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PSYCHIATRY ACADEMY

Unipolar vs Bipolar Depression

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Disclosures

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My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

I have consulted to NTT, and have received royalties from the following books:

- "ASK THE GENIUSES ABOUT THE FUTURE" (MAGAZINE HOUSE PUBLISHING),
- "SOCIAL JUSTICE" (BUNSHUN SHINSHO),
- "REAPPRAISAL" (JITSUGYO NO NIHONSHA),
- "PRESCRIPTION FOR DAILY MENTAL CRISES" (DAIWA SHOBO)
  "LIVING DEPRESSION" (BUNSHUN SHINSHO)
- "BECOMING A WORKING MOM" (KADOKAWA)
- "WHAT PARENTS NEED TO KNOW WHEN PARENTING FEELS CHALLENGING" (NIKKEI BP)

Diagnostic Criteria of Mood Disorders

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	Major Depressive Episode	Manic Episode	Hypomanic Episode	Mixed Episode
Major Depressive Disorder	+	-	-	-
Bipolar I Disorder	+/-	+ (or Mixed Episode)	-	+ (or Manic Episode)
Bipolar II Disorder	+	-	+	-

Depression in the Youth

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- When a child presents with symptoms of depression, both diagnoses of unipolar Major Depressive Disorder (MDD) and Bipolar major depression (BP MDD) need to be considered
- This is an important consideration because it affects treatment decisions:
  - Antidepressants could be effective for depression
  - BUT Antidepressants could also cause manic switches in individuals with underlying bipolar risk

Significance :
High rate of switching in children with MDD

- A large proportion **(up to 50%)** (Weissman 1999, Geller 1994) of children who initially present with depression (without previously having had a manic episode) will eventually develop mania or hypomania
- **Adult literature** has **consistently reported that "early onset" mood symptoms are a risk** of switching
- Their definition of "early onset" is **onset prior to age 25**

Manic Switches

- *Spontaneous s*witches can happen without any intervention

Manic Switches

- *Drug induced* Switches are those that develop after treatment with an antidepressant medication or other activating treatments
  - Biederman (2000) reported that up to half of children receiving antidepressants developed manic or hypomanic symptoms within a few months of treatment
  - Biederman (2000) reported that antidepressant treatment in BP children presenting with MDD resulted in manic exacerbation

Manic Activation in Children

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- 10 year old boy with depressive symptoms took an SSRI for the first time, and initially was observed to have improved mood. After 6 weeks, suddenly he became more impulsive, restless and silly. After 8 weeks, he became uncontrollably angry.
- 8 year old girl with some irritability was prescribed an SSRI. Initially she was seen to have less irritability and more positive outlook. After a month into the treatment, she became somewhat uncharacteristically chatty and had some thoughts such as “What would happen if I jumped out of the window?”

Manic Episodes in Children

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- **Manic Episode:**
- A) elevated, expansive or **irritable mood**
- B) >3/7 of following sxs (>4/7 if mood is irritable)
- **D**istractability
- **I**ndiscretion (e.g. sexual acting out *"bathroom humor" "exposing themselves"*, shopping sprees *"online shopping"*)
- **G**randiosity (i.e. "above all rules," disregard for adult authority)
- **F**light of Ideas
- **A**ctivities (increased goal directed activities)
- **S**leep (decreased need of sleep)
- **T**alkativeness

Summary of Risk Factors

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- **Family History of Psychiatric Illness**
  - Mood Disorders, Anxiety Disorders, ODD
  - Familial loading
  - Multigenerational FHx
- **Aggression, Conduct & Behavioral difficulties**
  - co-morbid conduct disorder or ODD
- **High Severity of Depression & Syndrome Congruent Impairment**
  - Suicidality, Hospitalizations, Low GAF
- **Psychiatric Co-morbidities & Psychosis**
- **Early Onset of Mood Symptoms**

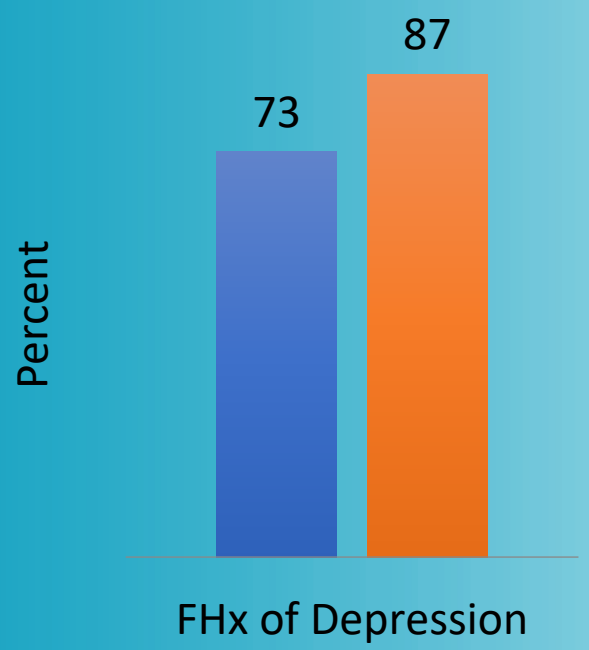
Family History

- **Geller et al 1994 & 2001** followed outpatient sample for 4 years and 10 years respectively
- The odds of having **3+ relatives** with mood disorders were **6 times greater** (p=.01) in switchers
- The odds of having **3 generations** of mood disorders were **5 times greater** (p=.02) in switchers
- **Parental and grandparental BP-I** predicted the switches in the 10 year follow up

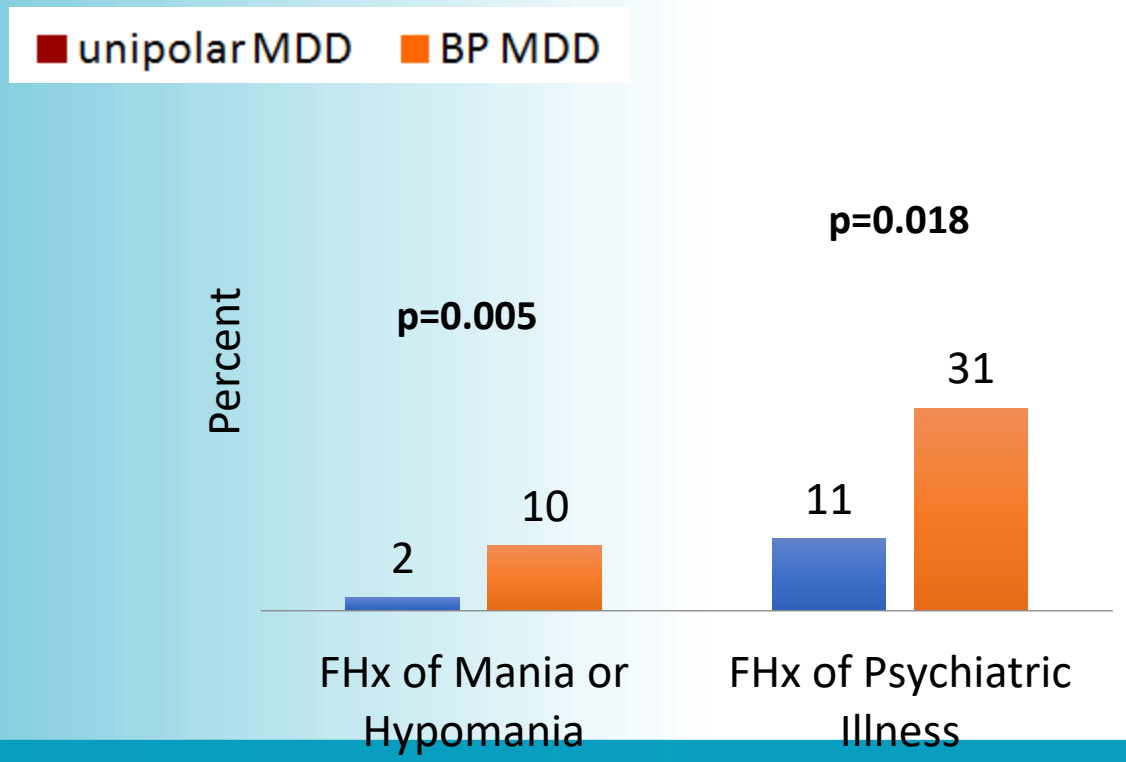
Family History

Merikangas, 2012

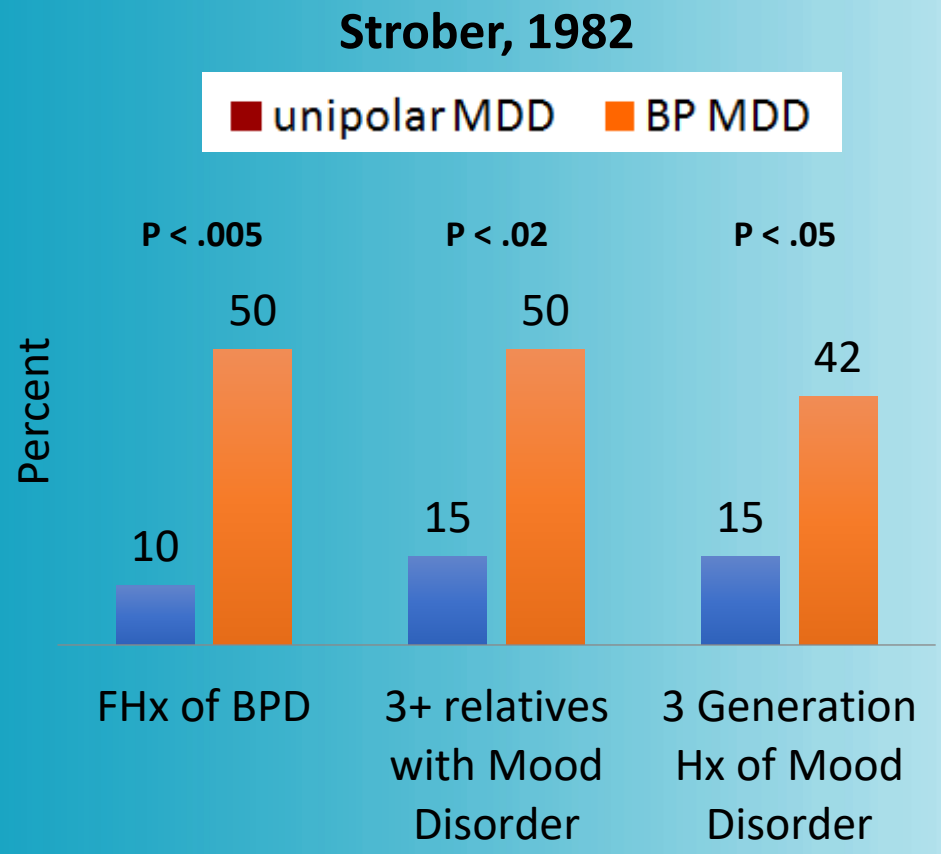
OR=2.4 [95%CI 1.19-4.84]



Shon, 2013



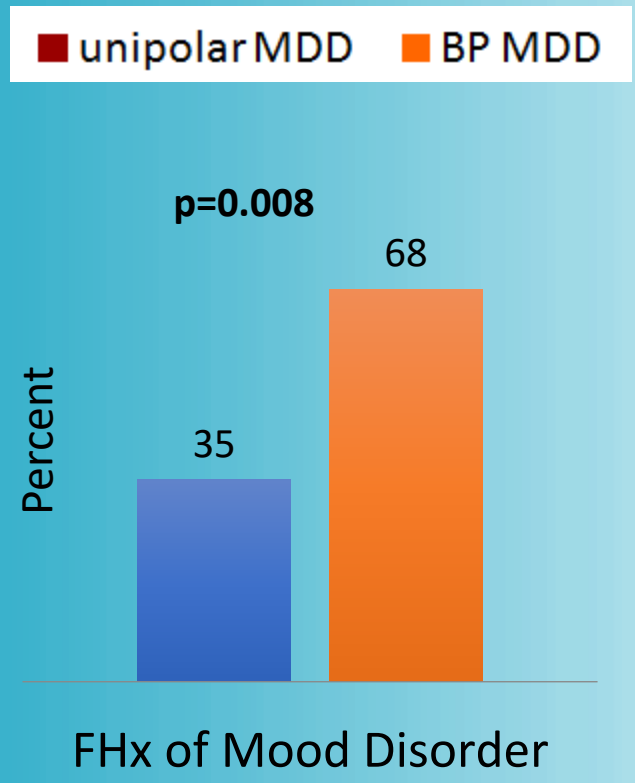
Family History



Strober (1982) followed inpatient adolescents for 4 years

Family History

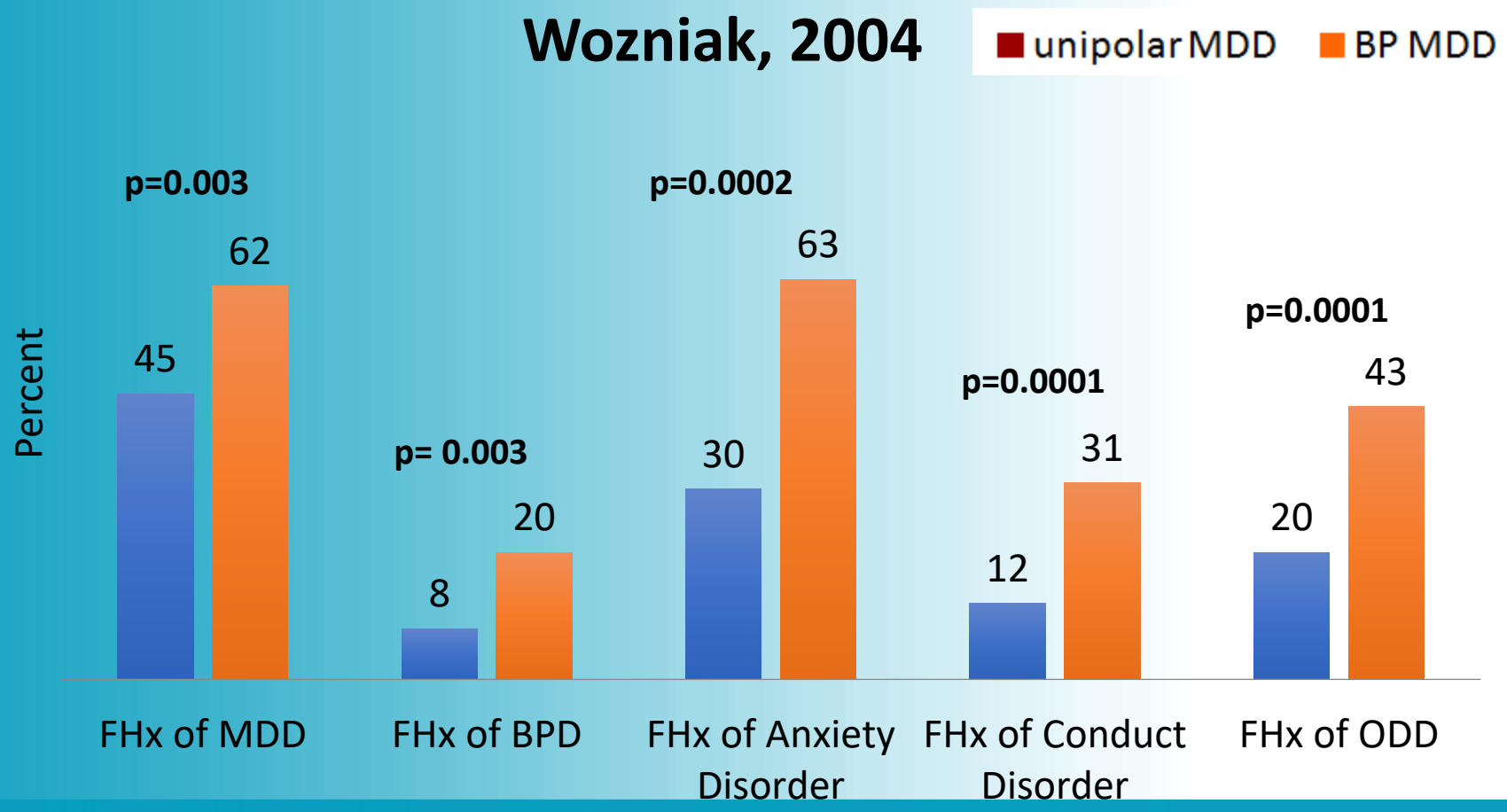
Biederman, 2009



Biederman (2009) used data from two large controlled longitudinal studies of children with and without ADHD and their siblings.

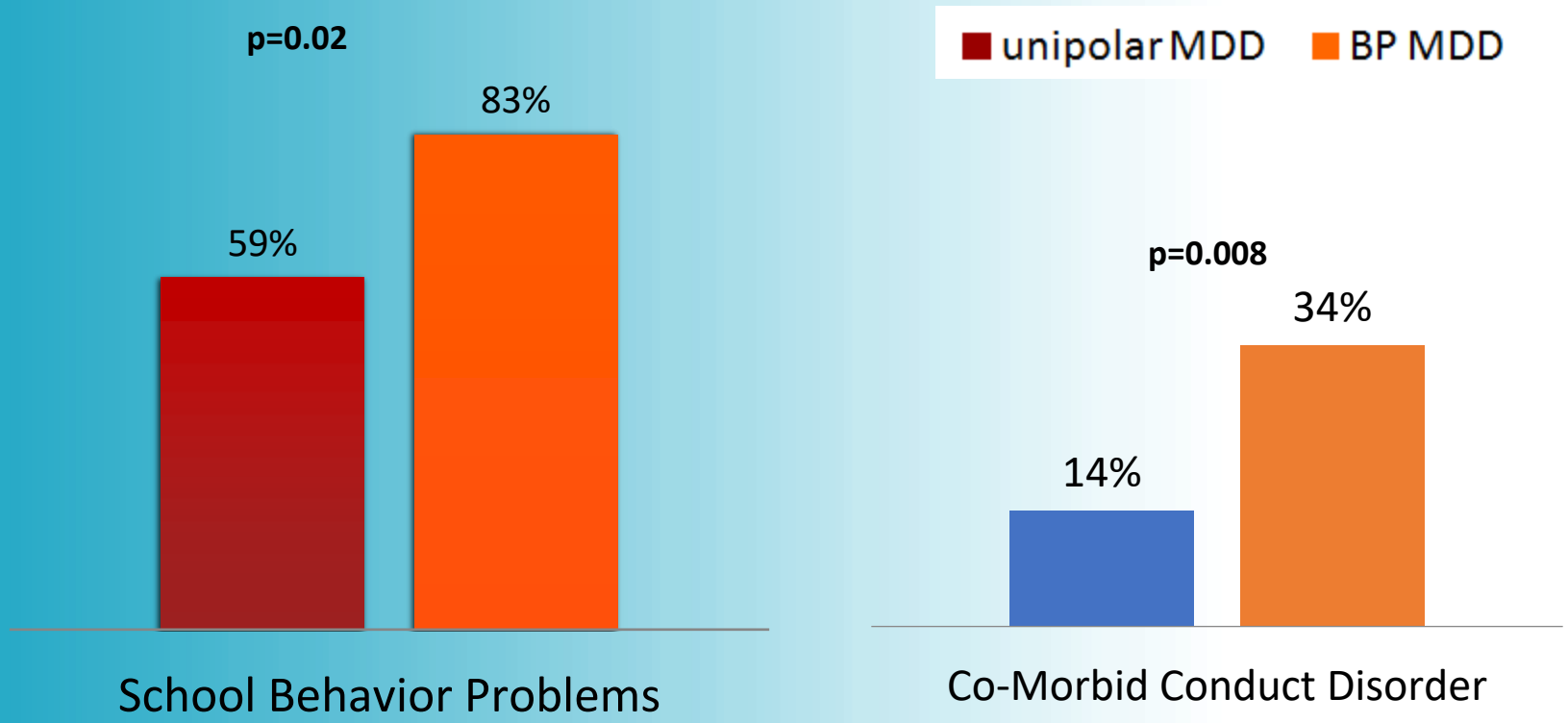
Subjects who switched had significantly higher rates of parental MDD and BP mood disorders

Family History

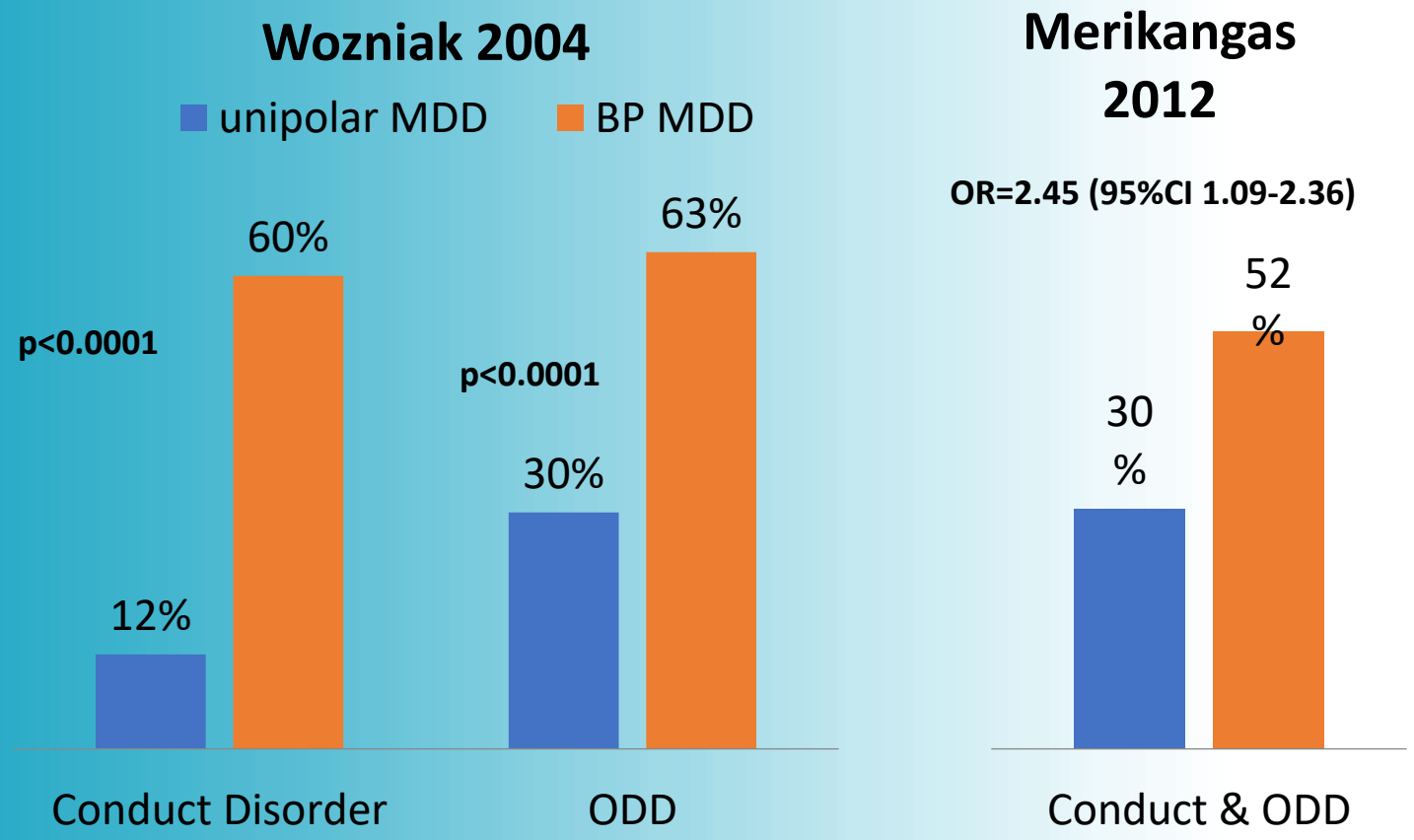


Aggression, Conduct, Behavioral Difficulties

Biederman 2009



Co-morbid Conduct Disorder or ODD



Conduct Disorder, ODD & Aggressive Behaviors

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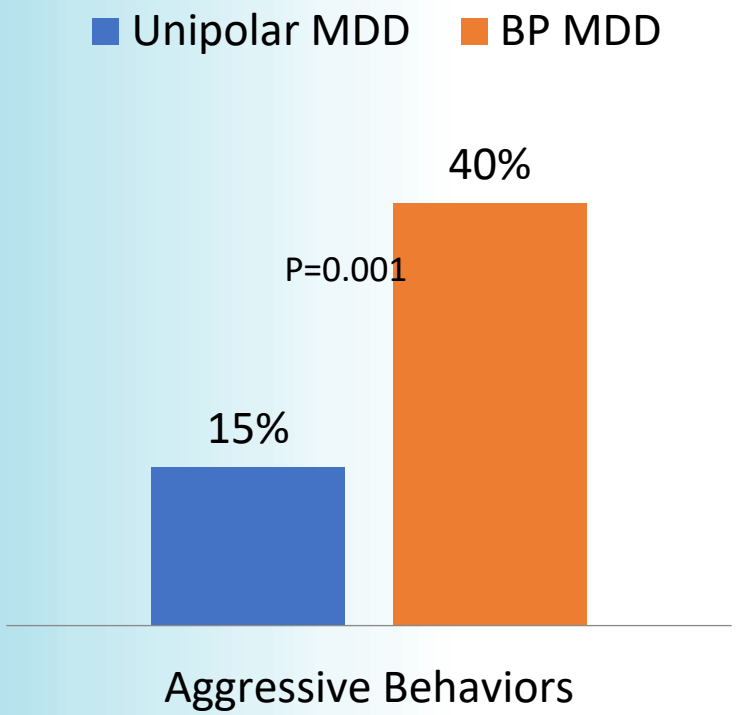
Luby 2008

Co-morbid Conduct Disorder
OR=54.4, P<0.001

Co-morbid ODD
OR=4.65
P<0.01

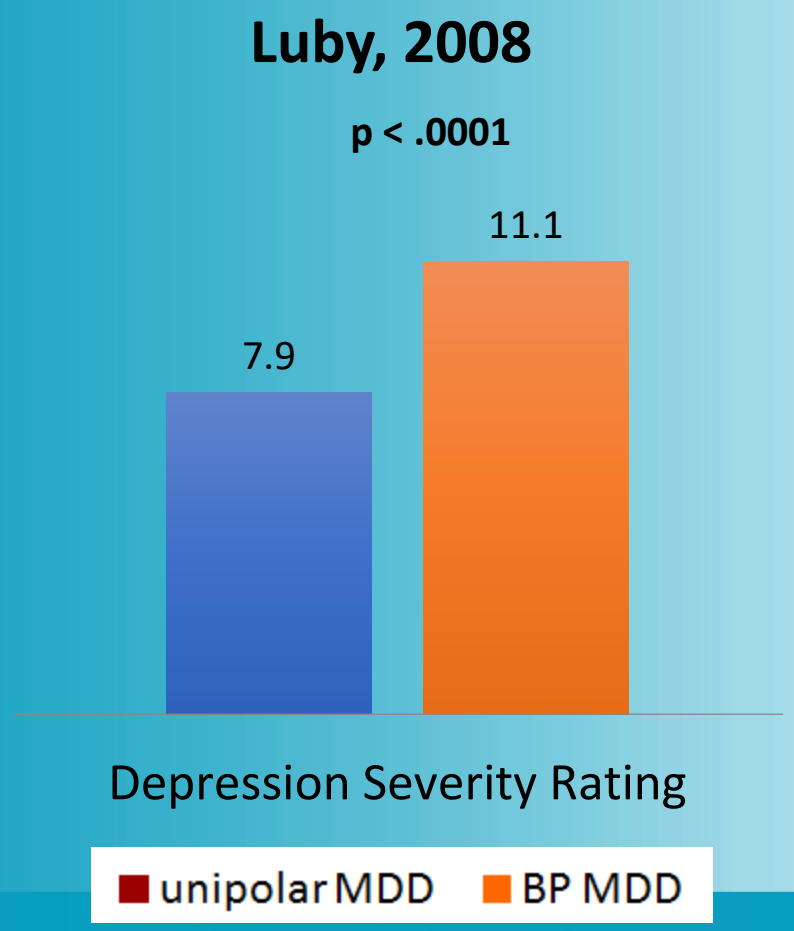
Shon 2013



Aggression, Conduct, Behavioral Difficulties

- **Geller (1994)** bullying behaviors was a significant predictor of switching (OR= 7.1, p=0.003)

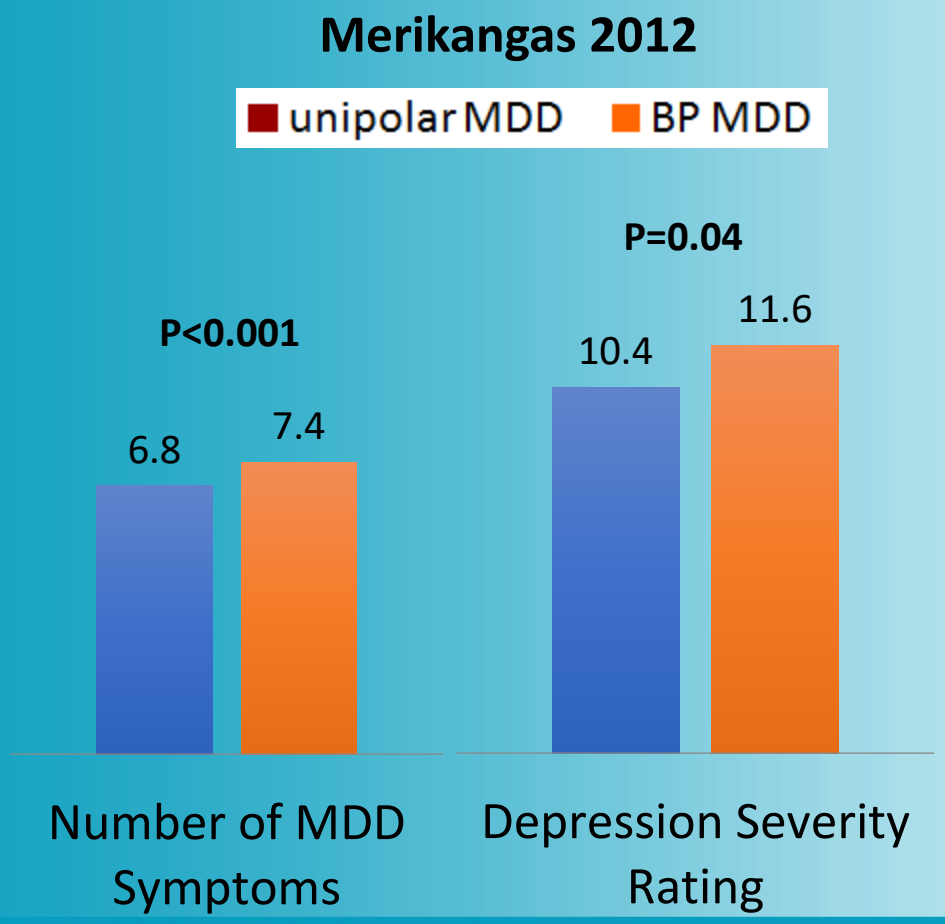
High Severity of Depression



Luby et al used a community sample of preschoolers.

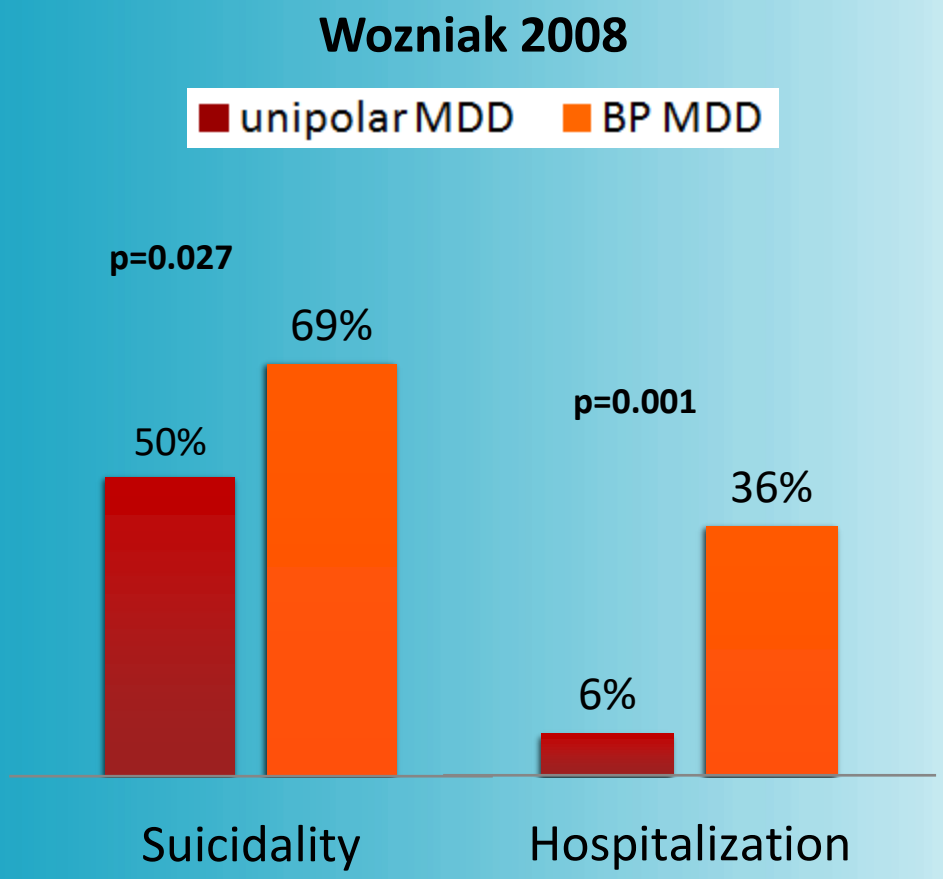
They found depression severity rating measured by *PAPA (Preschool Age Psychiatric Assessment)* was higher in the children with BP depression.

High Severity of Depression



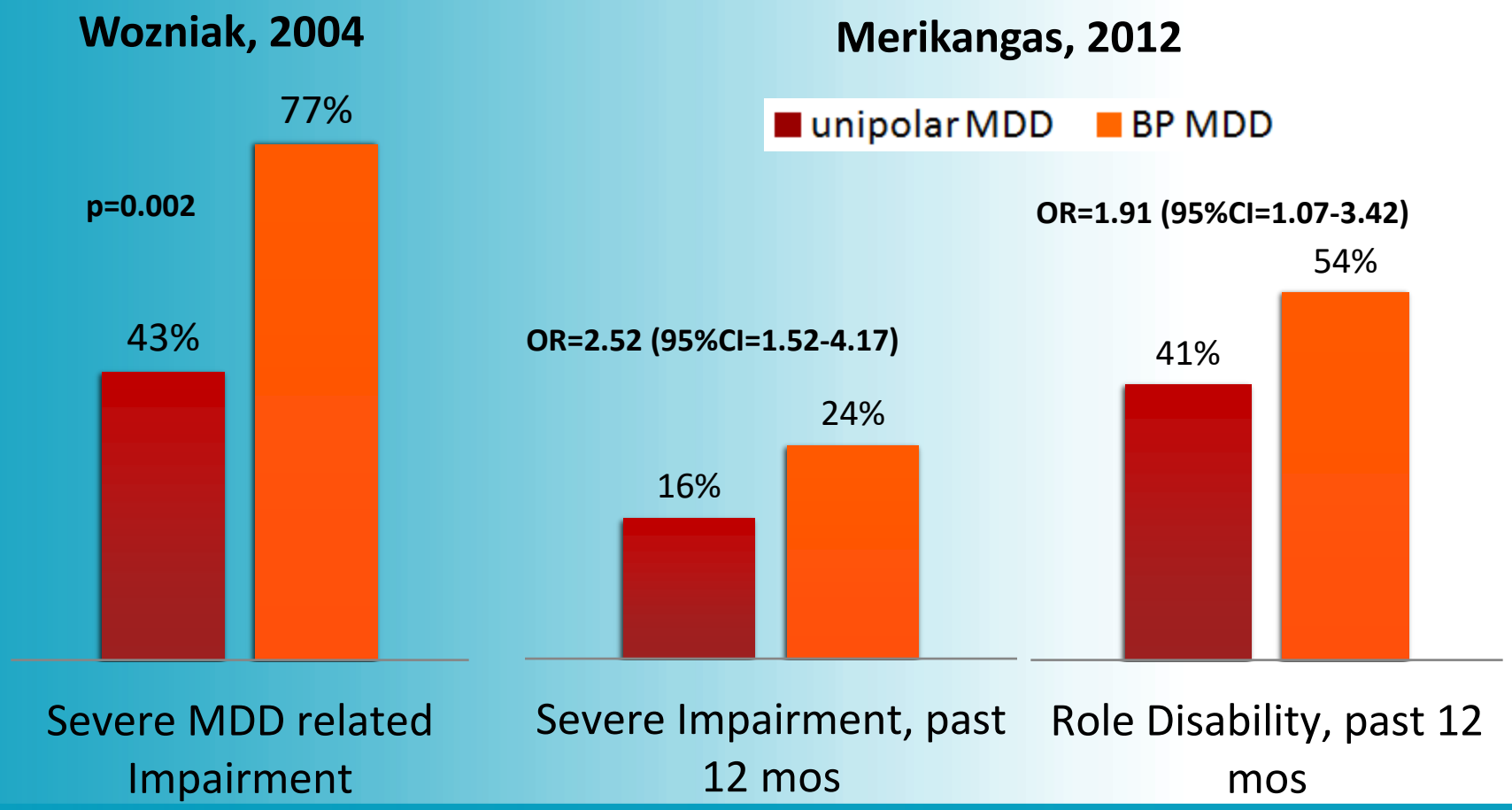
Number of MDD symptoms and Severity measured using the *Quick Inventory of Depressive symptomatology Self-Report (QIDS-SR)* were higher in BP MDD.

High Severity of Depression; Suicidality and Hospitalization

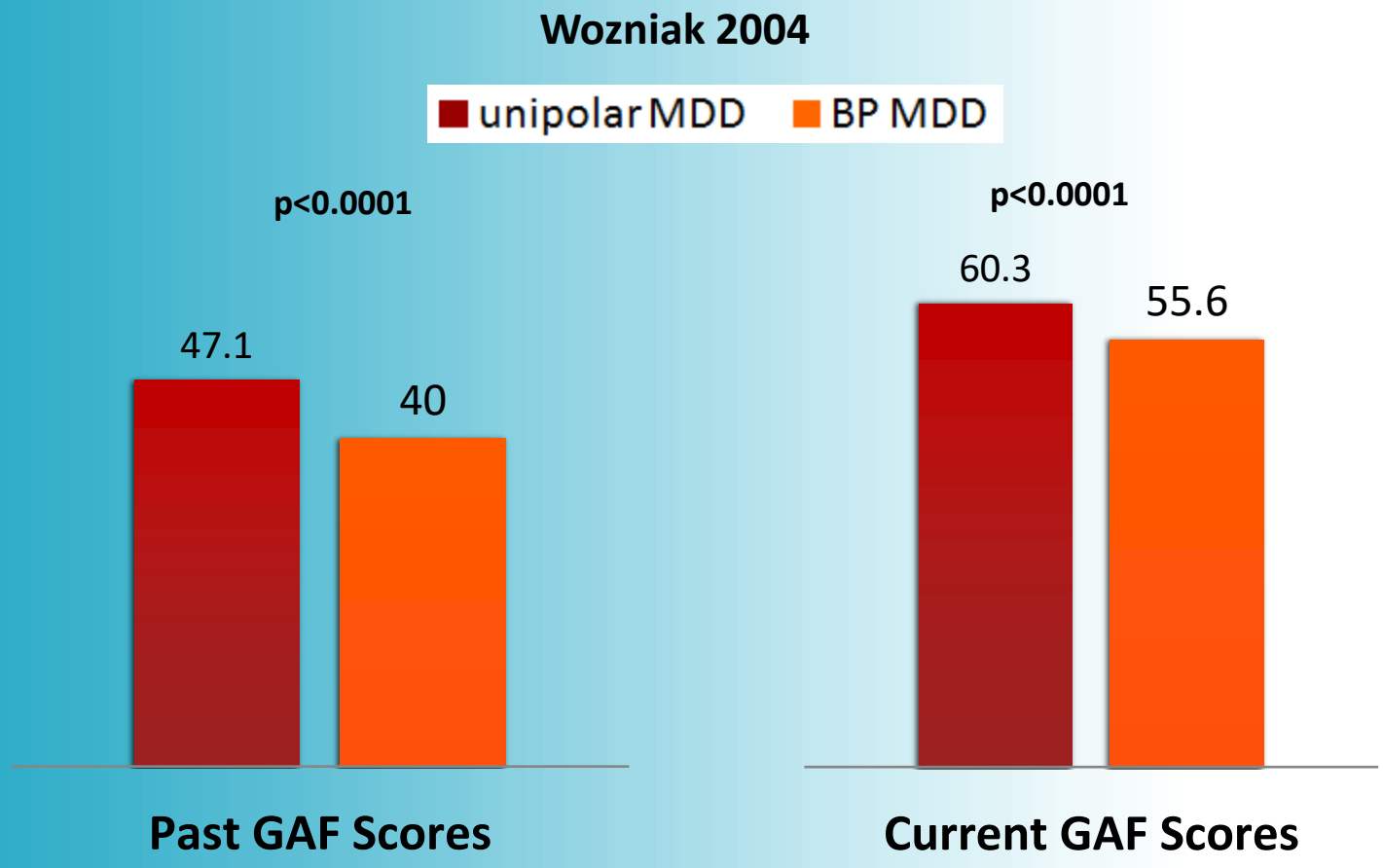


- Wozniak et al (2008) reported that rate of suicidality and hospitalization were higher in BP MDD.

Degree of Impairment



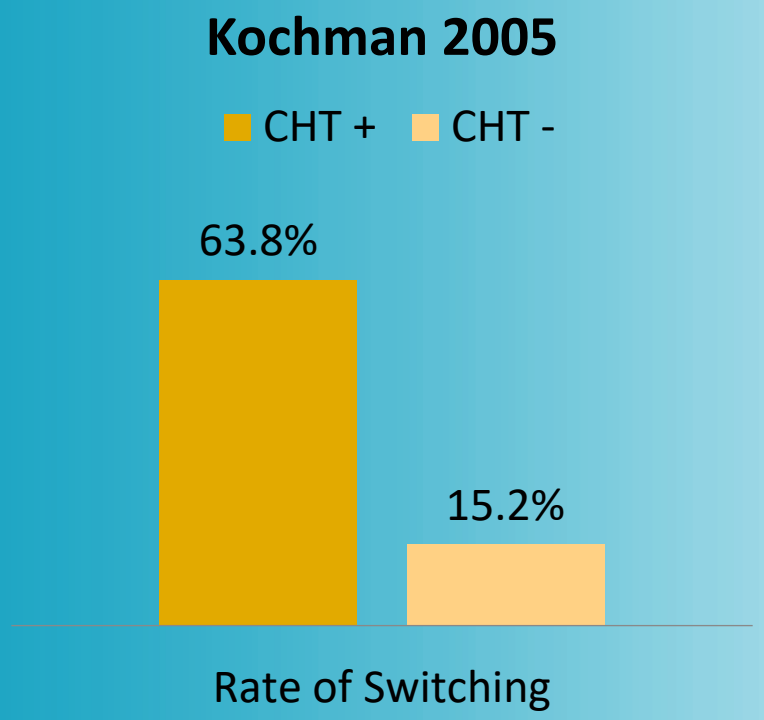
Degree of Impairment: GAF



Emotional Dysregulation

- **Kochman et al (2005)** followed 80 inpatients for 1 year
- Emotional dysregulation was reported in the form of **"Cyclothymic Hypersensitive Temperament (CHT)"** defined by *presence of high mood lability and emotional reactivity*

Emotional Dysregulation



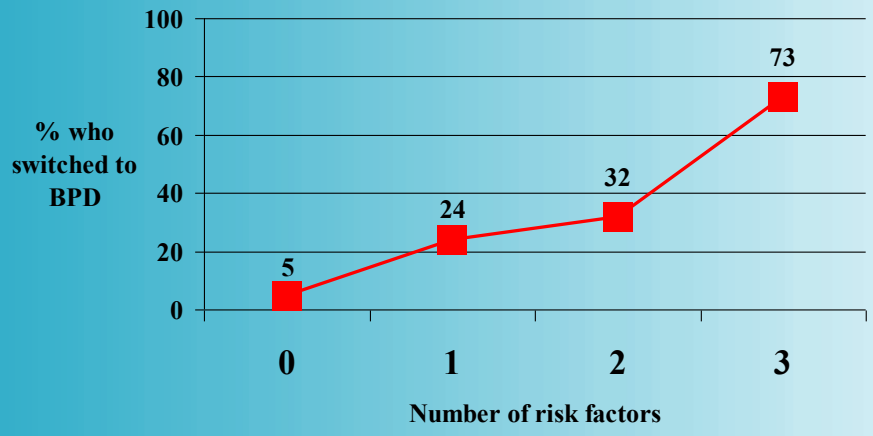
- 64% of children with CHT switched, vs. 15% of those without CHT ($p<0.0001$)
- Children with CHT also displayed a wider range of **aggressive behaviors** and a **higher rate of suicidality**

Emotional Dysregulation

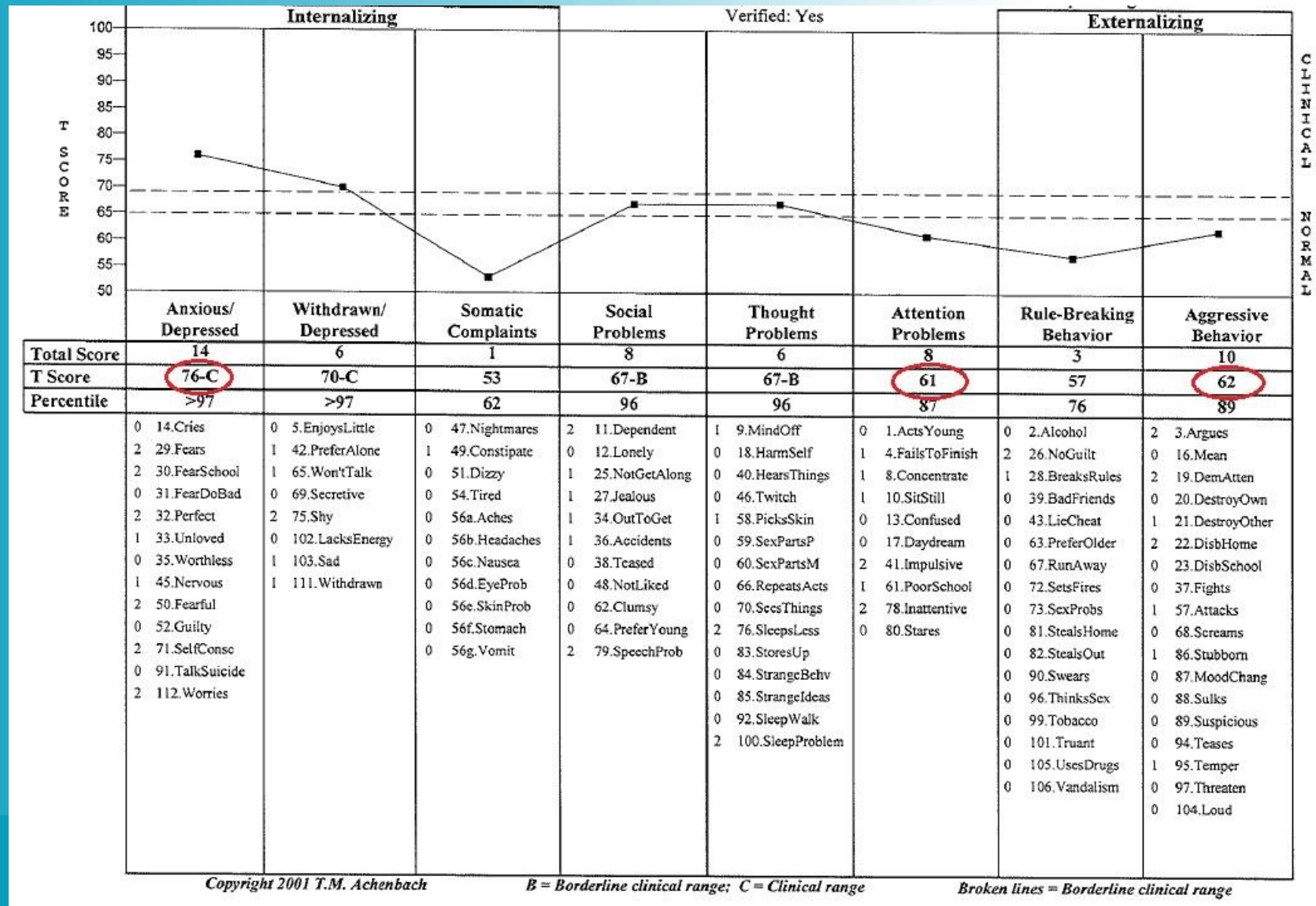
- **Biederman (2013)** examined emotional dysregulation (ED) using a profile in the Child Behavioral Check List CBCL
  - **Average of 1SD elevation** in the **Anxiety/ Depression, Aggression, and Attention subscales of the CBCL** (aggregate T score >180)
- ED was found to be a predictor of manic switching (**OR=3.54**, **p=0.037**).

Dose Response of Multiple Risk Factors

- Biederman (2009) reported the additive risk of significant predictors of switching (conduct disorder, school behavior problems and parental mood disorder).



CBCL scoring



Internalizing | Verified: Yes | Externalizing

T SCORE: 100, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50 — CLINICAL / NORMAL

	Anxious/ Depressed	Withdrawn/ Depressed	Somatic Complaints	Social Problems	Thought Problems	Attention Problems	Rule-Breaking Behavior	Aggressive Behavior
Total Score	14	6	1	8	6	8	3	10
T Score	76-C	70-C	53	67-B	67-B	61	57	62
Percentile	>97	>97	62	96	96	87	76	89
	0 14.Cries	0 5.EnjoysLittle	0 47.Nightmares	2 11.Dependent	1 9.MindOff	0 1.ActsYoung	0 2.Alcohol	2 3.Argues
	2 29.Fears	1 42.PreferAlone	1 49.Constipate	0 12.Lonely	0 18.HarmSelf	1 4.FailsToFinish	2 26.NoGuilt	0 16.Mean
	2 30.FearSchool	1 65.Won'tTalk	0 51.Dizzy	1 25.NotGetAlong	0 40.HearsThings	1 8.Concentrate	1 28.BreaksRules	2 19.DemAtten
	0 31.FearDoBad	0 69.Secretive	0 54.Tired	1 27.Jealous	0 46.Twitch	1 10.SitStill	0 39.BadFriends	0 20.DestroyOwn
	2 32.Perfect	2 75.Shy	0 56a.Aches	1 34.OutToGet	1 58.PicksSkin	0 13.Confused	0 43.LieCheat	1 21.DestroyOther
	1 33.Unloved	0 102.LacksEnergy	0 56b.Headaches	1 36.Accidents	0 59.SexPartsP	0 17.Daydream	0 63.PreferOlder	2 22.DisbHome
	0 35.Worthless	1 103.Sad	0 56c.Nausea	0 38.Teased	0 60.SexPartsM	2 41.Impulsive	0 67.RunAway	0 23.DisbSchool
	1 45.Nervous	1 111.Withdrawn	0 56d.EyeProb	0 48.NotLiked	0 66.RepeatsActs	1 61.PoorSchool	0 72.SetsFires	0 37.Fights
	2 50.Fearful		0 56e.SkinProb	0 62.Clumsy	0 70.SeesThings	2 78.Inattentive	0 73.SexProbs	1 57.Attacks
	0 52.Guilty		0 56f.Stomach	0 64.PreferYoung	2 76.SleepsLess	0 80.Stares	0 81.StealsHome	0 68.Screams
	2 71.SelfConsc		0 56g.Vomit	2 79.SpeechProb	0 83.StoresUp		0 82.StealsOut	1 86.Stubborn
	0 91.TalkSuicide				0 84.StrangeBehv		0 90.Swears	0 87.MoodChang
	2 112.Worries				0 85.StrangeIdeas		0 96.ThinksSex	0 88.Sulks
					0 92.SleepWalk		0 99.Tobacco	0 89.Suspicious
					2 100.SleepProblem		0 101.Truant	0 94.Teases
							0 105.UsesDrugs	1 95.Temper
							0 106.Vandalism	0 97.Threaten
								0 104.Loud

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CBCL – Emotinal Dysregulation Profile

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- CBCL Emotional Dysregulation Profile: >1SD (>180) aggregate T score of Attention, Anxiety/ Depression & Aggression subscales
- CBCL Severe Dysregulation Profile (Pediatric Bipolar Disorder Profile: > 2SD (> 210) aggregate T score of Attention, Anxiety/ Depression & Aggression subscales

CBCL- Emotion Dysregulation Profile and Risk for Bipolar Disorder

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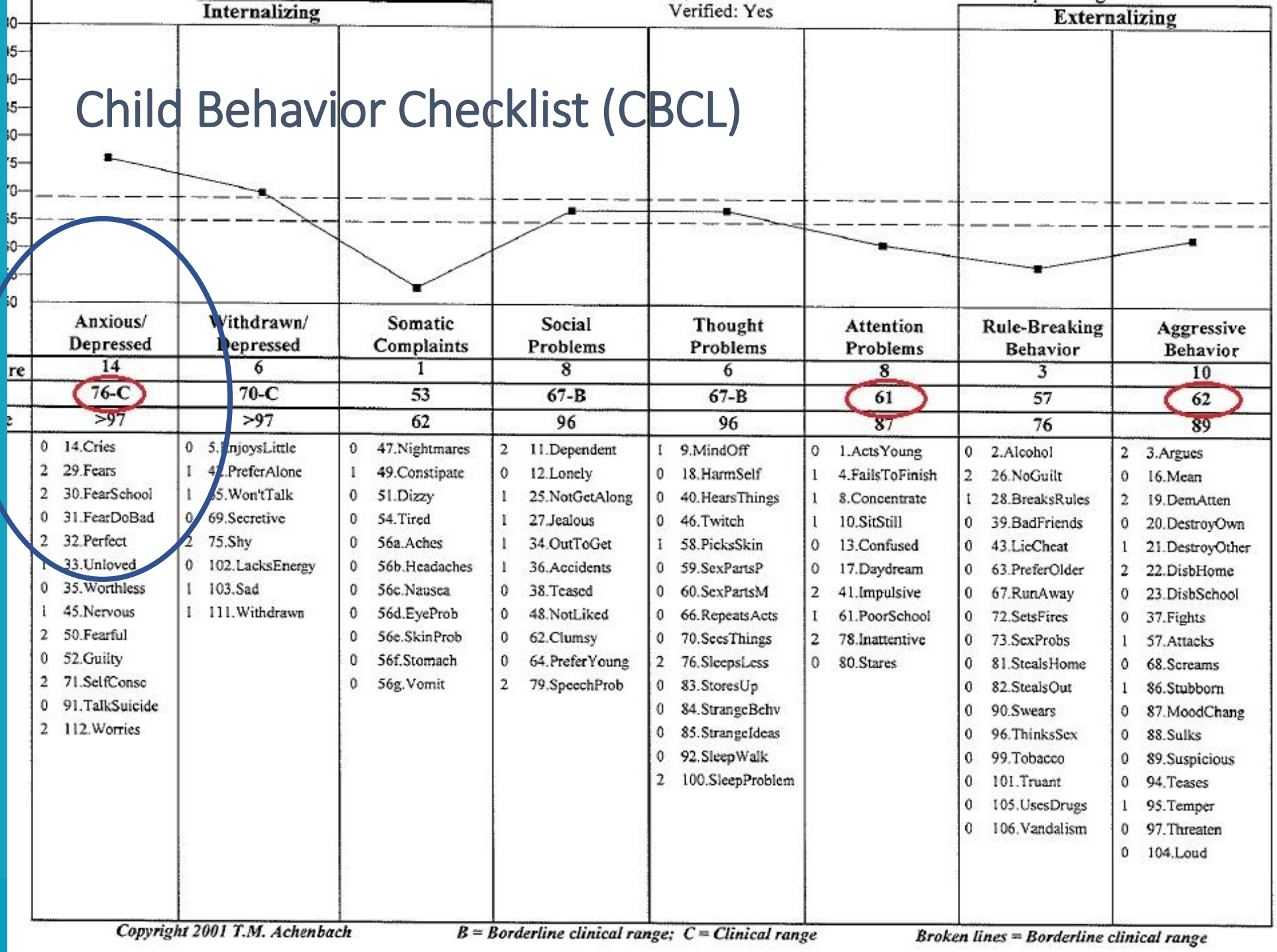
Personal and familiar correlates of Bipolar Disorder in children with CBCL – Emotion Dysregulation Profile *(Biederman, J of Affect Dis. 2013)*

CBCL severe emotion dysregulation profile was useful in differentiating children with bipolar disorder from children with ADHD *(Uchida, J of Affect Dis. 2014)*

ROC analysis of showed that a combined t-score of 195 on the CBCL-Emotion Dysregulation profile efficiently identified children with pediatric bipolar disorder *(Yule, Scandinav J of Child and Adolesc Psych and Psychology, 2019)*

Child Behavior Checklist (CBCL)



Internalizing | Verified: Yes | Externalizing

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Major Depressive Disorder Diagnosis Over the Developmental Years

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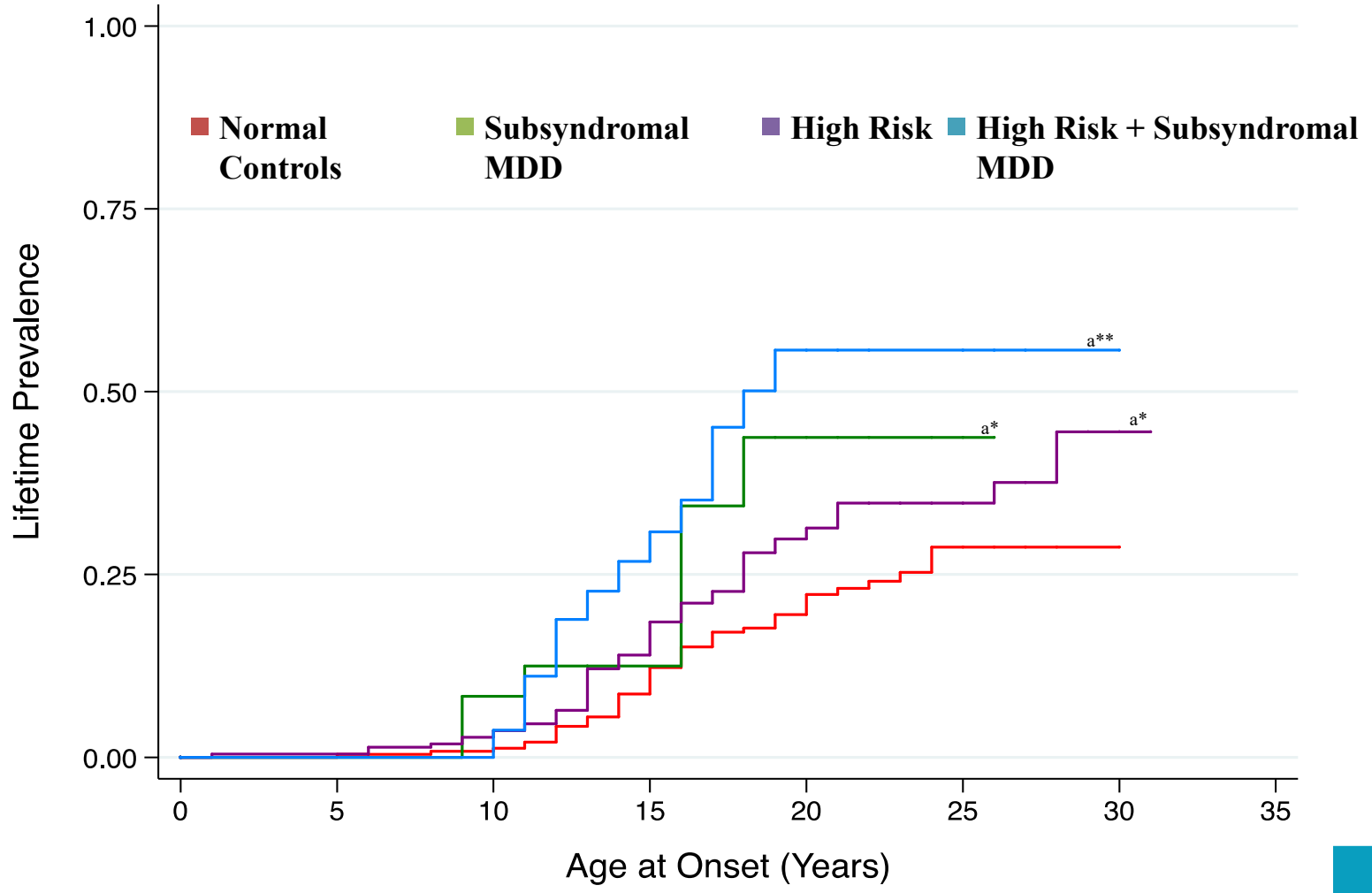

Bipolar Disorder Development

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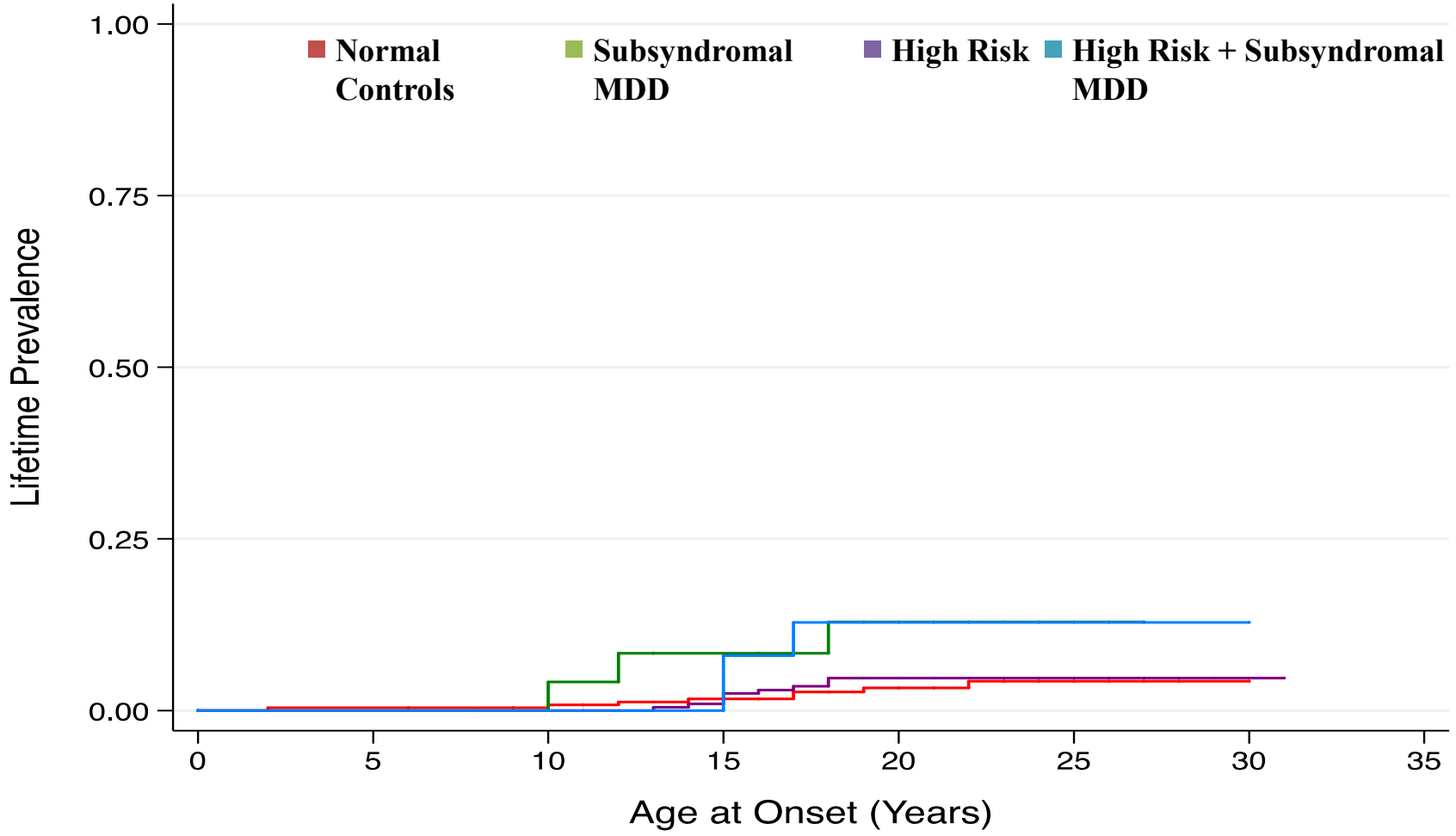
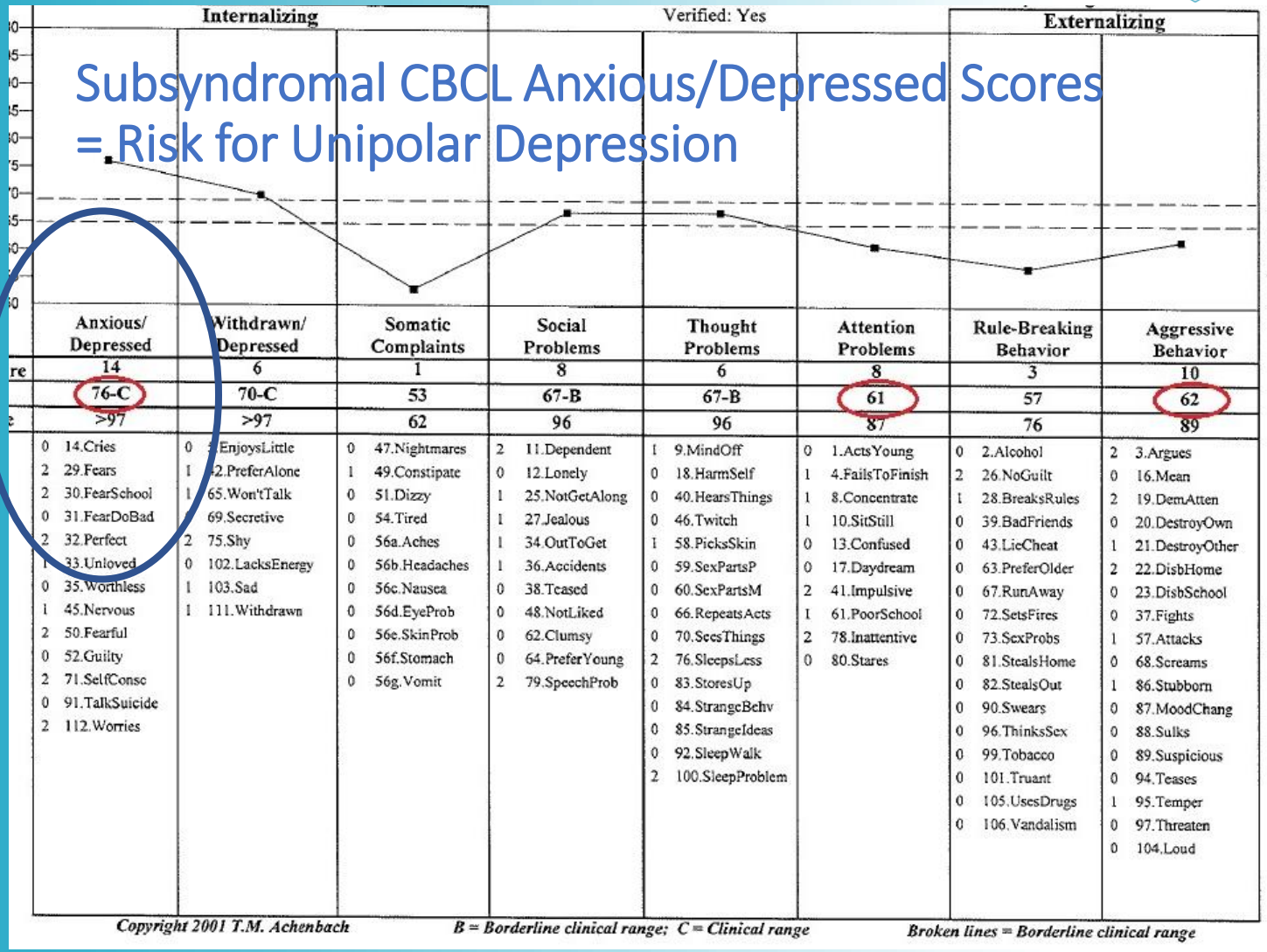


Subsyndromal CBCL Anxious/Depressed Scores = Risk for Unipolar Depression



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Aggregate Scores of CBCL Anxious/Depressed, Attention & Aggressive Behavior = CBCL Emotion Dysregulation Profile

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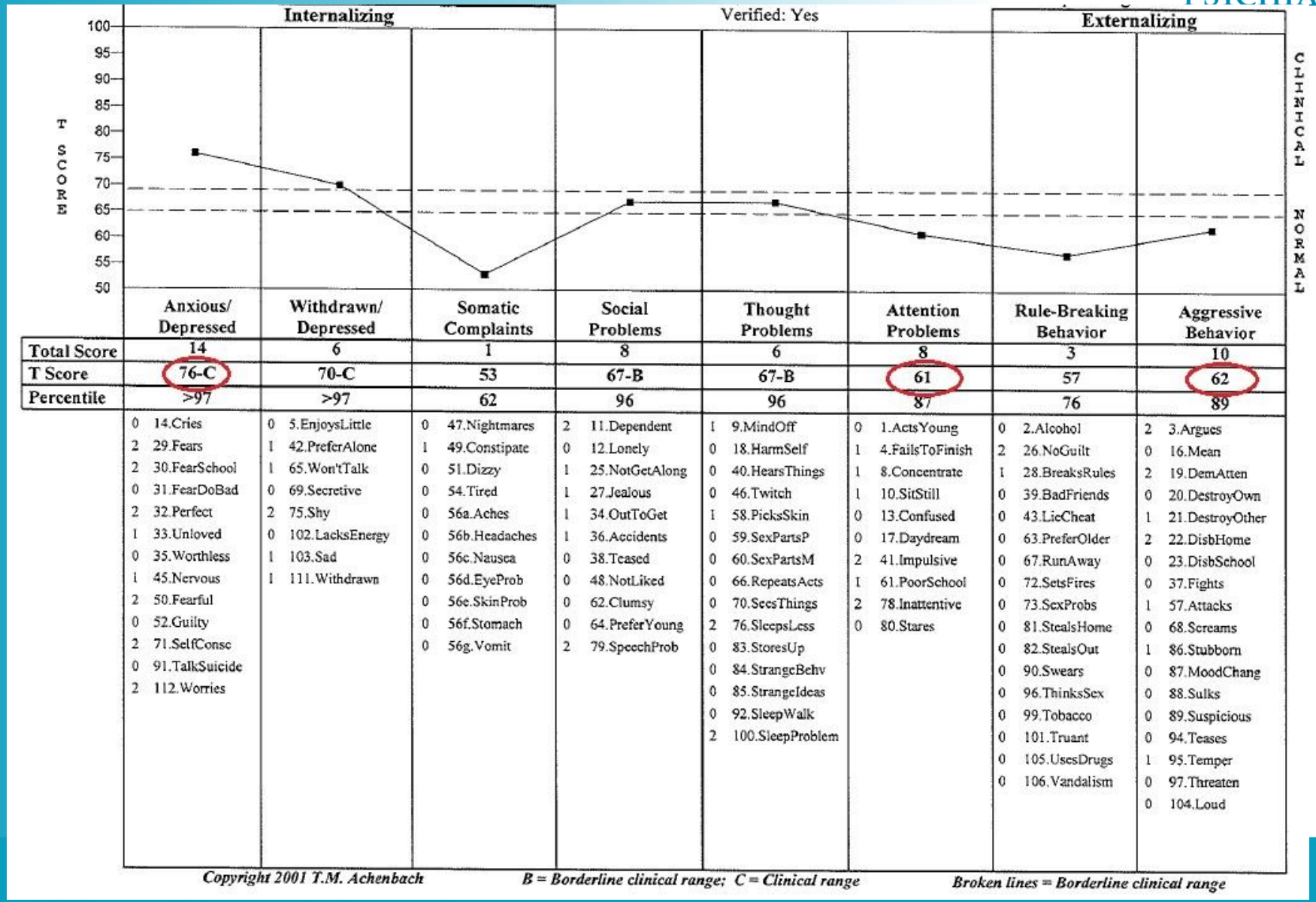

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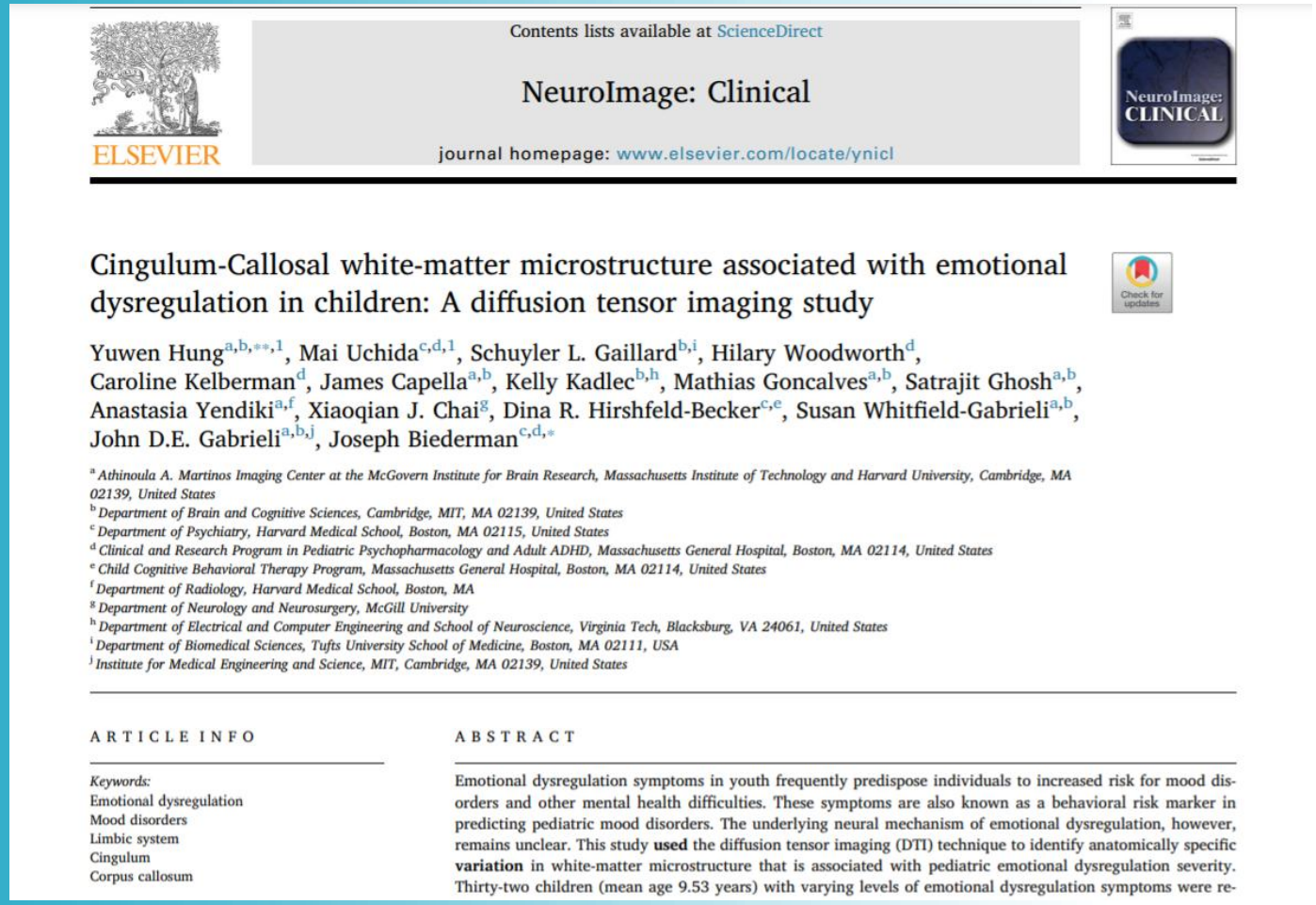
T Score	76-C	70-C	53	67-B	67-B	61	57	62
Percentile	>97	>97	62	96	96	87	76	89
	0 14.Cries	0 5.EnjoysLittle	0 47.Nightmares	2 11.Dependent	1 9.MindOff	0 1.ActsYoung	0 2.Alcohol	2 3.Argues
	2 29.Fears	1 42.PreferAlone	1 49.Constipate	0 12.Lonely	0 18.HarmSelf	1 4.FailsToFinish	2 26.NoGuilt	0 16.Mean
	2 30.FearSchool	1 65.Won'tTalk	0 51.Dizzy	1 25.NotGetAlong	0 40.HearsThings	1 8.Concentrate	1 28.BreaksRules	2 19.DemAtten
	0 31.FearDoBad	0 69.Secretive	0 54.Tired	1 27.Jealous	0 46.Twitch	1 10.SitStill	0 39.BadFriends	0 20.DestroyOwn
	2 32.Perfect	2 75.Shy	0 56a.Aches	1 34.OutToGet	1 58.PicksSkin	0 13.Confused	0 43.LieCheat	1 21.DestroyOther
	1 33.Unloved	0 102.LacksEnergy	0 56b.Headaches	1 36.Accidents	0 59.SexPartsP	0 17.Daydream	0 63.PreferOlder	2 22.DisbHome
	0 35.Worthless	1 103.Sad	0 56c.Nausea	0 38.Teased	0 60.SexPartsM	2 41.Impulsive	0 67.RunAway	0 23.DisbSchool
	1 45.Nervous	1 111.Withdrawn	0 56d.EyeProb	0 48.NotLiked	0 66.RepeatsActs	1 61.PoorSchool	0 72.SetsFires	0 37.Fights
	2 50.Fearful		0 56e.SkinProb	0 62.Clumsy	0 70.SeesThings	2 78.Inattentive	0 73.SexProbs	1 57.Attacks
	0 52.Guilty		0 56f.Stomach	0 64.PreferYoung	2 76.SleepsLess	0 80.Stares	0 81.StealsHome	0 68.Screams
	2 71.SelfConsc		0 56g.Vomit	2 79.SpeechProb	0 83.StoresUp		0 82.StealsOut	1 86.Stubborn
	0 91.TalkSuicide				0 84.StrangeBehv		0 90.Swears	0 87.MoodChang
	2 112.Worries				0 85.StrangeIdeas		0 96.ThinksSex	0 88.Sulks
					0 92.SleepWalk		0 99.Tobacco	0 89.Suspicious
					2 100.SleepProblem		0 101.Truant	0 94.Teases
							0 105.UsesDrugs	1 95.Temper
							0 106.Vandalism	0 97.Threaten
								0 104.Loud

B = Borderline clinical range; C = Clinical range

Broken lines = Borderline clinical range

DTI White Matter Structural Connectivity Associated With CBCL Anxiety/Depression vs CBCL Emotion Dysregulation Scores



Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cingulum-Callosal white-matter microstructure associated with emotional dysregulation in children: A diffusion tensor imaging study

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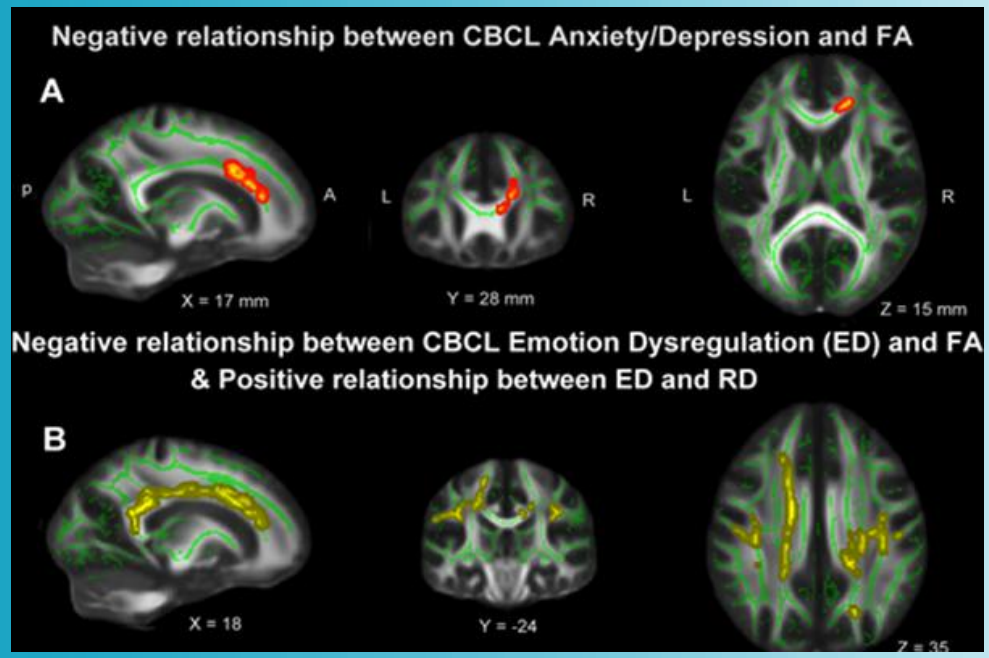
ARTICLE INFO

Keywords:
Emotional dysregulation
Mood disorders
Limbic system
Cingulum
Corpus callosum

ABSTRACT

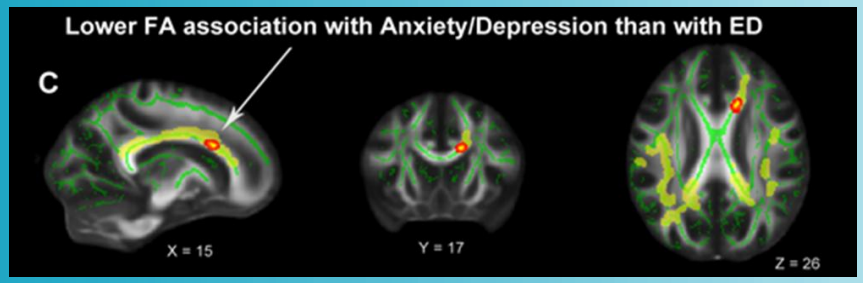
Emotional dysregulation symptoms in youth frequently predispose individuals to increased risk for mood disorders and other mental health difficulties. These symptoms are also known as a behavioral risk marker in predicting pediatric mood disorders. The underlying neural mechanism of emotional dysregulation, however, remains unclear. This study **used** the diffusion tensor imaging (DTI) technique to identify anatomically specific **variation** in white-matter microstructure that is associated with pediatric emotional dysregulation severity. Thirty-two children (mean age 9.53 years) with varying levels of emotional dysregulation symptoms were re-

DTI results of each CBCL Profile



- A: Negative correction between **CBCL Anx/Dep scores** and fractional anisotropy (FA) in the **anterior cingulum-callosal (CC-CG) region** (Red)
- B: Negative correlations between **CBCL Emotional Dysregulation** scores and the FA located in both the **anterior and posterior subdivisions of the CC-CG bundles**
- B: Positive correlations between **CBCL Emotional Dysregualtion** scores and the radial diffusivity (RD) located in both the **anterior and posterior subdivisions of the CC-CG bundles**

When compared DTI result of CBCL Anxiety/Depression vs CBCL Emotion Dysregulation



- C: Stronger **negative** association was found **between FA and CBCL-Anxiety/Depression scores** localized to the **right anterior cingulum-callosal conjunction (aCC+aCG)**.
- **Negative correlations between the CBCL-ED scores and FA** in both the **posterior cingulum and posterior cerebral cortex regions, were not seen** in examination of children with **CBCL-Anxiety/Depression elevation.**

J Psychiatr Res. 2022 Dec;156:261-267. doi: 10.1016/j.jpsychires.2022.09.051. Epub 2022 Oct 13.

MASSACHUSETTS GENERAL HOSPITAL PSYCHIATRY ACADEMY

Can machine learning identify childhood characteristics that predict future development of bipolar disorder a decade later?

Mai Uchida [1], Qasim Bukhari [2], Maura DiSalvo [3], Allison Green [4], Giulia Serra [5], Chloe Hutt Vater [3], Satrajit S Ghosh [6], Stephen V Faraone [7], John D E Gabrieli [2], Joseph Biederman [8]

Affiliations + expand

PMID: 36274531 PMCID: PMC9999264 DOI: 10.1016/j.jpsychires.2022.09.051

Free PMC article

- Data was derived from two MGH longitudinal family studies that were collected over 11 years
- Clinical Scales and Diagnoses were collected at baseline and at 11 year follow-up
- Children who already had diagnosis of Bipolar Disorder or Children with any missing values were excluded form the analysis
- 492 children, ages 6-17 at baseline, were included in the final analysis
- Of our sample, 45 children (10%) developed BP disorder.
- Extra Trees (Extremely randomized trees)

Results

	Predicted BPD	Predicted no BPD
Actual BPD	*7.71*	*1.63*
Actual no BPD	*10.71*	*79.95*

Confusion matrix in percentage using repeated sampling cross-validation of the 75% data

	Mean	*Standard Deviation*
Accuracy	*87.65*	*1.81*
Sensitivity	*82.56*	*7.48*
Specificity	*88.18*	*1.9*
ROC-AUC	*88.71*	*1.4*

Performance evaluation using repeated sampling cross-validation of the 75% data

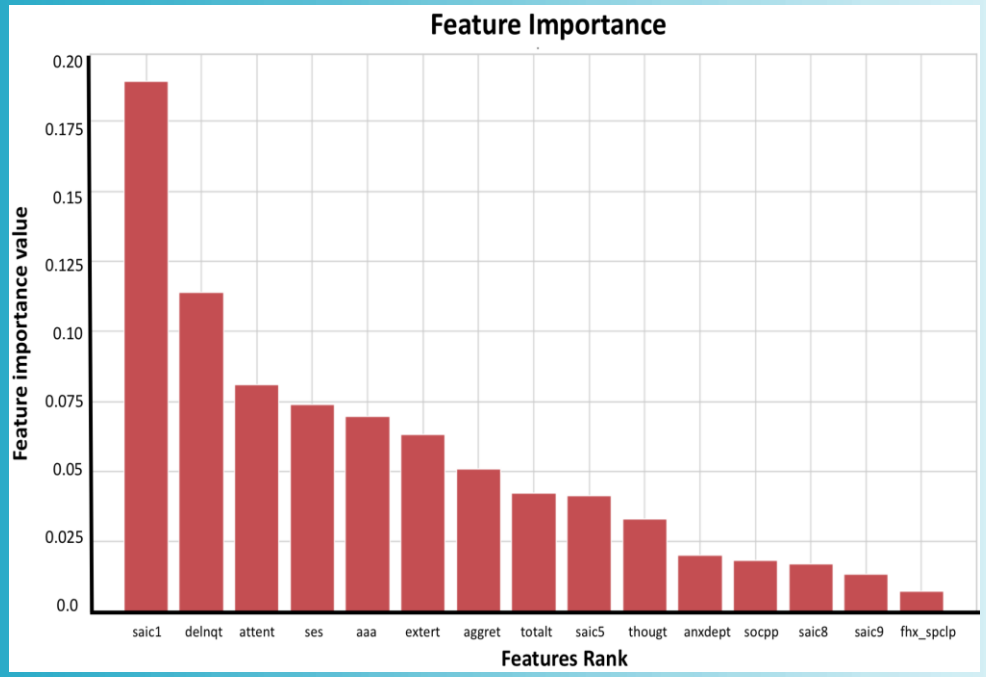
	Predicted BPD	Predicted MDD
Actual BPD	**35**	*8*
Actual MDD	*26*	***631***

Confusion matrix of the 25% data

Accuracy	*95.14*
Sensitivity	*81.39*
Specificity	*96.04*
ROC-AUC	*88.71*

Performance evaluation of the 25% data

Results: Feature Importance Ranking in Predicting Bipolar Disorder



Features at Baseline
SAICA school behavior problems
CBCL Rule Breaking t-score
CBCL Attention Problems t-score
SES
CBCL Externalizing t-score
CBCL-AAA score
CBCL Aggressive t-score
SAICA problems with peers
CBCL Total t-score
CBCL Thought Problems t-score

Our prediction model identified problematic school behaviors, conduct disorder symptoms, and emotional dysregulation as key predictors of BP disorder outcome with robust sensitivity, specificity and accuracy.

How do we pharmacologically manage them?

- Should we avoid antidepressants?
- SSRI + Antipsychotics?
- Antipsychotics only?
- SSRI only?
- Lamotrigine?
- FDA approved meds for bipolar depression?
- Are there other symptomatology that we can treat to mitigate the effect of depression?