Mental Illness

Computational models to improve psychiatry

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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 person's daily life and require treatment
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
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
Diagram

Figure 1.

A

B MDD: slower glutamate decay in vACC

C SSRI: vACC hyperpolarization through 5-HT\textsubscript{1A}R

5-HT\textsubscript{1A} \quad I_{K^+} \quad [K^+] \quad mV
Spiking model behaviors

- Integrate and Fire neuron model, Excitatory and Inhibitory
- Each subnetwork contained $NE = 800$ pyramidal cells and $NI = 200$ interneurons with membrane potential $V_m$ as

$$C_m \frac{dV_m}{dt} = -g_m(V_m(t) - V_L) - I_{syn}(t)$$

$$I_{syn}(t) = I_{AMP\Delta, ext}(t) + I_{AMP\Delta, rec}(t) + I_{NMD\Delta, rec}(t) + I_{GABA, rec}(t).$$

- $V_L = -70mV$ (leak), $V_{th} = -50mV$ (threshold) and $V_{res} = -55mV$ (reset)
Simulating MDD

- Simulate deficient glutamate reuptake by increasing time constant of synaptic glutamate decay.
  - $t_{AMPA} = 2.05\text{ms}, 2.1\text{ms}, 2.15\text{ms}$
- Simulate SSRI by hyperpolarization of excitatory cells
  - Reduced resting potential $VL = -70.6\text{mV}$
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
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
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)
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
MDD Conclusion

• The model shows:
  • glutamate dysregulation can cause aberrant brain dynamics
  • responds to treatment (SSRI)
  • can be reflected in EEG rhythms as biomarkers for detecting MDD
Questions?