Our Movement. Our Moment.

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2019 NAMI National Convention

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Bipolar Disorder: A Lifetime of Passion, An Unpredictable Journey

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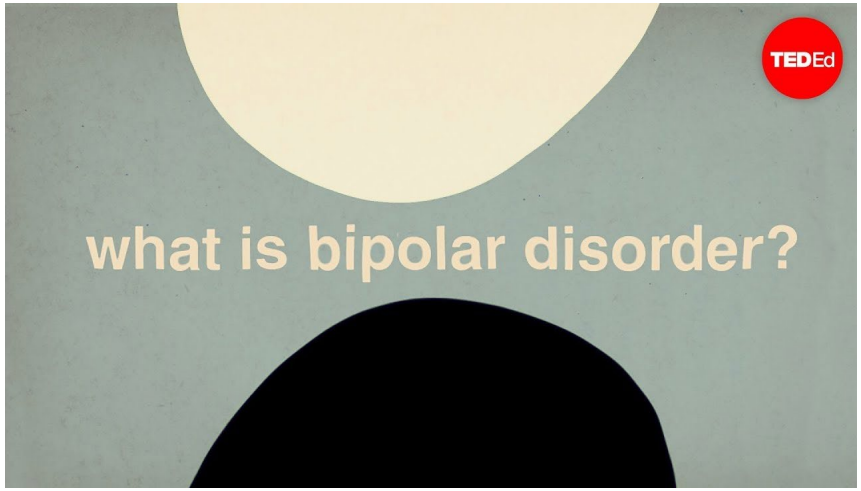
Associate Director, U-M Depression Center

Winner of the 2018 NAMI Research Award

HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM

MICHIGAN MEDICINE



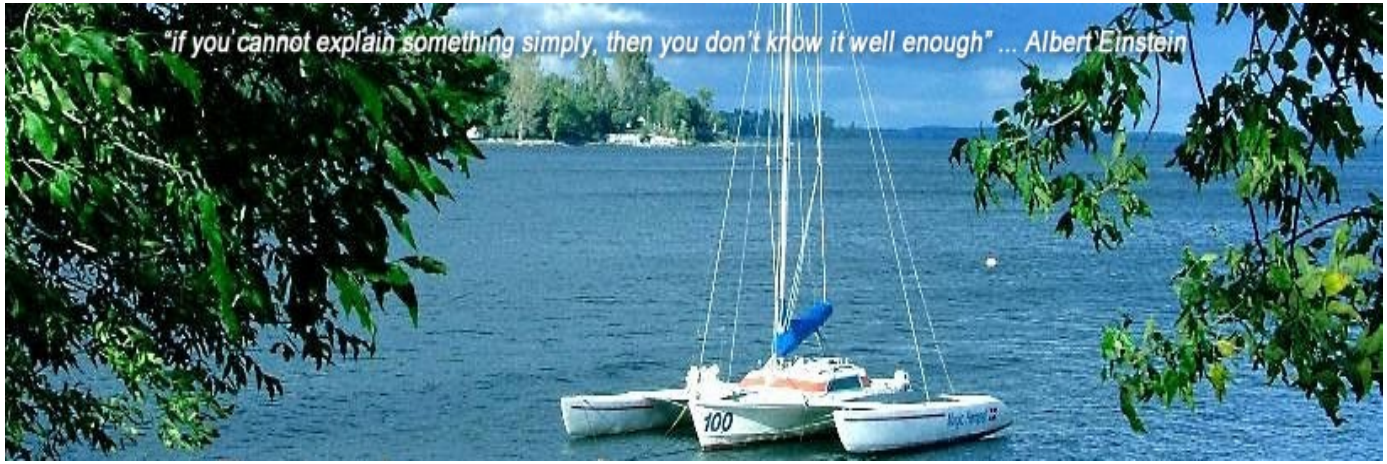
- Initially termed “manic depressive disorder”
- Clinical diagnosis: observed patterns
- Simple definition: recurrent periods of mania and depression

What is Bipolar Disorder?

- What is a clinical diagnosis?
  - Opinion based on observations
- What is a period?
  - Element of time between events
- What is an observed pattern?
- What is mania?
- What is depression?
- What is passion?

How can we simplify the approach to understanding Bipolar Disorder?

- Energy
- Emotion



Passion ……

Energy: Volition – Drive – Motivation

- All are vital to humanity
  - Personal
    - relationships
  - Social
    - society
  - Vocational
    - careers

*No shortcuts to the top

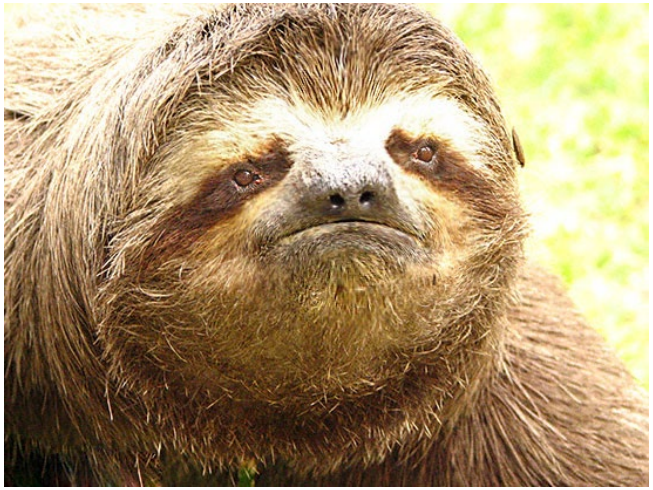
*Ed Viesturs

Energy Overcharged

The unpredictable journey…

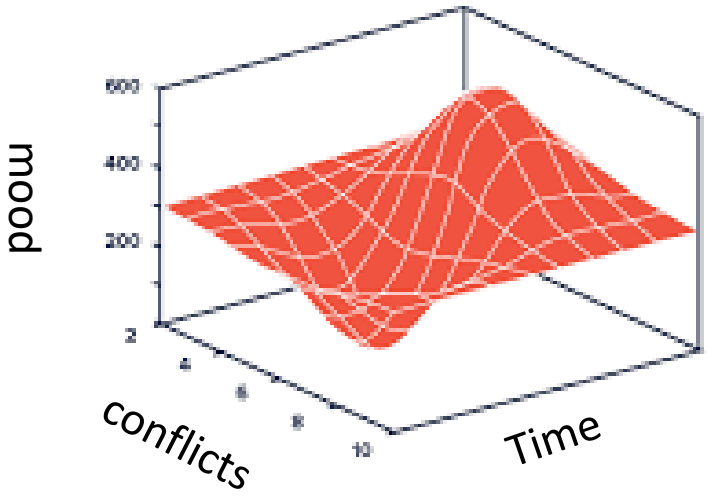
Emotions: Positive - - - - - - - Negative

- Many words to describe nuanced expressions and experiences of emotion
  - Joy – Sorrowful
  - Happy – Sad
  - Angry – Pleased
- Emotions are a personal experience

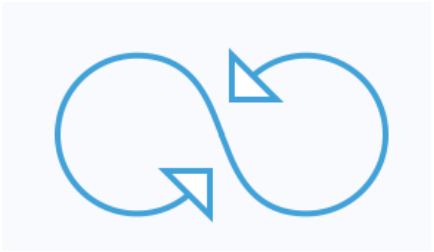


Passion = (Energy + Emotions)$^{2\cdots}$

- Dimensionality:
  - There is no 'black and white'
  - Multiple dimensions

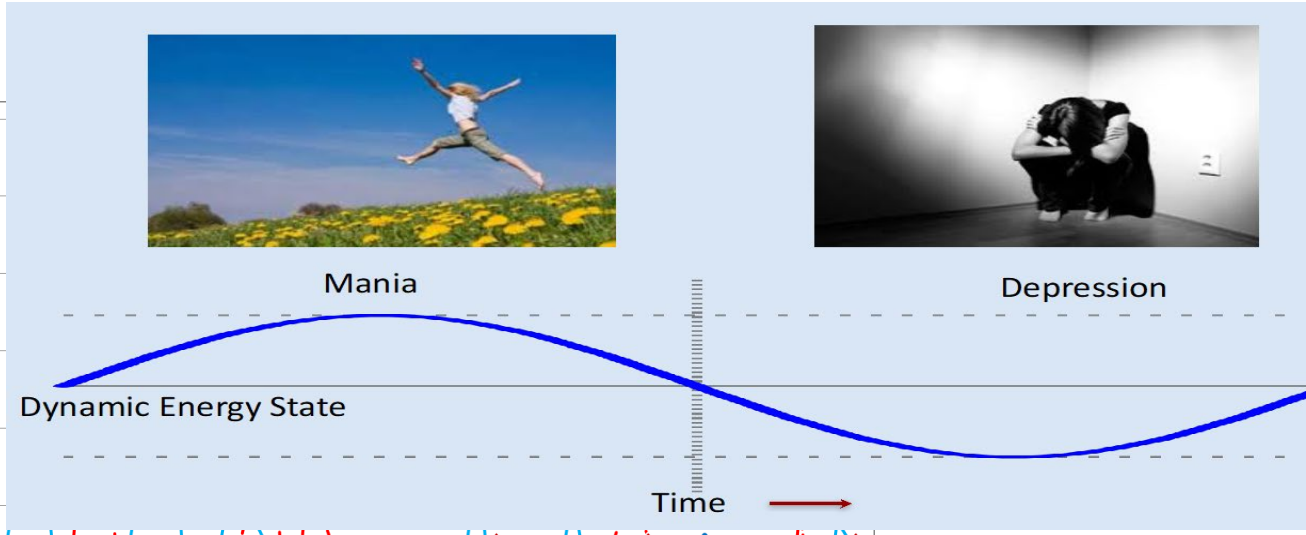


- Dynamic:
  - Ever changing states
  - Time and context influences the experience



The Bipolar Experience is ever changing – day to day – week to week.

Pathology of Energy & Emotion



Mania

Depression

Anticipate Change?

Pattern Description?

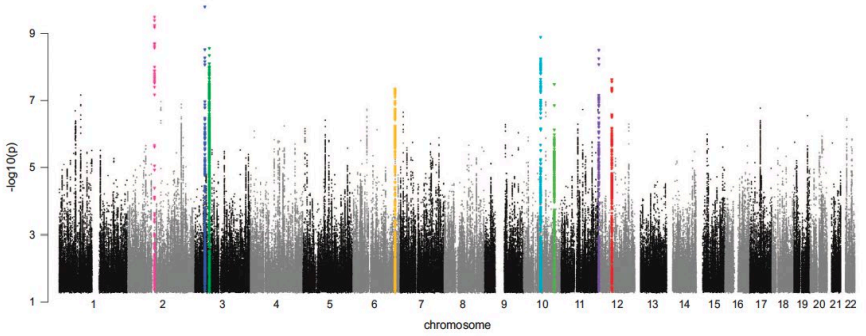
1 year

Overview of Bipolar Research

- Highly heritable
  - Clinical observations
- No established mechanisms
- Current medication for treating bipolar disorder is based on 1950's biochemistry

Challenges in Psychiatric Research

- ***Large samples available***: Psychiatric Genetics Consortium – Limited clinical and outcomes data



~31 loci; OR ~ 1.15
Stahl et al 2019

- Few long-term data collections available with detailed information (> 10 years with multiple data collections per year)

Goals…

- ***Discuss:*** longitudinal sample of the Heinz C. Prechter Bipolar Research Program at the University of Michigan Depression Center

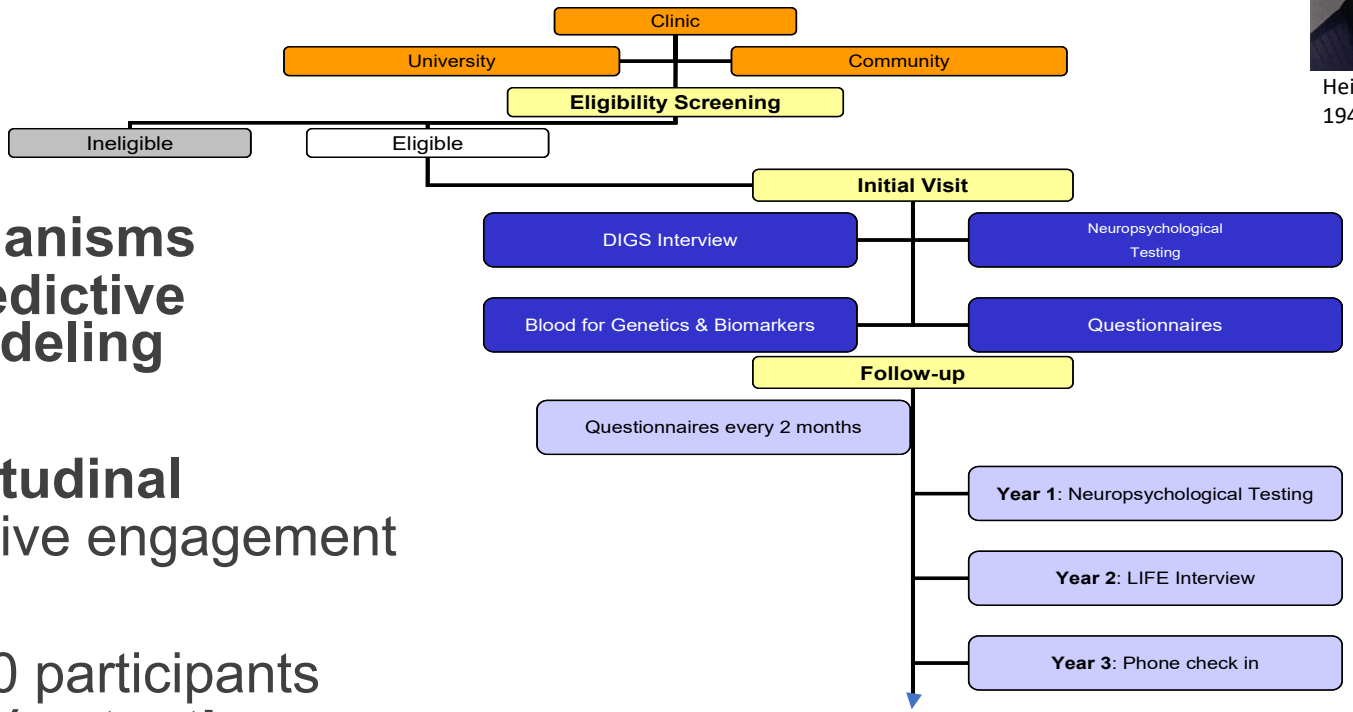
- Emphasis on ***Predictive Patterns*** of illness states
  - Bipolar disorder as a series of dynamic states (ever changing)

- ***Biological Mechanisms*** and modeling using induced pluripotent stem cells

Heinz C. Prechter Bipolar Research Program Precision Health


Heinz C. Prechter
1942 – 2001

- **Mechanisms**
  - **Predictive Modeling**
- **Longitudinal**
  - Active engagement
- > 1320 participants
  - **75% retention**



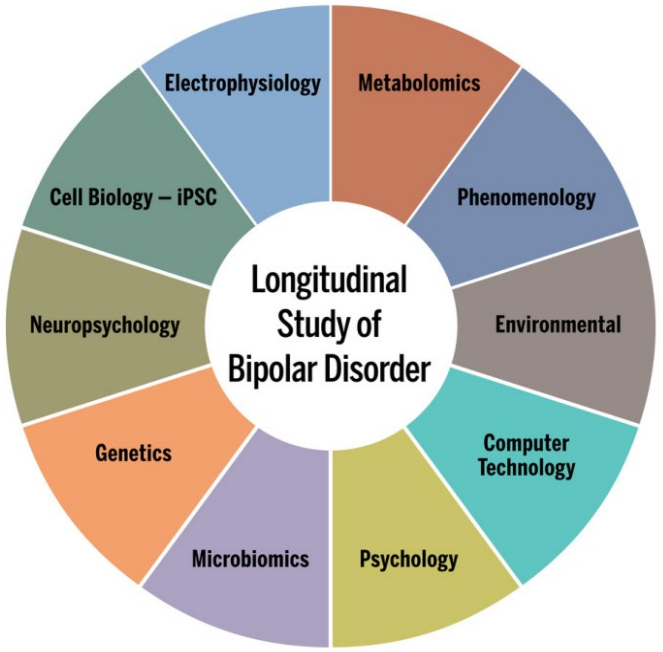
Entering Year 14

Ontology

Disciplines

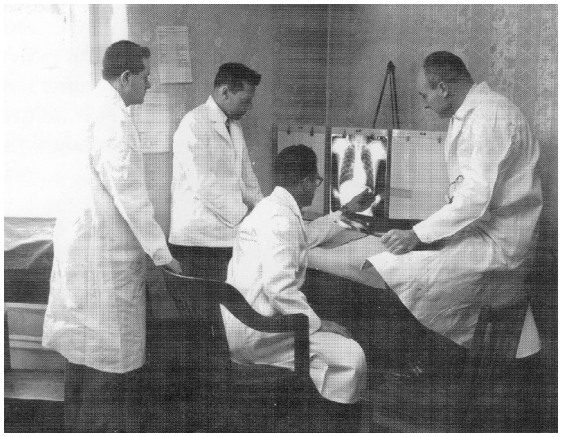
Clinical Phenotype **Classes**

-Disease
-Neurocognitive
-Temperament / Personality
-Motivated Behavior
-Life Story
-Sleep / Circadian
-Outcomes



Human Volunteer Participants

What is the importance of longitudinal data?

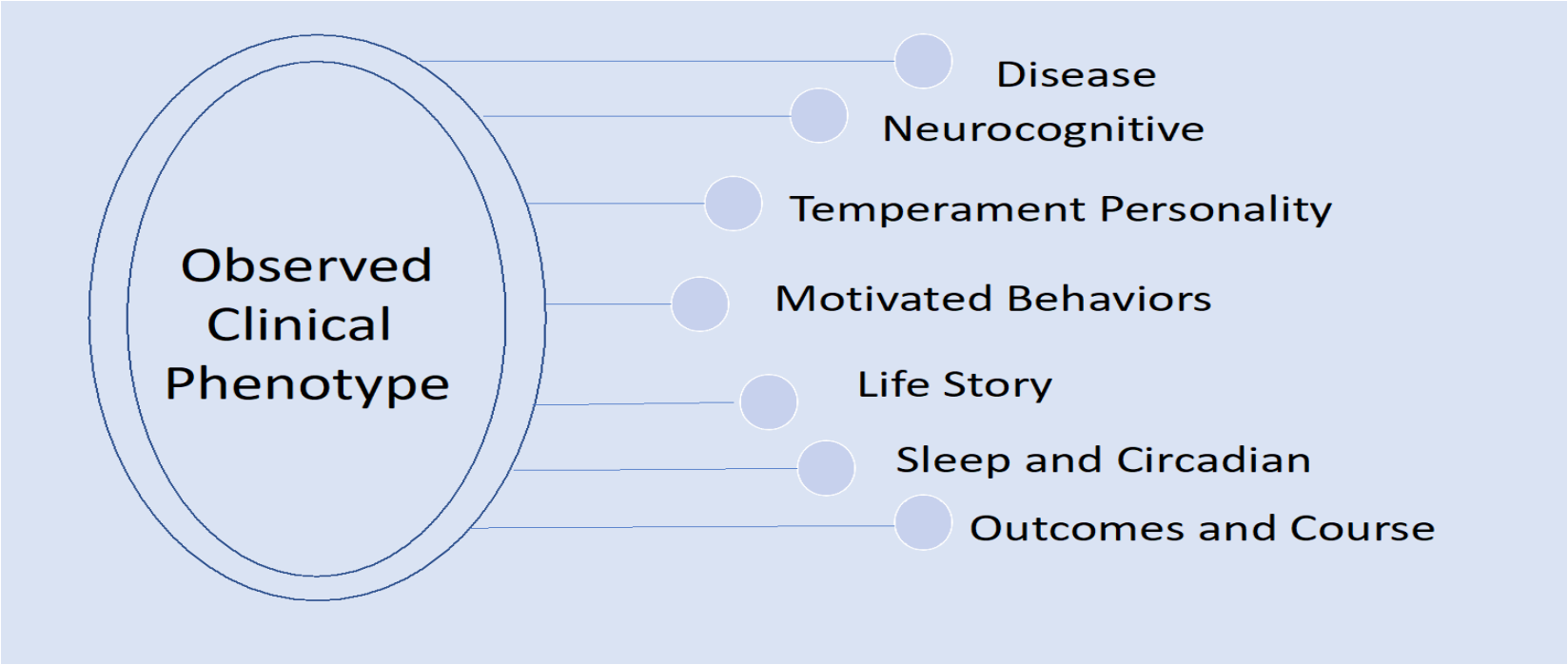


- Knowledge of ***course and outcome.***

  Framingham Heart Study
  - Began in 1948
  - Currently in 3rd Generation

- Everything that your physician advises you about heart disease is from FHS.
  - Smoking
  - Cholesterol
  - Weight
  - Exercise

Prechter cohort profile: 2018



Propose 7 Phenotype Classes that drive the Observed Clinical Phenotype

McInnis et al, 2018

Prechter phenotype classes

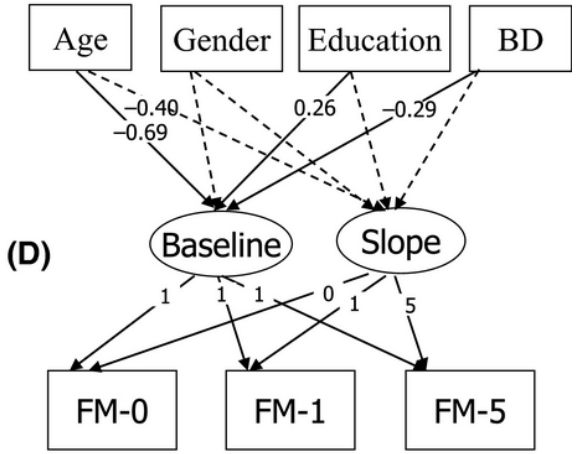
- **Disease**
  - Diagnostic Interviews
    - Presence of illnesses
- **Temperament / Personality**
  - Neuroticism
  - Extroversion
  - Impulsivity
  - Agressivity / Hostility
- **Motivated Behaviors**
  - Substances
  - Addictive Behaviors
- **Sleep & Circadian**
  - Sleep patterns
  - Circadian Rhythms
    - Larks vs Owls
  - Seasonality

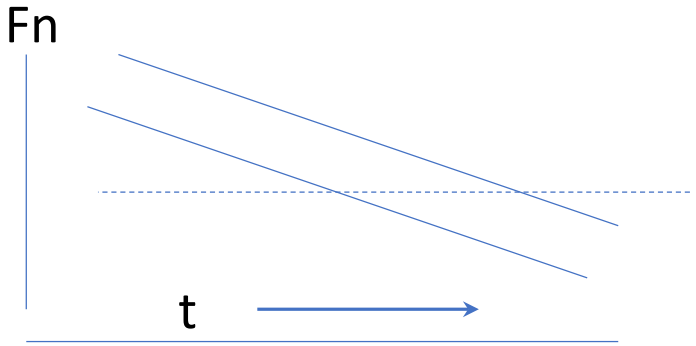
Prechter phenotype classes

- **Life Story / Experiences**
  - Life Events
  - Family supports
  - Traumas
  - Close relationships
  - Support vs. Undermining
- **Clinical outcomes**
  - Depression – mania symptoms
  - Anxiety
  - Drug responses
  - Functional / Occupational
- **Neurocognitive Function**
  - Capacity
  - Verbal / Physical
  - Logic and decision making
  - Emotion perception and processing
  - Memory

Trajectory of cognitive capacity*

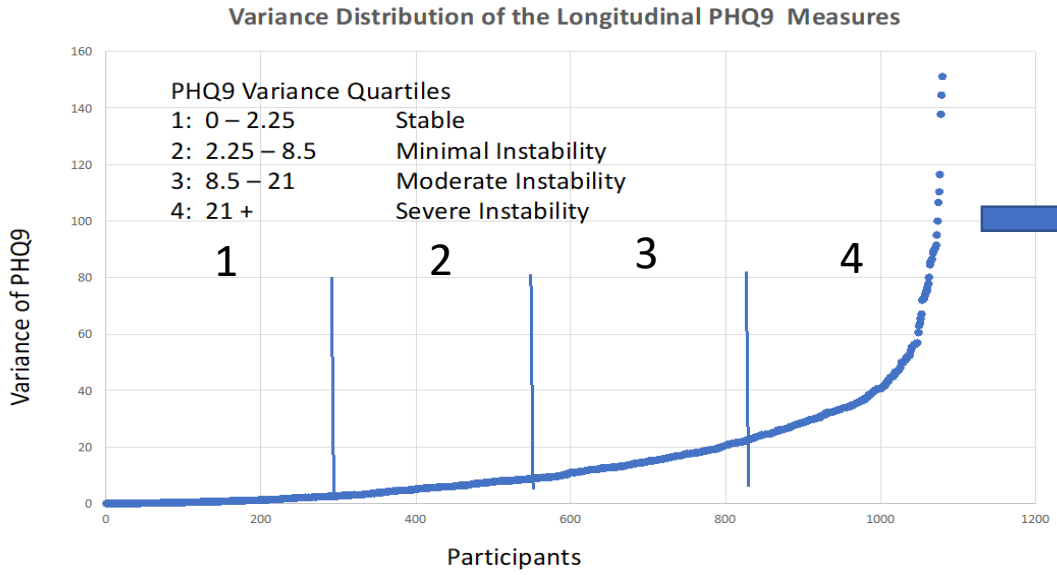
- Five year follow-up of cohort
  - Repeat testing
- Baseline function influenced by
  - Age, education level & diagnosis
- Slope
  - Limited effect from diagnosis
  - BP has similar slope as HC





* Ryan et al, Similar Trajectory of Executive Functioning Performance over 5 years among individuals with Bipolar Disorder and Unaffected Controls using Latent Growth Modeling> J Affect Disord. 2016. doi.org/10.1016/j.ad.2016.04.016

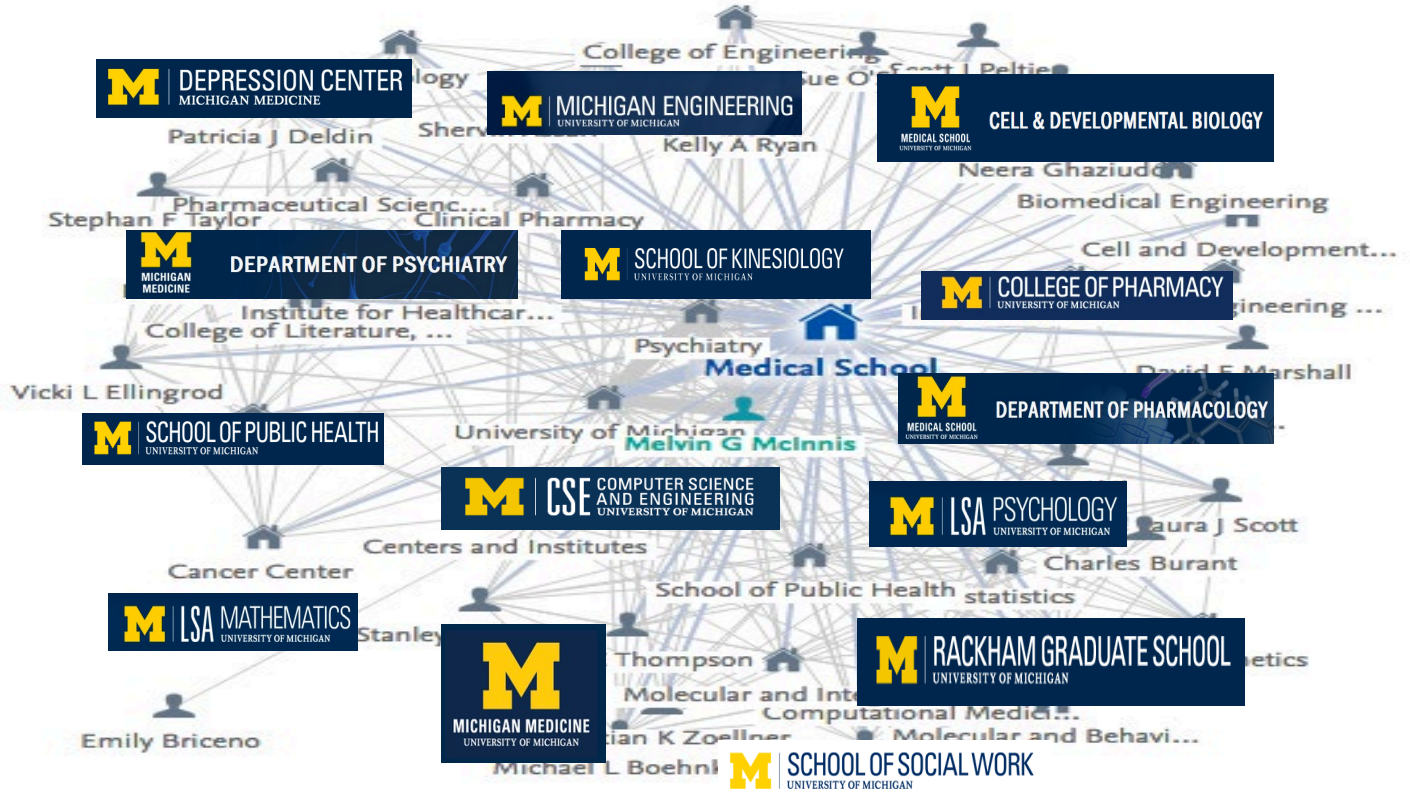
The Dynamic States of Bipolar



15% of Bipolar individuals have extreme variability in mood states

5 – 10 Years of Clinical Follow-up

HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM
MICHIGAN MEDICINE

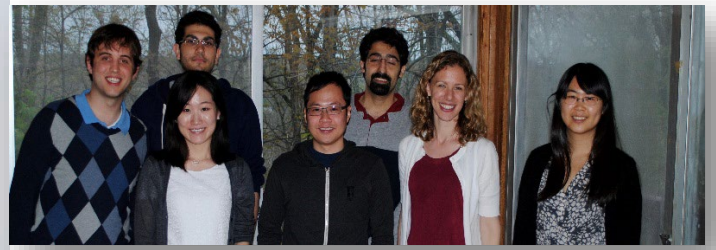


U-M experts: local network

> 92 peer reviewed publications with scientists from 7 U-M Schools

PRIORI

Predicting Individual Outcomes for Rapid Intervention



Emily Mower Provost, Ph.D.
Associate Professor of Computer Science & Engineering,
with her team

Conflict of Interest

- Melvin McInnis and Emily Mower Provost are inventors on US patent US9685174B2, *Mood monitoring of bipolar disorder using speech analysis*, held by the University of Michigan.

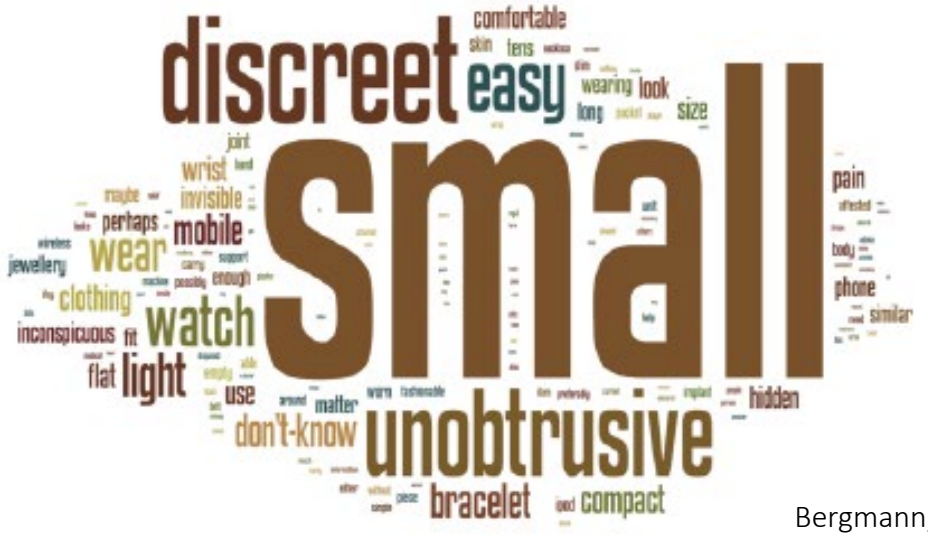
- Melvin McInnis and Emily Mower Provost are co-owners of ***priori ai LLC***, an artificial intelligence-based technology company in health care.

Early warning signs in bipolar - Useful

VERY close and intense clinical monitoring identifies problems early.
- Longer periods of wellness, decreased hospitalization & improved functioning

Sensors: A patient's perspective

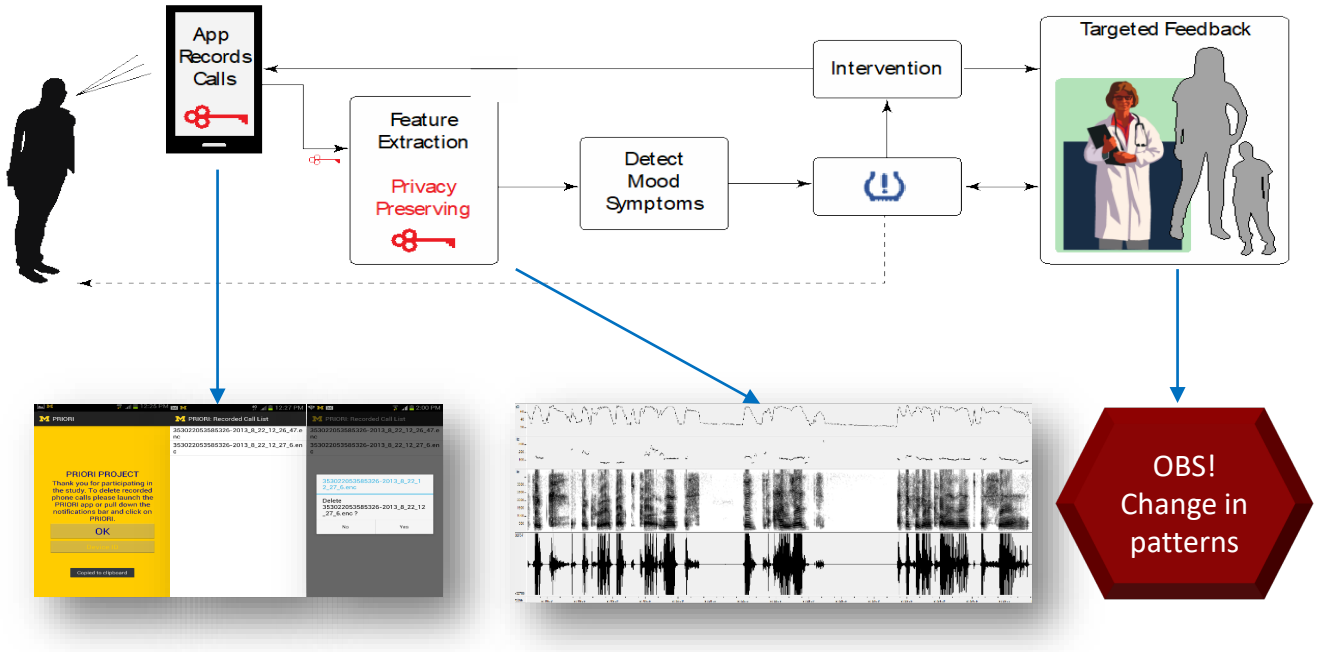
Patient preferences MUST be accommodated for sensor technology success.



Bergmann, et al, *Sensors* 2012

... small, discreet, unobtrusive and preferably incorporated into everyday objects…

PRIORI: Approach

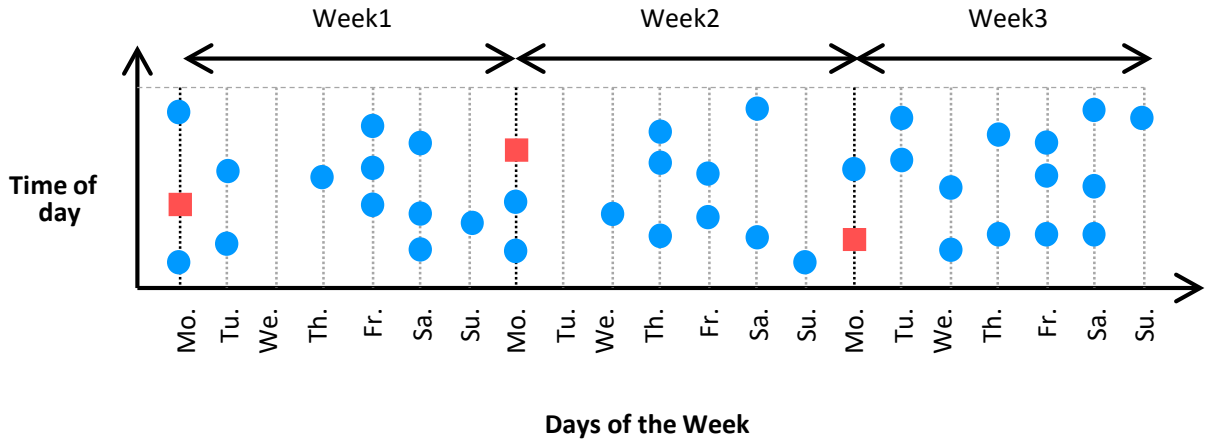


100 participants
~70,000 calls in data bases

PRIORI Database

Bipolar I or II

60 + min / week talk time on phone



- ***Assessment call:*** Weekly call: HamD and YMRS by researcher
- ***Personal Call:*** All other mobile calls made during the study period.

Speech for mood monitoring

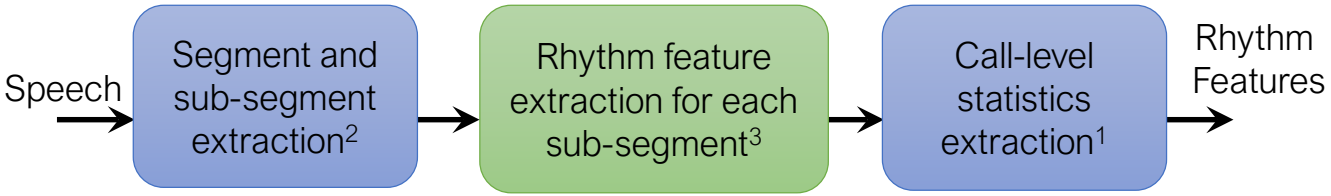
- ***Hypothesis***: Speech is a proxy measure emotional, mood and affective states
- **Why Speech?**
  - Reflects emotional state of speaker
  - Used in clinical assessment of psychiatric disorders

"Something's going on … I can hear it in his voice…. It scares me…" (family member of a patient)

I. Rhythm Features

Individuals with depression exhibit speech that is slowed [1]

Rhythm feature extraction system:



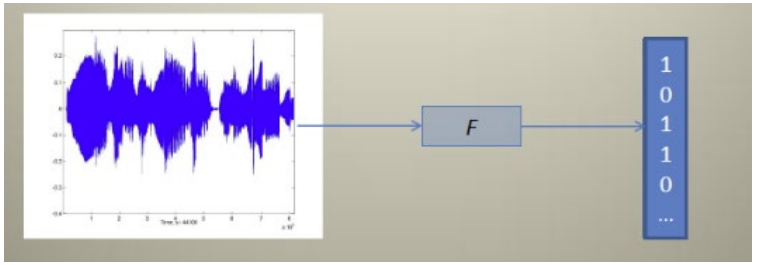
Analysis: Support Vector Machines to determine mania (YMRS), depression (HAMD)

AUC = 0.70

Gideon, Provost, McInnis., Mood state prediction from speech of varying acoustic quality for individuals with bipolar disorder, ICASSP, 2016: 2359-2363.

II. Identity Vectors (i-Vectors)

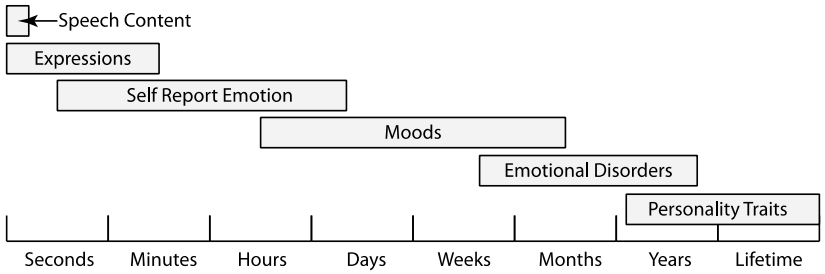
- Originally developed for speaker identification tasks
- Uses all available data
- Many applications of i-vectors are possible:
  - Language recognition
  - Accent / dialect recognition
- PRIORI used personal calls to study ***background patterns***



AUC = 0.78

III. Identifying intermediate features
Emotions

- Mood prediction is challenging:
  - Not directly observable
  - Long ***time scale***

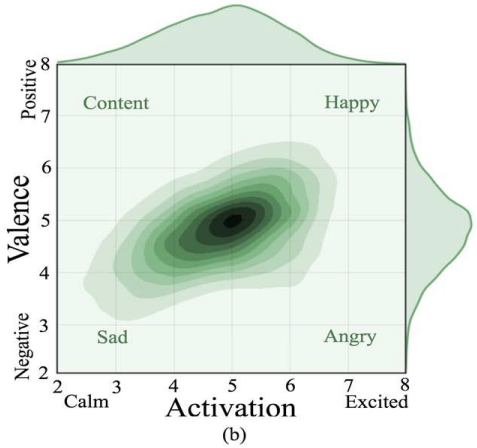


- Can ***Emotion*** simplify mood prediction?
  - Primary BP symptom: emotion dysregulation

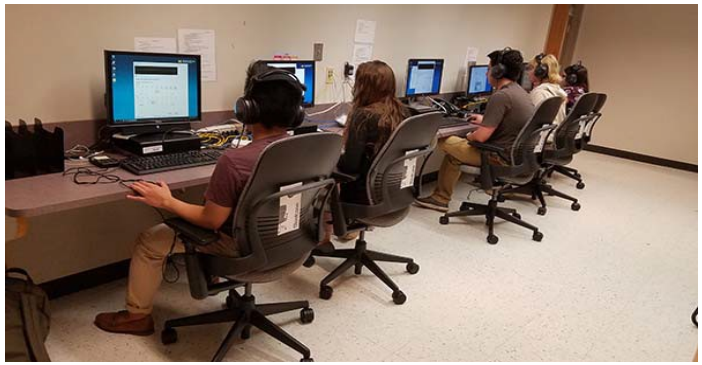
Khorram et al, Capturing Long-term Temporal Dependencies with Convolutional Networks for Continuous Emotion Recognition. Interspeech. 2017

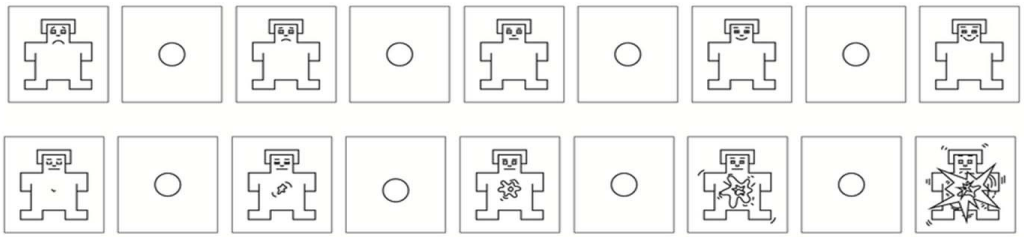
EMOTION

Emotion Annotation



Rating Emotional Content





Valence

Activation

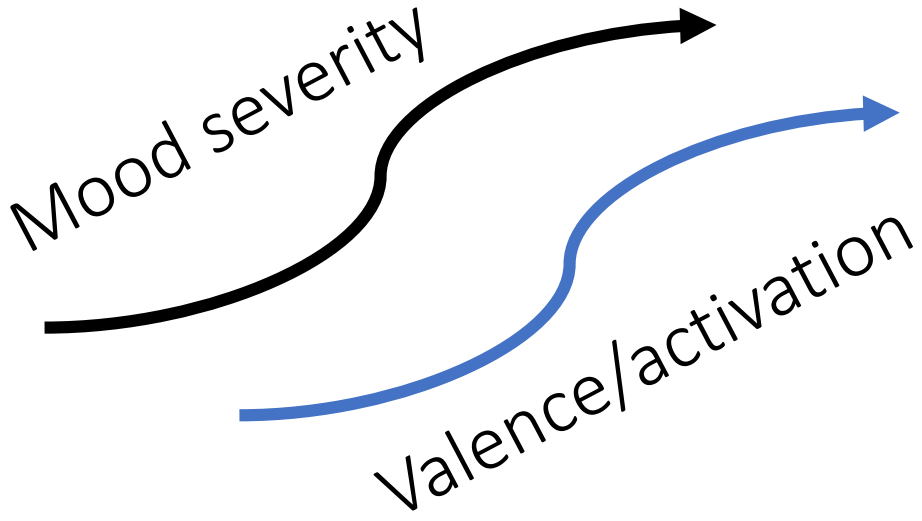
Annotators consider:

Acoustic characteristics, not content

Correlation between acoustic measures - activation 0.7; - valence 0.4

What is the link between mood and emotion?

- **Finding**: valence / activation are significantly correlated with mood severity



Valence: positive vs. negative
Activation: calm vs. excited

What does this give us?

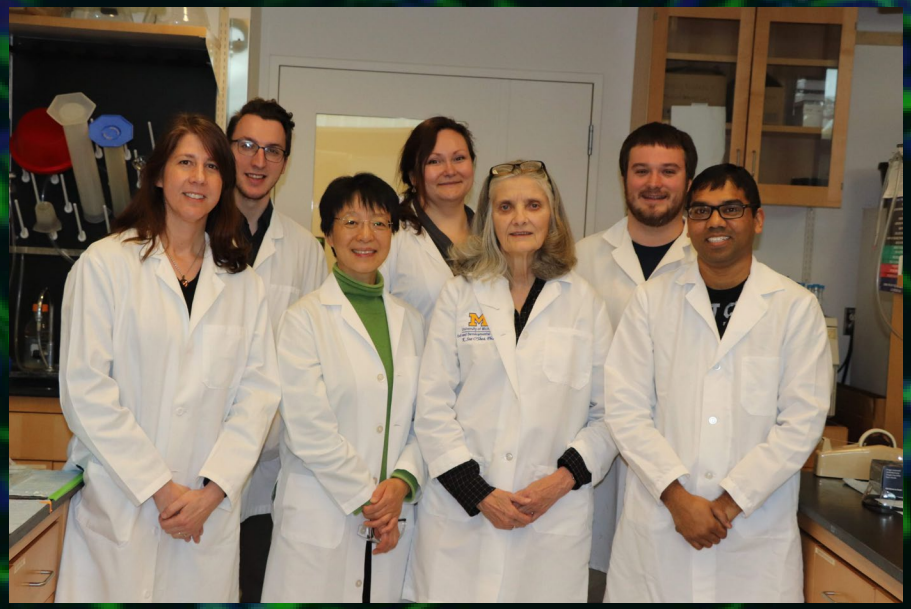
Behavior in daily life

Emotion variation

Mood variation

Human-Centered Computing:
Using Speech to **Measure** Behaviors, Moods & Emotions

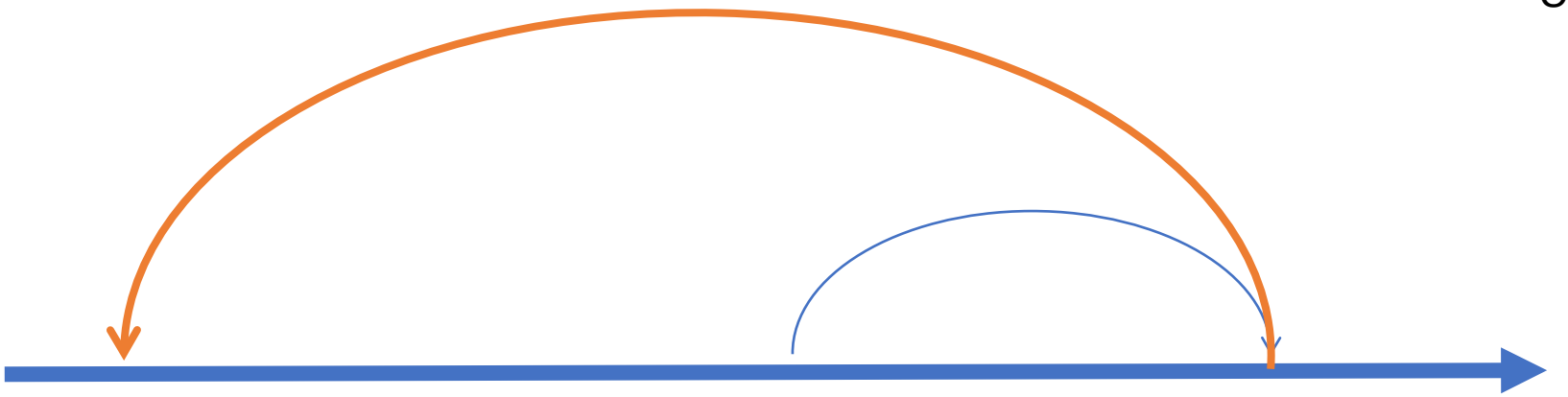
iPSC – Stem cell models of bipolar disorder



Sue O'Shea, Ph.D.,
Professor of Cell & Developmental Biology,
with her team

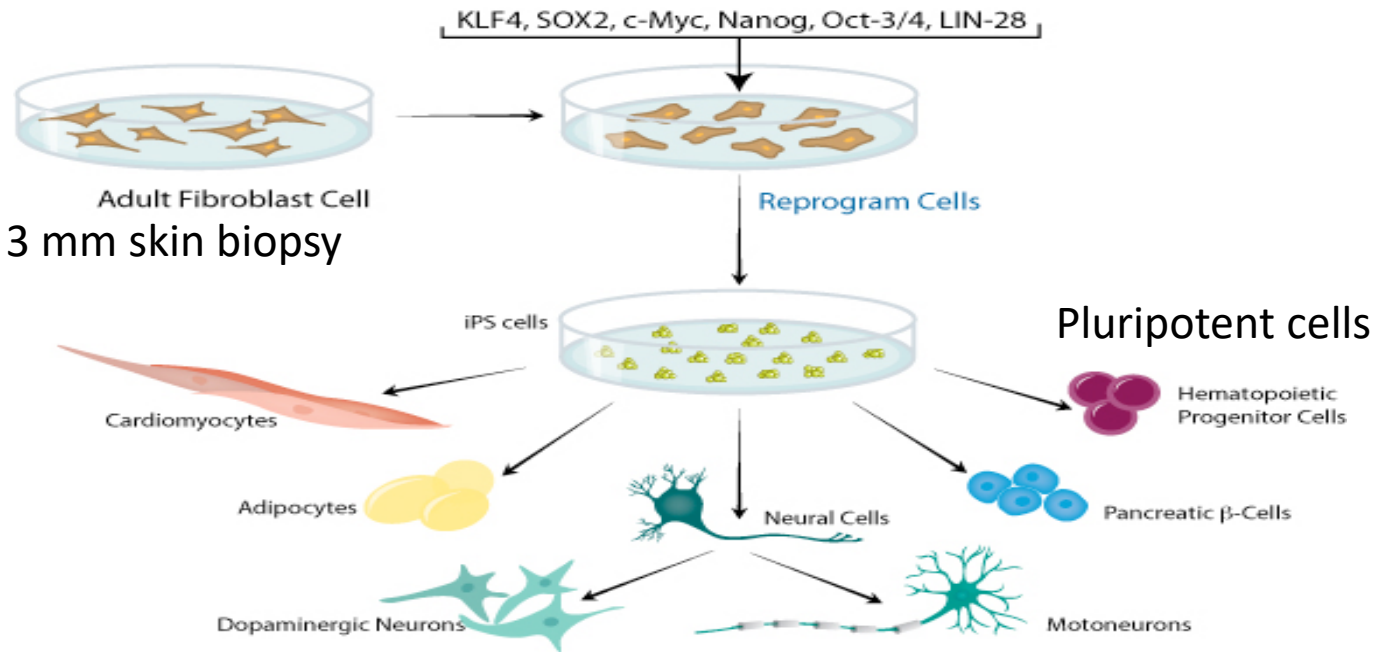
Brain disorders form early in development before first symptoms are present

O'Shea Lab



Stem cells provide for the study of the origins of BP

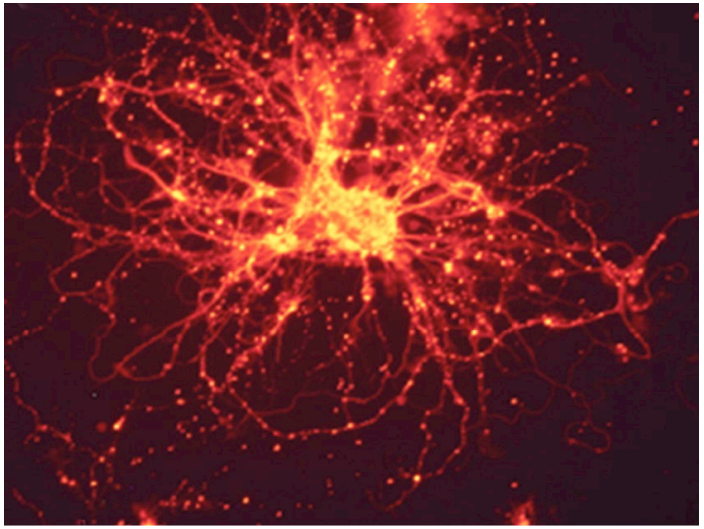
Induced Pluripotent Stem Cells (iPSC) 101

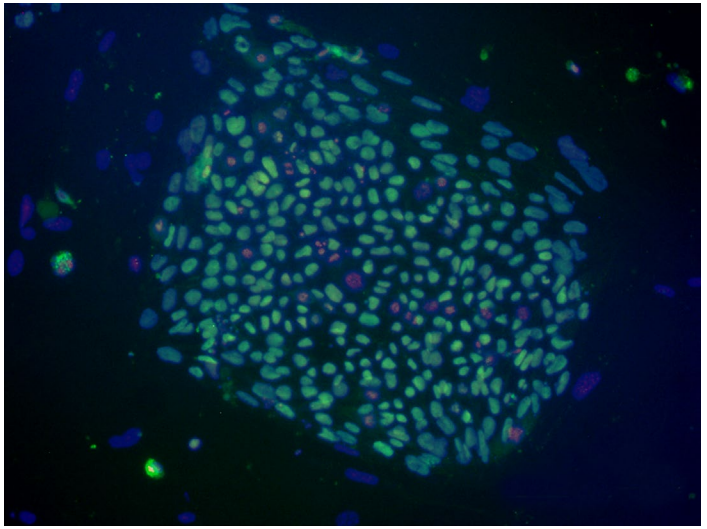


3 mm skin biopsy

Pluripotent cells

Advantages of induced pluripotent stem cells



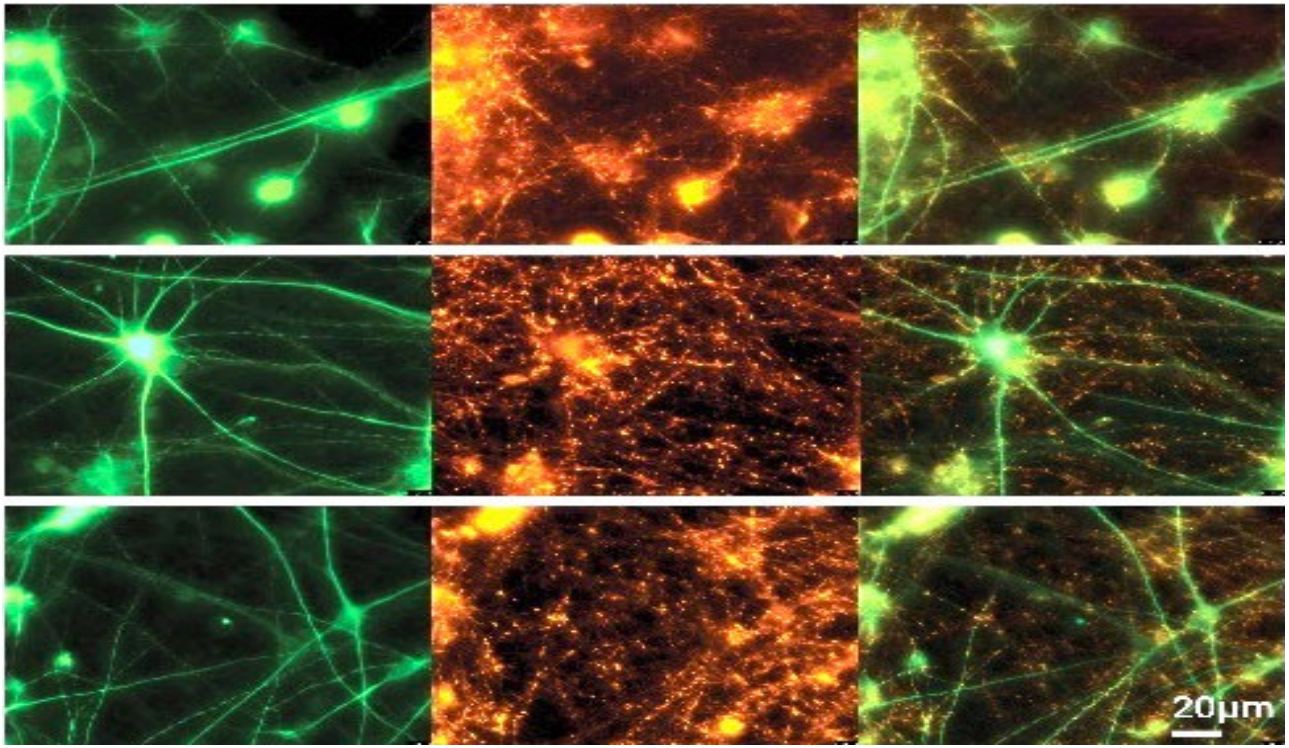


O'Shea Lab

- iPSC can be patient matched – personalized medicine – disease specific
- iPSC can be differentiated to the target cell type – "brain in a dish"
- study response to medicines, stress & condition perturbation

Morphology & Functionality

O'Shea Lab



The Roads…

Neuronal morphology

The Intersections …

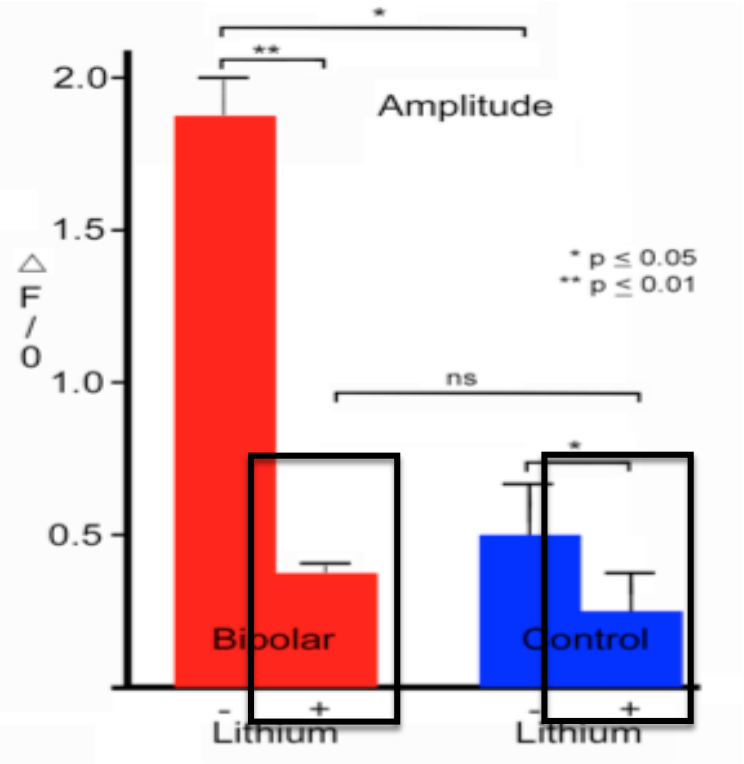
Synapses

The Map…

Overlay

Cindy DeLong

Excitable neurons

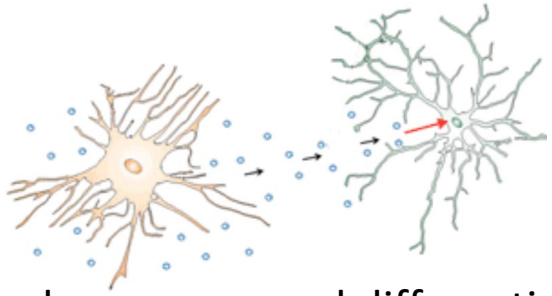


BP neurons more active than controls: lithium treatment normalizes signaling

Think: ***Energy*** ……

Chen et al, Translational Psychiatry 2014

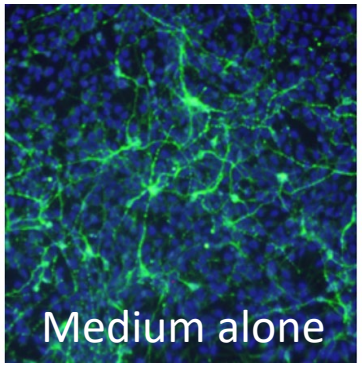
Astrocytes - exosomes (cellular health)

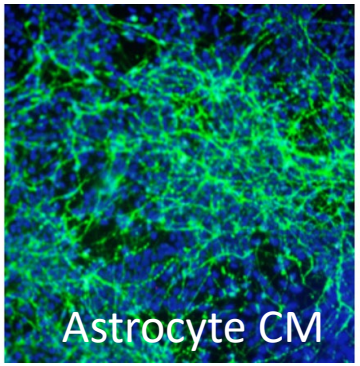


Astrocytes enhance neuronal differentiation

Think: Dept of Public Works

BIII Tubulin



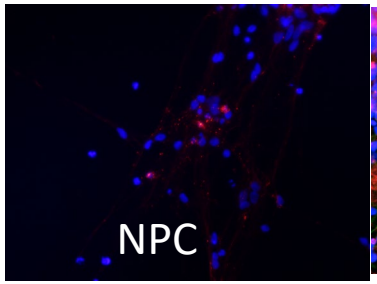


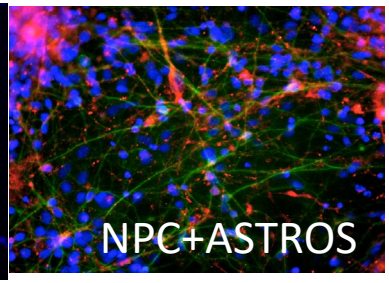
Analysis of 8 lines:

Exosomes, p < 1 x E-56, Rule….

Exosomes: 20-130 nm
Cell to Cell communication
Integral organelles of internal metabolism
Released on ***STIMULATION… (think Flushing...)***

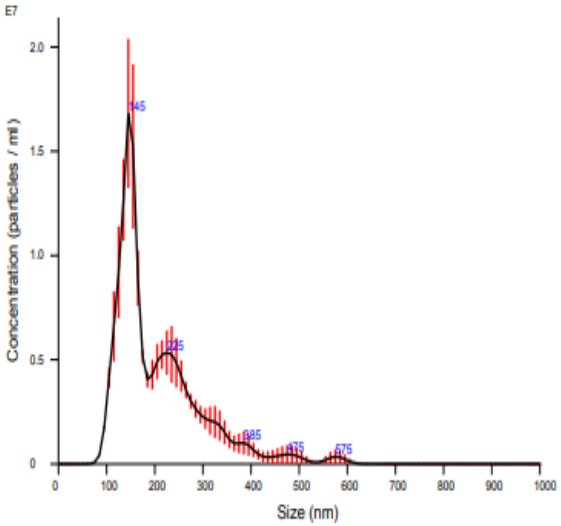
MAP2
Synapsin 1





Small particles released from cells: Extracellular vesicles or exosomes

O'Shea Lab



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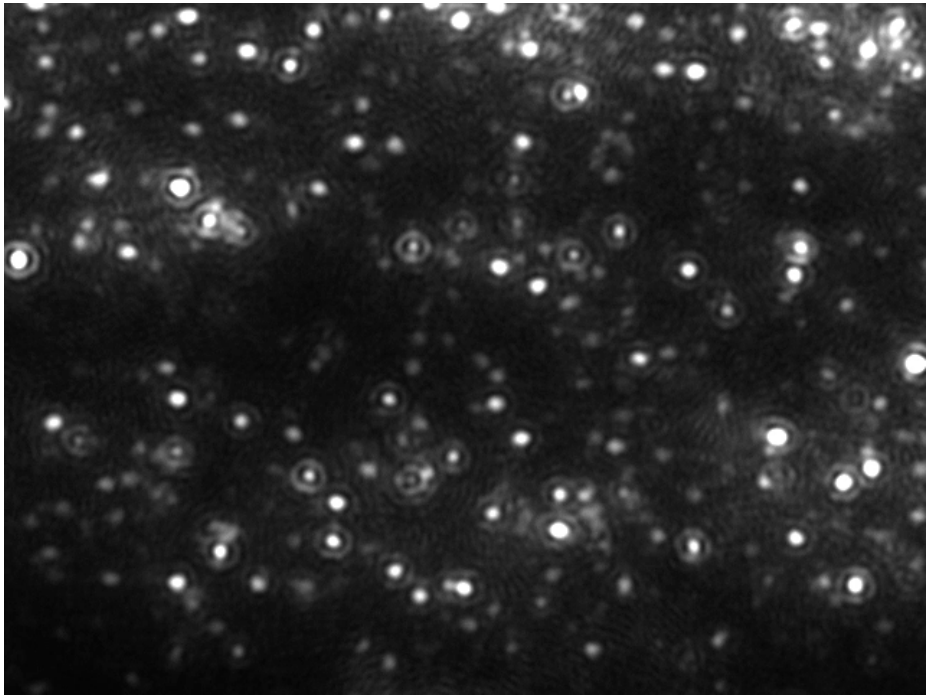
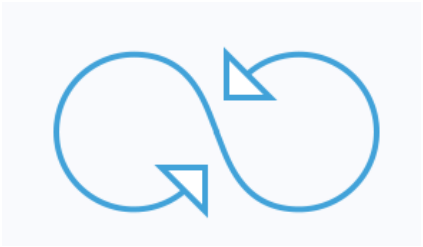


Medium from neurons or plasma from patients

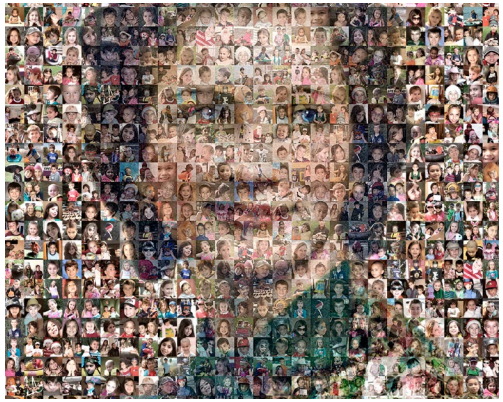
Durga Attili

Bipolar Disorder -  - Conclusions

- Bipolar Disorder is an illness of ***dynamic states*** that are ever changing clinically and biologically. It is difficult to predict patterns of change.
- ***Energy*** is a central feature of bipolar disorder and is evident in the activation levels of speech and reactivity of nerve cells.
- ***Emotion*** (valence) is the positive and negative quality of experience at a personal level and expressed internally (feelings) and externally in expressive features of communications (speech and language).
- ***Time*** is an essential element in monitoring people with bipolar.

So …. with all this re$earch – why don't we know more……

- The human body is a ***mosaic*** of different genomes
  - ***Mosaic***: composed of cells of genetically different types



This messy situation is the new normal …. The challenge is now to figure out up to what point we call something normal.

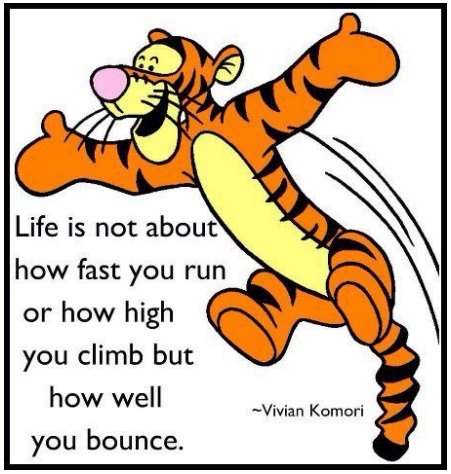
Yizhak, K. *et al. Science* **364**, 2019

There are multiple regions, cells and cell types within the brain.

The Mosaic Brain … Is there genetic diversity among cells of the brain?

The challenge may be to what point we call something normal…..

capacity to recover quickly from difficulties



Perhaps the road ahead is to learn more about:

- Why some individuals with bipolar do well.
- What features underline / predispose to 'doing well.'
  - What is doing well?
- What interferes with a positive course?
- What changes a negative course towards a positive course?

Heinz C. Prechter Bipolar Research Program at the University of Michigan

- Lab of Emily Mower Provost: Computer Science and Engineering
- Lab of Sue O'Shea: Cell and Developmental Biology
- Lab of Melvin McInnis: Department of Psychiatry

HEINZ C. PRECHTER BIPOLAR RESEARCH PROGRAM
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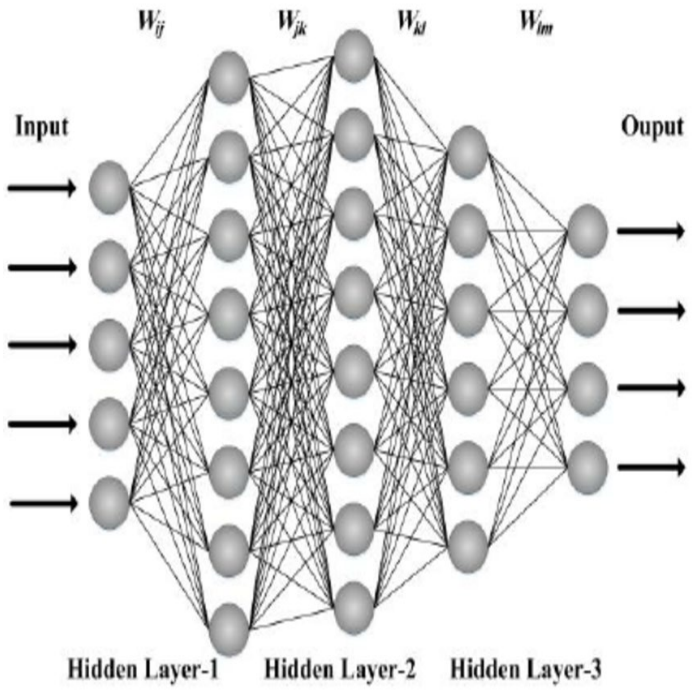

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