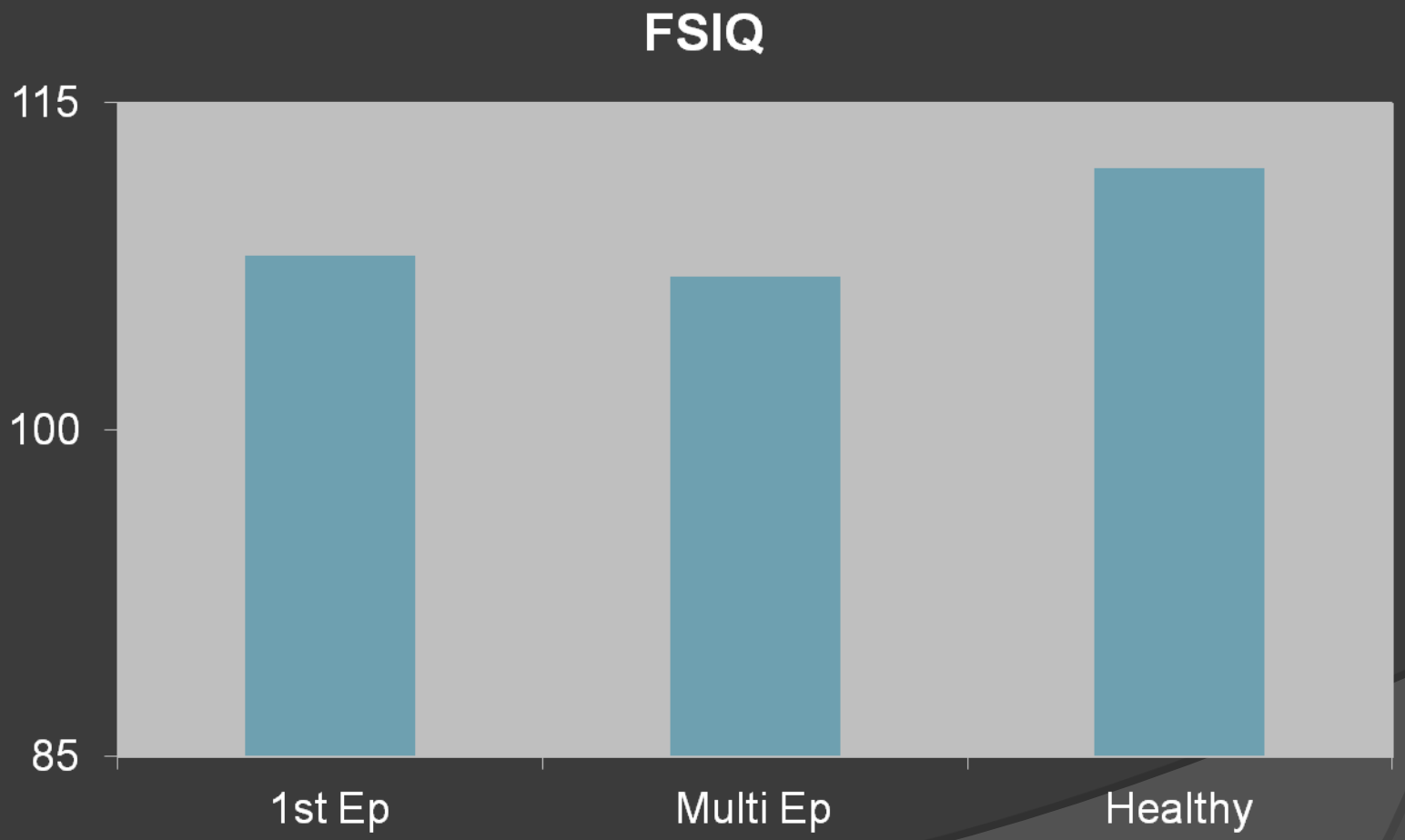
Lewandowski et al. 2011

Course of Intellectual Functioning in SZ



Mesholam-Gately et al. 2009

IQ Remains Intact in BPD

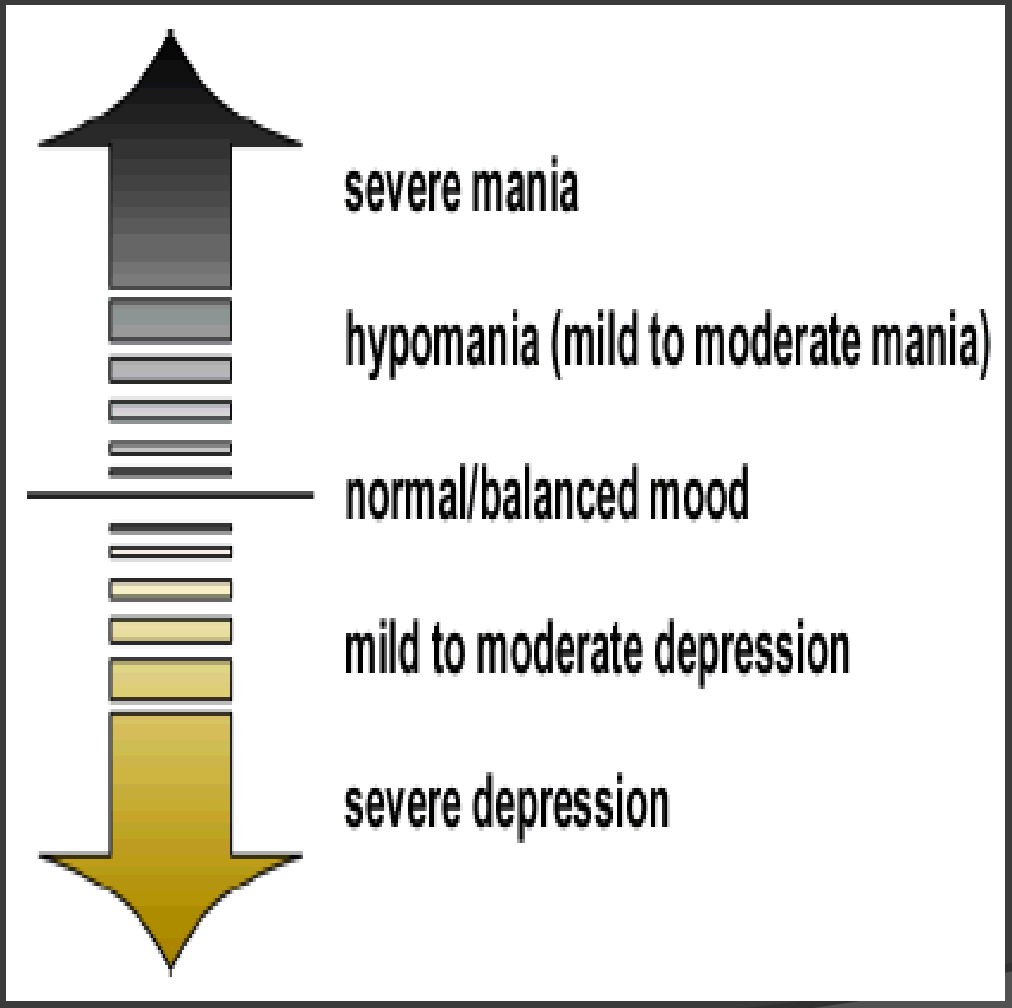


Hellvin et al. 2012

Cognitive Intervention *Challenges*

- Part I: Clinical complexity
  - Spectrum presentation
  - Course of illness
  - Comorbidities
  - Concomitant medications/polypharmacy
- Part II: Cognitive heterogeneity
- Part III: Measurement - No consensus battery for BPD

I) BPD Clinical/Diagnostic Challenges



- Episodic course
  - Natural fluctuations
- Mood state
  - Euthymia definition
  - Subsyndromal sxs
- Subtype
  - BPD I/BD II
  - Psychosis

Bipolar Subtype

Test	Study	BD I	BD II	*D*	*P*
Global cognition	8	293	233	0.26	0.004
Processing speed	6	246	187	0.28	0.005
Phonetic fluency	4	151	112	0	0.99
Stroop interference	3	129	83	0.26	0.10
TMT-A	3	130	98	0.08	0.56
TMT-B	4	152	131	0.25	0.10
Semantic fluency	4	167	131	0.31	0.01
Visual memory	6	218	183	0.38	0.01
Complex figure recall	3	107	72	0.66	<0.001
Verbal memory	7	260	198	0.52	<0.001
List learning	5	216	150	0.53	<0.001
List recall	5	188	141	0.48	<0.001
List recognition	7	267	197	0.49	<0.001
Attention	3	159	87	0.18	0.22
Omission errors	3	159	87	0.04	0.82
Commission errors	3	159	87	0.32	0.13
Planning	5	166	127	0.06	0.64
WCST cat	3	108	68	0.00	0.99
WCST per	3	108	68	0.03	0.86
Working memory	5	224	158	0.12	0.26
Digits forward	4	194	121	−0.01	0.92
Digits backward	3	129	83	0.20	0.16

Bora et al. 2011

Bipolar Subtype

Test	Study	HC	BD II	*D*	*P*
Global cognition	8	379	239	0.43	<0.001
Processing speed	6	300	193	0.55	<0.001
Phonetic fluency	4	216	118	0.47	<0.001
Symbol coding	3	112	100	0.68	<0.001
Stroop interference	3	187	89	0.72	<0.001
TMT-A	3	119	108	0.49	<0.001
TMT-B	4	148	137	0.51	<0.001
Semantic fluency	4	250	131	0.46	<0.001
Visual memory	6	227	125	0.58	<0.001
Complex figure recall	3	105	90	0.76	<0.001
Verbal memory	7	317	203	0.32	0.004
List learning	6	295	166	0.39	0.01
List recall	6	295	166	0.31	0.06
List recognition	6	300	193	0.22	0.05
Planning	4	143	108	0.29	0.05
Working memory	5	271	164	0.55	<0.001
Digits forward	3	221	102	0.39	0.06

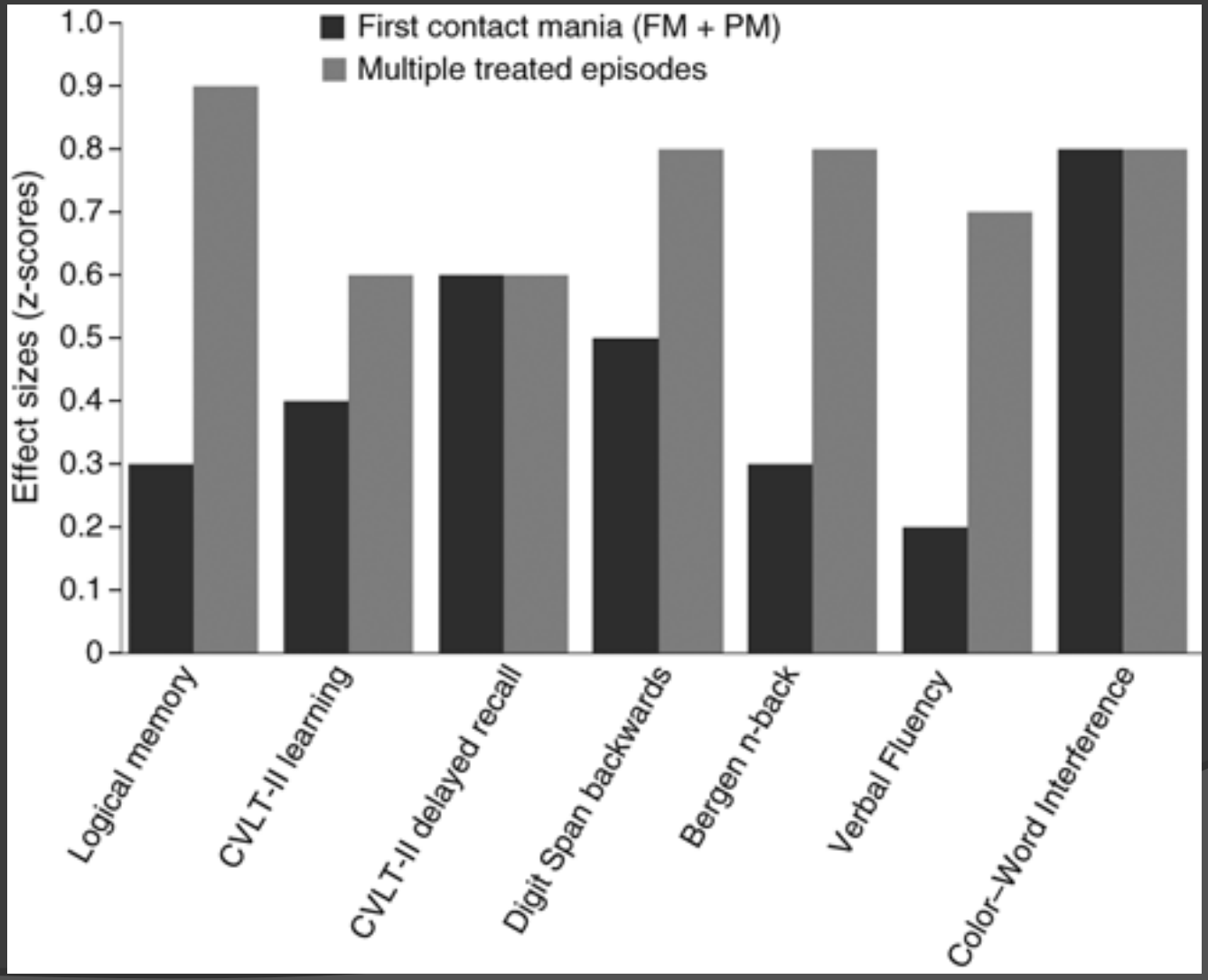
Bora et al. 2011

Psychosis History

Test	Study	BPD+	BDP−	*d*	95% CI	*Z*	*p*	Q-test *p*	Bias[a]
Global cognition	11	435	339	0.22	0.08–0.37	3.03	0.002	0.65	0.15
Global cognition[b]	10	360	291	0.30	0.14–0.46	3.72	<0.001	0.96	0.70
Attention	4	195	130	0.10	−0.12-0.32	0.88	0.38	0.69	0.14
Attention[b]	3	120	82	0.20	−0.08–0.48	1.37	0.17	0.87	0.38
Processing speed	7	278	230	0.20	0.02–0.37	2.15	0.03	0.59	0.91
Phonetic fluency	5	209	175	0.16	−0.05–0.37	1.53	0.13	0.88	0.003
Stroop	4	168	133	0.32	0.05–0.60	2.29	0.02	0.27	0.77
TMT-A	5	151	131	0.09	−0.16–0.34	0.68	0.50	0.34	0.97
TMT-B	5	151	131	0.30	0.06–0.55	2.48	0.01	0.75	0.43
Semantic fluency	5	202	168	0.37	0.15–0.58	3.39	<0.001	0.76	0.73
Visual memory	2	59	59	0.12	−0.24–0.48	0.64	0.52	0.96	
Verbal memory	6	227	192	0.39	0.18–0.59	3.83	<0.001	0.53	0.11
List learning	4	175	140	0.45	0.22–0.68	3.83	<0.001	0.70	0.72
List recall	5	209	175	0.34	0.13–0.54	3.18	0.001	0.86	0.86
List recognition	3	100	79	0.28	−0.02–0.58	1.85	0.06	0.92	0.99
Working memory	7	222	204	0.28	0.08–0.47	2.78	0.006	0.83	0.86
Digits forwards	4	105	104	0.23	−0.05–0.50	1.62	0.10	0.74	0.40
Digits backwards	5	145	135	0.30	0.08–0.52	2.72	0.006	0.46	0.92
Planning	8	303	241	0.31	0.07–0.54	2.54	0.01	0.009	0.001
Planning[b]	7	228	193	0.41	0.21–0.60	4.04	<0.001	0.81	0.13
WCST cat	6	216	171	0.33	−0.18–0.83	1.26	0.21	<0.0001	0.06
WCST cat[b]	5	141	123	0.55	0.30–0.80	4.33	<0.001	0.76	0.45
WCST per	7	269	206	0.31	0.12–0.49	3.21	0.001	0.70	0.03
WCST per[b]	6	194	158	0.36	0.15–0.57	3.26	0.001	0.72	0.09

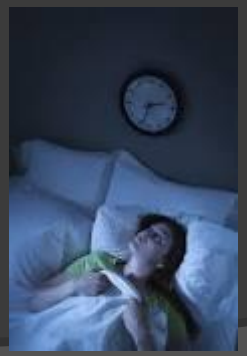
Bora et al. 2010

Effects of Repeated Episodes



Hellvin et al. 2012

BPD Clinical/Diagnostic Challenges



- Clinically complex with multiple common comorbidities that likely affect cognition
  - *Substance use d/o*
  - *Anxiety d/o*
  - *ADHD*
  - *Childhood trauma*
  - *Sleep disorders*

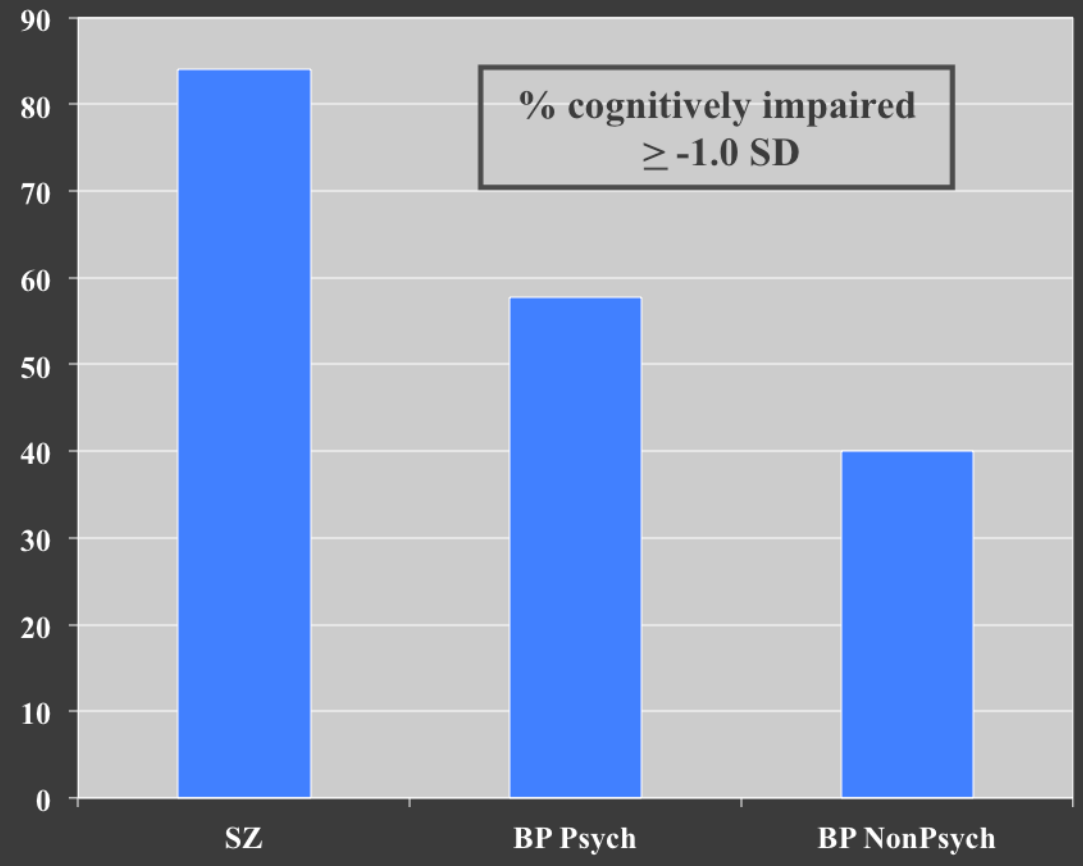
Cognitive Side Effects: Concomitant Meds

Agent	Adverse effects	Neutral or beneficial effects
Lithium	• Slowed motor speed • Impaired short- and long-term memory • Slowed reaction time • Diminished associative fluency	• No adverse effect on attention or sustained attention
Divalproex	• Mild attention impairment • Mild short- and long-term memory impairment • Delayed decision time • Slowed motor speed • Diminished cognitive flexibility	• No adverse effects on visuospatial function
Carbamazepine	• Mild short- and long-term memory impairment	• No adverse effects on motor speed
Lamotrigine	• None reported	• No reported adverse effects of attention, memory, motor speed
Antidepressants	• Anticholinergic effects of tricyclic agents associated sedation, cognitive dulling	• No published evidence of adverse cognitive effects associated with SSRIs, SNRIs, MAOIs, or bupropion
Atypical antipsychotics	• Noncontrolled studies have reported poorer executive function among bipolar patients taking SGAs as compared to those not taking SGAs	• Potentially better cognitive function with at least some SGAs than FGAs • Improvements reported with SGAs from baseline cognitive function in schizophrenia patients are modest, and also may reflect disease state differences relative to bipolar disorder

Goldberg and Chengappa, 2009

II) Heterogeneity in BPD

Cognitive Heterogeneity in BPD



- Acute state effects
- Cognitively heterogeneous when stable
- Not all patients will require intervention
- Defining threshold will be critical

Reichenberg et al. 2009; Bora et al. 2010

Psychological Medicine, Page 1 of 14. © Cambridge University Press 2014
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ORIGINAL ARTICLE

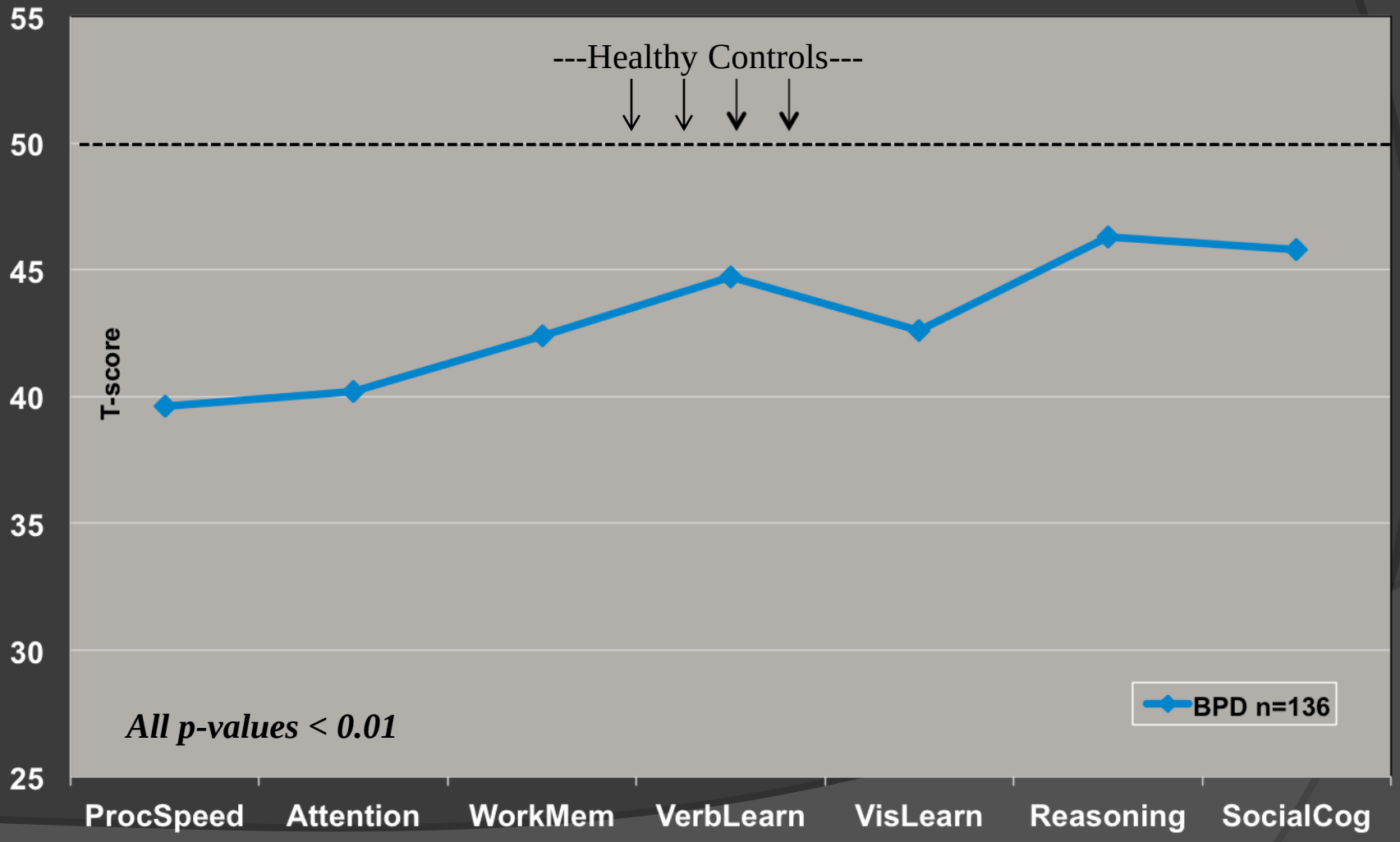
Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications

K. E. Burdick[1]*, M. Russo[1], S. Frangou[1], K. Mahon[1], R. J. Braga[2], M. Shanahan[1] and A. K. Malhotra[2]

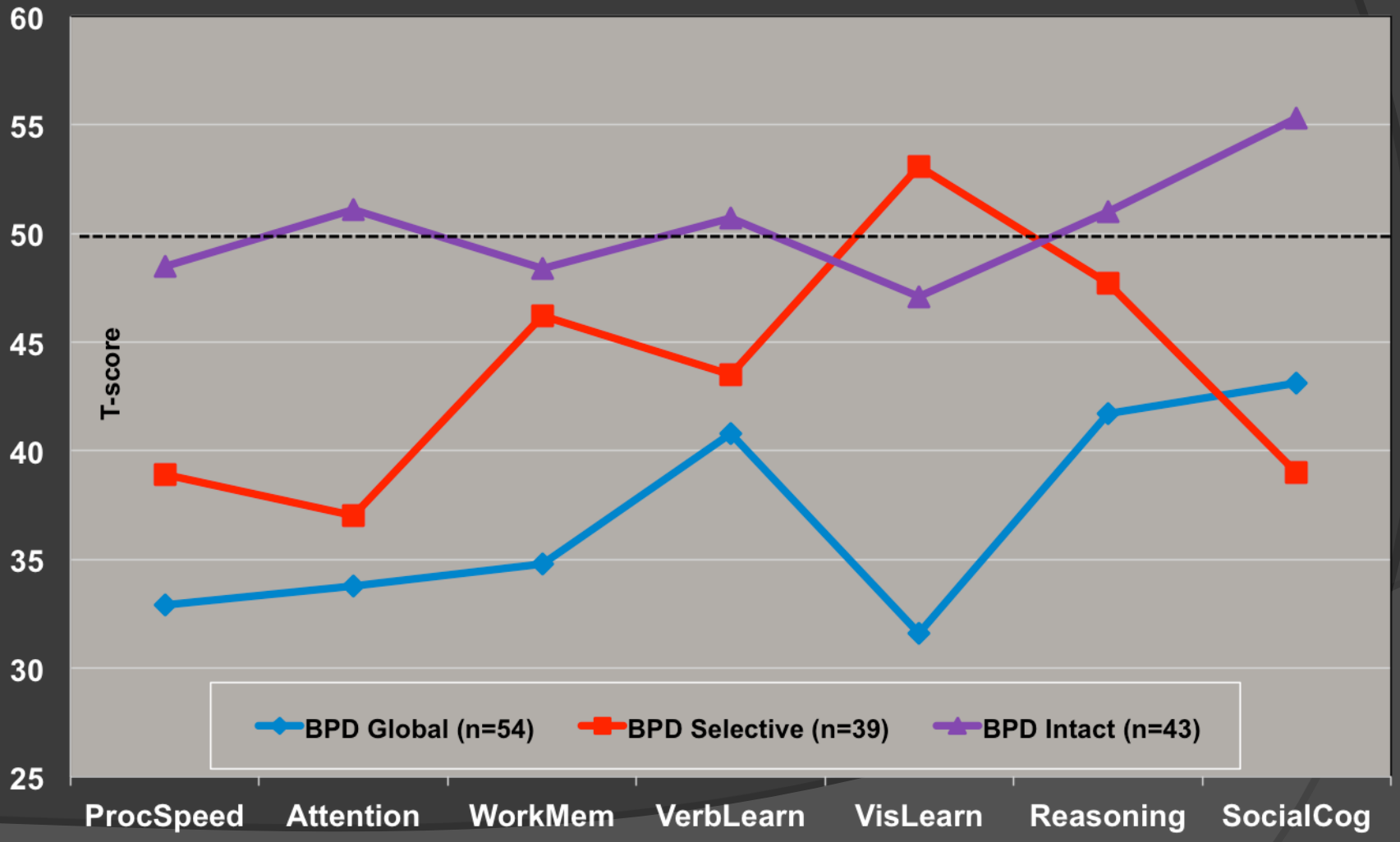
[1] *Departments of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA*
[2] *Zucker Hillside Hospital – North Shore Long Island Jewish Health System, Glen Oaks, NY, USA*

	BPD (n=136)	Healthy (n=148)	Statistic (p)
Age	40.8 (10.6)	41.6 (15.1)	0.26 (0.61)
Sex	50% female	43.9% female	1.10 (0.31)
Race	49% Caucasian	47% Caucasian	0.11 (0.74)
Premorbid IQ	97.6 (10.8)	102.2 (11.7)	10.70 (<0.01)
HamD	11.1 (8.5)	0.5 (1.3)	223.56 (<0.01)
CARS-M	5.5 (7.0)	0.3 (0.8)	81.56 (<0.01)
BPD subtype	105 BPI/31 BPII	----	----
Psychosis Hx	50.7% yes	----	----

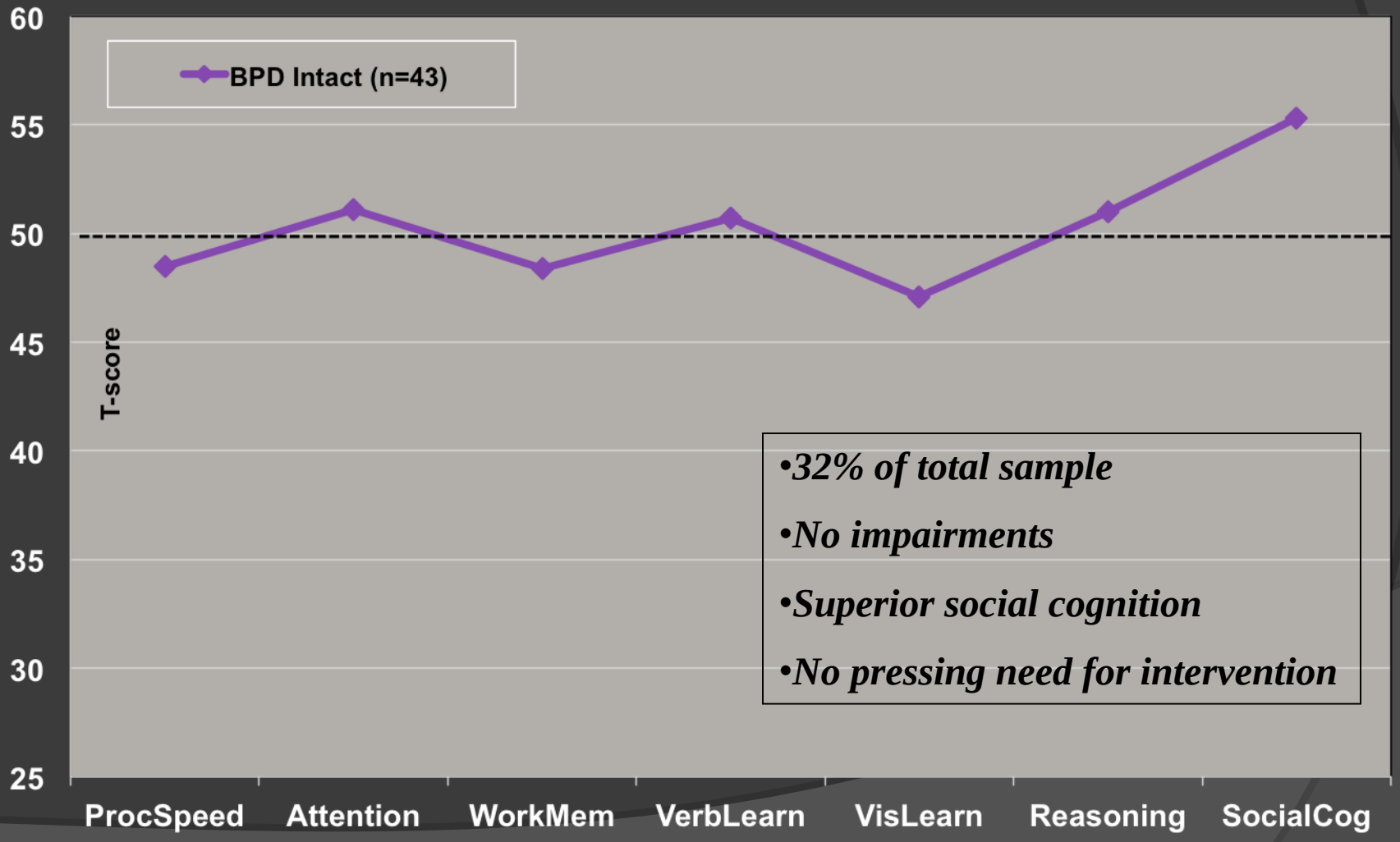
Cognitive Profile of all BPD Patients



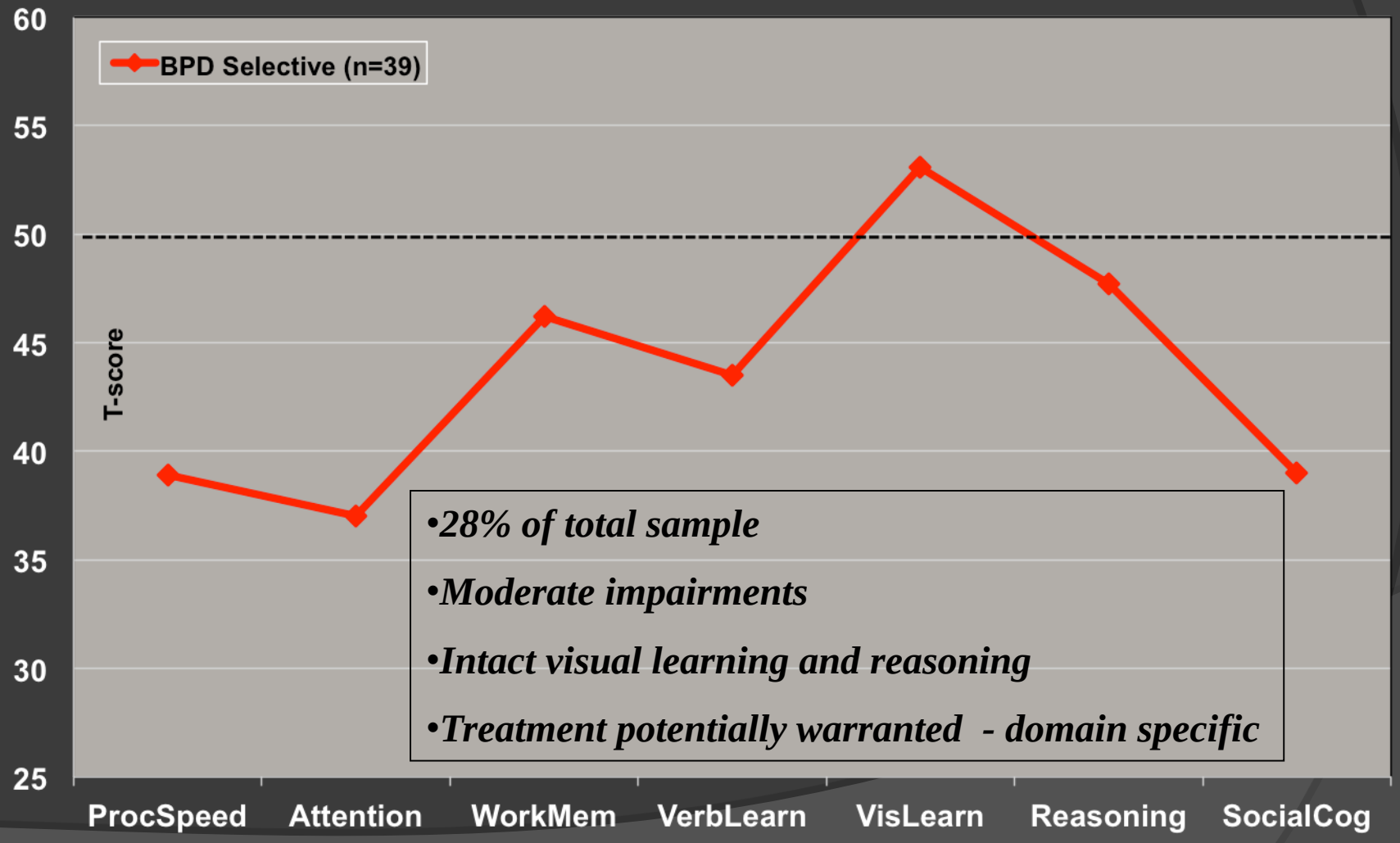
3 Cognitive Subgroups Exist



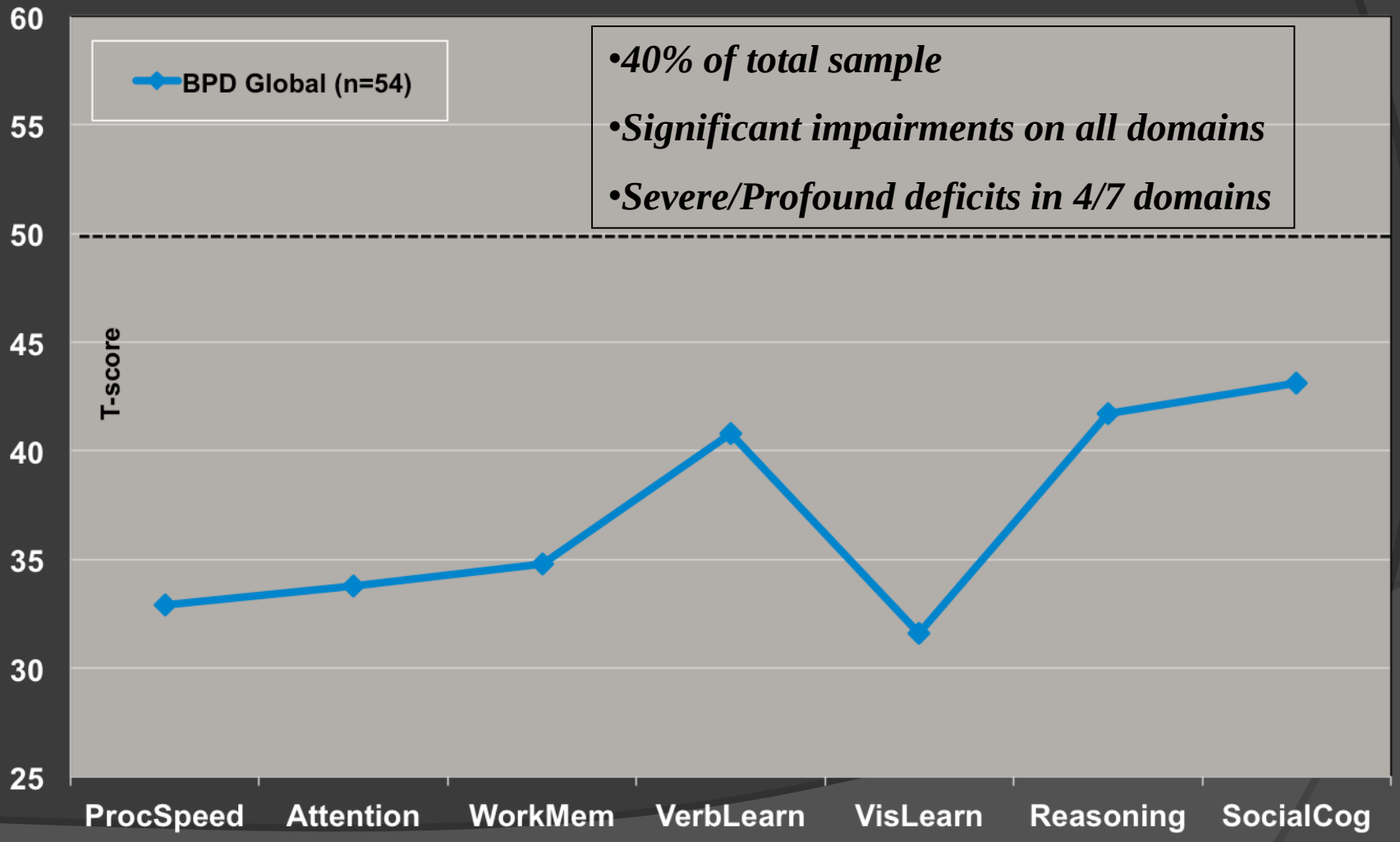
Cognitively Intact Subgroup



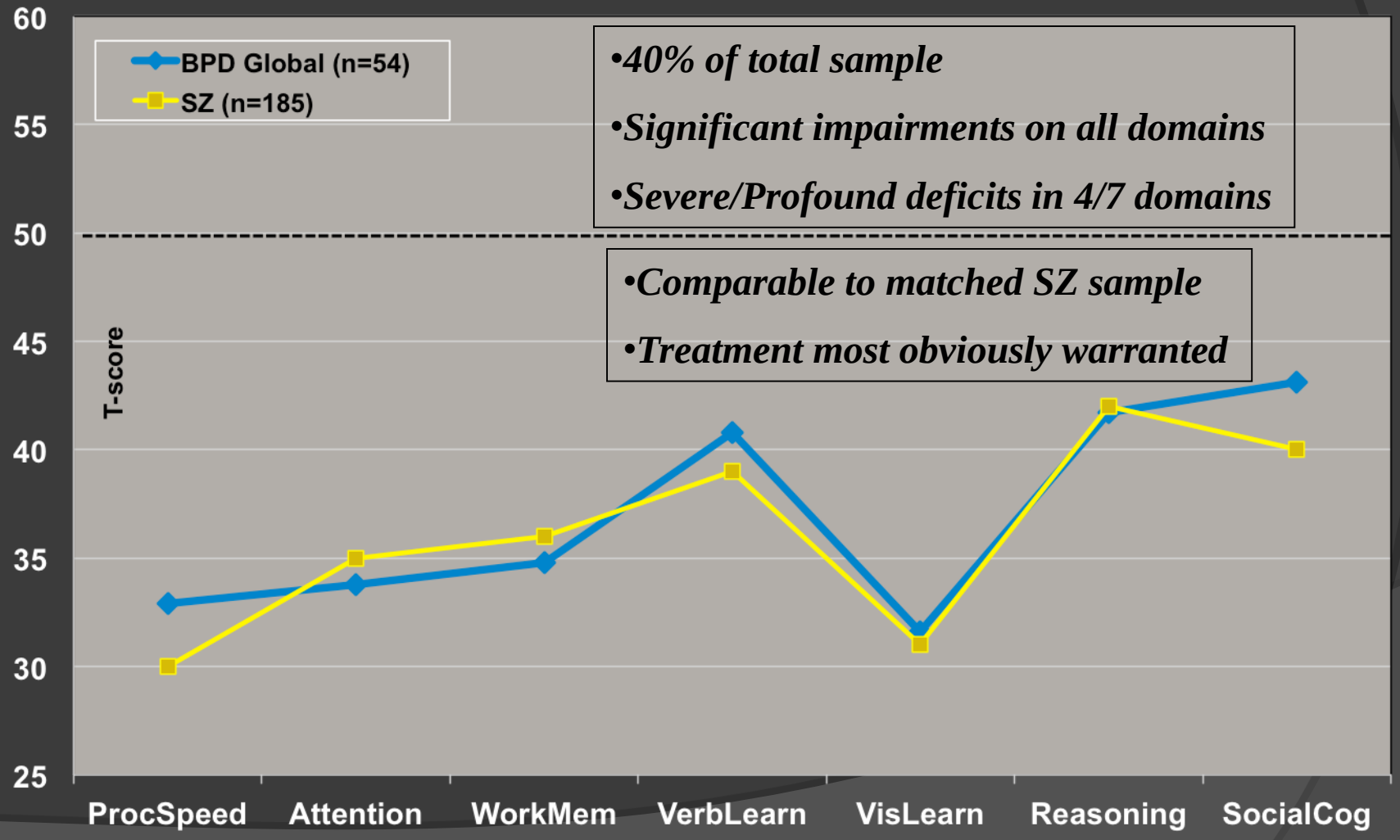
Selectively Impaired Subgroup



Globally Impaired Subgroup



Globally Impaired Subgroup



Hands on: Lessons Learned

Placebo-Controlled Adjunctive Trial of Pramipexole in Patients With Bipolar Disorder: Targeting Cognitive Dysfunction

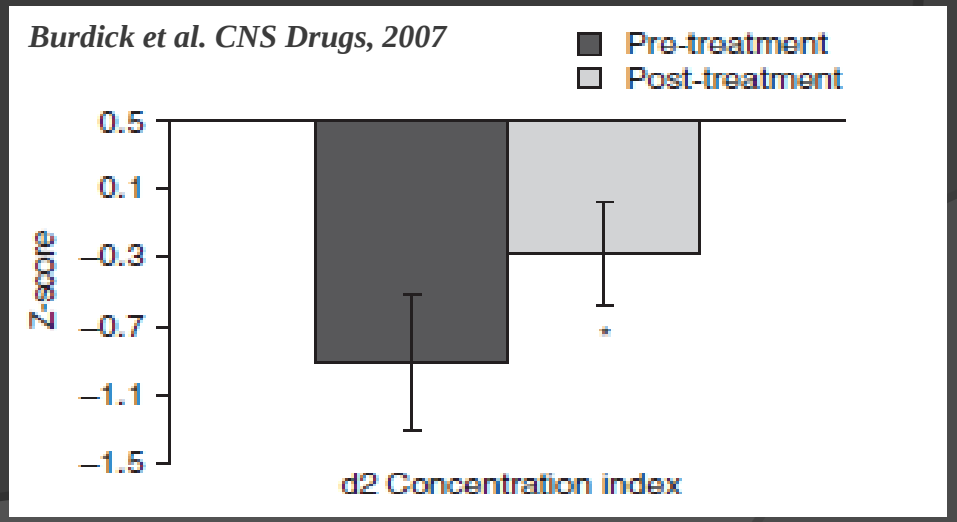
Katherine E. Burdick, PhD; Raphael J. Braga, MD; Charles U. Nnadi, MD; Yaniv Shaya, MA; Walter H. Stearns, MD; and Anil K. Malhotra, MD

- Pramipexole (Mirapex©) acts as a partial/full agonist at D_2/D_3 strongest affinity for D_3.
- FDA-approved for PD and RLS

- Although preliminary, our data are promising and suggest that improving neurocognitive functioning in patients with bipolar illness is a feasible ambition. Future studies of pramipexole and other agents will be important in continuing efforts to enhance treatment outcome and quality of life.

Preliminary Randomized, Double-Blind, Placebo-Controlled Trial of Pramipexole Added to Mood Stabilizers for Treatment-Resistant Bipolar Depression *(Am J Psychiatry 2004;*

- *Goldberg, Burdick, Endick (2004)*: (n=22): 12 active, 10 placebo
  - *67% pram response (50% decrease in HamD)*
  - *20% placebo response*
  - *Effect size d=0.77*
  - *Safe and effective*



Cognitive Enhancement in Bipolar Disorder (SMRI: Burdick and Malhotra): The Grant

- Funded for 2 year period
- 8-week randomized, double-blind, placebo-controlled trial (1.5 mg/day)
- Euthymic patients (HamD & CARS-M < 8)
- All-comers accepted – no requirement of objective impairment for inclusion
- No DA blockers

Cognitive Enhancement in Bipolar Disorder (Burdick et al. 2011): The Study

- Data collected from Aug 2005 to Mar 2010
- Euthymic patients (HamD & CARS-M < 8)
  - Stable not euthymic (HamD < 12)
- All-comers accepted – no requirement of objective impairment for inclusion
- No DA blockers
  - No first generations

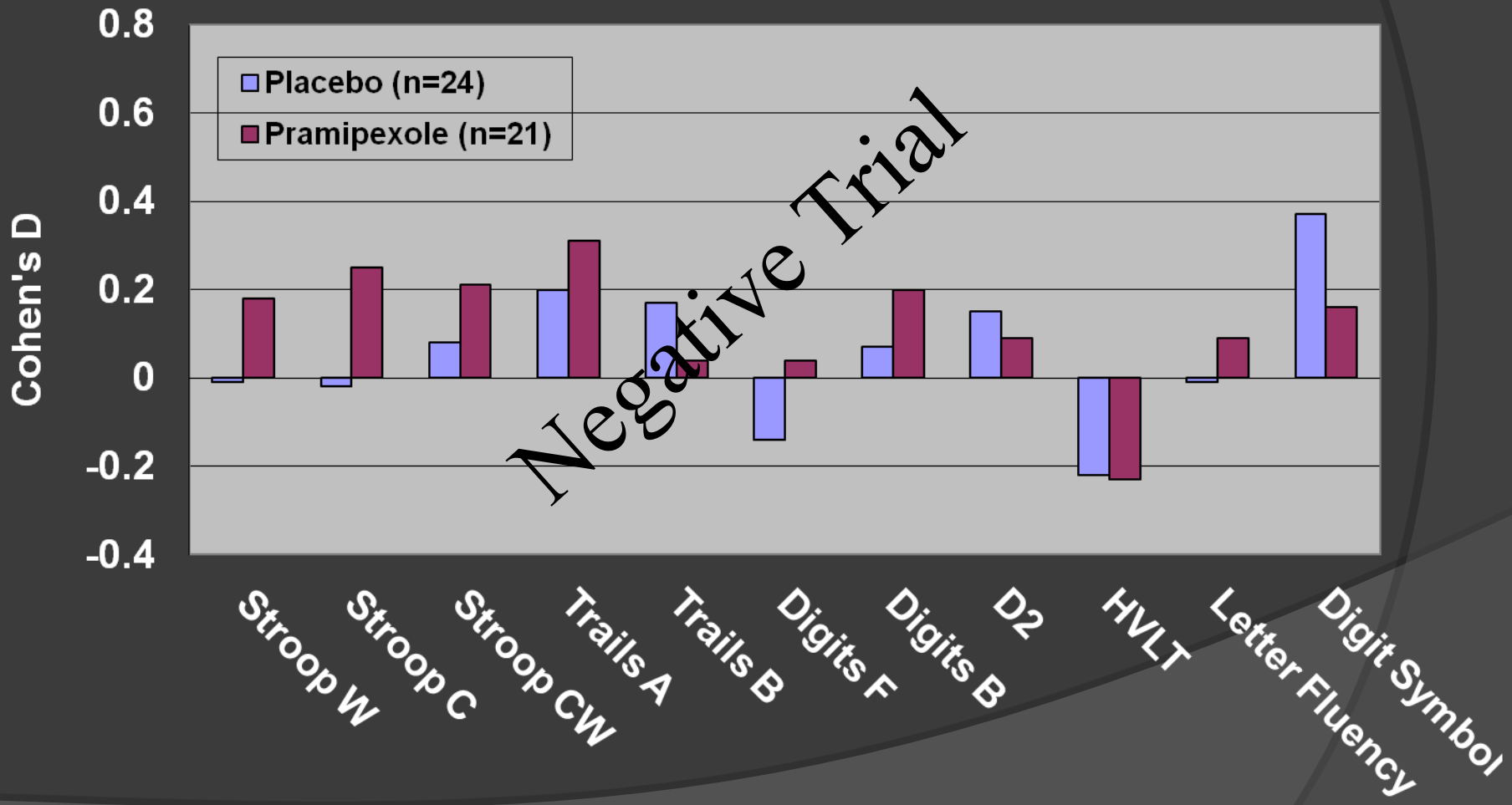
Placebo-Controlled Adjunctive Trial of Pramipexole in Patients With Bipolar Disorder: Targeting Cognitive Dysfunction

Katherine E. Burdick, PhD; Raphael J. Braga, MD; Charles U. Nnadi, MD; Yaniv Shaya, MA; Walter H. Stearns, MD; and Anil K. Malhotra, MD

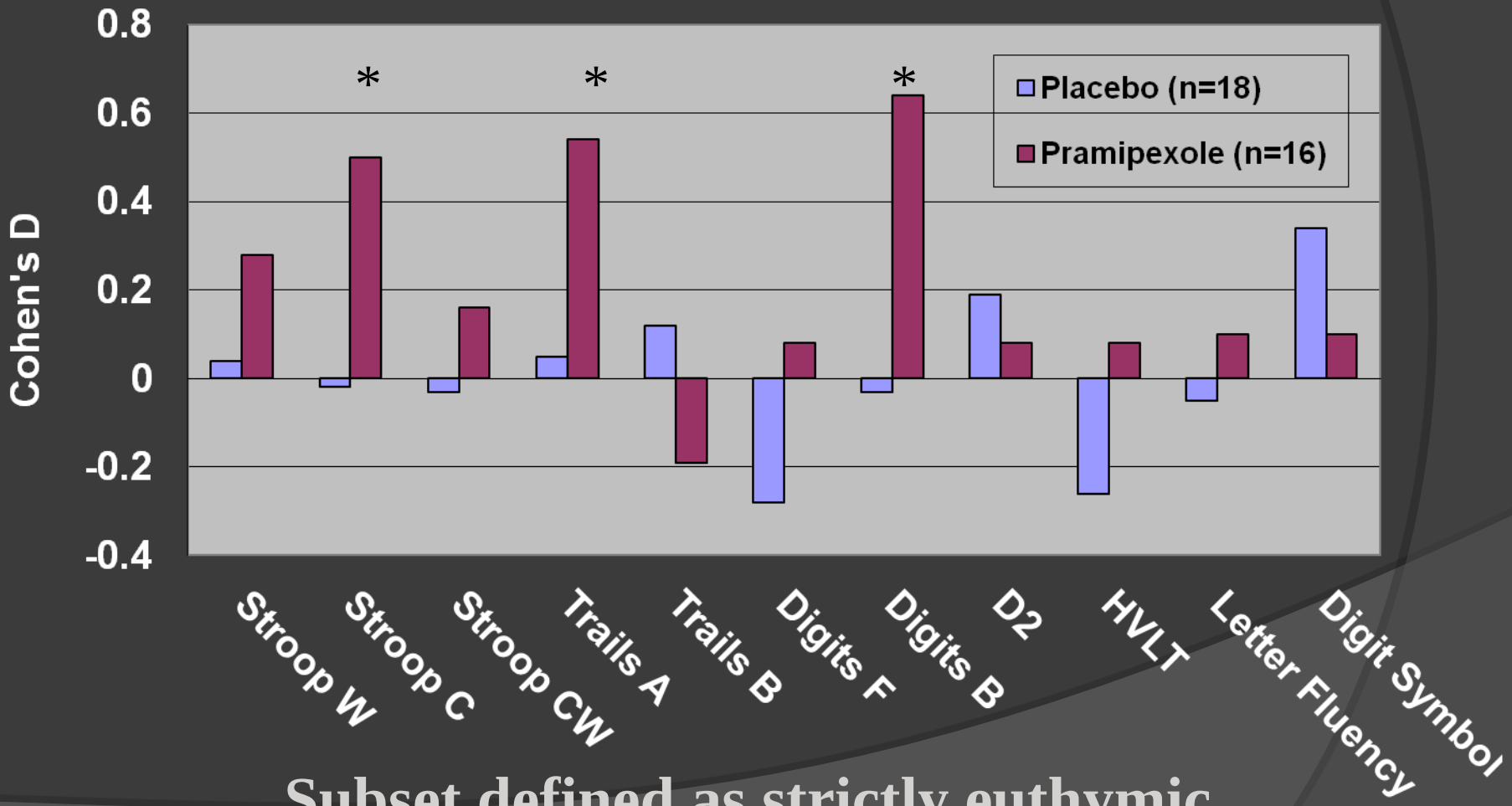
J Clin Psychiatry 2011;72(00):000–000

Feature	*Placebo (n=24)*	*Pram (n=21)*	*Statistic*	*p-value*
Mean Age (SD)	44.42 (12.2)	43.81 (9.4)	F=0.03	0.85
Sex	10male/14f	7male/14f	χ^2=0.33	0.57
Race	10white/14non	7white/14non	χ^2=0.33	0.57
Mean HamD Baseline (SD)	5.5 (3.5)	5.9 (3.4)	F=0.12	0.73
Mean CARS-M Baseline (SD)	2.5 (2.1)	3.1 (2.4)	F=0.92	0.34
Change in HamD (Week 8-Baseline)	-1.5 (3.2)	-0.9 (5.5)	F=0.23	0.63
Change in CARS-M (Week 8-Baseline)	-0.9 (3.0)	0.5 (4.0)	F=1.62	0.21
Mean Premorbid IQ (WRAT)	96.1 (13.3)	96.5 (12.7)	F=0.01	0.92

Effect in All Completers

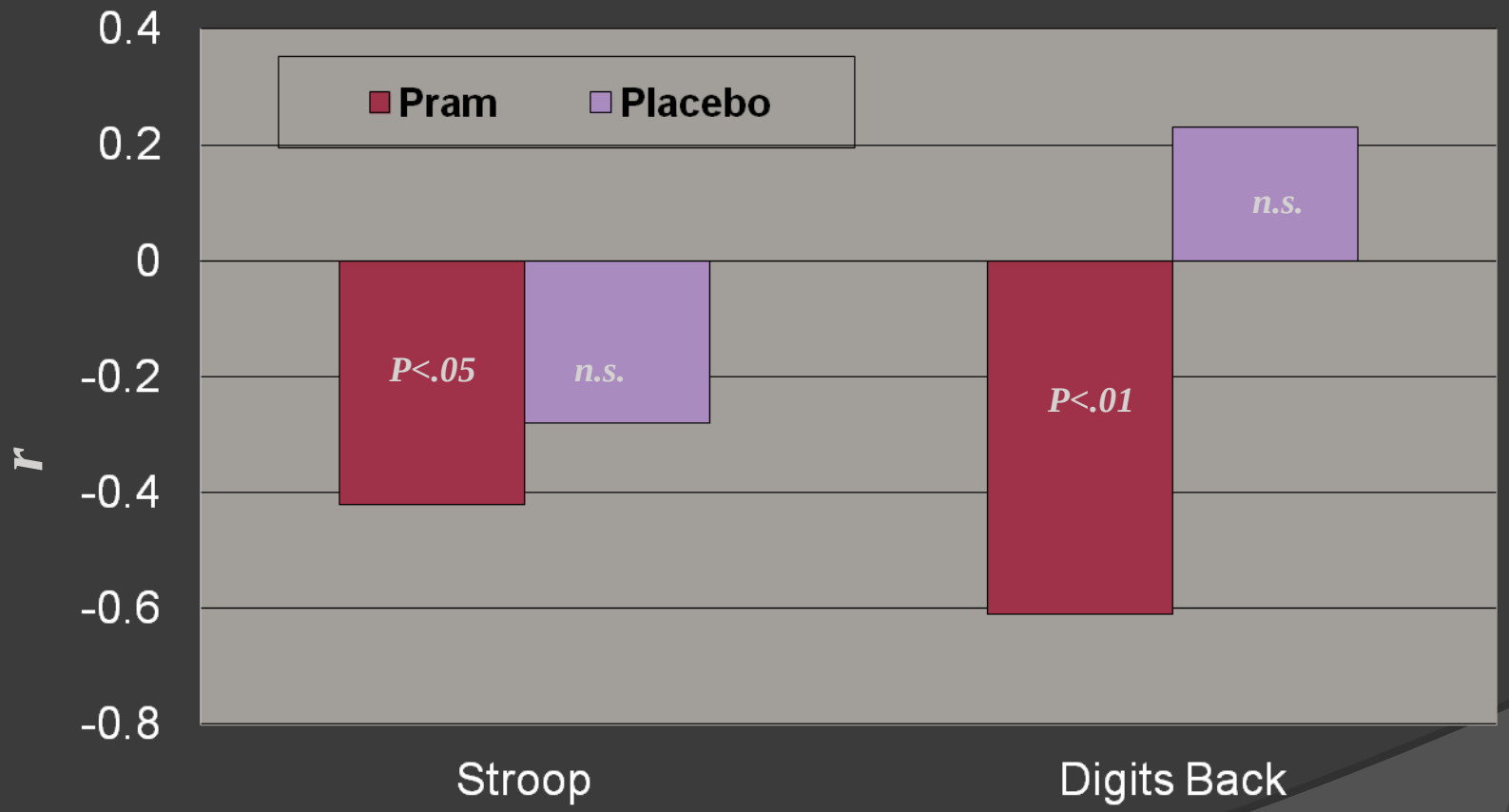


Influence of Baseline Affective Sxs



Subset defined as strictly euthymic

Influence of Baseline Deficit Severity

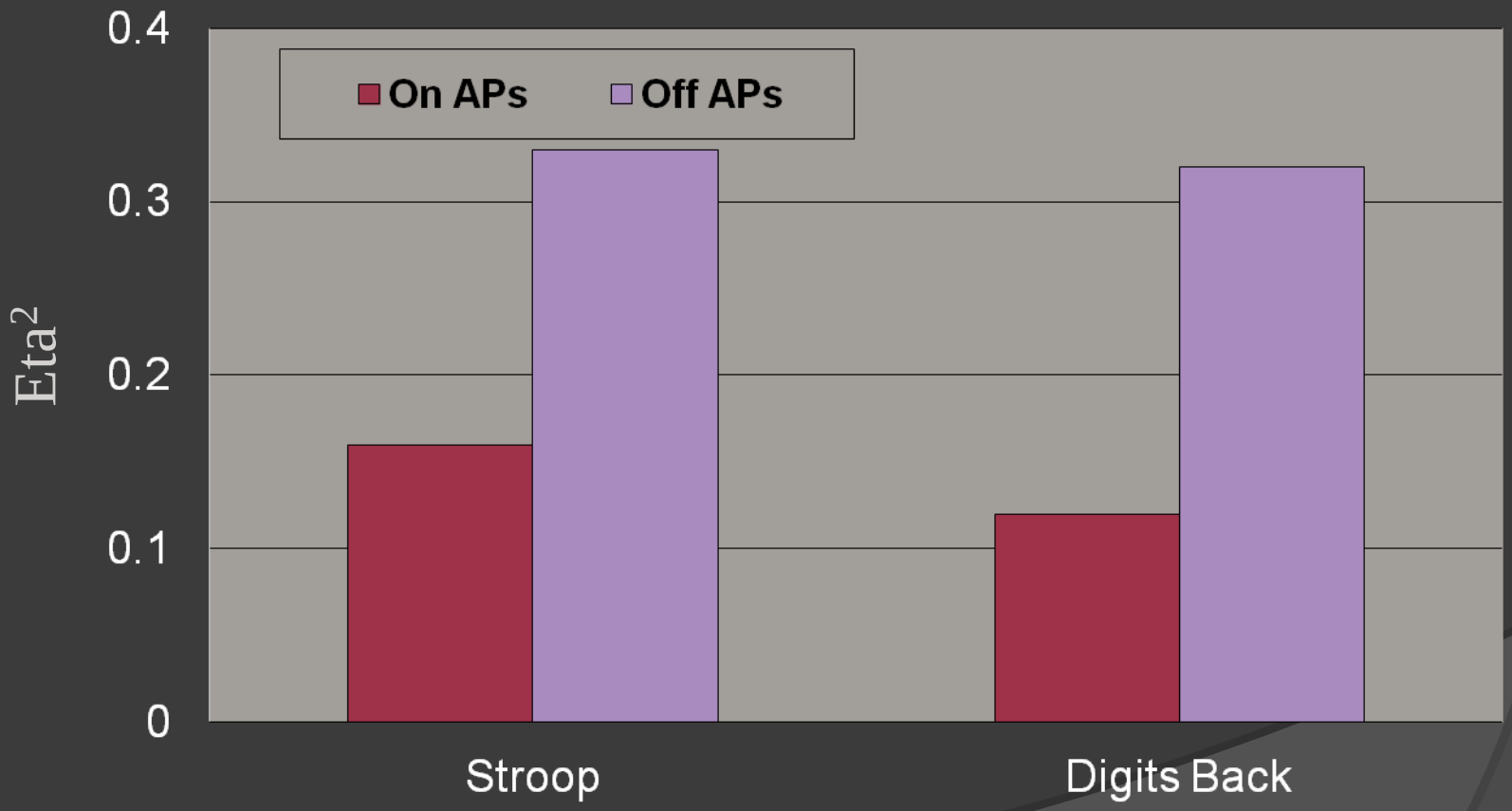


Supports the need to pre-screen for baseline cognitive impairment to identify subjects who will optimally benefit

Influence of Concomitant Meds

- Mean # of meds: 2.3 +/- 1.0
  - 40% lithium (Li+)
  - 64% antipsychotic (AP)
  - 44% antidepressant (AD)
  - 56% anticonvulsant (AC)
- Stratified (yes/no)
  - Cognitive benefit was greater in those taking AD or AC weaker in those on Li+ or AP

Influence of Concomitant Medications



%variance explained in Δ score significantly > in AP-free subjects

III) Measurement Issues in BPD

- Subjective (self-report) measures of cognitive functioning are not ideal and can be influenced by affective symptoms

Measure	Ham-D	YMR-S	CDS	CFQ	PAOF
Digit Span	0.12	0.22	0.16	0.15	0.04
Digit Sym	-0.04	0.19	-0.27	-0.26	-0.28
Trails A	0.05	-0.03	-0.29	-0.01	-0.24
Trails B	0.07	-0.10	-0.17	0.08	-0.11
CVLT-1-5	0.03	-0.17	0.08	0.18	-0.05
Global Z	-0.05	-0.15	-0.02	0.15	-0.10

Burdick et al. 2005

Criteria for Consensus Battery in SZ

Battery:

- Inclusion of the seven cognitive domains
- Valid assessment of cognition at the level of all individual major cognitive domains

Individual Tests:

- High test-retest reliability
- High utility as a repeated measure
- Demonstrated relationship to functional outcome
- Demonstrated tolerability and practicality

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MATRICS Consensus Cognitive Battery

Speed of Processing
- Category Fluency
- BACS Symbol Coding
- Trial Making A

Attention / Vigilance
- Continuous Performance Test
  Identical Pairs version

Working Memory
- Maryland Letter Number Span
- WMS Spatial Span

Verbal Learning
- Hopkins Verbal Learning Test

Visual Learning
- Brief Visuospatial Memory Test

Reasoning & Problem Solving
- NAB Mazes

Social Cognition
- MSCEIT Managing Emotions

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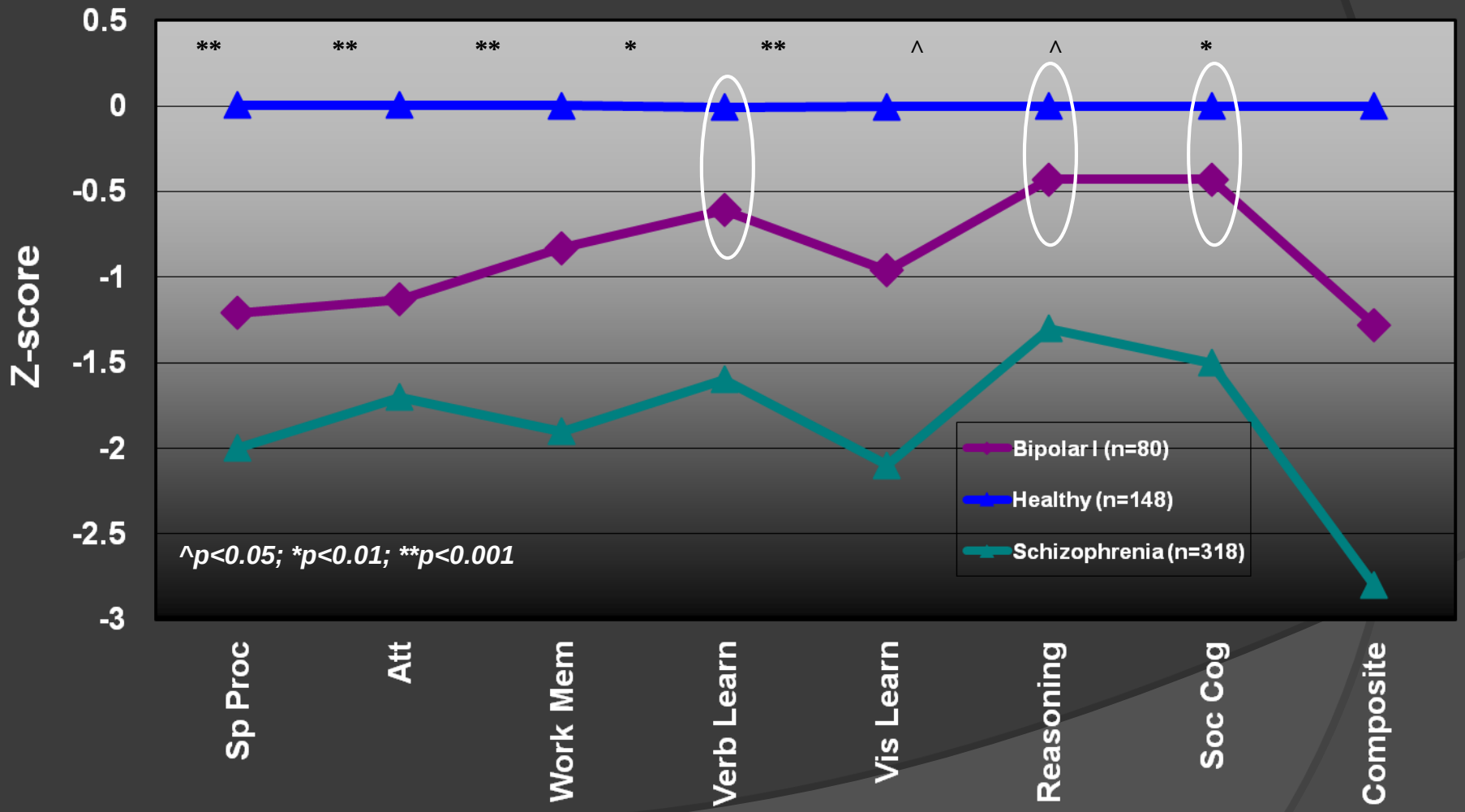
Relative Weaknesses of MCCB in BPD

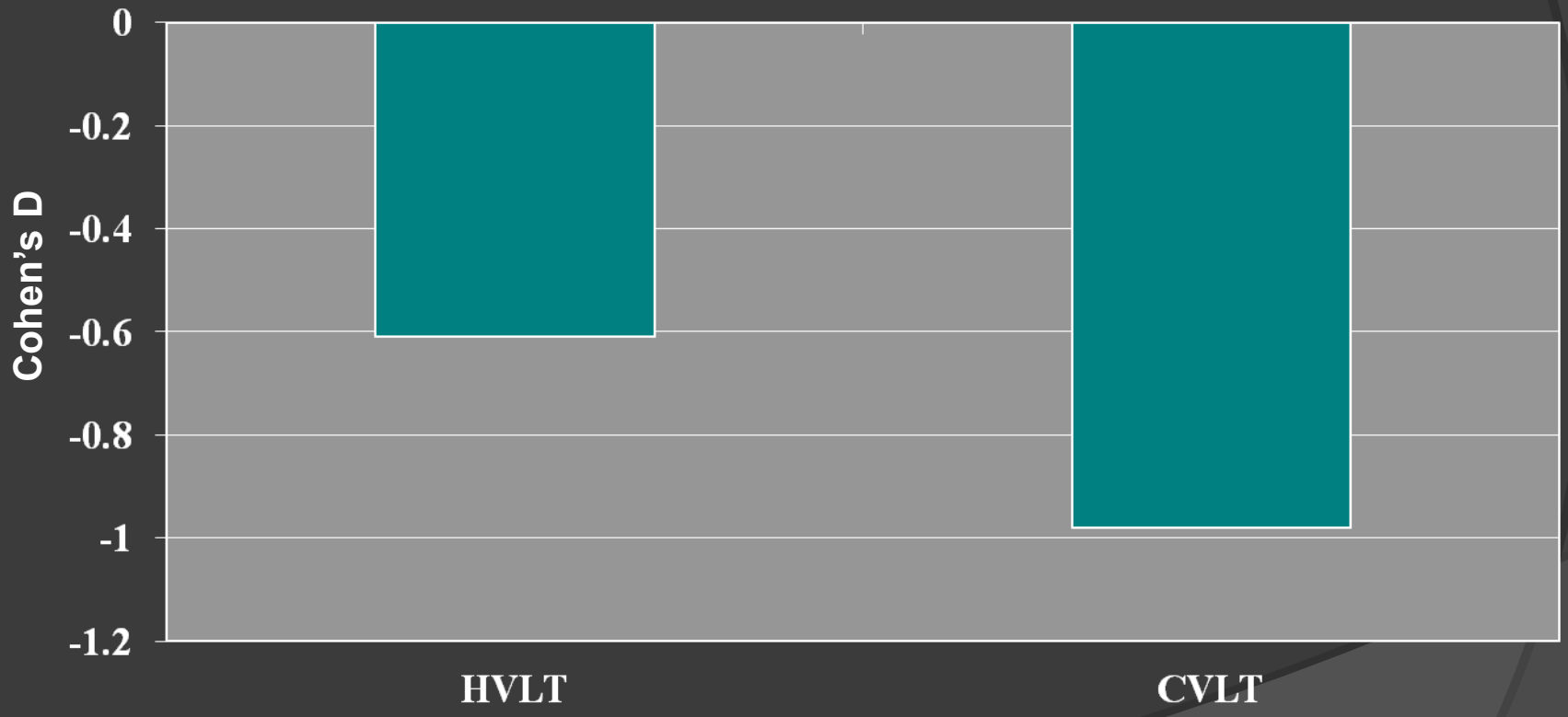


Burdick et al. 2011

Executive Functioning in BPD

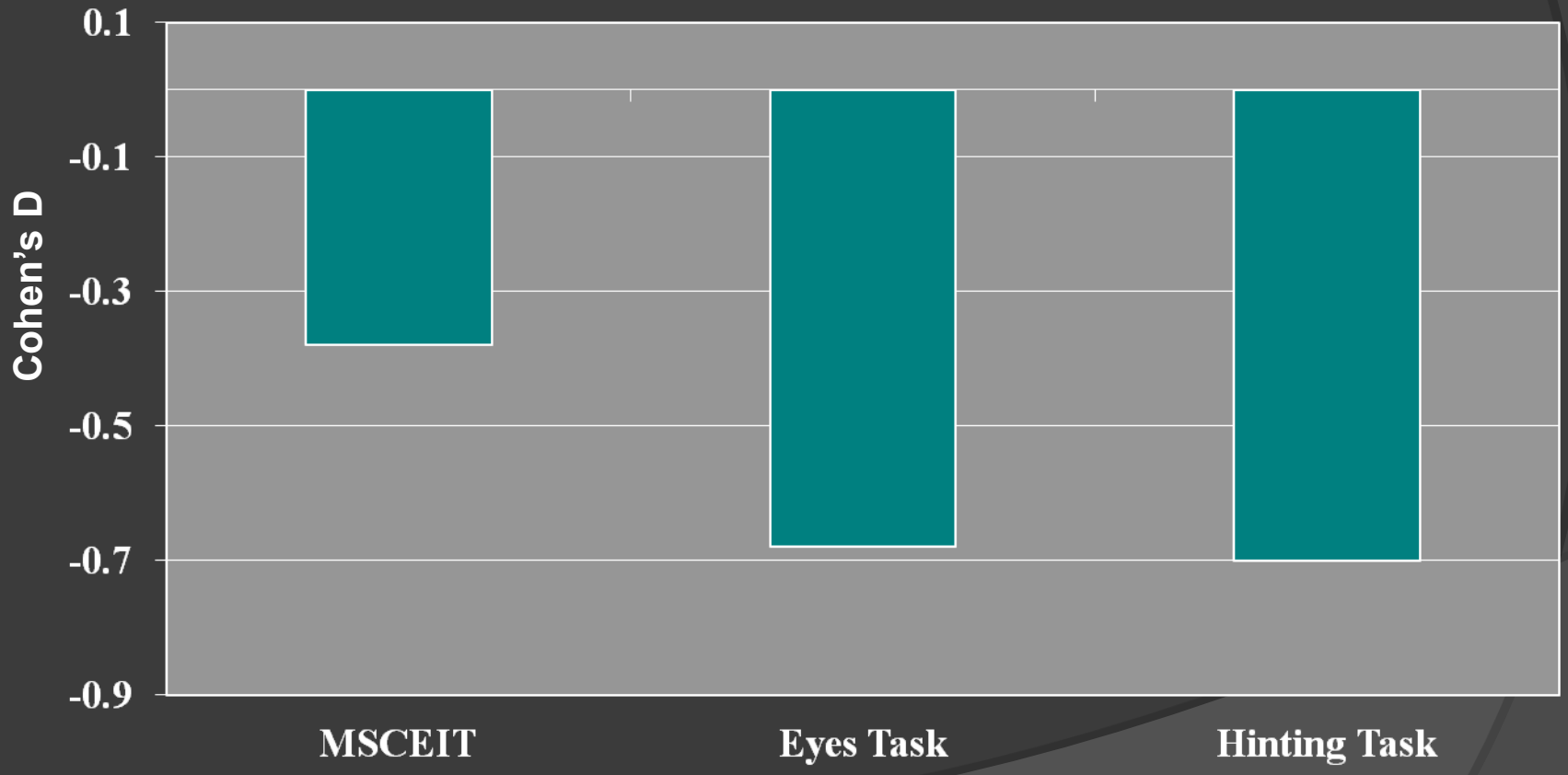
Meta-analytic data from Bora et al. 2008

Verbal Learning in BPD



Meta-analytic data from Bora et al. 2008

Social Cognition in BPD



Comparison data from Bora et al. 2005

Measurement Recommendations

- MCCB provides an ideal starting point
- MCCB “Plus” might include:
  - Substitution of tasks with less sensitivity or addition of tasks in these domains
  - Additional measures of affective-based cognition (Emotion recognition; Affective Stroop) that may be disease-specific
  - Decision-making and probabilistic learning tasks shown to activate brain regions implicated in affect regulation

The International Society for Bipolar Disorders–Battery for Assessment of Neurocognition (ISBD-BANC)

Table 4. Final proposed cognitive battery for bipolar disorder

Cognitive domain	Neuropsychological test	MCCB subtest	Subtest type	Duration (min)
Speed of processing	Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding	Yes	Core	3
	Category Fluency: Animal Naming	Yes	Core	2
	Trail Making Test–part A	Yes	Core	2
Attention/vigilance	Continuous Performance Test–Identical Pairs (CPT-IP)	Yes	Core	13
Working memory	Wechsler Memory Scale–3 Letter-Number Sequencing	Yes	Core	6
	Wechsler Memory Scale–3 Spatial Span	Yes	Core	5
Verbal learning/memory	Hopkins Verbal Learning Test–Revised	Yes	Substitute	5
Verbal learning/memory	California Verbal Learning Test	No	Substitute	10
Visual learning	Brief Visuospatial Memory Test–Revised	Yes	Core	5
Executive function	Stroop Test	No	Core	5
	Trail Making Test–part B	No	Core	5
	Wisconsin Card Sorting Test	No	Optional	20

Table 2. Promising cognitive tests that may be relevant to bipolar disorder

Test	Primary cognitive abilities involved
Hayling Sentence Completion Test (HSCT)	Inhibitory control
CANTAB IDED	Mental set shifting, reversal learning
Tower of London (and variants)	Planning, inhibition, working memory
Balloon Analogue Risk Task (BART)	Decision making/risk taking
Theory of Mind Advanced Test	Theory of mind

Consensus Article

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Preliminary Recommendations

- Patients to enroll should *ideally* be
  - Euthymic or subthreshold sxs controlled for at randomization
  - Cognitively impaired with objective evidence of deficit at screen
  - Mixed subtypes (BPI and BPII with and without psychosis history) provided they meet cognitive threshold defined
  - Limited comorbid diagnoses – where feasible
  - Limited in number of psychotropic medications (and/or type depending on agent being tested)

Preliminary Recommendations

- Trial design should consider
  - Duration of trial long enough to adequately test agent; short enough to avoid cycling
  - Treatment with adjunctive agent most feasible – monotherapy where appropriate
  - Measurement of cognitive outcome should be comprehensive
    - Sensitive/specific to BPD
    - Objective

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