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QEII CENTRE **LONDON** UK

KEYNOTE

**Dr Christopher
Palmer**

Integrative Medicine Psychiatrist;
Medical Director, Walden Behavioral
Care

 ipmcongress.com



integrative
mental health
CONFERENCE **23**

Brain Energy

The Metabolic Theory of Mental Illness



CHRISTOPHER M. PALMER, M.D.



McLean HOSPITAL
HARVARD MEDICAL SCHOOL AFFILIATE

**DIRECTOR, DEPARTMENT OF
POSTGRADUATE AND
CONTINUING EDUCATION**



HARVARD
MEDICAL SCHOOL

**ASSISTANT PROFESSOR
OF PSYCHIATRY**

Disclosures



**I RECEIVE ROYALTIES FOR A BOOK,
BRAIN ENERGY, BUT OTHERWISE, I HAVE NO
FINANCIAL RELATIONSHIPS RELATED TO THE
CONTENT OF THIS PRESENTATION.**

Mental Health Today



- Prior to the pandemic, mental and substance use disorders affected about 1 billion people throughout the world
- Rates are even higher now
- Mental disorders are one of the leading causes of disease burden and disability worldwide
- The problem is not always a lack of treatment; for some, it's that our treatments fail to work
- Rates of mental illness have been rising for decades across a wide range of diagnostic categories – autism, ADHD, bipolar, depression

Rates of Depression Reach New Highs



Rising Trends: Lifetime and Current Depression Rates

Has a doctor or nurse ever told you that you have depression?

Do you currently have or are you currently being treated for depression?

— % Yes, lifetime depression — % Yes, current depression



GALLUP®

What Causes Mental Illness?



NO ONE KNOWS.

WE ONLY KNOW RISK FACTORS.

The Biopsychosocial Model



- Biological Factors – neurotransmitters, genetics, hormones
- Psychological Factors – rigid beliefs, parental values
- Social Factors – trauma, stress, poverty, crime, lack of friends

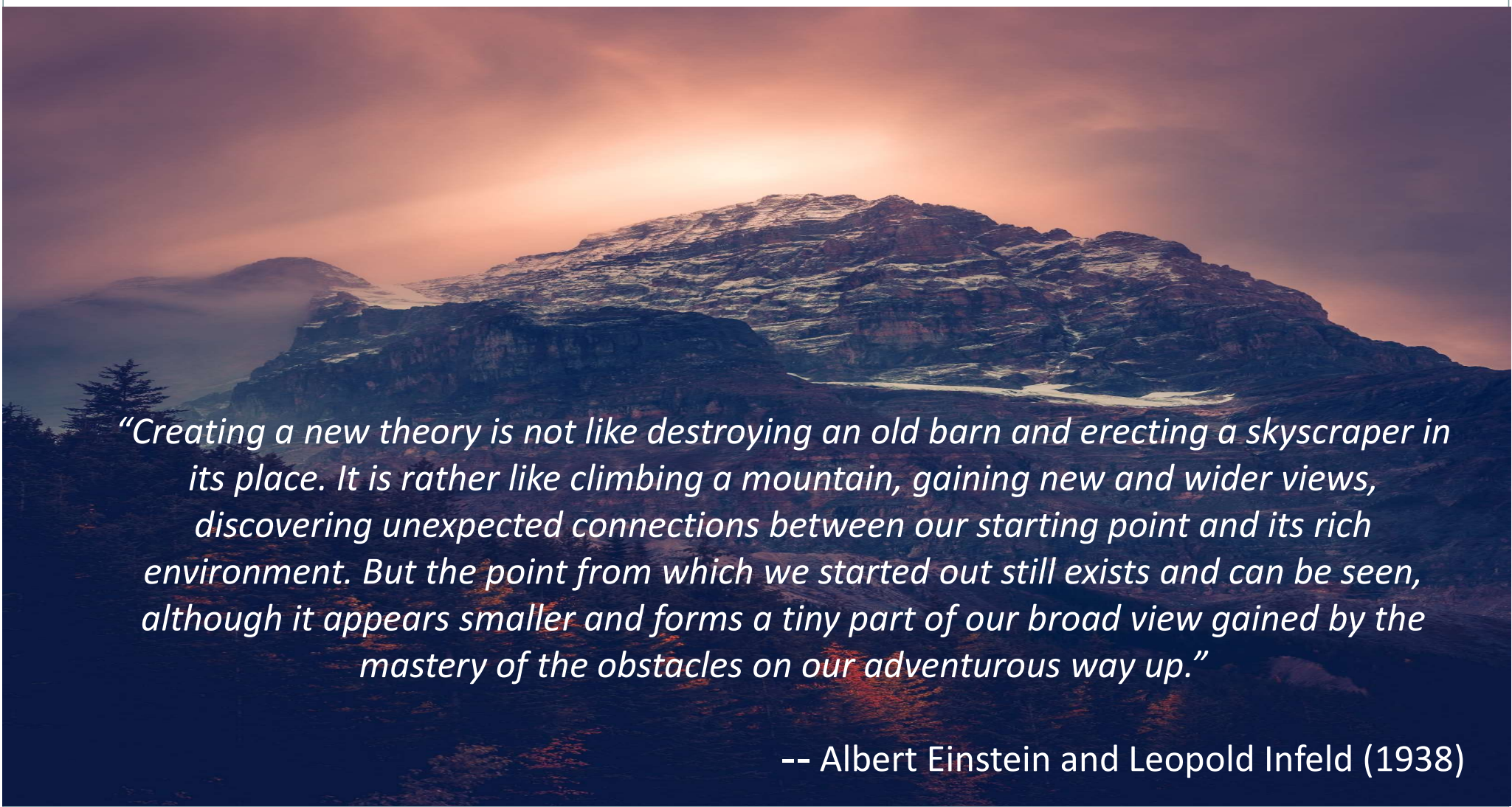
How do these all fit together to cause mental illness?

The Brain Energy Theory



Mental disorders are
metabolic disorders of the brain.

- All of the risk factors impact metabolism
- Metabolic dysfunction in cells can explain all the symptoms of mental illness
- Integrates the biopsychosocial risk factors
- Integrates “mental” and “physical” illness



“Creating a new theory is not like destroying an old barn and erecting a skyscraper in its place. It is rather like climbing a mountain, gaining new and wider views, discovering unexpected connections between our starting point and its rich environment. But the point from which we started out still exists and can be seen, although it appears smaller and forms a tiny part of our broad view gained by the mastery of the obstacles on our adventurous way up.”

-- Albert Einstein and Leopold Infeld (1938)

What should a new theory offer?



- Improved Understanding: A way to integrate and better understand existing research and empirical observations
- Precision
- Parsimony
- Explanatorily broad
- Falsifiable
- Promotes scientific progress

What *IS* Mental Illness?



Are DSM-5-TR Mental Disorders Distinct and Valid Constructs?

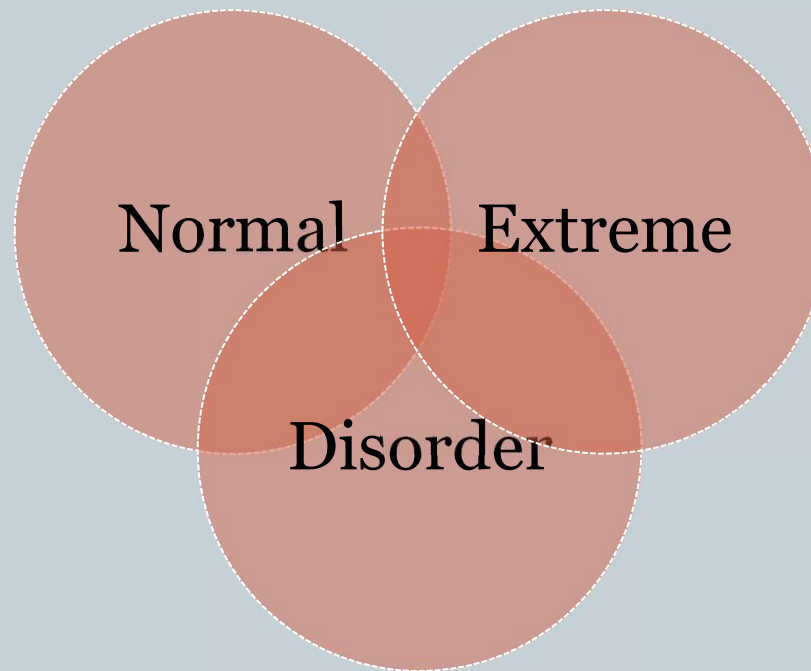


- Heterogeneity and Comorbidity
- Lack of validity
- Many lines of research suggest that mental disorders share a common pathway
 - 2012: Lahey suggests a “general factor” leading to all internalizing and externalizing mental disorders
 - 2018: Caspi and Moffit suggest a “p-factor” leading to **all** mental disorders
- NIMH: Research Domain Criteria (RDoC) - 2009
- Hierarchical Taxonomy of Psychopathology (HiTOP)

Mental States and Mental Disorders



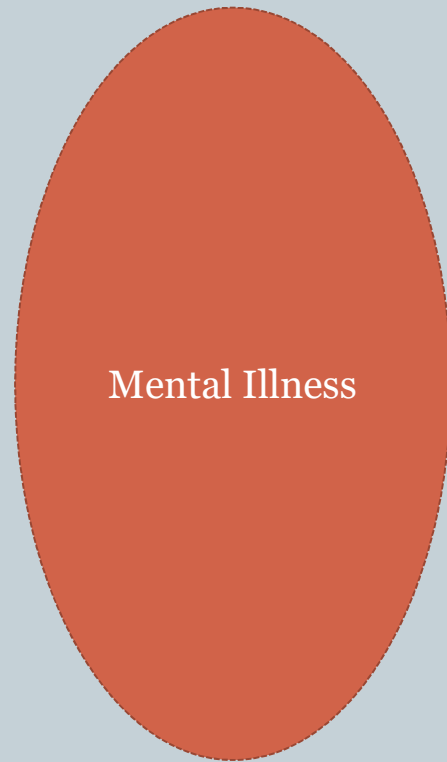
A simpler model...just like pain



The Mental and Metabolic Connection



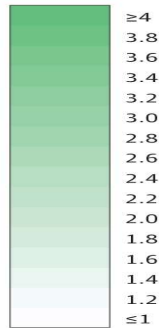
Mental or Metabolic?



Association Between Depression and Physical Conditions Requiring Hospitalization

UK Biobank data: depression is associated with 29 different “physical” conditions. At least 12 appear to be bi-directional relationships.

		Measures of depression							
		1	2	3	4	5	6	7	8
		Hazard ratio (95% CI) ^a by measure of depression							
Disease outcome ICD-10 chapter	ICD-10 codes	1	2 ^b	3	4	5	6	7	8 ^b
Infections	A01-B89		•	•	•	•	•	•	•
Cancer	C00-C97								
Diseases of the blood	D50-D89					•	•	•	•
Endocrine diseases	E00-E35			•	•	•	•	•	•
Mental and behavioral disorders	F00-F99		—	•	•	•	•	•	•
Diseases of the nervous system	G00-G99			•	•	•	•	•	•
Diseases of the eye	H00-H59					•		•	•
Diseases of the ear	H60-H99							•	•
Diseases of the circulatory system	I00-I99						•	•	•
Diseases of the respiratory system	J00-J99					•	•	•	•
Diseases of the digestive system	K00-K93		•				•	•	•
Diseases of the skin	L00-L99								•
Diseases of the musculoskeletal system	M00-M99						•	•	•
Diseases of the genitourinary system	N00-N99						•	•	•
Pregnancy complications	O00-O29							—	
Miscellaneous									
Circulatory and respiratory symptoms	R00-R09			•	•		•	•	•
Digestive and abdominal symptoms	R10-R19		•	•	•	•	•	•	•
Injury	S00-T35		•					•	•
Poisoning	T366-T65		•	•	•		•	•	•
Road injuries	V01-V99	—		—	—	—	—	—	
Falls	W00-W19						•	•	•



Frank et al., 2023, *JAMA Psychiatry*

Mental Illness and Mortality



Chronic Mental Illness is associated with increased mortality

LifeSpan

- Life expectancy is significantly reduced:
 - Schizophrenia – reduced 10-30 years
 - Bipolar Disorder – reduced 9-25 years
 - Major Depression – reduced 7-18 years
- ALL mental disorders are associated with reduced lifespan – avg 10 years for men, 7 years for women (Plana-Ripoll, *Lancet*, 2019)
- Mortality is primarily due to cardiac disease, diabetes, and cancer. Suicide rates are higher, but account for much less than these causes of death.

Why?



A 2016 World Health Organization report identified 3 broad categories of factors contributing to the problem of excessive mortality in severe mental illness:

1. Factors related to the individual's behavior and his or her disorder (e.g., diet and medication effects)
2. Problems at the health system level (e.g., absence of policy and investment and difficulties accessing care)
3. Wider societal issues (e.g., unemployment and limited social resources)

Are we missing the elephant in the room?

Metabolic Problems Often Precede SMI



- Longitudinal study of over 5,000 children followed from ages 1 – 24
- Those with the highest insulin levels beginning at age 9 were 5 times more likely to have “psychosis at-risk mental state” and 3 times more likely to already be diagnosed with a psychotic disorder.
- Children who gained the most weight around puberty were 4 times more likely to develop depression.

(Perry et al, 2021, JAMA psychiatry, 78(4), 416–425.)

Metabolic Problems in People with Mental Disorders



- Centuries of clinical and epidemiological evidence
- Basic research dates to 1940's
- Plethora of basic science, neuroimaging, and other studies
- Diagnoses include depression, anxiety disorders, PTSD, schizophrenia, bipolar disorder, anorexia nervosa, and alcohol use disorder



What does 'metabolic problem' mean?

- Differences in lactate, glucose metabolism, ATP/ADP, reactive oxygen species, redox markers, NAD⁺/NADH, inflammation, cortisol, brain insulin, and mitochondrial function

The Mental-Metabolic Feedback Cycle



What is Metabolism?

- It's more than just burning calories and more than metabolic syndrome.
- It's the process that all living organisms use to convert food into **energy** or **building blocks** to maintain or grow cells. It also includes the effective and efficient management of **waste** products.
- It's fundamental to the definition of life.

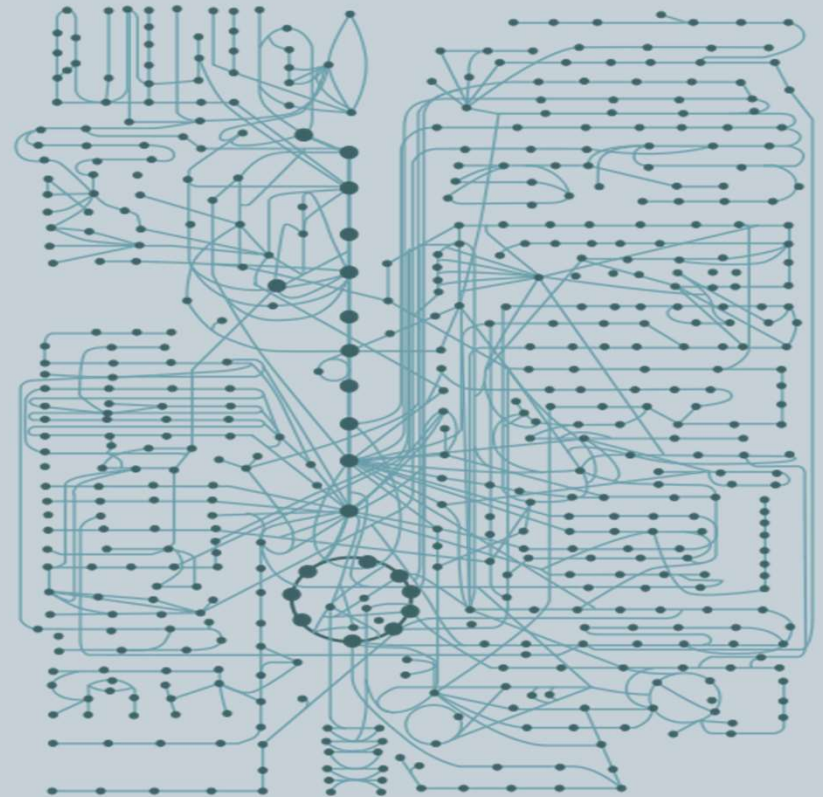


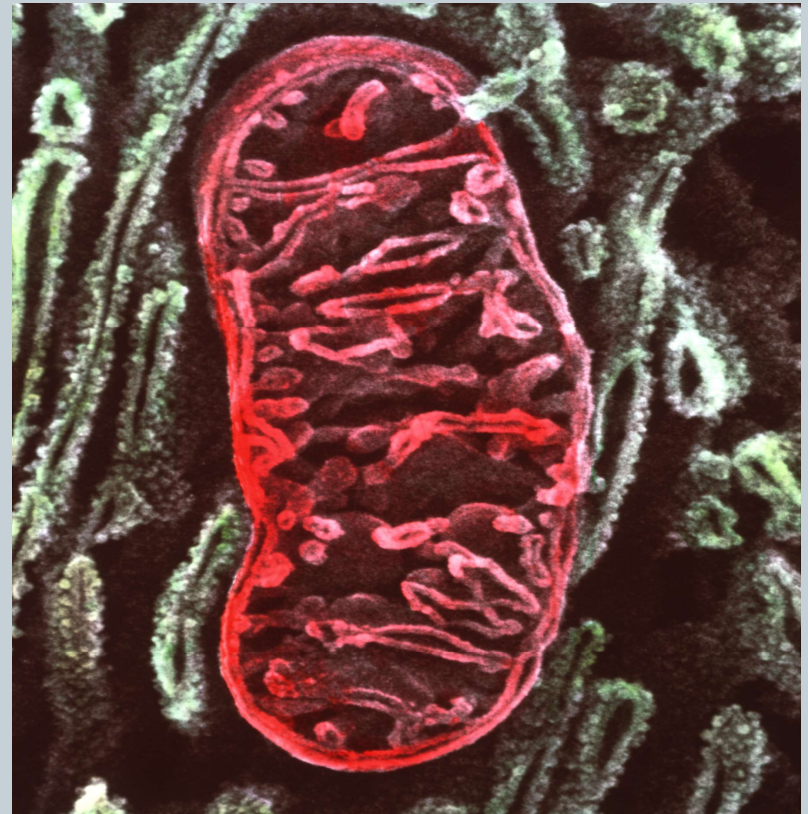
Image credit: "Metabolism diagram," by Zlir'a (public domain).

What Controls Metabolism?

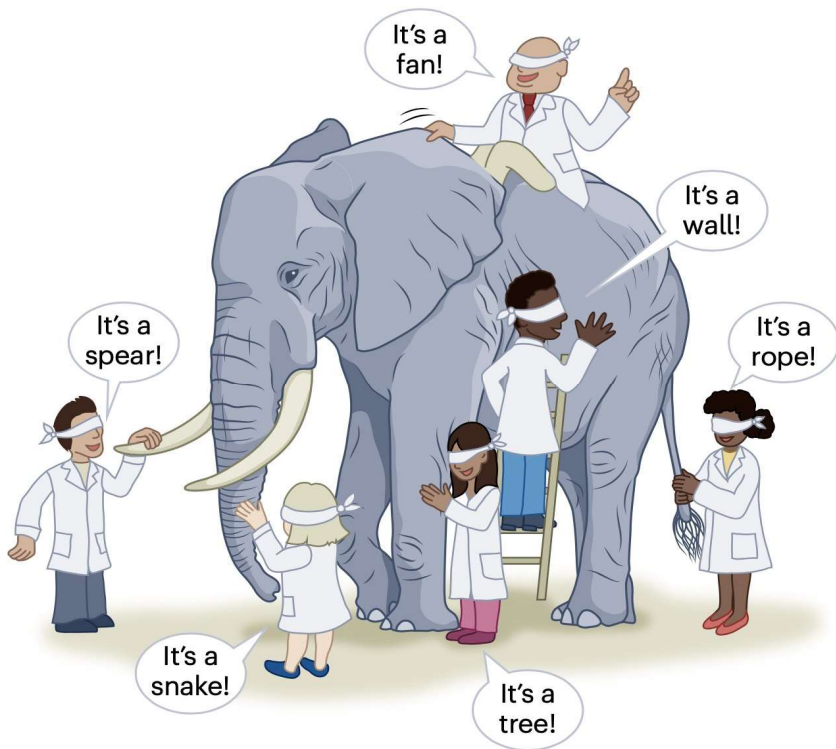


Mitochondria

- “The powerhouse of the cell” ... and so much more!
- Critical players in “metabolism”
- Hundreds or thousands of them in each cell
- Highly dynamic – movement, fusion, fission
- Involved in numerous cellular processes



Multidimensional Mitochondria



Biochemistry

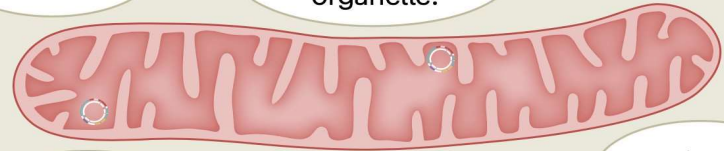
It's a powerhouse!

TEM

It's a bean-shaped organelle!

Live cell imaging

It's a dynamic network!



It's an endosymbiont bacterium!

It's a cell death inducer!

It's a signalling organelle!

Phylogenetics

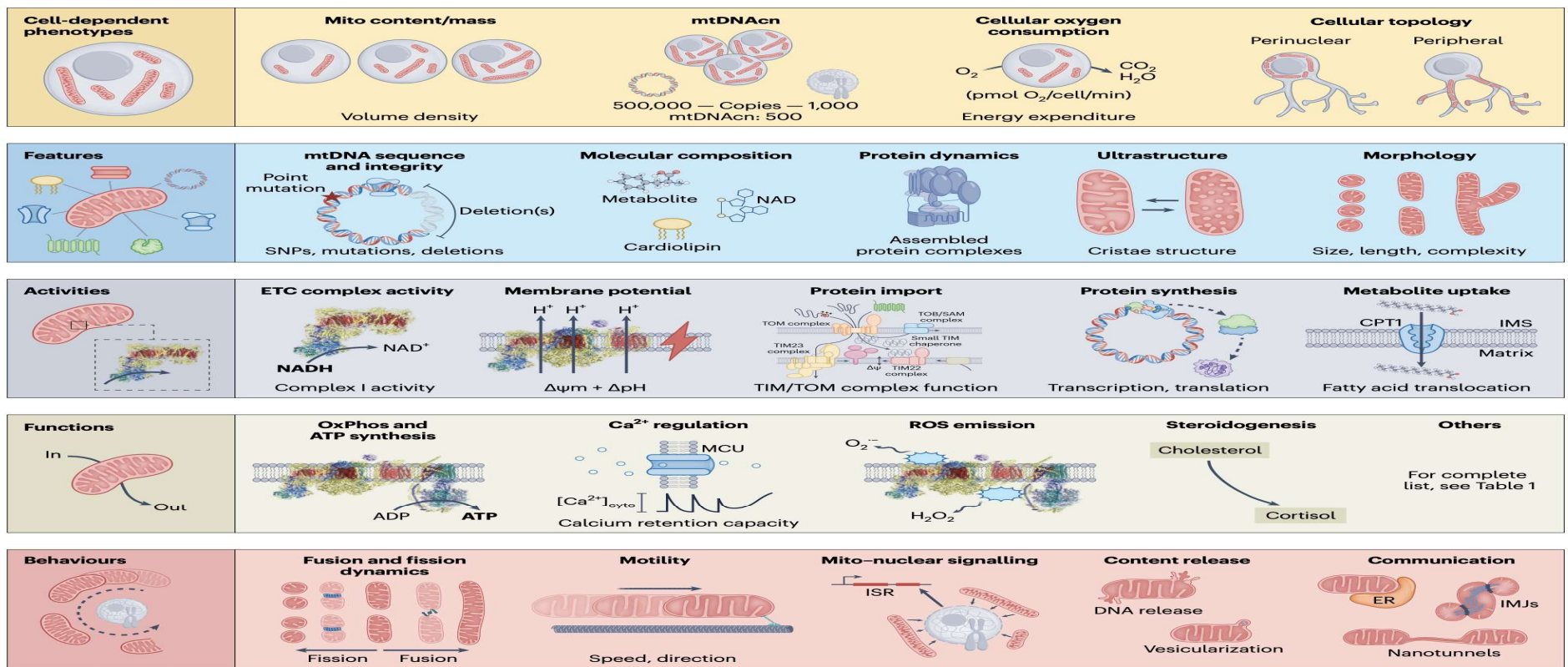
Cyt c release

Metabolomics

Integrated perspective

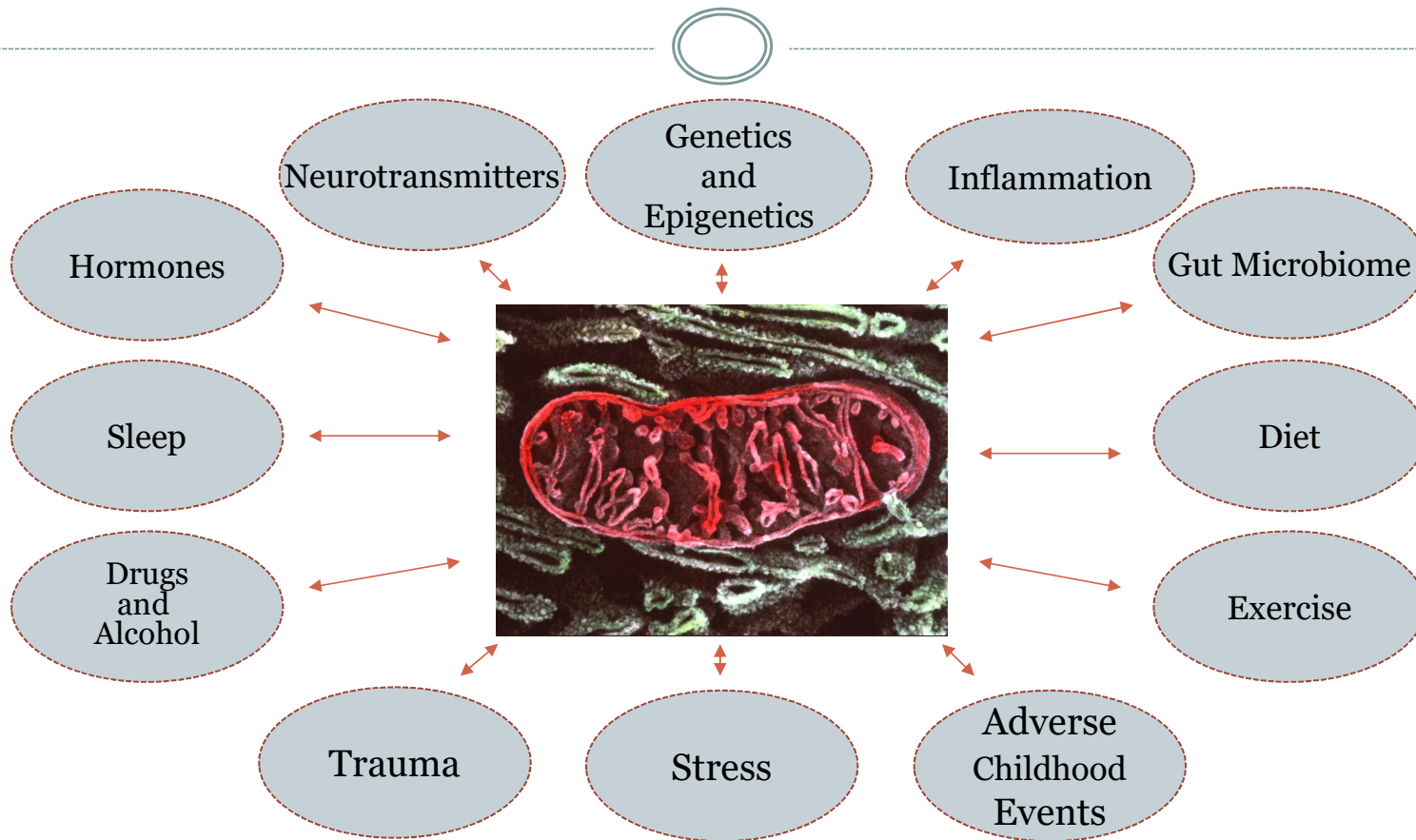
It's a family of organelles that exist as distinct mitochondrial phenotypes, defined by their molecular and morphological features, activities, functions and behaviours

Multifunctional Mitochondria



Monzel et al, 2023, *Nat Metab*

Mitochondria Are the Unifying Link



So, what causes mental illness?



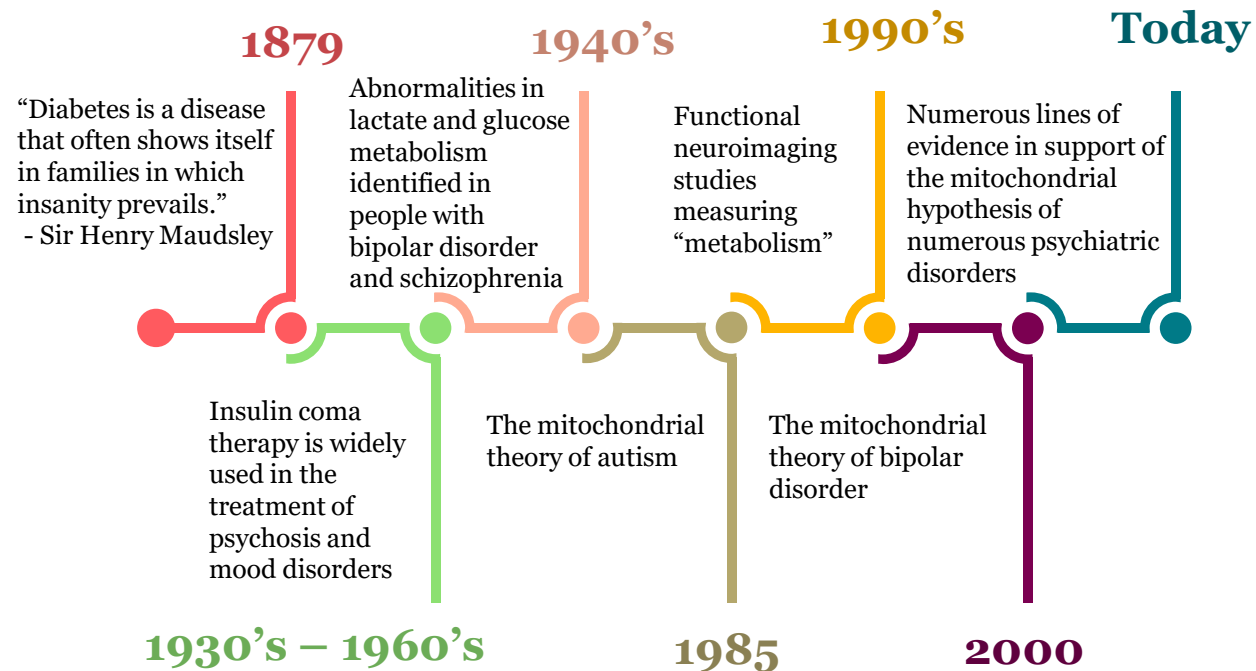
Metabolic and mitochondrial
dysfunction or dysregulation

What is Mitochondrial Dysfunction?



- Given the numerous roles of mitochondria in cells, it's difficult to define.
- Most research has focused on oxidative stress and reactive oxygen species.
- Free Radical Theory of Aging (1956) and the Mitochondrial Theory of Aging (1972) – Dr. Denham Harman
- Free radicals lead to damage and mitochondrial mutations, which then lead to more free radicals.
- But... it turns out that free radicals serve a useful purpose in addition to sometimes being harmful.

A Timeline of the Metabolic and Mitochondrial Hypotheses of Mental Illness



Can a Metabolic Treatment Play a Role in Treating Mental Illness?



The First Step — Assessment



- All of the usual mental health assessments ... Plus
- Weight
- Biomarkers of metabolic syndrome – lipids, BP, waist circumference
- Glucose levels –fasting glucose, HgA1c, fasting insulin, CGMs, etc.
- Sleep – many devices available
- Substance use
- Hormonal assessments – thyroid, estrogen, progesterone, testosterone
- Nutritional assessments
- Gut health
- Inflammatory biomarkers
- Prescription and non-prescription medications
- Exercise capacity
 - Pushups (at least 11 in men, ideally 40 for middle-aged men; at least 5 in women)
 - Grip strength (24kg in men; 16 kg in women)
- Relationships and purpose in life

Many Treatment Options



Exercise

Diet

Sleep

Substance use

Social
Connection

Psychotherapy

Stress
reduction

Psychiatric
medications

Metabolic
medications

Hormonal
Imbalances

Diet



Dietary Interventions - Goals



- Lose weight
- Gain weight
- Address nutritional deficiencies
- Remove allergens, toxins, chemicals, etc. – elimination diets
- “Healthy diets”
- Gut microbiome
- Change metabolism

The Ketogenic Diet: A Metabolic Treatment

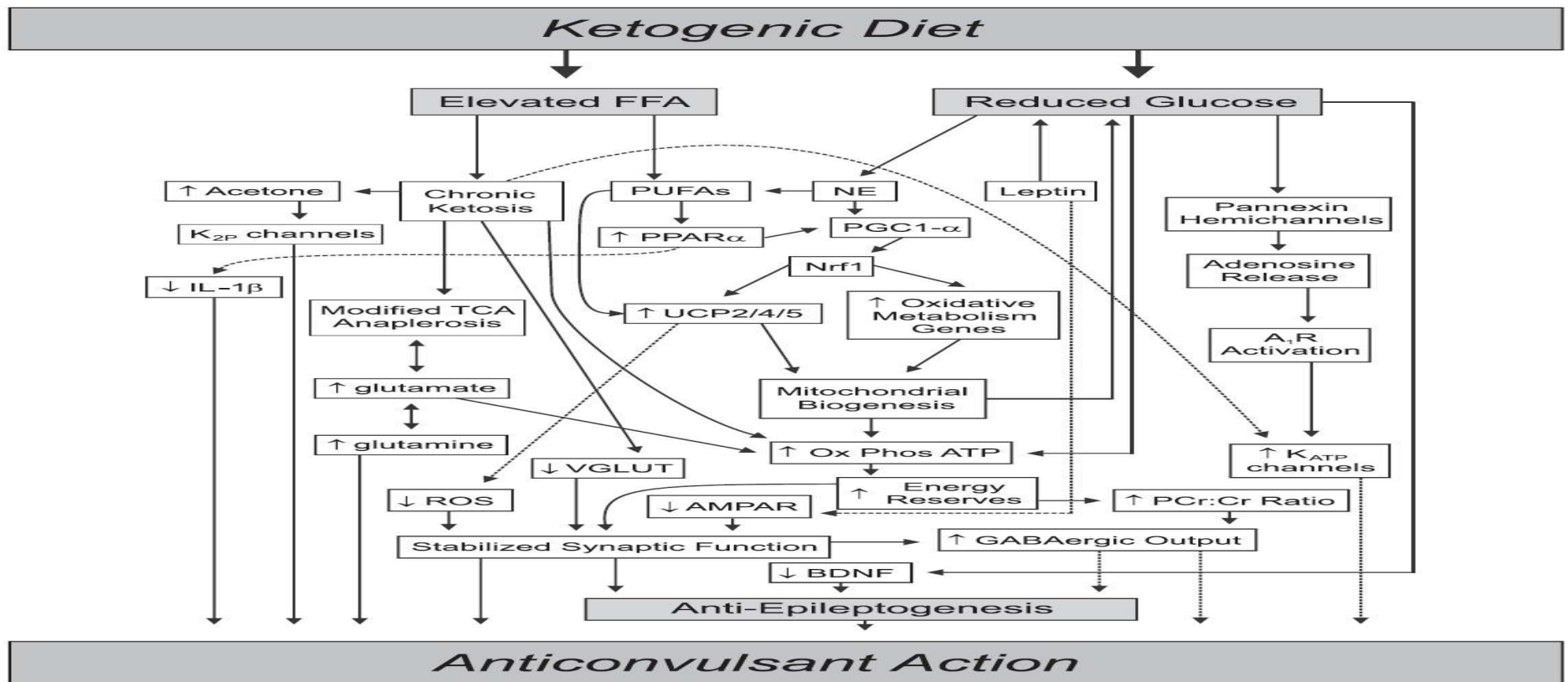


The Ketogenic Diet



- A high fat, low carbohydrate, moderate protein diet developed in the 1920's for the treatment of epilepsy
- Mimics the fasting state
- An evidence-based treatment for weight loss, type 2 diabetes, and epilepsy
- Epilepsy treatments are commonly used in psychiatry
- The ketogenic diet is a metabolic intervention with profound effects on brain function
- Emerging research suggests efficacy in treating mental disorders, particularly treatment-resistant disorders

Mechanisms of Action



Alzheimer's Disease



Randomized crossover trial of a modified ketogenic diet

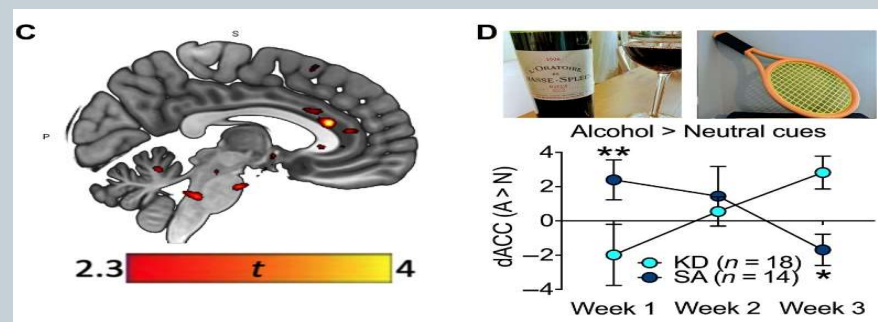
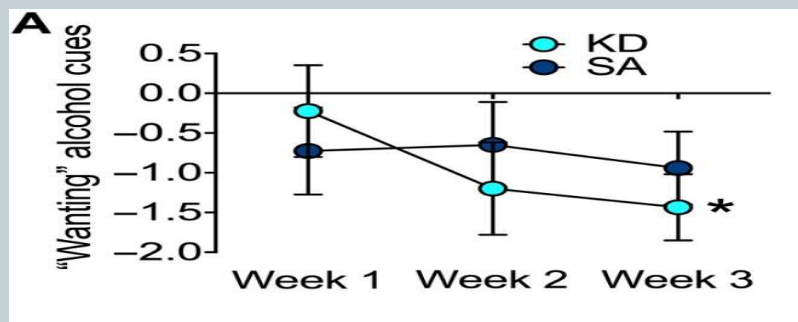
in Alzheimer's disease (Philips et al, 2021, *Alz Res Therapy*)

- 26 patients randomized to 12 weeks each of KD and low-fat diet, separated by 10-week washout



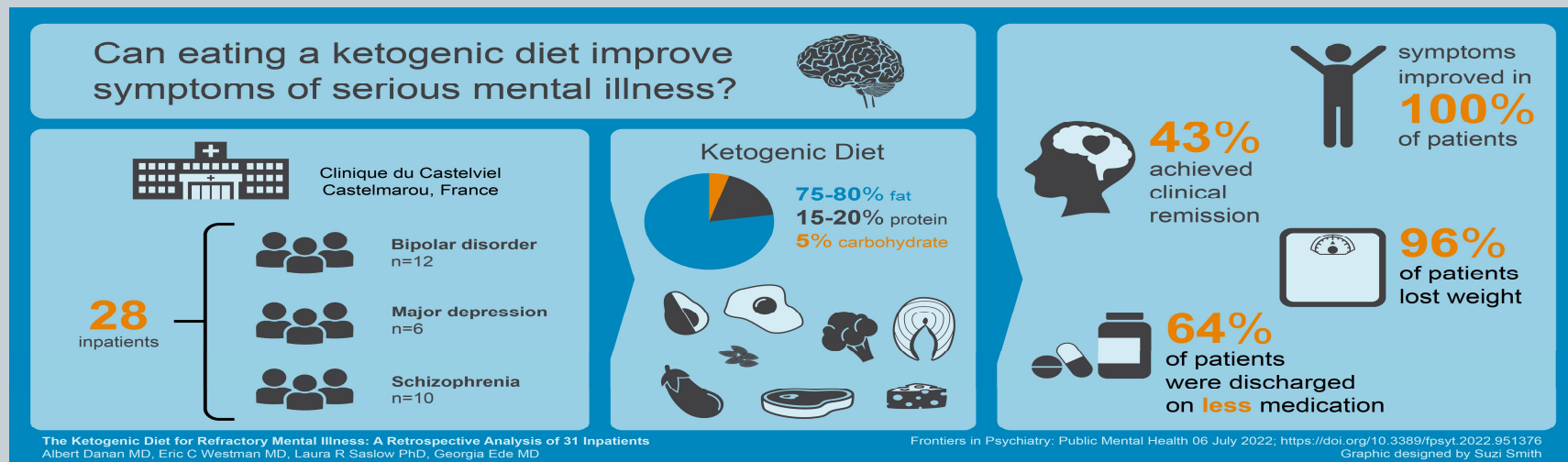
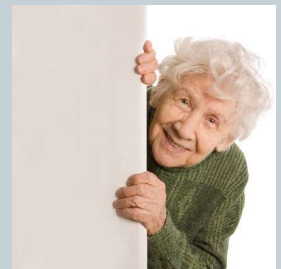
Alcohol Use Disorder

- AUD associated with brain glucose hypometabolism
- Animal models demonstrate reduced alcohol intake in rats on KD
- Ketogenic diet reduces alcohol withdrawal symptoms and changes brain metabolism (Wiers et al., Sci. Adv. 2021)
 - 3-week inpatient trial of KD vs SAD in people with AUD
 - KD required fewer benzos for detox



Schizophrenia, Bipolar Disorder, and Depression

- “The ketogenic diet and remission of psychotic symptoms in schizophrenia: Two case studies” (Palmer et al, *Schizophrenia Research*, 2019)
- “The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients” (Danan et al, *Front. Psychiatry*, 2022)



Implementing the Ketogenic Diet for Mental Illness



- Patients... please don't do this on your own!
- Risks in people with serious mental illness:
 - Adaptation, or “Keto flu,” can be dangerous. Can see:
 - ✦ Insomnia
 - ✦ Increased depression
 - ✦ Suicidality
 - ✦ Mania
 - ✦ Increased psychosis
 - These usually pass, but need to be safely managed
 - Hypomania and Mania are common, and usually unrecognized
- Psychiatric medications can interfere with the diet's effects and prevent a recovery, but are difficult and dangerous to reduce or stop
- Treatment includes more than just the diet – medications, sleep, daily routine, exercise, therapy/stress mgmt, drug/alcohol use, etc

The Future



Research already underway!

Schizophrenia, Bipolar Disorder, Depression, Alzheimer's Disease, Anorexia, PTSD, Alcohol Use Disorder, Opioid Use Disorder, Autism



Key Points



- Mental disorders are metabolic disorders of the brain.
- Mental health and metabolic health are inseparable.
- We can identify the root causes of mental disorders and treat them.
- Lifestyle strategies, such as diet, exercise, sleep, stress reduction, and relationships can play a powerful role in treating even serious mental disorders.
- We need to carefully consider the long-term effects of our treatments on metabolic and mental health.