

Is Bipolar Disorder an Energy Disorder? Evidence and Novel Treatments

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Disclosure Statement

Employee Of	Massachusetts General Hospital
Consultant For	Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Bristol-Myers Squibb, Cephalon, Clintara, Corcept, Eli Lilly & Co., Forest, Genaissance, Genentech, GlaxoSmithKline, Hoffman LaRoche, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Lundbeck, Medavante, Merck, Naurex, Novartis, PamLabs, PGx Health, Pfizer, Roche, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, Teva
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Honoraria From	MGH Psychiatry Academy in the past 3 years (Prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, J&J, Forest Pharmaceuticals, GlaxoSmithKline, Eli Lilly,, Shire, Wyeth-Ayerst), No speaker bureaus since 2003

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Disclosure Statement

Other Income	MBL Publishing for past services as Editor-in-chief of CNS Spectrums; Slack Inc. for services as Associate Editor of Psychiatric Annals; Editorial Board, Mind Mood Memory, Belvior Publications
Patents and Copyrights	Copyright joint ownership with MGH for Structured Clinical Interview for MADRS and Clinical Positive Affect Scale
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Outline

- Mitochondria
- PPARS and PGC-1 alpha
- New treatments

We are made of stars.

Moby



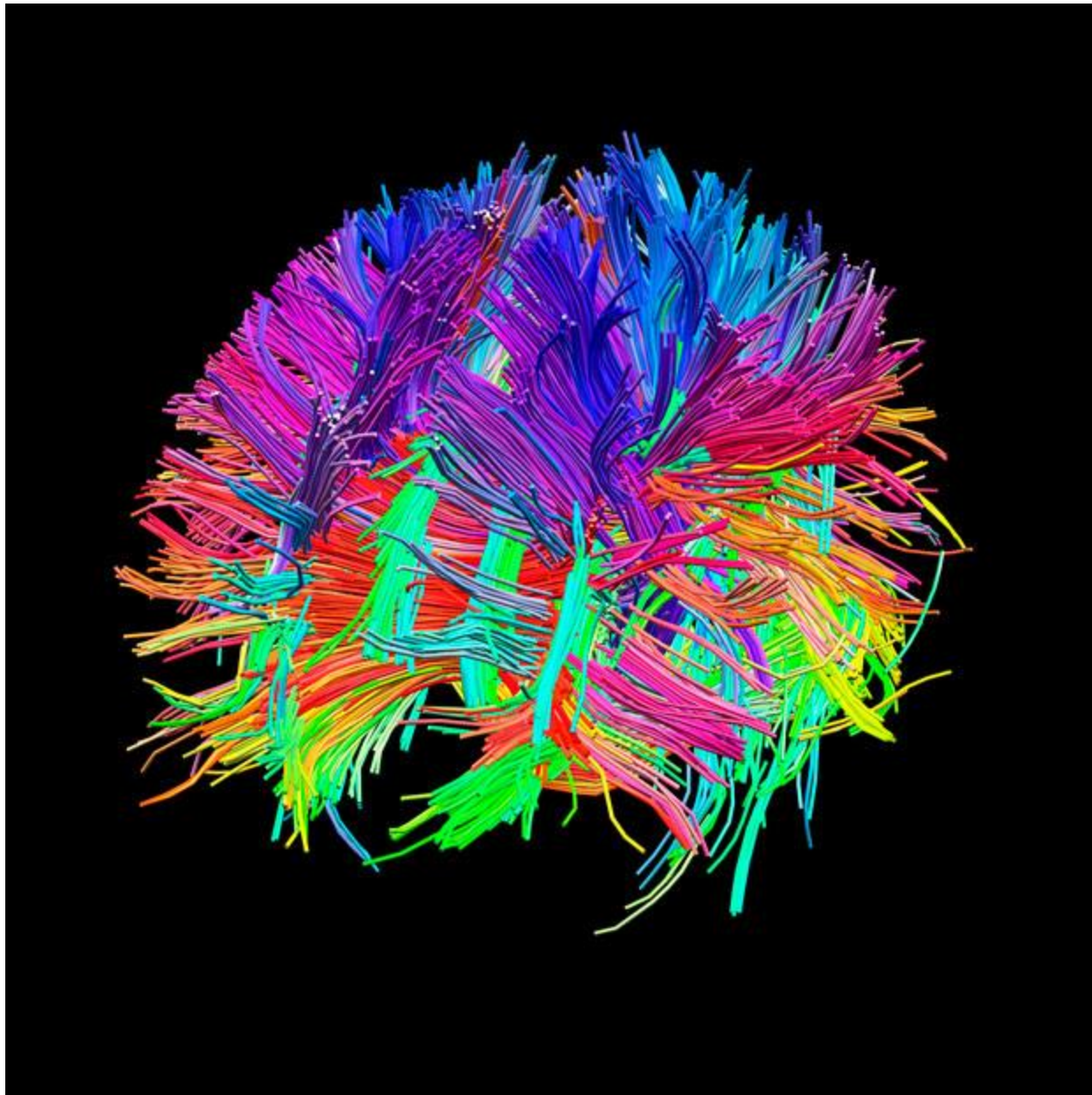
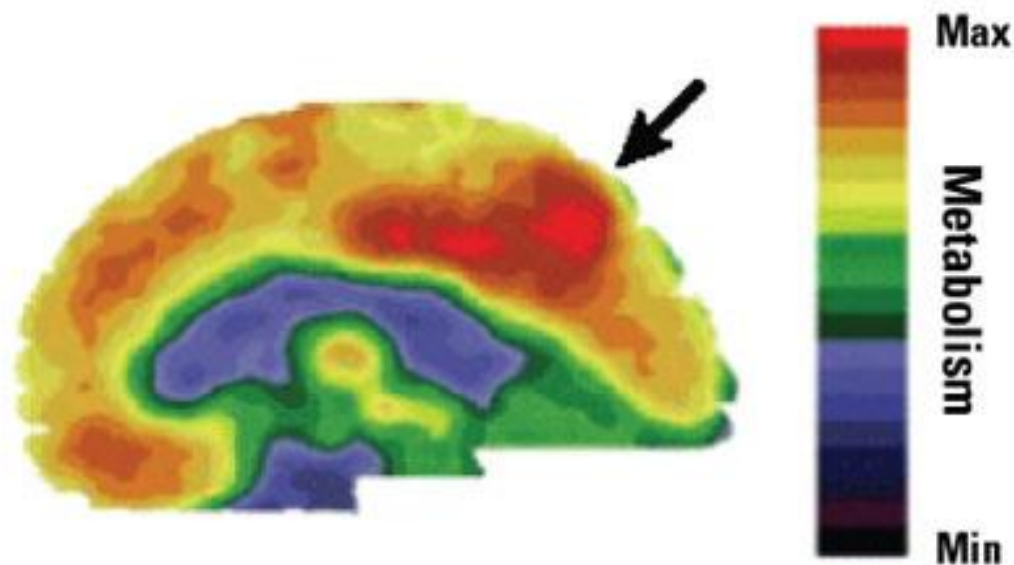


FIGURE 2.

The cortical areas associated with the highest resting metabolic rates in the conscious resting state are located in the posteromedial parietal cortex (posterior cingulate cortex and precuneus, arrow)¹⁶

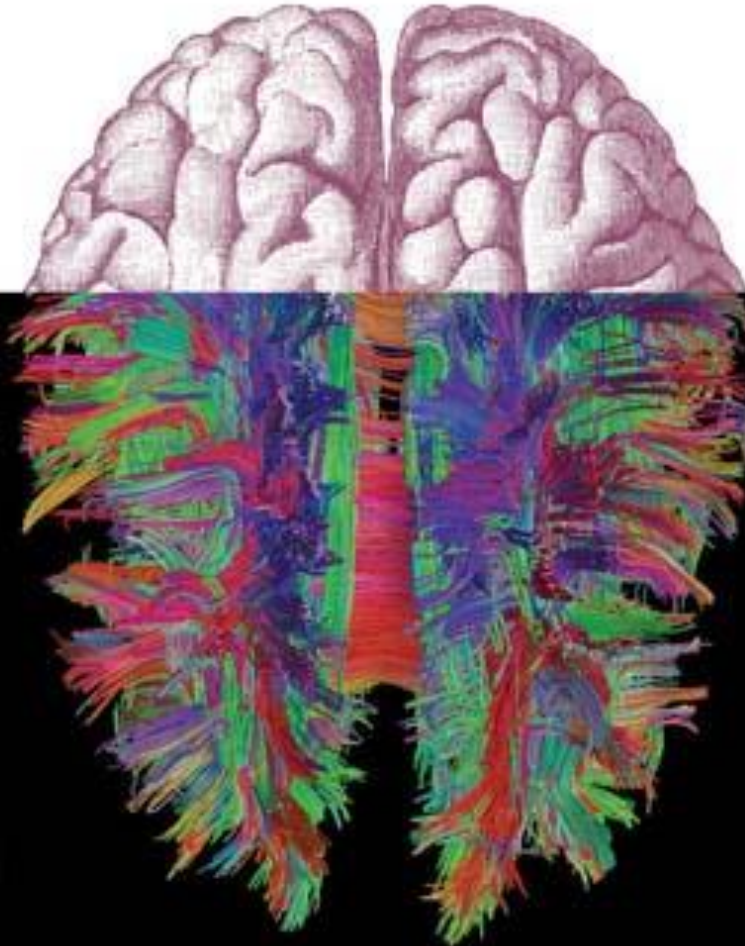


Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci.* 2001;2:685-694. Reprinted with permission.

Max=maximum; Min=minimum.

Cavanna AE. *CNS Spectr.* Vol 12, No 7. 2007.

Networks of the Brain



Olaf Sporns

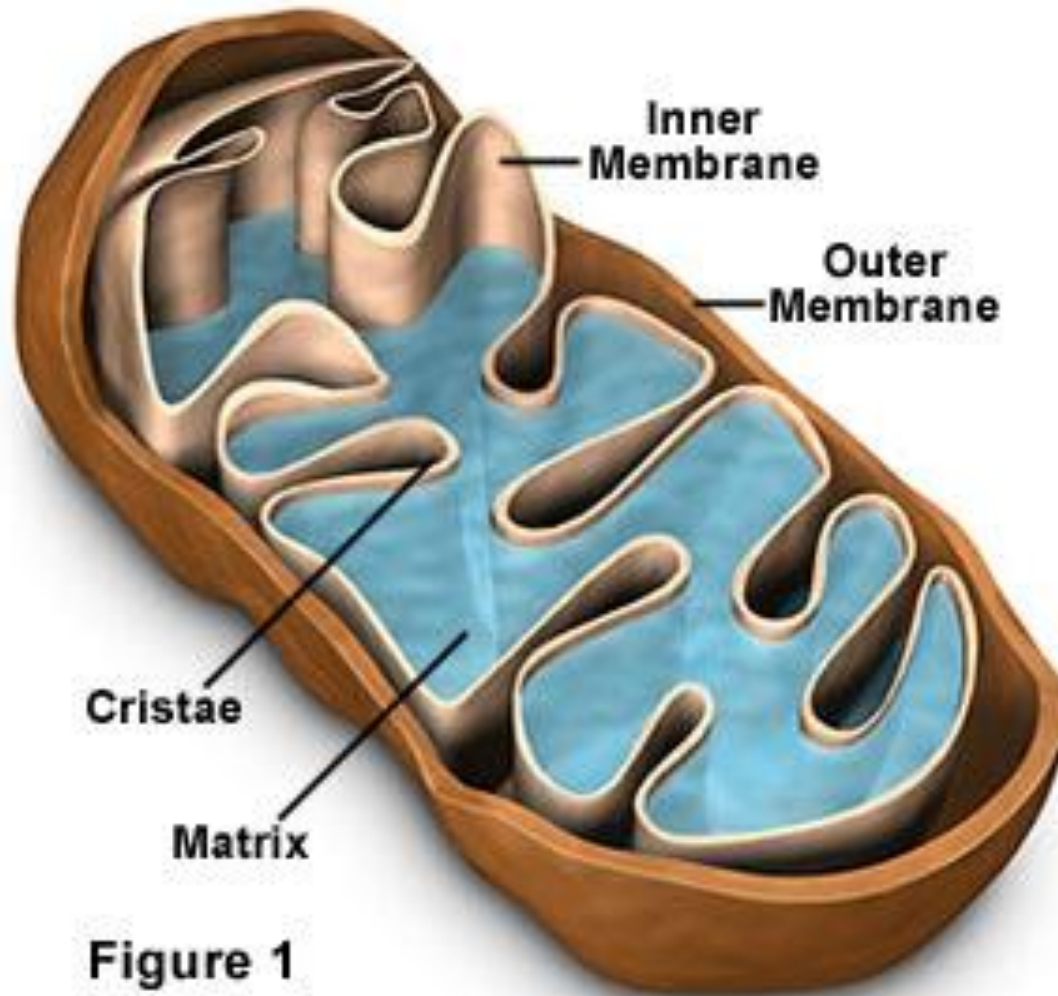
Mitochondria

Breathe

Eat

Energy

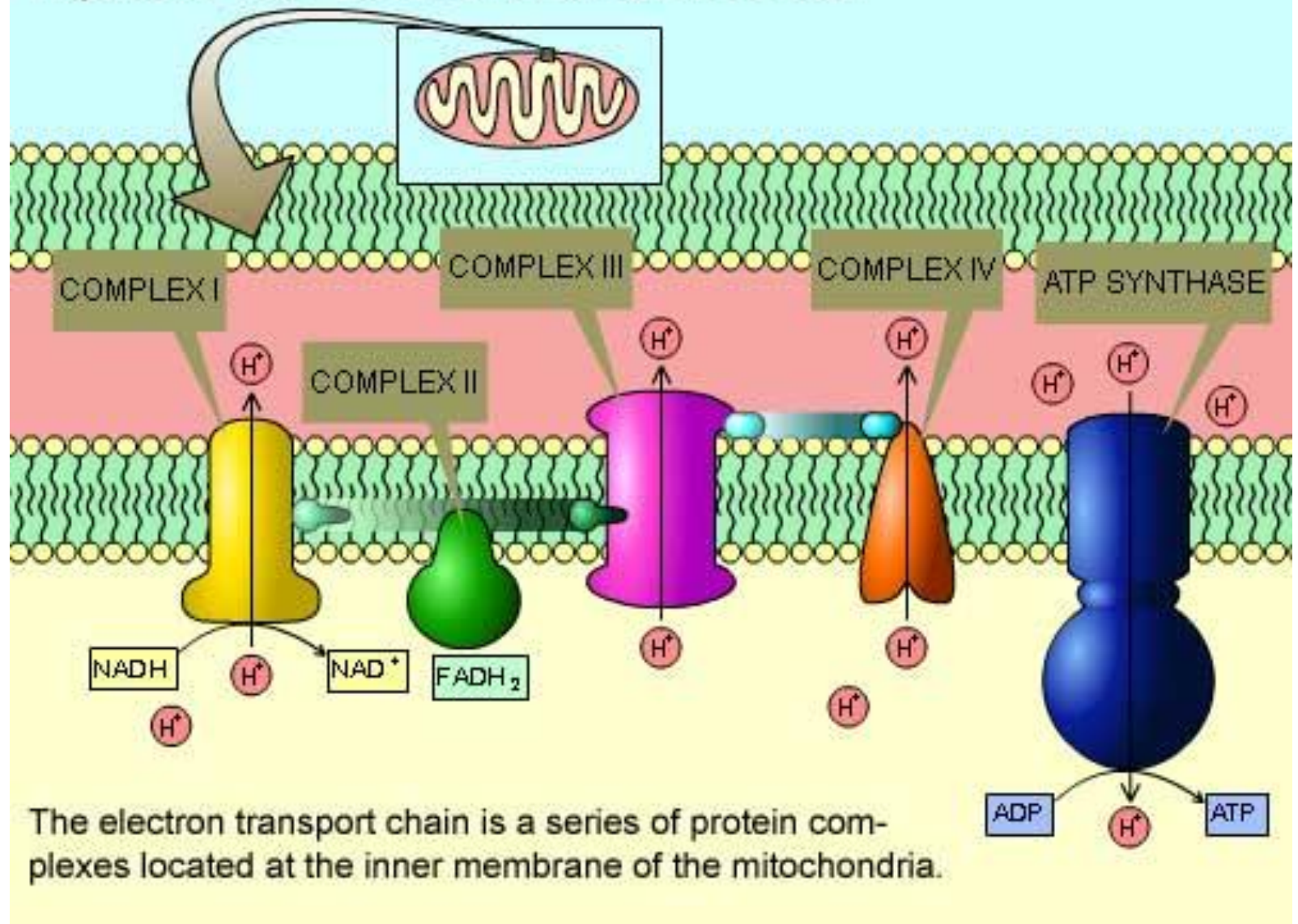
Mitochondria Inner Structure



Mitochondria

- Provide energy
 - Produce Adenosine TriPhosphate (ATP)
 - Stores energy
 - Produce proteins and membranes
- Allow neurons to change
 - New neurons
 - New dendrites
 - New synapses
 - Regulate cell survival
 - Regulate cell death

Figure J-13: Electron Transport Chain



Oxidative Stress



Oxidative Stress

- Natural Reactive Oxygen Species (ROS) from mitochondrial respiration
 - Superoxide anion
 - Nitric oxide
 - Hydrogen peroxide
- ROS can exceed metabolic capacity
 - Peroxynitrite
 - Hydroxy radical

Oxidative Stress

- Cellular dysfunction or death
- Non-physiologic ROS reactivity
 - Proteins
 - Nucleic acids
 - Carbohydrates
 - Lipids
- Due to dysfunctional electron flow in mitochondrial inner membrane

Oxidative Stress

- ROS damage mitochondria
- Decreased ATP and energy
- Damaged membrane
- Abnormal calcium sequestration
- Apoptosis (cellular death)
- Neurons especially susceptible

Mitochondrial Abnormalities in Bipolar Disorder

- Altered mitochondrial gene expression
- Decreased brain energy metabolism
- Altered calcium metabolism
- Bipolar calcium channel genes
- Decreased oxidative stress with lithium and valproate

PPARs and PGC-1 alpha

PPARs

(Peroxisome Proliferator
Activated Receptors)

PGC-1 alpha

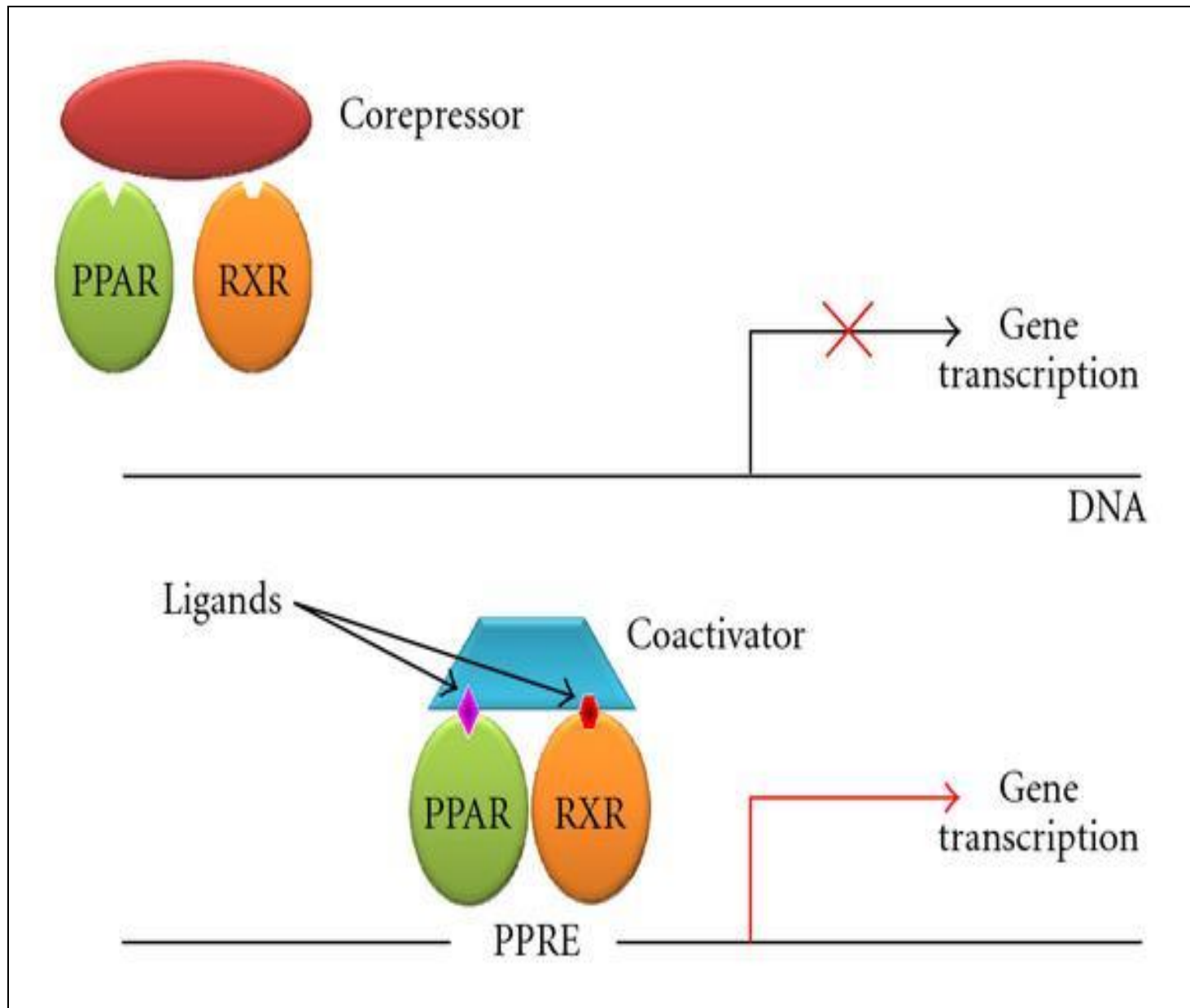
(PPAR Gamma Coactivator)

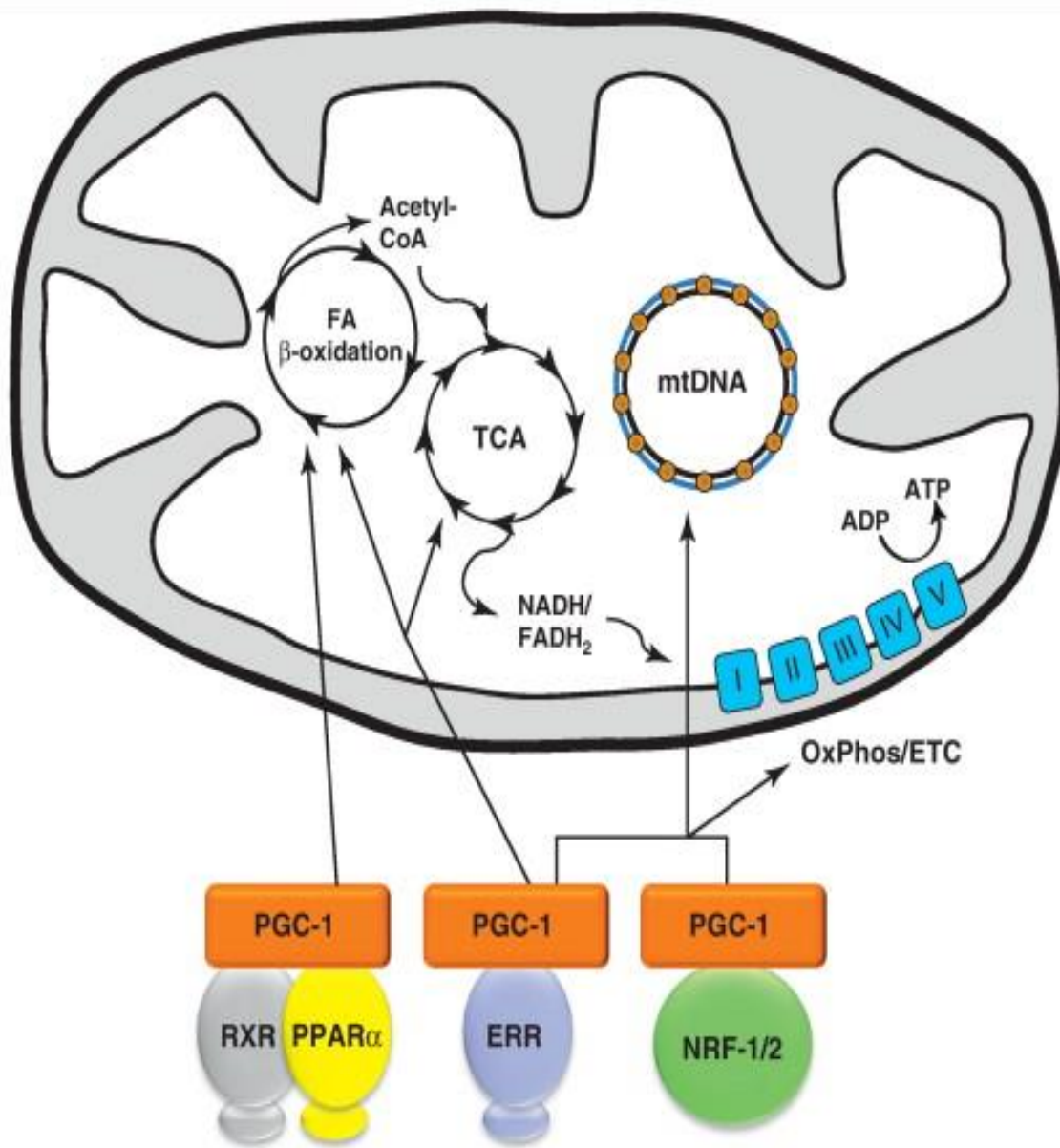
Peroxisome Proliferator-Activated Receptors

- Sit on DNA in nucleus
- Turn genes on and off
- Multiple functions
 - Regulate metabolism and fat
 - Anti-inflammatory and antioxidant
 - Protect neurons

PGC-1 alpha

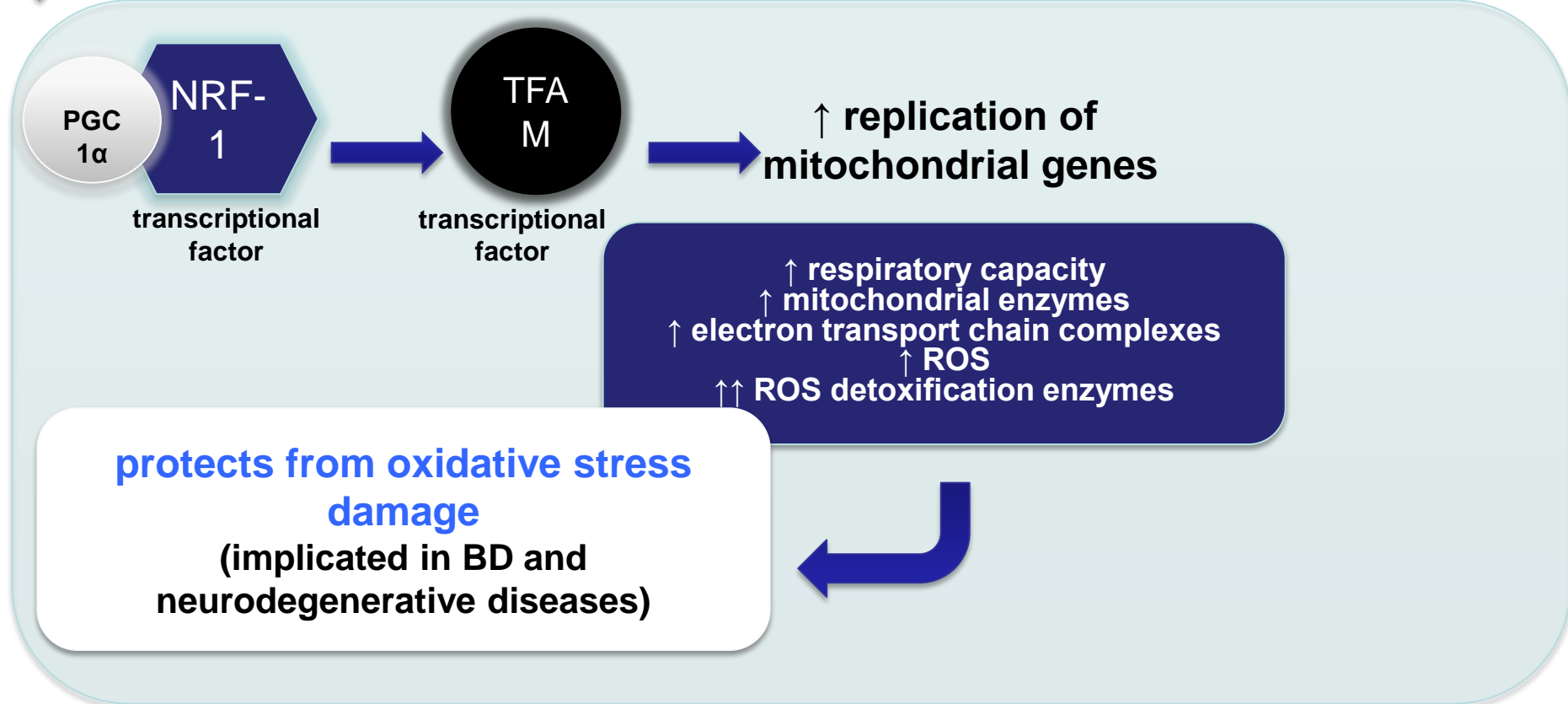
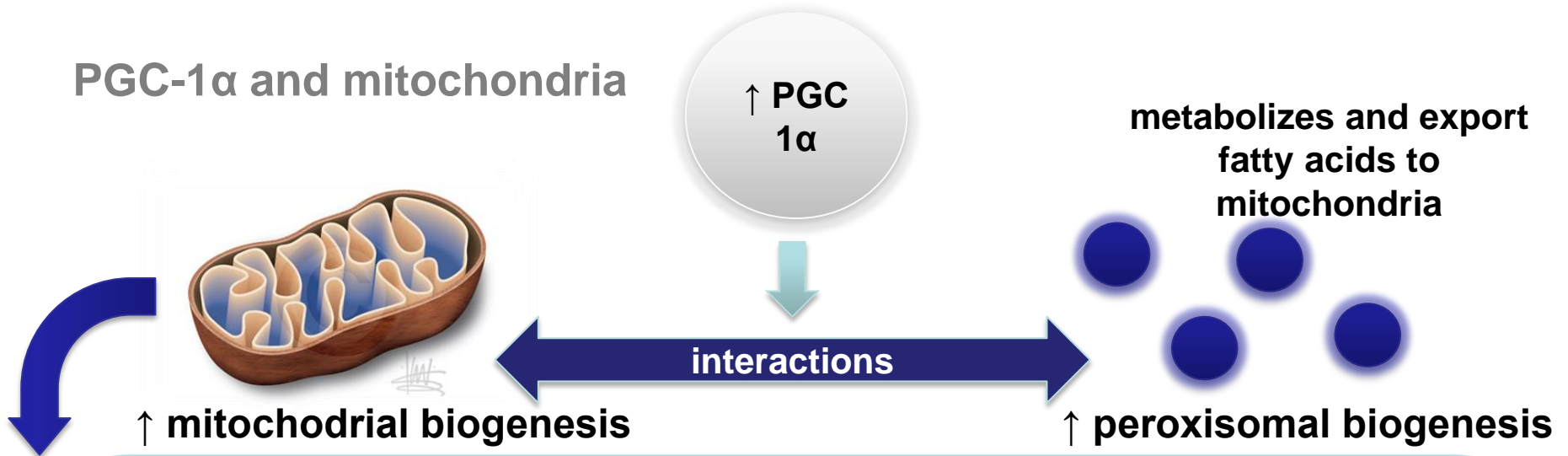
- Key co-factor
 - PPARs
 - Estrogen related receptors (ERR)
 - Nuclear regulatory factors (NRF)
- Broad metabolic effects
 - Carbohydrate metabolism
 - Lipid metabolism
 - Mitochondria
 - Link between exercise and health





TRENDS in Endocrinology & Metabolism

PGC-1 α and mitochondria



Can treatments that target
PPARs help with bipolar
disorder?

PPAR based treatments for Bipolar Disorder

- Anti-diabetic meds
- Anticholesterol meds

Anti-diabetic
Thiazolidinediones
(Glitazones)

Thiazolidinediones

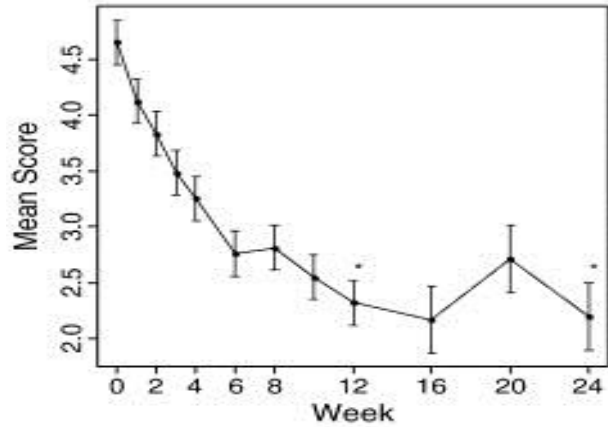
- Increase *PPARG* expression and stimulate PPAR-gamma transcriptional activity in adipose tissue;
- Upregulate genes involved in lipid metabolism;
- Enhance the incorporation of free fatty acids (FFAs) into adipose tissue
- Decreases serum FFa levels

Pioglitazone

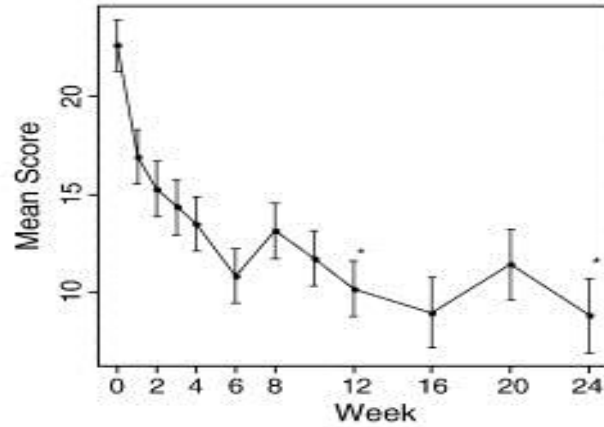
- PPAR gamma agonist
- Decrease insulin resistance
- Decrease HbA1c
- Decrease HDL, TG, inflammation
- Secondary prevention
 - MI and CVA
 - MI with CKD

Pioglitazone in Major Depression

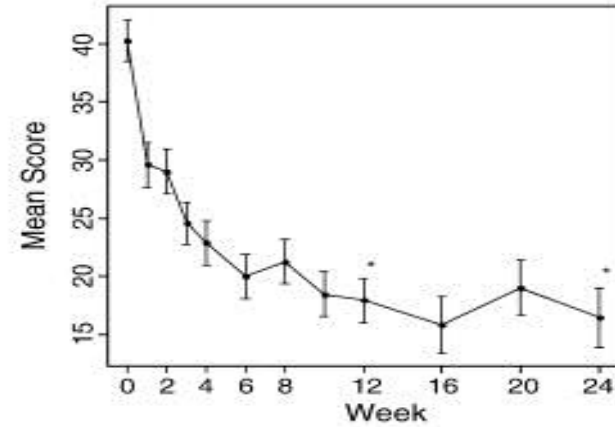
CGI Severity



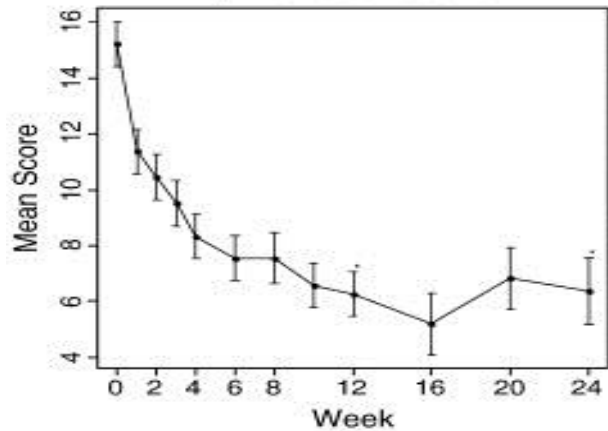
SIGH-A Total Score



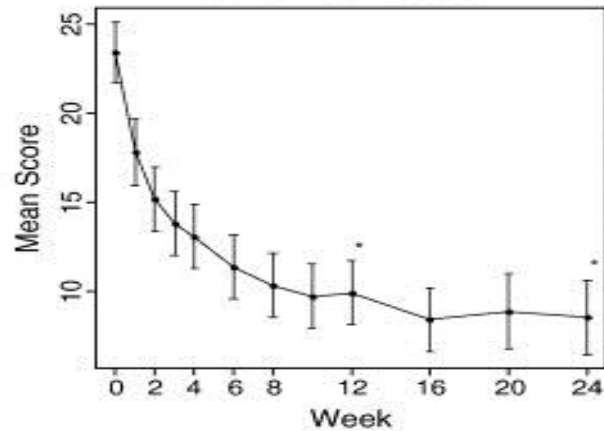
IDS-C Total Score



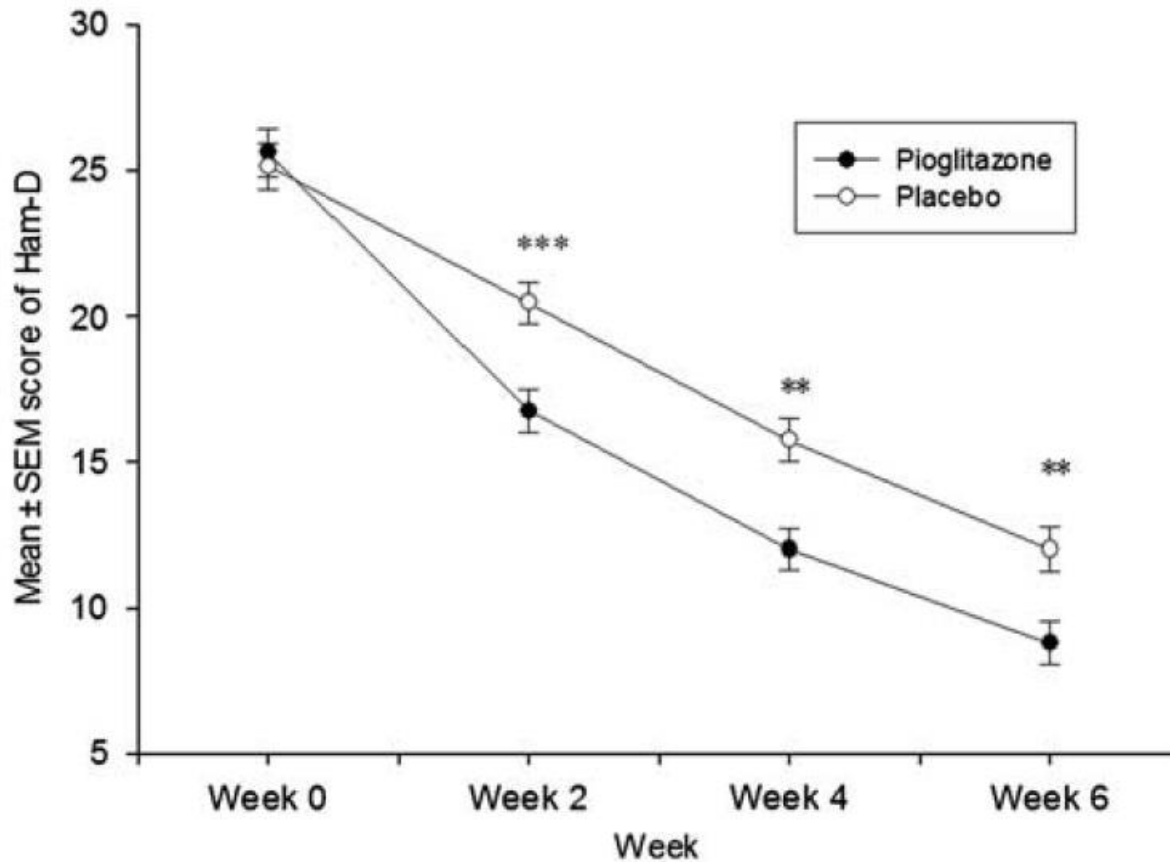
QIDS Total Score



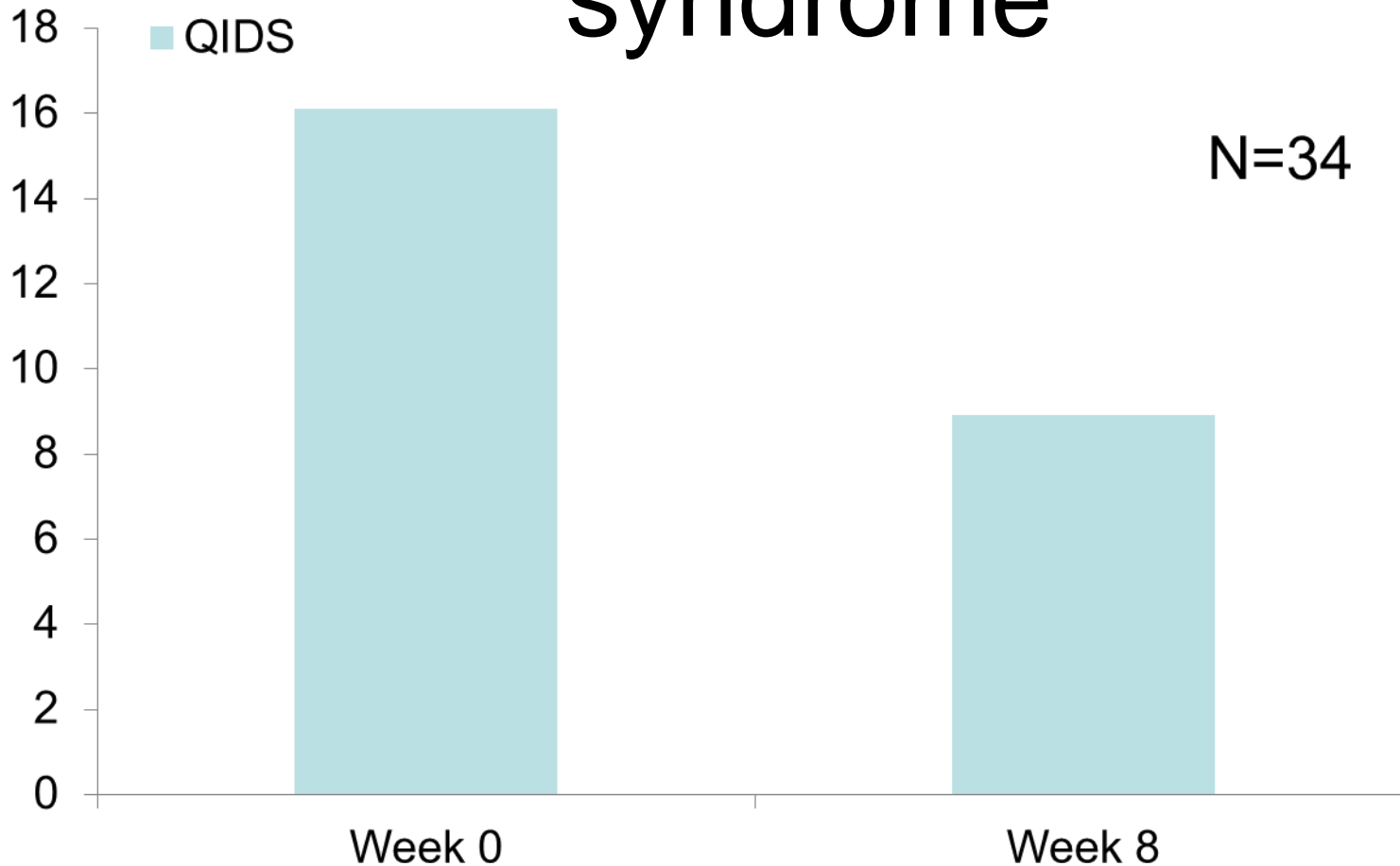
SDS Total Score



Pioglitazone for Major Depression



Pioglitazone for bipolar depression with metabolic syndrome



Anti-cholesterol Fibrates

Fibrates

- Old anticholesterol meds
 - Fenofibrate, clofibrate, gemfibrozil
- PPAR alpha agonists
- Neuroprotective
- Bezafibrate
 - Used for over 25 years in Europe
 - Safe
 - No weight gain

Bezafibrate

- Neuroprotective
 - Huntington's
 - Parkinson's
 - ALS
 - Traumatic Brain Injury

Bezafibrate Study

- Add to lithium for bipolar depression
- Measure
 - PGC-1 alpha gene expression
 - Mitochondria function
 - Brain Derived Neurotrophic Factor
 - fMRI brain circuits
 - Cognition
- Funding
 - Brain and Behavior Foundation Distinguished Investigator Award; Marriott Foundation

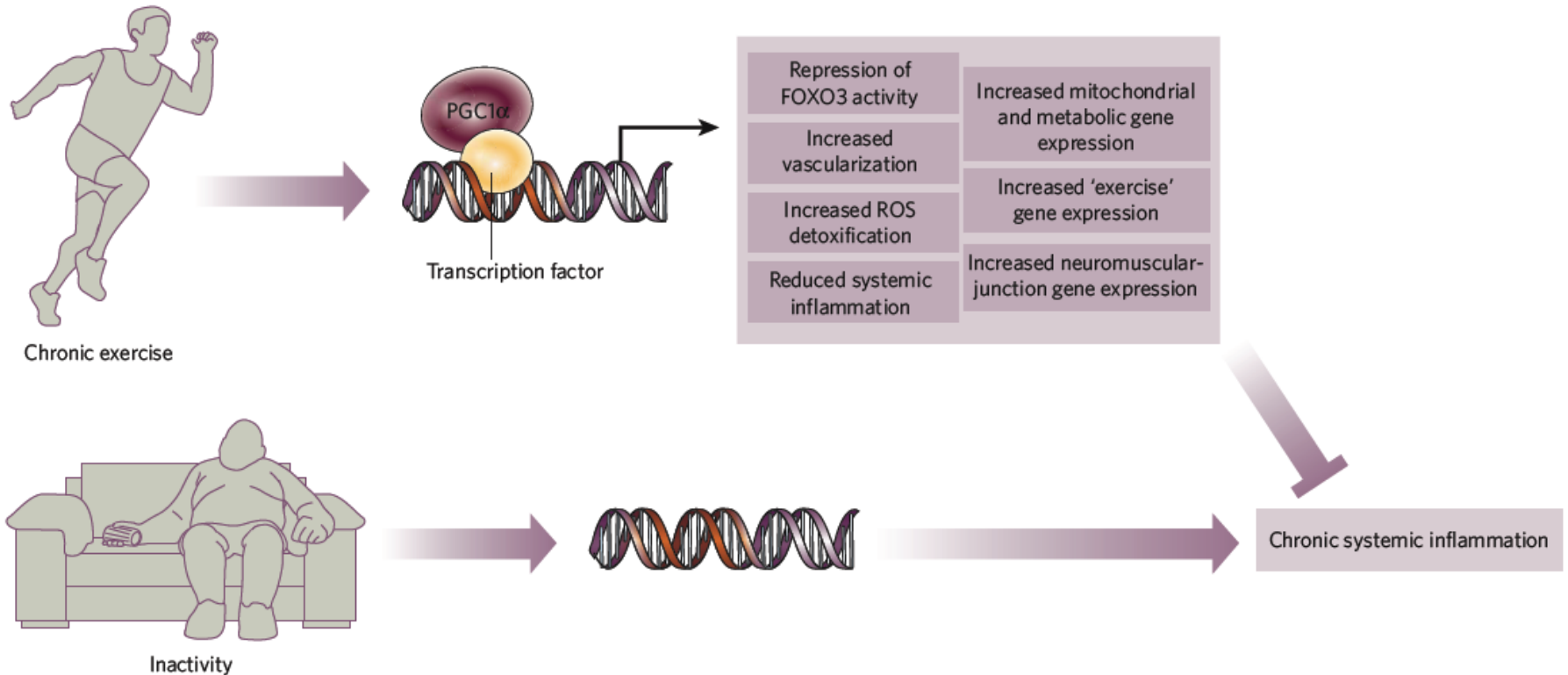
Exercise

“If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.”

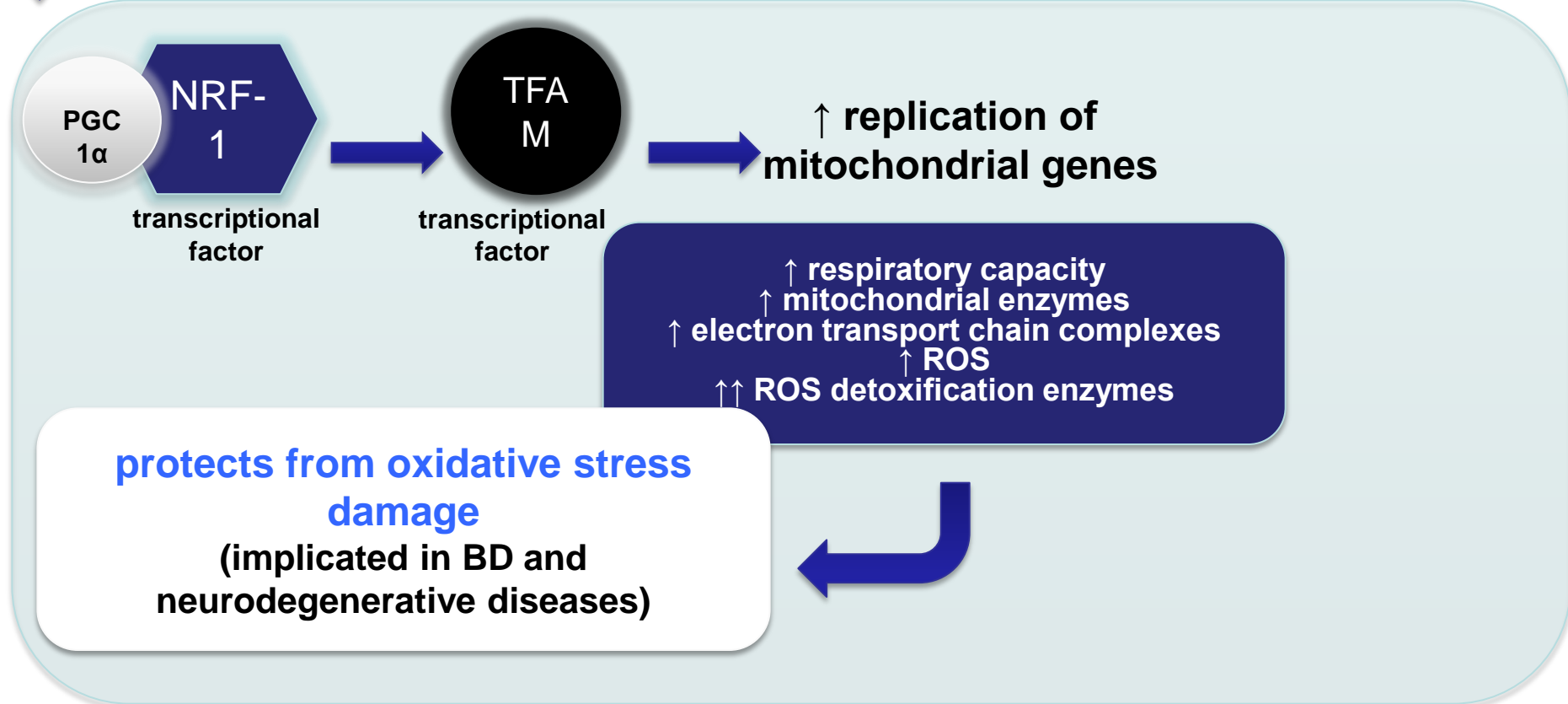
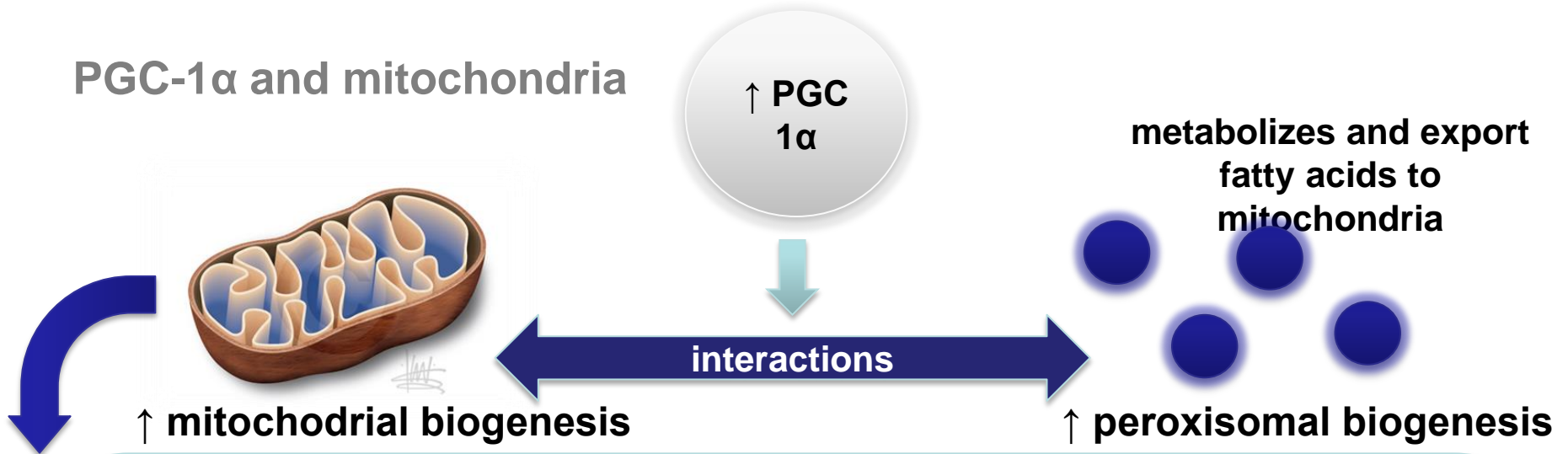
Hippocrates

Why is exercise
good for you?

Exercise increases PGC-1 alpha and decreases inflammation.

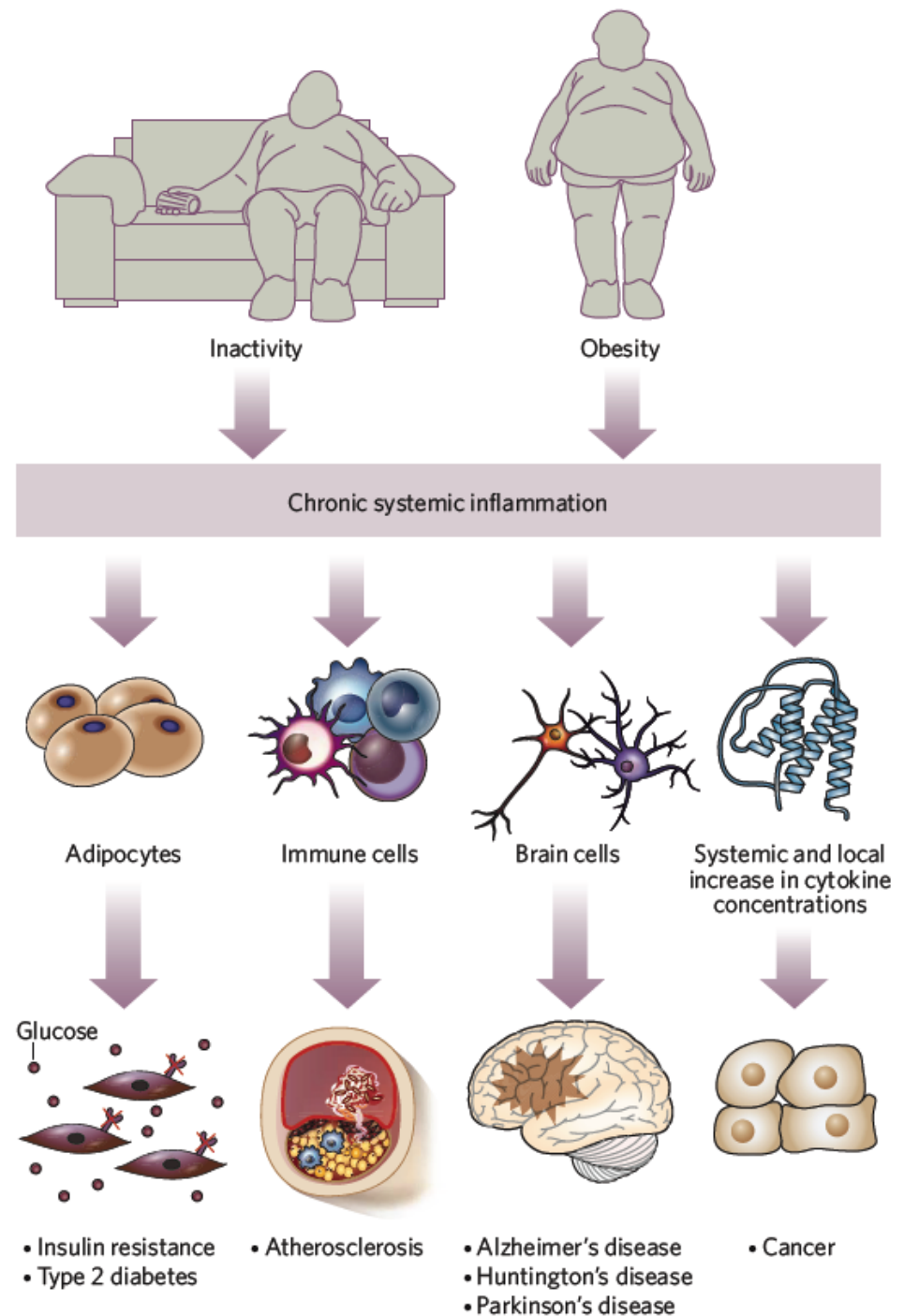


PGC-1 α and mitochondria



Why is too much tv bad for
you?

Inactivity plus obesity increases Inflammation.

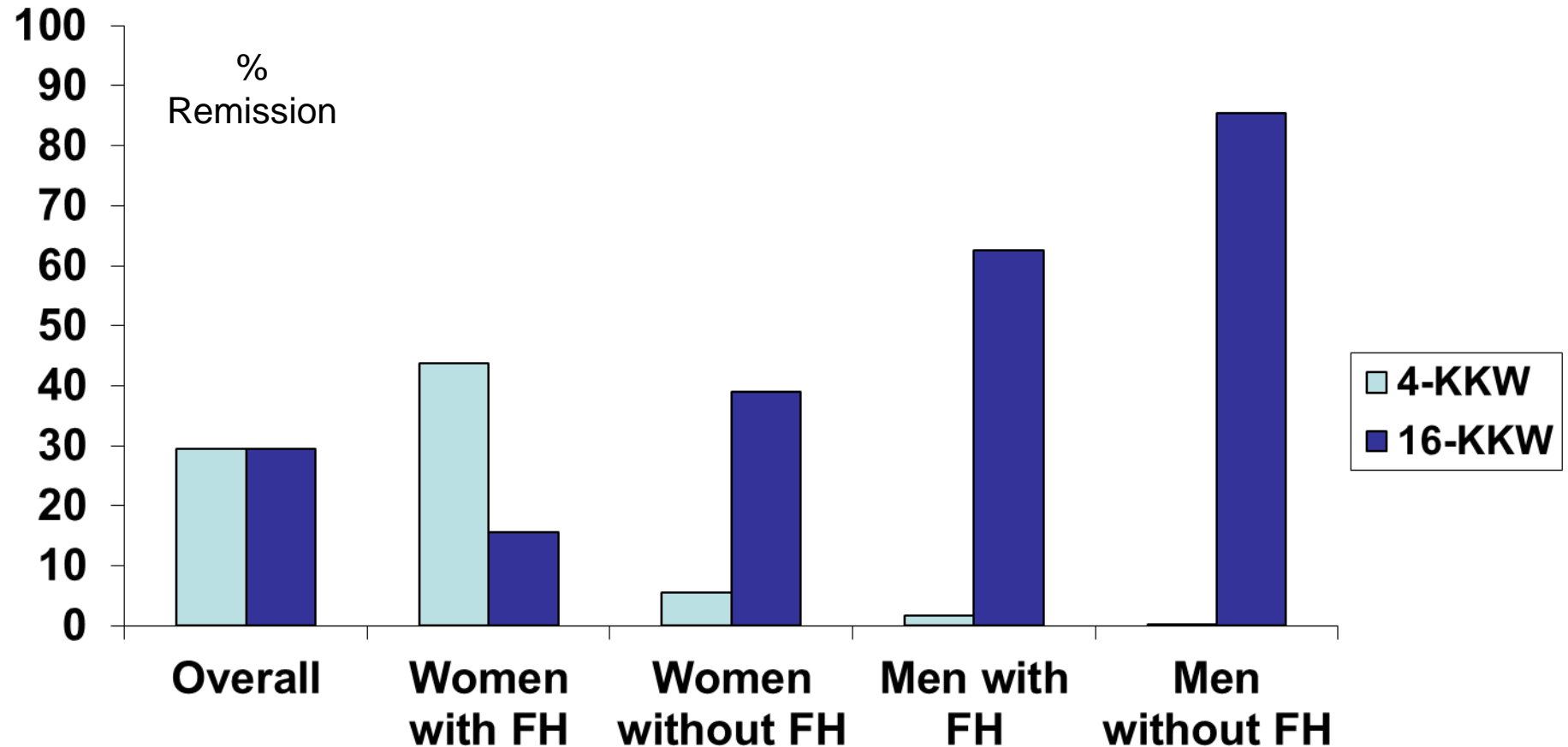


Handschin and Spiegelman.
NATURE|Vol 454|24 July 2008

Exercise

- Active muscles produce PGC-1 alpha
- PGC-1 alpha increases FNDC5
- FNDC5 increases Brain Derived Neurotrophic Factor (BDNF)
- BDNF
 - Brain fertilizer
 - Helps new and old neurons
- New neurons help with thinking
 - Increases ability to separate patterns

Sex and Family History Moderators of Exercise Augmentation for MDD



FH= Family history of mental illness; KKW=kilocalories/kg/week
Trivedi et al. J Clinical Psychiatry 2011;72(5):677-684

Weight Loss/Obesity

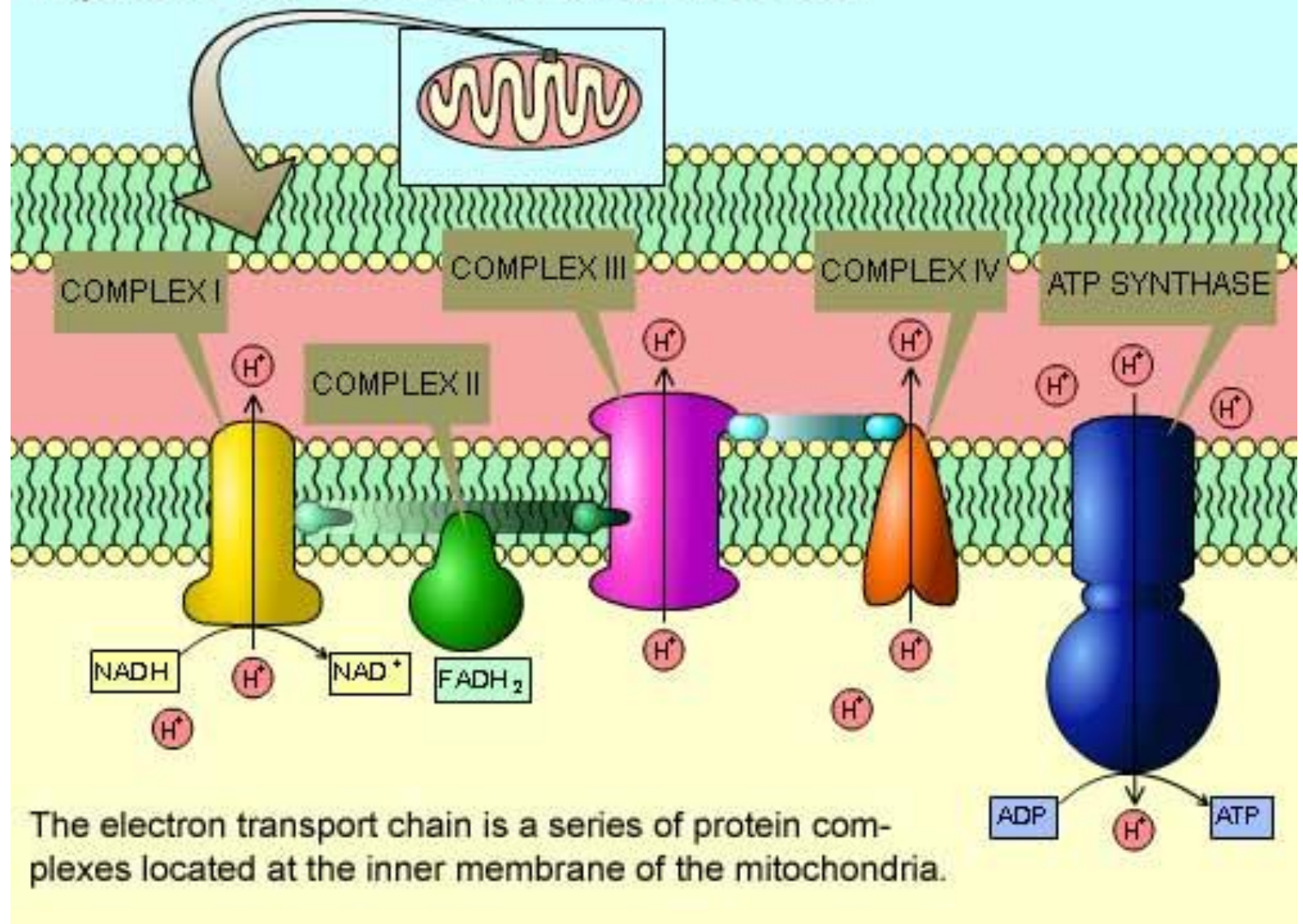
- NEW Tx associated with nearly 10 lb weight loss (5.7% of body weight)
 - Associated with improved mood and quality of life
- Obesity associated with depression and poor quality of life
- Weight loss associated with improved depression, quality of life, and cognition

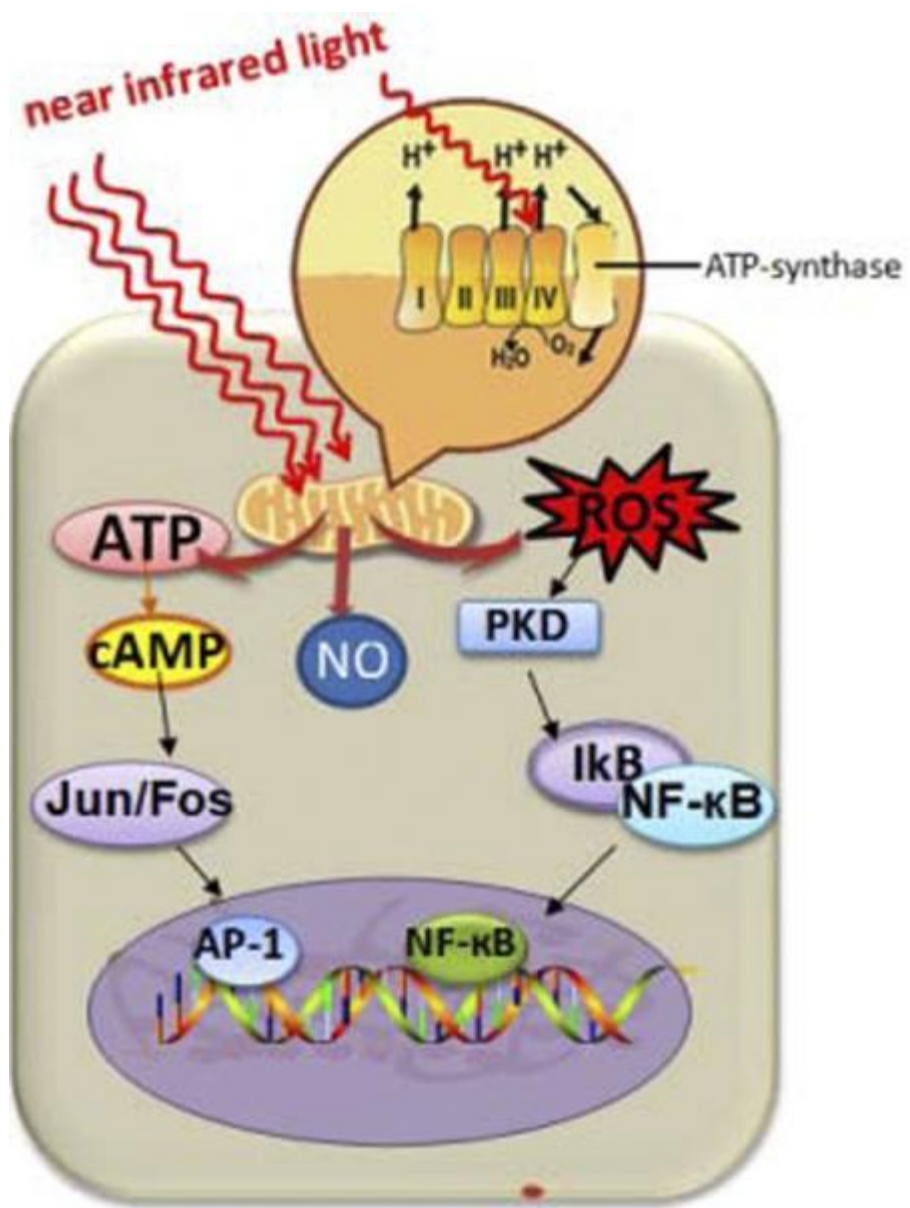
Transcranial Near-Infrared Light

Transcranial Near-Infrared Light

- Passes through skull
- Stimulates mitochondria
 - Provides photon to cytochrome oxidase
 - Protects neurons
 - Anti-inflammatory
- Preliminary data for depression
- No studies of bipolar depression
- Collaboration with Paolo Cassano, MD
- Supported by BBRF and private donations

Figure J-13: Electron Transport Chain

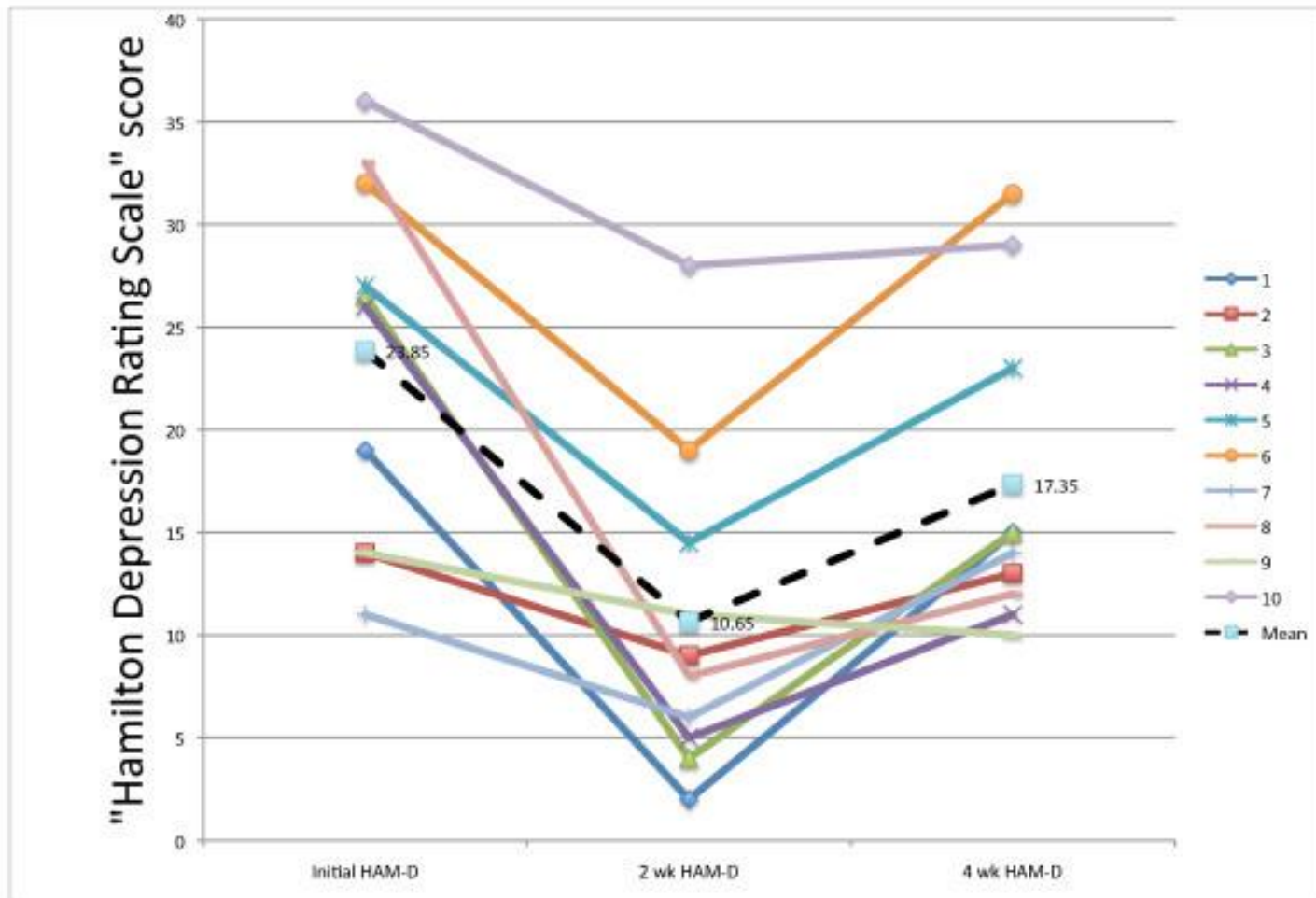








Near Infrared Light for Depression



Summary

- Mitochondria as a target for bipolar disorder
- PPARS and PGC-1 alpha
- New interventions
 - Anti-diabetic and Anti-cholesterol meds
 - Exercise
 - Light – transcranial near infrared radiation

Thanks

- Eduardo Maia, MD
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