Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

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Mood Disorders in Children and Adolescents

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Disclosures

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Learning Objectives

- Integrate evidence-based, best-practice options in children and adolescents for the:
  - Pharmacological and nonpharmacological management of depression (MDD)
  - Pharmacological and nonpharmacological management of bipolar disorder (BD)
- Review the efficacy and safety of early intervention strategies for treating youth with, and at high risk for, developing mood disorders.
- Discuss novel methods to investigate mechanisms underlying response to treatment and the development of treatment-emergent adverse events.

Audience Response

How confident are you in using the latest evidence in treating patients patients with mood disorders?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not confident at all

Audience Response

Which of the following are signs of bipolar disorder vs. ADHD?

A. Unstable mood, externally distracted
B. High energy, unstable mood
C. Stable mood, loses interest in fighting
D. Internally distracted stable mood

Mechanisms of Mood Disorders

Children vs. Adults

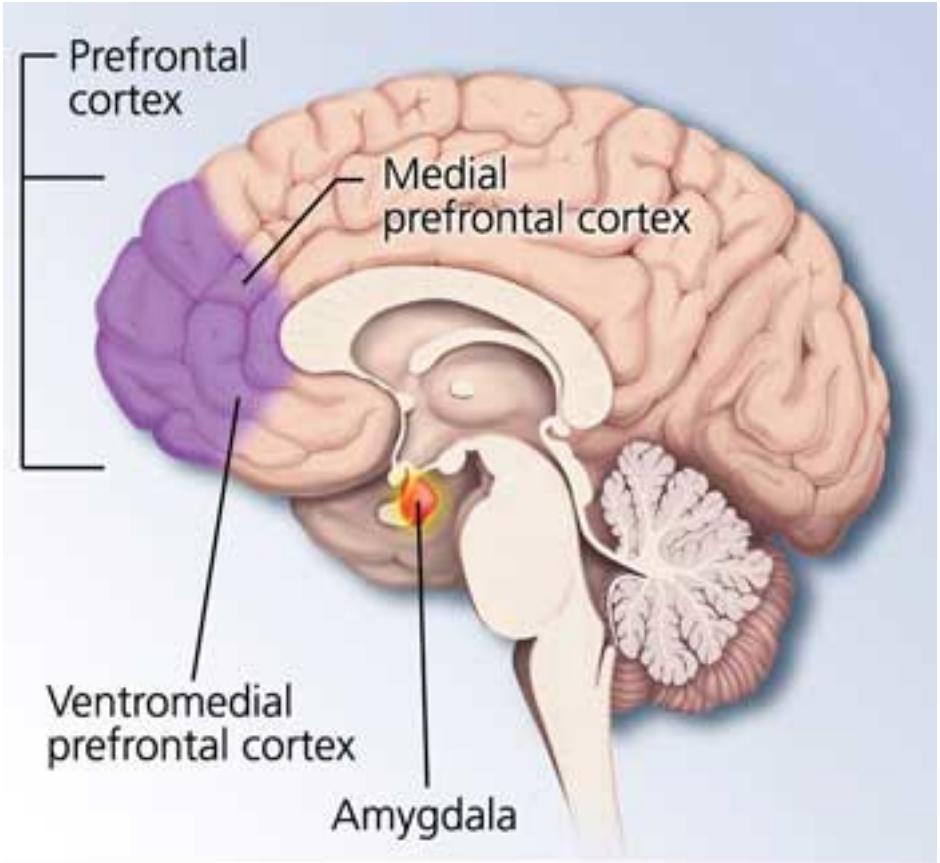
- Overall, the clinical picture of mood disorders in youths is similar to the clinical picture in adults
- Differences may be attributed to a child's physical, emotional, cognitive, and social developmental stages
  - Mood lability, irritability, low frustration tolerance, temper tantrums, somatic complaints, and/or social withdrawal instead of verbalizing feelings of depression
  - Fewer melancholic symptoms and delusions
  - More suicide attempts in adolescents than depressed adults

Birmaher B et al. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1575-1583..
Fergusson DM et al. *Psychol Med*. 2005;35:983-993.
Kaufman J et al. *Biol Psychiatry*. 2001;49:980-1001.
Nock MK et al., *JAMA Psychiatry*, 2013; 70(3):300-310.

Major Brain Mood Centers: Prefrontal Cortex and Limbic System (Amygdala)

Prefrontal cortex:

- Develops more in
- adolescence
- Executive function
- Regulates emotion



Brain Structures Involved in Dealing with Fear and Stress

Limbic system:

- Primitive
- Amygdala
- Controls moods
- Fight or flight

Treatment of Mood Disorders

Pediatric Depression

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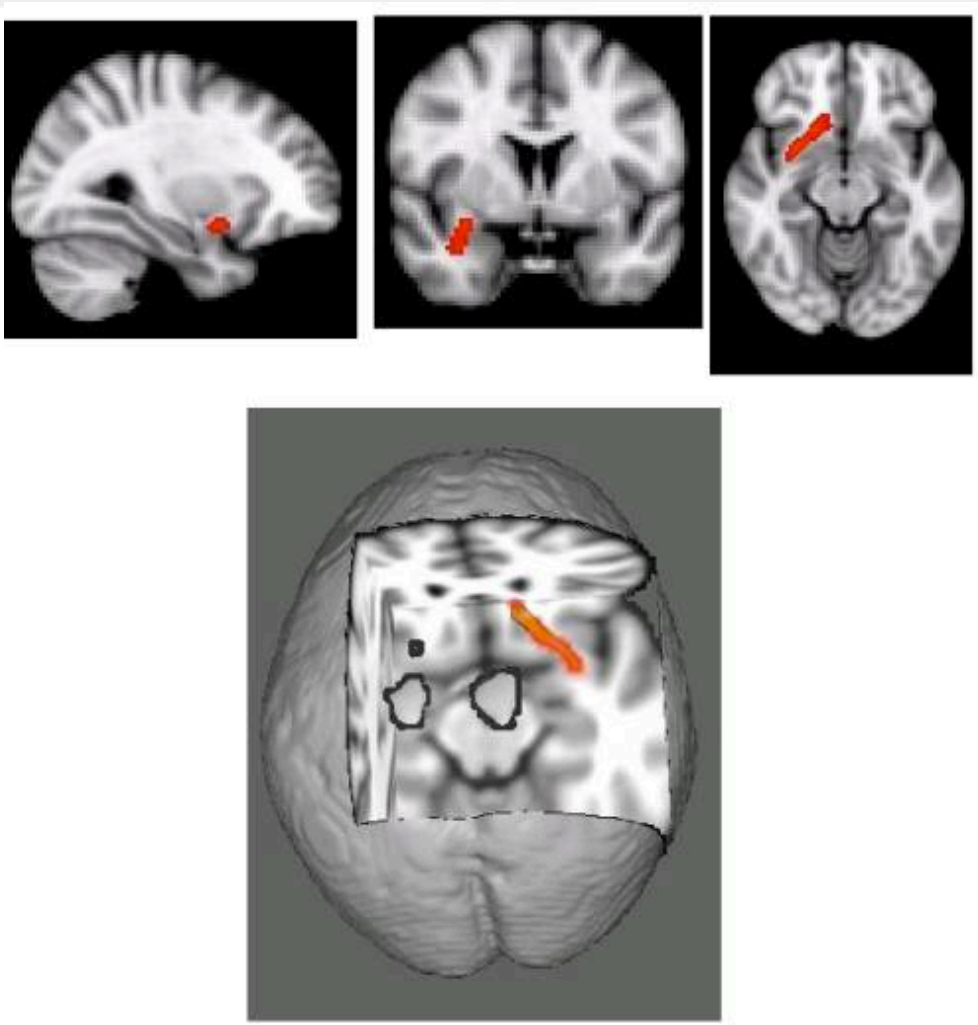
Altered White Matter Microstructure in Adolescent Depression



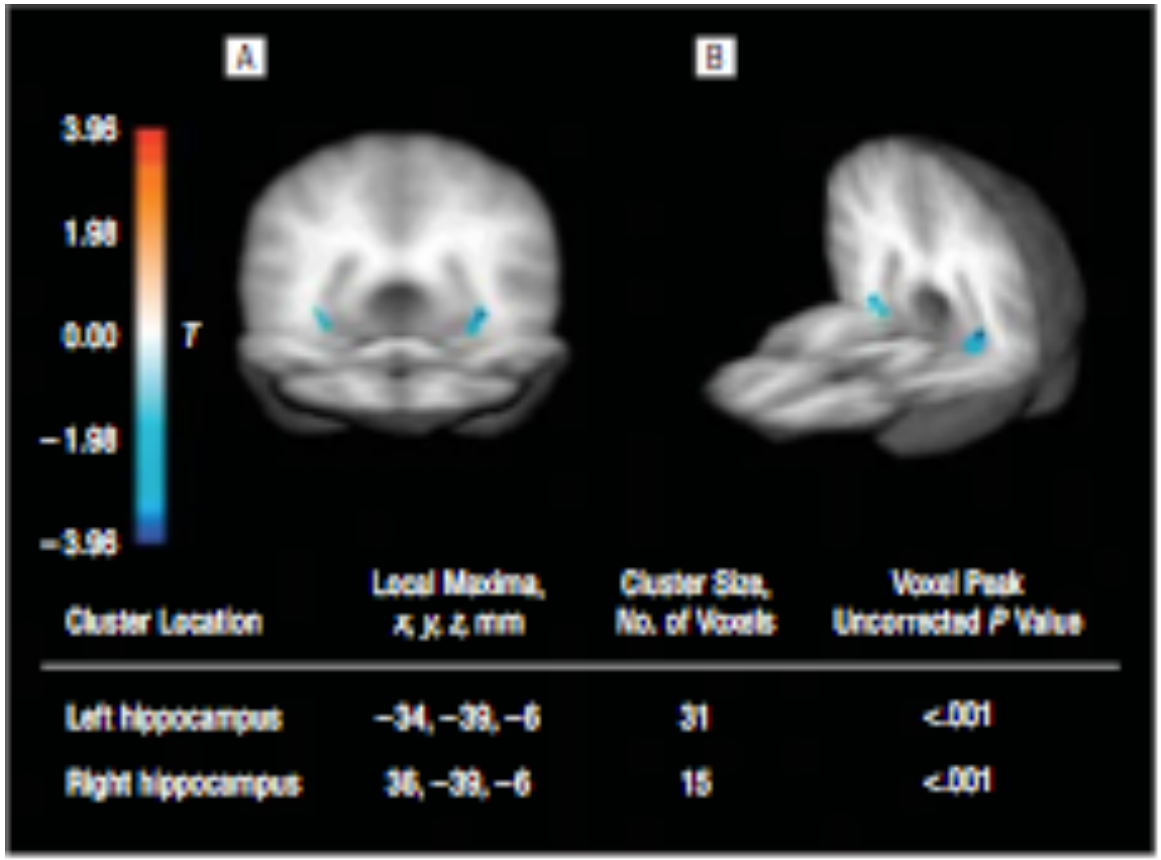
Cullen KR, et al., *J Am Acad Child and Adolesc Psychiatry,* 2010;49(2):173-183.e1.

Other Neural Abnormalities in Adolescent Depression

- Medication-naïve MDD adolescents show motivation that appears less capable of upregulating attention networks than healthy youths.[1]
- Adolescents with MDD have significantly decreased levels of inhibitory neurotransmitter GABA in the anterior cingulate cortex, particularly when they are anhedonic.[2]
- Adolescents with MDD have increased imbalance of resting-state brain activity between frontal cognitive control and (para) limbic-striatal emotional processing systems.[3]
- Topological properties of depressed adolescents' networks are significantly disrupted and the connectivity degree of amygdala related functional connection is positively correlated with duration of depression.[4]

1. Chantiluke K, et al., *Biol Psychiatry*. 2012;71(1):59-67. 2. Gabbay V, et al. *Arch Gen Psychiatry*. 2012;69(2):139-1494. 3.Jiao Q, et al. *PLoS One*. 2011;6(9):e25159. 4. Jin C, et al. *Neurosci Lett*. 2011;503(2):105-109.

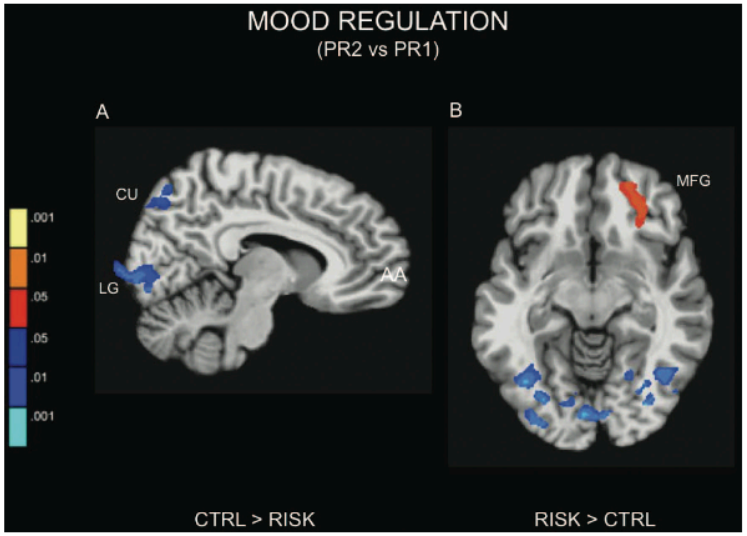
Reduced Hippocampal Volume and Risk for Depression



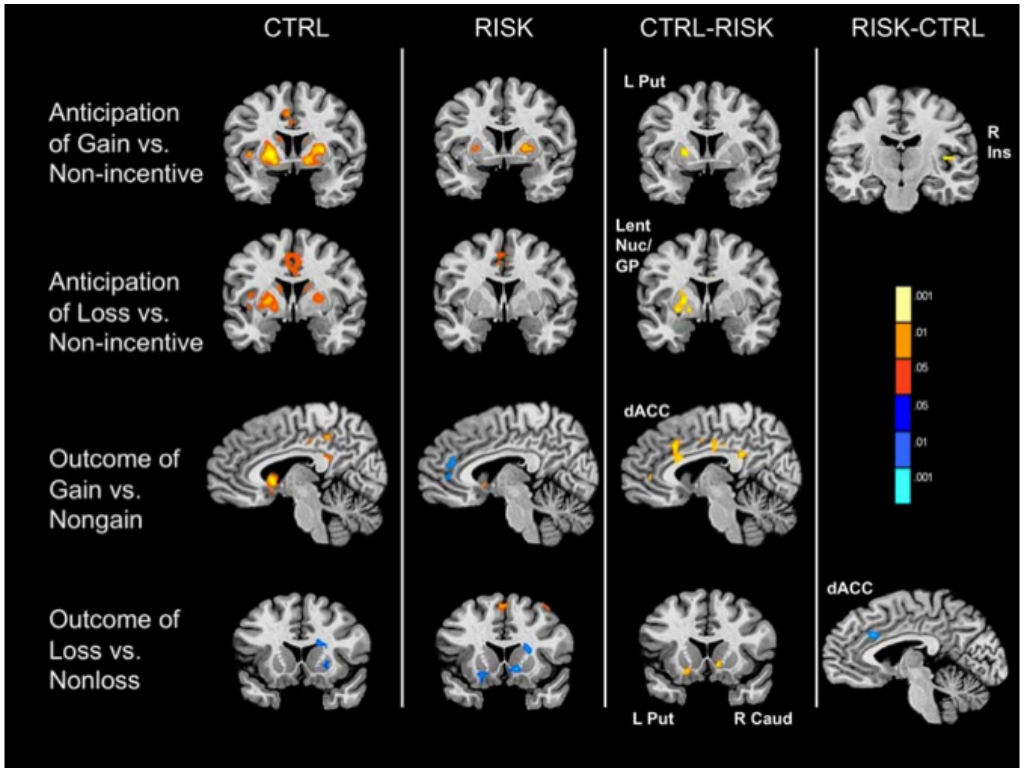
Cluster Location	Local Maxima, x, y, z, mm	Cluster Size, No. of Voxels	Voxel Peak Uncorrected *P* Value
Left hippocampus	−34, −39, −6	31	<.001
Right hippocampus	36, −39, −6	15	<.001

Chen MC, et al., *Arch Gen Psychiatry*, 2010;67(3):270-276.

Mood Regulation and Reward Processing and Risk for MDD



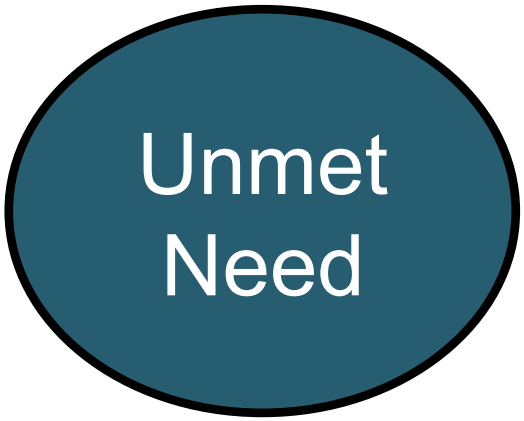
Joormann et al., *J Abnormal Psychology*, 2011



Gotlib IH, et al., *Arch Gen Psychiatry*. 2010;67(4):380-387.

FDA Approved Agents for Pediatric Depression

Acute Depression		Longer-Term	
Year	Drug	Year	Drug
2002	Fluoxetine (7-17 years)		
2009	Escitalopram (12-19 years)		



Antidepressants: The Old and the New

Generic Name	Approved Age
Clomipramine	10 and older (for OCD)
Citalopram	18 and older
Venlafaxine	18 and older
Escitalopram	12 and older (for depression)
Fluvoxamine	8 and older (for OCD)
Fluoxetine	7 and older (for depression)
Mirtazapine	18 and older
Nefazodone	18 and older
Doxepin	12 and older
Imipramine	6 and older (for bed-wetting)
Bupropion	18 and older
Sertraline	6 and older (for OCD)

CMS Medicaid Integrity Program. Antidepressant Medications: Use in Pediatric Patients. CMS Website. https://www.cms.gov/medicare-medicaid-coordination/fraud-prevention/medicaid-integrity-education/pharmacy-education-materials/downloads/ad-pediatric-factsheet.pdf. Published August 2013. Accessed May 20, 2016.

Controlled Pediatric MDD Studies

Table 1 Controlled pediatric MDD studies

	Medication	Reference	Ages	Number of studies
Positive studies*	Fluoxetine	Emslie et al. [16], Emslie et al. [17], TADS [19], Almeida-Montes & Friederichsen [15]	6–17	4
	Escitalopram	Emslie et al. [20]	12–17	1
	Sertraline	Wagner et al. [22] **	6–17	1 (a priori pooled analysis, individual trials negative)
Negative studies	Escitalopram	Wagner et al. [21]	6–17	1
	Citalopram	von Knorring et al. [23]	13–18	1
	Paroxetine	Keller et al. [25], Emslie et al. [27], Berard et al. [26], Paroxetine Trial 1 [28]	7–17	4
	Venlafaxine	Emslie et al. [29]**	7–17	2
	Mirtazapine	Mirtazapine Trials 1 & 2 [30]**	7–17	2

*On primary outcome measure

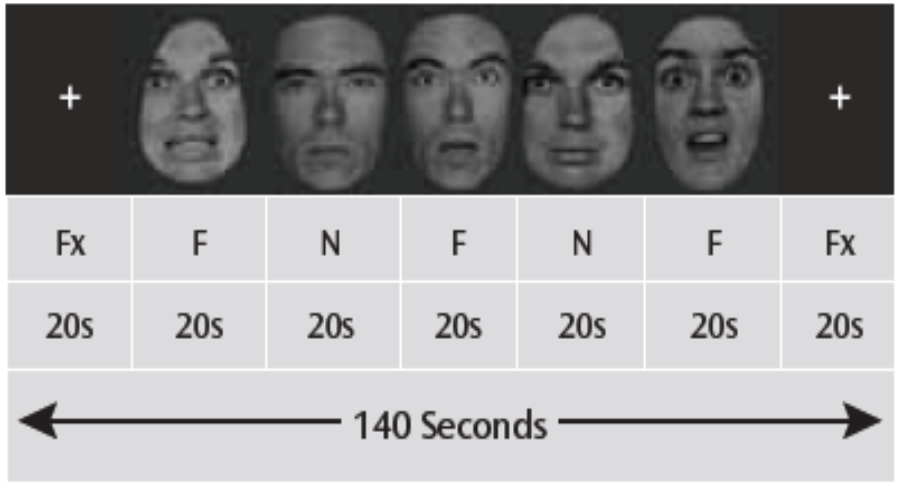
**References 22, 29 and 30 include two trials in one paper

Soutullo C, Figueroa-QuintanaA. *Curr Psychiatry Rep*. 2013 Jul;15(7):366.

Fluoxetine's Effect on Brain Function

- 19 depressed adolescents were presented a face paradigm before and 8 weeks after treatment with fluoxetine and compared to controls.

FIGURE 1. Face Paradigm in a Study of Depression in Adolescents[a]



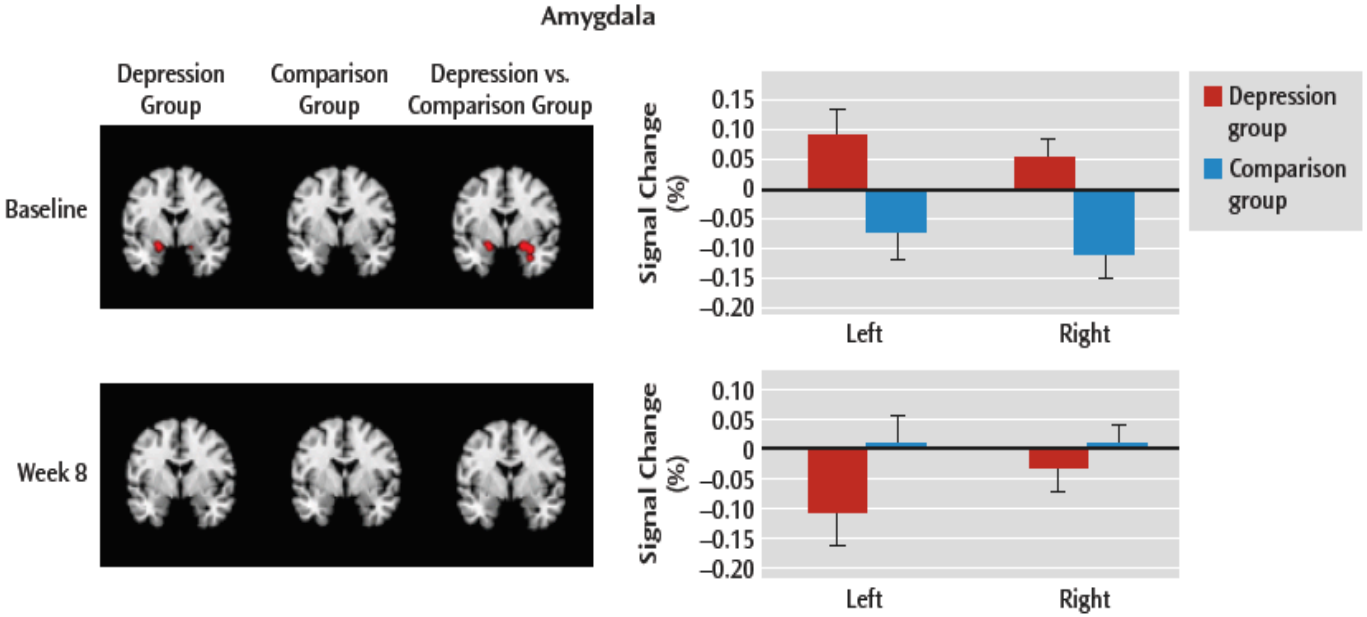
[a] The study used a block design, with a fixation block at the beginning and end of each run and five alternating fearful and neutral blocks in between. Fx=fixation; F=fearful faces; N=neutral faces.

Tao R, et al., *Am J Psychiatry*. 2012;169(4):381-383.

Fluoxetine's Effect on Brain Function

- 8 weeks of fluoxetine treatment normalized most regions of hyperactivity associated with adolescent depression

FIGURE 3. Activations at the Amygdala, Orbitofrontal Cortex, and Subgenual Anterior Cingulate Cortex in Adolescents With Major Depression and Healthy Comparison Subjects While Viewing Fearful and Neutral Facial Expressions[a]



Tao R, et al, *Am J Psychiatry*. 2012;169(4):381-383.

Medication for Teen Depression: SSRIs

Medication	Initial Dose	Incremental Dose Changes	Maximum Daily Dose	RCT Shows Efficacy/FDA Approved for Teen Depression
Fluoxetine	10 mg QD/ QOD	10-20 mg	60 mg	Yes/Yes
Escitalopram	5 mg QD/ QOD	5 mg	20 mg	Yes/Yes
Citalopram	10 mg QD/ QOD	10 mg	60 mg	No/No
Sertraline	25 mg QD/ QOD	12.5-25 mg	200 mg	Yes/No

Fluoxetine is the only SSRI approved for use in pre-teens. Doses listed here for teens and are not necessarily applicable for pre-teens.

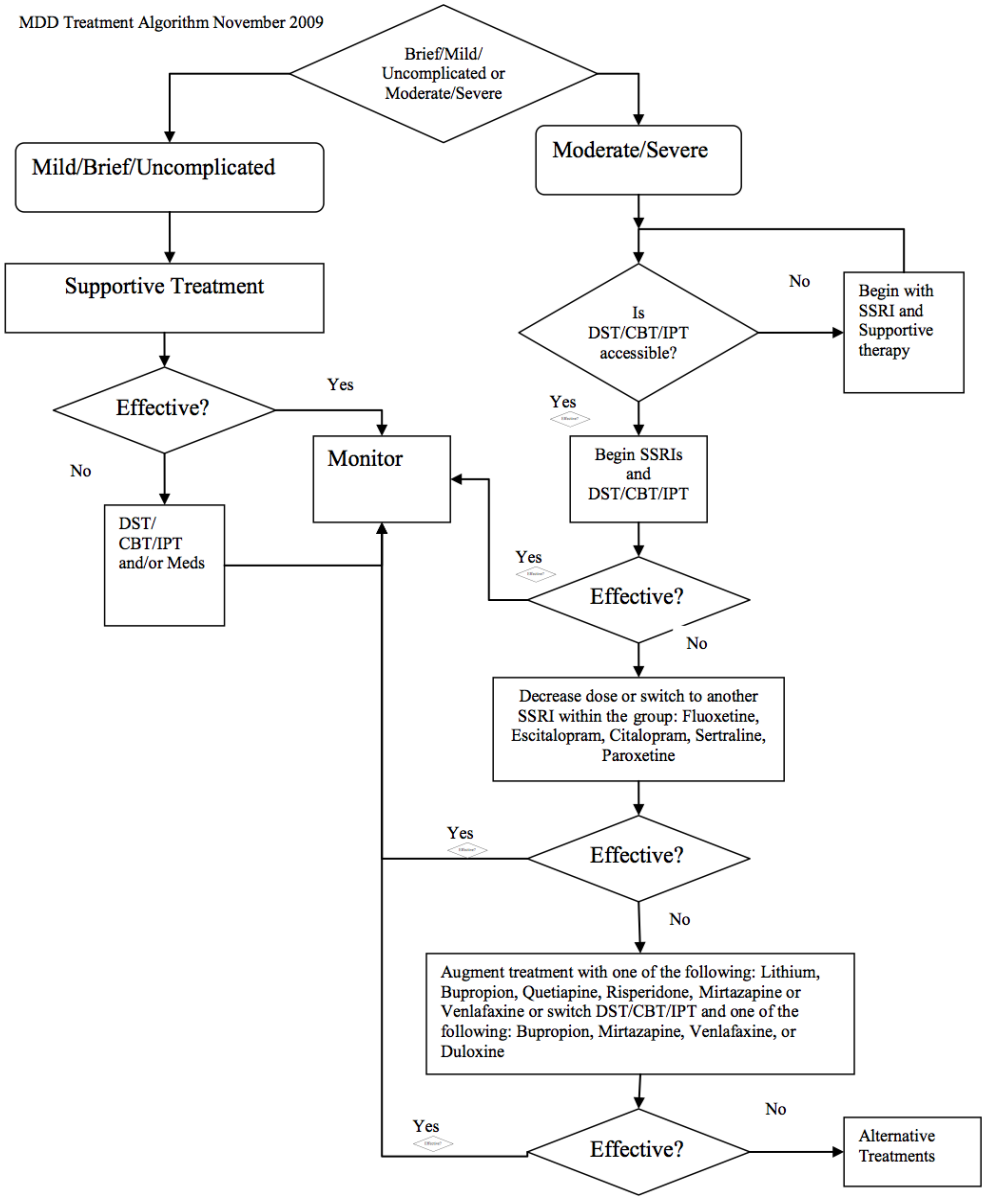
Bridge JA, et al. *JAMA*. 2007;297(15):1683-1696.

Pharmacotherapy for MDD: Other Agents

Medication	Initial Dose	Incremental Dose Changes	Maximum Daily Dose	RCT Shows Efficacy/FDA Approved for Teen Depression
Venlafaxine XR	37.5 mg	37.5 mg	75-225 mg	Yes/No
Trazadone	25 mg	25 mg	100-150 mg	No/No
Nefazadone	100 mg	50 mg	600 mg	No/No
Mirtazapine	7.5 -15 mg	15 mg	45 mg	No/No
Bupropion SR	150 mg	75 mg	300 mg	No/No
Bupropion XL	150 mg	75 mg	450 mg	No/No
Amytriptyline	25 mg	25 mg	100 mg	No/No
Nortryptaline	1-3 mg/kg/day	25 mg	150 mg	No/No
Imipramine	25 mg	25 mg	200 mg	No/No
Desipramine	25 mg	25 mg	100-150 mg	No/No

Bridge JA, et al. *JAMA*. 2007;297(15):1683-1696.

Texas Children's Medication Algorithm (TMAP) (2009)



American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct.

Treatment of Resistant Depression in Adolescents (TORDIA)

- Depressed adolescents who failed to respond to an 8 week trial with a SSRI were randomly assigned for another 12 weeks to:
  - Another antidepressant (citalopram/fluoxetine)
  - Venlafaxine, or
  - SSRI plus CBT,
  - Venlafaxine plus CBT
- Response rates were better for CBT+ antidepressant (55%) than antidepressants alone (41%)
- Predictors of response: less severe depression, less family conflict, no self-injurious behavior

Wagner KD, et al. *J Child Adolesc Psychopharmacol*. 2012;22(1):5-10.

Medication for Youth Depression: SSRI Side Effects

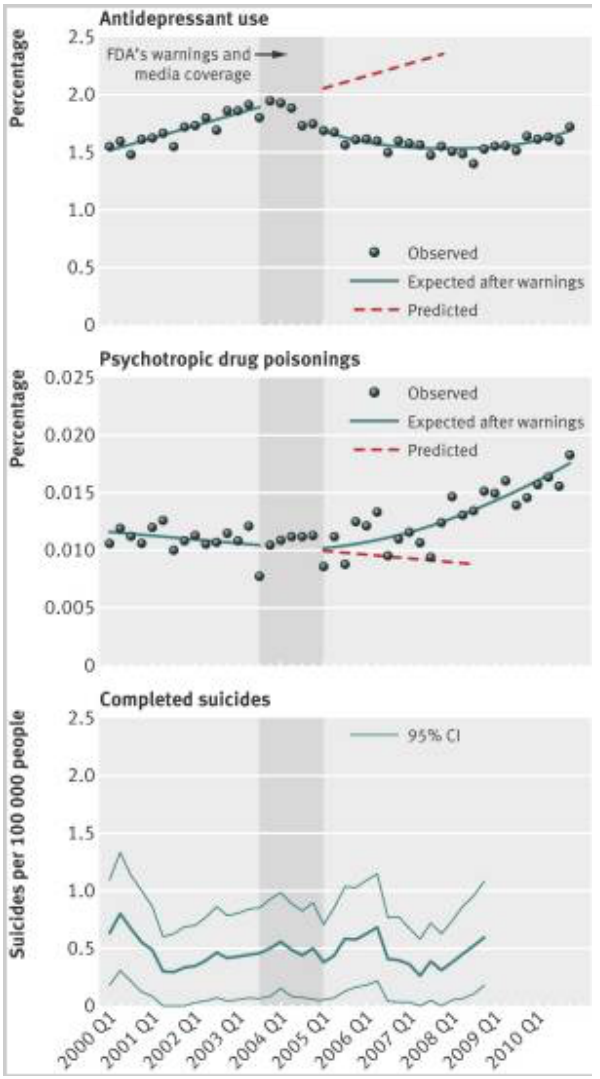
Number Needed to Harm (NNH) = 112

Side Effects of SSRIs, 5 HT Selective: May attenuate over several weeks. In general, any SSRI may cause: nausea, anxiety, agitation, anorexia, tremor, somnolence, sweating, dry mouth, headache, dizziness, diarrhea, constipation, sexual dysfunction				
Medication (generic)		**Anticholinergic Side Effects**	**Sedating Effect**	**Comments**
Fluoxetine		**+, esp nausea, sexual dysfunction, anorexia**	**+**	**FDA approved, stimulating**
Escitalopram		**+**	**+**	**FDA approved**
Citalopram		**+**	**+**	**Generic avail.**
Sertraline		**0, esp diarrhea & male sexual dysfunction**	**+**	**FDA Approved for Teen OCD**

Soutullo C, et al. *Curr Psychiatry Rep*. 2013;15(7):366.

Change in Antidepressant Use after FDA Warnings and Media Coverage

- October, 2003 - FDA orders black box warning on all SSRIs
- Trends in antidepressant use and poisonings changed abruptly after the warnings.
- Absolute reductions of 696, 1216, and 1621 dispensings per 100 000 people among adolescents, young adults, and adults, respectively.
- Simultaneously, there were significant, relative increases in psychotropic drug poisonings in adolescents (21.7%, 95% confidence interval 4.9% to 38.5%) and young adults (33.7%, 26.9% to 40.4%).



Lu CY, et al. *BMJ*, 2014; 2014 Jun 18;348:g3596.

Summary Recommendations for Antidepressants

- Minimize side-effects (nausea, diarrhea, appetite changes, headaches, restlessness, tremor, and changes in sleep)
- Prevent drug interactions
- Avoid withdrawal
- Monitor suicidality
- Diagnostic and treatment challenge: Rule out bipolar depression

Pediatric Bipolar Disorder (BD)

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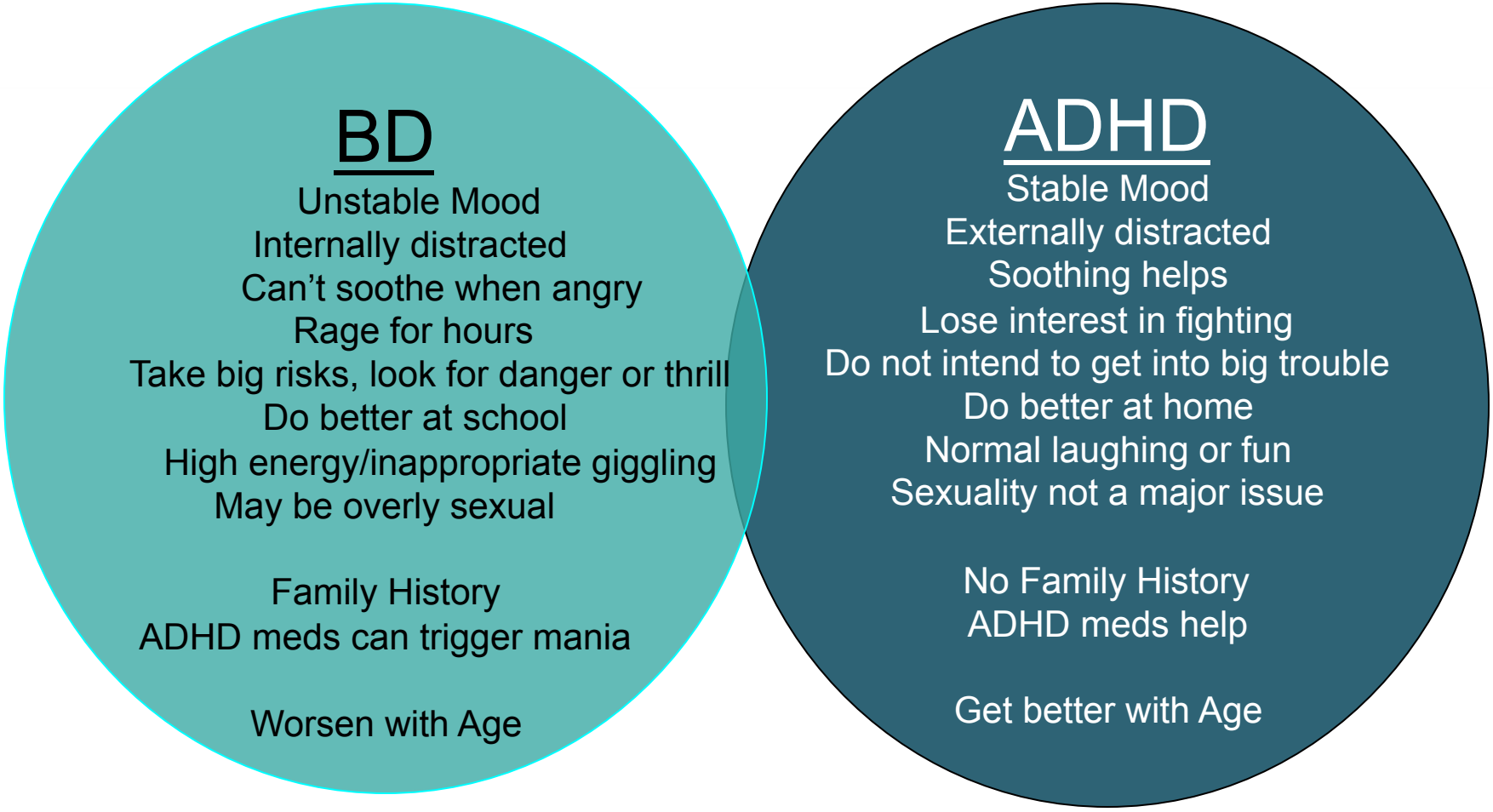
Pediatric Bipolar Disorder (BD)

- 1% lifetime prevalence[1,2]
- At risk for the 4 Ss:
  - School problems
  - Substance abuse
  - Social dysfunction
  - Suicide
- Bipolar disorder runs in families[3]
- Stronger genetic load in youth than adults[4]

Newsweek, May 2008

[1]Lewinsohn PM, et al., *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):454-463.; [1]Lewinsohn PM, et al.. *J Am Acad Child Adolesc Psychiatry*. 2000;39(7):888-95.; [2]Goodwin and Jamison, *Manic-Depressive* Illness, Oxford University Press, New York. 1990.; [3]Faraone SV, et al., *Biological Psychiatry*, 2003;1;53(11):970-977.

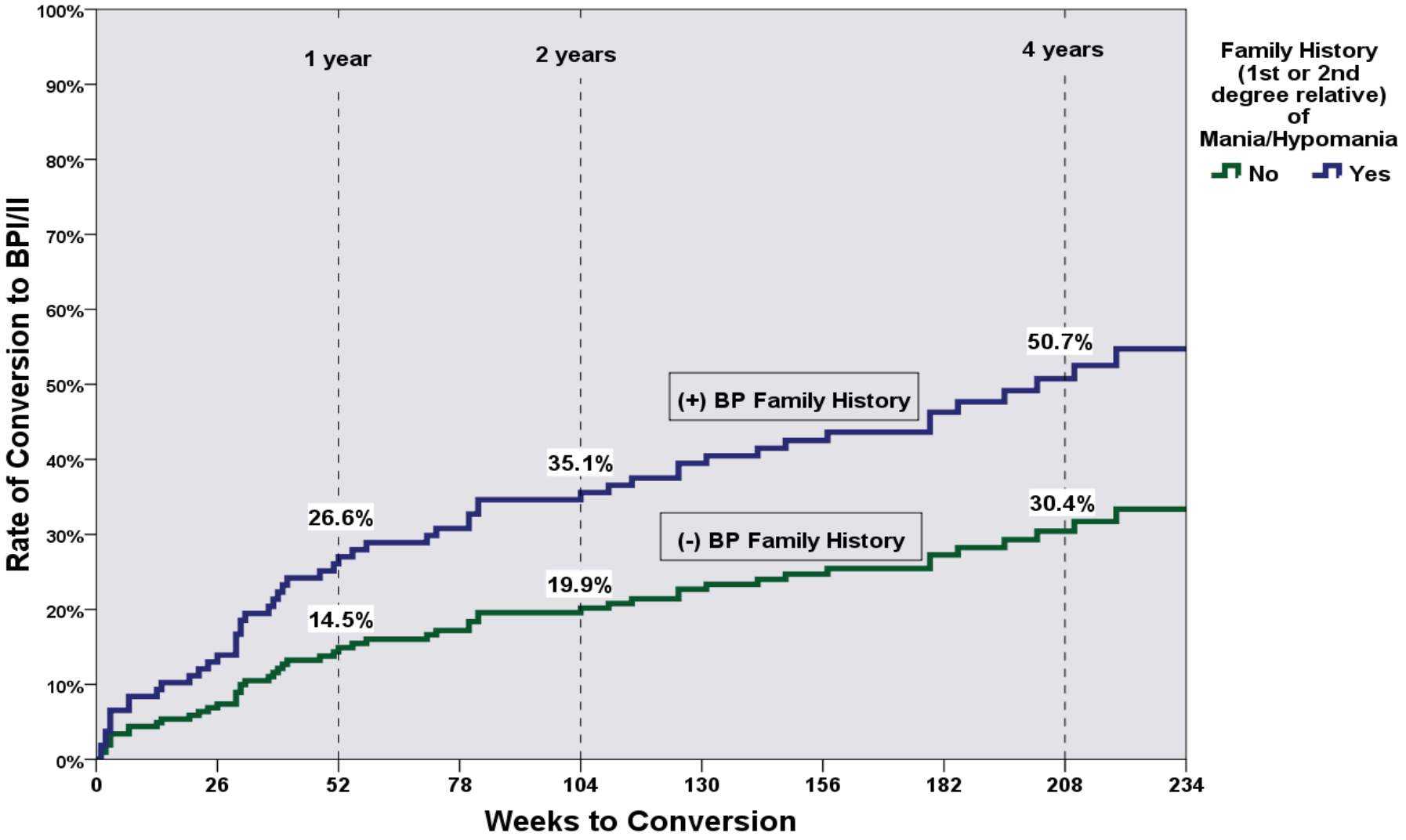
Diagnostic Challenge: Comparing Pediatric BD to ADHD



BD = bipolar disorder; ADHD = attention-deficit/hyperactivity disorder

Elmaadawi AZ, et al. *World J Psychiatry*. 2015;5(4):412-424.

Conversion from BD-NOS to BD-I/II Stratified by Family History of BD



Birmaher B, et al., *Arch Gen Psychiatry*. 2009;66(3):287-296.

Family Environment

- BD families with low cohesion and expressiveness
- BD families with low cohesion and organization, and high conflict

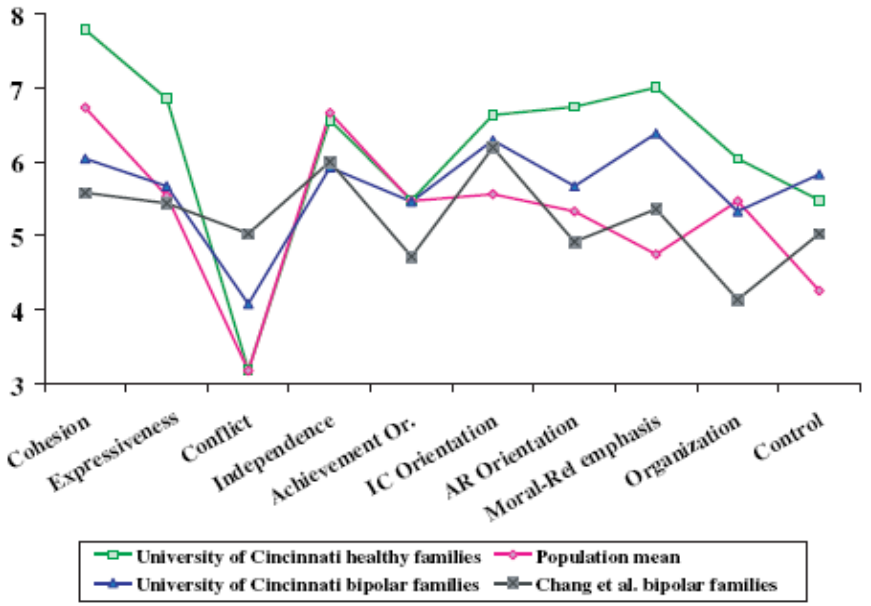


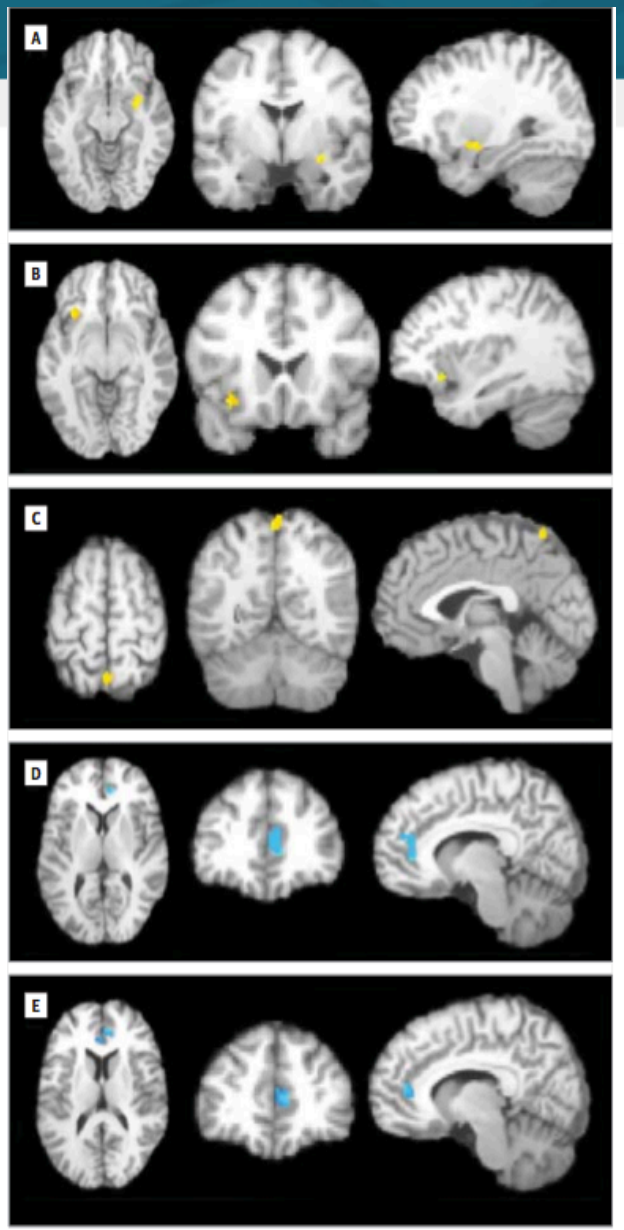
Fig. 1. Family Environment Scale (FES) subscale scores in bipolar (n = 24) and healthy families (n = 27), bipolar families from Chang et al. (12), and United States population means. Achievement Or = achievement orientation; IC Orientation = intellectual-cultural orientation; AR Orientation = active-recreational orientation; Moral Rel emphasis = moral religious emphasis.

Chang K, et al. *Am J Med Genet C Semin Med Genet.* 2003;123C(1):26-35.

Romero S, et al. *Bipolar Disord*. 2005;(6):617-622.

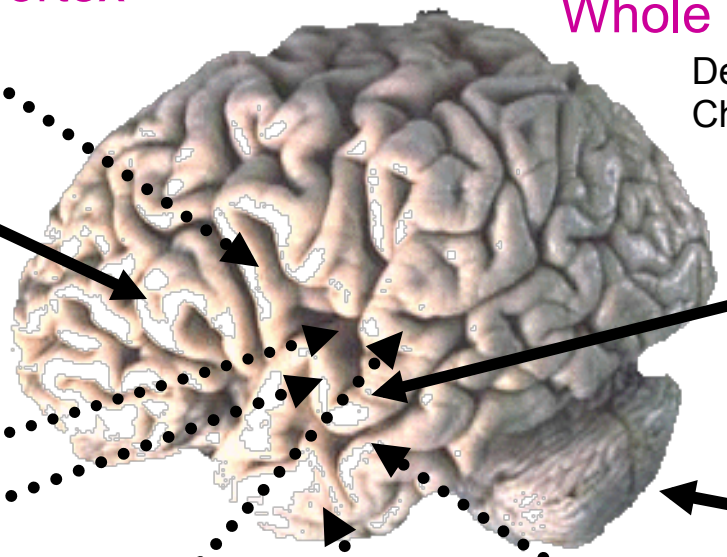
Bipolar Disorder in Children Looks Different from Adults

- Yellow indicates areas in the brain where youth with BD activate **MORE** than adults with BD (amygdala, inferior frontal gyrus, precuneus)
- Blue indicates areas in the brain where youth with bipolar disorder activate LESS than adults with bipolar disorder (anterior cingulate cortex)



Wegbreit E, et al., *Bipolar Disord*. 2015;17(5):471-485.

Structural Neuroimaging Studies in Pediatric Bipolar Disorder



Anterior Cingulate Cortex
Wilke, 2004 (↓)
Kaur, 2005 (↓)
Chiu, 2008 (↓)
Singh, 2012 (↓)

Prefrontal Cortex
Dickstein, 2005 (↓, DLPFC)
Sanches, 2005 (-)
Blumberg, 2006
(↓, VPFC, with age)
Najt, 2007 (↓, OFC, Males)

Corpus Callosum
Yasar, 2006 (-)

Striatum
DelBello, 2004 (↑Putamen)
Wilke, 2004 (↑Caudate)
Chang, 2005 (-)
Dickstein, 2005
(↓Nucleus accumbens)
Sanches, 2005 (-)
Ahn, 2007
(-,↑Nucleus accumbens)

Thalamus
DelBello, 2004 (-)
Chang, 2005 (-)
Frazier, 2005 (-)
Monkul, 2006 (-)

Amygdala
Chan, 2004 (↓)
DelBello, 2004 (↓)
Wilke, 2004 (↓)
Blumberg, 2005 (↓)
Chang, 2005 (↓)
Dickstein, 2005 (↓)
Frazier, 2005 (↓)

Hippocampus
Blumberg, 2003 (-/↓)
DelBello, 2004 (-)
Chang, 2005 (-)
Frazier, 2005 (↓)
Bearden, 2008 (↓)

Cerebellum
Monkur, 2008 (-/↓)

Superior Temporal Gyrus
Chen, 2004 (↓)

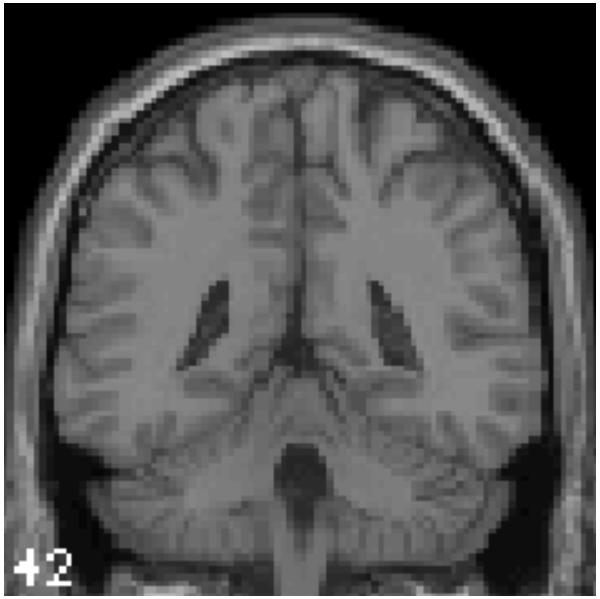
Whole Brain
DelBello, 2004 (↓); Frazier, 2005 (↓)
Chang, 2005 (-)

(-) = negative result; (↓) = decreased volume; (↑) = increased volume; (-/↓) = trend.

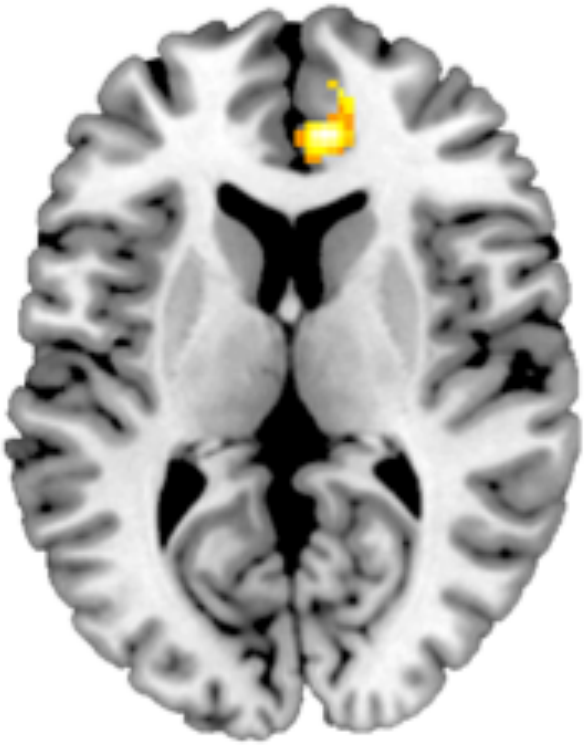
Who has bipolar disorder? Who will develop bipolar disorder?

Family history of bipolar disorder is a clear risk factor.

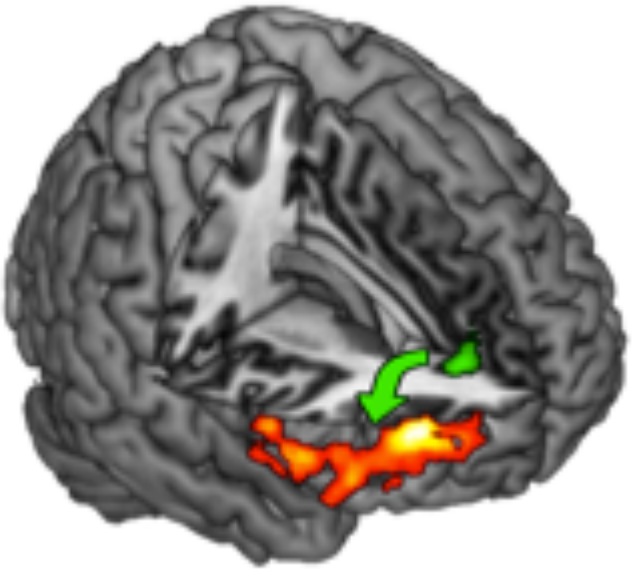
Some Children at High-risk for BD Show Brain Patterns of Vulnerability



Low-risk brain
(no family history)



High-risk brain
activity

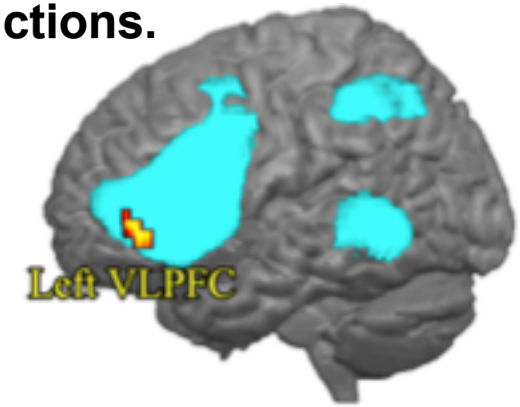


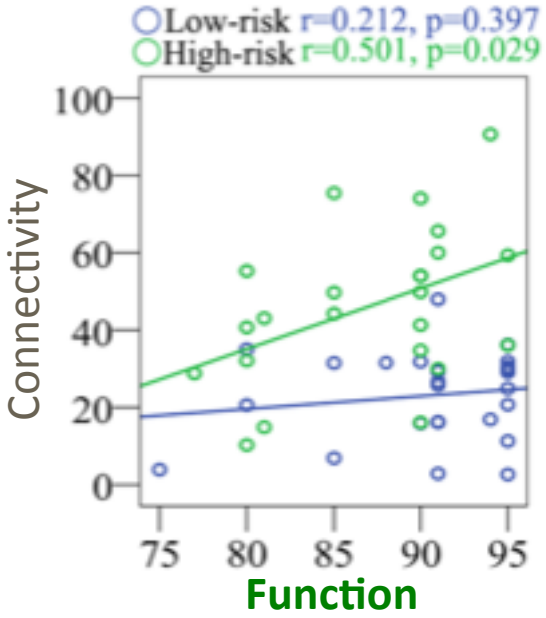
High-risk brain
connectivity

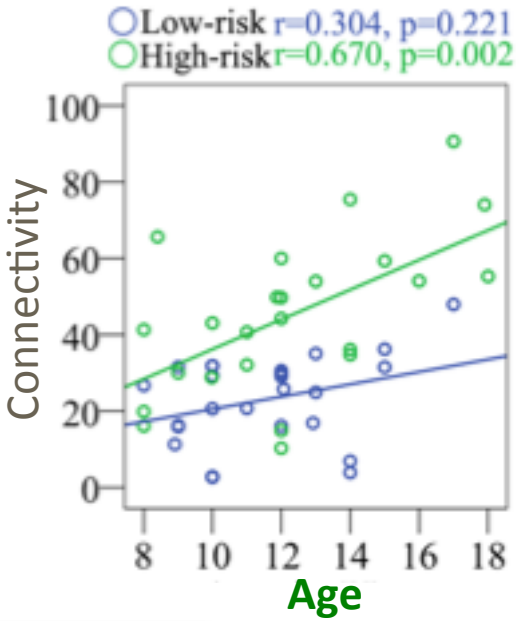
Singh MK, et al., JAMA Psychiatry 2014;71(10):1148-1156.

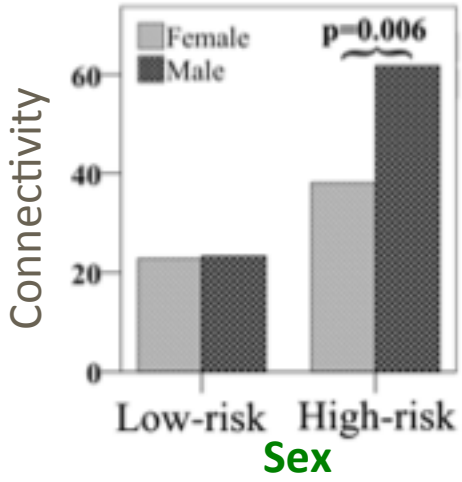
Some Children at High-risk for BD Show Brain Patterns of Resilience

Increased connections between the Ventrolateral Prefrontal Cortex (VLPFC) and the brain network that controls executive functions.



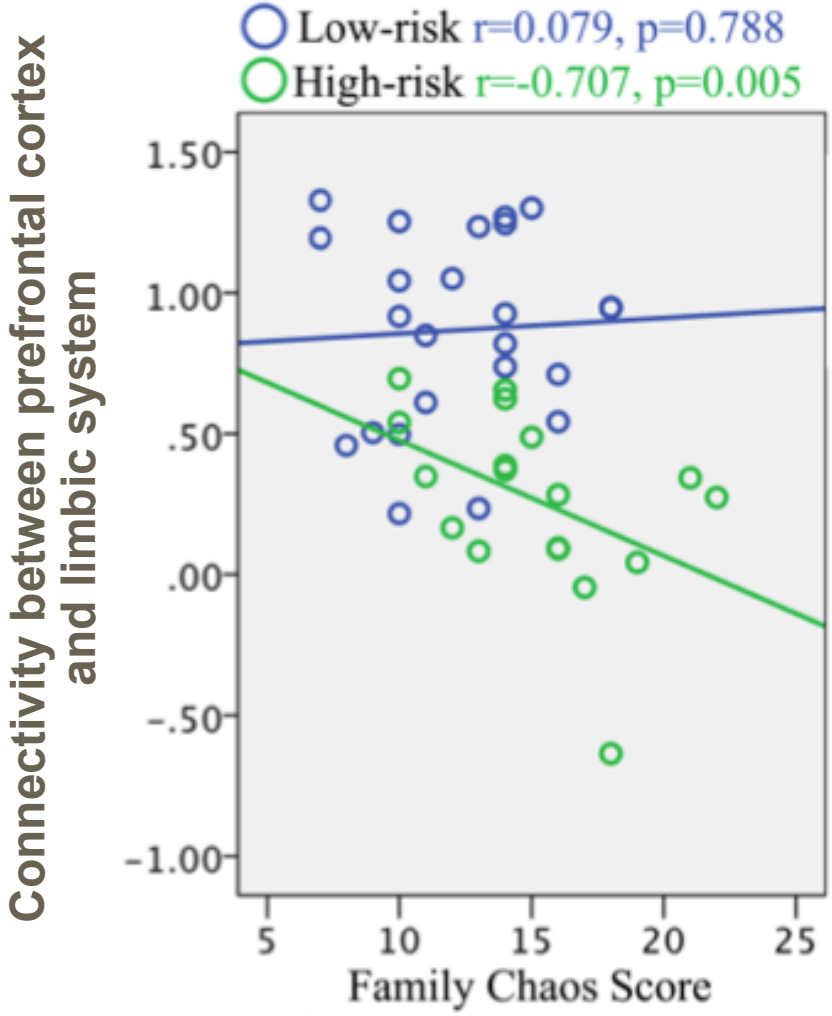






Singh et al. *Bipolar Disorders*, 2014;16(7):678-689.

Family Chaos is Associated with Disconnectivity in the Brain



Singh et al., *Bipolar Disorders,* 2014;16(7):678-689.

Treatment Challenge #1: How Should We Treat Depressed Youth Who are at High-Risk for BD?

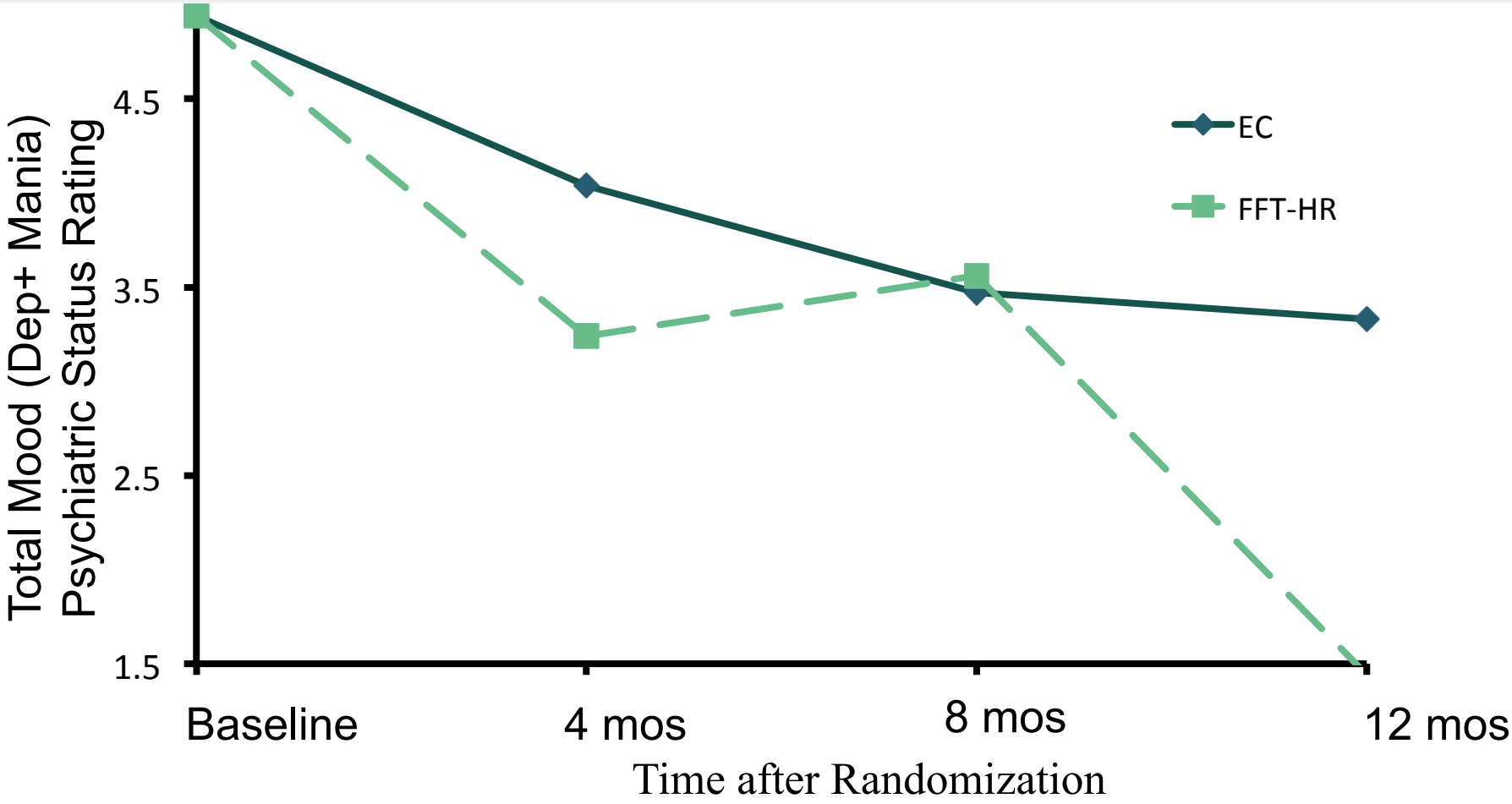
Well…definitely therapy first if possible… then…

- SSRI?
- Buproprion?
- Lamotrigine?
- Lithium?
- Quetiapine?

Psychotherapy Studies in High-Risk Bipolar Offspring

Authors	Sample Population &Size	Intervention	Design	Outcome
Miklowitz et al., 2011	13 children with a parent with Bipolar I or II Disorder and with active mood symptoms	Family Focused Therapy for Youth at High-Risk for Bipolar Disorder (FFT-HR)	Open, pilot 12 sessions over 4 mos	Improved depression, hypomania, and psychosocial functioning scores
Miklowitz et al., 2013	40 youth with BD-NOS, MDD or cyclothymia with a first degree relative with Bipolar I or II and active mood symptoms	12 sessions of Family focused therapy Youth at High-Risk for Bipolar Disorder (FFT-HR) or 1-2 sessions of Education Control (EC)	RCT of FFT-HR vs EC	More rapid recovery from initial mood symptoms, more weeks in remission, and a more favorable trajectory of YMRS scores over 1 year than youth in EC.
Goldstein et al., 2014	13 adolescents with a first degree relative with BD; 50% healthy at baseline, 50% with internalizing/ externalizing disorders	Interpersonal and social rhythm therapy (IPSRT)	Open, pilot 12 sessions over 6 months	High satisfaction but only attended about half of scheduled sessions due to parental BD illness severity. Less weekend sleeping in and oversleeping with treatment.
Cotton et al., 2015	10 high risk offspring with at least 1 bipolar parent and with anxiety symptoms	Mindfulness based cognitive therapy for children (MBCT-C)	Open, pilot 12 week	Reduced clinician-rated anxiety and youth-rated trait anxiety; Increased parent-rated emotion regulation; Increased mindfulness associated with decreased anxiety

Children at Risk for BD: A-LIFE Total Mood Scores Over 1 Year in FFT-HR and EC (N = 39)

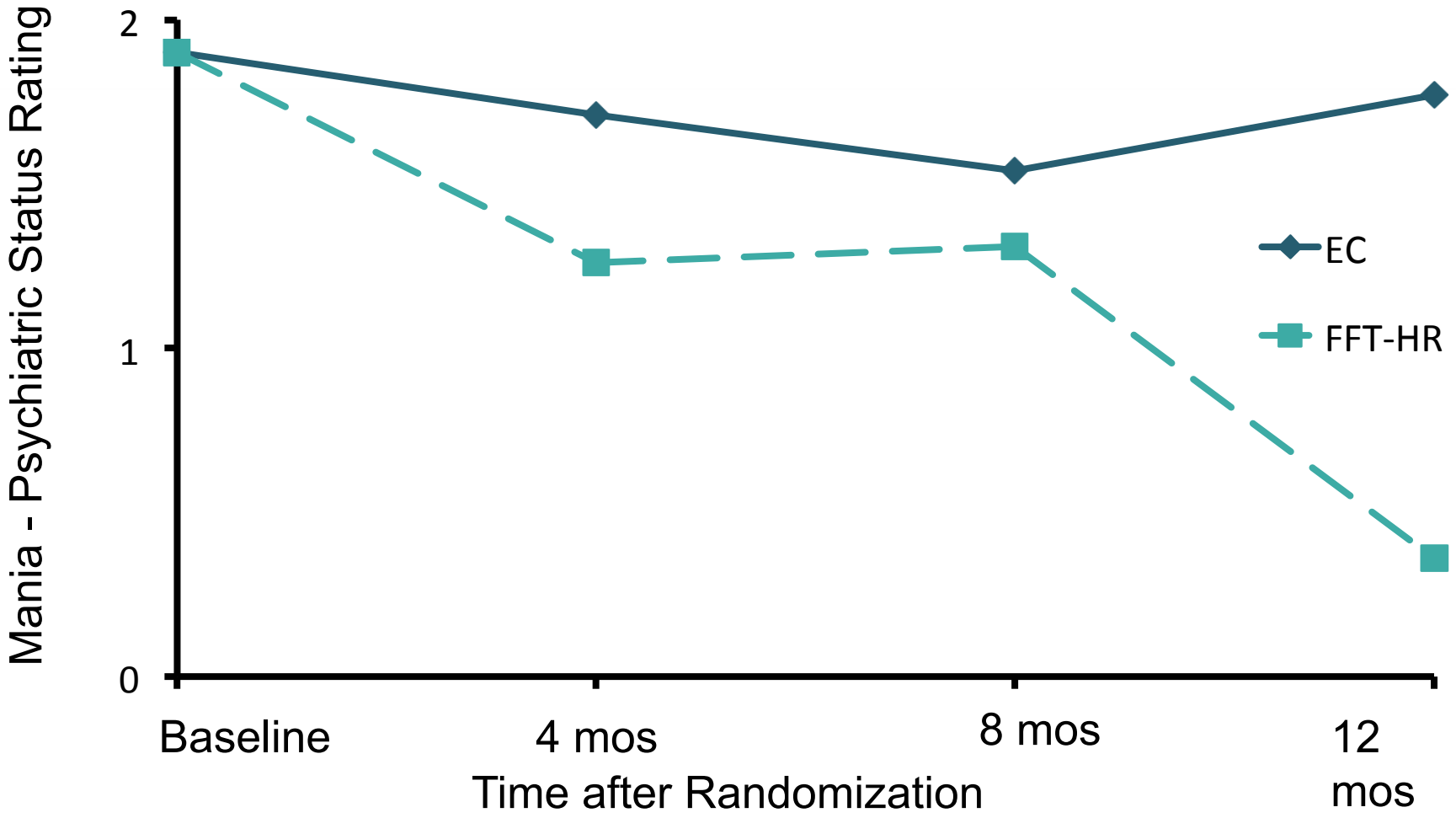


Treatment by time interaction, F = 14.23, *P* < .0001

EC = Educational control; FFT = family-focused therapy

Miklowitz DJ, et al. *Bipolar Disorders*, 2011;13(1):67-75.

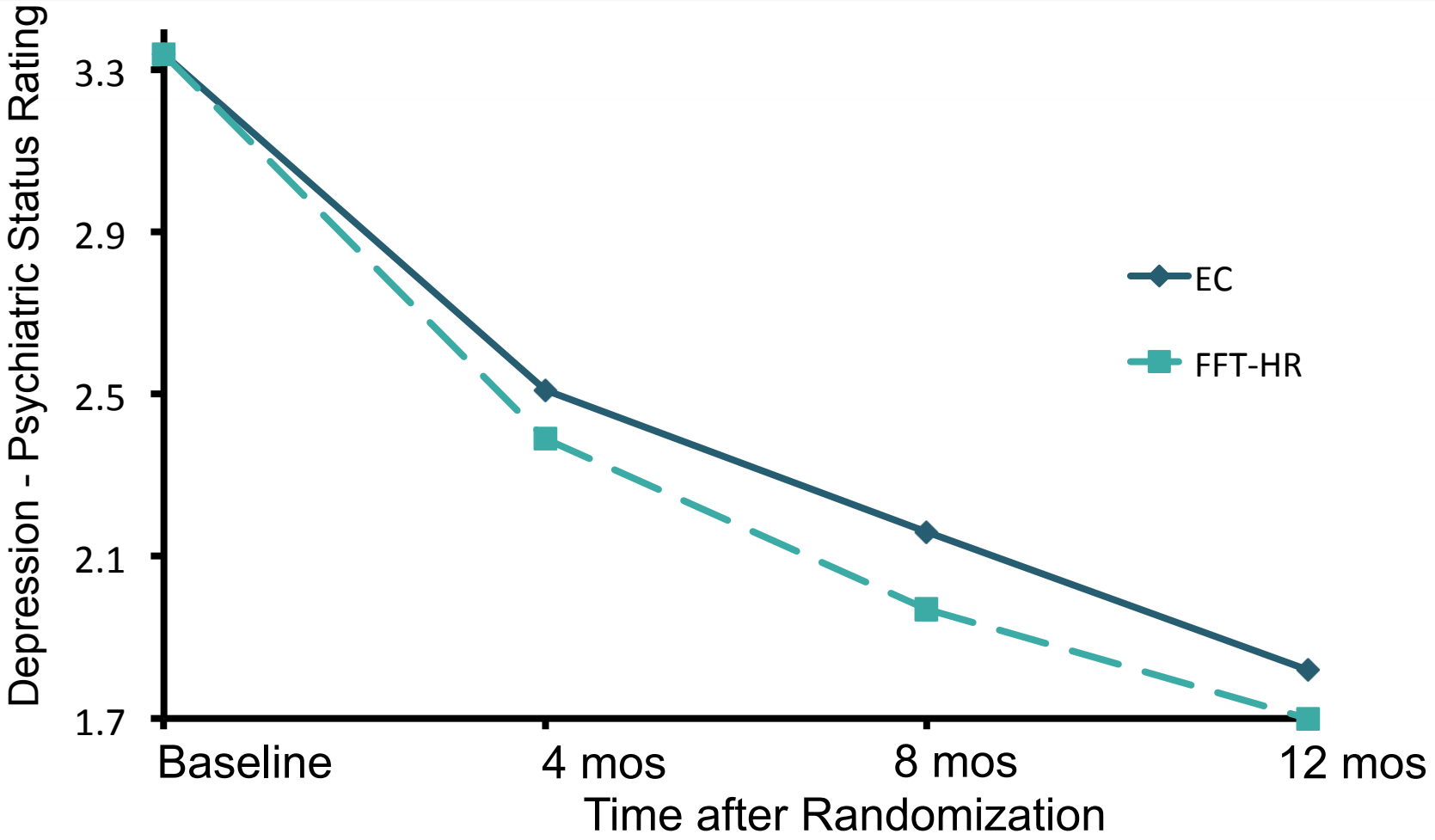
Children at Risk for BD: A-LIFE Mania Scores Over 1 Year in FFT-HR and EC (N = 39)



Treatment by time interaction, F = 24.83, *P* < .0001

Miklowitz DJ,et al. *Bipolar Disorders*, 2011;13(1):67-75.

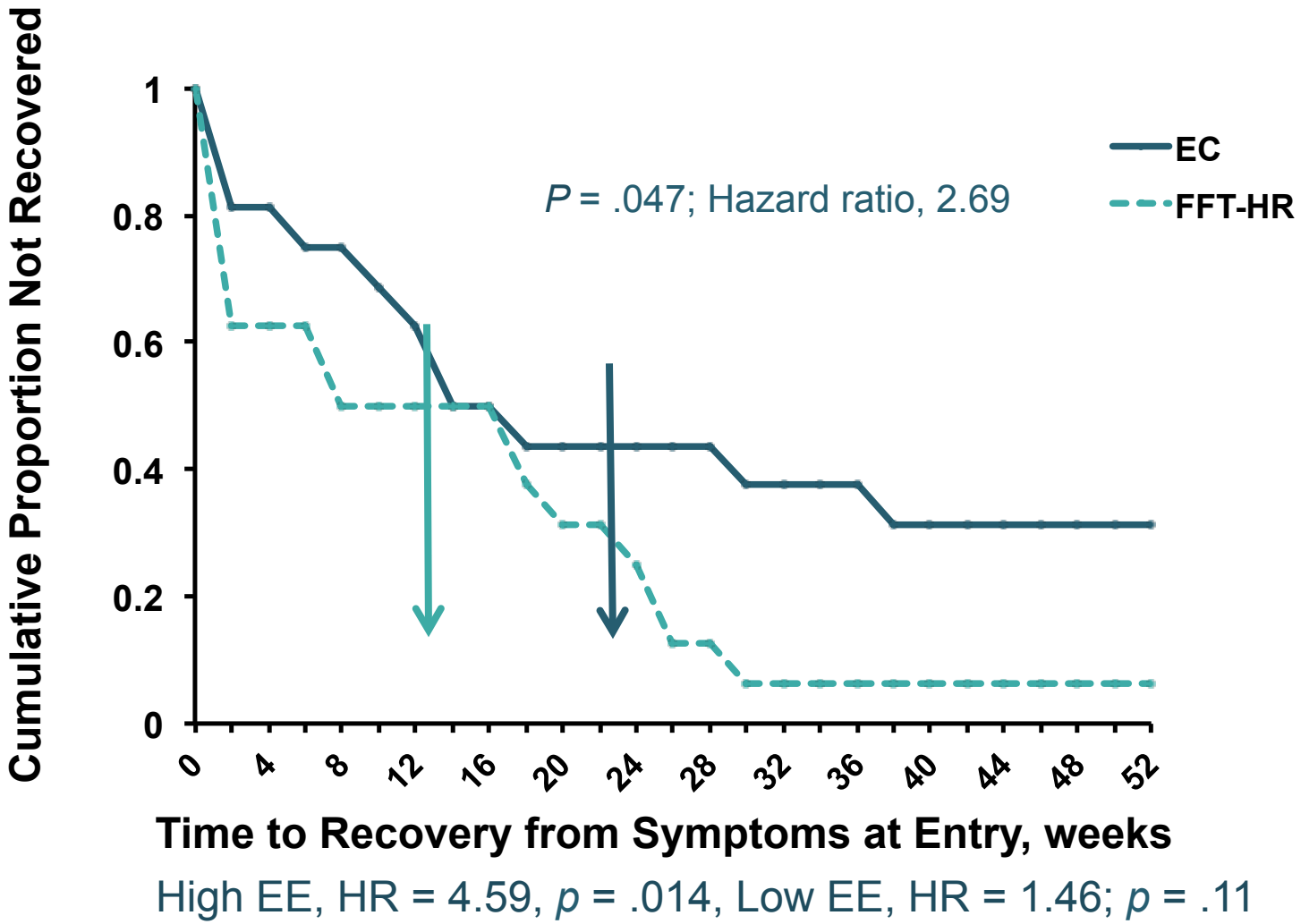
Children at Risk for BD: A-LIFE Depression Scores Over 1 Year in FFT-HR and EC (N = 39)



Treatment by time interaction, F = 2.8, *P* = .039

Miklowitz DJ,et al., *Bipolar Disorders*, 2011;13(1):67-75. PMID: 21320254.

Family Intervention Accelerates Recovery from Index Episodes in Youth at Risk for BD

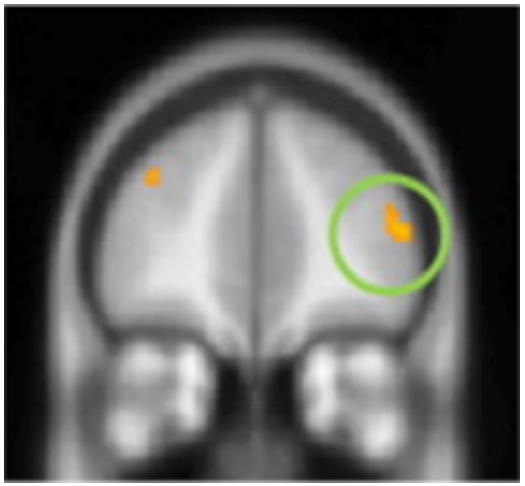


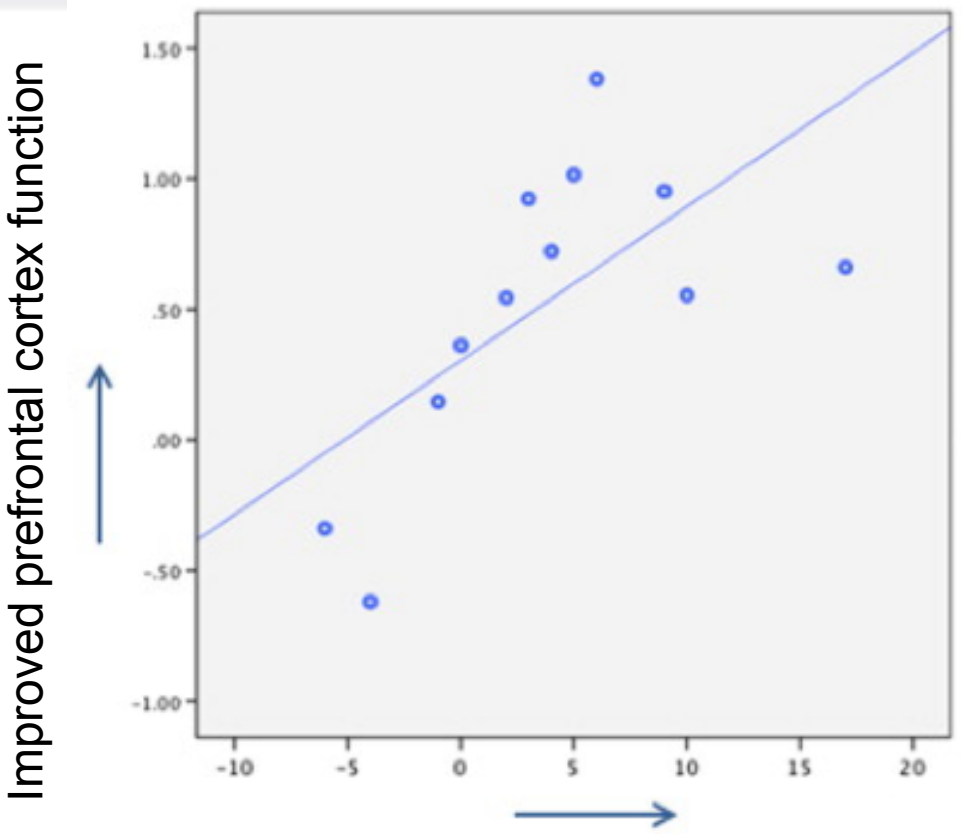
High EE, HR = 4.59, *p* = .014, Low EE, HR = 1.46; *p* = .11

EC = Educational control; FFT = family-focused therapy

Miklowitz DJ, Schneck CD et al. *J Am Acad Child Adolesc Psychiatry*. 2013;52(2):121-131.

FT Improves Mood and Prefrontal Cortex Function





Garrett AS, et al. *Prog Neuropsychopharmacol Biol Psychiatry*, 2015;56:215-220.

Mindfulness-Based Cognitive Therapy for Anxiety in BD Offspring

TABLE 2. Changes in mindfulness, emotion regulation, and anxiety before and after mindfulness-based cognitive therapy intervention

Variables	Before intervention		After intervention		Median change	*P*-value
	Mean	Range	Mean	Range		
Mindfulness (CAMM; *y*)	21.7 ± 8.5	9–39	24.0 ± 10.7	10–39	0.5	0.36
Emotional lability (ERC; *p*)	32.2 ± 4.1	27–40	29.0 ± 7.2	16–41	−6–4	0.08
Emotion regulation (ERC; *p*)	22.8 ± 3.8	15–28	25.1 ± 3.5	20–31	2.5	0.05
Emotion regulation composite (ERC; *p*)	68.9 ± 6.9	56–76	74.4 ± 9.5	65–92	5.0	0.05
Clinician-rated anxiety (PARS; *c*)	11.1 ± 2.3	8–15	4.3 ± 2.0	2–9	−–9	<.01
Child-rated state anxiety (STAI; *y*)	32.5 ± 6.4	22–41	31.8 ± 7.4	20–44	−0.5	0.34
Child-rated trait anxiety (STAI; *y*)	41.8 ± 7.6	25–50	34.0 ± 11.4	20–60	−6.4	0.03

Note. Means are shown ± their standard deviations; *P*-values are one-sided Wilcoxon signed rank test statistic for alpha = 0.05.
c, clinician rated; CAMM, Child and Adolescent Mindfulness Measure; ERC, Emotion Regulation Checklist; *p*, parent rated; PARS, Paediatric Anxiety Rating Scale; STAI, State-Trait Anxiety Inventory; *y*, youth rated.

Cotton S, et al. *Early Intervention in Psychiatry*, 2015; Jan 13. [Epub ahead of print].

Mindfulness-Based Cognitive Therapy for Anxiety in BD Offspring

TABLE 6. After-intervention parent feedback

Question	Response
Most notable changes in children after intervention	'My son is controlling anger and emotions more.' '(My daughter has) more patience'
Most helpful aspect of the programme	'She (my daughter) enjoys talking with other girls who go through the same thing.' 'Showing the children the difference between judgments and facts and making them understand it.' 'Teaching him (my son) how to relax.'
Most important thing their child took from the programme	'A different aspect on things; she (my daughter) is a little more easy-going and patient.' 'Trying to remember to learn to breathe when you're upset.'

Cotton S, et al., *Early Intervention in Psychiatry*, 2015; Jan 13. [Epub ahead of print].

Neural Effects of Mindfulness-based Cognitive Therapy for Anxiety in BD Offspring

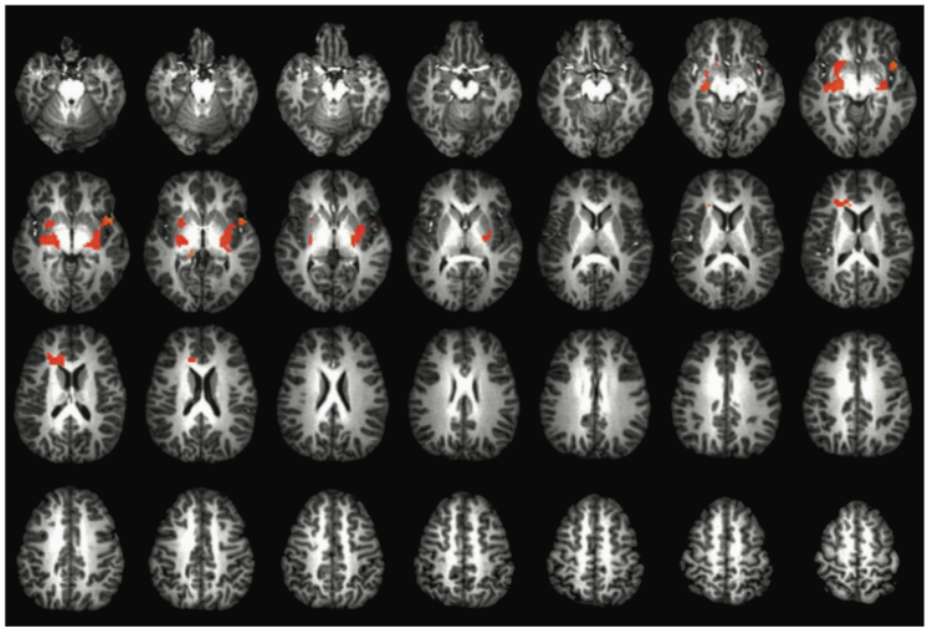


FIG. 1. Treatment-related changes in activation following mindfulness-based cognitive therapy (MBCT). Increased activation was observed in the bilateral insula and left thalamus as well as in the left anterior cingulate cortex following treatment with MBCT ($p < 0.05$, uncorrected; $p < 0.005$ corrected; cluster size, 37 voxels). A color version of this figure is available in the online article at www.liebertpub.com/cap.

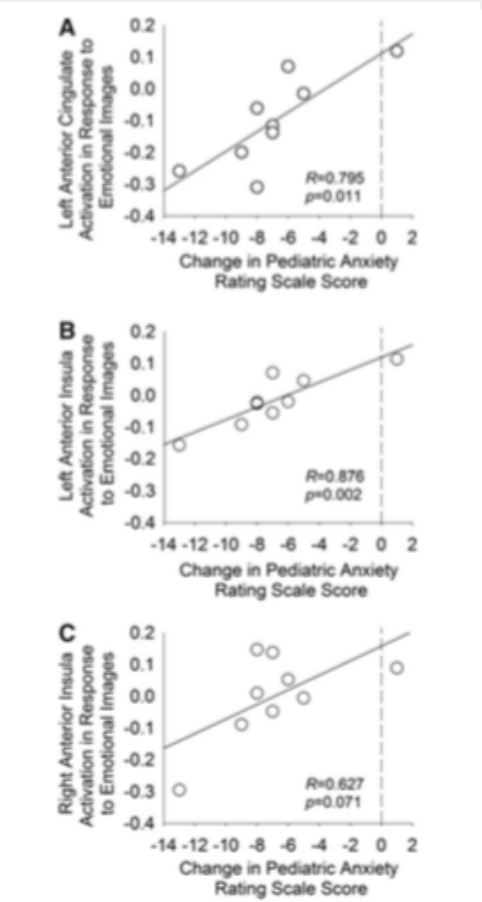


FIG. 2. Relationship between region of interest (ROI) activation in response to emotional images and anxiety symptom severity. Correlations between baseline activation in each ROI identified in the voxelwise analysis, and changes in symptom severity are shown for the left anterior cingulate (**A**) and for the insula, bilaterally (**B,C**).

Strawn JR, et al., *J Child Adolesc Psychopharmacol*. 2016;26(4):372-379.

Promoting Resilience to Optimize Outcome

- Know your patient's symptoms and triggers
- Promote healthy diet, physical exercise, and regular sleep
- Teach patients to train their brains – mindfulness
- Have them develop a plan to manage stress
- Preventive treatment continues for at least 2 years
- Combined medication(s) and psychotherapy often necessary
- whatmeds.stanford.edu

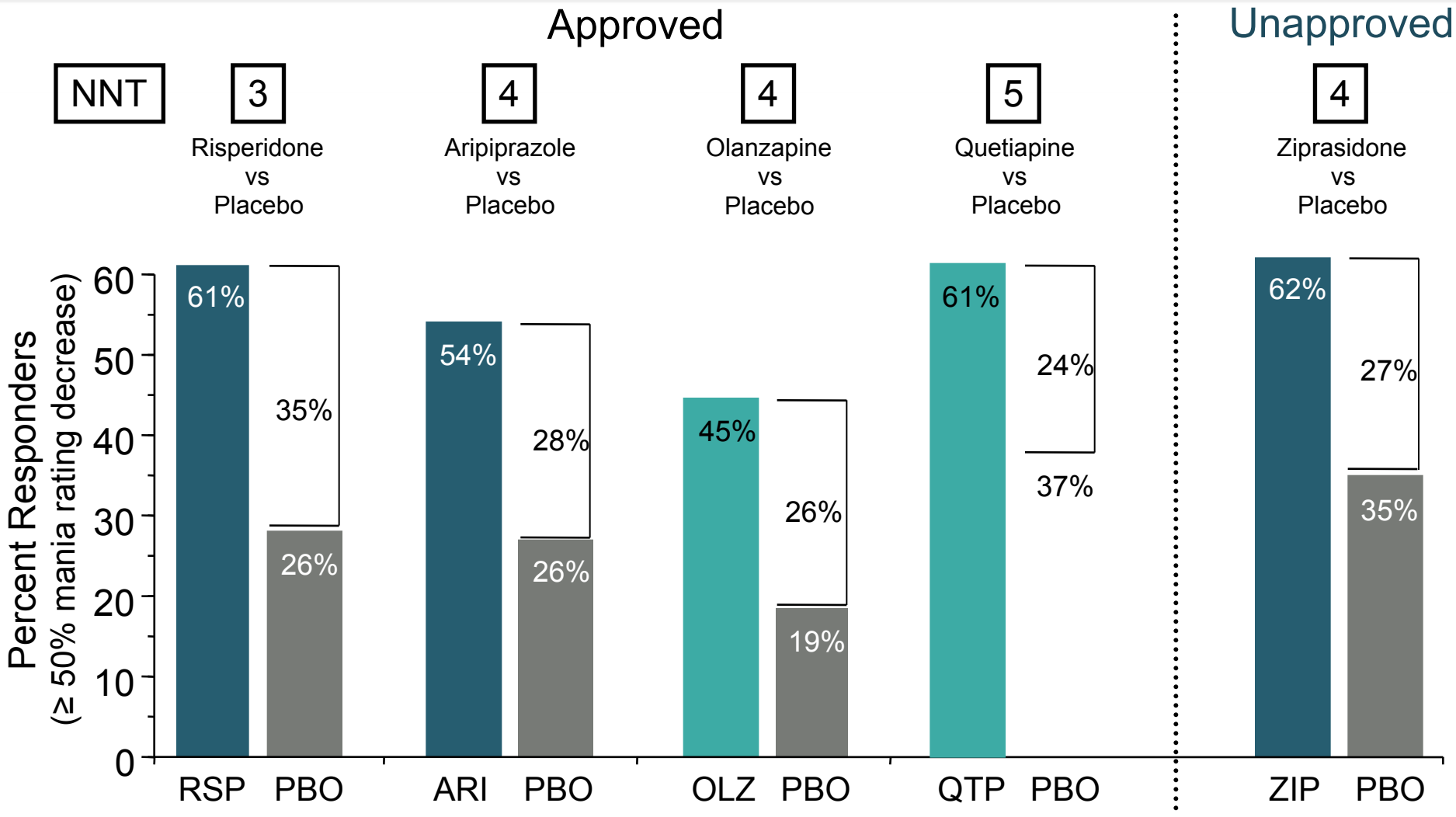
Treatment Challenge #2: Few Approved Agents for Acute and Long-Term Treatment of Pediatric BD

Acute Mania		Acute Depression		Longer-Term	
Year	Drug	Year	Drug	Year	Drug
1970	Lithium[a]	2014	OlanzapineFluoxetine[b]	1974	Lithium[a]
2007	Risperidone[b]			2008	Aripiprazole[(b->e)]
2008	Aripiprazole[b,(*->e)]				
2009	Quetiapine[b]				
2009	Olanzapine[c]				

*Adjunctive (and monotherapy);
[a]Age ≥ 12-17; [b]Age 10-17;
[c]Age 13-17;
[(->e)]Extrapolated indication

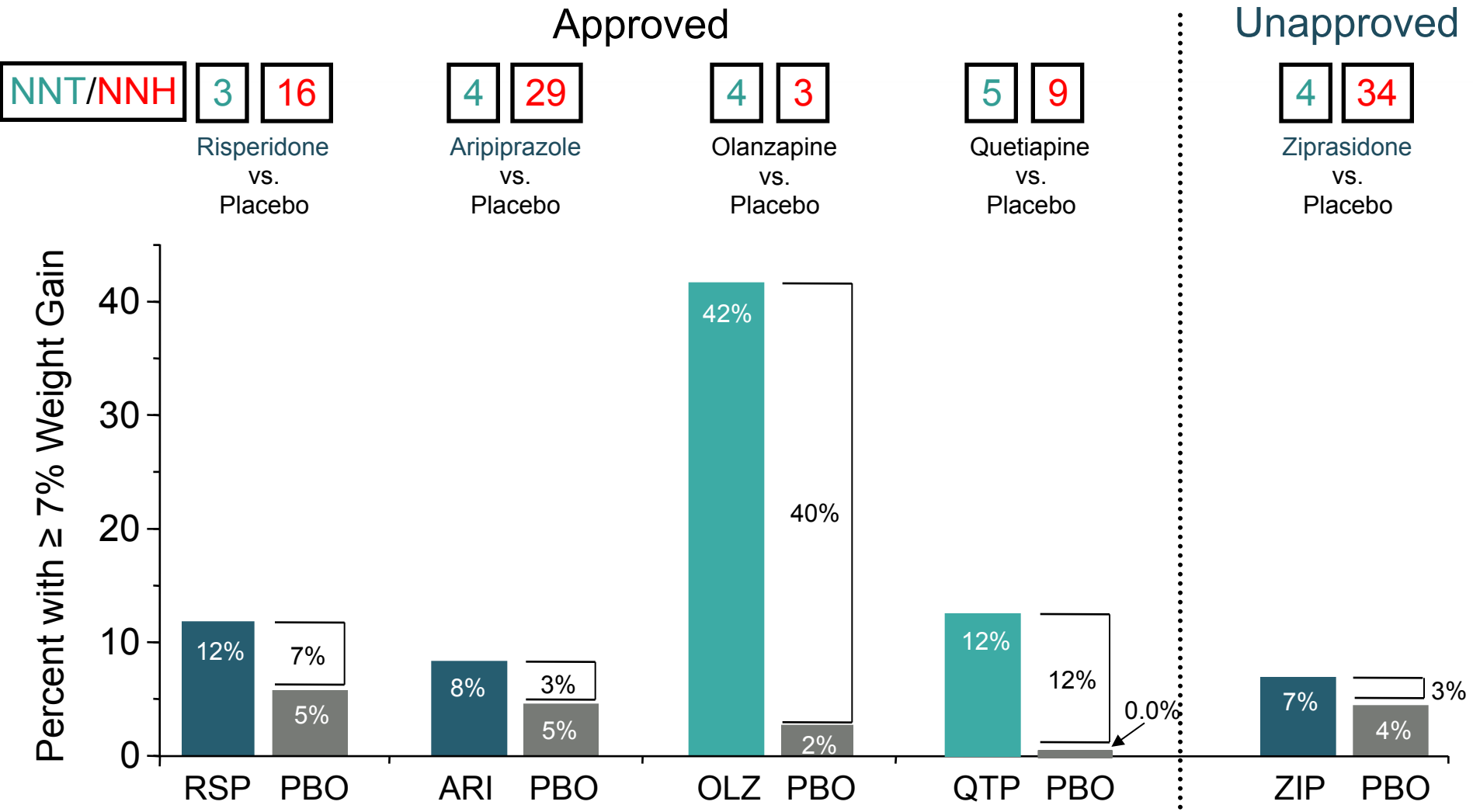
Ketter TA, Ed. *Handbook of Diagnosis and Treatment of Bipolar Disorders*. Arlington, VA: American Psychiatric Publishing, Inc; 2010.

Overview of Pediatric Acute Mania Studies Number Needed to Treat for Response, Rates



Adapted from Ketter TA (ed). Handbook Diag & Treat Bipolar Disord, Am Psych Pub, Inc., Washington, DC, 2010.

Overview of Pediatric Acute Mania Studies Numbers Needed to Treat and Harm, ≥ 7% Weight Gain Rates



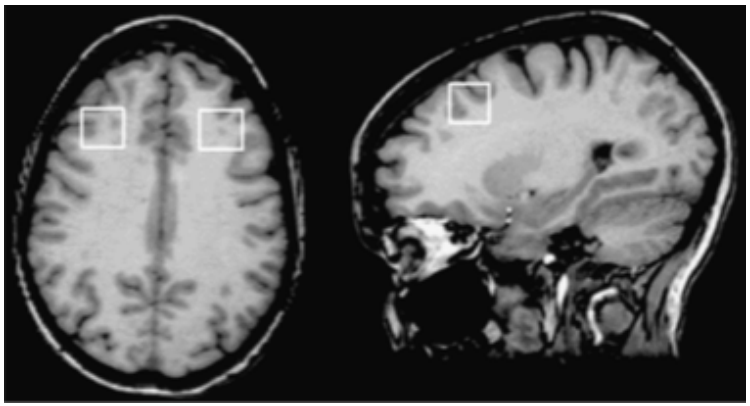
Adapted from Ketter TA (ed). Handbook Diag & Treat Bipolar Disord, Am Psych Pub, Inc., Washington, DC, 2010.

Pharmacological Studies in High-Risk Bipolar Offspring

Authors	Sample size and Population	Drug	Design	Outcome
Geller et al., 1998	30 Prepubertal (mean age 10.7 years) depressed children; 80% had Family History of BP-I or mania (40% of parents had BP-I or mania); and 20% with loaded or multigenerational MDD but no mania.	Lithium (N = 17) vs Placebo (N = 13)	Double-blind placebo controlled	No difference between active and placebo groups.
Chang et al., 2003	24 (6-18 year old) youth with mood and behavioral disorders, at least mild affective symptoms, and at least one parent with BD.	Divalproex	12-week Open-label	78% response rate. Well tolerated with no discontinuations due to adverse effects.
Findling et al., 2007	56 symptomatic youth (ages 5-17) with bipolar disorder not otherwise specified (NOS) or cyclothymia who also had at least 1 biological parent with bipolar illness.	Divalproex (N = 29) vs Placebo (N = 27)	Double-blind placebo controlled	No difference in survival time for discontinuation for any reason (p = .93) or due to a mood event (p = .55). Both groups had improved mood sx and psychosocial function.
DelBello et al., 2007	20 symptomatic adolescents (12-18 years old) at high risk for developing BD by virtue of having at least one first-degree relative with BD I.	Quetiapine	12-week single blind open label trial	87% responded (CGI-I < or = 2) at week 12. Decreased YMRS and CDRS scores from baseline to endpoint.
Findling et al., 2009	9 children (7-16 years old) with MDD and at least one parent with BD	Paroxetine vs Paroxetine + Divalproex	Open-label	Neither treatment was effective. 50% had mania symptoms.

Lingler J, et al. *J Child Adolesc Psychopharmacol*. 2008 Dec;18(6):615-21.

Neural Effects of Pharmacological Interventions in High-Risk Youth



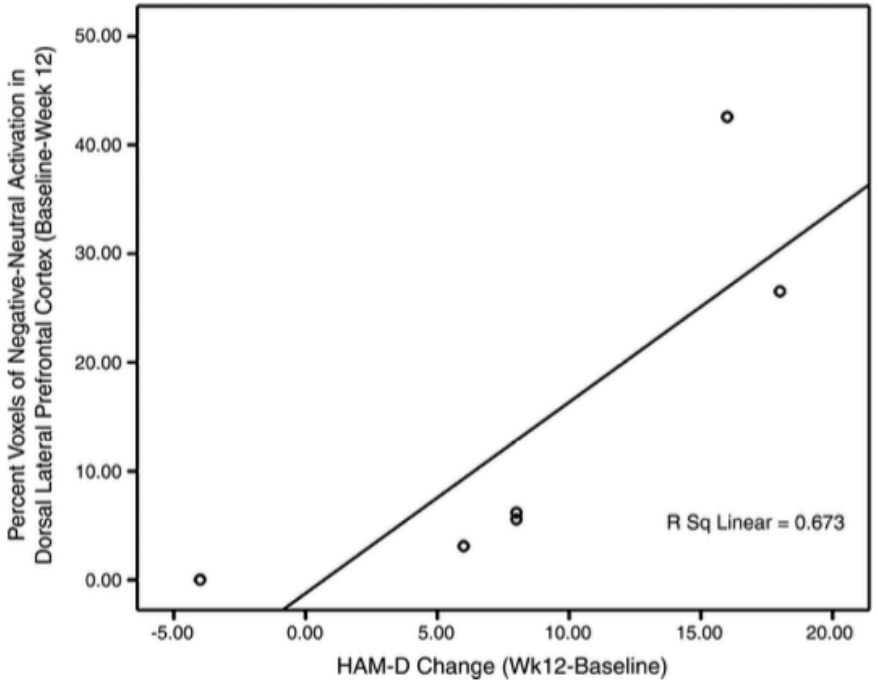


FIG. 3. Change in dorsolateral prefrontal cortex (DLPFC) activation versus change in Hamilton Rating Score for Depression (HAM-D) score in subsyndromal bipolar disease (BD) subjects.

Chang K, et al., *J Child Adolesc Psychopharmacol*. 2009;19(1):51-59.

Treatment Challenge #3: Certain Youth are Prone to Adverse Events with Antidepressants

- Children with BD and depressive symptoms referred to specialty clinic are 4x likely to improve with SSRI treatment, but 7x likely to become manic[1]
- 44% of outpatients evaluated at a mood disorders clinic with antidepressant-induced mania (AIM) and 14% with new-onset suicidal ideation[2]
- HMO database: most likely age group to switch from MDD to BD after starting SSRI was 10-14 years old[3]
- In ~4250 Medicaid enrolled 6-18 year old patients with bipolar depression both antidepressant monotherapy and polytherapy exhibited higher risk of manic switch than their alternatives[4]

[1]Biederman J et al. *J Child Adolesc Psychopharmacol*. 2000;10(3):185-192.; [2]Faedda GL et al. *J Affect Disord* 2004;82(1):149-158.; [3]Martin A et al. *Arch Pediatr Adolesc Psychopharmacol* . 2004;158(8): 773-780. [4]Bhowmik et al., *J Child Adolesc Psychopharmacology*. 2014;24(10):551-561.

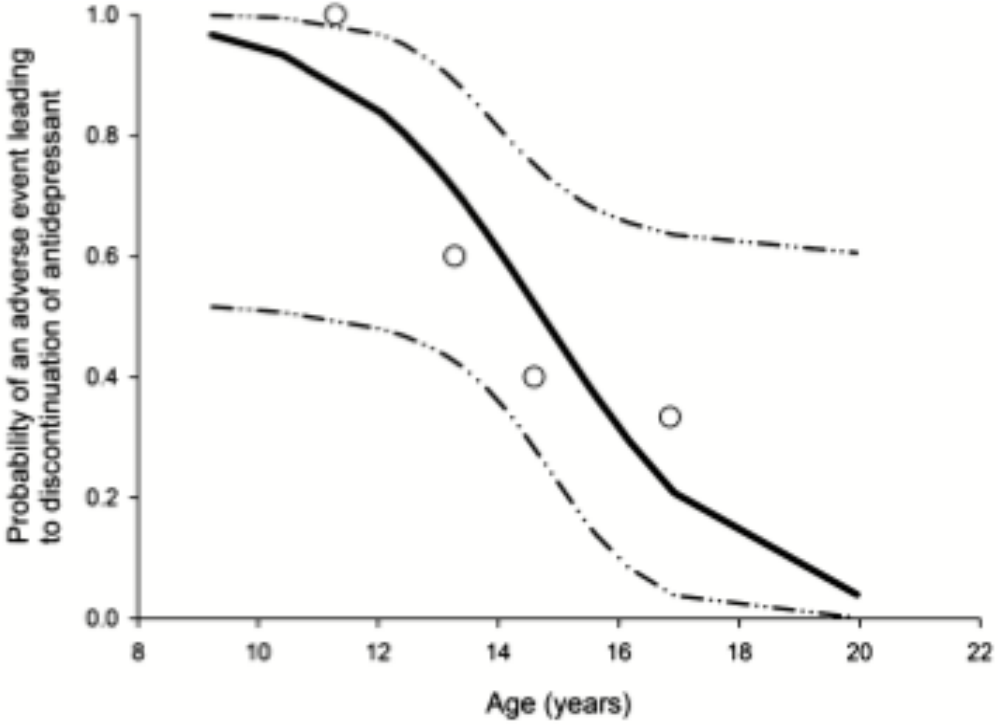
Mania in SSRI Trials in Youth

- At least 29 published case reports describe pediatric patients with treatment emergent mania or hypomania when exposed to SSRIs
- Pooled together these studies report hypomanic or manic symptoms that appear any time between two weeks to one year after initial SSRI exposure
- In 21% of such patients represented in these studies, there was a family history of BD

Goldsmith M, et al. *Paediatr Drugs.* 2011;13(4):225-243.

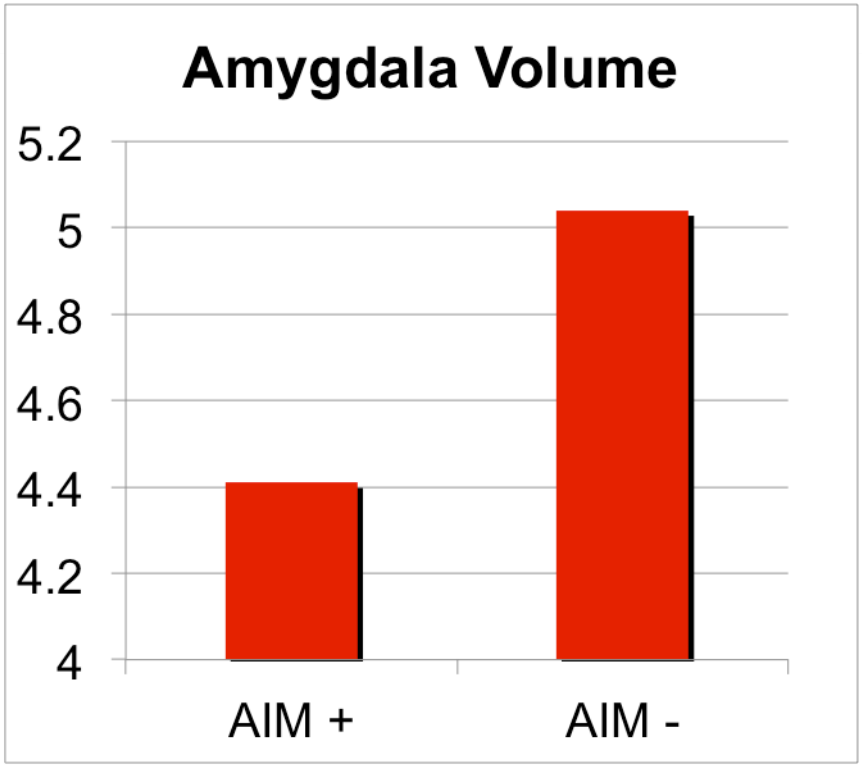
Younger High-Risk Youth are More Likely to Have to Discontinue an Antidepressant

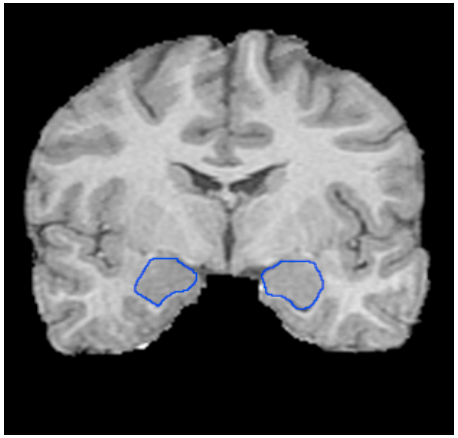
The probability and 95% confidence intervals of antidepressant-related adverse events leading to discontinuation in younger versus older high-risk patients ($p < .02$)



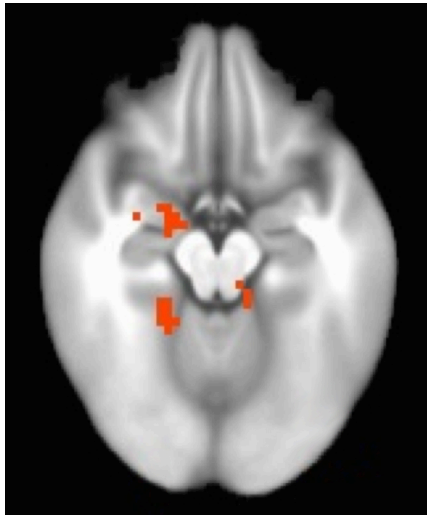
Strawn JR et al. *Bipolar Disord*. 2014;16(5):523-530.

Aberrant Amygdala Structure and Function in High Risk Youth Exposed to Antidepressants





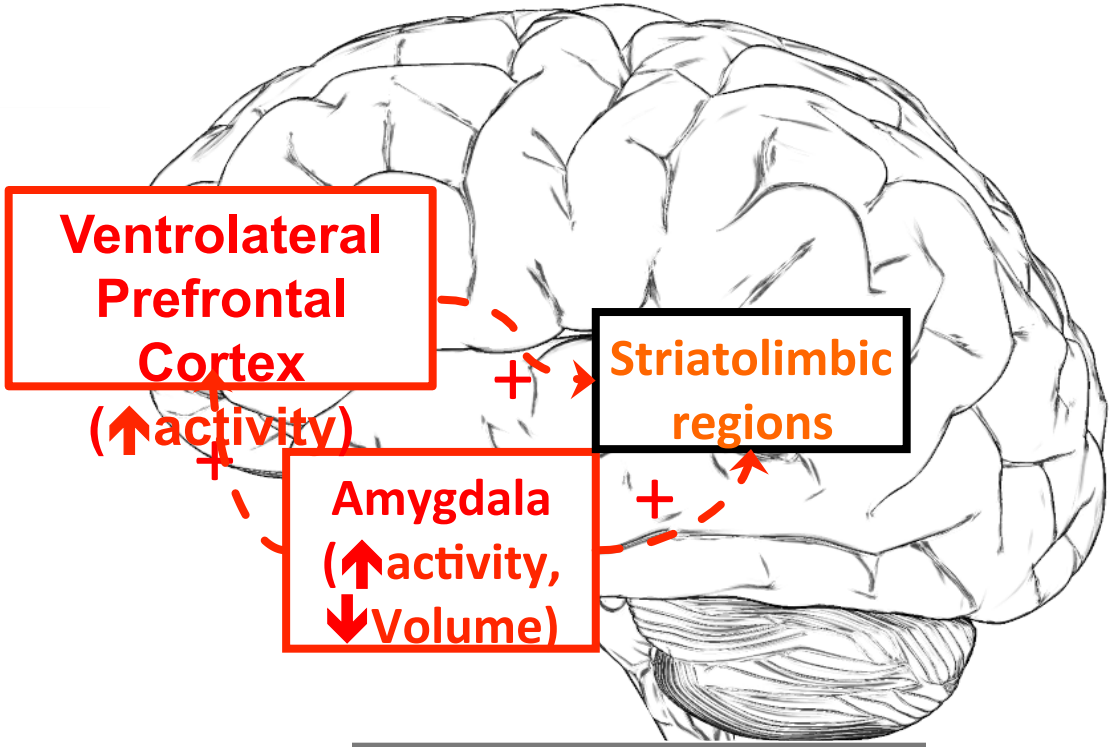
Reduced amygdala volume in high risk youth with antidepressant-related mania-like symptoms
(t = 2.9 *p* = .01)



Amygdala hyperactivity during emotion processing in high risk youth with with antidepressant-related mania-like symptoms
(*p* = .05, FWE-corrected)

Strawn JR et al. *Bipolar Disord*. 2014;16(5):523-530.

Neural Mediators of Antidepressant-Related Adverse Events



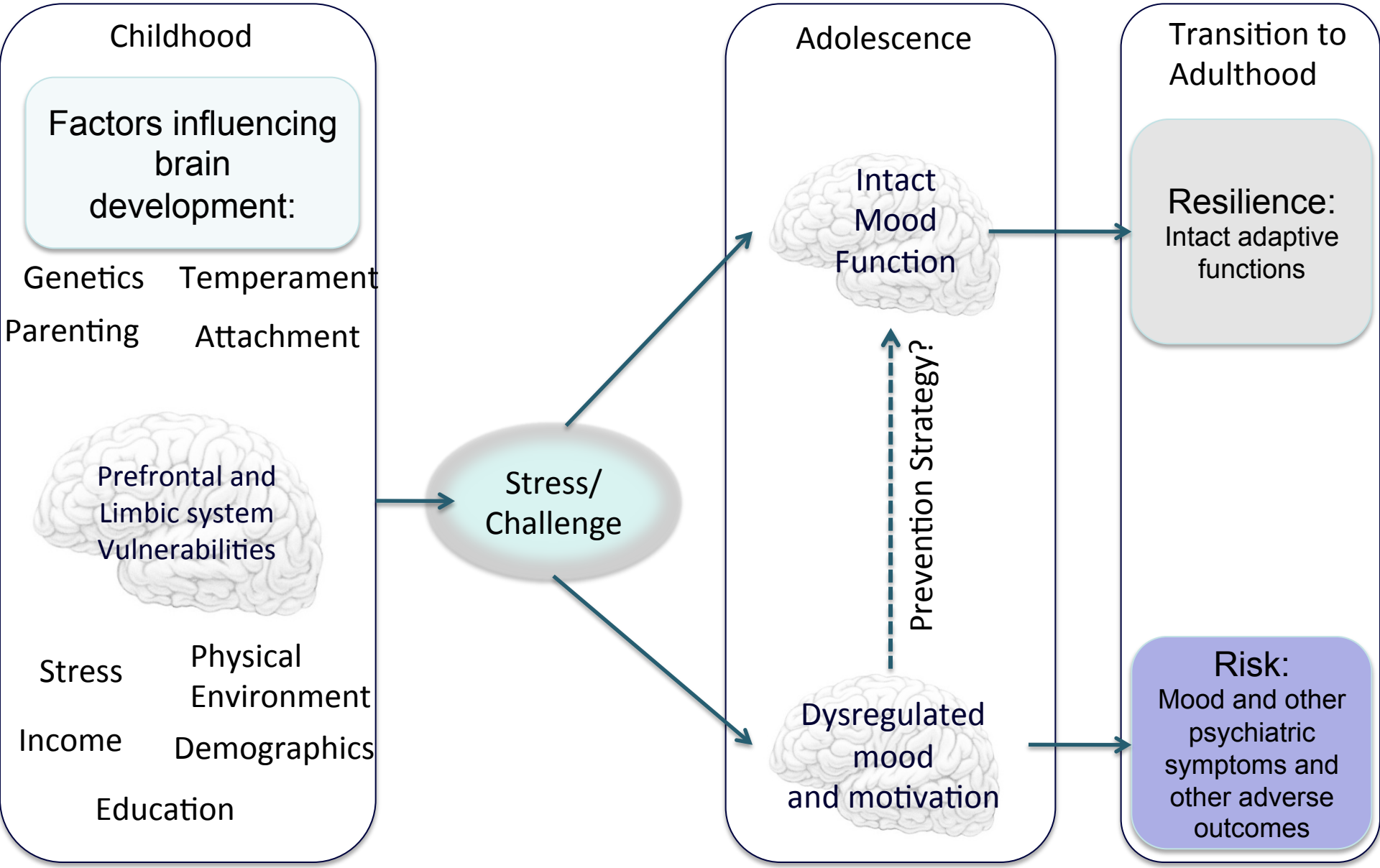
Antidepressant (MED/No MED) → Change in Neural Circuitry → Antidepressant Related Adverse Event

Kelley R, et al., *Bipolar Disord*. 2013 Nov;15(7):795-802.

Theories for Why Antidepressant-Related Adverse Events Occur

- Ignition hypothesis: Antidepressant interacts with genetic predisposition to trigger mania
- Scar hypothesis: No genetic predisposition, but new predisposition created by antidepressant
- Side effect hypothesis: Simply an adverse effect, no scar created
- Natural course hypothesis: Coincidence of mania naturally following depression

Joseph, MF, et al. *Future Neurol*. 2009;4(1):87-102.


Childhood
Factors influencing brain development:
Genetics
Temperament
Parenting
Attachment
Prefrontal and Limbic system Vulnerabilities
Stress
Physical Environment
Income
Demographics
Education
Stress/ Challenge
Adolescence
Intact Mood Function
Prevention Strategy?
Dysregulated mood and motivation
Transition to Adulthood
Resilience:
Intact adaptive functions
Risk:
Mood and other psychiatric symptoms and other adverse outcomes

Conclusions

- Mood disorders commonly begin in childhood and adolescence
- Early signs of problems with mood may reflect a change in brain function
- Interventions may prevent or potentiate the natural course of mood problems before reaching adulthood

Audience Response

Which of the following are signs of bipolar disorder vs. ADHD?

A. Unstable mood, externally distracted
B. High energy, unstable mood
C. Stable mood, loses interest in fighting
D. Internally distracted stable mood

Audience Response

Based on the evidence presented, how confident are you now in using the latest evidence in treating patients patients with mood disorders?

A. Extremely confident
B. More confident
C. Somewhat confident
D. Not confident at all

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