



Neurocognitive Aspects of Primary Psychiatric Disorders

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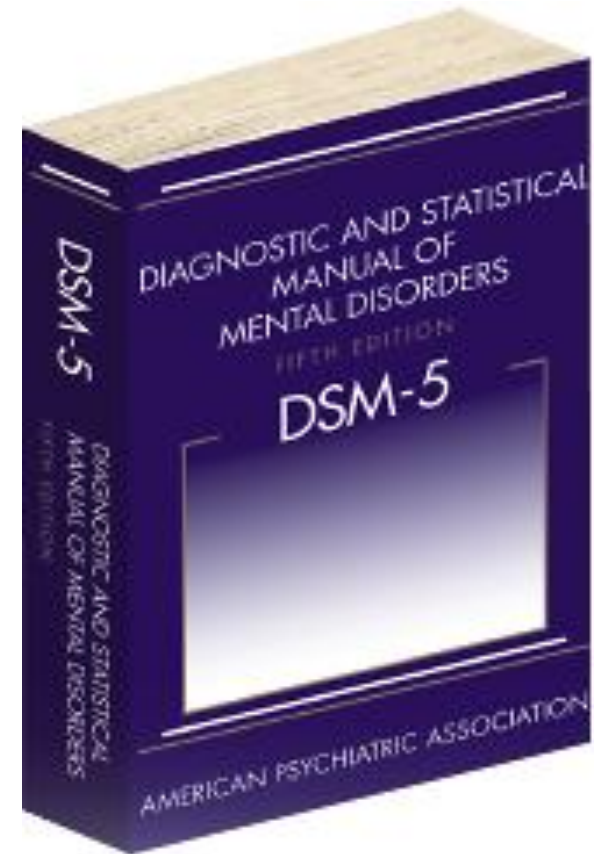
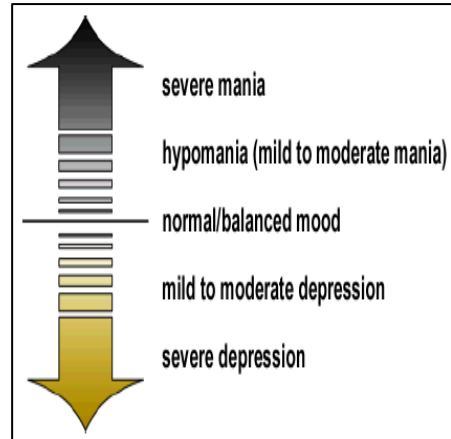
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A historical perspective



Why does cognition matter?

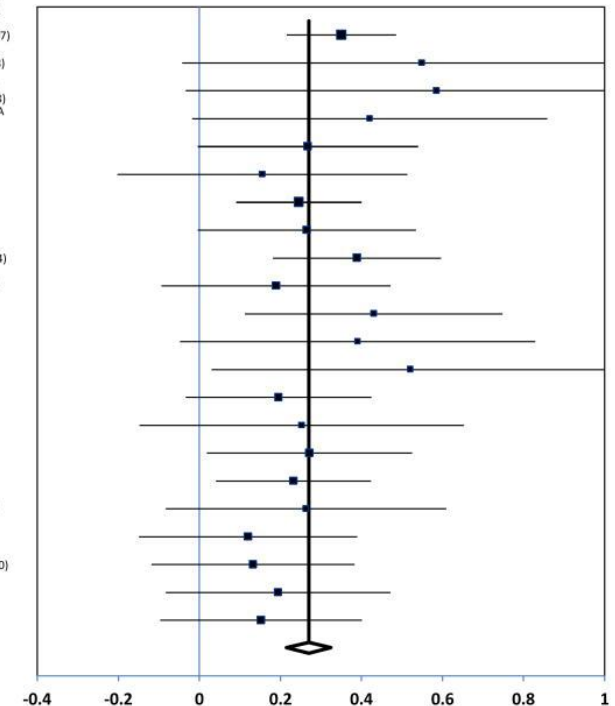
Ten Leading Causes of Disability in the World

Type of Disability	Cost (in DALYs)	Cumulative % of Cost
Unipolar major depression	42,972	
Tuberculosis	19,673	
Road traffic accidents	19,657	
Alcohol use		23.2
Self-inflicted injuries		26.7
Bipolar Disorder	11,189	29.8
War	13,134	32.9
Violence	12,955	36.0
Schizophrenia	12,542	39.0
Iron deficiency anemia	12,511	42.0

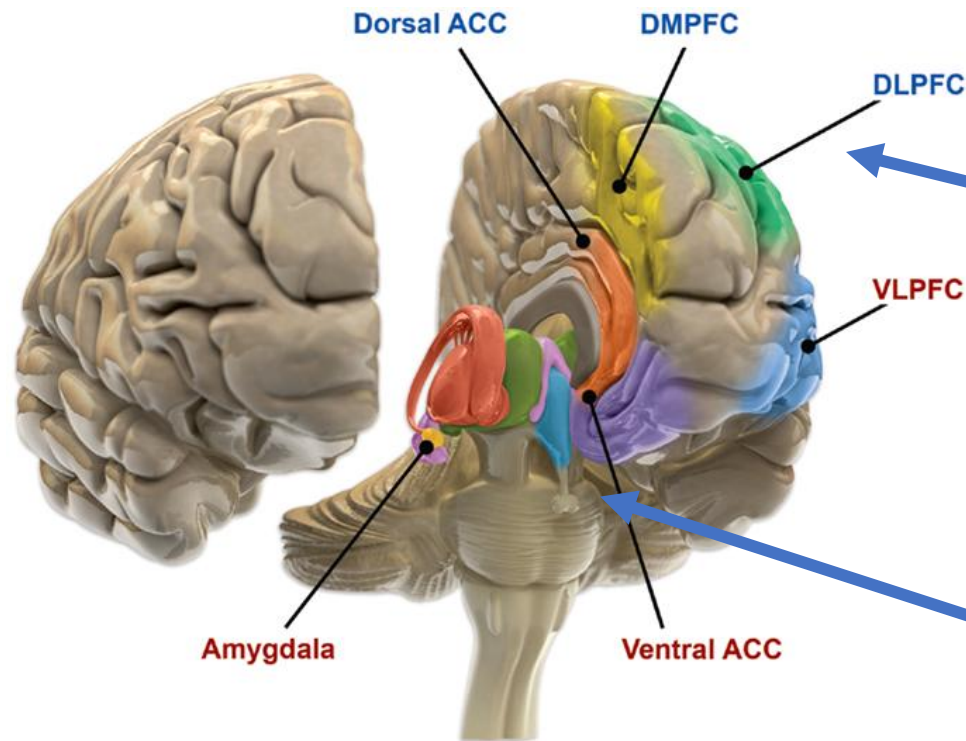
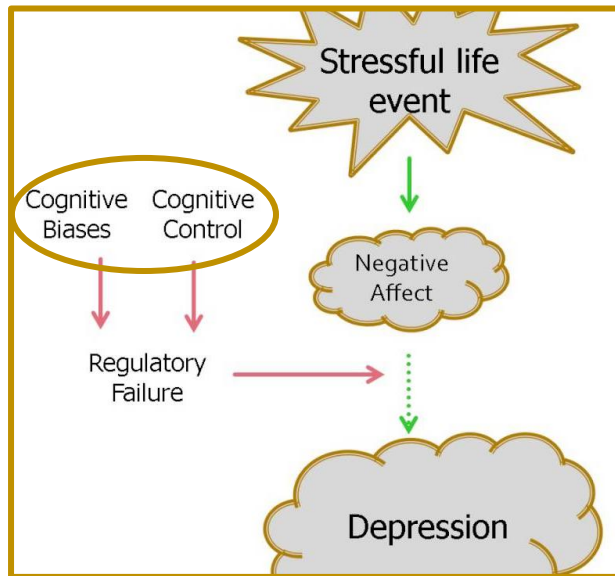
If full recovery is the goal, cognitive impairment must be addressed

Reference, Author (year)

- 28. Altschuler et al. (2007)
- 29. Altschuler et al. (2008)
- 30. Atre-Vaidya et al. - Community Sample (1998)
- 30. Atre-Vaidya et al. - VA sample (1998)
- 31. Brissos et al. (2008)
- 1. Burdick(2010)
- Depp (2010)
- 17. Depp et al. (2007)
- 32. Dickerson et al. (2004)
- 33. Dittman et al. (2007)
- Forcada (2010)
- Giglio (2010)
- Gildengers (2009)
- Jabben (2010)
- Laes (2006)
- Levy (2010)
- 10. Martinez-Aran et al. (2004)
- 36. Martino et al. (2009)
- Simonsen-nonpsychotic (2010)
- Simonsen-psychotic (2010)
- 37. Torres et al. (2010)
- 38. Wingo et al. (2010)

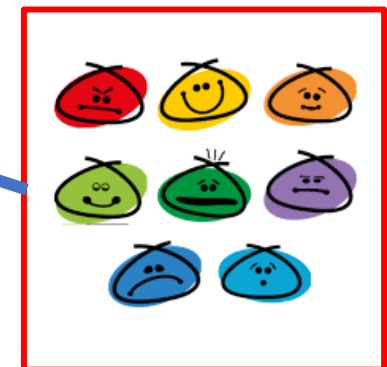


Cognition's role in affective (dys)regulation



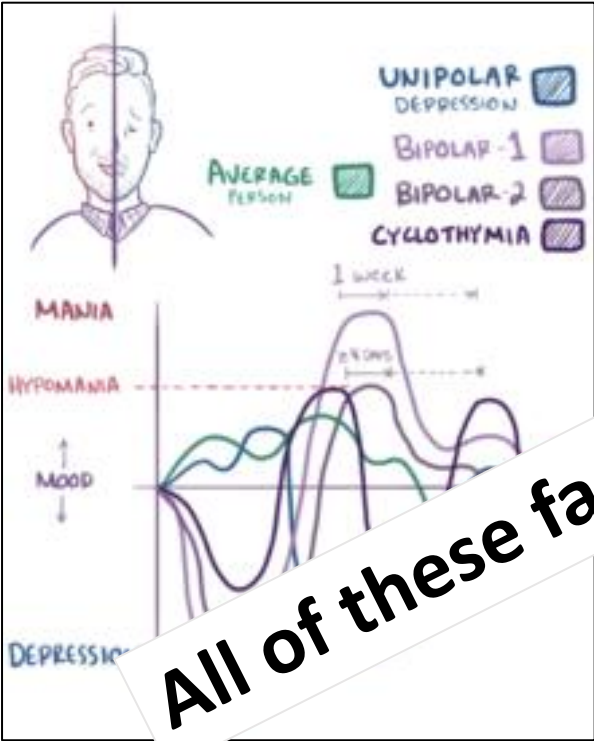
DLPFC: Dorsolateral prefrontal cortex
VLPFC: Ventrolateral prefrontal cortex

DMPFC: Dorsomedial prefrontal cortex
ACC: Anterior cingulate cortex

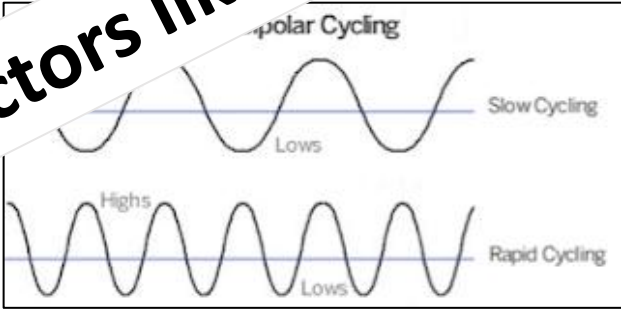


Psychiatric illness is EXCEPTIONALLY complex: BD as an example

Clinical heterogeneity: Recognized subtypes



WHAT IS PSYCHOSIS?
PSYCHOSIS DISTORTS A PERSON'S PERCEPTIONS AND THOUGHTS THROUGH HALLUCINATIONS AND DELUSIONS



Comorbidities



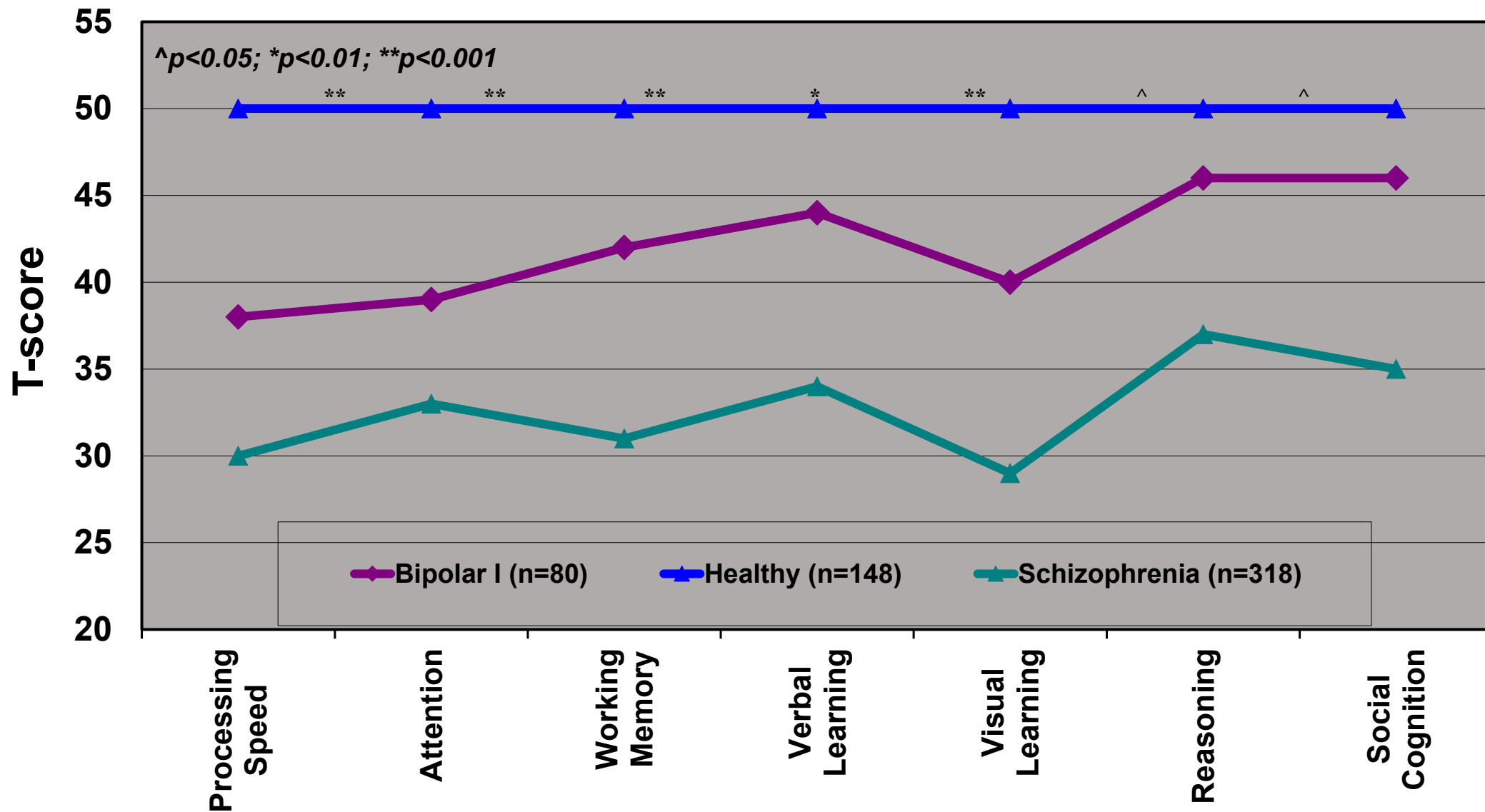
Anxiety Symptoms

ausea, brain zaps, falling sensation, sweating, shaking, weak legs, difficulty breathing, el like, headaches, cold chills, knot in stomach, twitching, muscle tension, eye strain, chest tightness, restless legs, blurred vision, numbness, tingling, facial tic, head pressure, body pain, dizziness, body jolts, hot flash, night sweats.

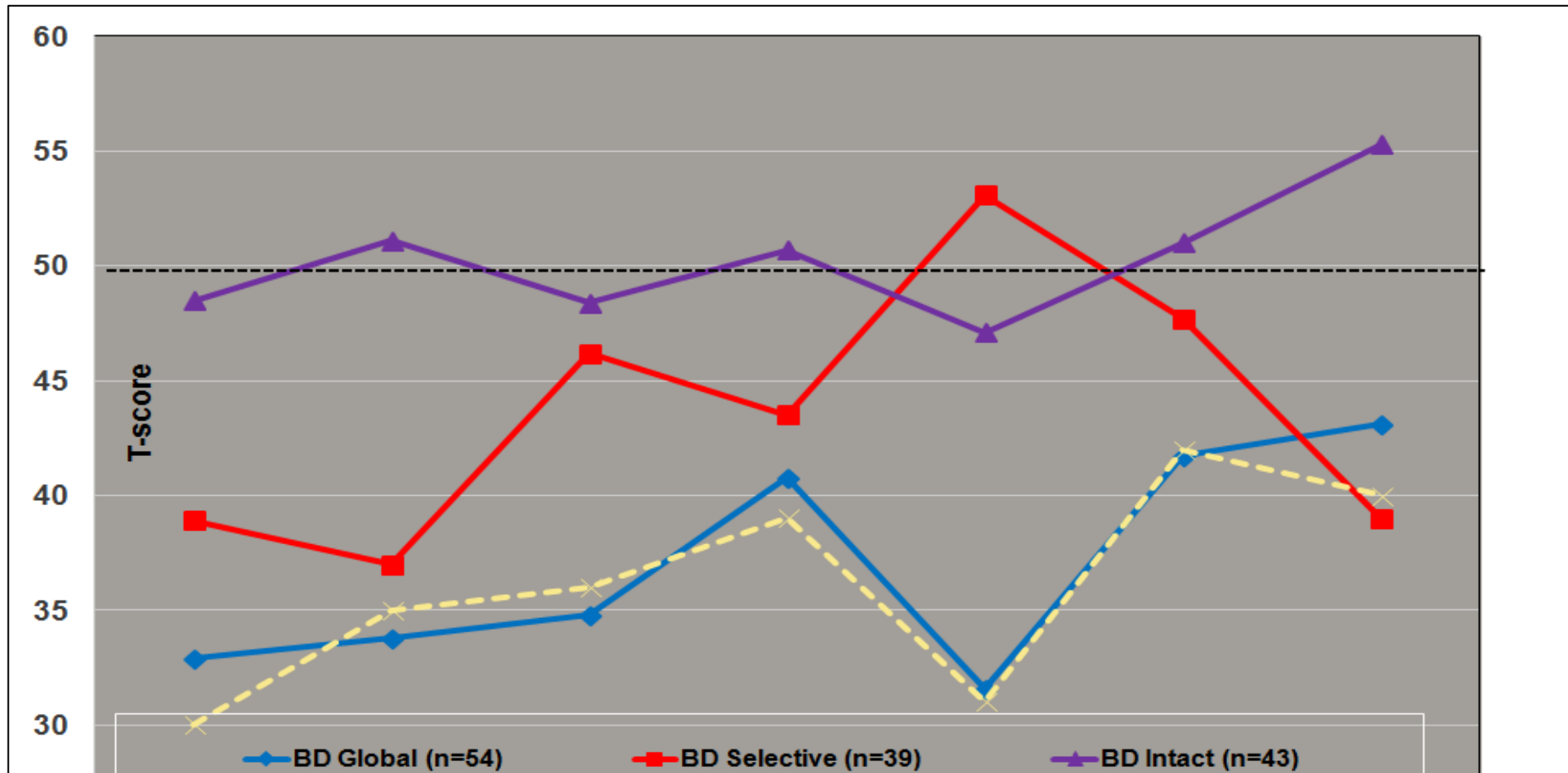


There are 100s of *different* combos of sxs that can result in a dx of BD

Traditional diagnostic classification: Cognition



Cognition-based subtypes in bipolar disorder



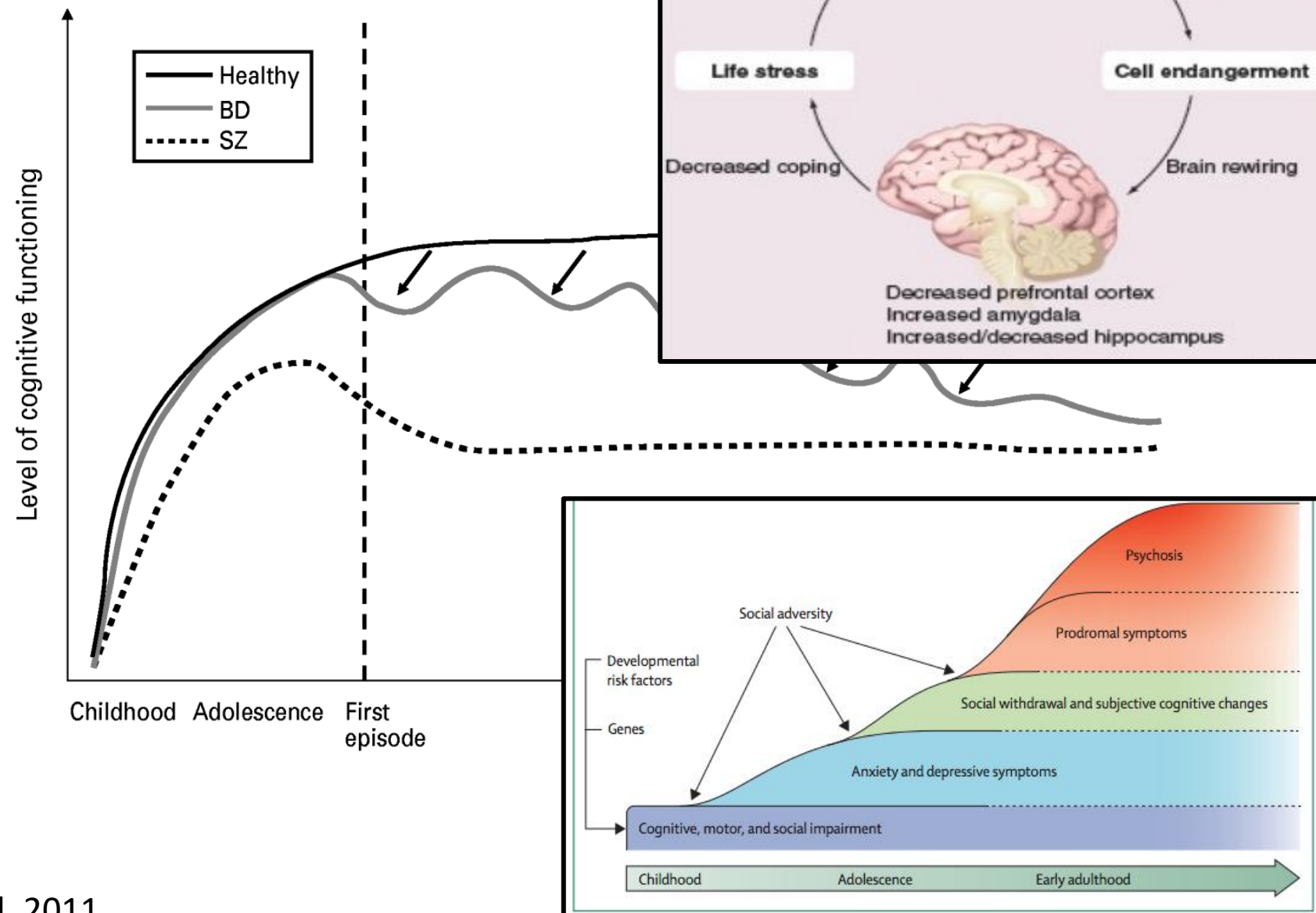
Burdick et al. 2014

Does this type of classification tell us anything *new* about bipolar disorder?

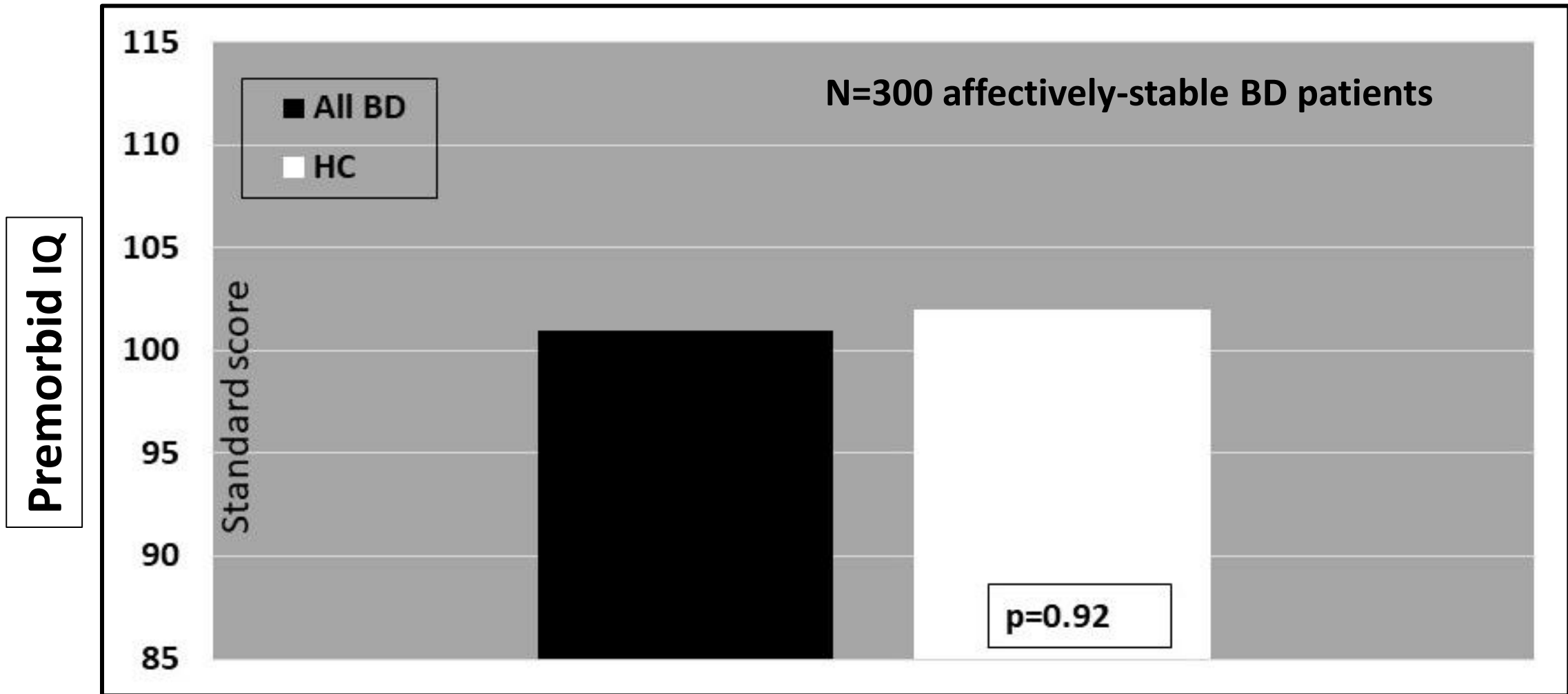
Functional heterogeneity in BD



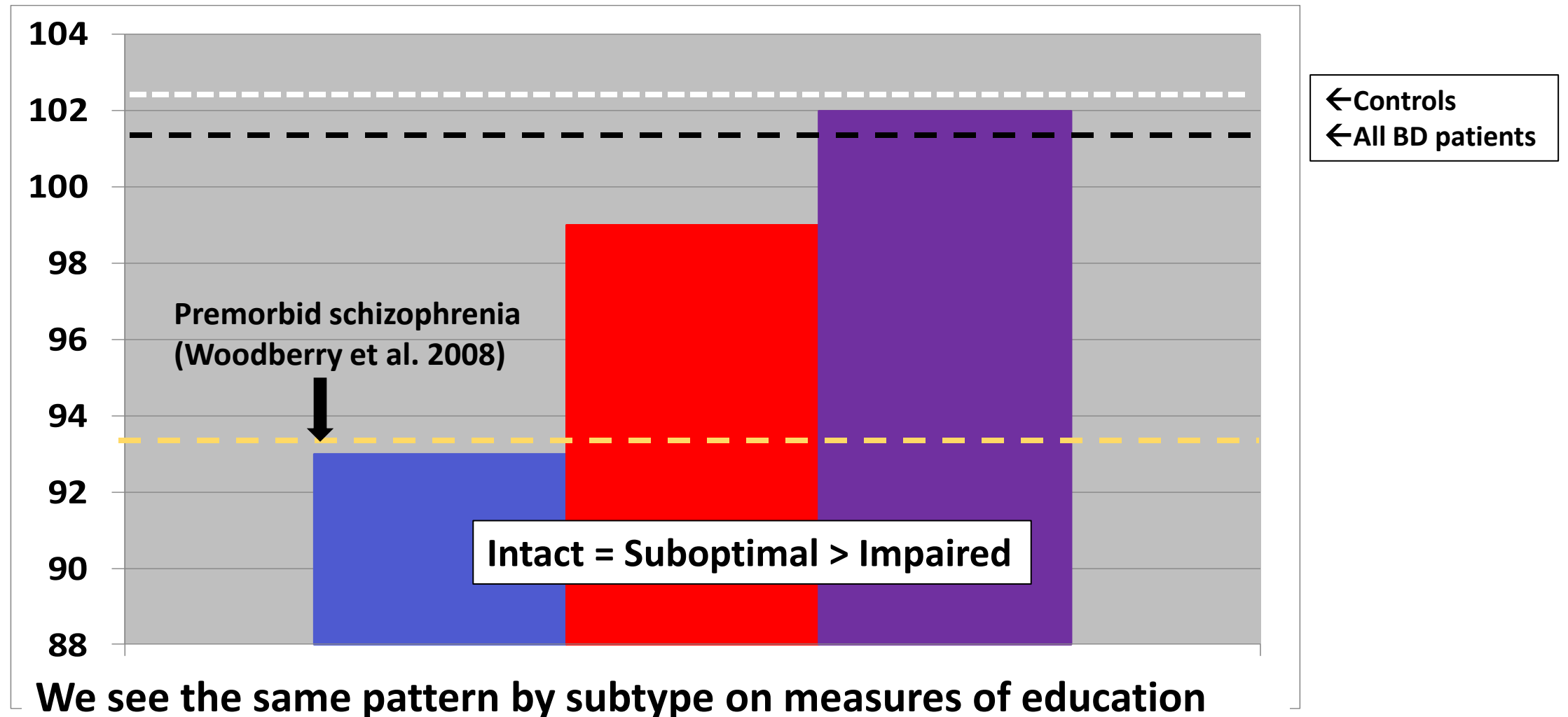
Hypothesized Trajectories by DSM-diagnosis



Traditional diagnostic classification: Premorbid IQ

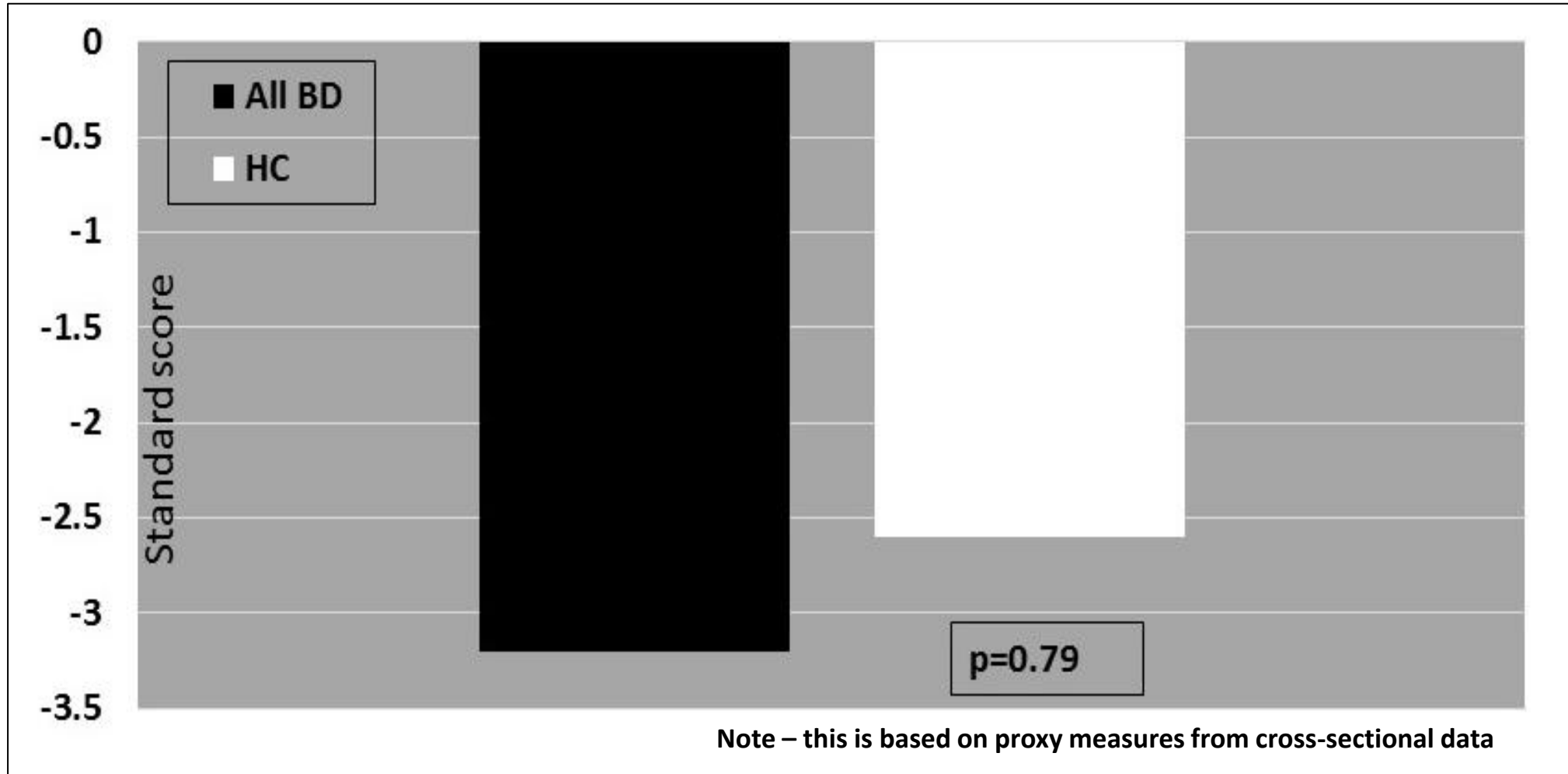


Cognitive subtyping: Premorbid IQ



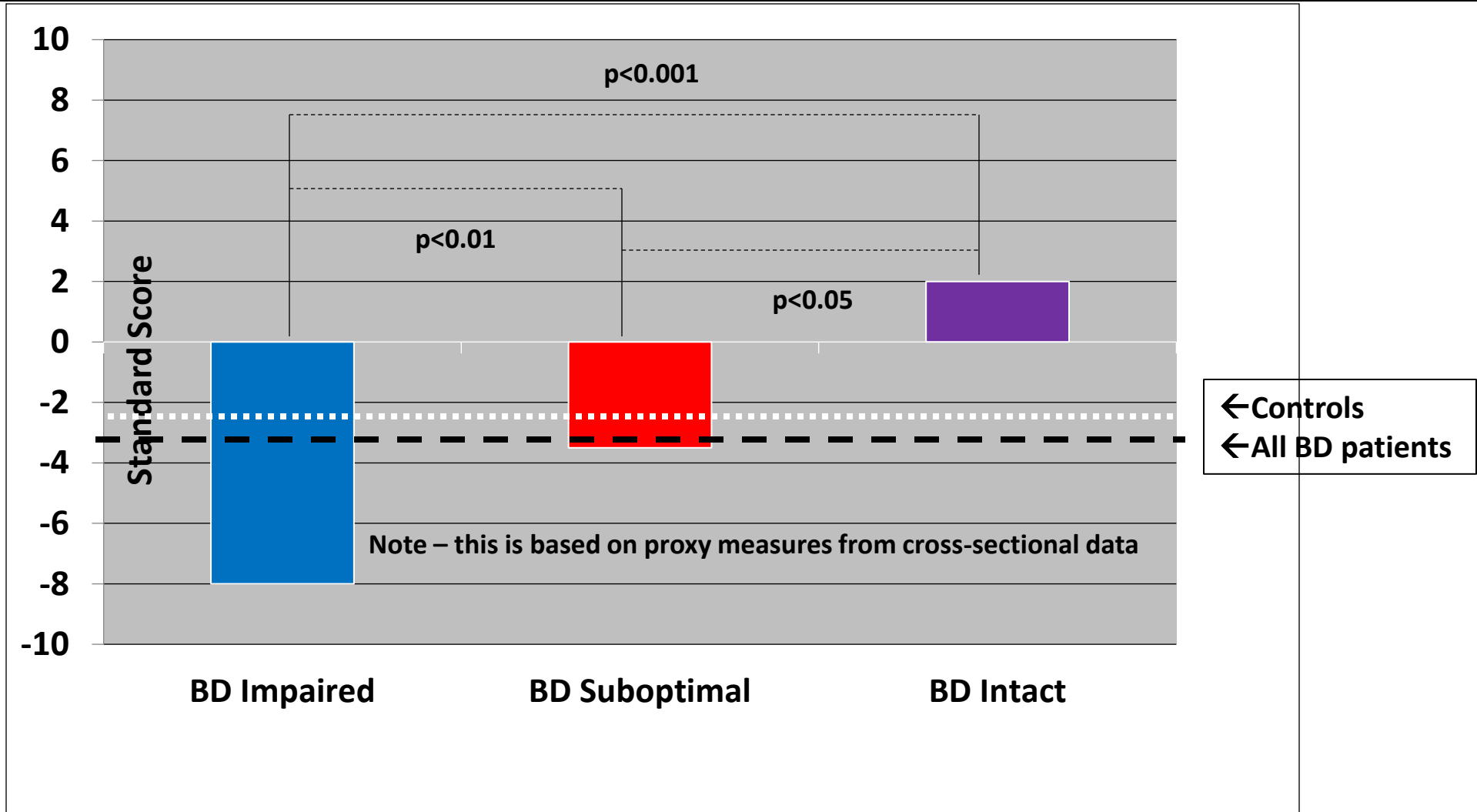
Traditional diagnostic classification: Cognitive decline

Proxy “Change” in IQ



Consistent with meta-analyses (Bora et al. 2017; Szmulewicz et al. 2020); do not account for heterogeneity

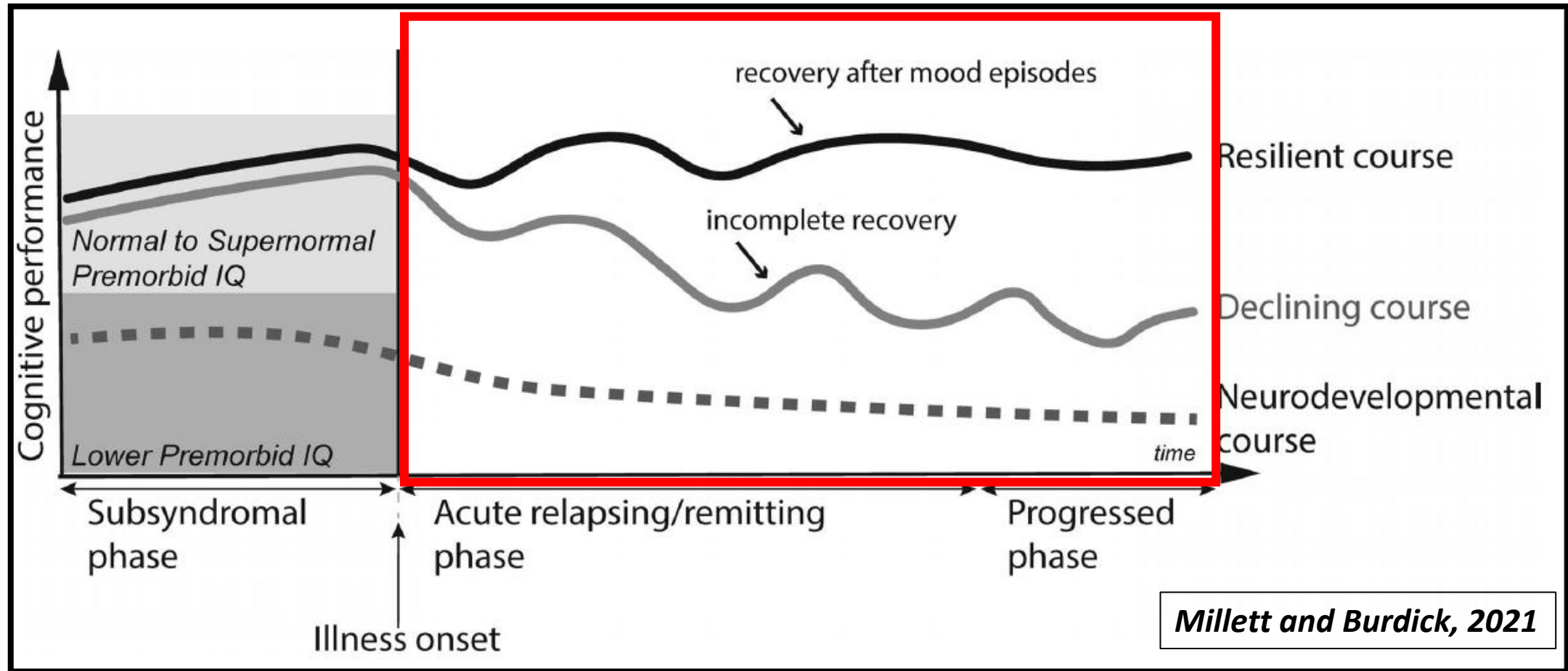
Cognitive subtyping: Cognitive decline



Suggests that *some* BD patients show a declining course and some do not

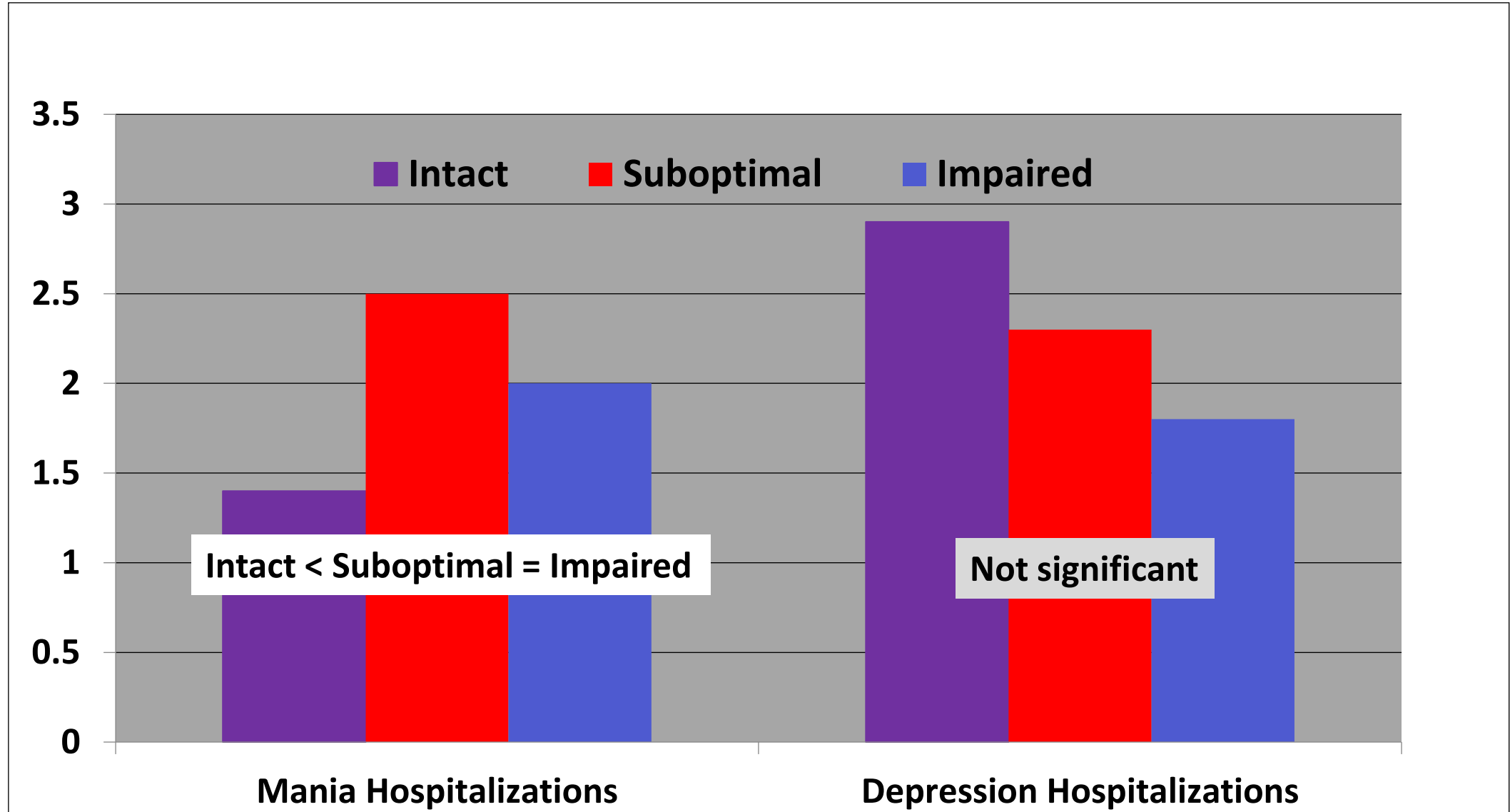
Cognitive subtyping in BD: A revised model

Window of opportunity



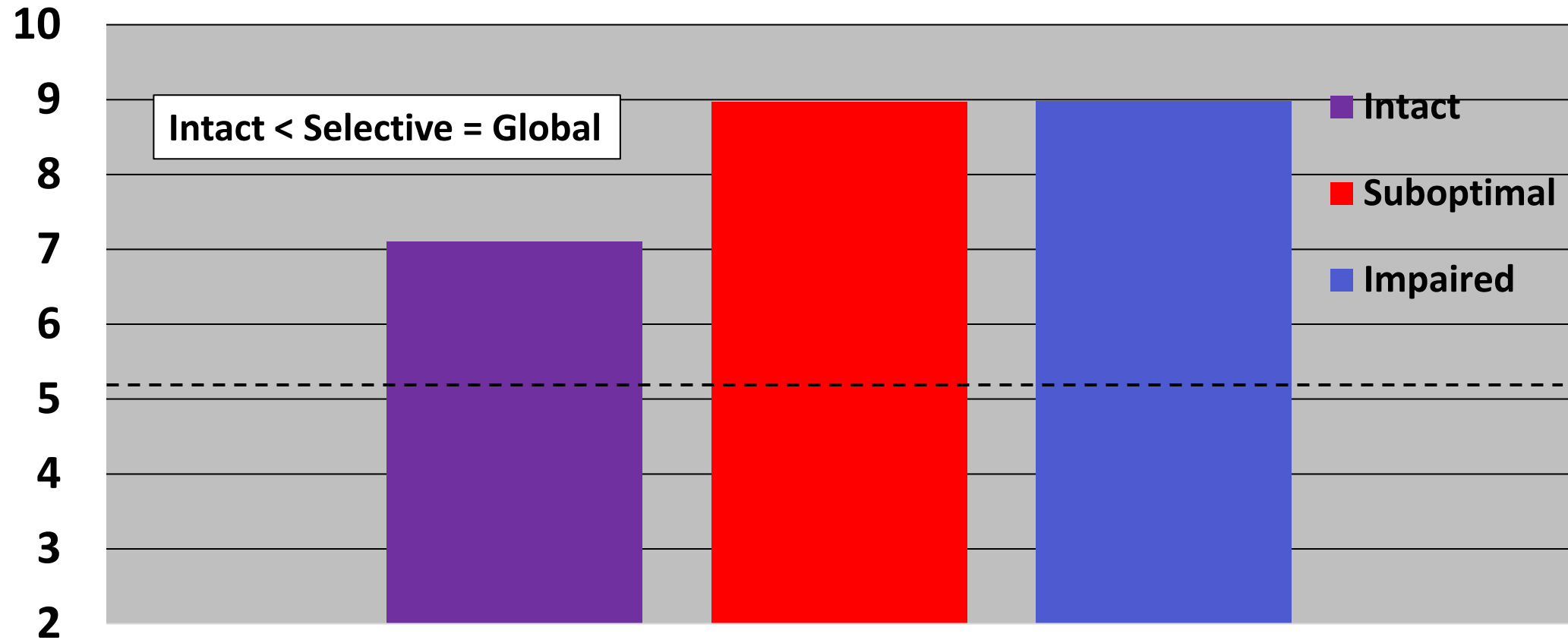
Can we use this new information to identify modifiable risk factors for poor outcome in BD?

Cognitive subtyping: Recurrence rate



Cognitive subtyping: Sleep quality

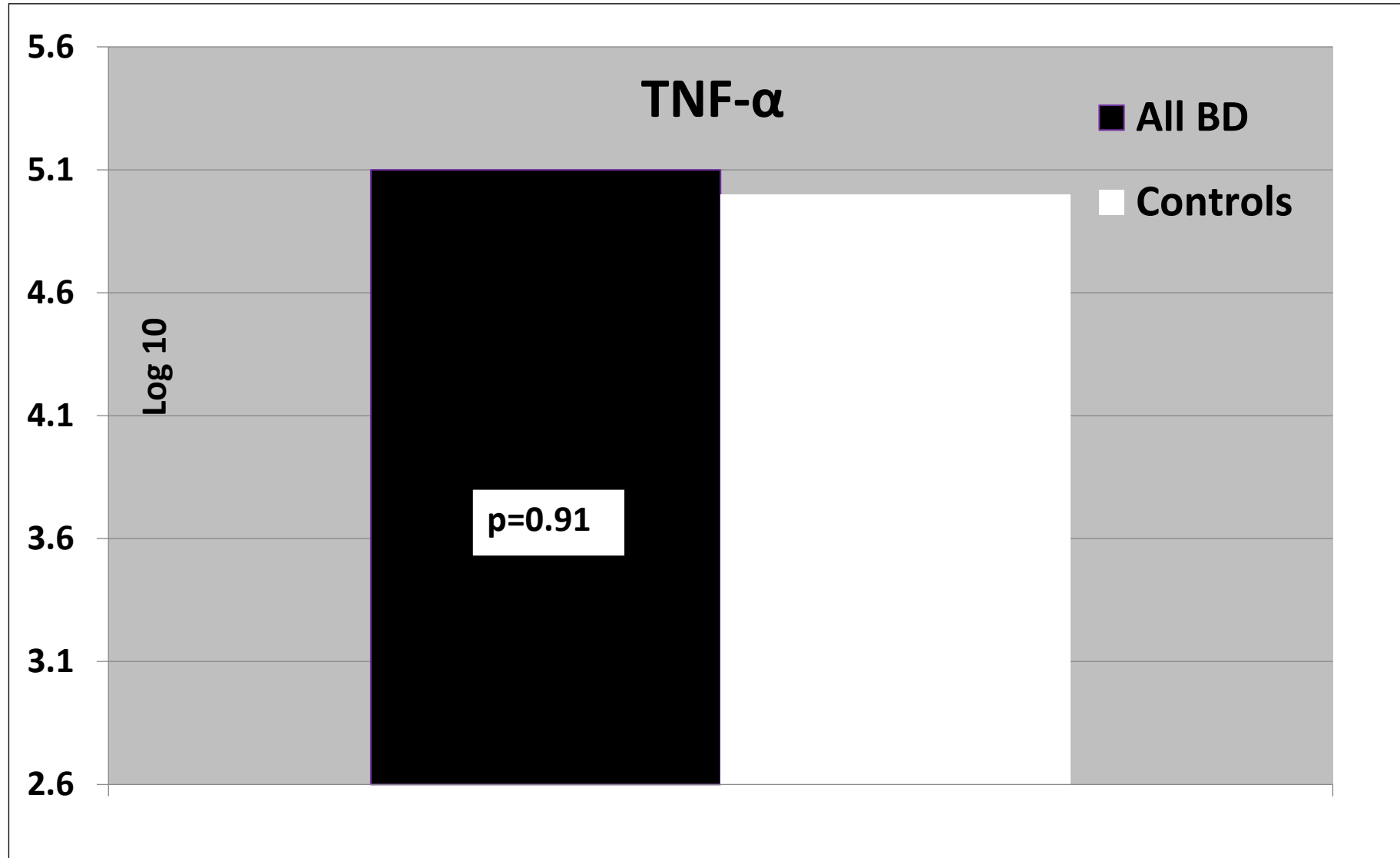
Pittsburgh Sleep Quality Index



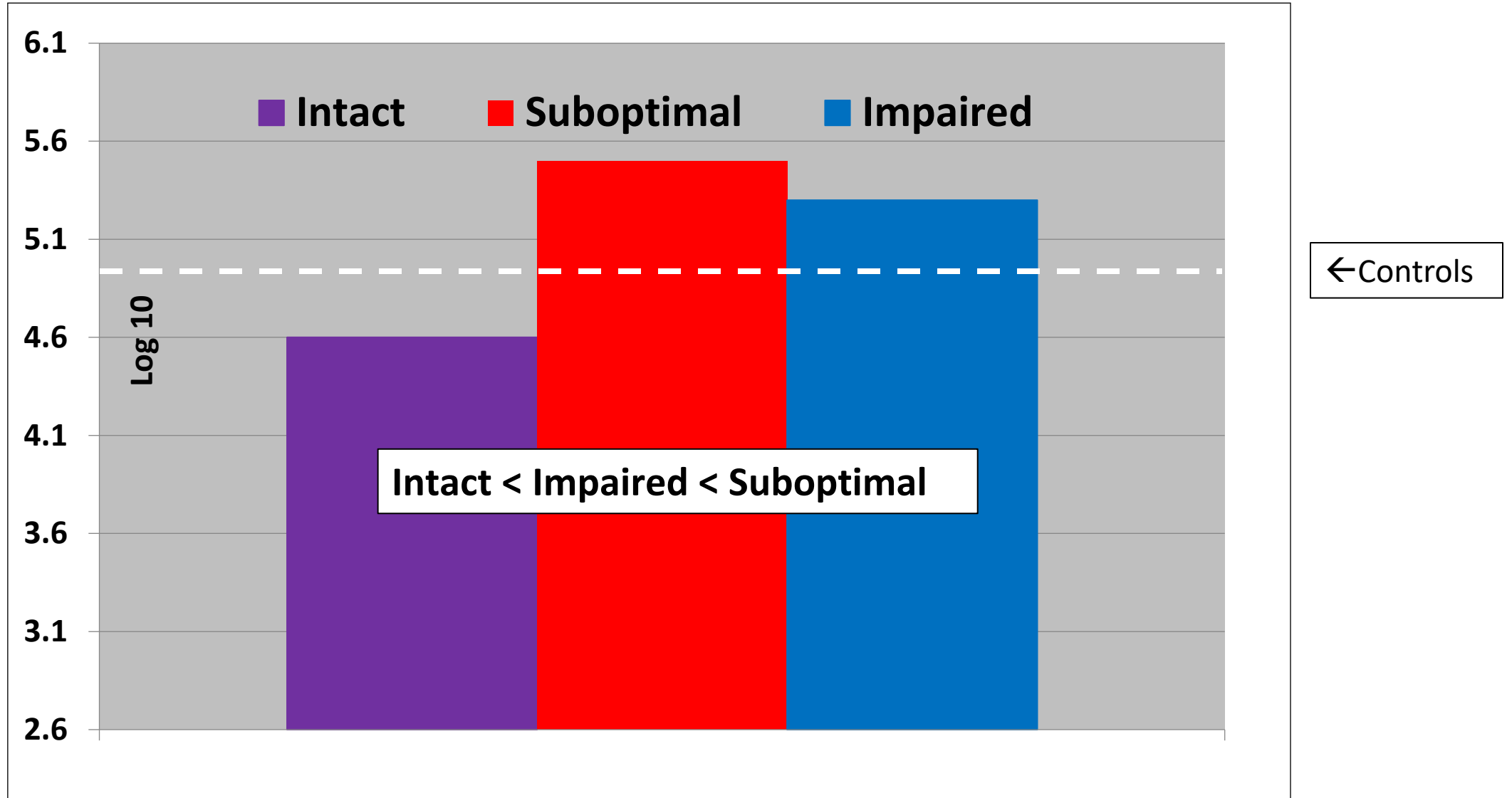
Traditional diagnostic classification: Inflammation

Plasma-based biomarkers of peripheral inflammation were collected at the time of assessment

Tumor necrosis factor – alpha (TNF- α) – a pro-inflammatory cytokine – is shown



Cognitive subtyping: Inflammation (TNF- α)



Cognition-based subtypes in bipolar disorder

Intact subtype	Suboptimal subtype	Impaired subtype
Normal premorbid IQ No evidence of decline ---- Fewer manias Better sleep Less substance use d/o ---- Low levels of inflammation	Normal IQ Some evidence of decline ---- More manias Poor sleep Higher substance use d/o ---- High levels of inflammation	Impaired Premorbid IQ Evidence of decline ---- More manias Poor sleep Higher substance use d/o ---- High levels of inflammation
Not all patients are the same!		

Should cognition be routinely (clinically) assessed for BD?

- Conduct formal screening assessment of cognition for *all patients in partial or full remission* whenever possible since subjective and objective cognition measures can diverge early

- Mood symptoms will muddy clinical picture when stable
- Persistent “trait-like” impairment is a concern
- Differentiate cognitive impairment from mood symptoms

- Assess cognitive function to: (i) detect cognitive impairment, (ii) address and in some cases may require referral for comprehensive neuropsychological evaluation, (iii) identify those who are cognitively intact, and (iii) track cognition, ideally at least every 5 years or whenever there is a reason to anticipate the assessment

- Identify those who need further follow-up
- Identify those who are functioning in the “normal” range
- Longitudinal tracking is critical in an episodic life-long disorder

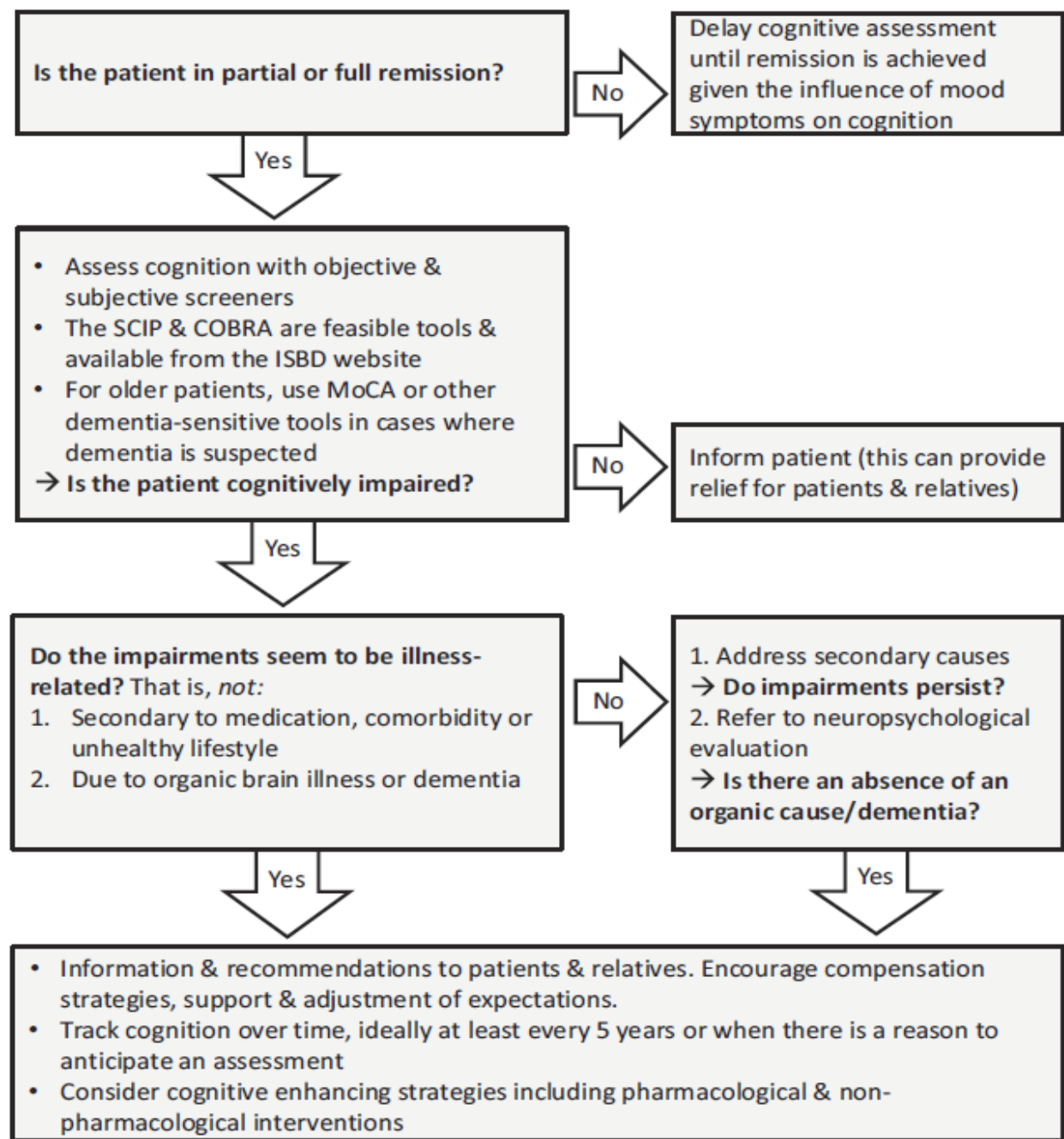
YES!!!!

What are the most feasible tools?

- Use brief, feasible tools that include objective and subjective cognition measures such as the Screen for Cognitive Impairment in Psychiatry (SCIP) and Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)
- Standardized measures with normative values are optimal
- Established cut-offs are not yet available
- Always interpret in context (age, premorbid IQ, current mood state)
- Obtain the SCIP and COBRA—which exist in multiple languages and are freely available—through the ISBD website at www.isbd.org/cognitive-assessment
- Freely available
- Ongoing studies/use will allow for additional norming

What are the most feasible tools?

- SCIP is a brief 5-test battery
 - *Verbal working memory; verbal learning; verbal fluency and psychomotor speed*
 - *10-15 minutes*
 - *3 alternate forms – repeatable*
 - *Available in multiple languages*
- COBRA is a 16-item subjective scale
 - *i.e. Do you find it hard to concentrate while reading?*
 - *Correlates with some objective tests - used alone is not highly sensitive/specific: use with objective measures*
 - *Can point to secondary causes of complaints (e.g. subthreshold mood that needs more aggressive tx)*



What are the clinical implications of cognitive testing in BD?

- Evaluate the potential impact of medication, comorbidity and symptoms when impairment is detected to discriminate between "secondary" and "primary" causes of cognitive impairments—and adjust medication if necessary to reduce cognitive side effects
- Assess when initiating a new tx to allow objective evaluation of cognitive side effects or cognitive benefit
- Opportunity to psycho-educate around substance abuse
- Consider referral for more comprehensive neuropsychological evaluation when there is a substantial impairment in the screening, when there is concern about organic brain illness, comorbidity, or cognitive decline, when there is a need to evaluate multiple cognitive domains in greater detail, when there is a question of poor effort affecting validity of test results, or when premorbid/developmental/learning problems may be complicating the cognitive picture

What are the clinical implications of cognitive testing in BD?

- Inform patients and relatives about the nature and possible consequences of patients' cognitive impairments and encourage compensation strategies, support and adjustment of expectations
 - Reduce frustration; set realistic expectations
 - Reduce interpersonal conflict
 - Encourage patients to implement good habits, including regular sleep and exercise, and to build up their cognitive reserve by engaging in education and vocational activities
-
- Although premorbid factors establish baseline cognitive reserve, there is evidence that this is modifiable

State of the Field – Cognitive treatment in Psychiatry

Not long ago, cognition was ONLY a target in schizophrenia (SZ)

- Now recognized as independent target in BD, MDD

In SZ – hundreds of trials over past two decades – no approvals

- Atypicals as beneficial – flawed designs → practice effects
- MATRICS (2003) – many RCTs followed, none with compelling results
- More recently, agents with new MOA show promise (e.g., KarXT, Alto-101)

In BD and MDD, still very few trials; many pilot-level; underpowered; no replication

A few exceptions – e.g., vortioxetine - only antidepressant with a regulatory-endorsed cognitive indication

The good news? The field is rallying

Conclusions: I

- Cognitive dysfunction is common and disabling in many patients with BD
- Once remitted, cognitive impairment is the strongest predictor of how patients' function
 - ✓ Treatments need to target this disabling symptom domain
 - ✓ Mood stabilization is often not enough to promote full recovery
 - ✓ Not all patients are impaired – precision approaches are needed
- Many factors contribute to good/poor cognitive and functional outcomes
 - *Some of these represent modifiable treatment targets*
 - *Episode reduction*
 - *Sleep improvement*
 - *Anti-inflammatory approaches*
- *In order to identify those patients who need treatment, routine clinical care must begin to address this*
 - *Screening can be done in clinical settings: referral may be needed*

Conclusions: II

- *In order to identify those patients who need treatment, routine clinical care must begin to address this*
 - *Screening can be done in clinical settings; referral may be needed*
 - *One of the next steps for the task force is to develop an online, freely available battery to streamline assessment in the clinic*
 - *It is imperative that clinicians acknowledge this as a priority for care*