The Neurobiology of Mood and Psychotic Disorders

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Overview of talk

• Genetics: Consistent evidence for overlap across disorders
• Gene x Environment interactions, epigenetics
• Abnormalities in brain structure and function, neurochemistry and inflammation
• Summary
Disease Incidence and Overlap

- **Major Depressive Disorder (MDD)**
  - Overall lifetime incidence: 17% in the U.S. (lower in other countries, e.g., in Japan 3%)
  - Among those with MDD, **lifetime incidence of psychosis: ~18%**

- **Bipolar Disorder (BD)**
  - Overall lifetime incidence: ~4% (including Bipolar I & II and subthreshold); 1% for Bipolar I
  - Among those with BD, **lifetime incidence of psychosis: 25%**

- **Schizophrenia (SZ)**
  - Overall lifetime incidence: 0.7%, ~3% defined broadly (with 5+ fold variation in incidence across the world, highlighting the importance of environmental factors)
  - Among those with SZ, **lifetime incidence of MDD: 25%**

- Genetics and neuroimaging studies show evidence of biological **overlap** – dimensional/symptom-focused approaches are now gaining favor in biological research
Many shared genetic risk variants across disorders
Genetic overlap observed with an ever increasing number of disorders such as OCD, PTSD, TS…
Overlap with personality traits too: polygenic scores for neuroticism explain 15% of the variance in neuroticism and predict MDD
Heritability of
Schizophrenia: 80%
Bipolar Disorder: 90%
Major Depression: 40%

Mood Disorders: childhood trauma

Schizophrenia:
-in utero events, such as infections, nutritional deficiencies
-childhood trauma/bullying
-urban living
-minority status/discrimination
-cannabis use
Epigenetic mechanisms
1) those that alter DNA directly, i.e., via methylation
2) histone modification
3) non-coding RNAs, e.g., microRNA, that modify gene expression
Increased BDNF promoter methylation in the Wernicke area of suicide victims
G x E interactions underlying depression

Example: 5HTTLPR gene x stressful life events

Greater sensitivity to adverse life events

S carriers: reduced structural and functional connectivity and hyperactivity of the amygdala

Caspi et al, Science 2003

Pezawas et al, Nat Neurosci 2005
Genetic variation in the FKBP5 gene x early adversity

1. Early life adversity + risk genotype = Primed stress response
2. Differences in FKBP5 epigenetic regulation based on genotype
3. Psychopathology onset
4. FKBP51 "disinhibition" subtype

Figure legend:
- de-methylated
- methylated
- glucocorticoid receptor
- mRNA
- n1360780 A/T (risk allele)
- n1360780 G/C (resilient allele)

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Genetic variation in the FKBP5 gene and early adversity can affect stress response and psychopathology onset. The figure illustrates the influences of FKBP5 expression on early life, adulthood, and psychopathology development.

Matosin et al. Biol Psych 2018
G x E interactions underlying schizophrenia

Example: DRD2 gene x cannabis use

Relative risk for a psychotic disorder

Relative risk for a psychotic disorder
Interaction between increased genetic risk for schizophrenia and obstetric (intra-uterine) complications
GWAS signal for depression (3 significant loci) only in women with no reported adversity →
contribution of genetics to depression may be more heterogeneous for those with histories of adversity

Peterson et al, Am J Psych 2018
genetic vulnerability, present from birth

changes in brain structure/function

symptoms and impaired functioning

prenatal or later-in-life events, effects depend on developmental stages/critical periods
Ventricular enlargement and brain volume loss in schizophrenia

Ventricular size in patients and controls.
Each point represents average of four measurements on photographs.

Johnstone et al, Lancet 1976
Ventricular enlargement $\rightarrow$ widespread cortical thinning in schizophrenia

Kuperberg et al, Arch Gen Psych 2003
Abnormally High Neuronal Density in the Schizophrenic Cortex

A Morphometric Analysis of Prefrontal Area 9 and Occipital Area 17

Lynn D. Selemon, PhD; Grazyna Rajkowska, PhD; Patricia S. Goldman-Rakic, PhD
Excessive pruning and loss of cortical connections over time → increased vulnerability to psychosis
Schizophrenia risk proportional to the C4 allele’s tendency to increase C4A expression, which mediates pruning.
Similar pattern of “excessive pruning” in adolescents with low level psychotic symptoms

Satterthwaite et al JAMA Psych 2016
Specific types of therapy (e.g., cognitive enhancement treatment) may reverse or prevent progressive changes in the brain during the early stages of schizophrenia.
Fetal fortification exposure alters cortical development during adolescence

Eryilmaz et al, JAMA Psych 2018
A key circuit affected in neuropsychiatric disorders
Abnormalities of the subgenual cingulate gyrus in major depression

Ressler & Mayberg, Nat Neurosci 2007
Greater frontal-amygdala connectivity in resilient (vs. non-resilient) female adolescents

Fischer et al, JAMA Psych 2018
The finding of amygdala hyperactivity in unipolar and bipolar depression has been highly replicated.
Overactivity of the amygdala in children of patients with depression has been observed in 3 studies (Monk et al, 2008; Swartz et al, 2014, Chai et al, 2015)

A. FH-

Also found in young adults with a first-degree relative with depression

B. FH+

C. FH+ > FH-

Amygdala

Face W > Face A

Face A > Face W

Barbour et al, under review
Overactivity of the amygdala in youth with subclinical, psychotic-like symptoms
Abnormally sustained hippocampal response to emotional stimuli in schizophrenia

Holt et al, Biol Psych 2005
Levels of subclinical delusions predicted the resting activity (perfusion) of the hippocampus bilaterally.

These data, which resemble similar findings in patients with psychotic disorders, suggest that the phenomenology and biology of subclinical and clinical psychosis are on a continuum.

Wolthusen et al, Biol Psych CNNI, 2018
What are the molecular and cellular mechanisms underlying these changes in the brain?

**Dopamine** synthesis is elevated in schizophrenia and bipolar disorder patients compared to healthy subjects, and correlates with positive symptom severity.

![Graph](image)
Cellular model of schizophrenia

[Diagram of cellular model of schizophrenia showing Prefrontal cortex, Striatum, and Mesencephalic DA cell nuclei with arrows indicating excitatory and inhibitory activity, and receptors such as NMDA, GABA, and DA activity]
Neuroinflammatory pathways in the pathogenesis of depression

External and internal stress → Sympathetic nervous system activation → Cytokines

Cytokines → Sympathetic nervous system activation

Neuroinflammatory pathways

5HT-transporter expression in hippocampus

IDO-enzyme activation

Kynurenine-pathway activation

Central serotonin availability

GR resistance

HPA-axis dysfunction

Cortisol

Monoamine hypothesis

Neurotransmitter-depletion pathway

Neuroendocrine pathway

Depression

Neuronal cell apoptosis → Neuronal damage

Neurotrophin BDNF

Antioxidant protection → Inflammation

Change in NMDA receptor

Synaptic glutamate

Glutamatergic excitotoxicity

Apoptosis in hippocampus

Neural plasticity pathway

Neurodegeneration

Neurogenesis

Oxidative and Nitrosative stress

Autoimmune reaction
Changes in cytokines in schizophrenia, bipolar disorder and depression

Goldsmith et al, Mol Psych 2016
STRESS
Early adversity
Interpersonal conflict
Social isolation

↑ excitotoxicity
↓ monoamines
↓ trophic factors

NF-κB
CRH
Hypothalamus
Pituitary

↑ pro-inflammatory cytokines
↑ Chemokines
↑ Adhesion molecules
↑ Acute phase reactants

ACTH

Adrenal gland
Pons
Vagus n.

Inflammation

Immune system
Macrophage
Sympathetic chain

Miller et al Biol Psych 2009
Conclusions/Discussion

- genetic vulnerability, present from birth
- changes in brain structure/function
- symptoms and impaired functioning

prenatal or later-in-life events, effects depend on developmental stages/critical periods