Brain anatomy and activity are often abnormal in schizophrenics
- many studies have found the ventricles in schizophrenic patients enlarged (see below).
- at the structural level, several brain areas have been shown to be different in schizophrenics:
  - ______________________________ has fewer neurons;
  - temporal lobe (parahippocampal gyrus, dentate gyrus, and hippocampus) have __________________;
  - the pyramidal cell layer of the__________________ is disorganized, as revealed by post-mortem analysis;
  - striatum, especially the __________________, has a significant volume reduction.
- these brain abnormalities are most often observed in patients displaying __________________ (flat affect, socially withdrawn, poverty of speech, and lack of energy and drive).

- functional brain imaging studies of normal and schizophrenic patients performing abstract reasoning tasks show ____________________________ in schizophrenic patients (PET, MRI, CT).
- example of normal individuals and schizophrenic patients performing a simple number task or the Wisconsin Card Sorting (WCS) task.
- note the large difference in cerebral blood flow between the normal and schizophrenic subjects, as measured with magnetic resonance imaging (MRI), especially in response to the WCS task.
- prefrontal hypofunction is again correlated more highly with the negative symptoms of schizophrenia (social withdrawal, flat affect, etc).

Maps of Regional Cerebral Blood Flow
Schizophrenia and heredity:
- the children of schizophrenic parents are much more likely to develop schizophrenia during their lifetime (__%) than children of non-schizophrenic parents (1%).

- monozygotic (identical) twin studies: if one member of the pair develops schizophrenia, the other member has ____________ of developing schizophrenia.

- this is much higher than in ____________ ( dizygotic), where the concordance is only about 17%.

- also, in discordant pairs of identical twins (only one twin develops schizophrenia) having children, the normal twin is just as likely as the schizophrenic twin to produce schizophrenic children - suggests an inheritable component, even if not expressed in parent.

```
<table>
<thead>
<tr>
<th>General</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shared</td>
<td>17.5%</td>
</tr>
<tr>
<td>First cousins</td>
<td>2%</td>
</tr>
<tr>
<td>Uncles, aunts</td>
<td>1%</td>
</tr>
<tr>
<td>Grandchildren</td>
<td>1%</td>
</tr>
<tr>
<td>Parents</td>
<td>1%</td>
</tr>
<tr>
<td>Siblings</td>
<td>1%</td>
</tr>
<tr>
<td>Children</td>
<td>10%</td>
</tr>
<tr>
<td>Potential twins</td>
<td>1%</td>
</tr>
<tr>
<td>Identical twins</td>
<td>49%</td>
</tr>
</tbody>
</table>
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However, even some of the monozygotic twin high concordance can be explained by non-genetic mechanisms.

- recently, it has been shown that the concordance in monozygotic twins is related with the intrauterine environment and development rather than genes:

- twins sharing the same amniotic sac and placenta (monochorionic) are much more likely to be concordant than twins having independent placenta (dichorionic)

- the concordance in dichorionic twins is ____________.

- the concordance in monochorionic twins is ____________.

Thus, the intrauterine environment and development appears to account for a significant percentage of schizophrenic concordance, leaving a small percentage to genetic factors alone.
Schizophrenia and the environment:
- genetics at best explains 50% of schizophrenic diagnoses, so the other factors must be present in the environment.

- link to parental behavior, particularly the mothers: conflicting and unreliable evidence makes it doubtful that __________ are responsible for schizophrenic development.

- several environmental theories have been put forward, such as __________ schizophrenia, but none of these theories have been confirmed.

- some examples of associations with virally-mediated schizophrenia include the observation that pregnant women contracting the Influenza type A virus during the second trimester are much more likely to give birth to babies who will go on to develop schizophrenia.

- famines associated with the second World War in some European countries have also been associated with a higher incidence of schizophrenic births.

- severe emotional stress during the second trimester of pregnancy has also been associated with a higher incidence of schizophrenia: because stress inhibits the immune system, it is conceivable that this observation is also linked to virally-mediated instances of schizophrenia.

- thus, there is increasing evidence for a developmental factor associated with schizophrenia;
- for yet unknown reasons, the fetal brain of schizophrenic individuals might not develop the right connections between various parts of the brain.
- these faulty connections only come to bear on behavior during or after the last maturation of the brain with adolescence (hormonal switch??).

- the stigma attached with the schizoid diagnostic has been proposed as one source for the development of full-blown schizophrenia; however, several studies dispute this fact, particularly in societies where such stigmas have not developed (Esquimos, for instance).
Dopamine hypothesis of schizophrenia
States that schizophrenia is caused by ________________________________
______________________________________________________________
______________________________________________________________

Some of the clues that have led to the dopamine hypothesis of schizophrenia include:
- drug-induced psychosis in otherwise healthy individuals, produced by drugs that specifically _______ dopamine at the synapse such as amphetamine, cocaine, and the dopamine agonist apomorphine.
- these drugs also readily produce ________________ in individuals who have been diagnosed with schizophrenia.
- the drugs that are most effective at reducing the symptoms of schizophrenia and drug-induced psychosis all act at dopamine receptors (______________________).

Dopamine systems in the brain
The three (3) major dopamine pathways in the brain:

1. ____________________ - cells of origin located in substantia nigra
   - project mostly to striatum. Shown below.

2a. ____________________ - (similar to 2b. below).
2b. ____________________ - cells of origin located mostly in ventral tegmental area and substantia nigra;
   - project to many forebrain limbic (ex. hippocampus), and cortical areas (ex. prefrontal cortex). Shown below.

3. ____________________ - cells of origin in arcuate and periventricular hypothalamic nuclei;
   - project to the anterior pituitary to control prolactin release (inhibits). Not shown.

Review of dopaminergic biochemistry
Dopamine system alterations in Schizophrenia

Most evidence suggest that the overactivity of the dopaminergic system observed with schizophrenia is associated with an alteration in

- there are 2 general classes of post-synaptic receptors that are responsive to dopamine:
  A. ________________: includes the D1 and D5 dopamine receptor subtypes - they respond to dopamine by __________ the production of the second messenger cyclic adenosine monophosphate (cAMP). They are therefore ____________.
  - D1 receptors are found in highest concentrations in the nigrostriatal pathway (striatum, nucleus accumbens, and substantia nigra).
  - D5 receptors are not found in high concentrations anywhere in the brain.

  B. ________________: includes the D2, D3, and D4 dopamine receptor subtypes - they respond to dopamine by __________ the production of the second messenger cAMP (also metabotropic receptors).
  - D2 receptors are found in high concentrations in many of the same regions as the D1 receptor subtype (see above).
  - D3 receptors are found in high concentrations in the nucleus accumbens, the islands of Cajal, and in olfactory areas.
  - D4 receptors, which exist in several isoforms, are found in highest concentrations in the prefrontal cortex, amygdala, diencephalon, brainstem, and olfactory bulbs.
  - importantly, the D2 receptor subtypes are found presynaptically and function as ____________.

Dopamine system alterations in Schizophrenia (continued)

Evidence for dopamine receptor upregulation (increased receptor numbers):

<table>
<thead>
<tr>
<th>Receptor density</th>
<th>Normal control</th>
<th>Patient - never medicated</th>
<th>Patient - medicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Low</td>
<td>*</td>
<td>*</td>
<td>*</td>
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</tbody>
</table>

Most effective treatment so far, as discussed above, are dopamine receptor antagonists that are specific against the D2 receptor family, the antipsychotics, also known as neuroleptics.

- neuroleptics are believed to act both on D2 post-synaptic receptors and pre-synaptic receptors.

- D2 pre-synaptic receptor activation by dopamine produce:
  1) ________________,
  2) ________________.

- blocking these receptors can therefore ________________.
Schizophrenia and drug therapy

Early studies investigating the effectiveness of drug therapy indicated a clear advantage to drug treatment over placebo effects.

In addition, patients maintained on antipsychotic drug therapy were

Schizophrenia and drug therapy (continued)

Drug Treatment

Neuroleptics: older term referring to the ability to _______________________.

What are the two major subtypes of dopamine antagonist available as antipsychotics?

1. _______________________________________________________

2. _____________________________________________________

What family of dopamine receptor do they work on? _______________

What is their direct mechanism of action? _______________________

If their action is to block D2 receptors (immediate effect), why does it take 1 - 2 weeks to obtain a clinical effect?
- in animals, the effects of D2 pre-synaptic receptor blockade will excessively increase activity of dopamine neurons and DA release
- this high level of activity cannot be sustained; these neurons undergo ________ after roughly 1 - 2 weeks of D2 receptor antagonist treatment.
- the depolarization block-induced reduction in DA neurons’ activity roughly coincides with ________.
- evidence for a reduction of DA activity in schizophrenia is impossible to obtain directly - indirect measures of a metabolic product of dopamine, homovanillic acid (HVA) that ends up in the blood and CSF, show that the greatest declines in HVA in schizophrenic patients correlate with greater symptoms improvements.
Drug Treatment: Side-effects

All the drugs used to treat schizophrenia act significantly upon the dopaminergic system. However, specific neuroleptics achieve these effects at different potencies and also have actions on different neurotransmitter systems:

1. Because of their direct mechanisms of action, neuroleptic drugs often produce ___________________________) by blocking dopamine receptors.
   - the incidence of these side-effects can be as high as in 90% of patients treated with neuroleptics.

   These extrapyramidal symptoms are correlated with ___________________________, thus, drugs that inherently possess anticholinergic activity (some butyrophenones and clozapine) will usually produce fewer extrapyramidal side-effects.
   - however, anticholinergic activity in the periphery produces side-effects as well (__________________________________________).

   The popularity of clozapine can be associated with a lower incidence of extrapyramidal side-effects (thus the name "atypical" antipsychotic).
   - this is achieved by the drug binding more significantly to __________ producing little changes in D2 receptors in the nigrostriatal system.
   - however, its anticholinergic side-effects can be undesirable in some patients.
   - a recently popular antipsychotic with many advantages of clozapine and fewer anticholinergic side-effects is ____________(Risperdal ™).

2. Another significant side-effect is ____________________________; neurological abnormality associated with prolonged use of antipsychotic drugs.
   - characterized by _____________________________________________________________.
   - the occurrence of tardive dyskinesia is correlated best with age (later incidence in all treated population: 10-20%; incidence in patients over 60 jumps to above 50%) and sex (women being at higher risks).
   - the mechanism of action for the development of TD is not understood but may include D2 receptor upregulation in the striatum (increased receptor number), and ultrastructural changes in the striatum (increased dendritic branching and synaptic contacts).
   - unfortunately, _____________________________________________, although some atypical antipsychotics (clozapine and risperidone) produce a lower incidence of TD.

   Additional side-effects of many antipsychotic drugs:
3. __________________________; milk production and ejection in non-lactating women (small incidence of 10% in men)
   - produced by inhibition of D2 receptors in the anterior pituitary.
   - normally dopamine release in the pituitary (tuberohypophyseal system) _____________________________, but antipsychotics blocks this effect, allowing higher than normal prolactin production.

   4. __________: sudden decrease in blood pressure when a patient stands up after sitting or lying down for a while.
   - due to blockade of noradrenergic receptors, common to almost all antipsychotic drugs.
5. ________________: sometimes lethal suppression of bone marrow functions - leads to loss of white blood cells, therefore increasing susceptibility of patients to serious infections.
- incidence is about 1:2000 or lower for phenothiazines and butyrophenones, but 1:50-200 for clozapine.
- need for close monitoring of patients treated with clozapine.

6. ________________: normally observed at the beginning of treatment, it is characterized by fever, rigidity, altered consciousness, and autonomic system instability (heart rate, blood pressure).
- can be fatal if drug treatment not discontinued immediately.
- incidence is about 0.5-1% of patients treated with neuroleptics.

Schizophrenia: Drug vs. Psychotherapy
The best empirical studies have shown that acute phase schizophrenia is best treated with drug therapy.

However, once the active phase is under control, maintenance is best obtained ________________________________.