The Neurobiology of Mood and Psychotic Disorders

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Disease Incidence

- **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
Overview of talk

- The big picture: Gene x Environment interactions in mood and psychotic disorders

- Schizophrenia:
  - Abnormalities in brain structure and function
  - Abnormalities in neurochemistry
  - Genetics and epigenetics

- Mood disorders:
  - Abnormalities in brain structure and function
  - Abnormalities in neurochemistry
  - Genetics and epigenetics

- Summary
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
The Overall Model

- Genetic vulnerability, present from birth
- Changes in brain structure/function
- Symptoms and impaired functioning

E

Prenatal or later-in-life events, effects depend on developmental stages/critical periods
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
G x E interactions underlying schizophrenia

Example: DRD2 gene x cannabis use

Relative risk for a psychotic disorder

[Bar chart showing the relative risk for a psychotic disorder between GG subjects and T carriers based on different cannabis use levels.]

Colizzi et al Schiz Bull 2015
Abnormalities in brain structure and function in schizophrenia

• Enlarged ventricles and loss of brain volume
  – Localized or diffuse?
  – Static or progressive? Reversible?
  – Role of antipsychotics?
  – How early do these start? (During the prodrome or earlier?)

• Inefficient function and abnormal connectivity ("dysconnectivity") of the brain
  - Related to impairments in cognition? Social cognition?
  - A fundamental expression of the pathophysiology, or secondary to having the illness or its treatments?
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

[Graphs showing neuronal and glial density comparisons between normal and schizophrenic groups for Areas 9 and 17.]
Brain volume reductions may be progressive during the early years of psychosis

An active pathological process, which may be reversible?
Also likely a contribution of antipsychotic medications
Specific types of therapy (e.g., cognitive enhancement treatment) may reverse or prevent progressive changes in the brain during the early stages of schizophrenia. Eack et al, Arch Gen Psych 2010
The stages of psychotic illness

Note: ~25-30% of people who are “clinically high risk” develop schizophrenia

Fusar-Poli, JAMA Psych 2013
Excessive pruning and loss of cortical connections over time → increased vulnerability to psychosis
Much evidence (from diffusion tensor imaging, EEG & resting-state connectivity studies) for “dysconnectivity” in schizophrenia.

Holt et al, Biol Psych 2011
Thalamic dysconnectivity in both the prodromal and full-blown illness stages of psychosis

Anticevic et al JAMA Psych 2015
An abnormally small hippocampus is one of the most replicated findings in schizophrenia → the whole hippocampus, or just a subregion?

Can divide the human hippocampus into its subregions (including the subfields) using MRI
Hyperactivity of the hippocampus, particularly CA1, in psychosis
Hyberactivity of the CA1 subfield of the hippocampus predicts CA1 atrophy in at-risk prodromal patients

20 prodromal patients; 10 developed psychosis during the follow-up period (mean 2.4 years)

Also modeled this pattern of changes in ketamine-treated mice - showed that excessive extracellular glutamate plays a role.

Schoebel et al, Neuron 2013
Atrophy of the hippocampus in schizophrenia begins in the CA1 subfield and then spreads to involve the other subfields over the course of the illness.
Abnormalities in neurochemistry in schizophrenia

- Dopamine
  - Increase in presynaptic synthesis and release
- Glutamate
  - Hypofunction of glutamate NMDA receptors
- GABA
  - Deficits in the fast-spiking parvalbumin-containing interneurons
- Neurotrophic factors
- Inflammation
Dopamine neurotransmission is dysregulated in schizophrenia
In vivo evidence for the dopamine hypothesis of schizophrenia: excessive dopamine release in acutely psychotic patients

Laruelle et al, Biol Psych 1999
Cellular model (unified hypothesis?) of schizophrenia

**NMDA receptor hypofunction**
(due to a reduction in dendritic spines, increased pruning, neuroinflammation) → **deficit in functioning of GABAergic interneurons** (fast spiking, parvalbumin-containing) → “**disinhibition**” of hippocampal pyramidal cells, thalamic nuclei, dopamine neurons → Increases in extracellular glutamate → further atrophy, loss of connections
Abnormalities in genetics/epigenetics in schizophrenia

• Schizophrenia is highly polygenic → GWAS with > 36K patients and > 100K controls: 108 SNP “hits” meeting significance threshold
  – Still these loci only account for 3.4% of the liability for schizophrenia
  – Loci in genes encoding synaptic proteins, calcium channels, glutamate receptors, the D2 dopamine receptor, the major histocompatibility complex (MHC)
  – many common alleles with very small effects

• 11 rare copy number variants (CNVs) identified: large deletions or duplications that confer a relatively high amount of risk for schizophrenia, can be de novo, incidence of clinically relevant ones ~5% (use of chromosomal microarray analysis as a diagnostic test?)

• High degree of pleiotropy in common SNPs and CNVs— one gene or allele affecting multiple phenotypic traits— i.e., common risk variants for schizophrenia, bipolar disorder and major depressive disorder

Owen et al, Lancet 2016
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*
Schizophrenia risk proportional to the C4 allele’s tendency to increase C4A expression, which mediates pruning.
Epigenetic mechanisms—accounting for “missing heritability?”:
1) those that alter DNA directly, i.e., via methylation
2) histone modification
3) non-coding RNAs, e.g., microRNA, that modify gene expression
Abnormalities in brain structure and function in mood disorders

- Hypofunction of the prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC), and striatum
- Overactivity of the amygdala
  - also present in first-degree relatives
  - correlations with levels of childhood adversity
- Overactivity of the subgenual cingulate cortex and anterior insula
- Reduced volume of the hippocampus - correlations with the number of episodes/chronicity and treatment resistance
- Clinical heterogeneity and state vs. trait effects may account for inconsistent findings → ongoing work identifying mood disorder subtypes related to specific symptoms and treatment response
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-

B. FH+

C. FH+ > FH-

Also found in young adults with a first-degree relative with depression
Model of mood disorders: reduced prefrontal function leads to disinhibition of the amygdala and other limbic structures.
A meta-analysis showed an average of increased connectivity between the subgenual prefrontal cortex and default network in depression: a model of rumination.

**Figure 1.** Regions showing reliably increased connectivity with the default-mode network in major depressive disorder.
Abnormalities of the subgenual cingulate gyrus in major depression

Ressler & Mayberg, Nat Neurosci 2007
Abnormalities in neurochemistry in mood disorders

• **Monoamines:** post-mortem, PET, CSF and neuroendocrine studies demonstrate a reduction in activity of serotonin neurons in depressed patients (with reductions in serotonin transporter binding sites and receptor densities); alterations in norepinephrine and dopamine as well.

• **Cortisol:** Many depressed patients hypersecrete cortisol; the dexamethasone suppression test (DST), plus the cortisol releasing factor (CRF) stimulation test, indicate hyperactivity of the HPA axis in these patients—may be due to a tendency (genetically mediated) towards CRF hypersecretion, which may lead to overactivity of the immune system. However, both hypercortisolemia and hypocortisolemia can be observed in depressed patients.

• **Chronic inflammation:** levels of cytokine activation correlate with depression severity; anti-inflammatory agents have therapeutic effects.

Saveneau & Nemeroff, Psych Clin N Am 2012
Abnormalities in neurochemistry in mood disorders

• The “neurotrophic hypothesis” of depression is based on:
  • Reduced hippocampal BDNF in postmortem samples of depressed patients
  • Impairment of BDNF signaling \(\rightarrow\) depression-related behaviors in rodents; facilitation of BDNF \(\rightarrow\) antidepressant effects

• **Gender** effects (explaining 2-fold higher incidence of depression in females compared to males): Estrogen has antidepressant effects but testosterone administered during puberty to rats reverses depression-associated behaviors

• Abnormalities in **energy homeostasis and metabolism**

Krishnan & Nestler, Am J Psych 2010

**Euthymic**
Synaptic homeostasis

**Depressed**
Synaptic dysconnectivity

**Remitted**
Synaptic formation

- Stress: EAAT, BDNF, mTORC1
- Ketamine: Glu surge, AMPA, Extrasynaptic NMDA
- BDNF

Coping, exercise, enrichment

Depression relapse
Abnormalities in genetics/epigenetics in mood disorders

• GWAS of patients with depression have not produced significant findings thus far; likely underpowered
• Genetically, depression has great overlap with anxiety (GAD), and some (but less) with bipolar disorder
• Role of clinical heterogeneity in depression genetics: more heritable in women; possibly 3 genetic factors underlying psychomotor/cognitive, mood and neurovegetative features of depression, respectively
• GWAS of bipolar patients have identified significant loci in genes encoding for subunits of calcium channels (L-type alpha), cell surface proteins, extracellular matrix glycoproteins; some bipolar disorder risk alleles also increase risk for schizophrenia and some are disease specific
• Different from schizophrenia: few copy number variants (CNVs) associated with bipolar disorder so far
• G x E interactions observed for mood disorders may be accounted for by epigenetic mechanisms

Craddock & Sklar, Lancet 2013; Flint & Kendler, Neuron 2014
Increased BDNF promoter methylation in the Wernicke area of suicide victims
Histone deacetylation → condenses chromatin → limits transcription; HDAC inhibitors prevent this

Increased deacetylation of H3 in socially defeated mice and depressed humans

All of these changes were reversed by treatment with an HDAC inhibitor, similar to the effects of fluoxetine

Covington et al, J Neurosci 2009
Summary/Conclusions

- 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