Application of Cognitive Assessment Methods for Bipolar Clinical Trials

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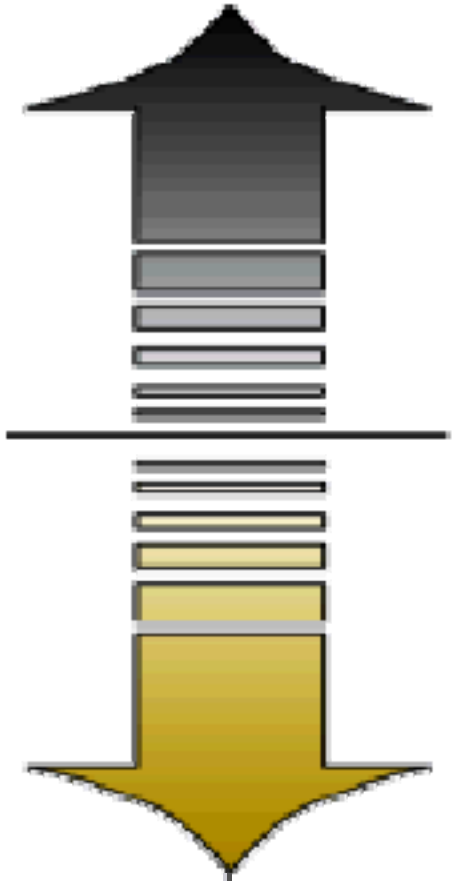
Bipolar Disorder

- 1.6% prevalence
- Alternating periods of depression and mania
- Depression: Sad mood, changes in appetite, sleep, activity
- Mania: Heightened mood/irritability, changes in appetite, sleep, activity, rapid speech, flight of ideas, and some psychosis

Bipolar Disorder



Bipolar I

severe mania

Bipolar II

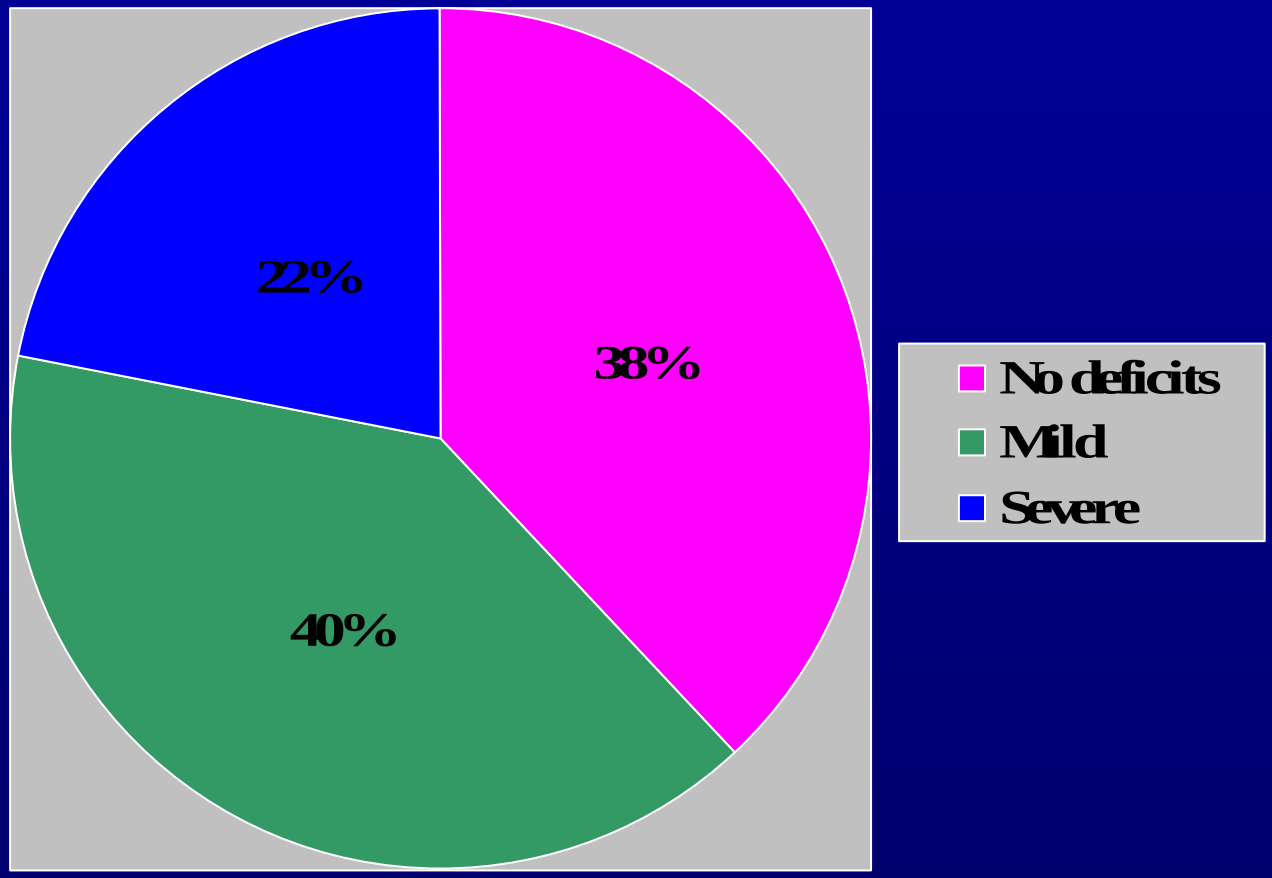
hypomania (mild to moderate mania)

normal/balanced mood

mild to moderate depression

severe depression

Cognitive Heterogeneity in Bipolar Disorder



A majority of bipolar patients (but not all) have significant cognitive impairment, even when euthymic.

Martino et al. 2008

Causes of Cognitive Deficits in BPD?

- State-related phenomena
  - Depressive and manic symptoms: acute and subsyndromal
- Course of illness features
  - Age of onset, Number of Manias/Hospitalizations
  - Psychosis History
  - Comorbid substance abuse/dependence
- Genetic predisposition?

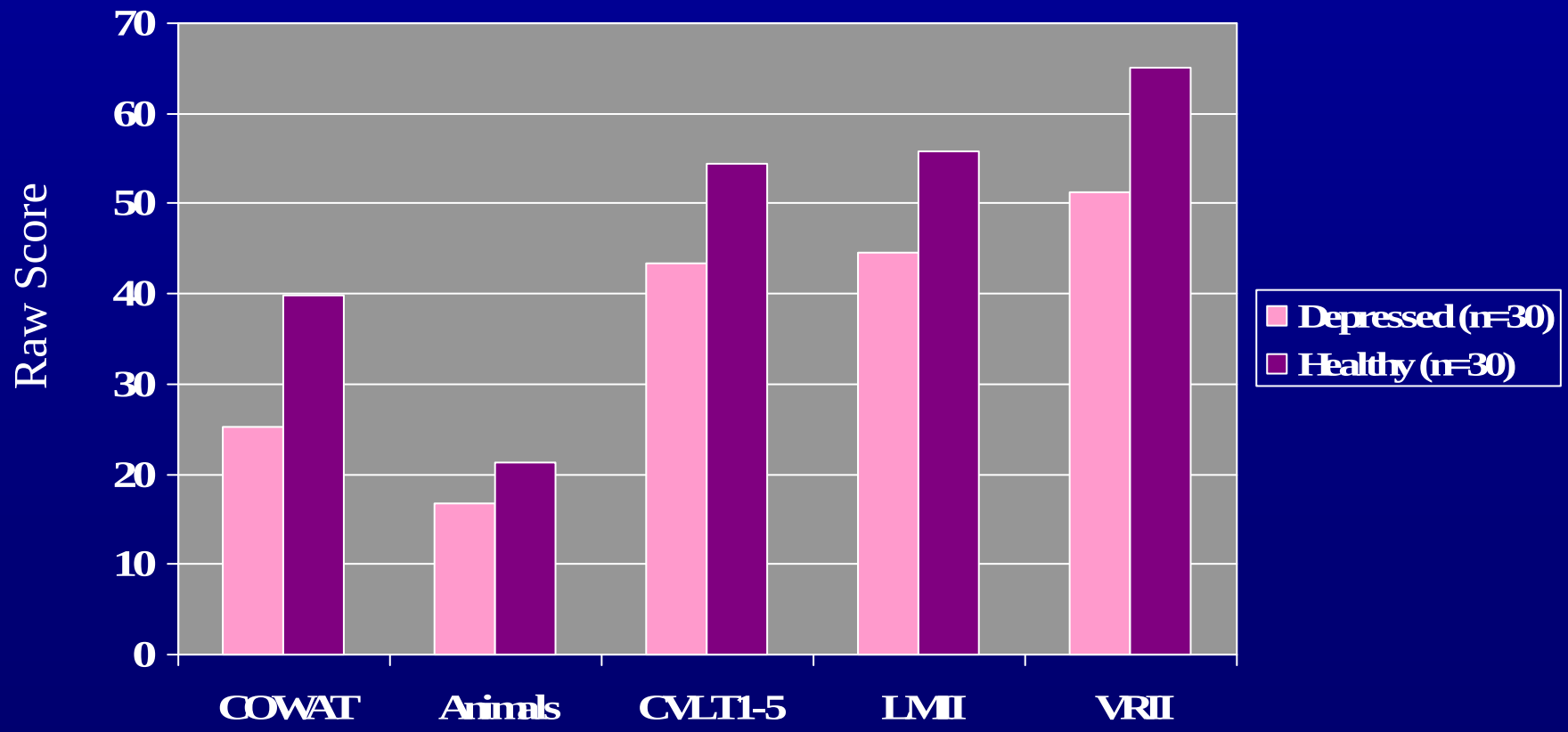
The Long-term Natural History of the Weekly Symptomatic Status of Bipolar I Disorder

Lewis L. Judd, MD; Hagop S. Akiskal, MD; Pamela J. Schettler, PhD; Jean Endicott, PhD; Jack Maser, PhD; David A. Solomon, MD; Andrew C. Leon, PhD; John A. Rice, PhD; Martin B. Keller, MD

2-year weekly follow-up data

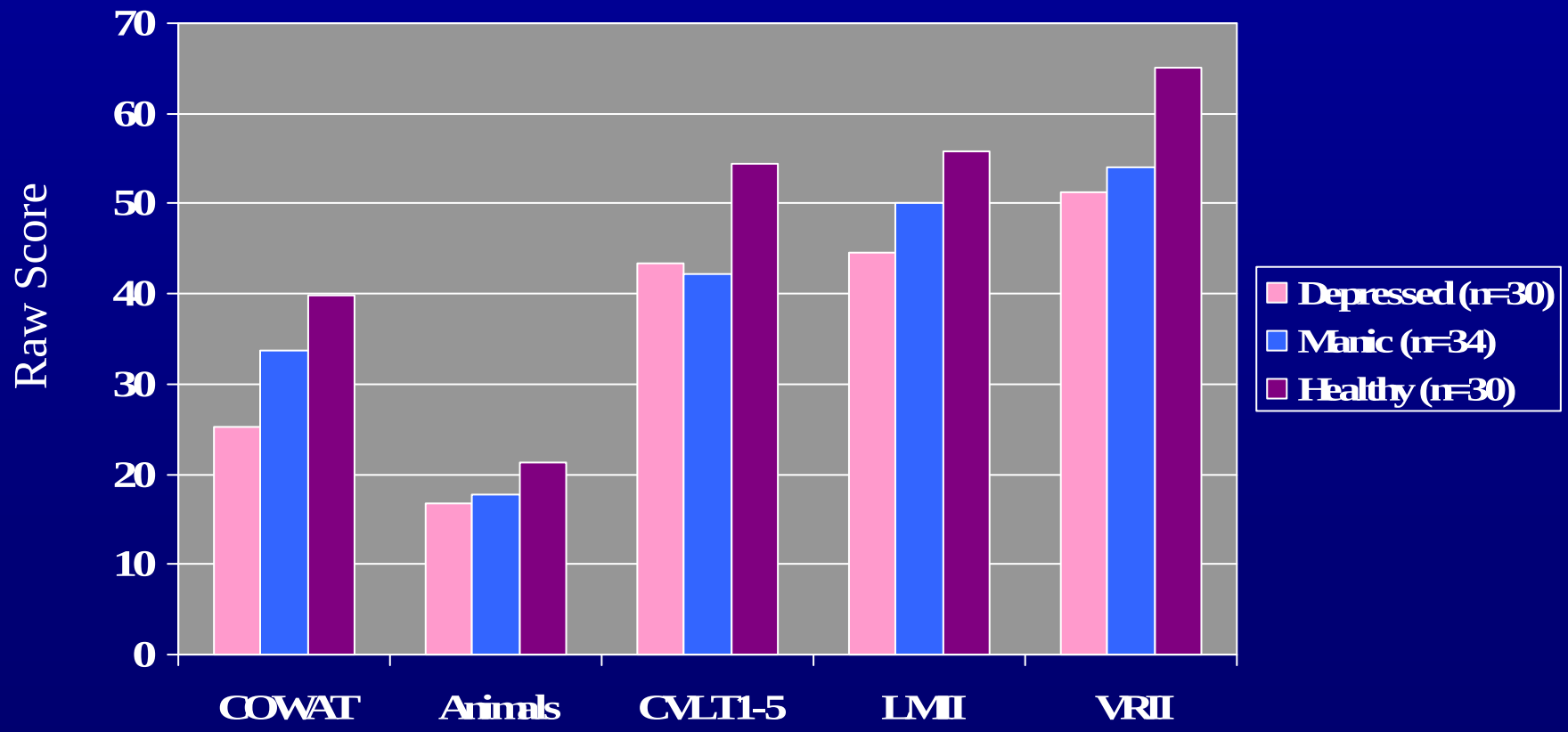
Affective Symptom Severity Level	Percentage of Follow-up Weeks Spent at Each Level: Mean (SD)	Median (Range)
Weeks asymptomatic (no depression or mania/hypomania)	52.7 (34.0)	62 (0-99)
Weeks with pure depression (no mania/hypomania)	31.9 (29.9)	23 (0-99)
Pure subsyndromal depression	9.4 (14.7)	3 (0-82)
Pure minor depression/dysthymia threshold	13.5 (17.3)	7 (0-82)
Pure major depression threshold	8.9 (12.5)	5 (0-63)
Weeks with pure mania/hypomania (no depression)	9.3 (15.6)	2.5 (0-82)
Pure subsyndromal mania/hypomania	2.4 (6.8)	0 (0-38)
Pure hypomania threshold	4.6 (9.9)	1 (0-81)
Pure mania threshold	2.3 (4.0)	1 (0-37)
Weeks with cycling/mixed affective	5.9 (14.2)	0 (0-94)

Affective Symptoms Influence Cognition in Bipolar Disorder



Martinez-Aran et al. 2004

Affective Symptoms Influence Cognition in Bipolar Disorder



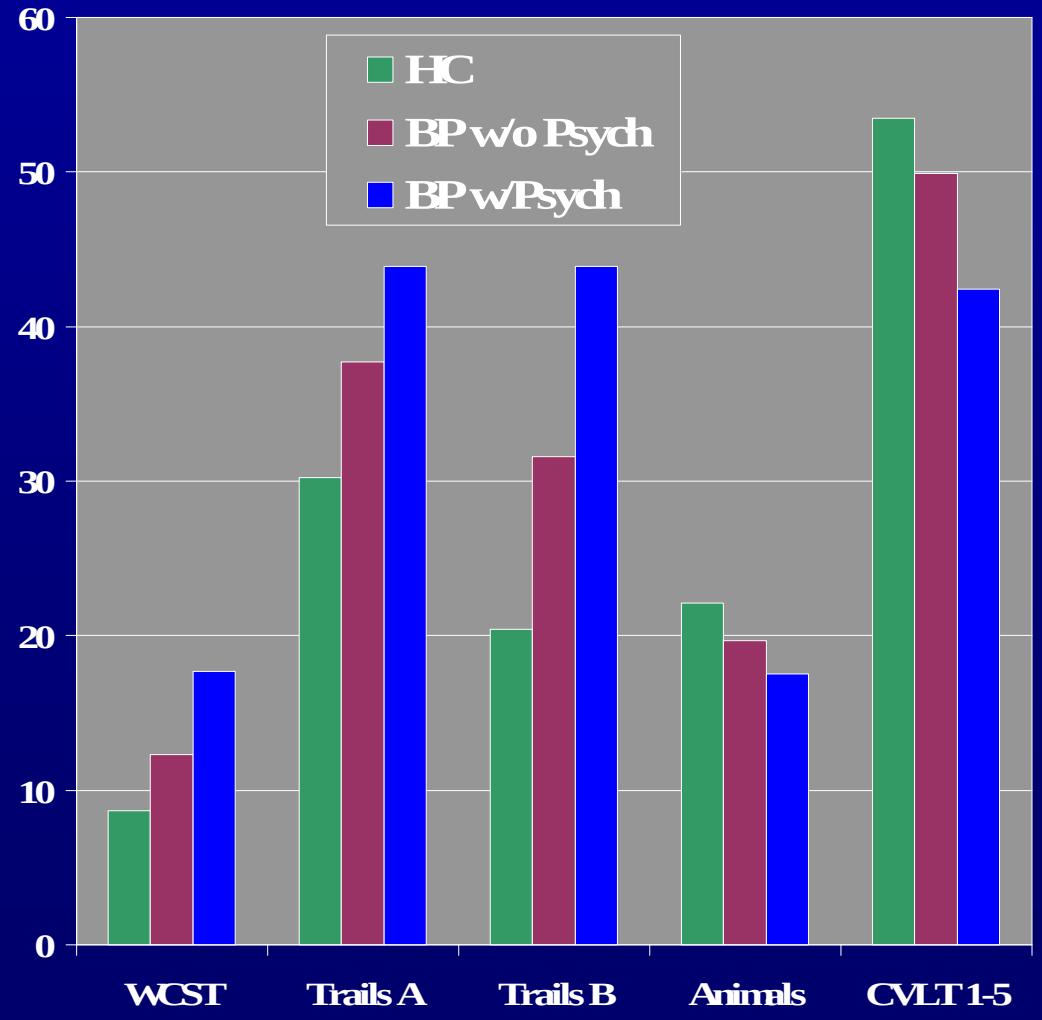
Martinez-Aran et al. 2004

Course of Illness Influences Cognition in Bipolar Disorder

Study	Manic episodes	Depressed episodes	Hospitalizations			Age at onset
			Total	Manic	Depressed	
Van Gorp et al. (5)	−0.01 to **−0.8** (3/12)**	+0.24 to −0.43 (0/12)	–	–	–	–
Krabbendam et al. (7)	ns (0/11?)		–	–	–	–
Rubinsztein et al. (8)	ns (0/3)	ns (0/3)	**−0.5** (1/3)*[b]	–	–	–
El-Badri et al. (9)	**−0.49** to **−0.66** (4/11?)***[c]		–	–	–	ns (0/11?)
Zubieta et al. (11)	+0.18 to **−0.6** (2/6)*	− 0.03 to **−0.55** (2/6)*	–	− 0.03 to **−0.66** (2/6)*	+0.2 to −0.38 (0/6)	+0.49 to −0.41 (0/12)
MacQueen et al. (10)	ns (0/24)	**−0.43** to **−0.62** (6/24)	–	–	–	–
Clark et al. (12)	− 0.09 to **−0.48** (2/6)*	−0.12 to **−0.48** (4/6)*	+0.01 to −0.22 (0/6)	−0.06 to −0.12 (0/6)	+0.37 to **−0.42** (1/6)*	–
Cavanagh et al. (13)	−0.5 to **−0.9** (4/5)***[d]	+0.5 to +0.2 (0/5)[d]	+0.2 to −0.1 (0/5)	–	–	–
Fleck et al. (14)	–	–	–	–	–	–
Deckersbach et al. (15)	**−0.56** to **−0.57** (2/2)***	**−0.51** to **−0.63** (2/2)***	–	–	–	−0.32 to −0.34 (0/2)
Deckersbach et al. (17)	**−0.42** to **−0.5** (2/2)*	**−0.44** to **−0.52** (2/2)**	–	–	–	−0.09 to −0.26 (0/2)
Martínez-Arán et al. (16)	+0.03 to **−0.35** (2/9)*	ns (0/9)	+0.07 to **−0.38** (3/9)*	–	–	+0.12 to **−0.47** (2/9)**
Thompson et al. (18)	**+0.35** to −0.17 (1/15)**	+0.15 to **−0.30** (1/15)*	+0.1 to **−0.48** (6/15)***	–	–	+0.15 to −0.17 (0/15)
Clark et al. (19)	–	–	–	–	–	–
Kieseppä et al. (20)	ns (0/16?)[a]		–	–		

Robinson and Ferrier, 2006

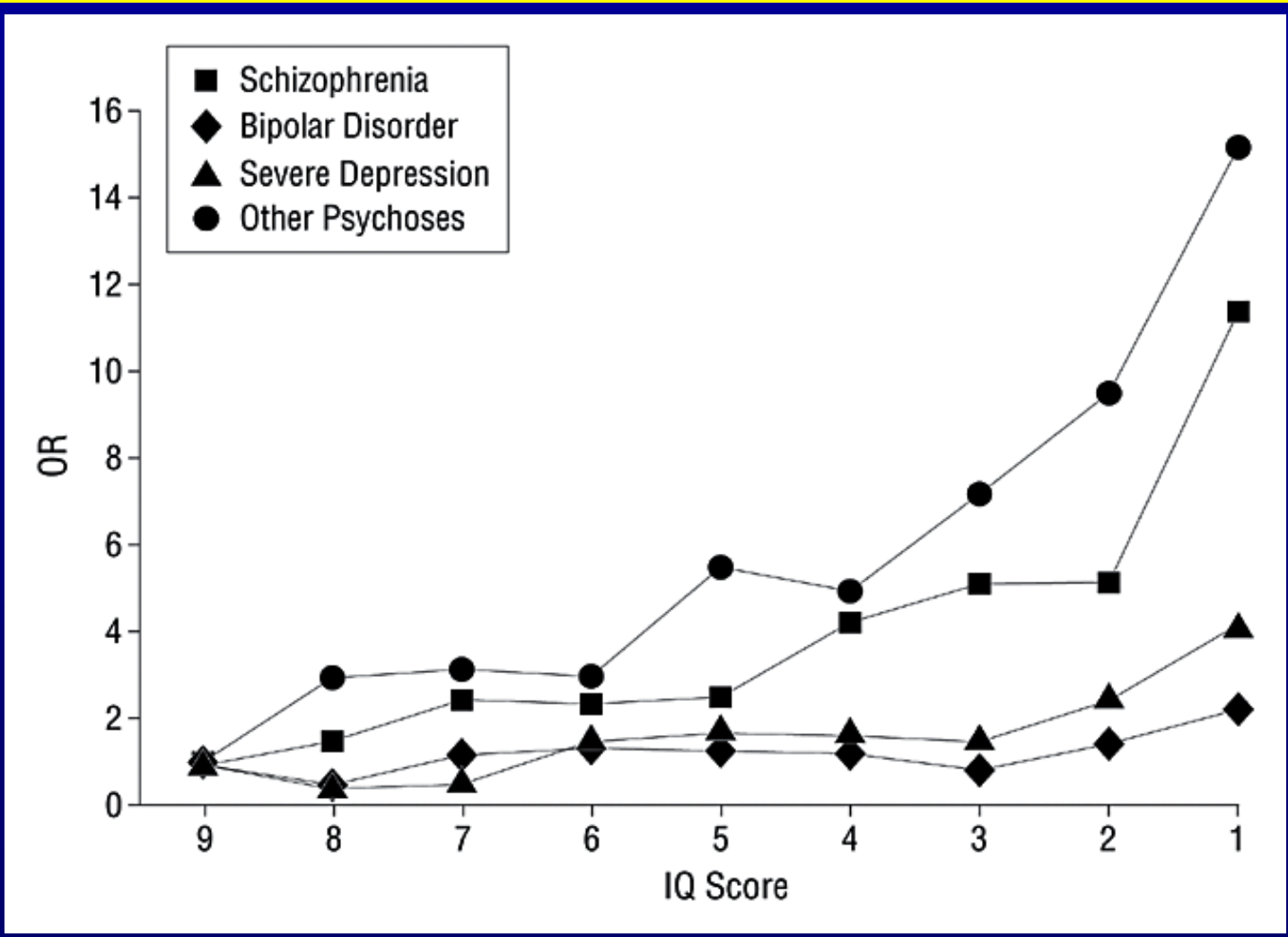
Psychosis History Influences Cognition in Bipolar Patients



- ~50% prevalence in mania
- Remits completely during euthymia
- Aggregates in bipolar patients with a family history of SZ
- May suggest a different genetic background

Martinez-Aran et al. 2008

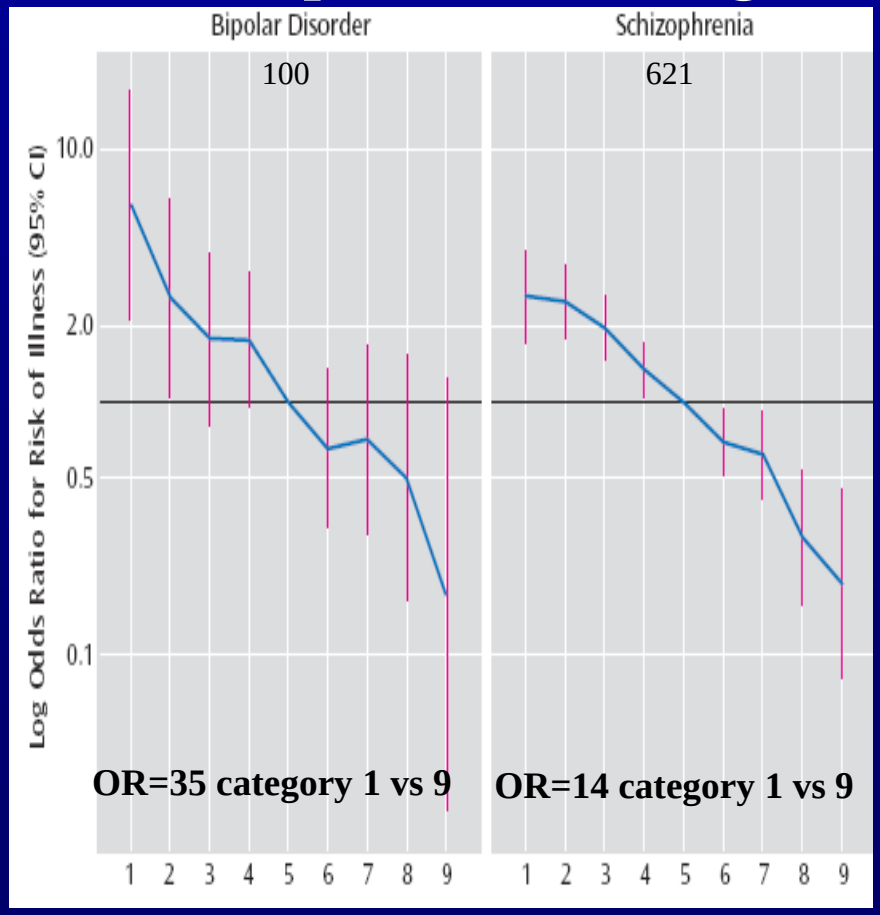
When Do Cognitive Deficits Emerge?



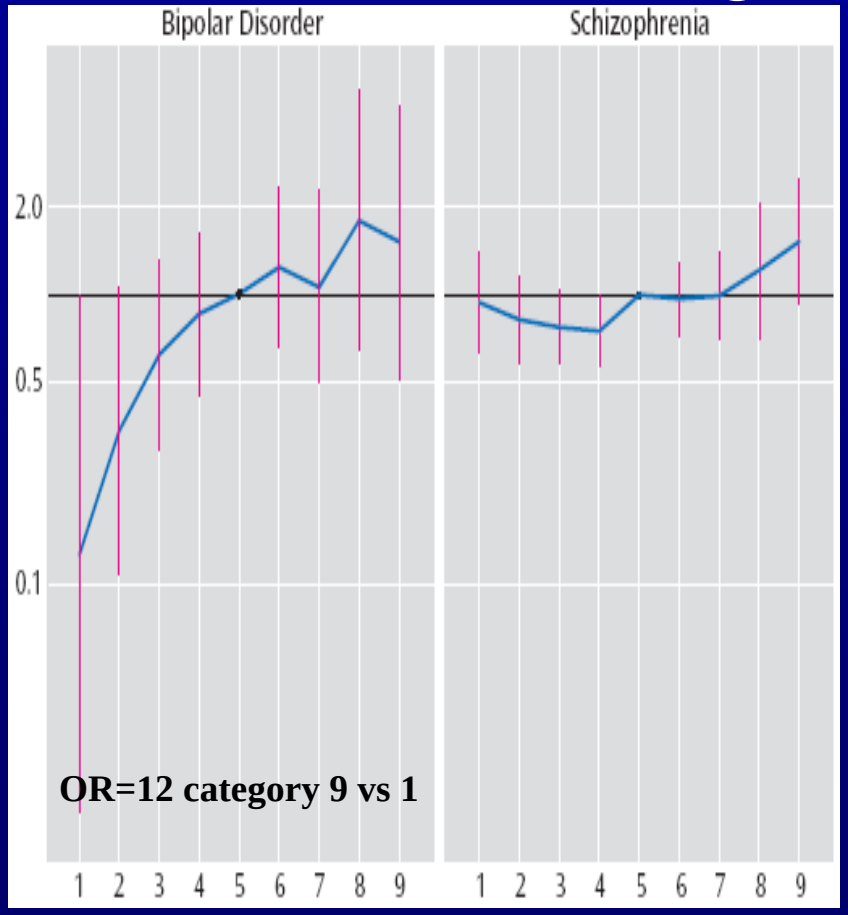
Zammit et al. 2005

When Do Cognitive Deficits Emerge?

Visuospatial Reasoning



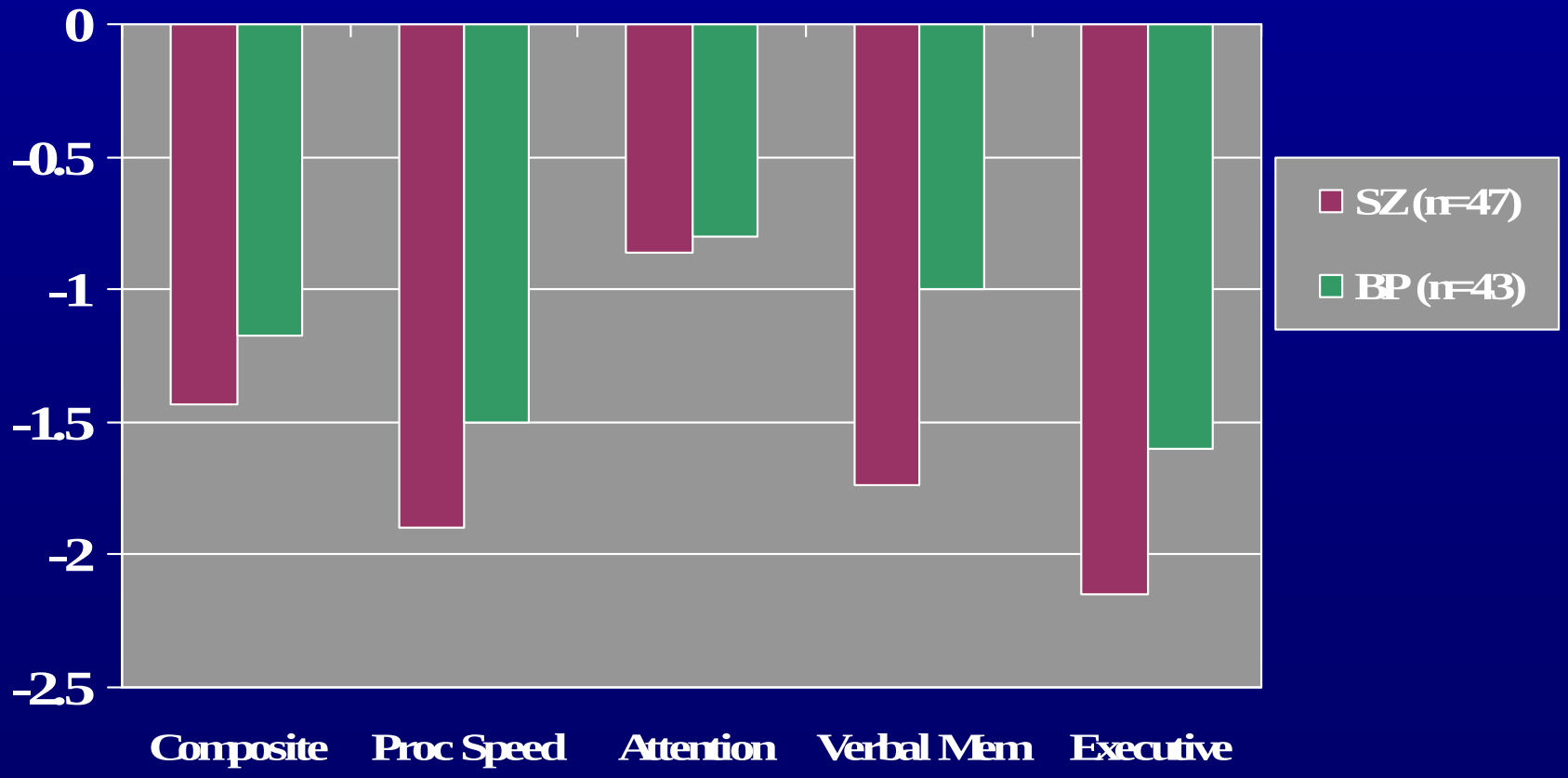
Arithmetic Reasoning



Category of Performance 1=lowest; 9=highest

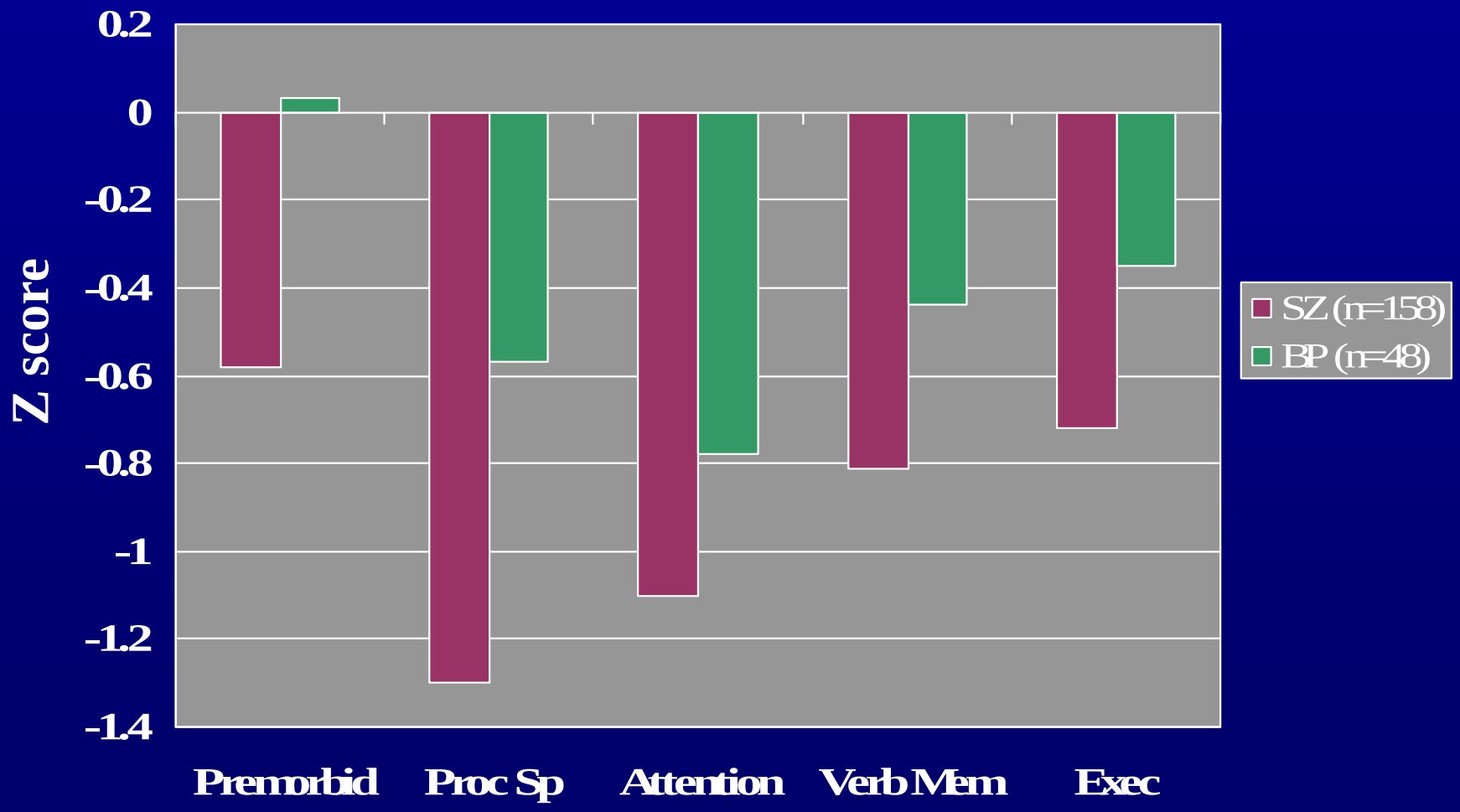
Tiihonen et al. 2005

Cognitive Impairment in Bipolar Disorder Relative to Schizophrenia

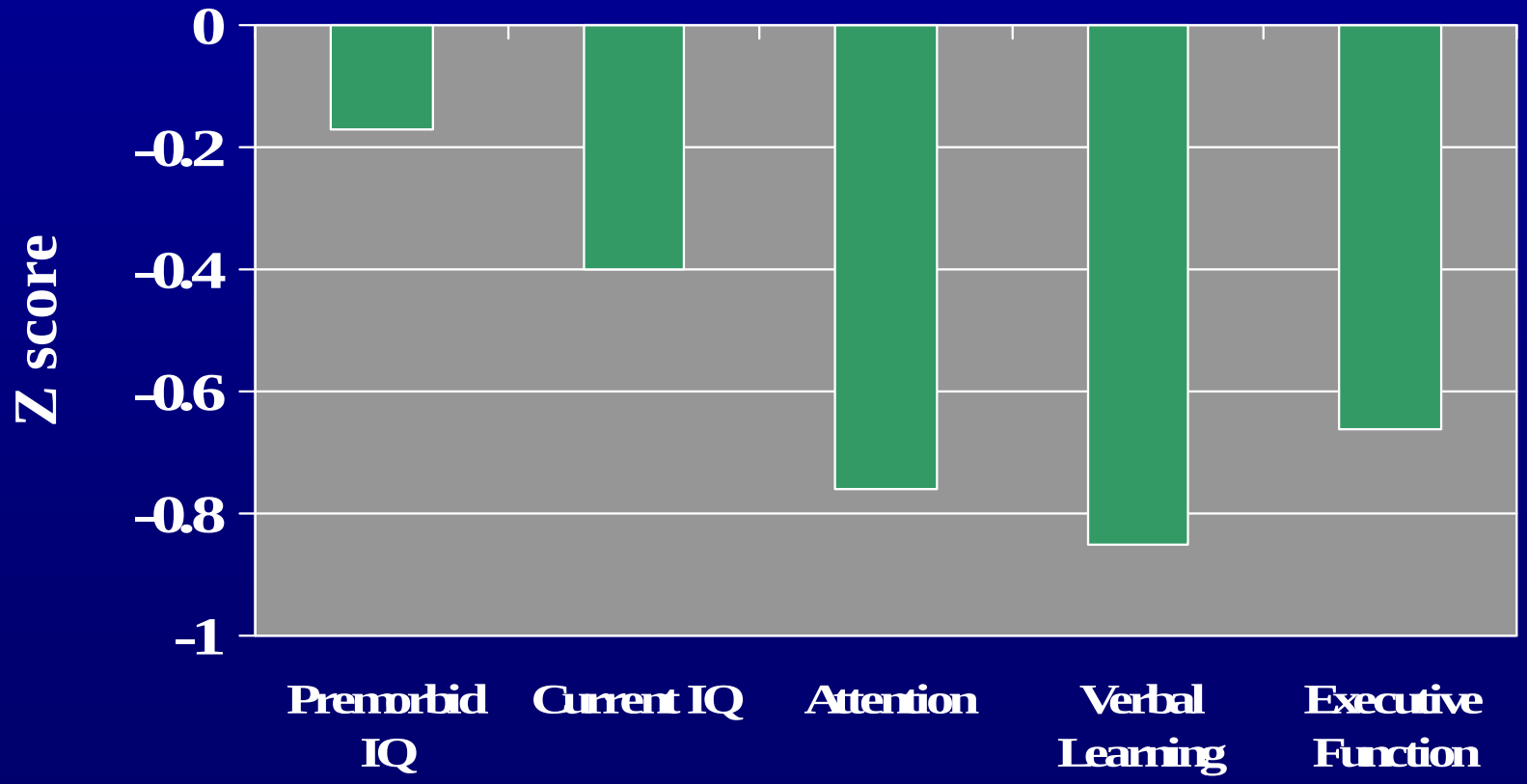


Tabares-Seisdedos et al. 2008

Cognitive Deficits during Remitted States (ZHH Sample)



Cognitive Performance in 1423 Euthymic Bipolar Patients: Meta-Analysis



Bora et al. 2008

Cognition-Function Relationship in Euthymic Bipolar Patients (n=30)

	WHO-Quality of Life	
MEASURE	***Environment***	***Social***
Stroop	.38	.25
Similarities	.54	.30
Trails B	.54	.40
ToH	.51	.33
HDRS Total	.36	.20

Brissos et al. 2008

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

- **Dopamine**
  - Pramipexole: (*Burdick et al. 2007*)-Significant improvement on d2 test of attention but n=7 and depressed at baseline (pseudospecificity?)
- **Glutamate**
  - Lamotrigine: (*Khan et al. 2004*)-Self reported cognitive improvement but open-label monotherapy and adjunctive combined and no objective tests employed
  - Lamotrigine vs. carbamazepine or VPA (*Daban et al. 2006*)-LMT associated with improvement in letter fluency but not randomized, not monotherapy, and groups were not matched on illness features (i.e. illness duration)

Cognitive Dysfunction in Bipolar Disorder

Future Place of Pharmacotherapy

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CNS Drugs, 2007

- **Acetylcholine**
  - Donepezil (*Jacobsen & Comas-Diaz, 1999*)-Self reported improvement but no objective tests, unipolar and bipolar combined, open trial, induced mania.
  - Galantamine (*Schrauwen & Ghaemi, 2006*)-Self reported improvement but n=4, no objective tests and retrospective case series design
- **Glucocorticoid**
  - Mifepristone (*Young et al. 2004*)-Significant improvement in spatial WM, recognition, and verbal fluency but cross-over design with possible order effects and testing conducted 14 days post tx

Issues to Consider for Future Trials

- 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

Issues to Consider for Future Trials

- Objective measures
  - MATRICS provides an ideal starting point
  - MATRICS “Plus” might include additional measures:
    - Affective-based cognition (Emotion recognition; Affective Stroop) that may be more disease-specific
    - Decision-making and probabilistic learning tasks shown to activate brain regions implicated in affect regulation
  - Other batteries for SZ have been adapted to incorporate some of these additional tasks (i.e. BAC-S and BAC-A)

Issues to Consider for Future Trials

- Subject selection considerations
  - Euthymic at baseline
  - Rule out comorbid substance use disorders and clear history of ADHD
  - Careful assessment of history of illness including age of onset, number of episodes, history of psychosis—match groups accordingly
  - Demonstrable cognitive impairment on ‘screening’ measures; alternatively performance suggestive of decline from premorbid functioning

Conclusions

- Bipolar illness is complex, with multiple subtypes and several clinical features that impact directly upon cognition.
- Some aspects of cognitive dysfunction may represent a core feature of bipolar disorder, as they persist during euthymia.
- Evidence supports a relationship between these persistent deficits and functional disability, making this a treatment priority.
- The identification of homogeneous samples or bipolar ‘subtypes’ that may optimally benefit from cognitive enhancement trials will be critical.

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