



Leading the Integration of Physical and Mental Health Care

CONFERENCE 2020

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Heart Matters: Bipolar Disorder as a Vascular Disease

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None.



Learning Objectives

1. Recognize the increased cardiovascular risk associated with bipolar disorder
2. Identify different factors that may explain this association
3. Consider how the heart-bipolar link may inform monitoring, treatment, and stigma-reduction in bipolar disorder



Bipolar Disorder


- Also known as manic-depressive illness
- Recurrent, severe mood disorder; episodes of mania/hypomania and depression
- Affects 1-5% of Canadian population
- Sex ratio: 1:1, except 2:1 F:M in adolescents
- Functional and neurocognitive impairment
- High direct and indirect health care costs



Early-onset Bipolar Disorder

- 32-65% of adults have onset ≤ 18 yo
- More comorbid anxiety, substance abuse
- More episodes and symptoms
- More psychosis, suicidality, and violence
- Longer delay until treatment
- Greater functional impairment
- Earlier recurrence after remission
- **Less time well**

Goldstein & Levitt, *Am J Psychiatry* 2006; Leverich et al. *J Pediatr* 2007; Perlis et al. *Biol Psychiatry* 2004; Perlis et al, *Bipolar Disord* 2009

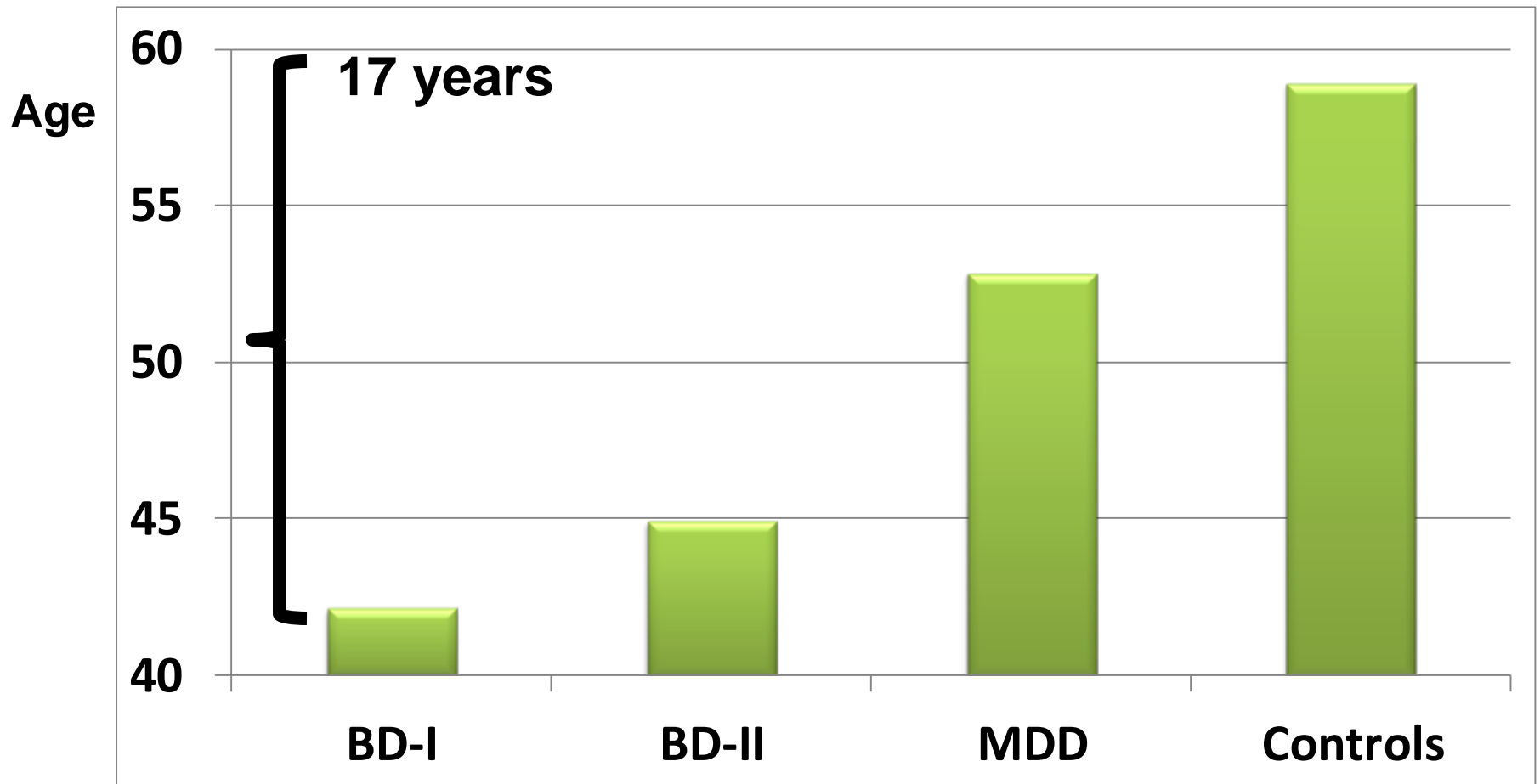


Bipolar Disorder among Canadian Adolescents and Young Adults

	15-18yo	19-24yo
Female	64.9%	52.3%
White	72.7%	77.7%
Anxiety disorder	41.8%	48.6%
Substance abuse	32.1%	46.0%
Suicidality	54.6%	48.6%
Received treatment	45.8%	60.3%



Mean Age at Wave 1 of Adults with New-onset Cardiovascular Disease at Wave 2 in the NESARC





***“Not at all infrequently
and in comparative youth
arteriosclerosis is present”***

—Emil Kraepelin, 1921



AHA Scientific Statement

Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease

A Scientific Statement From the American Heart Association

Benjamin I. Goldstein, MD, PhD, Chair; Mercedes R. Carnethon, PhD; Karen A. Matthews, PhD, FAHA;
Roger S. McIntyre, MD; Gregory E. Miller, PhD; Geetha Raghuvver, MD, FAHA;
Catherine M. Stoney, PhD; Hank Wasiak, BA, MBA; Brian W. McCrindle, MD, MPH, FAHA, Co-Chair;
on behalf of the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth
Committee of the Council on Cardiovascular Disease in the Young

Circulation
Volume 132(10):965-986
September 8, 2015





Step 1: Risk Stratification by Disease Process

Tier I: High Risk

- Diabetes mellitus, type 1 and type 2
- Chronic kidney disease/end-stage renal disease/post kidney transplant
- Post heart transplant
- Kawasaki disease with current coronary artery aneurysms

Tier II: Moderate Risk

- Kawasaki disease with regressed coronary aneurysms
 - Chronic inflammatory disease
 - HIV
 - Nephrotic syndrome
 - **Major depressive disorder or bipolar disorder (NEW)**
- } $\approx 0.5\%$
- } $\approx 10\%$



Step 2: Assess Cardiovascular Risk Factors

- Family history of early CVD in expanded 1st degree pedigree ($\sigma \leq 55y$; $\text{♀} \leq 65y$)
- Fasting lipid profile*
- Smoking history*
- Blood pressure (BP), 3 separate occasions, interpreted for age/sex/height percentile
- Height, weight, body mass index (BMI)*
- Fasting glucose (FG)
- Diet, physical activity/exercise history*

*Increased prevalence among adolescents with bipolar disorder

If ≥ 2 Risk Factors, move to Tier I

Reasons for Excessive and Premature Cardiovascular Disease among People with Bipolar Disorder

Pathophysiology

- Inflammation
- Oxidative stress
- Autonomic dysfunction
- Endothelial dysfunction

Behavior and Environment

- Early adversity/abuse
- Sleep disturbance
- Sedentary lifestyle
- Suboptimal nutrition
- Tobacco, alcohol, and substance use

Medication

- Anti-depressants: weight gain (mild)
- Second generation antipsychotics: weight gain (significant), dysglycemia, dyslipidemia

CVD

```
graph TD; P([Pathophysiology]) --> B[• Inflammation<br>• Oxidative stress<br>• Autonomic dysfunction<br>• Endothelial dysfunction]; BE([Behavior and Environment]) --> BEB[• Early adversity/abuse<br>• Sleep disturbance<br>• Sedentary lifestyle<br>• Suboptimal nutrition<br>• Tobacco, alcohol, and substance use]; M([Medication]) --> MB[• Anti-depressants: weight gain (mild)<br>• Second generation antipsychotics: weight gain (significant), dysglycemia, dyslipidemia]; B --> CVD([CVD]); BEB --> CVD; MB --> CVD;
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Primary Reasons that Medications Do Not Fully Explain the Bipolar-Cardiovascular Link

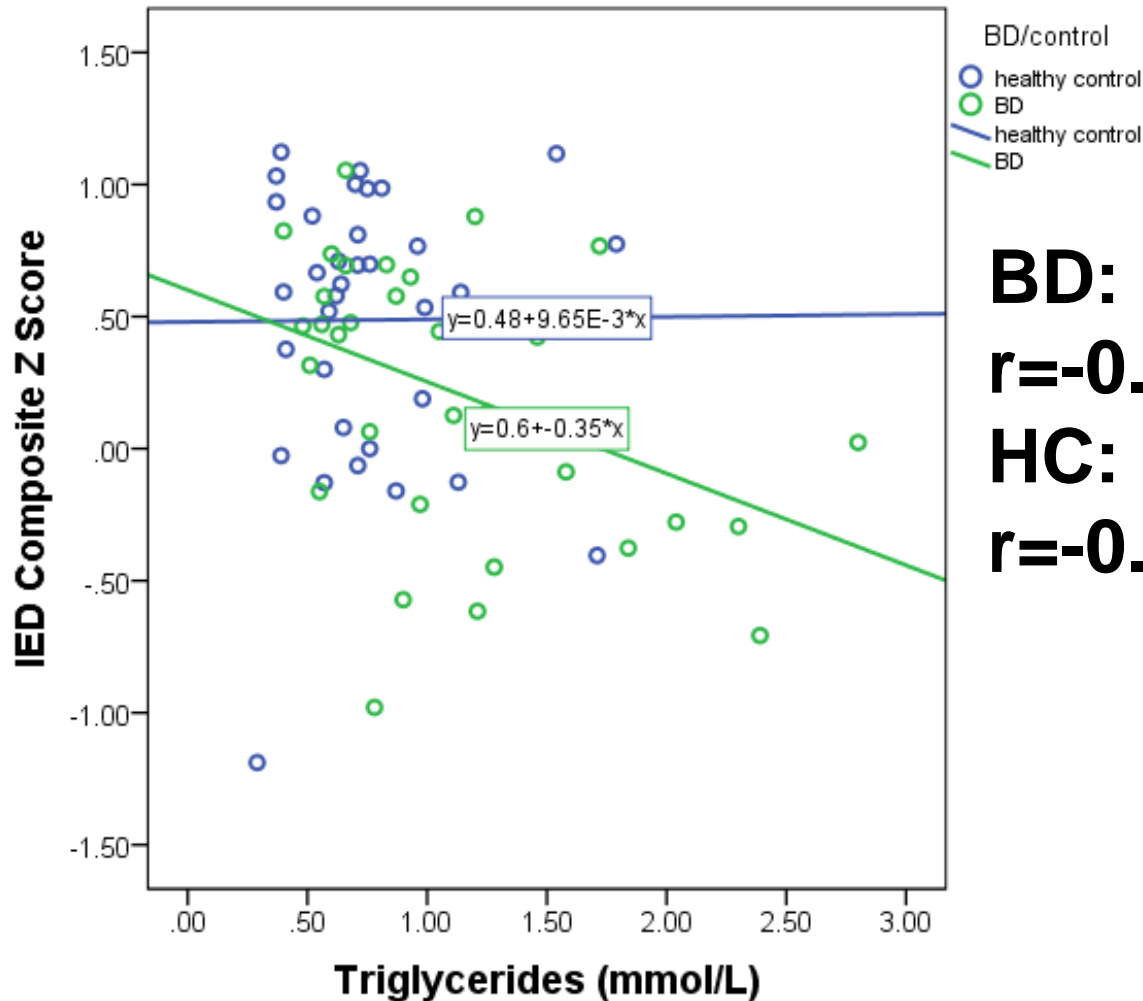
1. Medications may increase CVD risk factors, but increased risk of CVD is independent of CVD risk factors
2. Bipolar-CVD link described decades before the advent of medications
3. Most people in population studies had not received any treatment for mood disorders, let alone pharmacological treatment



Psychiatric Correlates of Cardiovascular Risk Factors in Bipolar Disorder

- More suicide attempts
- More manic and depressive episodes
- More psychiatric hospitalization
- Worse global symptom severity
- Worse global functional impairment
- What is the direction of this association?

Elevated Triglycerides are Associated with Reduced Executive Function

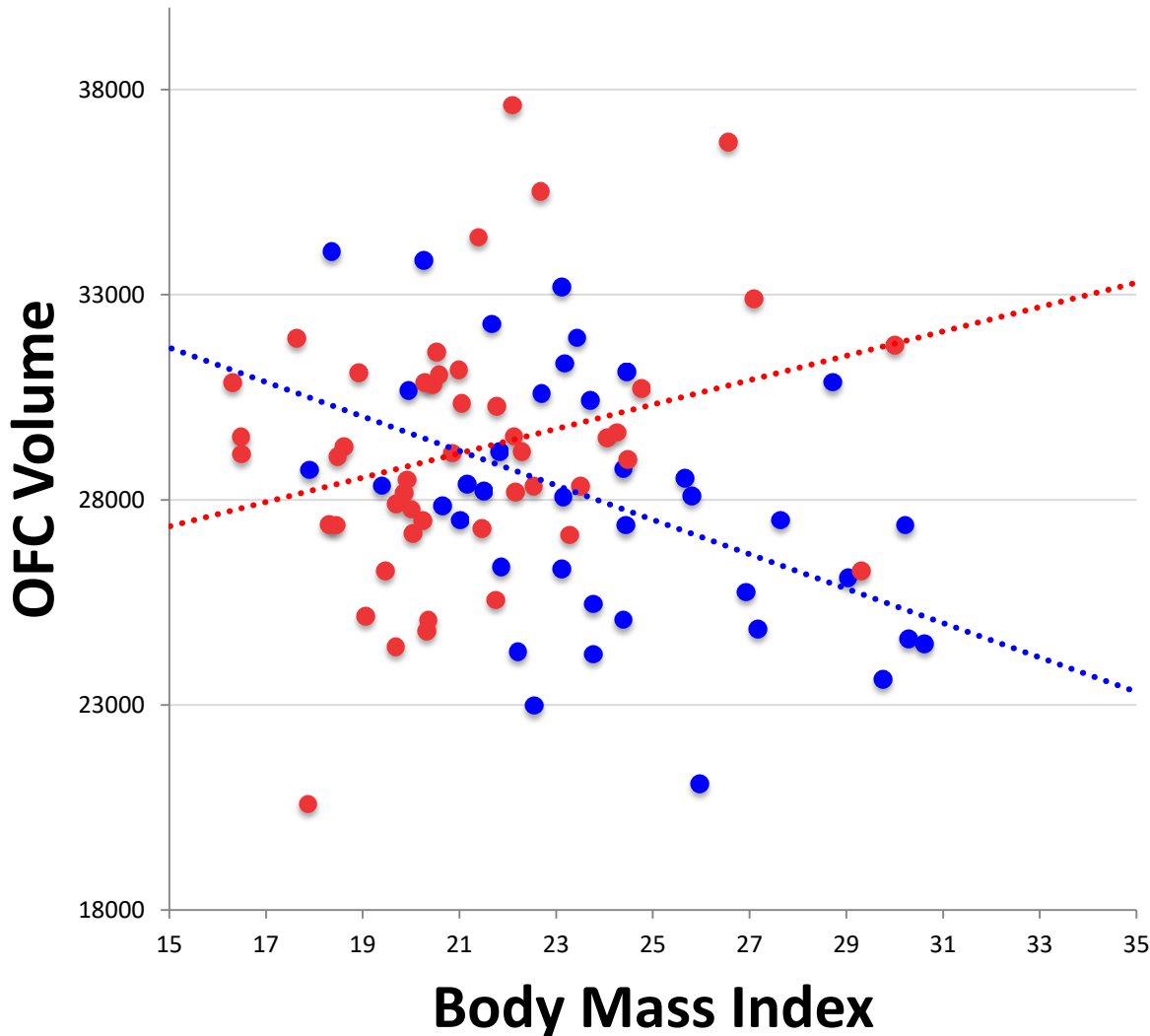


BD:
 $r = -0.396$, $p = 0.020$
HC:
 $r = -0.057$, $p = 0.744$





Greater BMI Correlates with Lower Frontal Cortical Thickness and Volumes



- BD
- HC
- Linear (BD)
- Linear (HC)

$\beta=161.54, \eta^2_p=0.041, p=0.182$

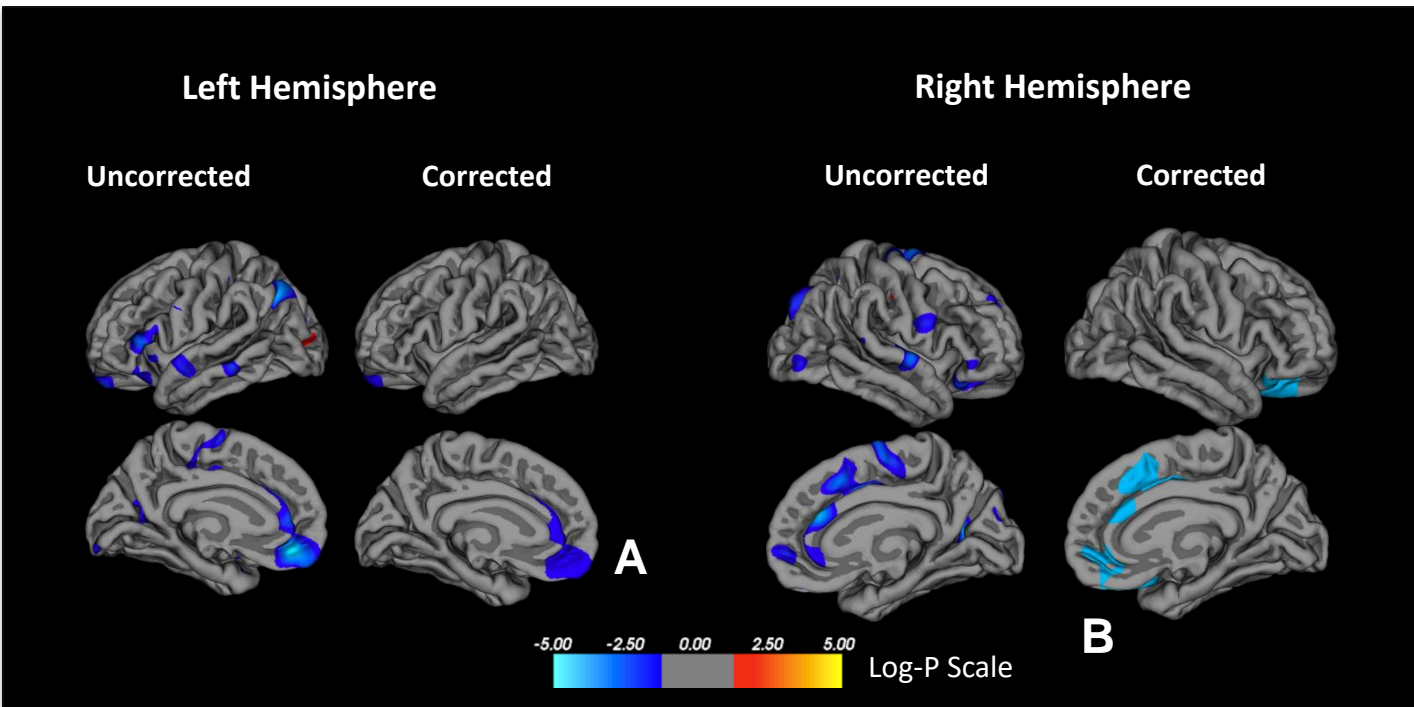
Group-BMI interaction

P=0.005

$\beta=-269.48, \eta^2_p=0.195, p=0.007$



Whole-brain analyses (BD>HC): BMI-Cortical Volume correlation



[A] CW P-value=0.027
Size (mm²) = 1544.41
Cluster peak: **Medial OFC**
Encompasses: Caudal and Rostral ACC,
Superior Frontal

[B] CW P-value=0.0001
Size (mm²) = 3197.35
Cluster peak: **Caudal ACC**
Encompasses: Posterior cingulate, superior
frontal, rostral ACC, medial & lateral OFC



ELSEVIER

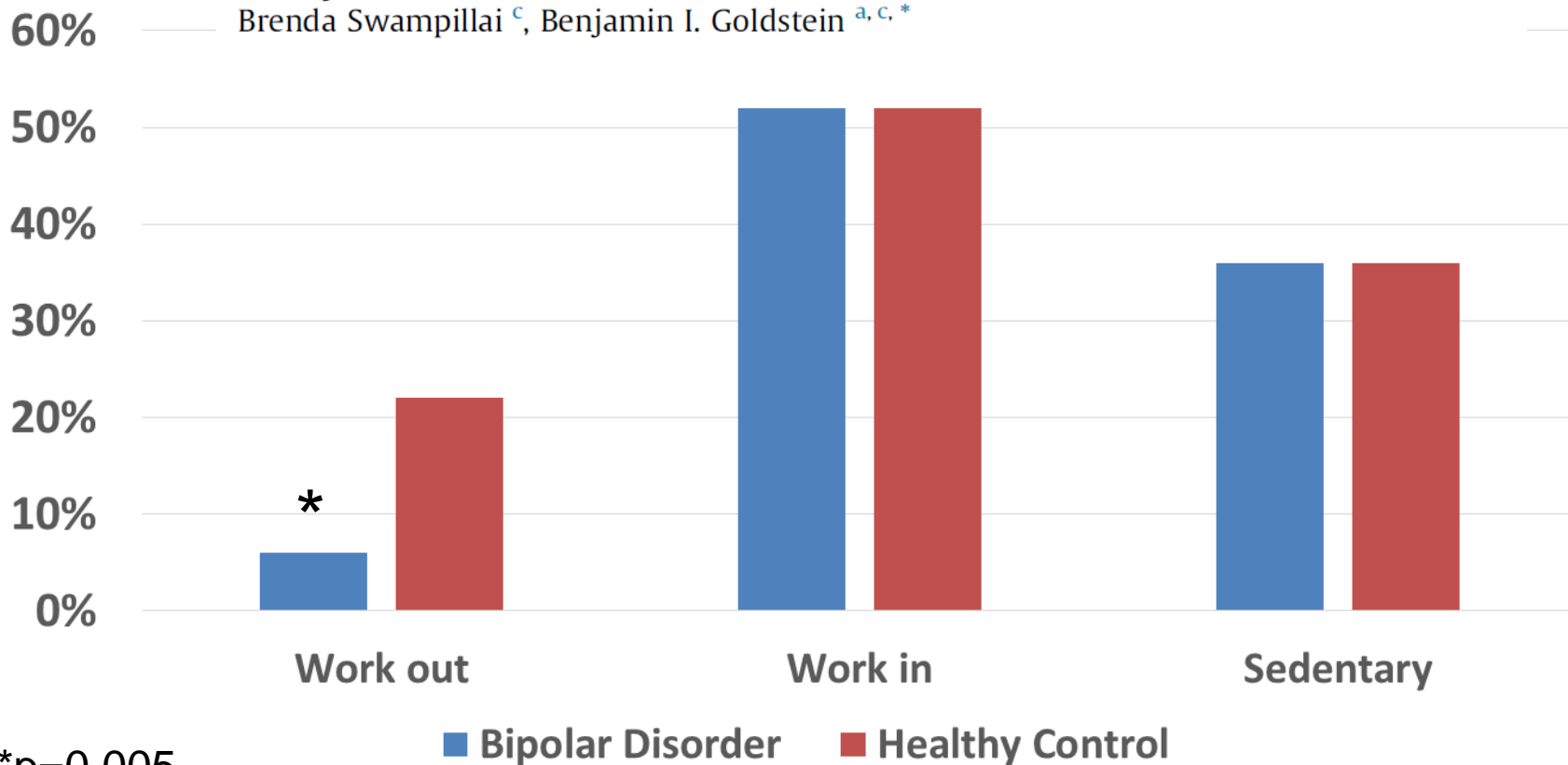
Contents lists available at ScienceDirect

Mental Health and Physical Activity

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

Preliminary evidence of disparities in physical activity among adolescents with bipolar disorder

Laura Jewell ^a, Robert Abtan ^b, Antonette Scavone ^c, Vanessa Timmins ^c,
Brenda Swampillai ^c, Benjamin I. Goldstein ^{a, c, *}



Exercise as Treatment in Bipolar Disorder

Neuromol Med (2009) 11:328–336
DOI 10.1007/s12017-009-8079-9

ORIGINAL PAPER

Exercise and Bipolar Disorder: A Review of Neurobiological Mediators

Mohammad T. Alsuwaidan · Aaron Kucyi ·
Candy W. Y. Law · Roger S. McIntyre

Exercise Treatment for Bipolar Disorder: Potential Mechanisms of Action Mediated through Increased Neurogenesis and Decreased Allostatic Load

Louisa G. Sylvia · Rebecca M. Ametrano · Andrew A. Nierenberg

frontiers in
PSYCHOLOGY

REVIEW ARTICLE

published: 04 March 2015
doi: 10.3389/fpsyg.2015.00147

USA

A brief review of exercise, bipolar disorder, and mechanistic pathways

Daniel Thomson¹, Alyna Turner^{2,3,4*}, Sue Lauder^{3,5}, Margaret E. Giggleswick⁶,
Julie A. Pasco^{2,8}, Michael Berk^{2,3,9,10} and Louisa Sylvia^{6,11}

Aerobic Physical Exercise as a Possible Treatment for Neurocognitive Dysfunction in Bipolar Disorder

Aaron Kucyi, BSc¹
Mohammad T. Alsuwaidan,
MD, FRCPC^{1,2}
Samantha S. Liauw¹
Roger S. McIntyre, MD,
FRCPC^{1–4}

Abstract

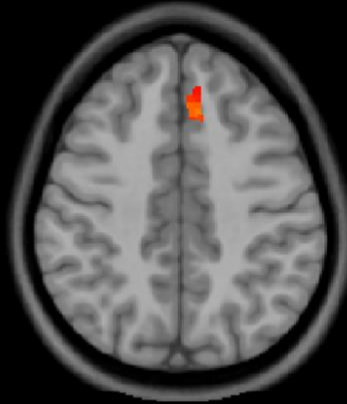
Background: Neurocognitive dysfunction associated with bipolar disorder (BD) is pervasive, persistent across illness phases, and is demonstrated to predispose and portend psychosocial impairment. Moreover, no approved therapies for various phases of BD have been shown to reliably improve any dimension of neurocognitive performance. In this article, we emphasize that aerobic physical exercise is a viable neurocognitive-enhancing adjunctive treatment for patients with BD. The overarching aim of this review is to emphasize that aerobic physical



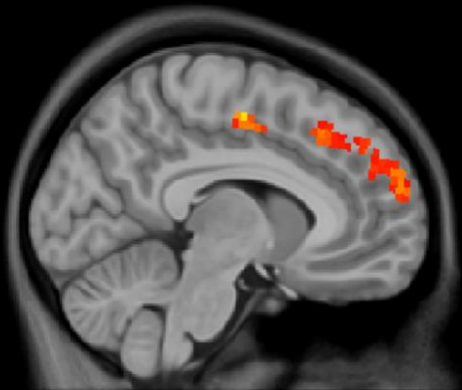
Baseline CBF: increased in BD compared to controls



Y=-10



Z=44



X=-8

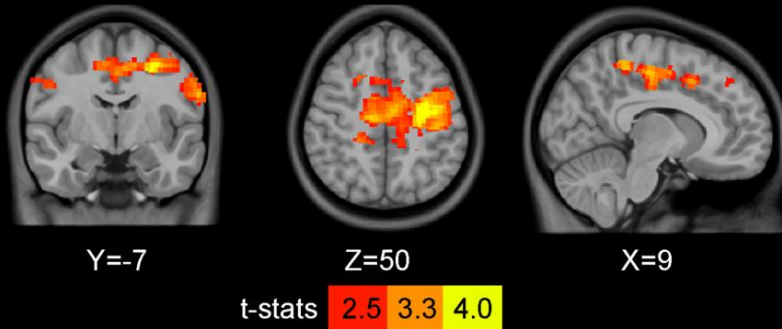


- Increased baseline frontal CBF in two left medial frontal regions and bilateral middle cingulate
- These findings were not related to volumetric frontal differences, BMI, mood, SGAs

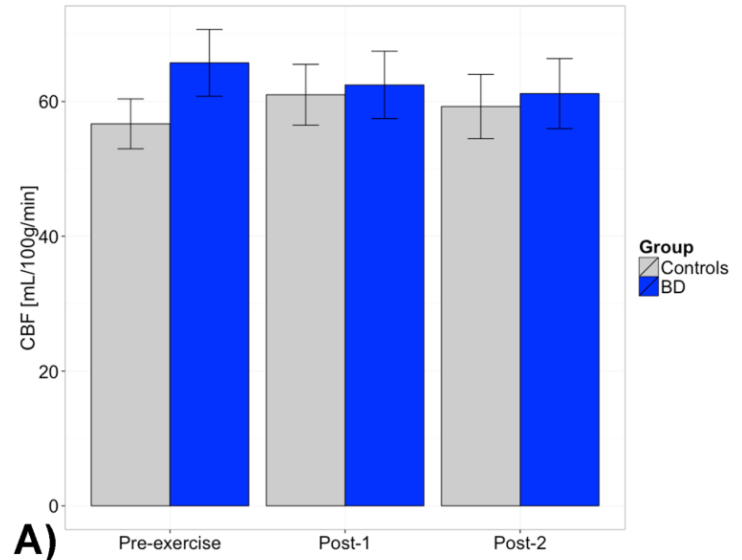
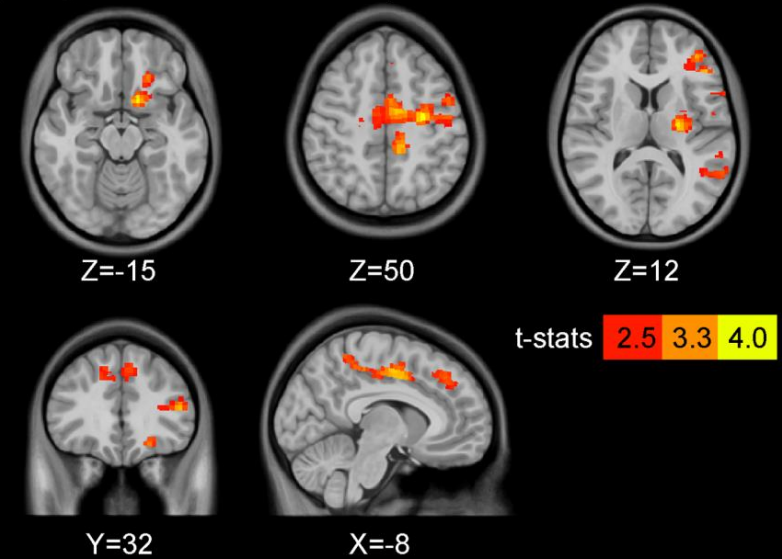


Elevated Cerebral Blood Flow among Adolescents with Bipolar Disorder

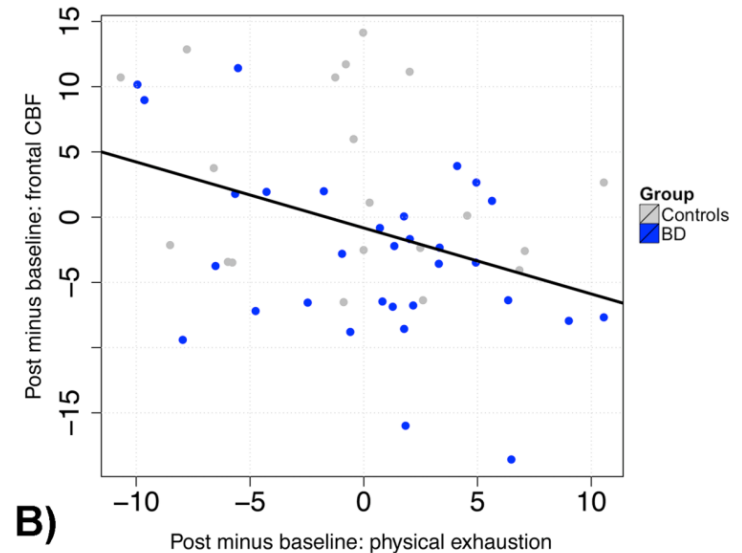
A) Larger CBF decreases at post1 in BD



B) Larger CBF decreases at post2 in BD

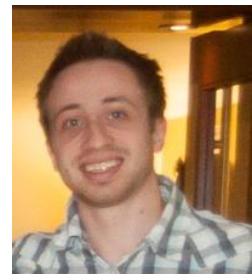
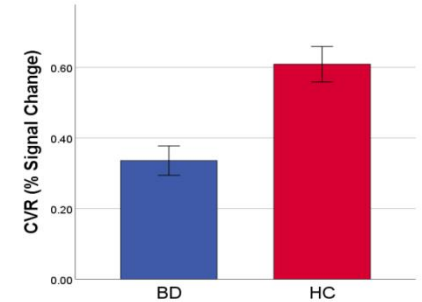
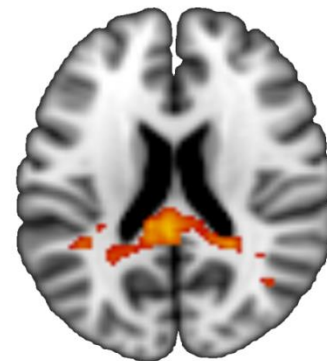
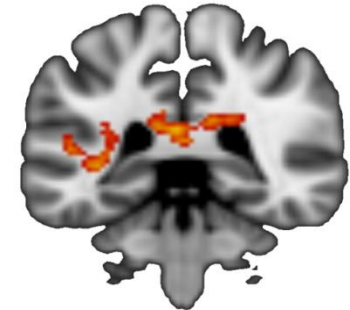
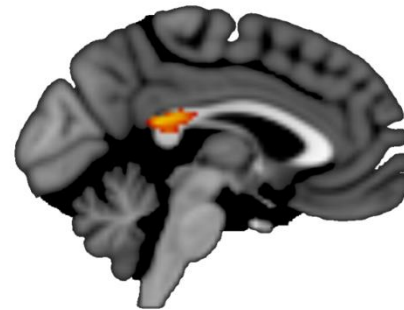
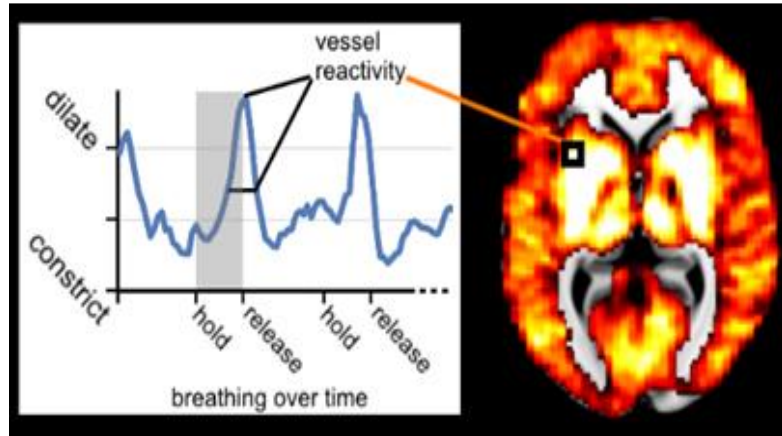


A)



B)

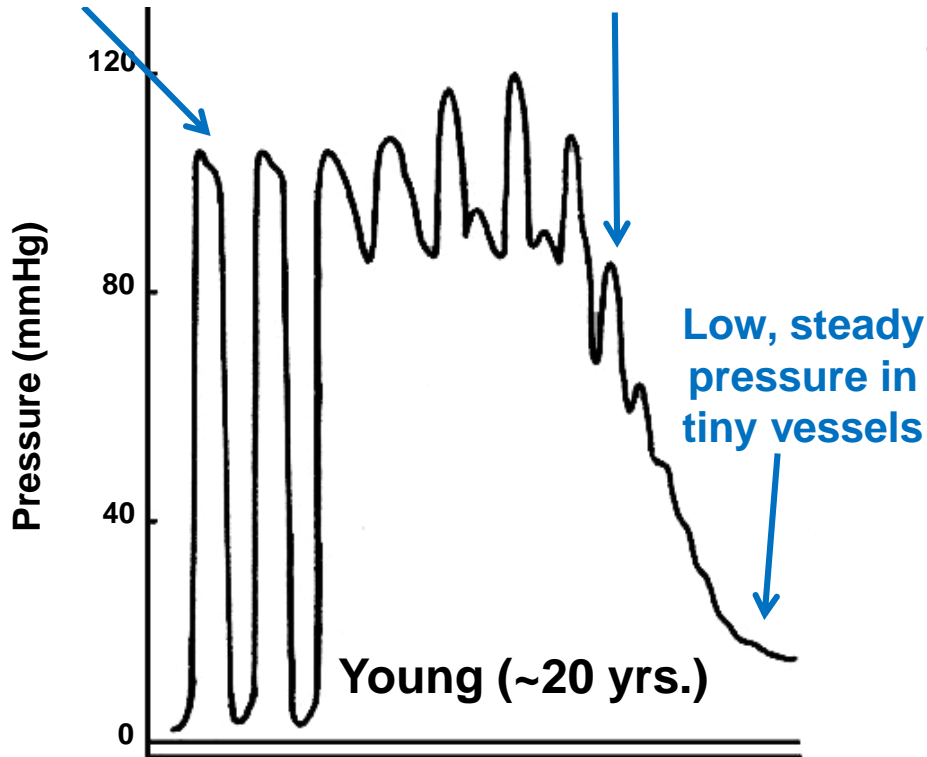
Lower Cerebrovascular Reactivity in White Matter among Adolescents with Bipolar Disorder



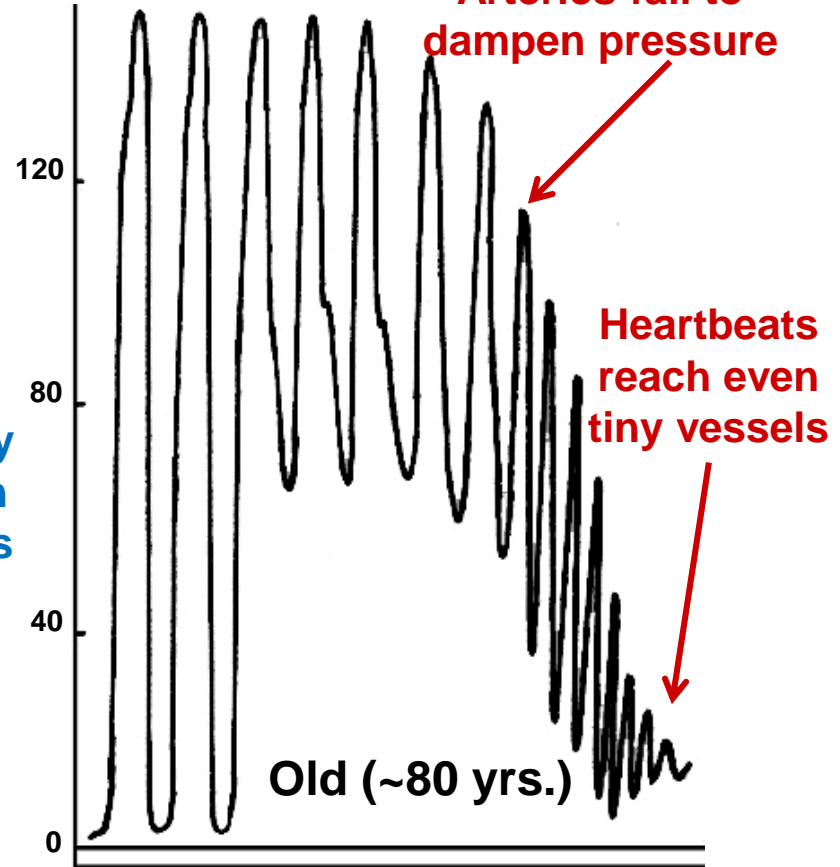
How Do Heartbeats Affect the Brain?

Cyclic pressure from heartbeats

Healthy small blood vessels dampen pressure

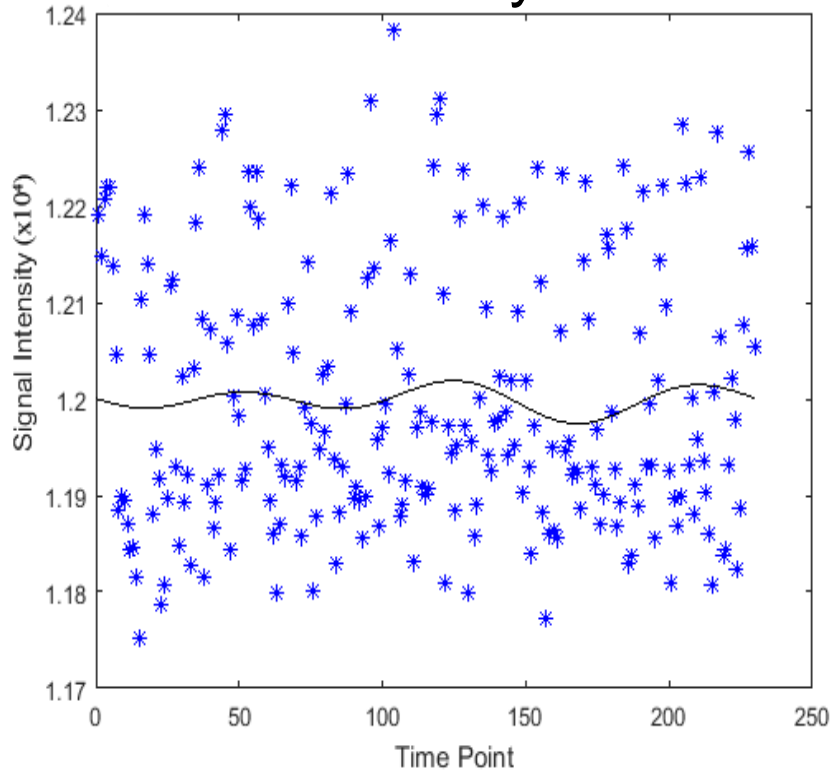


Arteries fail to dampen pressure



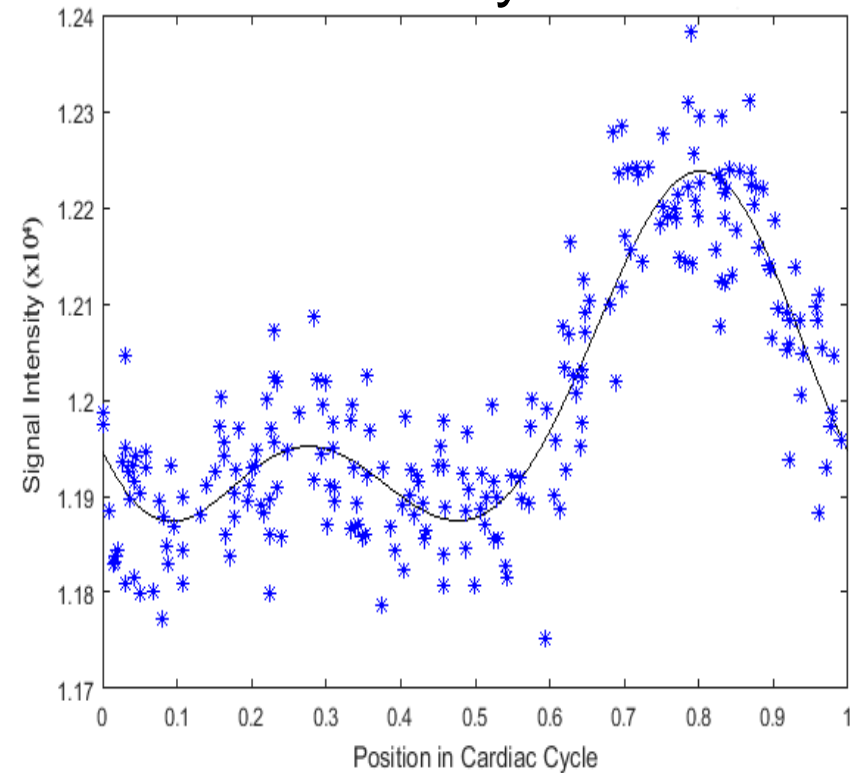
How Do Heartbeats Affect the Brain?

fMRI sorted by time



$R^2 = 0.007$

fMRI sorted by heartbeat



$R^2 = 0.793$

	Group (BD>HC)	Session (Pre>Post)	Group x Session
Gray Matter	.01	.002	.11
White Matter	.004	.009	.16

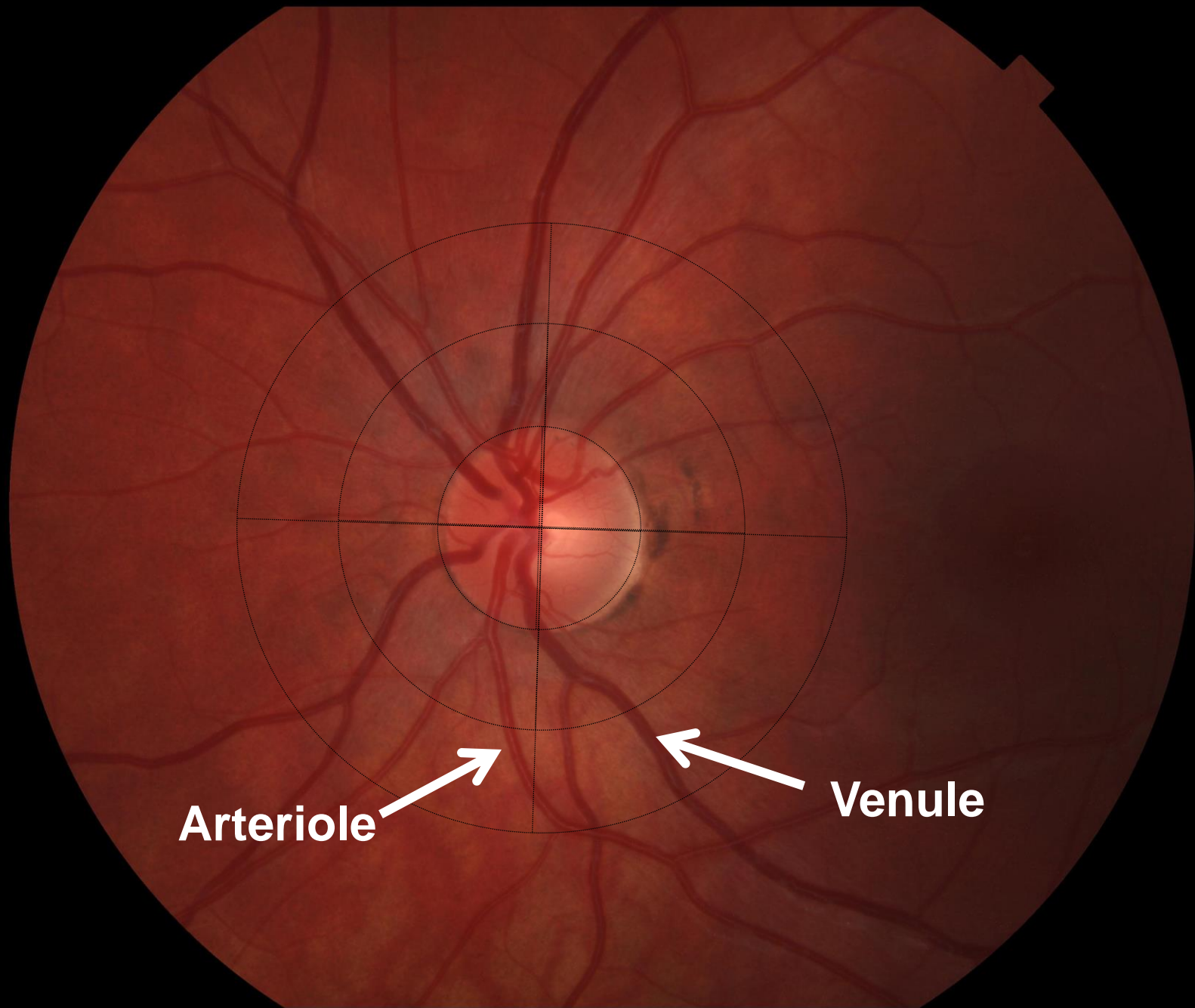


Research paper

Retinal photography: A window into the cardiovascular-brain link in adolescent bipolar disorder

Melanie R. Naiberg^{a,c,h}, Jessica K. Hatch^{a,c,h}, Beth Selkirk^{d,h}, Lisa Fiksenbaum^{a,h}, Victor Yang^{b,e,h}, Sandra Black^{b,e,f,h}, Peter J. Kertes^{d,g,h}, Benjamin I. Goldstein^{a,c,h,*}





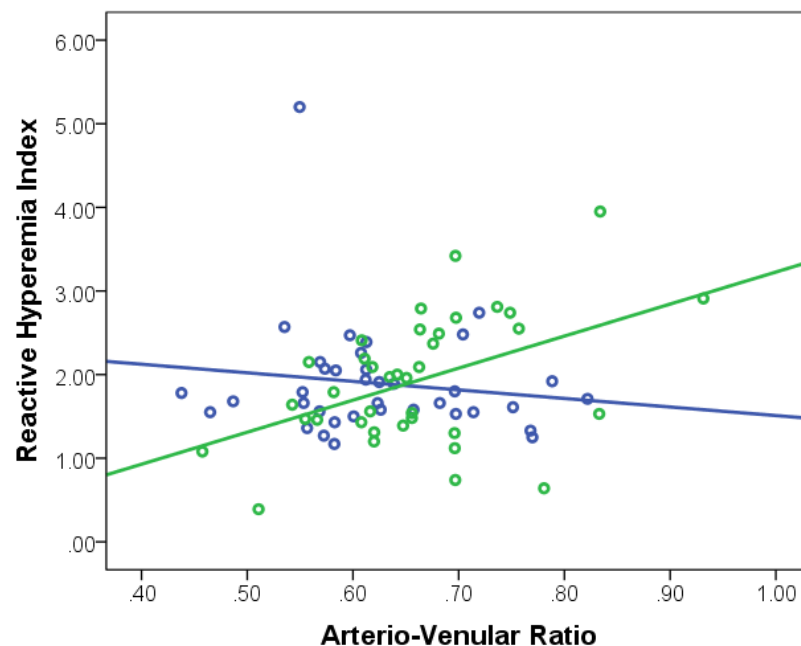
Arteriole

Venule

Retinal Photography: Window to Examine Brain Blood Vessels in Bipolar Disorder

In adolescents with BD, but not healthy adolescents, retinal vessels associated with:

- Blood pressure
- Fingertip blood vessel function
- Mood symptoms

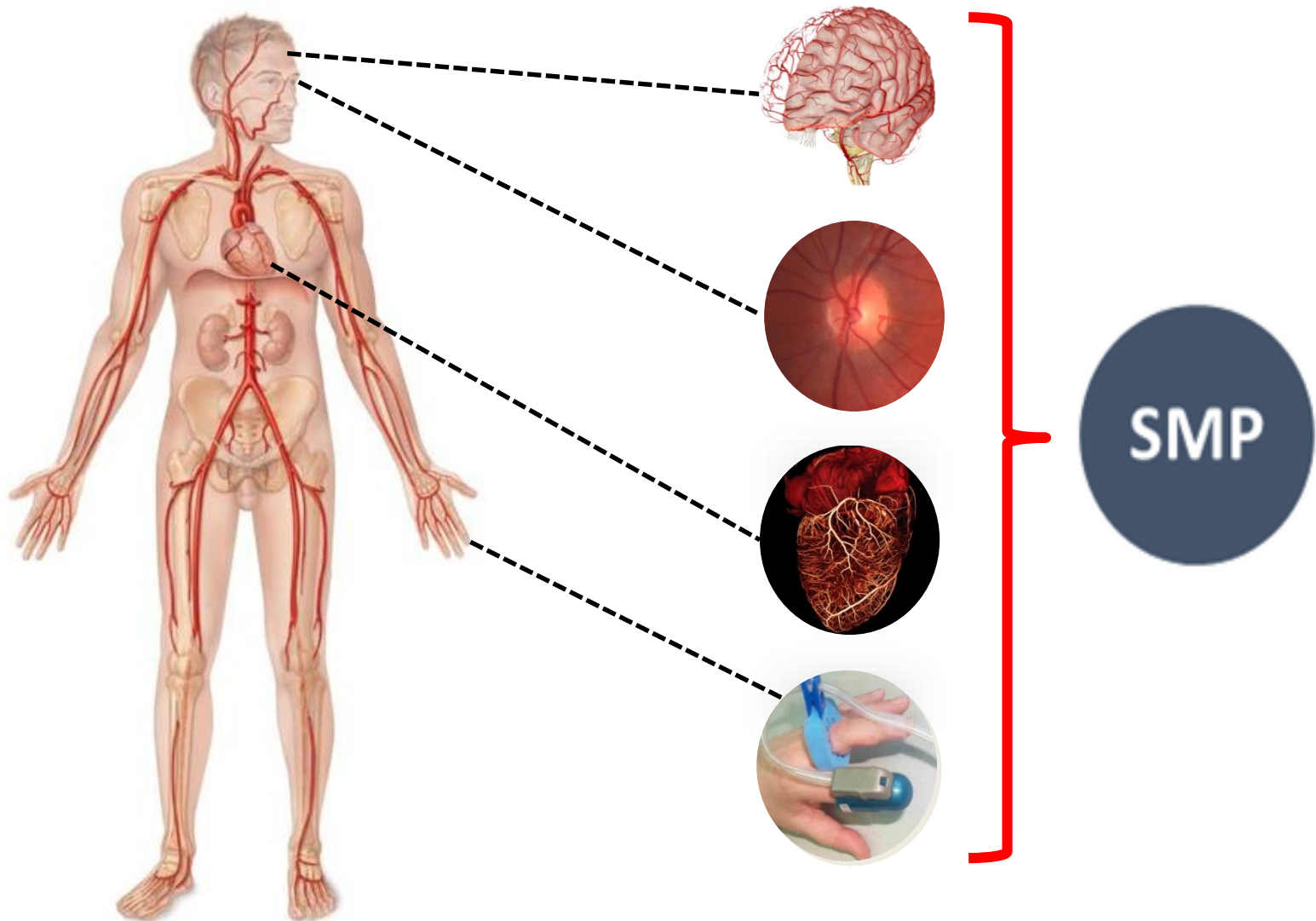


BD group: $r=0.458$, $p=0.004$

HC group: $r=-0.077$, $p=0.649$



Next Steps: Systemic Microvascular Phenotype (SMP)



Next steps: Nitrous Oxide for Bipolar Disorder

Readily available +

Inexpensive +

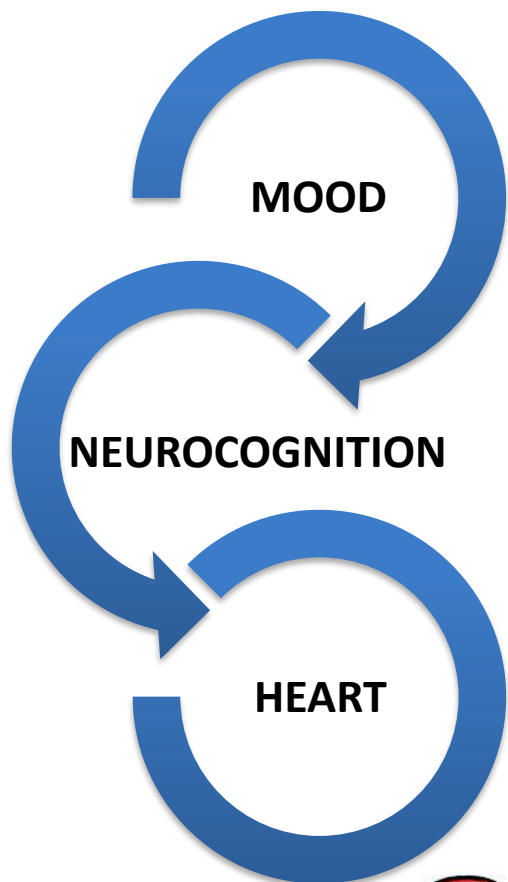
Generally safe +

Ease of administration

= Potential game-changer for bipolar depression

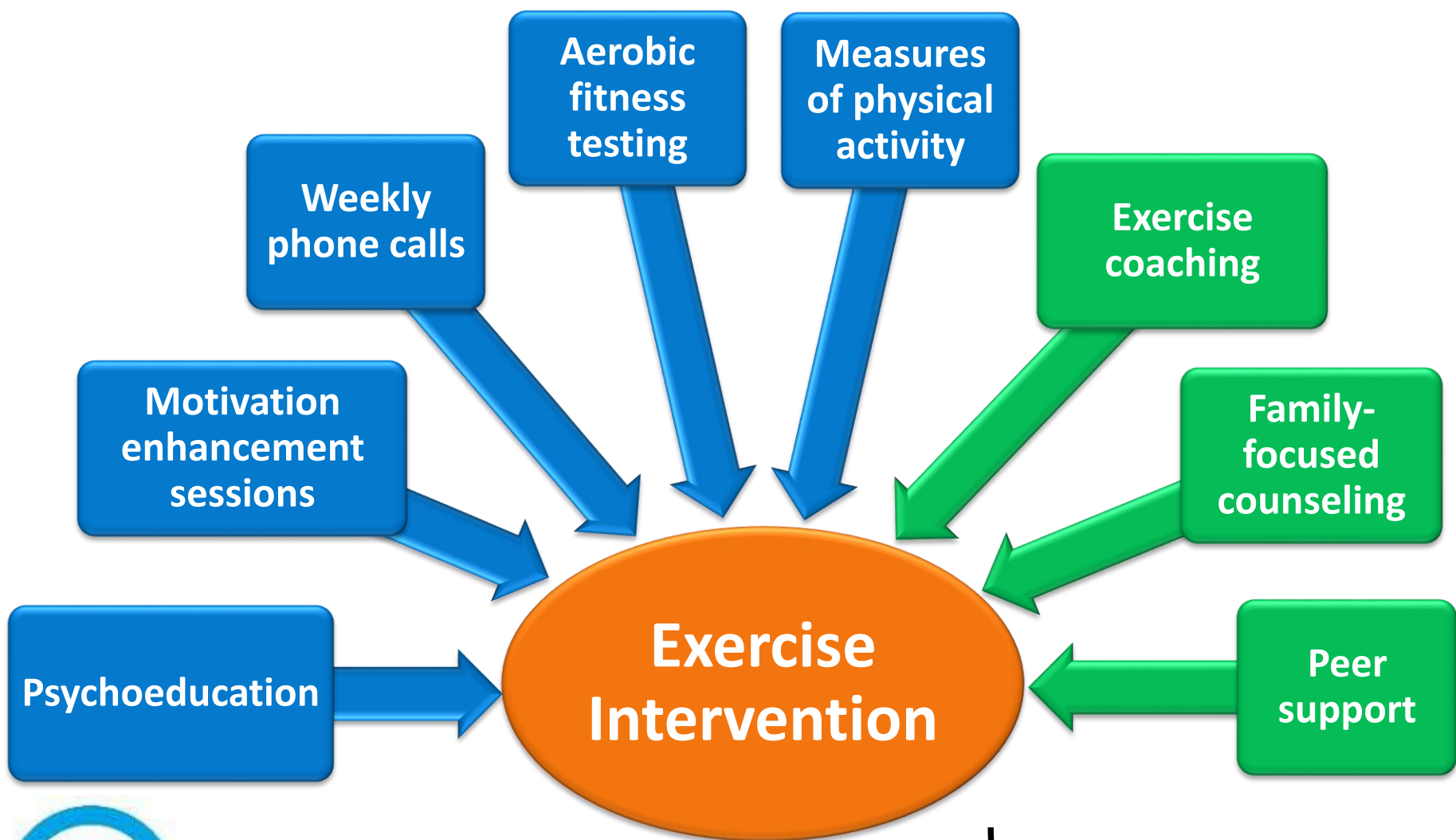


Next Steps: Aerobic Exercise for Bipolar Disorder



- Low rates of aerobic exercise among youth with bipolar disorder
- Multiple potential benefits on brain, mind, heart
- Benefits are within reach for vast majority, regardless of weight loss
- Greatest benefits come to those who are most aerobically unfit

Toward Exercise as Medicine for Adolescents with Bipolar Disorder (TEAM-BD)



Research Emphasizes Integrative Care

WEDNESDAY, DECEMBER 23, 2015

Study Suggests Mental Disorders Increase Risk of Subsequent Chronic Physical Conditions



Findings from a study published today in *JAMA Psychiatry* suggest that mental disorders increase the odds of later range of chronic physical chronic pulmonary disease disorders being most prev

Researchers from the Univ Australia analyzed retros generated from the World more than 47,000 adults in 17 countries.

JAMA | Viewpoint | December 22, 2015

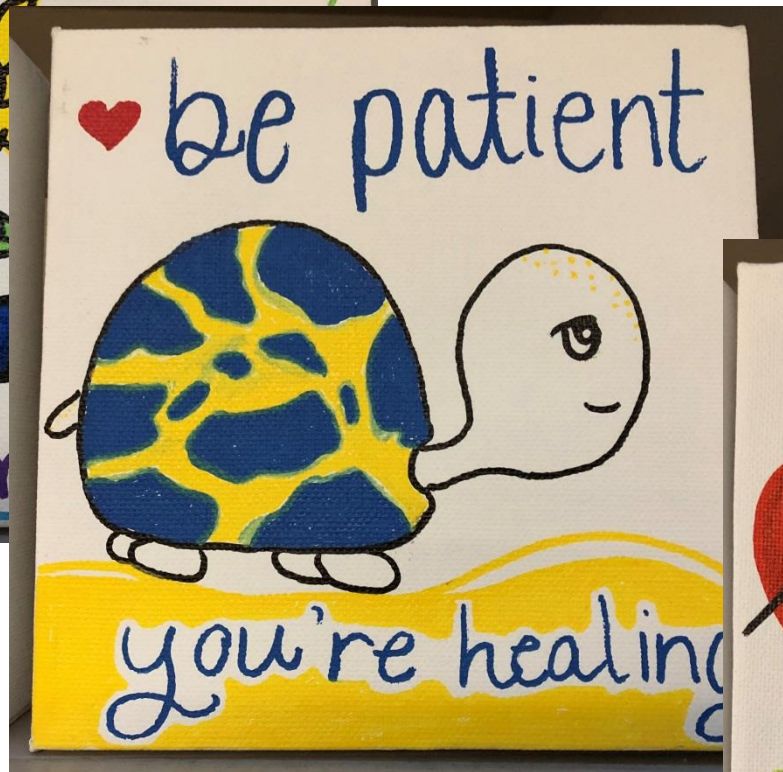
Making Physical Activity Counseling a Priority in Clinical Practice: The Time for Action Is Now

Kathy Berra, MSN, NP-BC; James Rippe, MD; JoAnn E. Manson, MD, DrPH
JAMA. 2015;314(24):2617-2618. doi:10.1001/jama.2015.16244.

“...given the early onset...treatment of all mental disorders should optimally incorporate **attention to physical health and health behaviors**, with this parallel focus on physical health **beginning as early in the course of the mental disorder as possible.**”

Scott et al, *JAMA Psychiatry* 2015

Messages of Hope





Conclusions

- Adolescents with bipolar disorder have increased cardiovascular risk from a convergence of factors
- Cardiovascular risk factors among adolescents with bipolar disorder are associated with brain structure and function
- Cerebrovascular function appears to be impaired among adolescents early in their course of bipolar disorder
- The heart-bipolar link may offer clues toward novel biomarker and treatment approaches



Acknowledgments


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Keynote Response

*Audience Questions
and Answers*

with Dr. Benjamin Goldstein

Moderated by Dr. David Gratzner