Psychotic Disorders and their Treatment

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Psychotic disorders are characterized by substantial abnormalities of thought, perception, mood and behavior:

- Delusions (odd and erroneous beliefs)
- Hallucinations (False sensory percepts)
- Disorganized/illogical thinking and speech
- Odd, inappropriate or disorganized behavior
- Inappropriate or extreme mood and affect
While there are many causes of psychosis, most of our patients are classified as having either:

**schizophrenia**, typified by a chronic course and more complex delusions and hallucinations

or

**bipolar disorder**, typified by a recurrent course and extremes of mood.
However, it may be incorrect to think of bipolar disorder and schizophrenia as either distinct or homogeneous disorders.

Many factors may interact to produce a range of conditions with various features of the syndromes of bipolar disorder and schizophrenia.
Genetics

The inheritance of risk for psychotic disorders appears best to fit a model including multiple, interacting genes.

We are collaborating with the Broad Institute to identify such genes, but at present no common risk genes are well documented.
Subtle changes in the brain, especially in areas associated with complex thinking and emotion, can be seen in bipolar disorder and schizophrenia.
## Examples of MR Findings in Schizophrenia, Bipolar Disorder and Major Depression

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>Bipolar Disorder</th>
<th>Major Depression</th>
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</thead>
<tbody>
<tr>
<td><strong>MRI</strong></td>
<td>↑ VBR</td>
<td>↓ Cerebellum</td>
<td>↓ Hippocampus</td>
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<tr>
<td><strong>MRS</strong></td>
<td>↓ NAA (Temporal Lobe)</td>
<td>↑ Lac, Glx (Gray Matter)</td>
<td>↓ β-NTP (Basal Ganglia)</td>
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<tr>
<td><strong>fMR</strong></td>
<td>↓ PFC</td>
<td>↑ Amygdala</td>
<td>↓ Anterior Cingulate</td>
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Activity in the Right Medial Dorsal Thalamus during a Verbal Fluency Task in Healthy Controls and Patients with Schizophrenia

Cohen and Yurgelun-Todd
Cerebral Blood Volume Changes in the Thalamic Region After Risperidone Treatment

Cohen and Yurgelun-Todd
Currently available antipsychotic and mood stabilizing medications are effective but work slowly, produce many side effects and often achieve only partial symptom relief.
The Stanley Research Center at McLean Hospital supports a multidisciplinary team of basic and clinical scientists devoted to discovering new treatments for bipolar disorder, schizophrenia and related illnesses.

Techniques and discoveries arise from clinical, laboratory and brain imaging components.
Why are treatment studies relevant to studies of cognition and brain functioning?

- Medication and other treatment trials provide an opportunity to study subjects when they are more and less symptomatic.
- The effects of medication can clarify the mechanism by which the brain processes information in health and illness.
Stanley Research Center at McLean
Major Preclinical Projects

Kappa agents
Low Field Magnetic Stimulation (LFMS)
Trace amine modulators
Neuroregenerative agents
Bone marrow derived stem cells
Stress reducing agents to prevent relapse
Kappa agonists in mania
Secretin
D-Serine
Omega 3 fatty acids plus cytidine
Taurine in mania
SAMe for bipolar depression
Low field magnetic stimulation
MR Biofeedback
Research by McLean investigators suggests that kappa receptor agonists, antagonists and partial agonists may have antimanic, antidepressant and mood stabilizing effects.
Increasing CREB Reduces the Effects of Antidepressants in Rats

Blocking kappa receptors mimics the effects of antidepressants in rats

Carlezon et al
Dynorphin may also be important in mediating the effects of antipsychotic/antimanic drugs.
Nucleus Accumbens Clozapine Treated Rat

Separate red and green staining indicates that cells responding to antipsychotic drugs are not glia (GFAP) or cholinergic (VACHT).

Combined red and green staining to produce yellow indicates that activated cells are dynorphinergic neurons.

Ma et al., 2003
• Unlike current medications, agents acting at kappa receptors may have rapid effects on mania and depression

• No currently available drugs are specific kappa receptor modulators

• We are synthesizing kappa specific agents and testing available drugs in the meantime
(+/-) Pentazocine Hydrochloride

**Action at Opiate Receptors**

<table>
<thead>
<tr>
<th></th>
<th>kappa ($\kappa$)</th>
<th>mu ($\mu$)</th>
<th>delta ($\delta$)</th>
<th>sigma ($\sigma$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nearly full agonist</td>
<td>mostly antagonist</td>
<td>weak agonist</td>
<td>partial agonist</td>
<td></td>
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</tbody>
</table>
Pentazocine Induced Change in Acute Mania or Sedation Symptom Score

in 10 subjects