Mental Illness

Computational models to improve psychiatry

Ryan Weiss
4/28/17

Mental Illness/Disorder

- Mental illness is any disease or condition that influences the way a person thinks, feels, behaves, and/or relates to others and to his or her surroundings.

- Symptoms can vary from mild to severe and are ongoing

- Symptoms negatively affect a persons daily life and require treatment

THE UNIVERSITY OF TENNESSEE KNOXVILLE

Causes of Mental Illness/Disorder

- Biological
  - Chemical imbalance in neurotransmitters

- Hereditary
  - Combination of genes

- Psychological
  - Triggered by trauma

- Environmental
 - Stressors, life changing

List of Mental Illness

- Addiction

- Anxiety

- ADHD/ADD

- Bipolar

- Depression

- Eating

- OCD

- Schizophrenia

- PTSD

- Dissociative

- Tourette's

- Personality

- Insomnia

- Narcolepsy

Diagnosing Mental Health

- A physical exam
  - Rule out physical problems
- Lab tests
  - Thyroid function and drug screen
- Psychological evaluation
  - Explain symptoms like thoughts, feelings, behavior in questionnaire

Computational Psychiatry and RDoC

- Behavioral tasks

  - Index different psychological processes

- Computational models

  - Fit general psychological process

- Parameter estimation

  - Fitting models to subjects

- Machine learning clustering methods

  - Identify clinically significant conditions
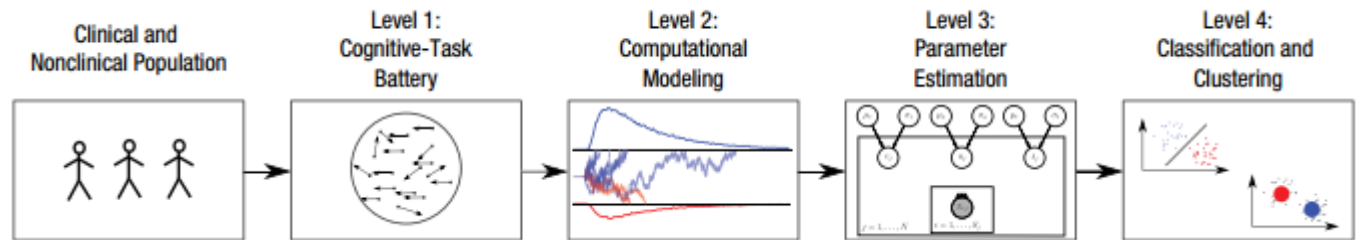
Research Domain Criteria

- Aim to identify neural correlation of psychiatric disorder, bottom-up approach

- Key Matrix of Data

  - Columns represents units of analysis, including genes, cells, behavior

  - Rows represent research domains, including cognitive systems, arousal/regulatory systems

- Three claims

  - Mental illness as disorders of brain circuits

  - Identifiable with tools of clinical neuroscience

  - Biosignatures allow for clinical management

THE UNIVERSITY OF TENNESSEE KNOXVILLE
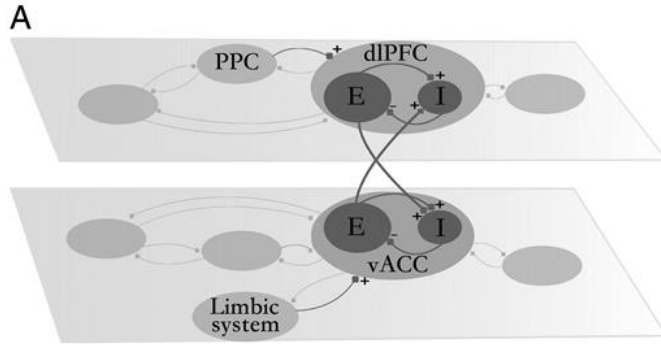
Major Depression Disease (MDD)

- Dysfunction of multimode brain networks

  - Reciprocal interaction between midline limbic regions (ventral anterior cingulate cortex, vACC) and dorso-lateral prefrontal cortex (dlPFC)

  - Interaction between emotion and cognition

  - Abnormal glutamate metabolism in vACC

  - Treatment success in selective serotonin reuptake inhibitor, SSRI, and deep brain stimulation

- No current mechanistic framework describes network dynamics, glutamate, and serotonin interaction
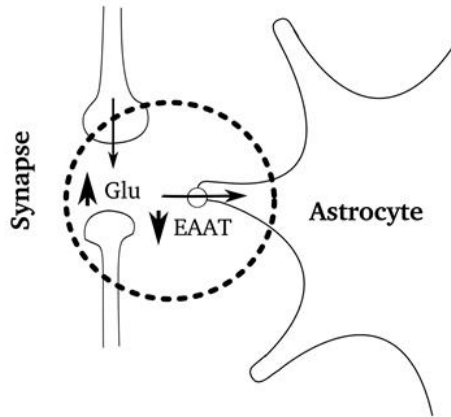
Computational Model of MDD

- Biophysical model of vACC and dlPFC
  - Switch between emotional and cognitive processing
- Simulate slowing glutamate decay
  - Sustained vACC activity
- Hyperactivity of vACC not suppressed by dlPFC
  - Mimics cognitive dysfunction seen in MDD
- Deep brain stimulations or SSRI counteract vACC activity
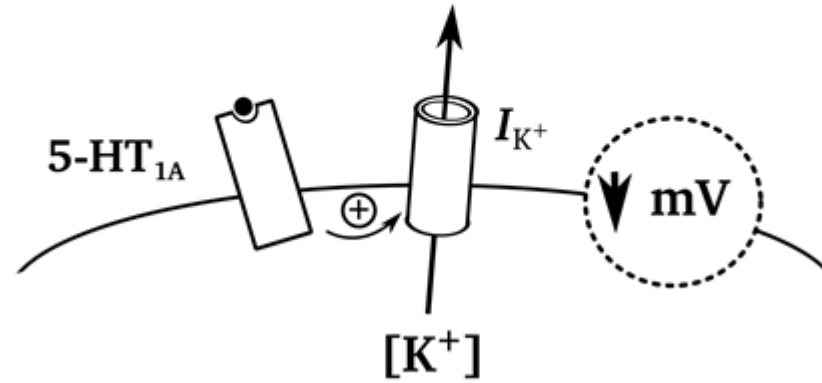- Theta and beta/gamma oscillations switch-like operation in network

THE UNIVERSITY OF TENNESSEE KNOXVILLE

Diagram

Figure 1.

A

PPC — dlPFC
E — I

E — I
vACC

Limbic system

B MDD: slower glutamate decay in vACC

Synapse — Glu — EAAT — Astrocyte

C SSRI: vACC hyperpolarization through 5-HT$_{1A}$R

5-HT$_{1A}$ I_{K^+} mV

[K$^+$]

THE UNIVERSITY OF TENNESSEE KNOXVILLE

Spiking model behaviors

- Integrate and Fire neuron model, Excitatory and Inhibatory

- Each subnetwork contained NE = 800 pyramidal cells and NI = 200 interneurons with membrain potential Vm as

$$C_\mathrm{m}\frac{dV_\mathrm{m}}{dt} = -g_\mathrm{m}(V_\mathrm{m}(t) - V_\mathrm{L}) - I_\mathrm{syn}(t)$$

$$I_\mathrm{syn}(t) = I_\mathrm{AMPA,ext}(t) + I_\mathrm{AMPA,rec}(t) + I_\mathrm{NMDA,rec}(t) + I_\mathrm{GABA,rec}(t).$$

- Vl = -70mV (leak), Vth = -50mV (threshold) and Vres = -55mV (reset)

# Simulating MDD

- Simulate deficient glutamate reuptake by increasing time constant of synaptic glutamate decay.

    - tAMPA = 2.05ms, 2.1ms, 2.15ms

- Simulate SSRI by hyperpolarization of excitatory cells

    - Reduced resting potential VL = -70.6mV

Model tasks

- Strong conflicting emotional and cognitive demand task per epoch

    - Purely emotional (sadness provocation task SP)

    - Purely cognitive (working memory task WM)

- Healthy has two stable states

    - SP epoch vACC responds persistent activation

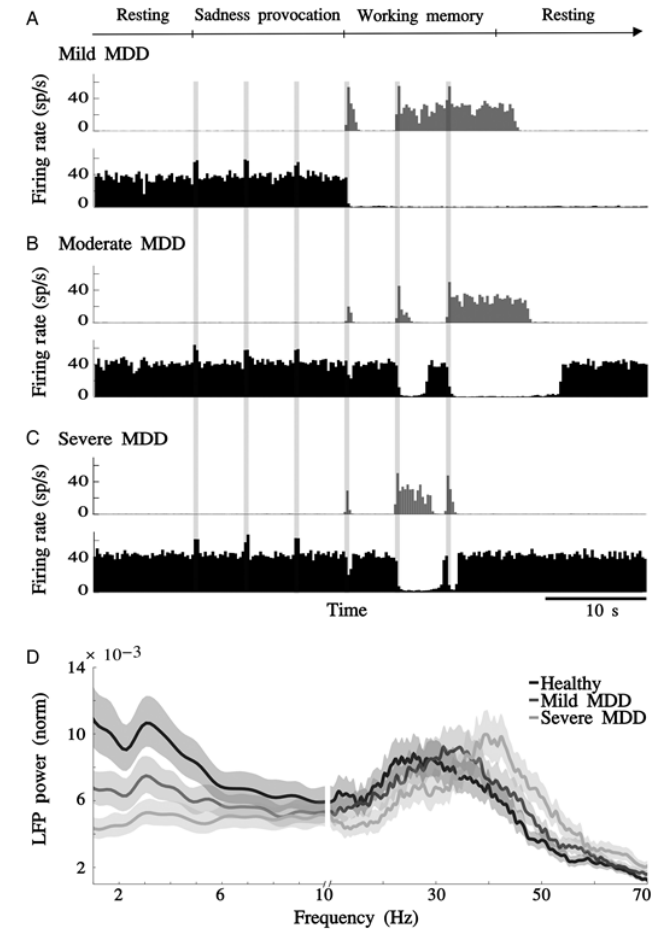   - WM epoch dlPFC responds persistent activation

Figure 2.
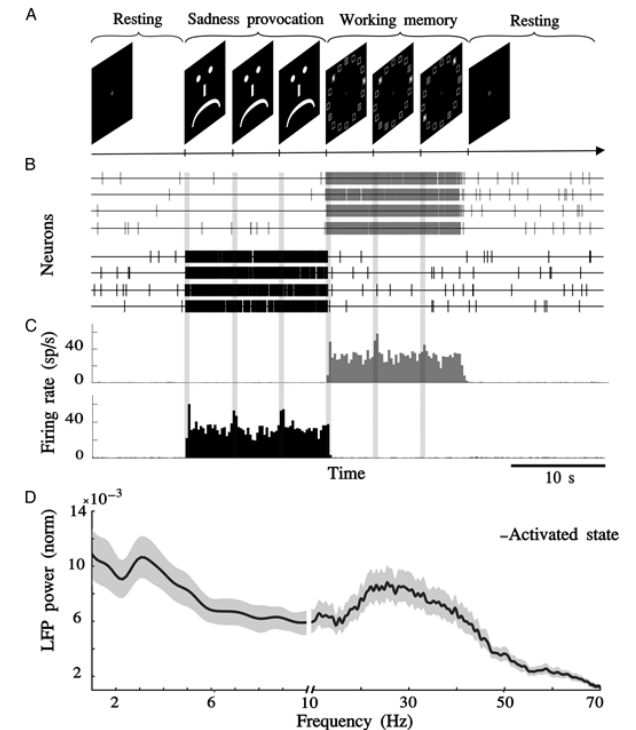
Model MDD

- Adding slower glutamate reuptake
  - 2.5% slowdown showed slight alterations (mild)
  - 5% slowdown disruptions in vACC and
    barely any dlPFC response (moderate)
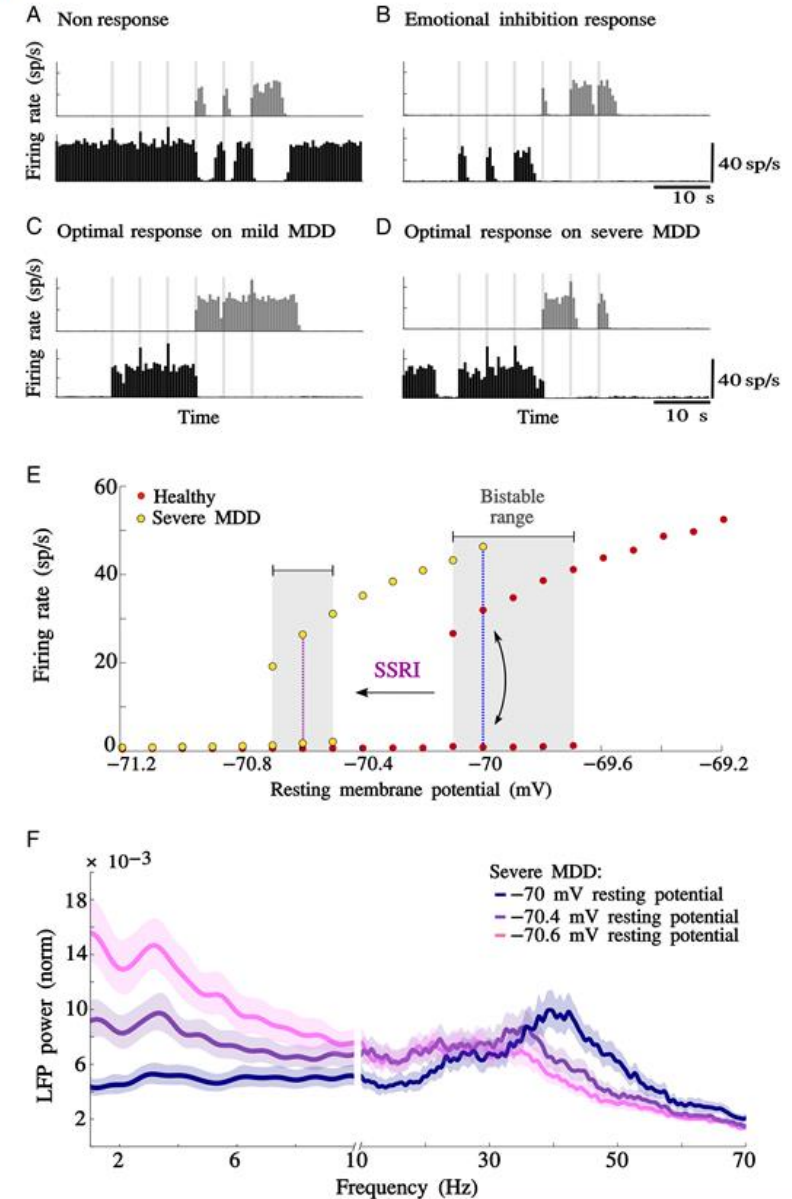 - Further slowdown causes severe disruptions

Figure 3.

Treatment (SSRI)

- Simulate effects of SSRI treatment
  - Non response
  - optimal response
  - emotional inhibition
- SSRI affects VL
  - Low dose of SSRI VL = -70.05mV
  - High dose of SSRI VL = -70.5mV
  - Optimal VL = -70.18mV (mild)
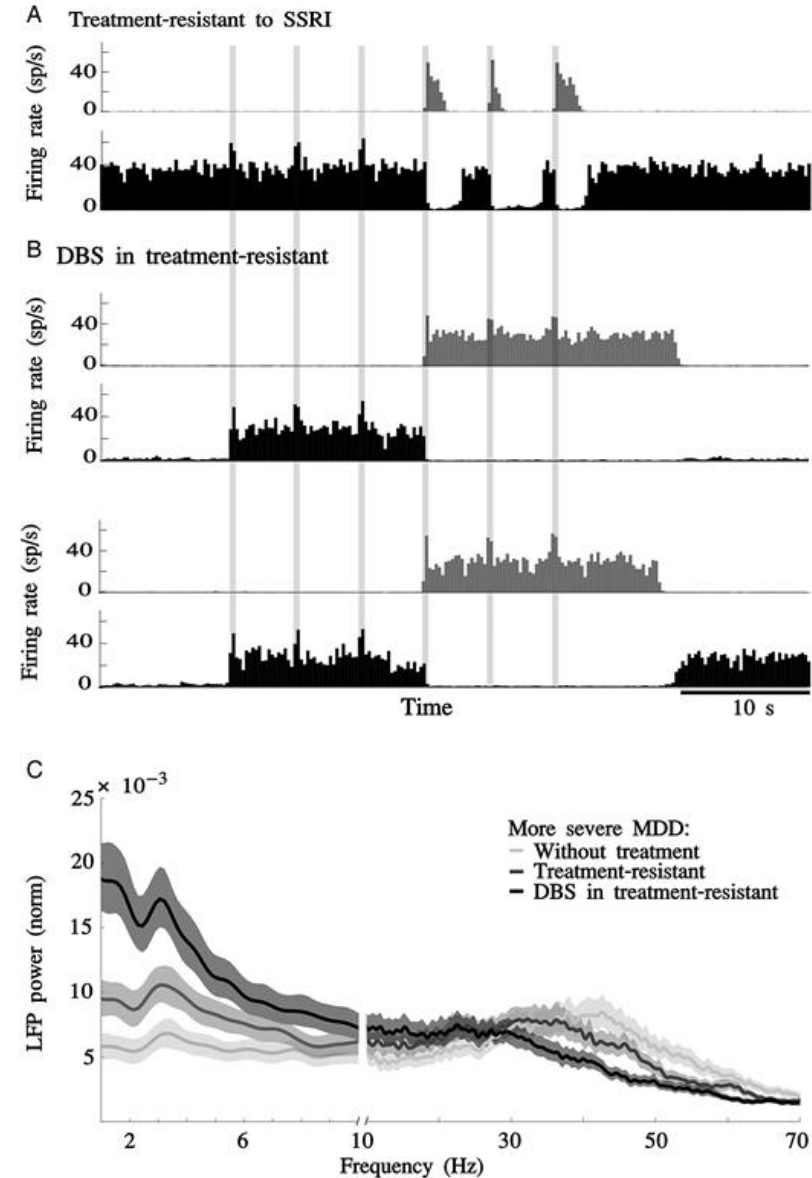 - Optimal VL = -70.6mV (severe)

Figure 4.

THE UNIVERSITY OF
TENNESSEE
KNOXVILLE

Treatment (DBS)

- Adding Deep brain stimulation to SSRI treatment recovered oscillatory dynamic characteristics of a healthy activated state

  - Enhanced theta oscillations and suppressed rhythmic activity in the beta/gamma band

Figure 5.

THE UNIVERSITY OF TENNESSEE KNOXVILLE

MDD Conclusion

- The model shows :
    - glutamate dysregulation can cause aberrant brain dynamics
    - responds to treatment (SSRI)
    - can be reflected in EEG rythms a biomarkers for detecting MDD

Questions?