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.
Overlap/comorbidity?

- **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 also show evidence of biological overlap – dimensional/symptom-focused approaches are now gaining favor in biological research
Genetic pleiotropy is high across disorders—many shared genetic risk variants.
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
## Heritability of Common Illnesses

<table>
<thead>
<tr>
<th>Illness</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington’s Disease</td>
<td>100%</td>
</tr>
<tr>
<td>Autism</td>
<td>90%</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>80%</td>
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<tr>
<td>Schizophrenia</td>
<td>80%</td>
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<tr>
<td>Asthma</td>
<td>80%</td>
</tr>
<tr>
<td>ADHD</td>
<td>70%</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>65%</td>
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<tr>
<td>Hypertension</td>
<td>62%</td>
</tr>
<tr>
<td>Major Depression</td>
<td>40%</td>
</tr>
<tr>
<td>Alcoholism (in males)</td>
<td>35%</td>
</tr>
</tbody>
</table>
genes x E → brain function x E → symptoms x E

- 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
One environmental influence on schizophrenia risk: Minority status increases the risk of developing schizophrenia 2-4 fold, unrelated to ethnicity or socioeconomic status.

The increase in risk correlates with discrimination rates.

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Experiences of interpersonal discrimination</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morocco</td>
<td>42%</td>
<td>High</td>
</tr>
<tr>
<td>Netherlands-Antilles</td>
<td>30%</td>
<td>Medium</td>
</tr>
<tr>
<td>Surinam</td>
<td>26%</td>
<td>Medium</td>
</tr>
<tr>
<td>Other non-Western</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>8%</td>
<td>Low</td>
</tr>
</tbody>
</table>

Relative rate (compared to average rate) of developing schizophrenia:

- Morocco: 4 x
- Netherlands-Antilles: 2 x
- Surinam: 1.5 x
- Other non-Western: 1.5 x
- Turkey: 1.5 x

Discrimination, urban living, bullying, childhood abuse = social stress

Greater social stress-induced activation of the brain in minority participants compared to controls, which correlated with discrimination levels.
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
- Relative risk for a psychotic disorder
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 prefrontal cortex and other regions**
  - Related to impairments in cognition? Social cognition?
  - A fundamental expression of the pathophysiology, or secondary to having the illness or its treatments?
  - A large-scale network coordination problem – frontoparietal attention network vs. default network

- Abnormalities in subcortical structures may drive other changes: e.g., hippocampus
- Sensory/perceptual abnormalities may play an important role: bottom up vs. top down?
Neuroimaging: Across Space and Time
Anatomy, Physiology, Metabolism, Electrophysiology, Neurochemistry

High-Field fMRI
Optical Imaging
Anatomic MR
PET
EEG/MEG
TMS
Cortical Stim

Courtesy of Bruce Rosen
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

Selemon et al, Arch Gen Psych 1995
Brain volume reductions may be progressive during the early years of psychosis.

An active pathological process, which may be reversible?

Also 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.
The stages of psychotic illness

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

Fusar-Poli, JAMA Psych 2013
Timeline of Human Brain Development

Thompson & Nelson, American Psychologist 2001
Excessive pruning and loss of cortical connections over time → increased vulnerability to psychosis

*Graph showing synaptic connectivity over age with key points for normal development, possible paths to schizophrenia, and psychosis threshold.*
Similar pattern of “excessive pruning” in adolescents with low level psychotic symptoms

Satterthwaite et al JAMA Psych 2016
Much evidence (from diffusion tensor imaging, EEG & resting-state connectivity studies) for “dysconnectivity” in schizophrenia.

One example: reduced functional connectivity between mid/posterior and dorsal anterior cingulate cortex in schizophrenia.

Holt et al, Biol Psych 2011
An abnormally small hippocampus is one of the most replicated findings in schizophrenia localized to a subregion of the hippocampus?

Can segment the human hippocampus into its subfields using MRI
Hyperactivity of the hippocampus, particularly CA1, in psychosis
Hypermetabolism 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.

Ho et al, Mol Psych 2016
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*

Nature 2014
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 is 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

Barbour et al, under review
Overactivity of the amygdala in first-degree relatives of patients with depression may be linked to low resilience.

Barbour et al, under review
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 reduced 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 → depression-related behaviors in rodents; facilitation of BDNF → 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

- Synaptic vesicles
- Stress
- EAAT
- BDNF
- mTORC1
- Coping, exercise, enrichment

**Depressed**
Synaptic dysconnectivity

- NMDA
- GABA
- Glu surge
- AMPA
- Extrasynaptic NMDA
- Depression relapse

**Remitted**
Synaptic formation

- NMDA
- AMPA
- mTOR
- BDNF
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 $\rightarrow$ condenses chromatin $\rightarrow$ 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/Conclusion

- 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