Current Hypotheses on the Etiology of Schizophrenia
Molecules, Neural Networks and Behavior

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Background Literature and Slides
• The Schizophrenia Research Forum online:
  http://www.schizophreniaforum.org
• Lecture slides available at:
  http://www.case.edu/med/galanlab/teaching.html

Outline
• First Lecture
  • Introduction
    • What we know about Schizophrenia
    • Hypotheses on the etiology of the disease
      • Dopamine hypothesis
      • Glutamate (or NMDAR) hypothesis
      • GABA hypothesis
      • Genetic hypothesis
      • Synthesis of most of the above: A systems level perspective
  • Second Lecture
    • Discussion of a research paper

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Basic Facts
• Schizophrenia has a heterogeneous presentation, with disorganized, positive (delusion, hallucinations), and negative symptoms (avolition, apathy, blunted affect, cognitive deficits) having different levels of prominence across time and across individuals.

• Schizophrenia is relatively common, affecting approximately 0.7% of the world’s population.

• Prevalence is greater in men throughout most of adulthood, but is equal by the end of the risk period.

Basic Facts
• Schizophrenia has a peak of onset in young adulthood and is rare before adolescence. Onset also interacts with sex, such that men are likely to become ill earlier in life than women.

• Liability to schizophrenia is highly heritable (~80%), and concordance between identical twins is almost 90%, suggesting a role for environmental or stochastic influences as well.

• All drugs with established anti-psychotic effects decrease dopamine neurotransmission, but anti-psychotic drugs are not effective for all schizophrenia symptoms.
**Etiological Facts**

- Linkage studies (which identify regions of the genome where schizophrenia genes might be found) suggest a number of regions that show genome-wide significance (1q, 6p, 6q, 13q, 17p), with several other regions found across multiple studies.
- Association studies (which identify which form of a particular gene or part of a gene is associated with risk) suggest alleles in a number of promising genes confer risk, including RGS4, DISC1, DTNBP1, NRG1, DAOA, and COMT.
- A number of early neurological insults and later life stressors confer additional risk for schizophrenia and other neurological disorders. Obstetrical complications and migrant status illustrate two of the largest effects known at this time.

**Pharmacological Facts**

- While antipsychotics lead to some immediate improvement for many individuals, the time course varies widely and a minority of patients do not show a medication response until a month after beginning treatment.
- Chronic exposure to amphetamine, a dopamine agonist, can result in schizophrenia-like symptoms in some individuals.
- A single exposure to phencycline (PCP) and other NMDA receptor antagonists (such as ketamine) can result in schizophrenia-like symptoms in some individuals.

**Pathological Facts**

- In post-mortem studies, pyramidal neurons in input layers of prefrontal cortex have a reduced dendritic spine density; whereas hippocampal neurons appear to be abnormally oriented with signs of arrested migration.
- Even in first-episode patients, the lateral and third ventricles are somewhat larger, whereas total brain volume is slightly smaller.
- Medial temporal lobe structures such as the hippocampus, and superior, temporal, and prefrontal cortices, as well as the thalamus tend to be smaller in patients with schizophrenia.

**Pathological Facts**

- Overall grey matter and hippocampal volumes are also slightly smaller in healthy relatives of patients with schizophrenia.
- Functional abnormalities occur in a number of brain systems, including prefrontal and temporal cortices and subcortical structures.

**Behavioral Facts**

- Cognitive tests are challenging for many, but not all, patients. The greatest deficits appear on tasks such as verbal memory, performance IQ, and short-term memory tasks.
- Longer duration of untreated psychosis is associated with a poorer treatment response.
- Patients have a 4.9% rate of suicide, which is far greater than the average risk in the United States.

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Dopamine hypothesis

- The dopamine hypothesis is the oldest of the schizophrenia hypotheses. Although clearly not sufficient to explain the complexity of this disorder, it offers a direct relationship to some symptoms and their treatment.
- The first formulation of the dopamine hypothesis of schizophrenia proposed that hyperactivity of dopaminergic transmission was responsible for the disorder (Rossum, 1966). This was based on the early observations that dopamine receptors are activated by psychostimulants. Indeed, most antipsychotics bind to D2 receptors.

Dopamine hypothesis

- Given the predominant localization of dopaminergic terminals and D2 receptors in subcortical regions such as the striatum and the nucleus accumbens, the classical dopamine hypothesis of schizophrenia originally focused on subcortical regions.
- More recently, functional imaging studies that these symptoms might arise from altered prefrontal cortex function.

Dopamine hypothesis

- The dopamine hypothesis provides an explanation for the cause of positive symptoms.
- However, it does NOT provide a satisfactory explanation for the negative symptoms, for which the antipsychotics are not clinically effective.

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Glutamate hypothesis

- The glutamate hypothesis of schizophrenia posits that the function of the N-methyl-D-aspartate (NMDA) receptor is compromised in this disease.
- NMDA receptors are a major subtype of glutamate receptors and mediate slow excitatory postsynaptic potentials (EPSPs). These slow EPSPs are considered critical for the proper expression of complex behaviors, such as associative learning, working memory, behavioral flexibility, and attention, many of which are impaired in schizophrenia.
- NMDA receptors also play an essential role in the development of neural pathways, including pruning of cortical connections during adolescence, making them a critical component of developmental processes whose malfunction may lead to schizophrenia.
Glutamate hypothesis

- The idea of a glutamatergic abnormality in schizophrenia was first proposed by Kim, Kornhuber, and colleagues in 1990 based on their findings of low cerebrospinal fluid glutamate levels in patients with schizophrenia.
- This theory was not well received because: 1) these findings could not be replicated in subsequent studies and, 2) our limited knowledge of the glutamate system at the time suggested that disruptions in glutamate neurotransmission would result in overt toxicity and gross developmental abnormalities, something not seen in schizophrenia.
- In the last two decades, however, basic and clinical evidence has been accumulating to support the idea that aberrant NMDA receptor function subserves many aspects of molecular, cellular, and behavioral abnormalities associated with schizophrenia.

Glutamate hypothesis

- Postmortem studies show changes in glutamate receptor binding, transcription, and subunit protein expression in the prefrontal cortex, thalamus, and hippocampus of subjects with schizophrenia.
- Recent imaging studies using a novel tracer for the NMDA receptor have reported reduced NMDA receptor binding in the hippocampus of medication-free patients. While this study remains to be replicated in a larger group of patients, it represents the first direct demonstration of NMDA receptor deficiency in schizophrenia.
- Glutamate neurons regulate the function of other neurons that have been strongly implicated in the pathophysiology of schizophrenia. These include GABA interneurons, whose morphology has been altered in schizophrenia, and dopamine neurons, which are the target of antipsychotic drugs.

Glutamate hypothesis

- Two key pharmacological clues to the pathophysiology of schizophrenia—clinical efficacy of D2 receptor antagonist and increased probability of developing schizophrenia after cannabis use during adolescence—are consistent with deficient NMDA receptor function in schizophrenia.
- Cannabinoid CB1 receptor and D2 receptors are localized presynaptically on glutamate terminals and work to inhibit the release of glutamate.
- Cannabis, therefore, reduces glutamate release, in particular in corticostriatal regions, leading to deficient activation of NMDA receptors, whereas reduced D2 receptor function produces modest increases in glutamate release.

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GABA hypothesis

- Tissue concentrations of the mRNA that encodes the 67 kiloDalton isoform of glutamic acid decarboxylase (GAD67), an enzyme that synthesizes GABA, are reduced in the DLPFC of individuals with schizophrenia.
- By contrast, mRNA and protein levels of GAD65, another enzyme that synthesizes GABA, are not altered in the DLPFC of people with schizophrenia, and the density of GAD65-immunoreactive axon terminals also remains unchanged.
- Interestingly, elimination of the Gad65 gene in mice does not alter cortical levels of GABA, whereas reductions in Gad67 mRNA are associated with marked decreases in cortical GAD activity and GABA content.
**GABA hypothesis**

- In individuals with schizophrenia, most GABA neurons in layer 3–5 (but not 6) of the prefrontal cortex express normal levels of GAD67 mRNA. However, ~25–30% of GABA neurons do not express this transcript at a detectable level.

- In the same cohort of individuals, expression of the GABA membrane transporter 1 (GAT1), a protein responsible for reuptake of released GABA into nerve terminals, was also decreased with almost identical cellular patterns.

- Therefore, in schizophrenia, both the synthesis and reuptake of GABA seem to be greatly reduced in a subset of inhibitory neurons, at least in the prefrontal cortex.

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**GABA hypothesis**

- In the prefrontal cortex of individuals with schizophrenia, the density of pyramidal-neuron axon initial segments that are immunoreactive for the GABA a2 subunit is increased by >100% compared with control subjects.

- This seems to reflect higher levels of a2 subunits at the axon initial segment rather than an increase in the density of pyramidal neurons or of their axon initial segments.

- Since the a2 subunit endows the GABAAergic synapses with slower kinetics, it seems that the postsynaptic neuron is trying to compensate for the lack of released neurotransmitter, by increasing the time window over which chloride ions flow through the synapse.

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**Genetic hypothesis**

- The gene DISC1 (Disrupted In Schizophrenia - 1) was identified in the late 60’s in a large Scottish family that segregates with schizophrenia and other mental disorders.

- DISC1 is a scaffold protein that has a multifaceted impact on neuronal development.

- Exogenous manipulation of DISC1 in mice results in a spectrum of neuronal abnormalities, depending on the timing and locus of the perturbation.

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**Genetic hypothesis**

- During embryonic cortical development, knockdown of DISC1 at E13 accelerated cell cycle exit and neuronal differentiation whereas at E14.5 leads to inhibition of neuronal migration and disorganized dendritic arbors.

- During adult neurogenesis, suppression of DISC1 also leads to decrease proliferation of neural progenitors and an array of neuro-developmental defects in newborn dentate granule cells, including hypertrophy, misplacement, impaired axonal targeting, and accelerated dendritic growth and synaptogenesis.
Glutamate

A systems-level synthesis attempt

- In modern accounts of schizophrenia, researchers have proposed that the disorder arises from a failure to integrate the activity of local and distributed neural circuits.
- Recently there has been a considerable amount of interest in the role that glutamate-mediated NMDA receptor activation plays in neuronal circuitry, and how this relates to understanding the etiology and pathophysiology of schizophrenia.
- Hypothalamus-amygdala interactions may play a role in the regulation of many of the cognitive and behavioral abnormalities that characterize schizophrenia.
- Gamma oscillations represent the synchronization of neural firing and are thought to mediate representations and selection of information in the brain, and thus play an important role in the expression of schizophrenia.
- Consistent with the notion that neuronal synchronization may be impaired in schizophrenia, a growing number of studies have reported abnormal gamma oscillations associated with schizophrenia.

Genetic hypothesis

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A systems-level synthesis attempt

- In animals, NMDA receptor blockade has been found to reduce the number of parvalbumin-immunoreactive neurons in entorhinal cortex. This reduction is accompanied by robust disruption in gamma rhythms.
- These effects may be mediated primarily by the NR2A subunit. In a recent study, in a primary neuronal culture system, Kinney and colleagues have found that NR2A is particularly enriched in PV-containing GABA cells at both the transcript and protein levels, when compared to pyramidal cells.
- NR2A, but not NR2B selective antagonists, down-regulate parvalbumin mRNA and protein expression and expression of GAD67 mRNA in parvalbumin-containing cells. In light of these findings, it is indeed very interesting that, in schizophrenia, GAD67 mRNA expression has been found to be selectively reduced in PV-containing neurons.

A systems-level synthesis attempt

- The normal interaction between pyramidal cells and parvalbumin-positive interneurons is thought to be a “push-pull” mechanism that generates oscillations of neuronal activity in the cortex.
- This push-pull mechanism seems to be defective in schizophrenia.

A systems-level synthesis attempt

- These findings lead to the following hypothesis:

  Hypofunction of NMDA receptors on GABAergic interneurons, especially those that contain parvalbumin, disrupts the synchronization of neural circuits in the gamma frequency (40-100 Hz) by altering inhibitory control of pyramidal cell networks.
Neural interactions that putatively lead to gamma oscillations

NMDAR dysfunction alters the PC drive to the IN

...which in turn alters the feed-back from the IN onto the PC

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Paper for discussion

• J. A. Matta et al. (2013). Developmental origin dictates interneuron AMPA and NMDA receptor subunit composition and plasticity. *Nature Neuroscience*, 16: 8, p. 1032-1042.