Pro-cognitive strategies in Bipolar Disorder: Challenges and New Directions

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Challenges

1. Conceptual challenges

   Relationship between cognitive changes and clinical symptoms

   Measurement of cognitive function

   Measurement outcome

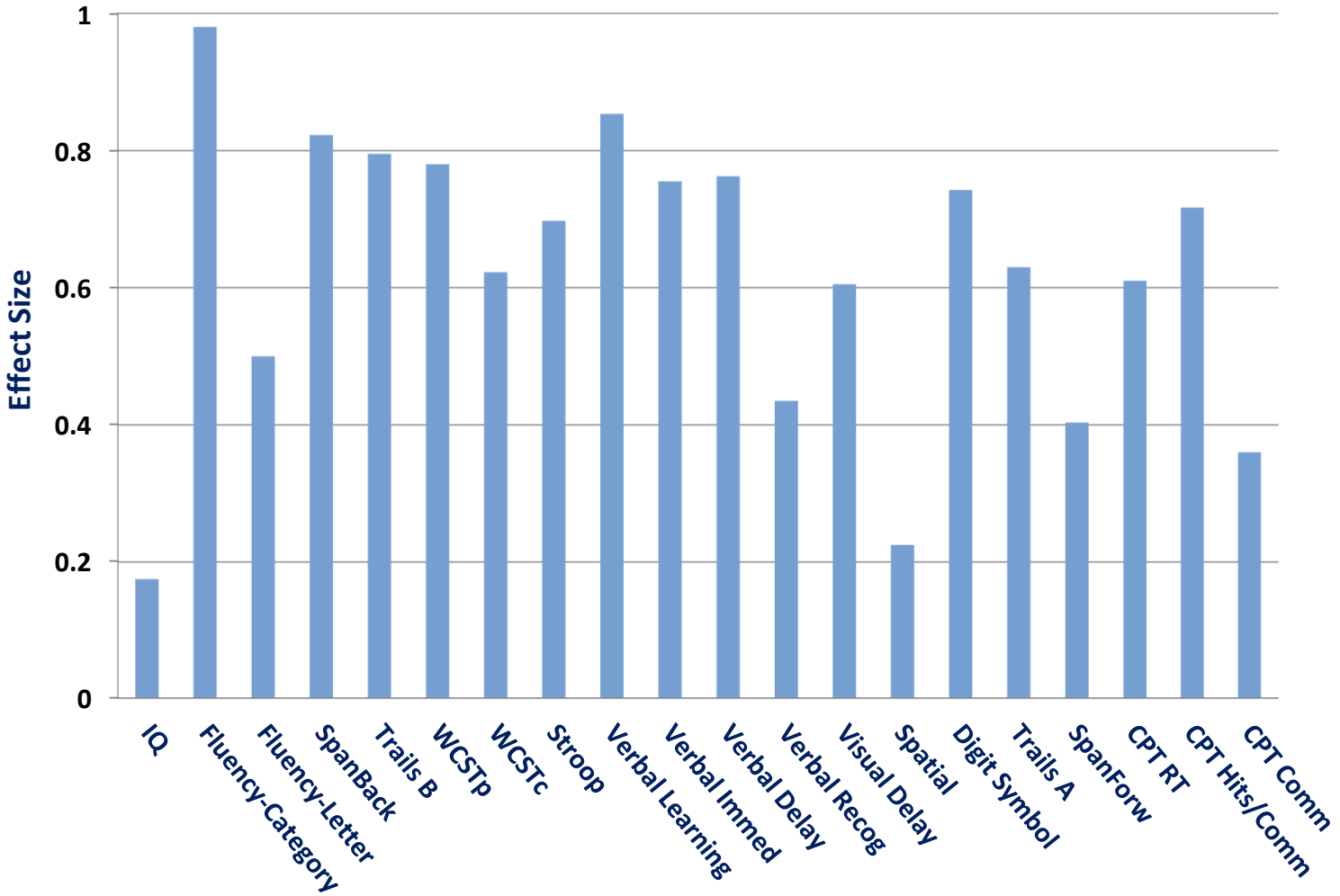
2. Limitations of current pro-cognitive interventions

New Directions

3. neural and Cellular basis of cognitive (dys)function

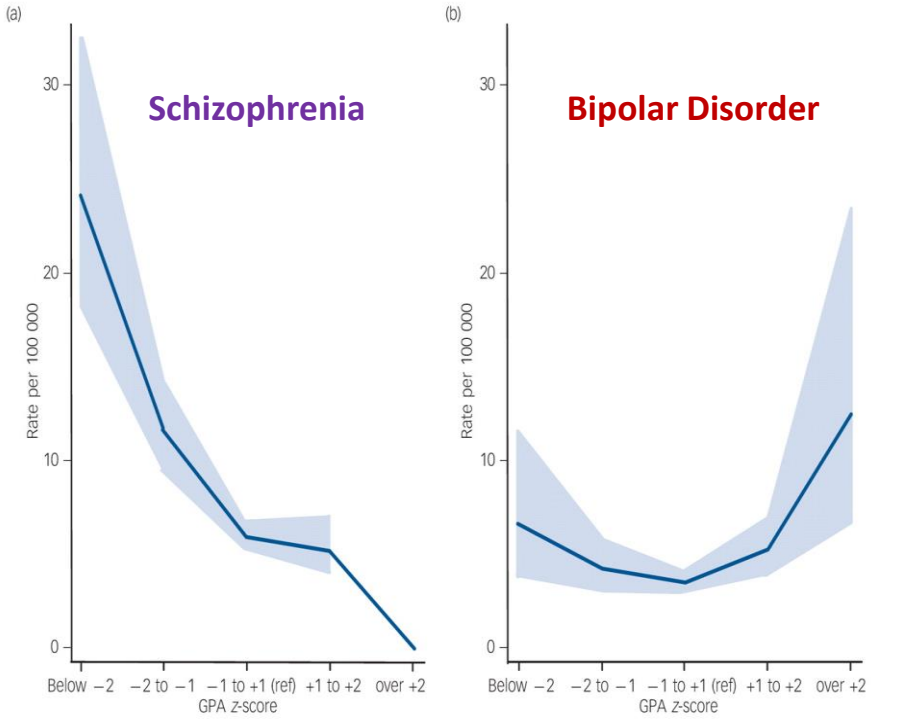
4. Potential neural and cellular targets

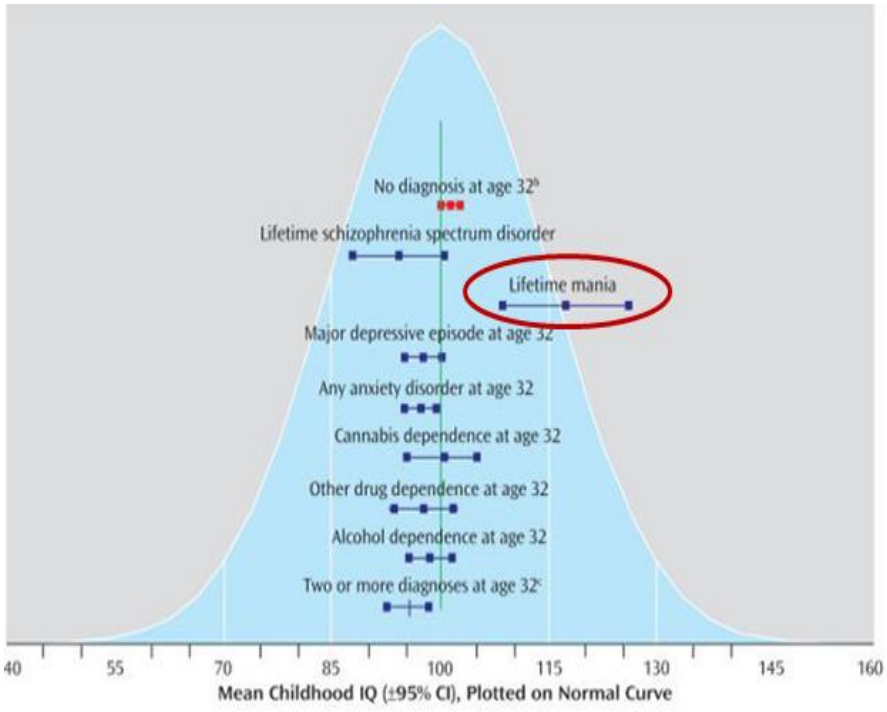
Cognitive Profile of Bipolar Disorder Inter-episode



Based on 4 meta-analytic studies: Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009

Premorbid phase: Population studies



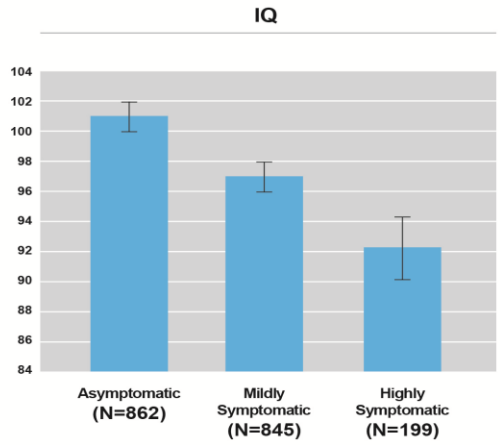


MacCabe et al. Br J Psychiatry 2010

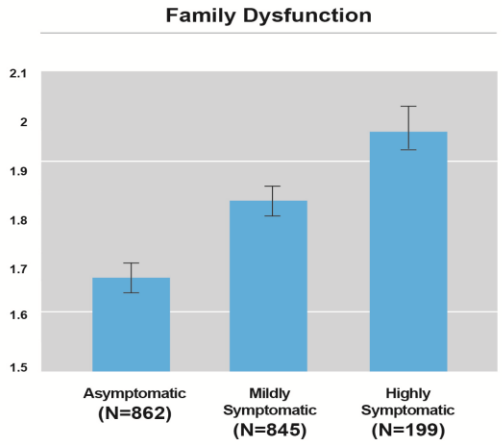
Koenen et al. Am J Psychiatry 2009

Multiple developmental pathways

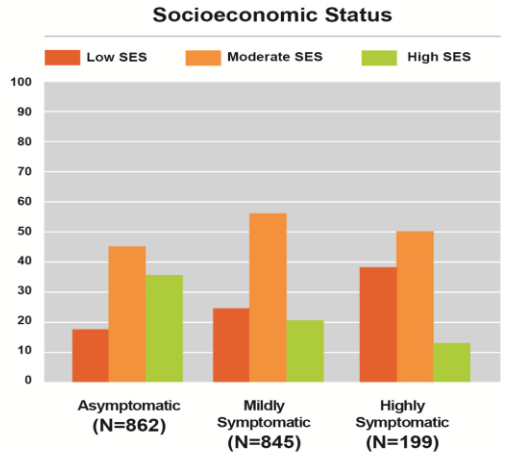
Figure 2. Cognitive, Socioeconomic and Family Characteristics of the Asymptomatic, Mildly Symptomatic and Highly Symptomatic Classes



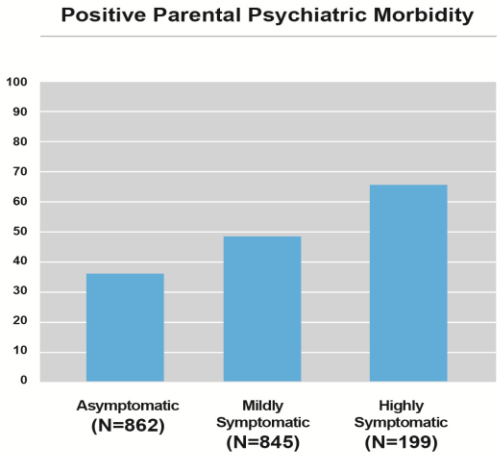
Data shown as Mean ±2(Standard Error); p values from multiple comparisons <0.001



Data shown as Mean ±2(Standard Error); p values from multiple comparisons <0.001



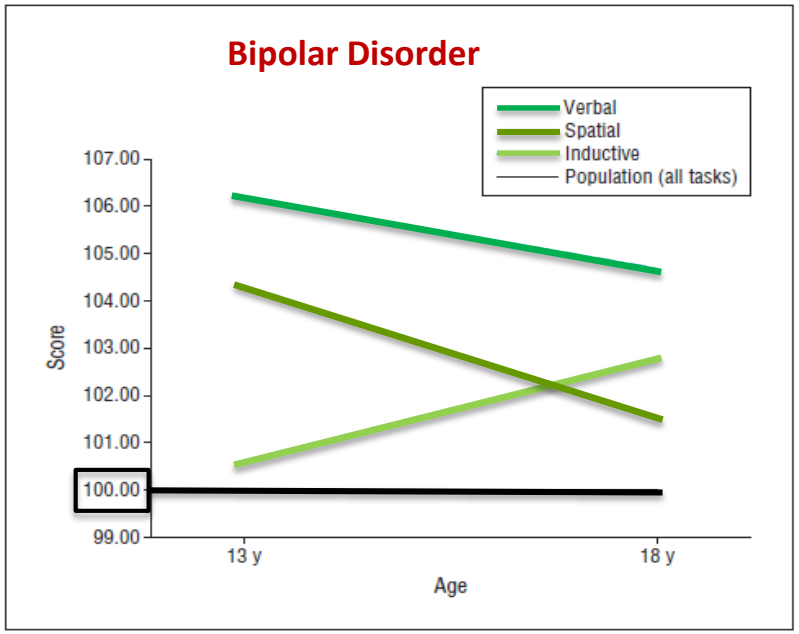
Data shown as % within classes; all p values <0.001



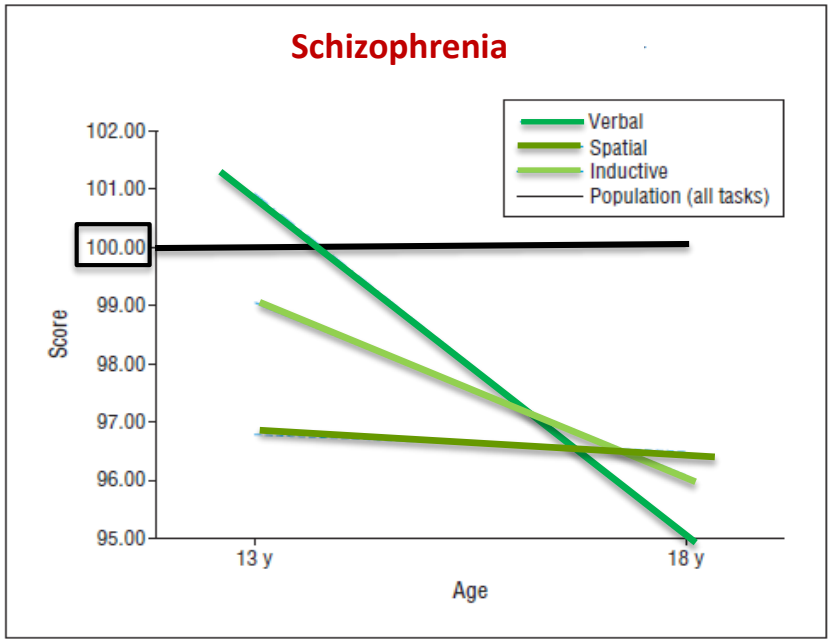
Data shown as % within classes; all p values <0.001

Papachristou et al. AJP

No evidence of premorbid decline in Bipolar Disorder



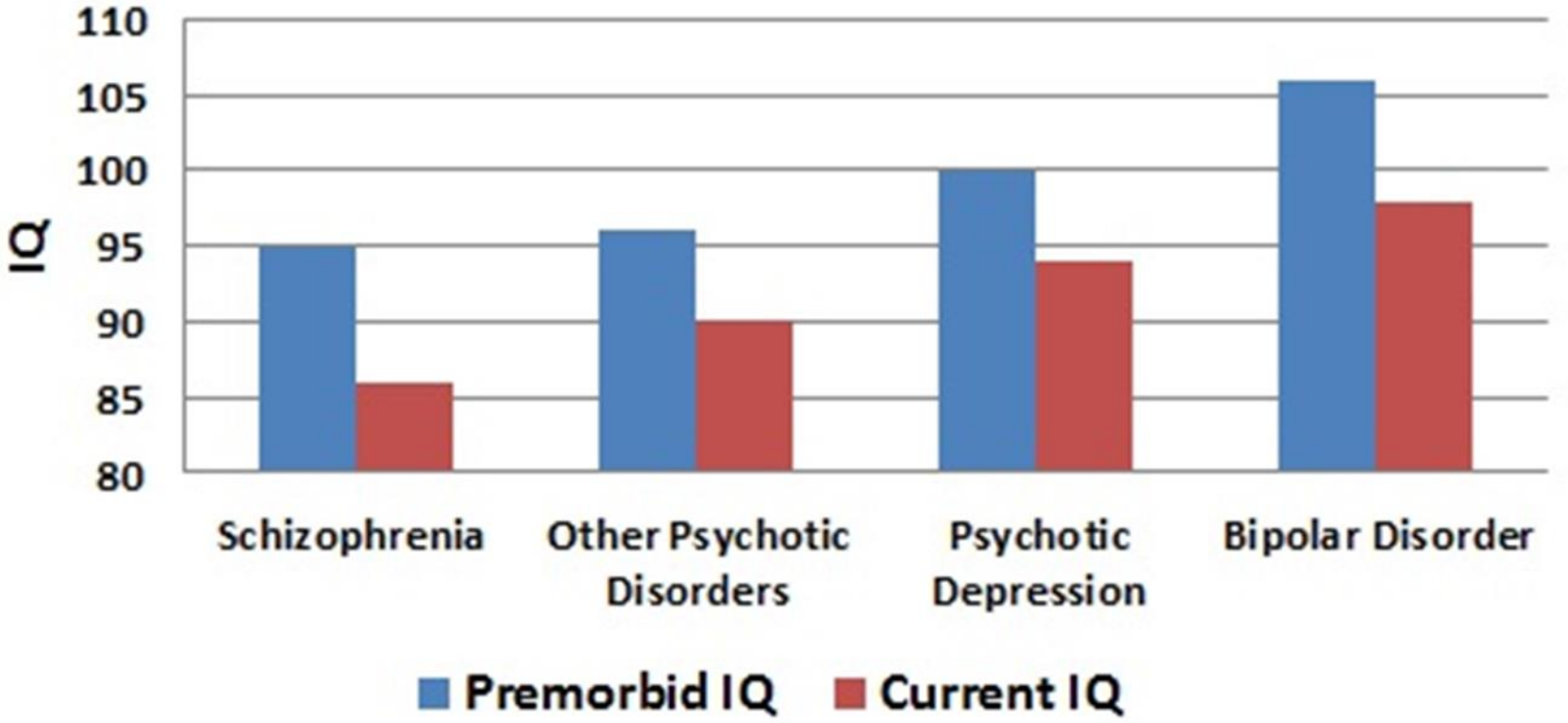
Premorbid cognitive functioning in adolescents and young adults who later develop bipolar disorder. Scores are standardized to a population mean (SD) of 100 (15).



Premorbid cognitive functioning in adolescents and young adults who later develop schizophrenia or schizoaffective disorder. Scores are standardized to a population mean (SD) of 100 (15).

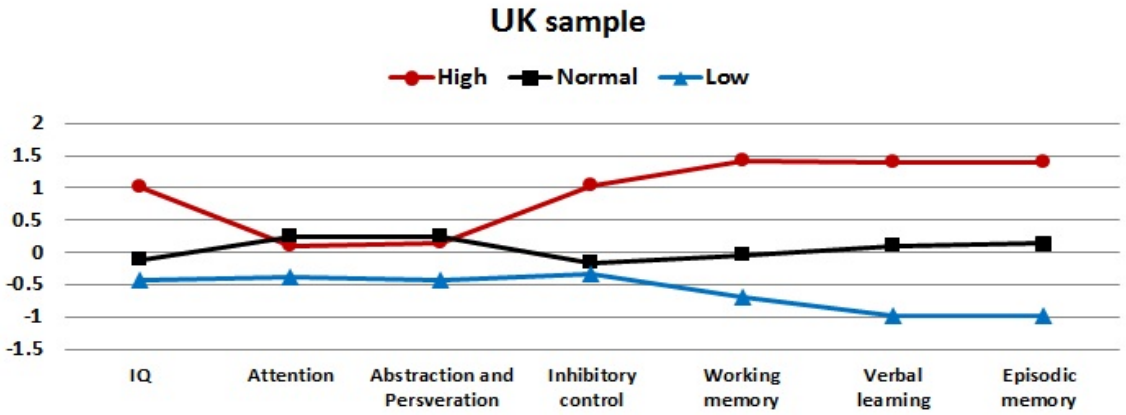
MacCabe et al, JAMA Psychiatry 2013

Estimates of Premorbid and Current IQ in First Episode Psychosis

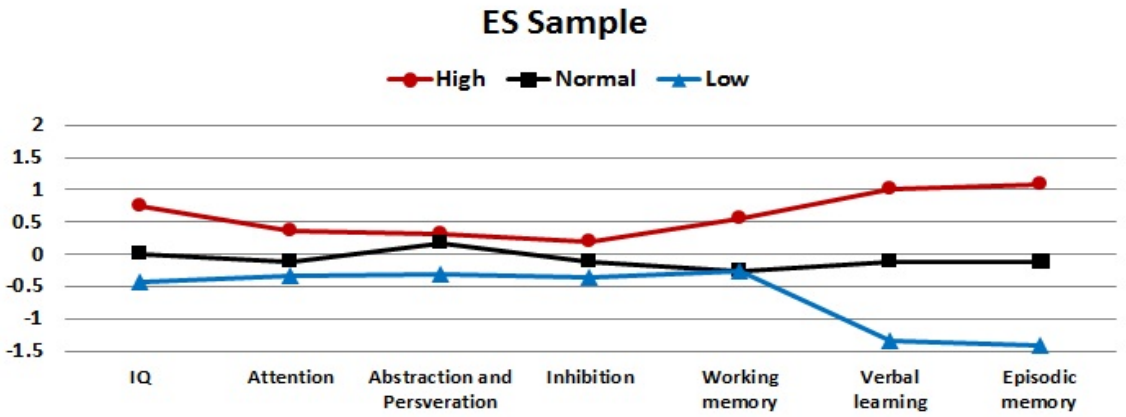


Zanelli et al. Am J Psychiatry 2010

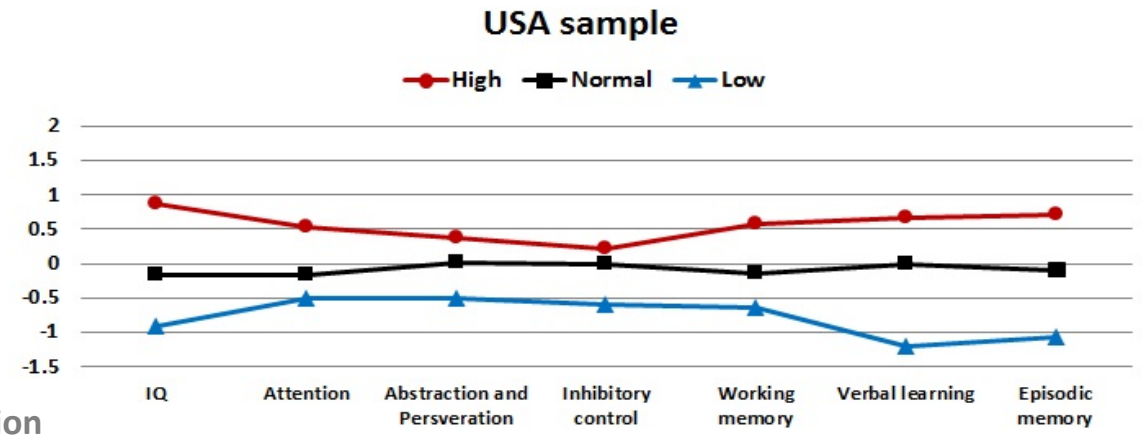
High: 17%
Normal: 49%
Low: 34%



High: 30%,
Normal: 51%
Low: 19%

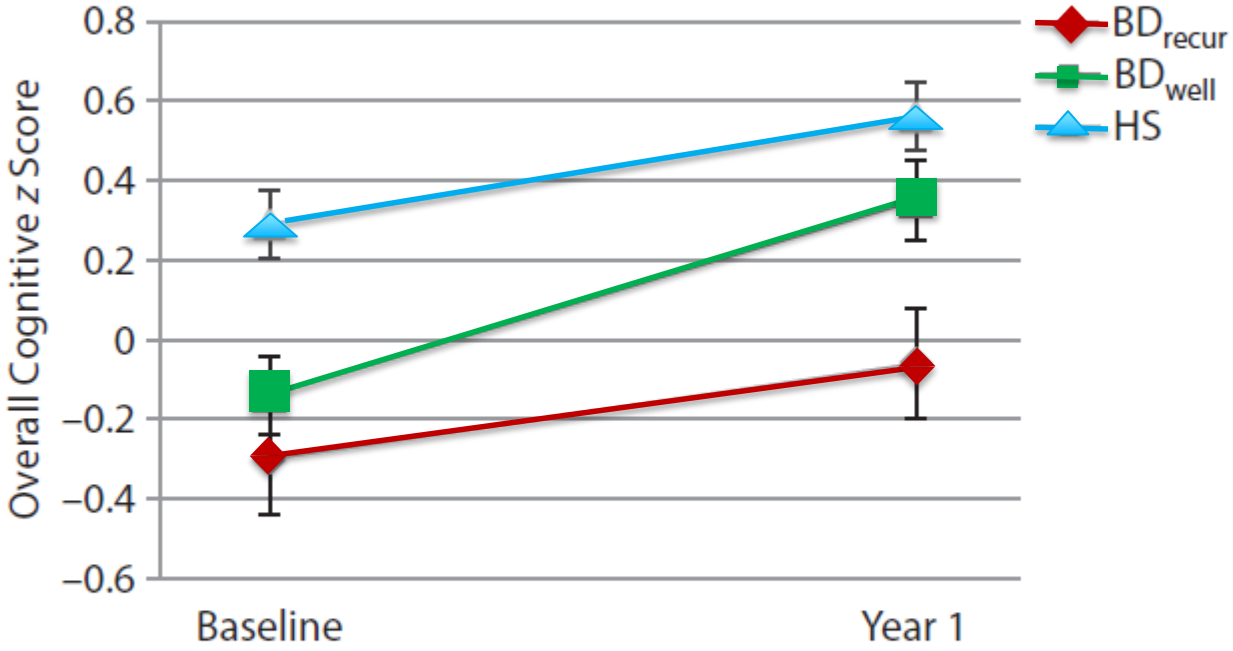


High: 32%,
Normal: 50%
Low: 18%.



Reinares et al. in preparation

Figure 1. Baseline and Follow-Up Cognitive Performance in Patients and Healthy Subjects[a]



[a]Data points represent mean and standard error.

Abbreviations: BD_{recur} = bipolar disorder patients with at least 1 mood episode over follow-up, BD_{well} = bipolar disorder patients who remained well over follow-up, HS = healthy subjects.

Kozicky et al. J Clin Psych, 2014

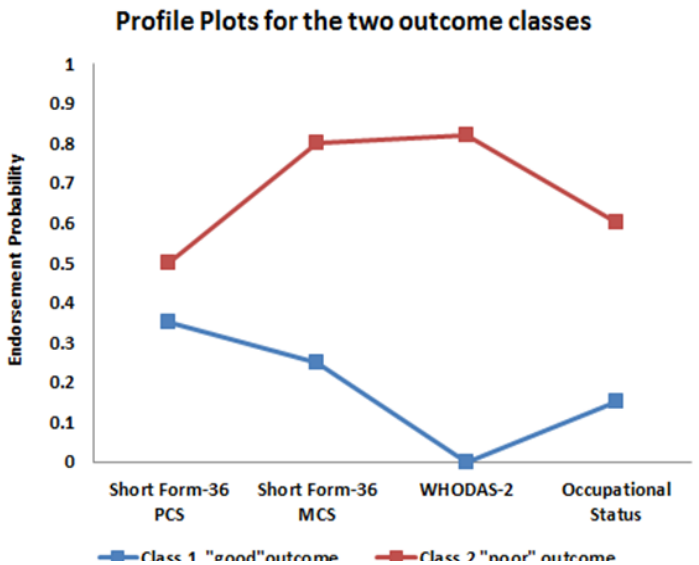
Post Disease Onset: Cognition as a predictor of outcome

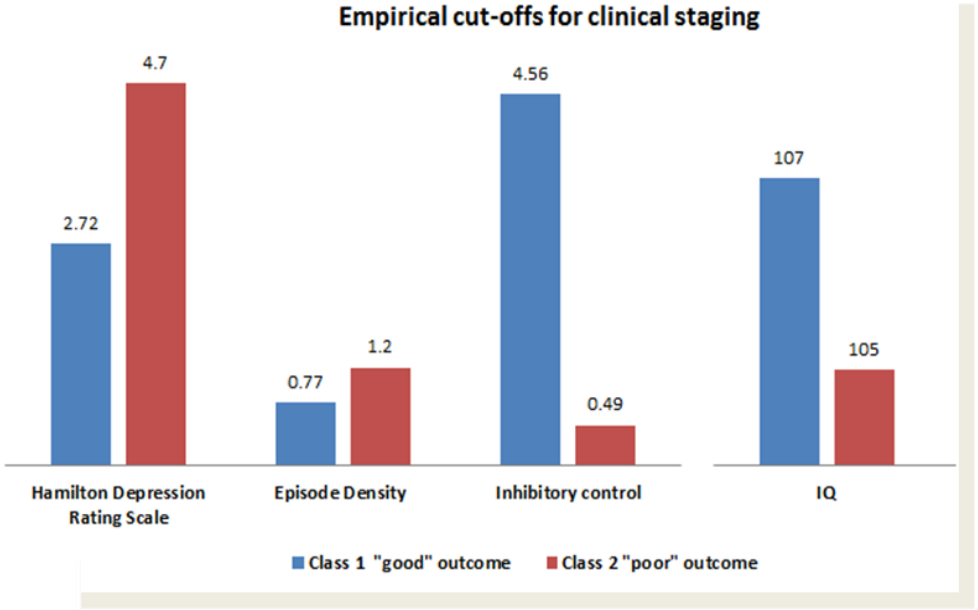
Table 1
Characteristics of the sample.

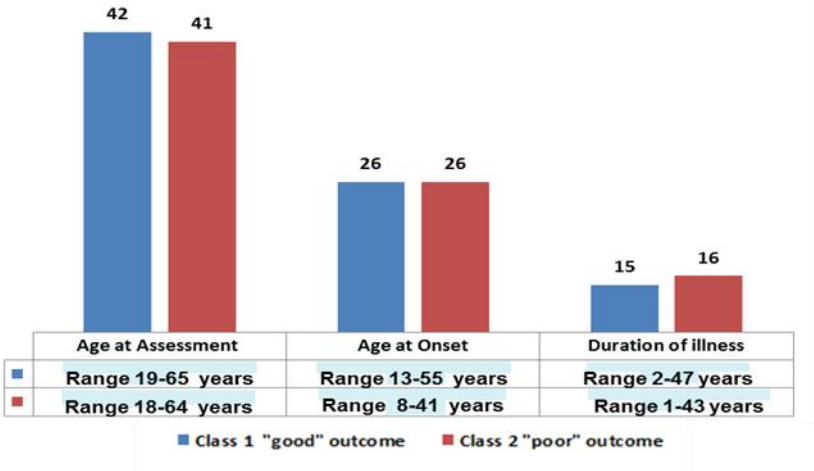
Variables	Mean (sd) or n (%)
Demographic and clinical variables	
Age (years)	41 (11.39)
Gender (Female)	52 (49%)
Years of education	14.71 (3.61)
Age of onset (year)	25.83 (8.15)
Total number of episodes	14.49 (24.87)
Number of manic episodes	2.48 (2.58)
Number of hypomanic episodes	4.56 (12.78)
Number of depressive episodes	6.73 (13.06)
Number of mixed episodes	0.71 (1.51)
Number of hospitalisations	1.90 (1.94)
Lifetime history of psychotic symptoms	77 (72.6%)
History of suicide attempts	29 (27%)
Family history of affective disorder	72 (68%)
Comorbidity of axis I or II disorders	24 (23%)
Comorbidity axis III	60 (56%)
Hamilton Depression Rating Scale	3.43 (2.44)
Young Mania Rating Scale	1.22 (1.58)
Medication	
Number of medications	2.78 (1.15)
Lithium (number of patients)	64 (59%)
Antiepileptics (number of patients)	52 (49%)
Antipsychotics (number of patients)	58 (55%)
Antidepressants (number of patients)	31 (29%)
Cognitive variables	
Estimated verbal intelligence	106.4 (10.03)
Stroop Colour Word Test—interference score	2.41 (8.28)
Wisconsin Card Sorting Test—categories achieved	5.15 (1.60)
Wisconsin Card Sorting Test—number of perseverative errors	13.72 (12.84)
Digit Span—Forward	8.71 (2.27)
Digit Span—Backward	6.09 (1.93)
Trails Making Test—Part A	39.06 (17.27)
Trails Making Test—Part B	88.45 (41.05)
FAS letter fluency (number correct)	34.48 (9.71)
California Verbal Learning Test—List A (total)	49.21 (9.98)
California Verbal Learning Test—Free short recall	10.46 (3.31)
California Verbal Learning Test—Cued short recall	11.86 (2.64)
California Verbal Learning Test—Free delayed recall	11.33 (3.15)
California Verbal Learning Test—Cued delayed recall	12.12 (2.79)
California Verbal Learning Test—Recognition hits	14.64 (1.94)
Processing Speed index	102.39 (12.37)
Functional variables	
WHO Disability Assessment Schedule-2	16.07 (12.44)
Short Form-36—Mental Component Score	45.35 (11.52)
Short Form-36—Physical Component Score	51.03 (7.33)

Reinares et al. JAD 2013

Empirical Clinical Staging in Bipolar Disorder







106 patients with naturalistic follow-up
Barcelona Bipolar Disorders Program

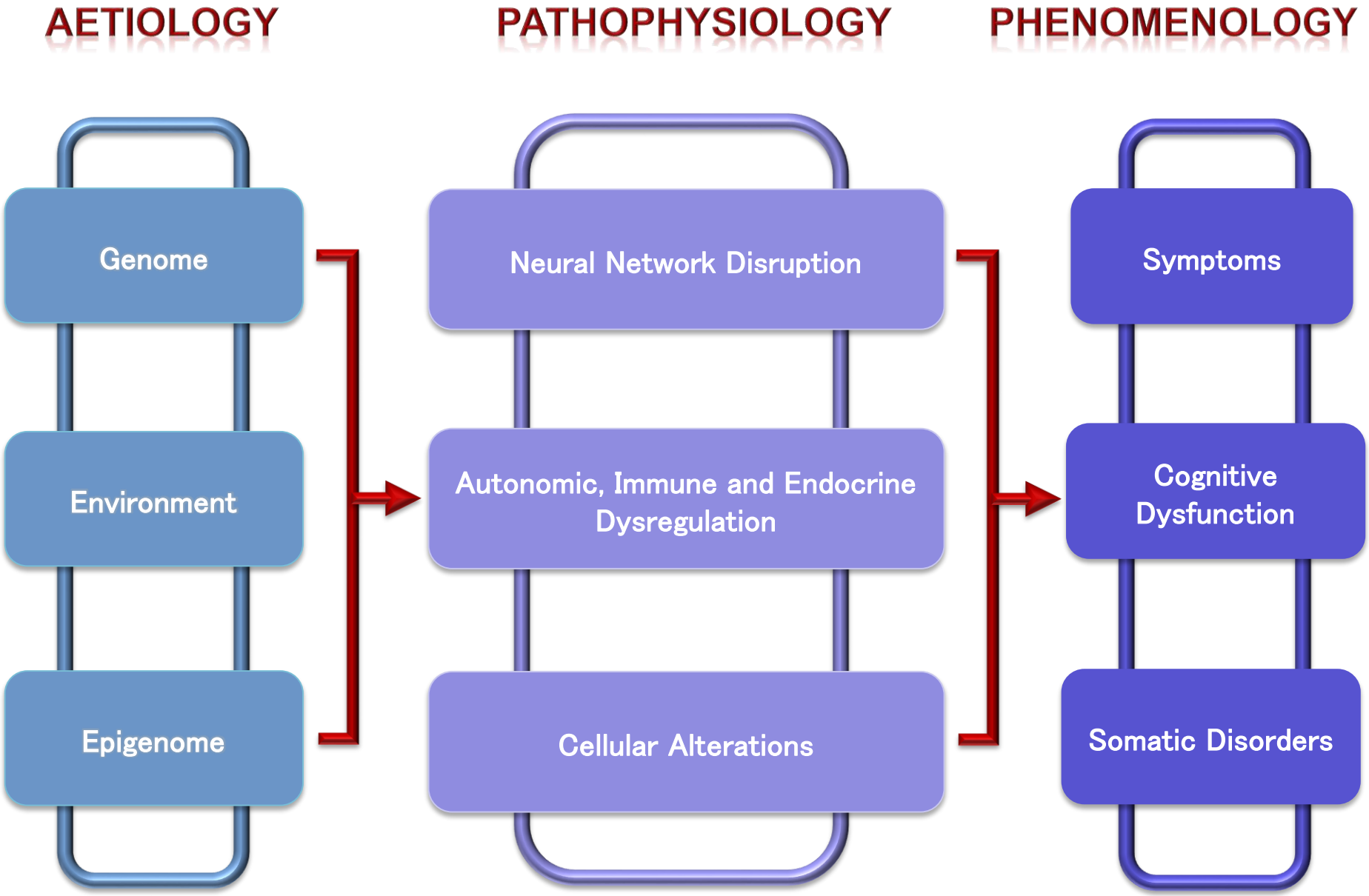
Reinares et al. JAD 2013

Cognitive Dysfunction in Bipolar Disorder: Relationship between cognitive and clinical features

- General intellectual ability is not compromised prior to syndromal onset in the majority of patients
  - Some evidence of premorbid heterogeneity
- No evidence for significant premorbid decline
- Cognitive dysfunction is present at syndromal onset in the majority of patients
  - Evidence of post-onset patient heterogeneity
  - Magnitude of cognitive impairment seems linked to clinical severity

Pro-Cognitive Strategies in Bipolar Disorder

New Directions


AETIOLOGY
PATHOPHYSIOLOGY
PHENOMENOLOGY
Genome
Environment
Epigenome
Neural Network Disruption
Autonomic, Immune and Endocrine Dysregulation
Cellular Alterations
Symptoms
Cognitive Dysfunction
Somatic Disorders

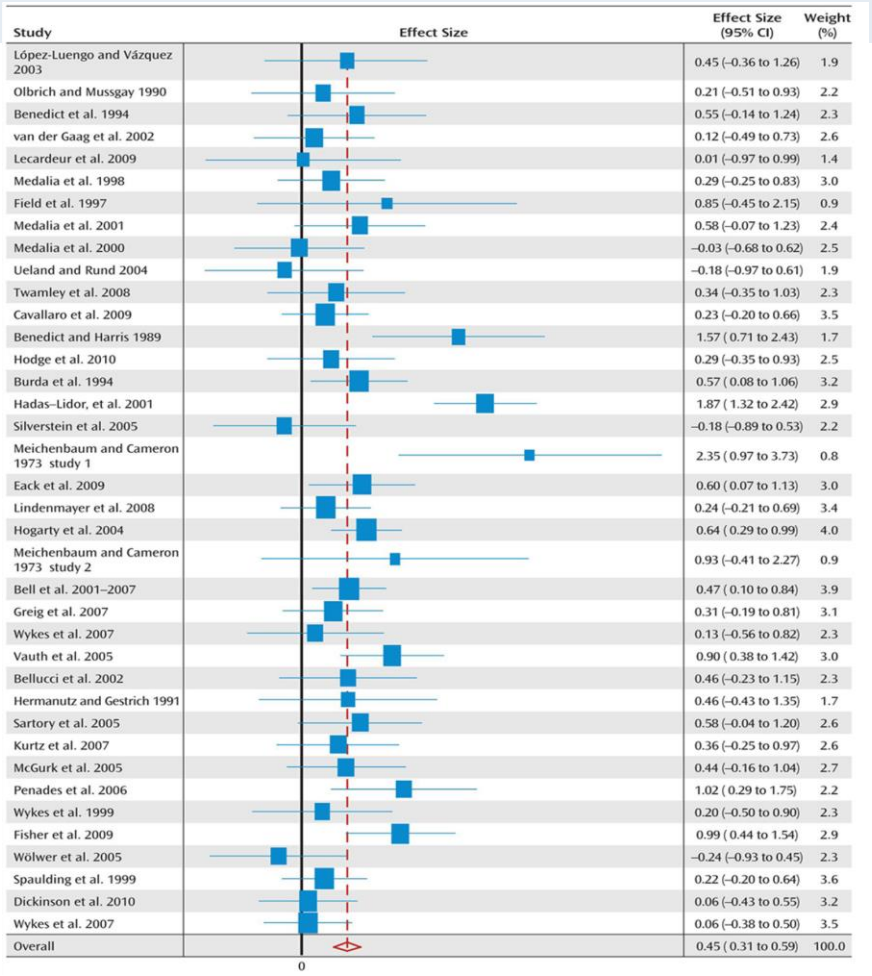
Neural Network Targets

THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

From: A Meta-Analysis of Cognitive Remediation for Schizophrenia: Methodology and Effect Sizes

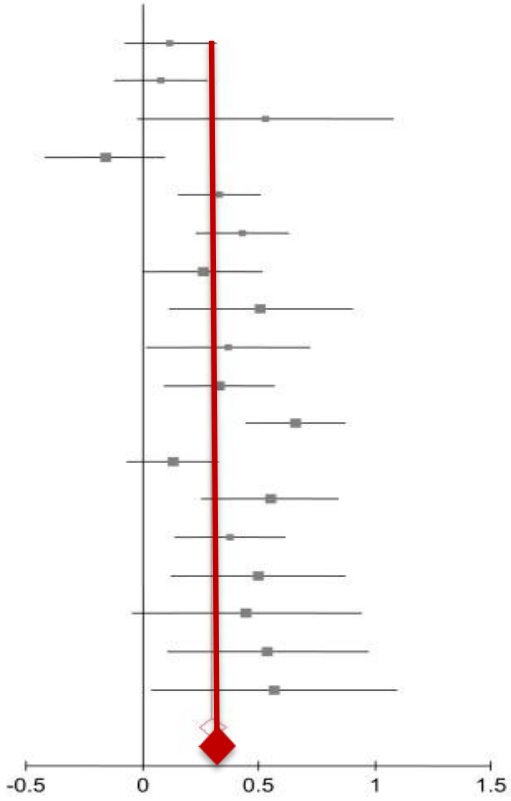
Am J Psychiatry. 2011;168(5):472-485. doi:10.1176/appi.ajp.2010.10060855



Forest Plot of Global Cognition Among Studies in Cognitive Remediation Therapy

A systematic review of cognitive remediation for schizo-affective and affective disorders

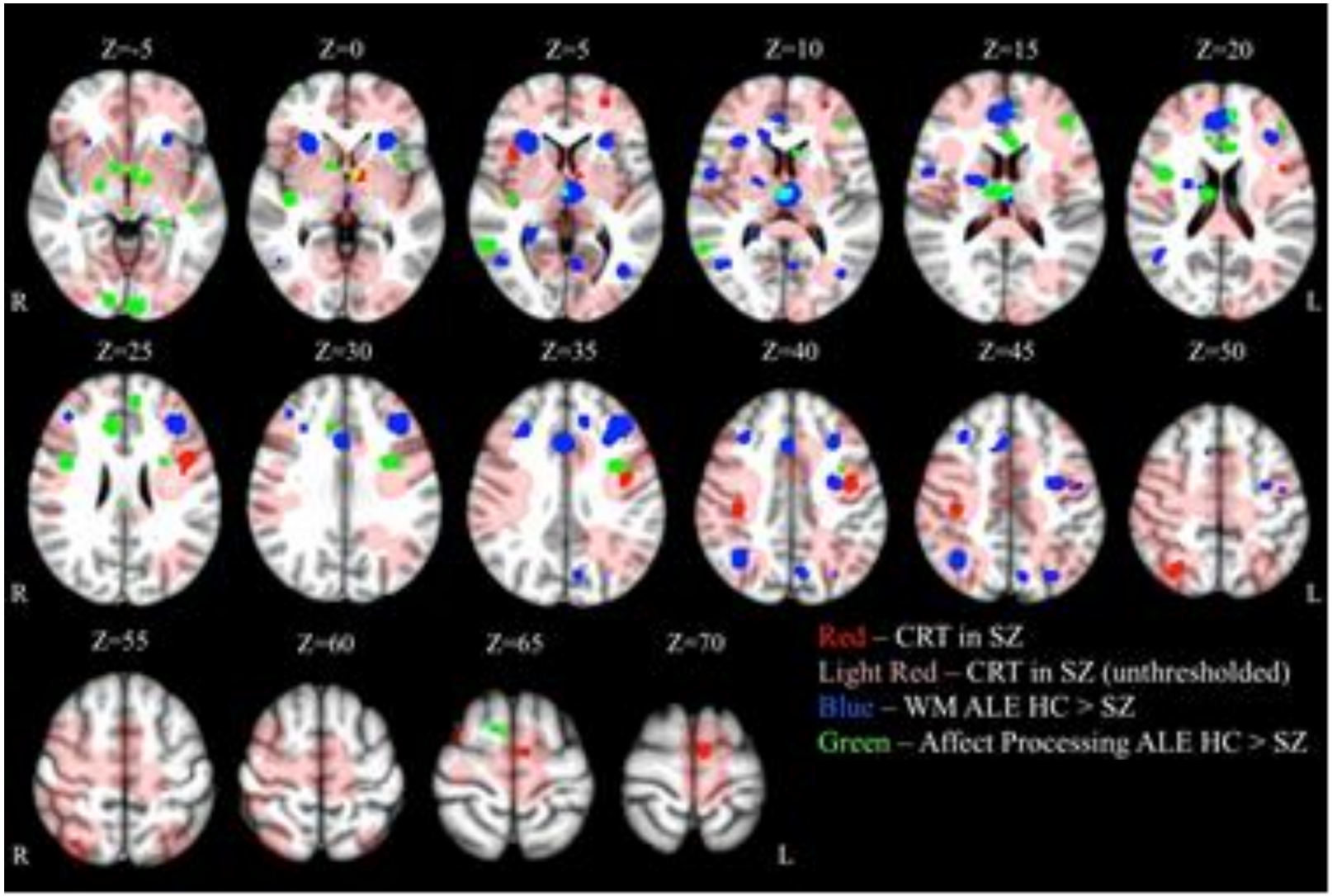
Study ID	Year	% Schizophrenia	Effect Size (95% CI)
BARBIERI	2006	93%	0.12 (-0.08 to 0.32)
SPAULDING	1999	86%	0.08 (-0.12 to 0.28)
DICKINSON	2010	79%	0.53 (-0.02 to 1.08)
MEDALIA	2000	76%	-0.16 (-0.41 to 0.09)
MCGURK	2005	73%	0.33 (0.15 to 0.51)
HOGARTY	2004	73%	0.43 (0.23 to 0.63)
MCGURK	2009	71%	0.26 (0.01 to 0.51)
BURDA	1994	68%	0.51 (0.12 to 0.9)
UELAND	2005	68%	0.37 (0.02 to 0.72)
BELL	2003	67%	0.33 (0.09 to 0.57)
EACK	2009	66%	0.66 (0.44 to 0.88)
CASSIDY	1996	62%	0.13 (-0.07 to 0.33)
CHOI	2005	56%	0.55 (0.26 to 0.84)
TWAMLEY	2008	47%	0.38 (0.14 to 0.62)
BELLUCI	2002	56%	0.5 (0.13 to 0.87)
NAISMITH	2010	0%	0.45 (-0.04 to 0.94)
ELGAMAL	2007	0%	0.54 (0.11 to 0.97)
DECKERBACH	2009	0%	0.57 (0.04 to 1.1)
			0.31 (0.24 to 0.37)



Meta-analysis of cognitive remediation studies that include patients with schizoaffective and affective disorders. Mean weighted effect sizes (95% confidence intervals) are shown for individual studies ranked according to proportion of study sample with schizophrenia

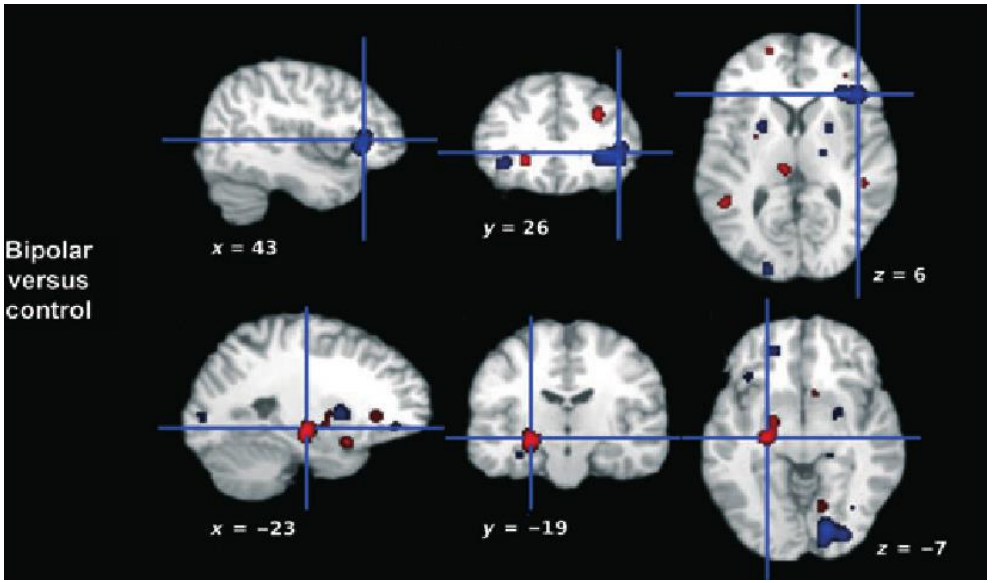
Anaya et al JAD 2012

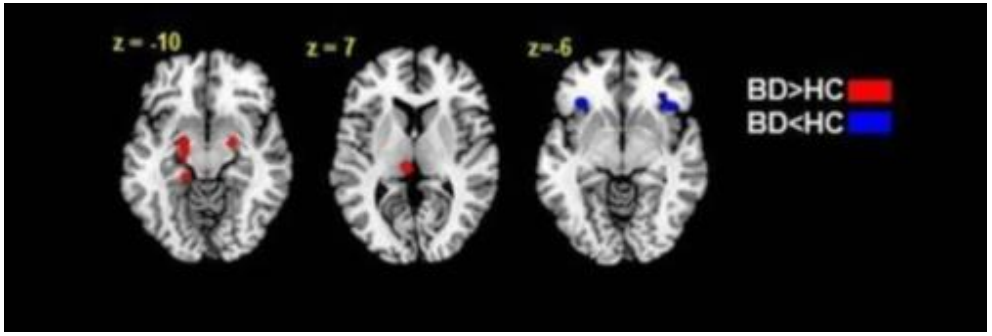
ALE analysis of cognitive remediation training in schizophrenia



Ramsay et al , University of Minnesota, unpublished data

Meta-analyses of brain functional changes in Bipolar Disorder





Ventolateral PFC (VLPFC)
Links emotion with contextually appropriate action
Supports inhibitory control

. **Amygdala**
Signals salience/ambiguity

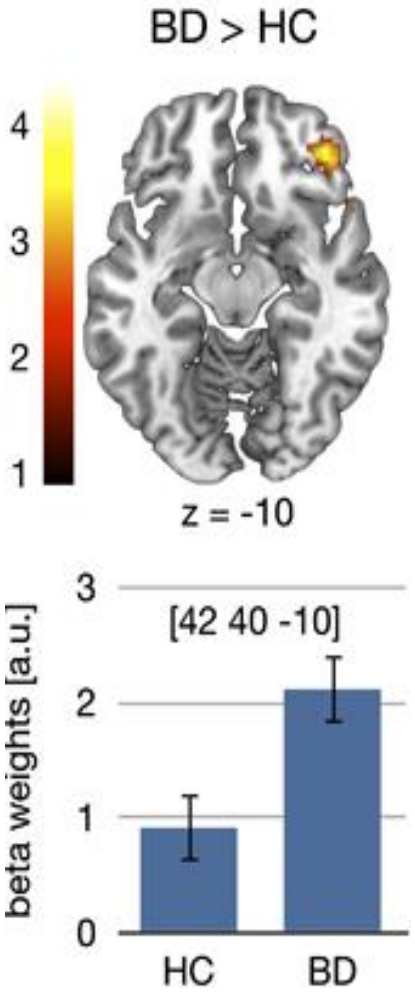
. **Parahippocampal gyrus**
Appraisal of emotional stimuli

. **Pulvinar /Putamen**
Amplification of processing affective stimuli

Chen et al. Bipol Disord 2011 *Delvecchio et al. Eur Psychopharmacol 2011*

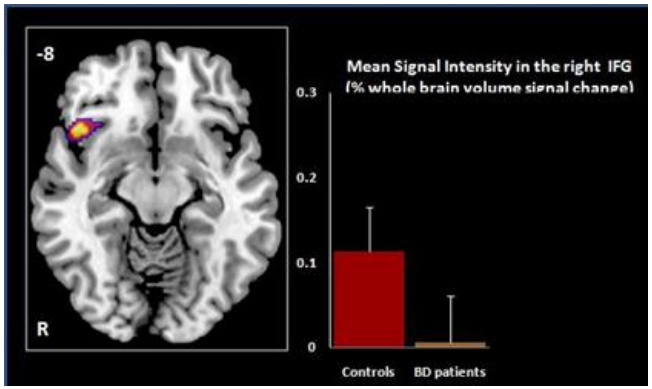
Ventrolateral PFC inefficiency/hypoactivation may have a central pathogenetic role in Bipolar Disorder

Emotional Downregulation



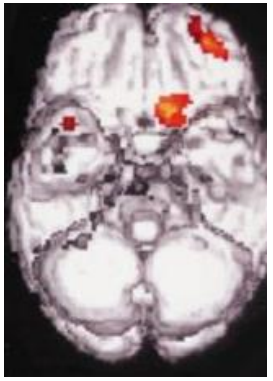
Morris et al. Transl Psychiatry. 2012

Inhibitory control in remission

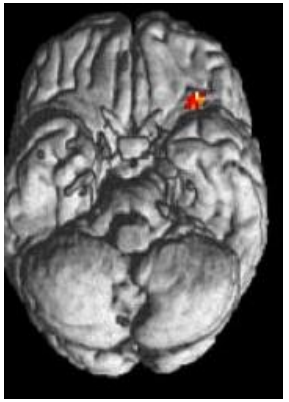


Pompei et al. Neuroimage 2011

Syndromal Episodes

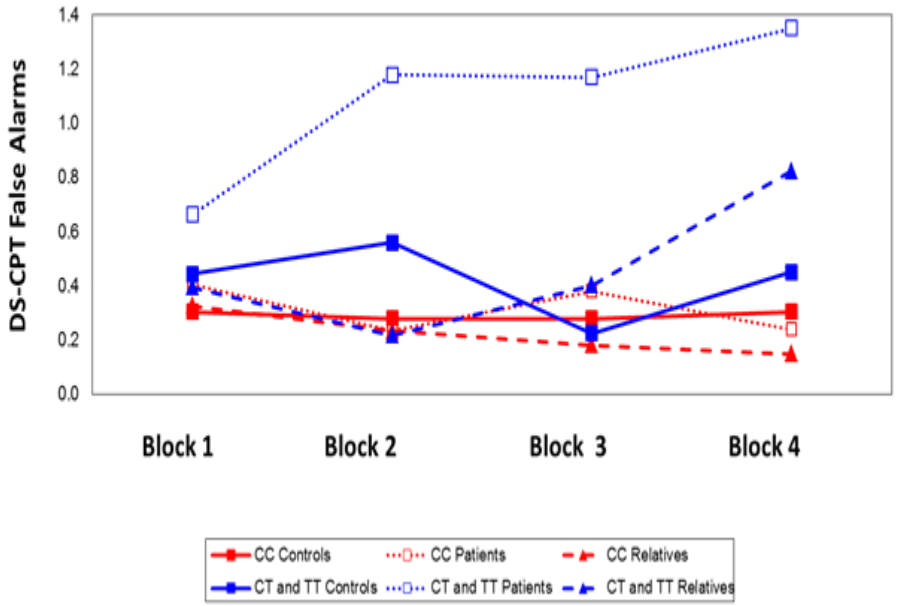


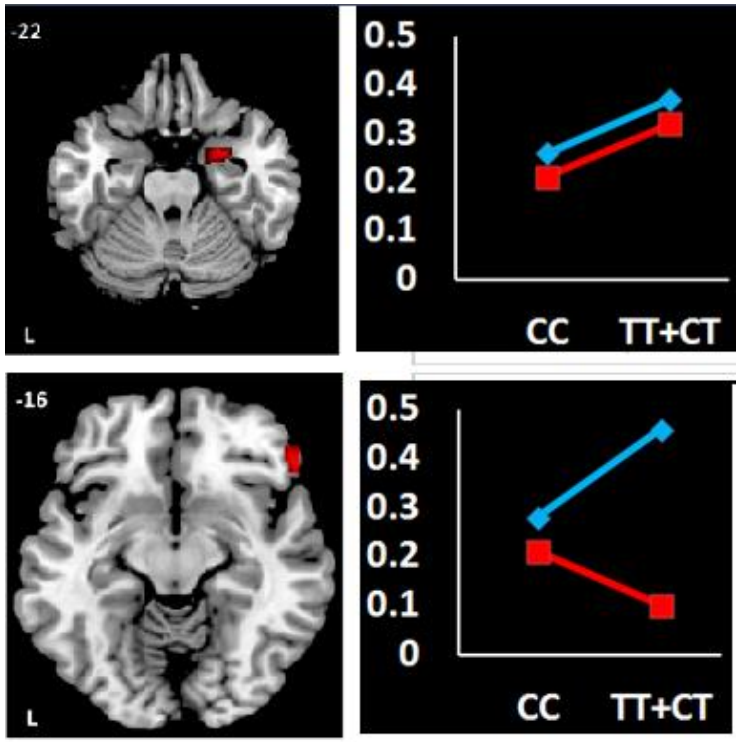
PET, Blumberg et al.
Am J Psychiatry, 1999



fMRI, Altshuler et al.
Biol Psychiatry, 2005

ANK3 rs10994336 polymorphism

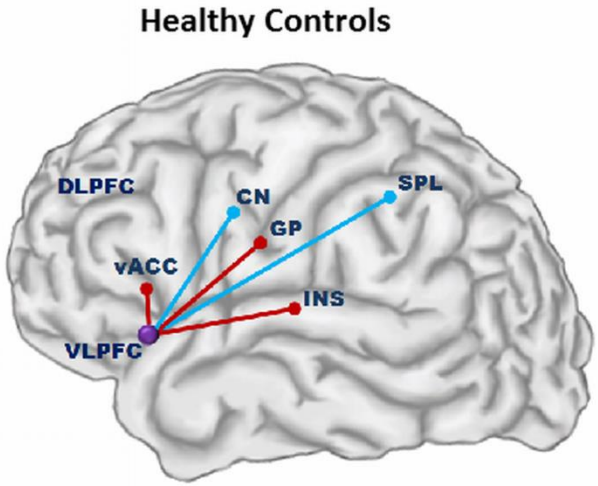


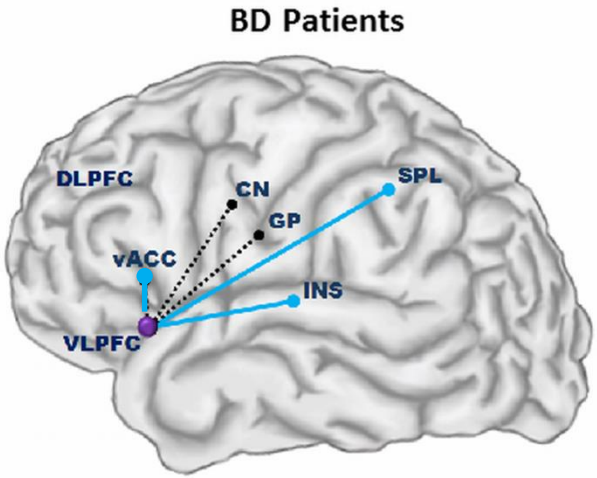


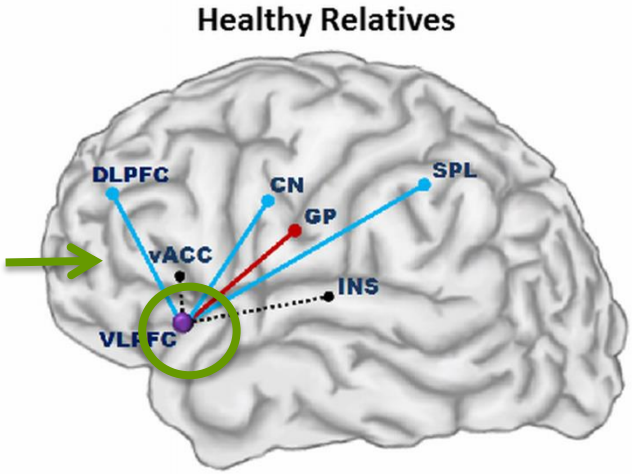
Ruberto et al. PLoS One, 2011

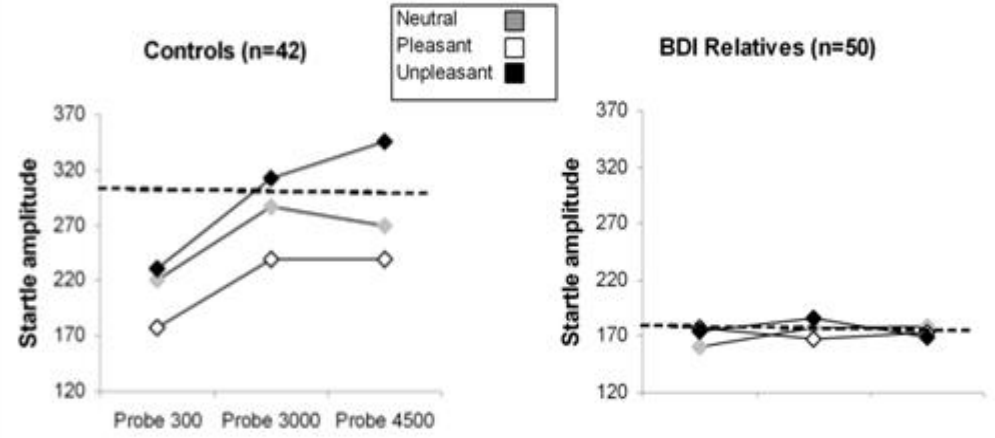
Dima et al. JAMA Psychiatry 2013

Lessons from resilience









Pompei et al. Neuroimage 2011

Giakoumaki et al. Psychophysiology 2010

Target Remediation Interventions

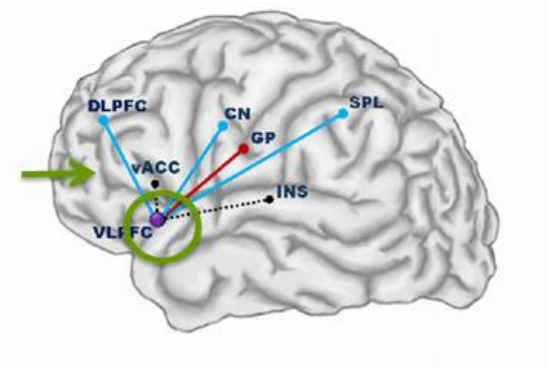
Increase DLPFC engagement

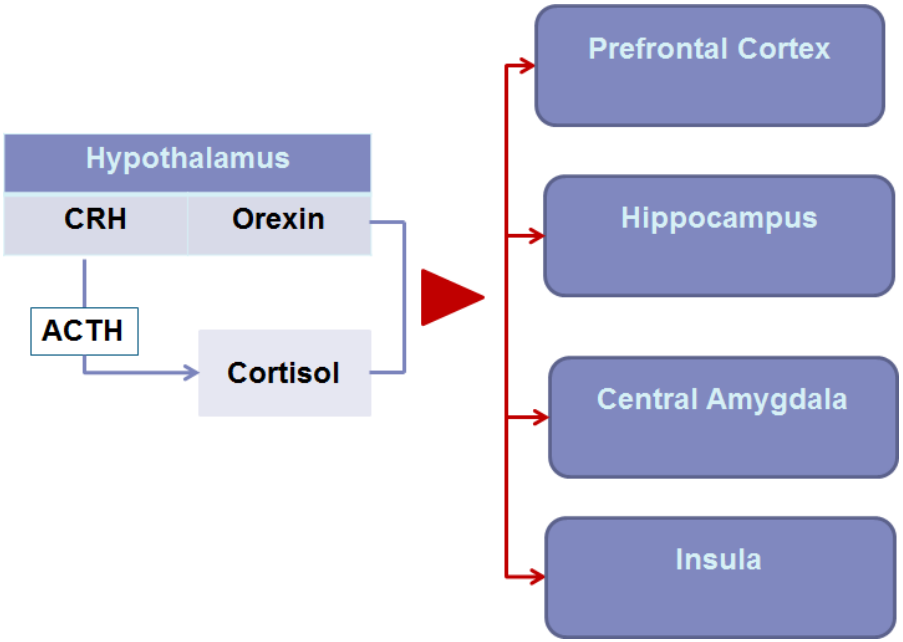
Goal Management Training

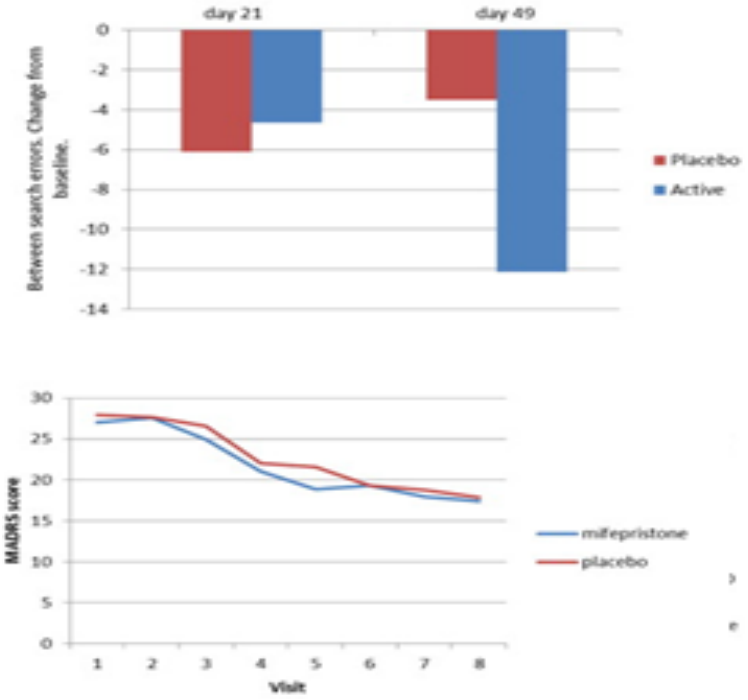
Decreased Stress Reactivity

Stress Management Training

HPA / Orexin System



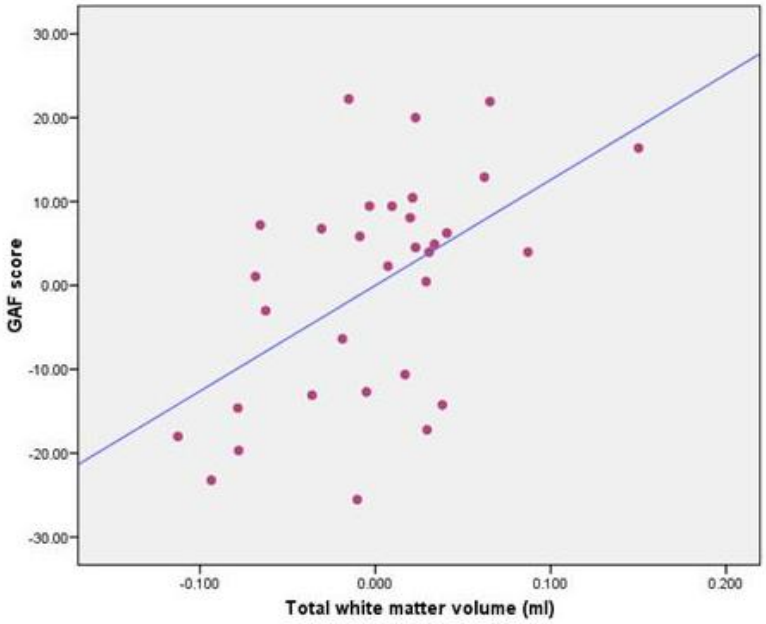




Watson et al. Biol Psychiatry. 2012

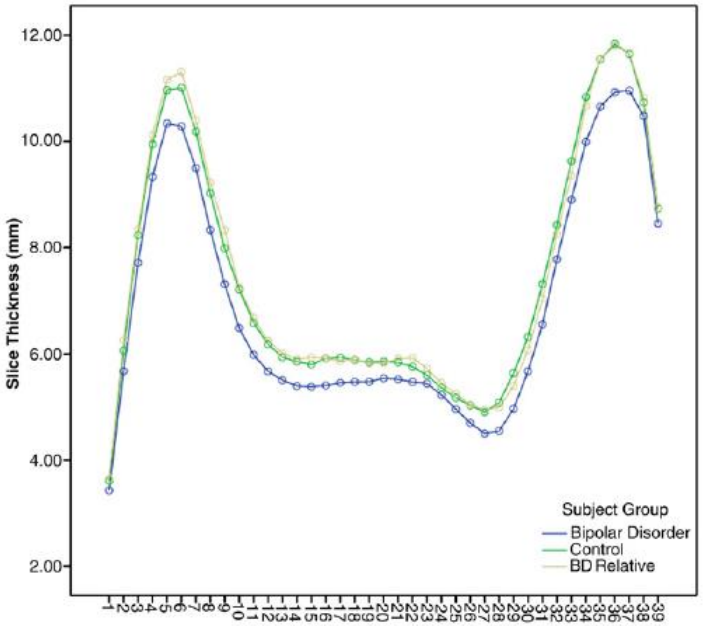
Cellular Targets

White Matter Abnormalities in Bipolar Disorder



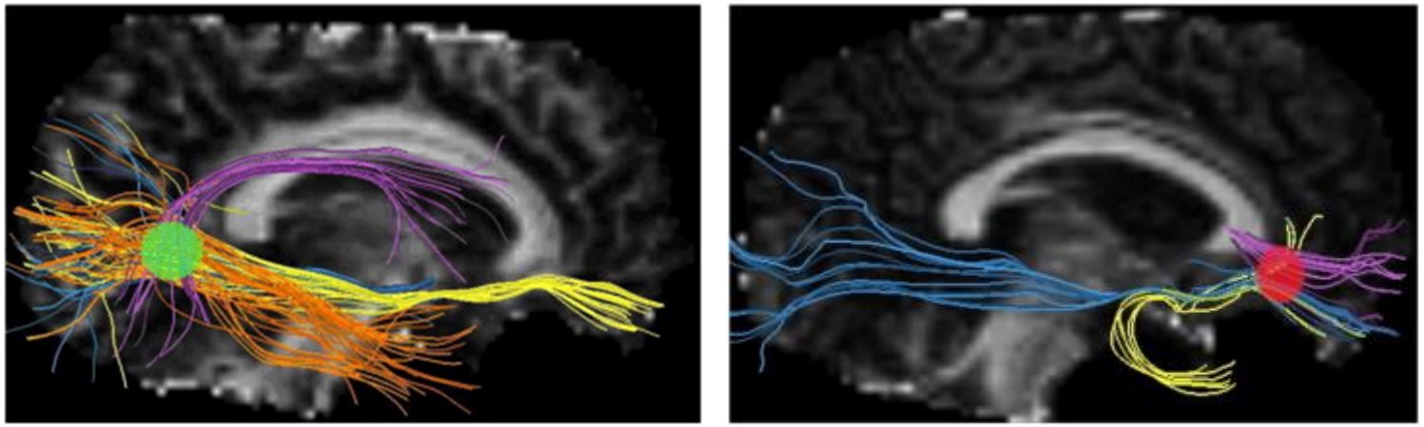
Total white matter volume predicts functional outcome in patients with Bipolar Disorder but not their health relatives

Forcada et al. J Affect Disord. 2011



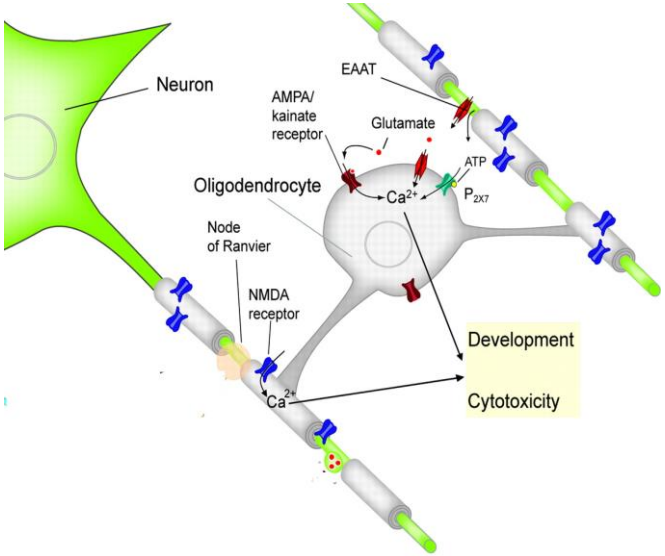
Callosal thickness reduced in patients with Bipolar Disorder but not their healthy relatives

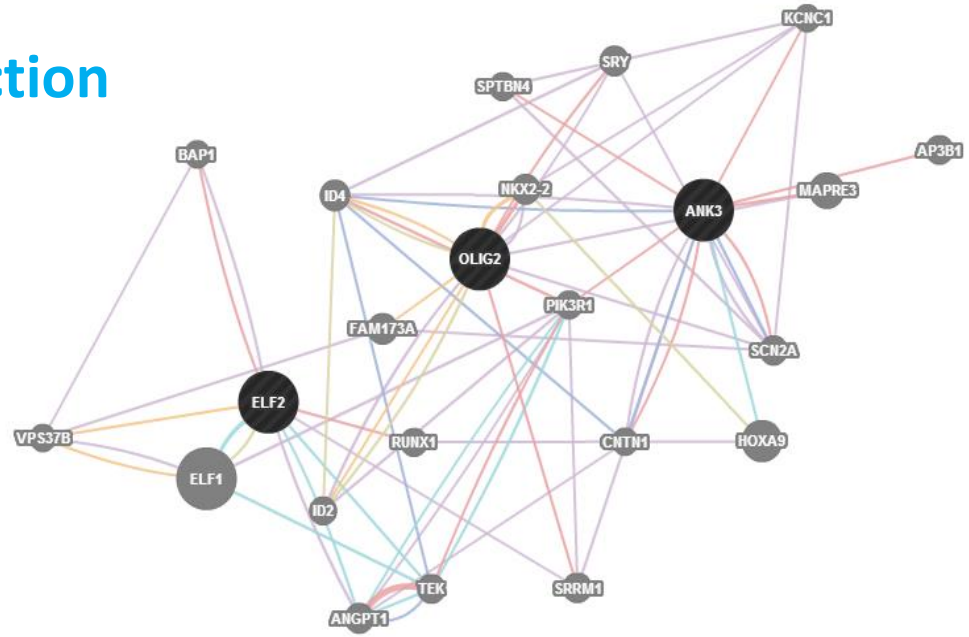
Walterfang et al. Prog Neuropsychopharmacol Biol Psychiatry. 2009

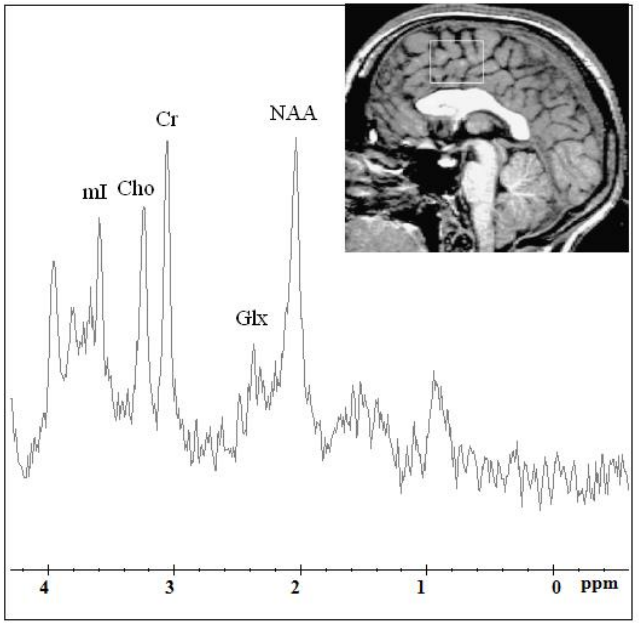


Vederin et al. Prog Neuropsychopharmacol Biol Psychiatry. 2013

Oligodendrocyte dysfunction



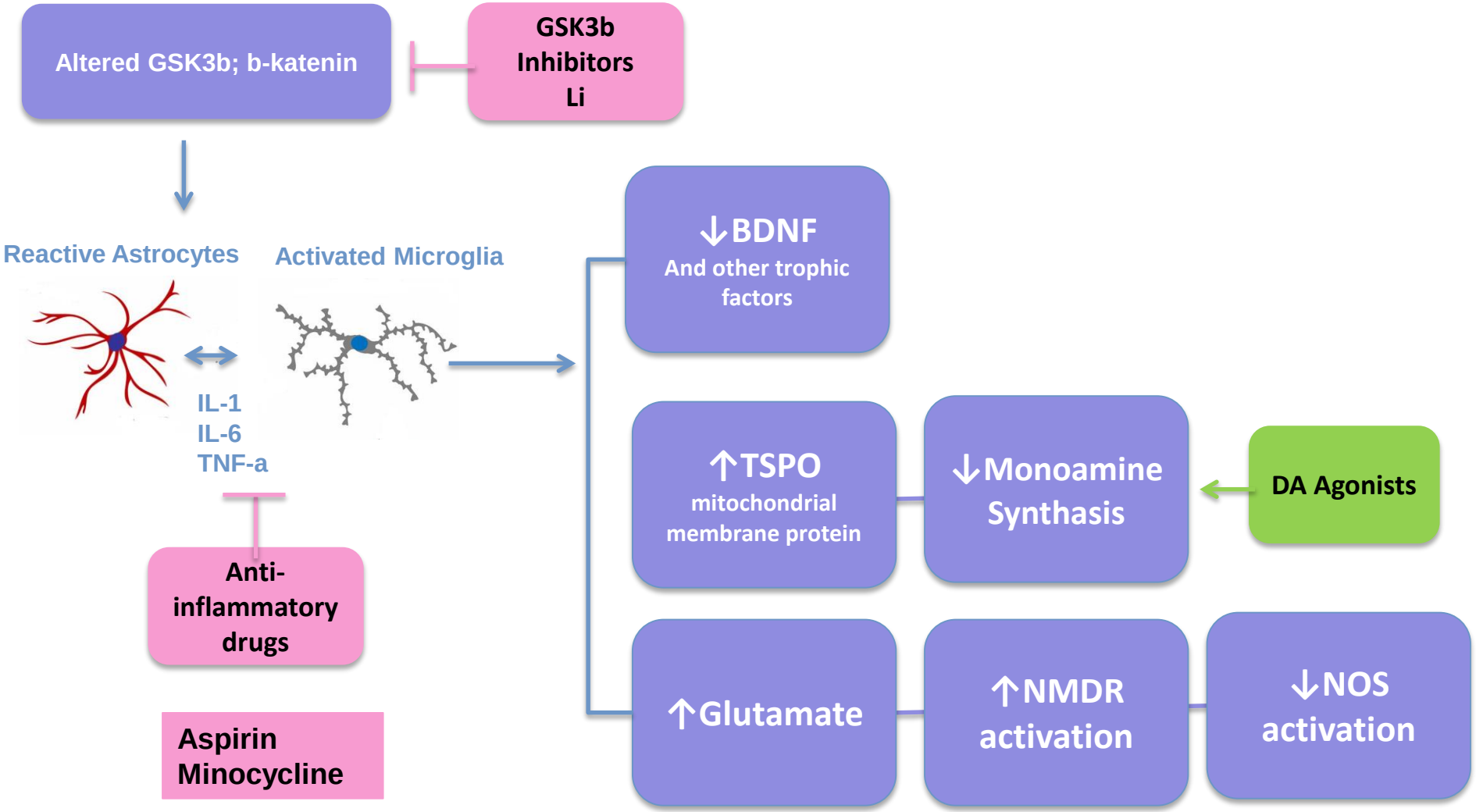




- Reduction in oligodendrocytes PFC and ACC
- Reduced oligodendrocyte-related gene expression

Frangou et al. J Psychopharmacol 2007

Neuroinflammation



Concluding Remarks

1. Premorbid general intellectual ability is preserved in the majority of patients with BD
2. At the time of syndromal onset patients present with a number of cognitive difficulties
3. Cognitive deficits may predominantly cluster within subgroups of patients

Concluding Remarks

1. Cognitive dysfunction and clinical symptoms are emerging phenomena reflecting altered neural network function
2. Cognitive and clinical symptoms may involve overlapping circuits
3. Remediation strategies should be neuroscience informed
    - Anchored on neural circuitry dysfunction
    - Targeting underlying cellular abnormalities