

Medications and Psychotherapy to Target Neural Networks in Youth at High-Risk for Bipolar Disorder

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Impact of Pediatric Bipolar Disorder

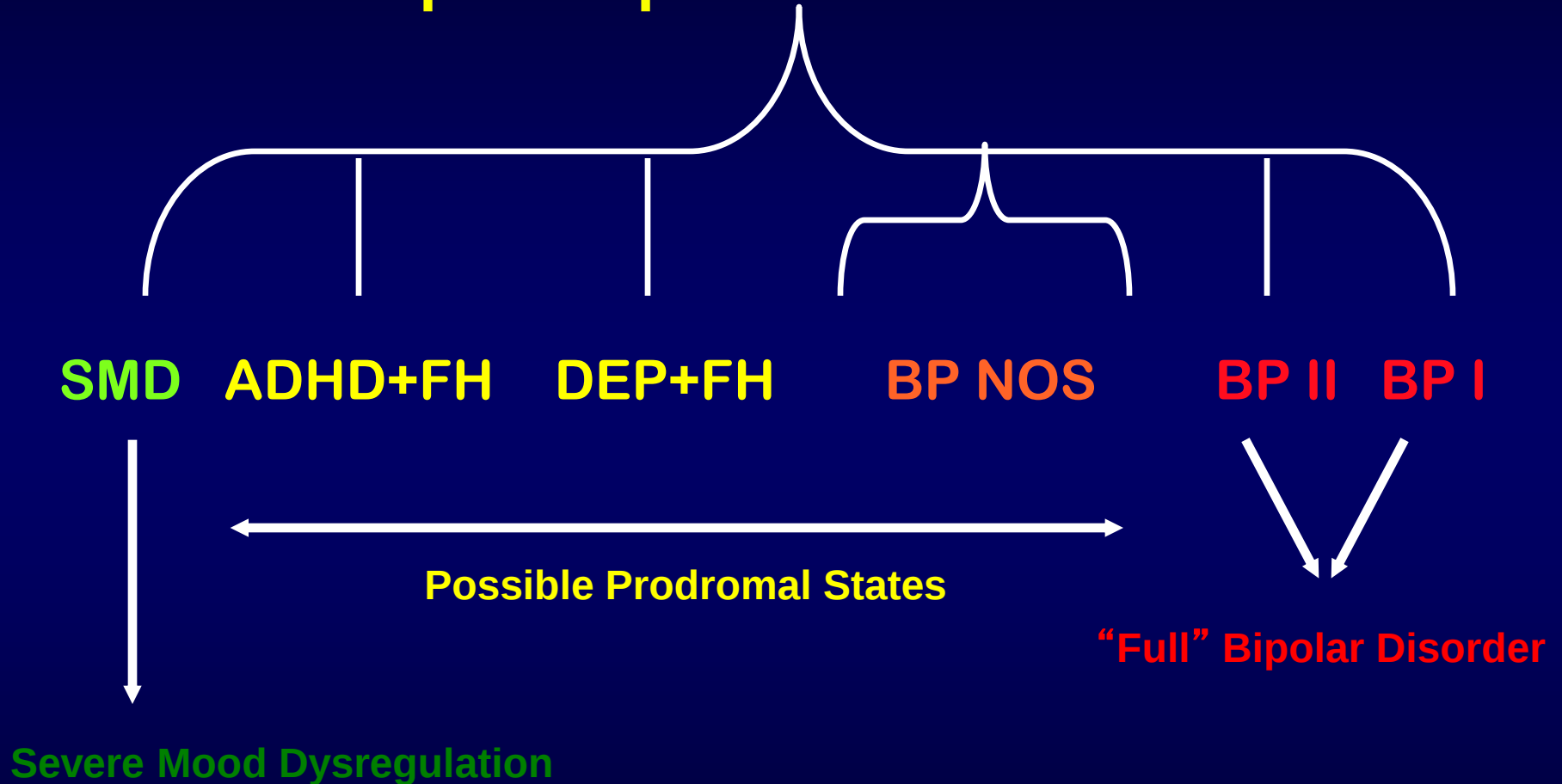
- Bipolar onset begins in childhood or adolescence 50-67% of the time¹
- 420,000 – 2,072,000 U.S. children could suffer from bipolar I or II disorder²
- Community diagnosis has increased 40x in past 10 years³
- Children with BD have poor psychosocial outcomes: higher rate of substance use, suicide attempts, school failure^{4,5}

¹ Perlis 2004; Leverich 2007; ²Post & Kowatch, 2006

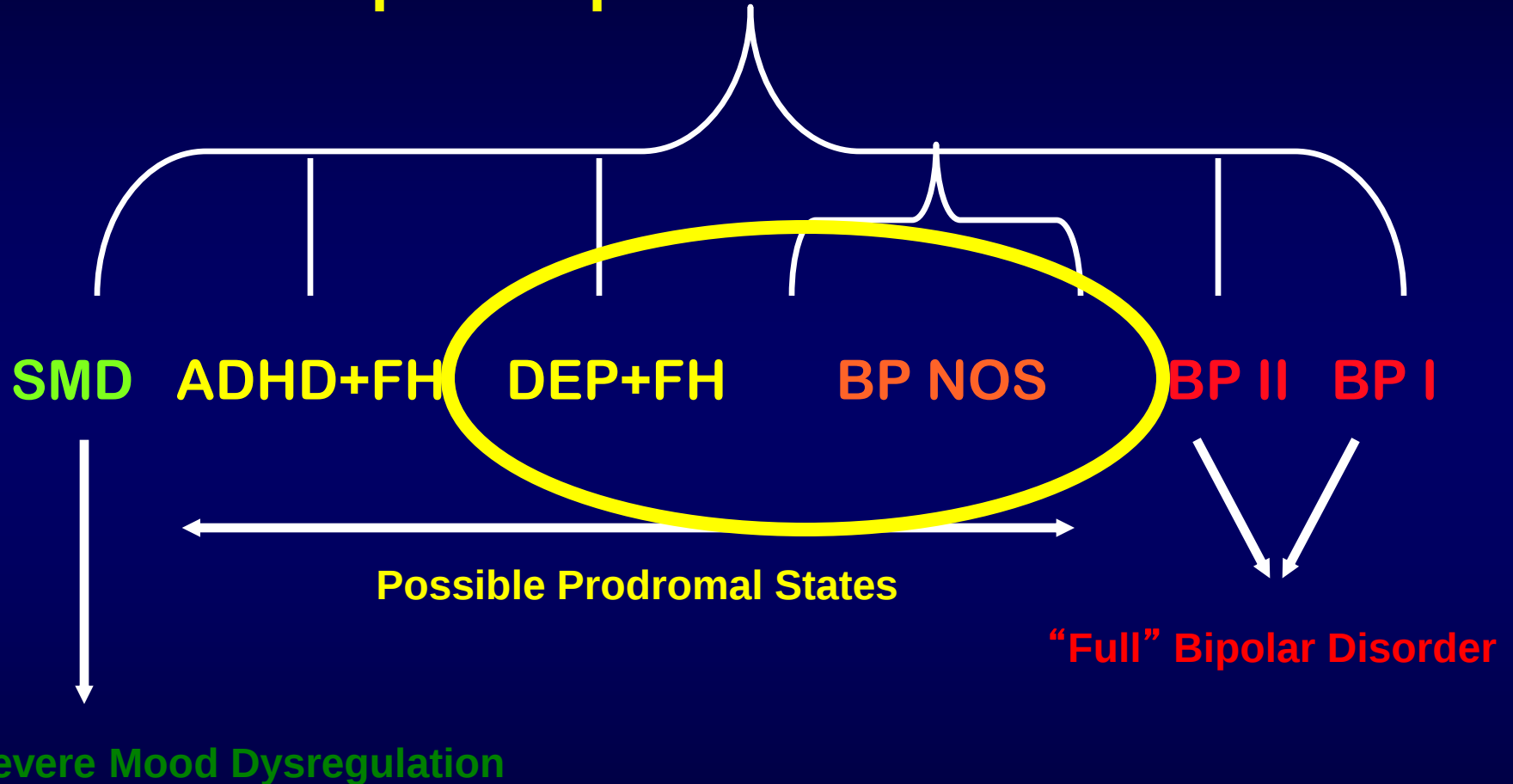
³ Moreno, Archives, 2007

⁴Carter 2003; ⁵Leverich 2007

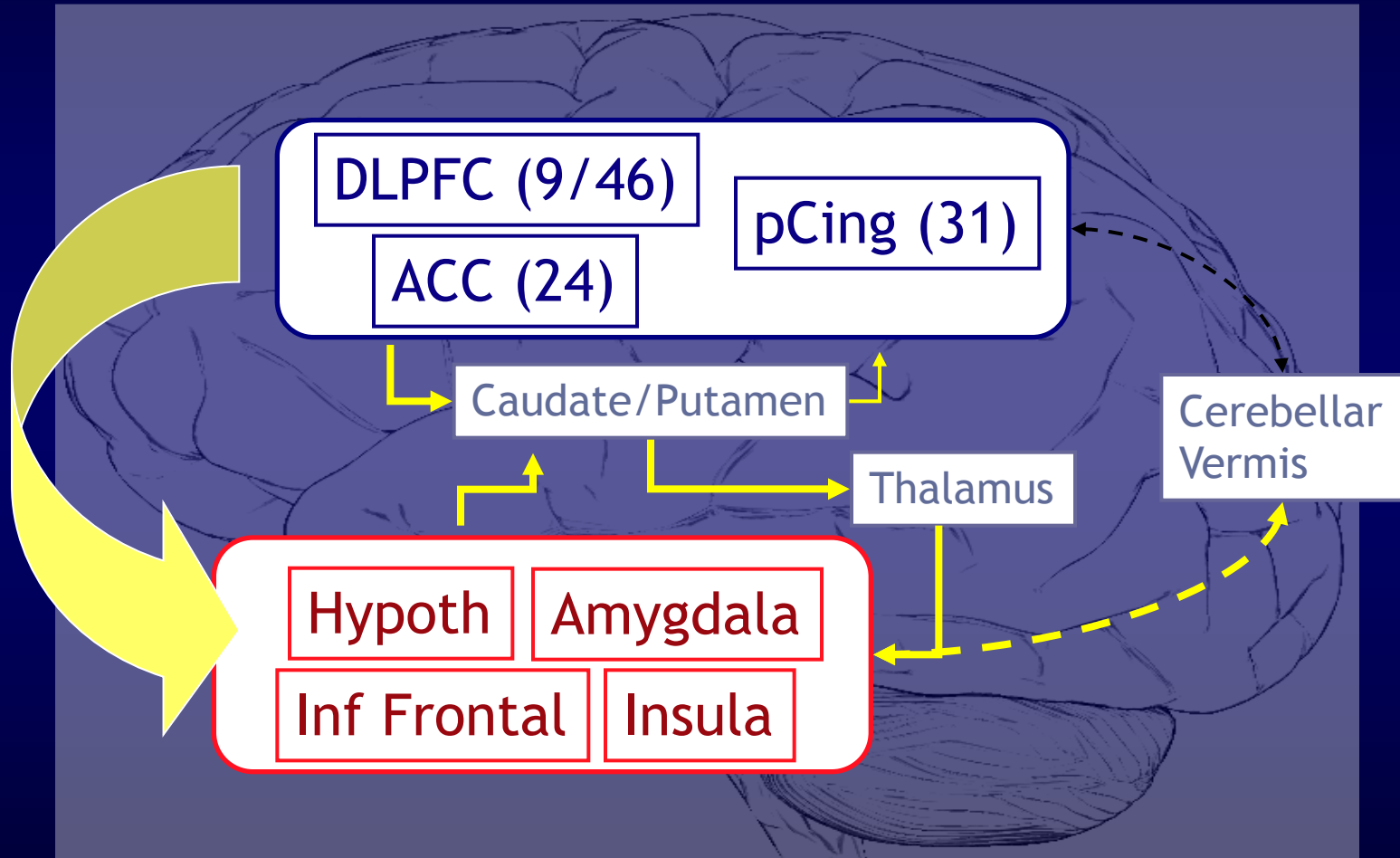
Bipolar Spectrum in Children



Bipolar Spectrum in Children



Corticolimbic Control in Bipolar Disorder



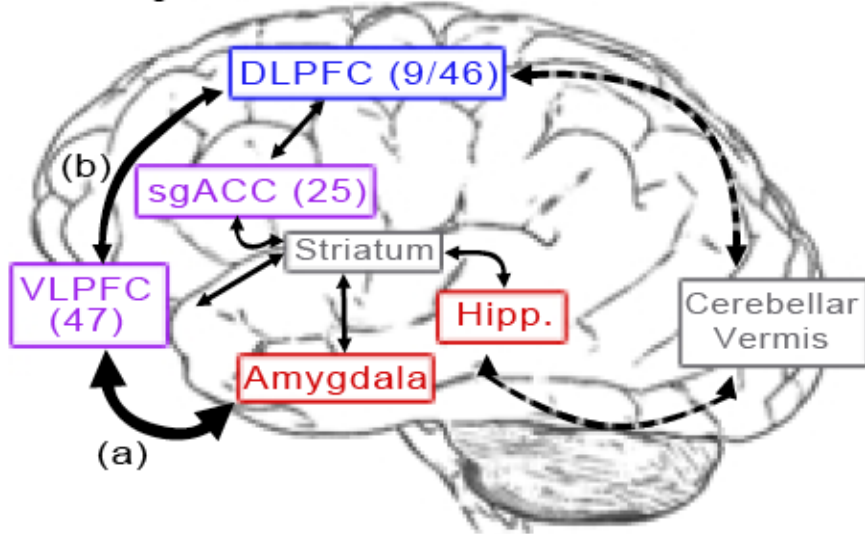
ACC=anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; Hypoth=hypothalamus; Inf=inferiors; pCing=posterior cingulate cortex.

Chang K et al. *Arch Gen Psychiatry*. 2004;61:781-792.

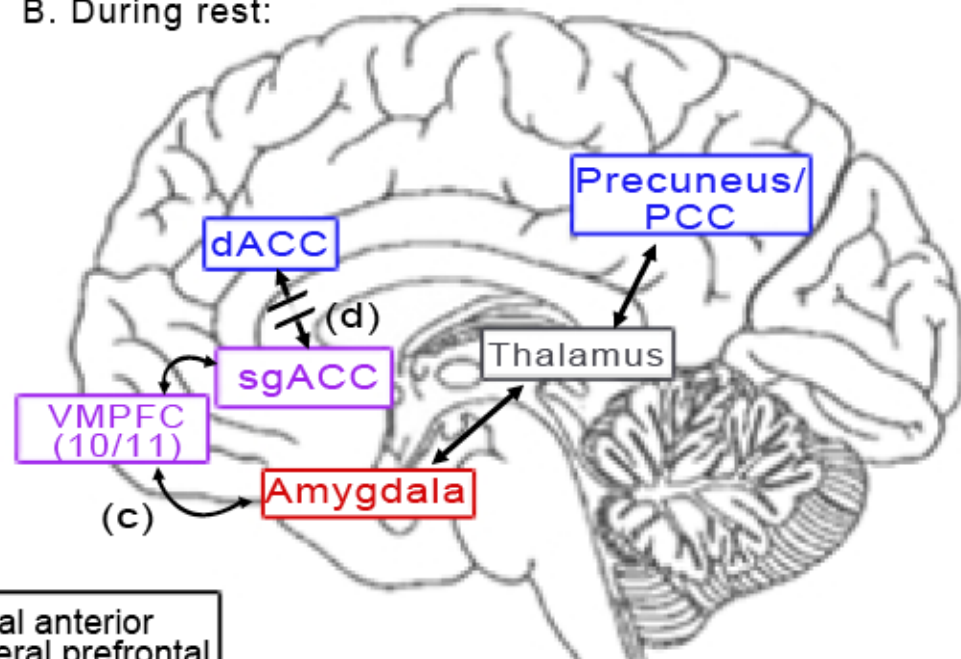
Functional Connectivity in High-Risk Youth

Figure 1. Functional connectivity in youth at risk for BD

A. During emotion task:

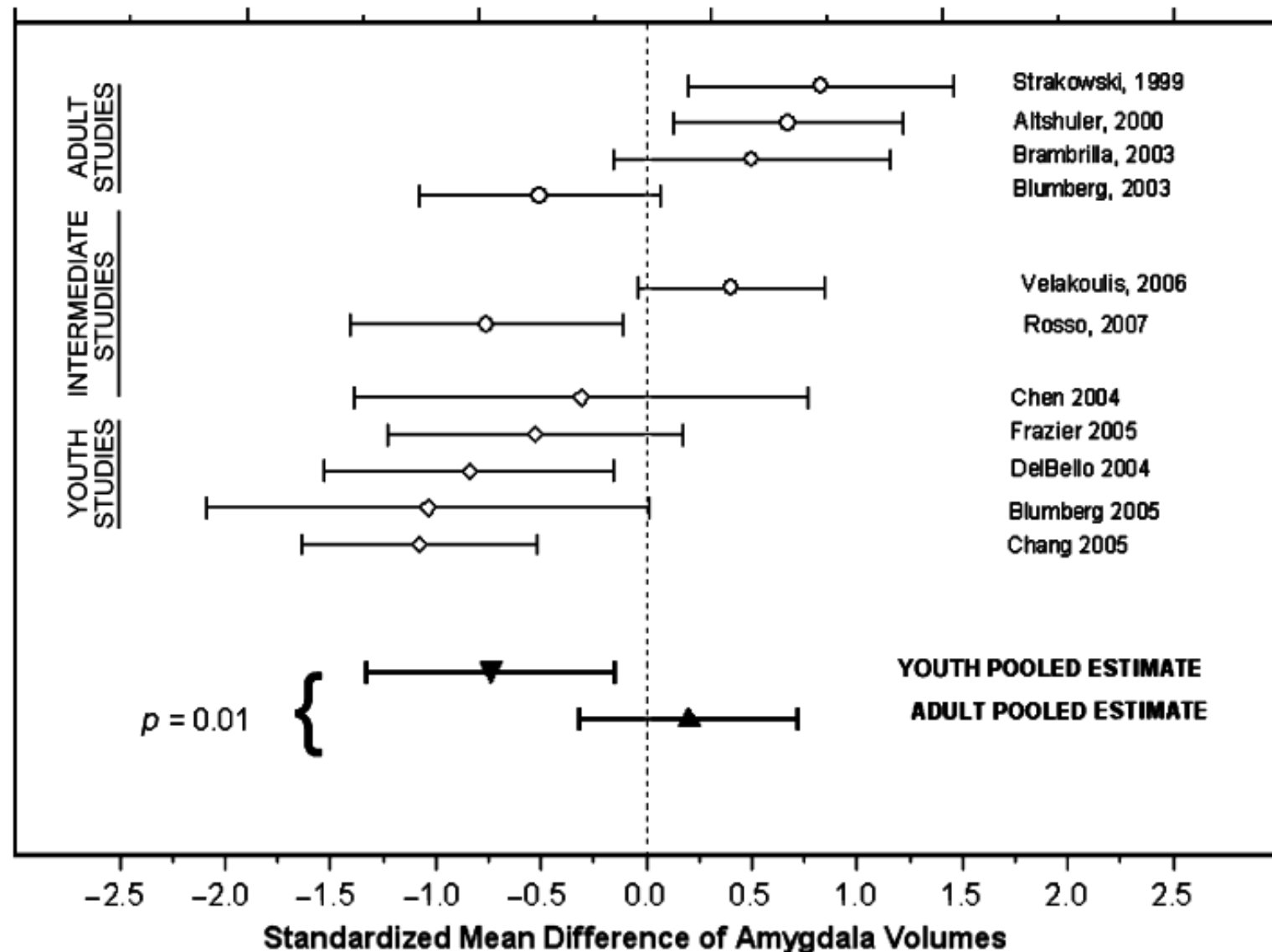


B. During rest:

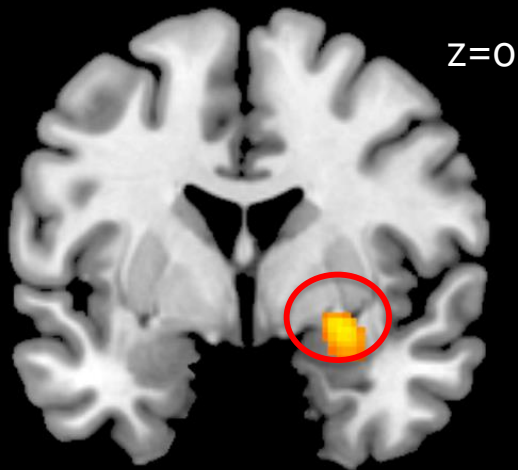


DLPFC = dorsolateral prefrontal cortex; sgACC = subgenual anterior cingulate cortex; Hipp.= hippocampus; VLPFC = ventrolateral prefrontal cortex; VMPFC = ventromedial prefrontal cortex; dACC = dorsal ACC; PCC = posterior cingulate cortex

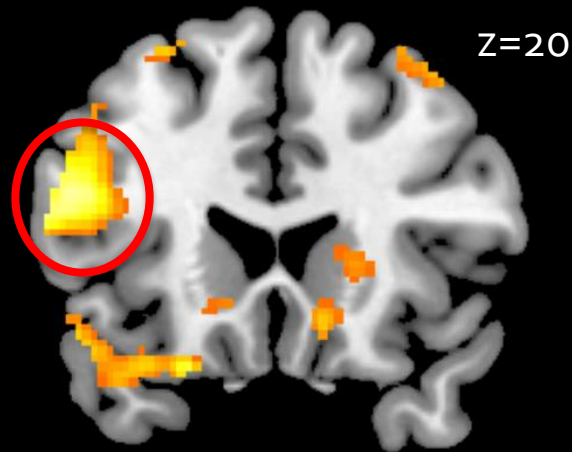
Amygdala Volumes in BD by Age



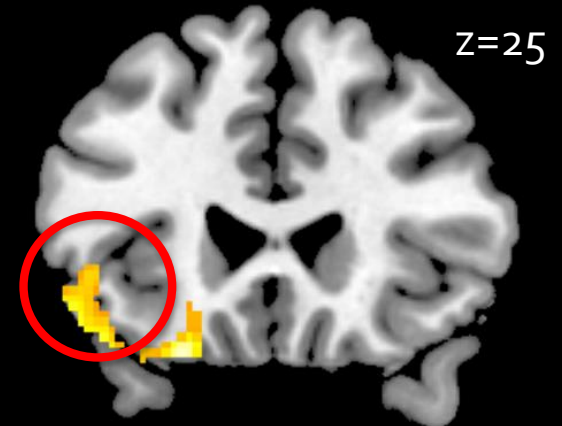
HR>HC Fear-Calm



Right Amygdala



Left DLPFC (BA 9)

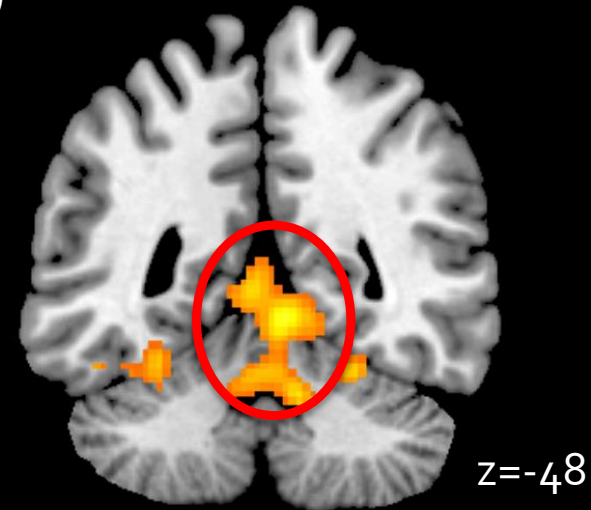
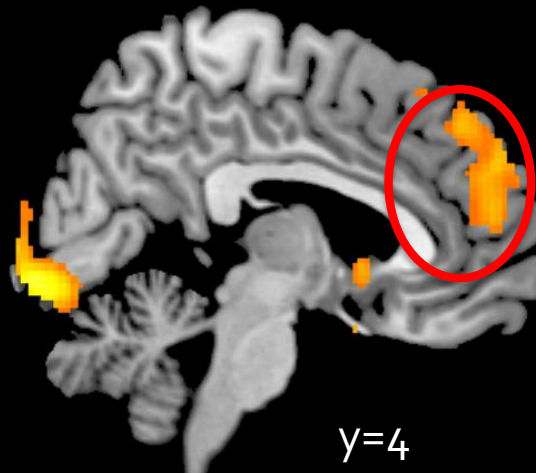
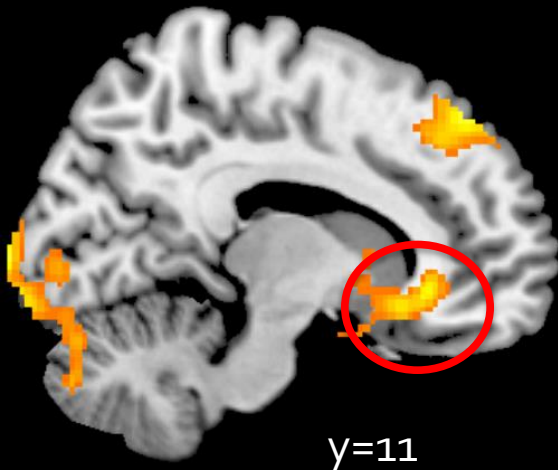


Left VLPFC (BA 47)

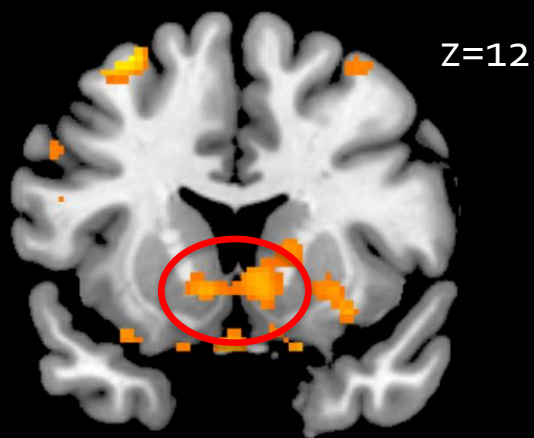
L Subgenual Cingulate (BA 25)

R Medial Frontal Gyrus (BA 10/11)

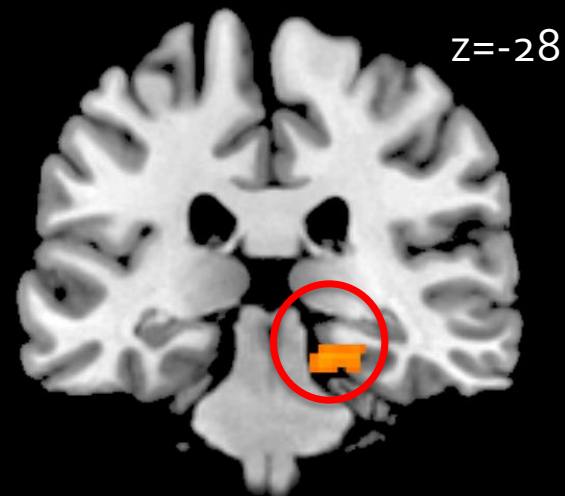
Cerebellar Vermis



HR>HC Fear-Calm



Bilateral Caudate/VS



Right Parahippocampal Gyrus

Treatment/Early Intervention

Early Interventions in Children at High Risk for BD

Study	N	Reduction of Manic Sx	Reduction of Depressive Sx	Beat Placebo?
Lithium vs Pbo ¹	30	+	+	No
Divalproex, ² Open-label	24	+	+	N/A
Divalproex vs Pbo ³	53	+ (prevented relapse)	+ (prevented relapse)	No (only with ++ Fam Hx)
Quetiapine, ⁴ Single-blind, prospective	20	+	+	N/A

1. Geller B et al. *J Affect Disord*.1998;51:165; 2. Chang KD et al. *J Clin Psychiatry*. 2003;64:936;
3. Findling RL et al. *J Clin Psychiatry*. 2007;68:781; 4. DelBello MP et al. *J Clin Psychiatry*. 2007;68:789

Family-Focused Treatment (FFT) for High Risk Youth

- ♦ Time-limited: 12 outpatient sessions over 4 months
- ♦ Begins with assessment of family
- ♦ Three component modules:
 - **Psychoeducation** about mood disorders (*symptoms, early recognition, etiology, treatment, self-management*)
 - **Communication skills training** (*behavioral rehearsal of effective speaking and listening strategies*)
 - **Problem solving skills training**

Miklowitz DJ and Goldstein MJ. *Bipolar Disorder: A Family-Focused Treatment Approach*. NY: Guilford Press, 1997

Our pilot study demonstrated that neural changes accompany symptom change

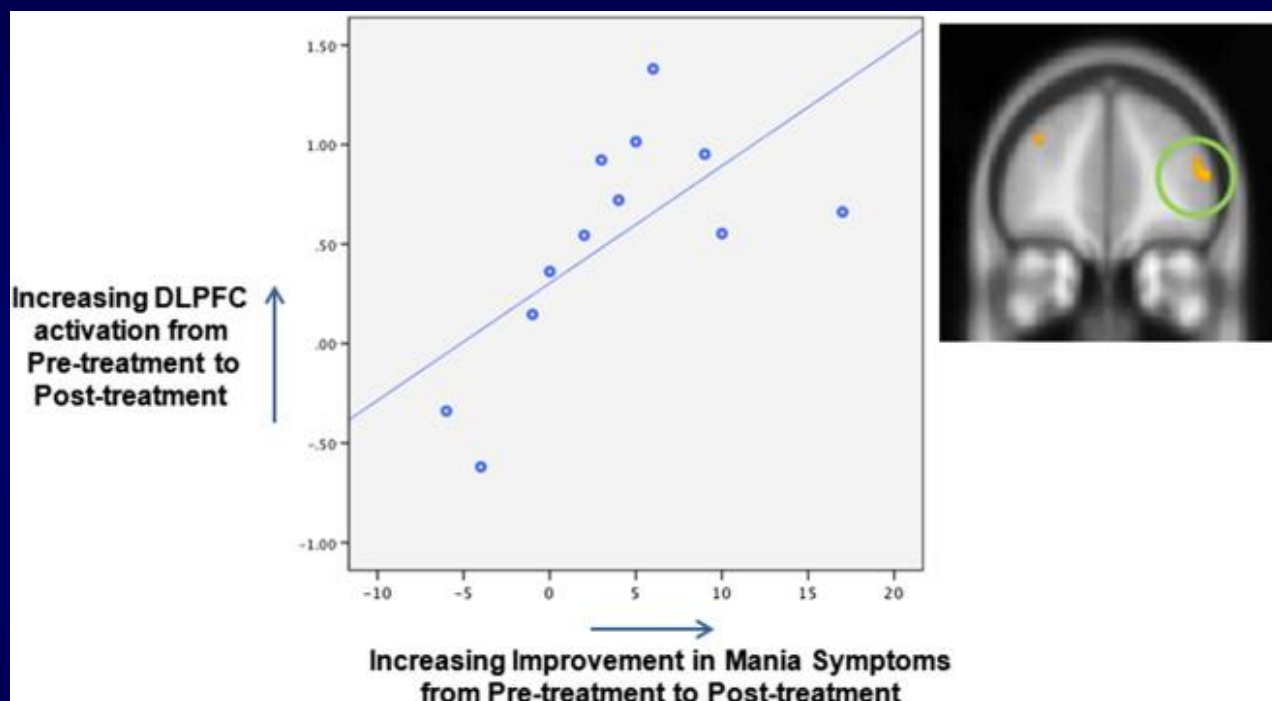
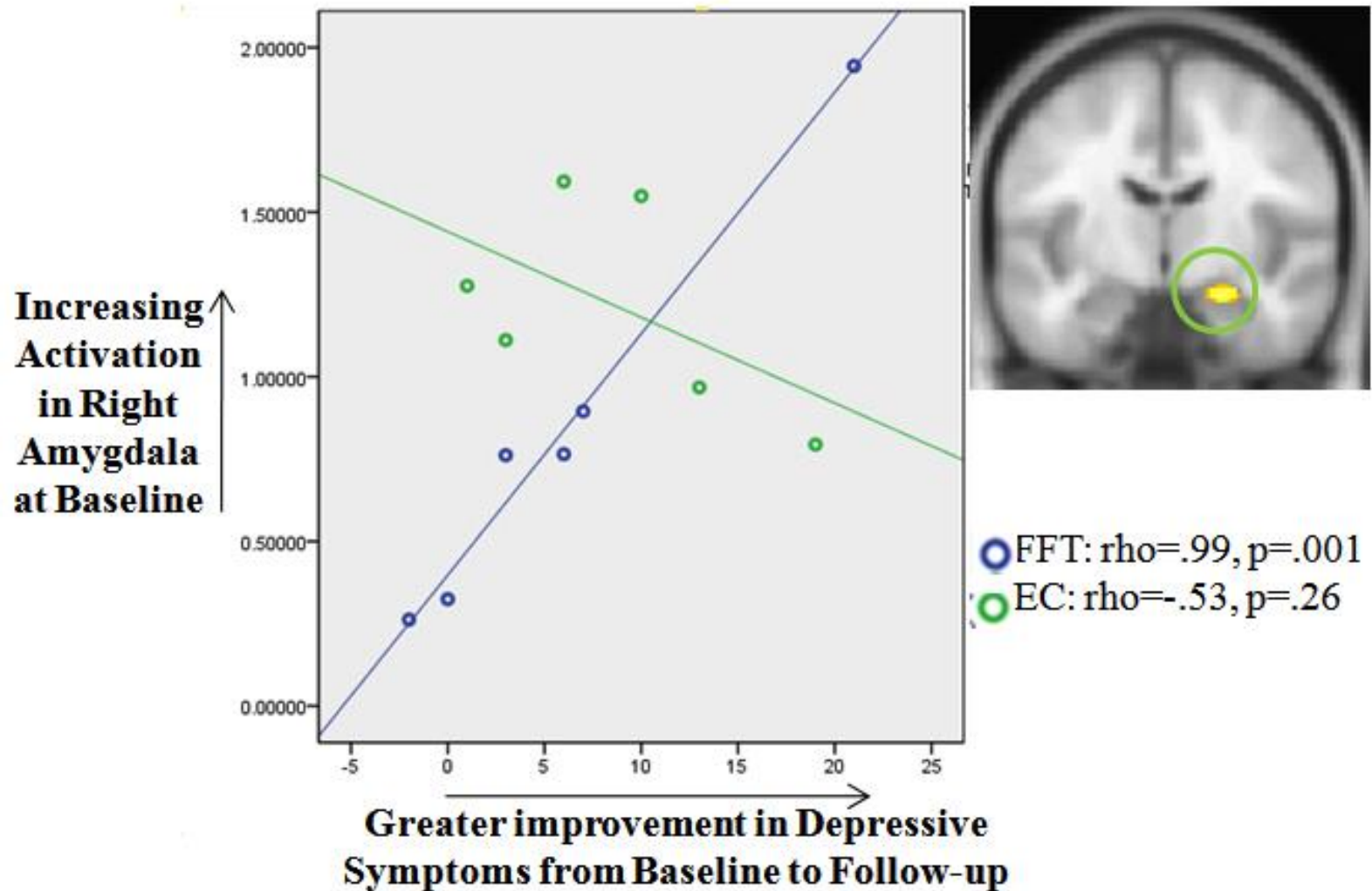


Fig. 1. Scatterplot showing the significant correlation between increasing activation in the dorsolateral prefrontal cortex (DLPFC) and improvement in symptoms of mania from pre- to post-treatment (Spearman's $\rho = .72$, $p = .008$).

Garrett, A. S., Miklowitz, D. J., Howe, M. E., Singh, M. K., Acquaye, T. K., Hawkey, C. G., Glover, G. H., Reiss, A. L., Chang, K. D. 2015; Changes in brain activation following psychotherapy for youth with mood dysregulation at familial risk for bipolar disorder. *Prog Neuropsychopharm & Biol Psych* 56: 215-220 .

Right Amygdala Activation at Baseline Predicts Response to FFT-HR, But Not EC



Conclusions

- Bipolar disorder is common in children and adolescents (1%)
- Children, adolescents, and adults usually have a prodromal phase before the first manic episode
- Targeted pharmacologic and psychotherapeutic interventions *at the right time* may help restore healthy neuronal connectivity/function
- Long term follow up to determine *prevention* is necessary.

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