Learning & Memory (Ch.17) V

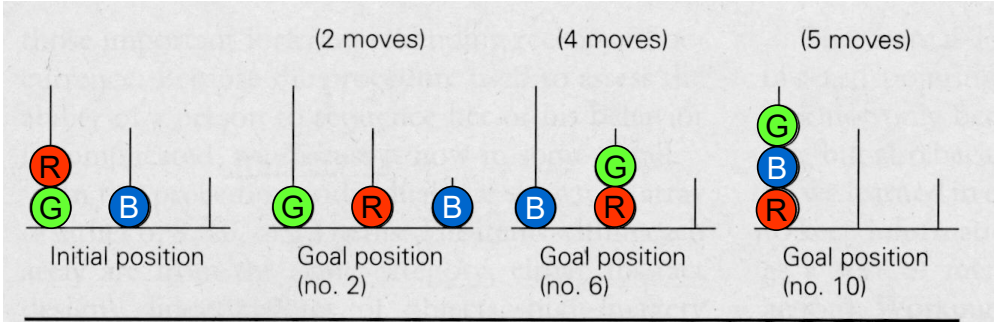
- The Prefrontal Cortex
  - Planning

- And Later- Schizophrenia

Prefrontal Cortex and Planning (II)

➢ **Tower of London task:**

- Assesses planning of movement sequences
- "Move the balls from the start position to this final position in as few moves as possible."



- PFC patients need many more moves to reach goal position; often, they don't reach goal at all

➢ **Dinner Party Problem":** subjects given "real-world" planning task

- •Given 6 errands to run (e.g.: buy loaf of bread, etc)
- •Also told to get answers to 4 questions (e.g.; price of tomatoes).
- •Explicitly told **not** to enter shops unnecessarily finish as quick as possible

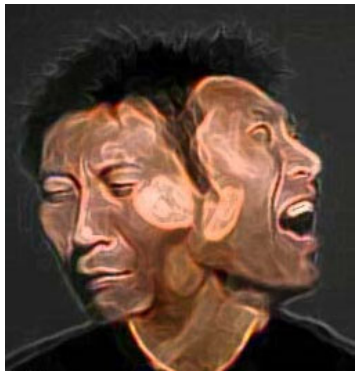
- PFC damaged patients very inefficient: broke rules (entered unnecessary shops) and failed on many tasks
- All patients remembered and understood rules and attempted to comply
- NOT a memory deficit, but a deficit in integrating memory to form plan of action

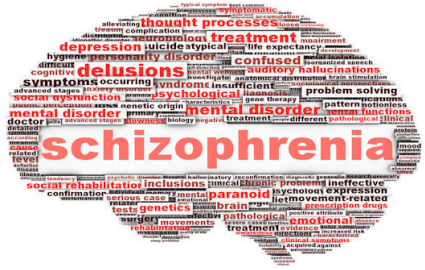
Psychopathology (Ch.16)

- Schizophrenia
  - Symptoms, Epidemiological factors
  - Causes
    - Genetic, Neurodevelopmental
  - Cognitive and Brain Abnormalities

Schizophrenia: What is it?

- Described originally by Kraeplein as *dementia praecox* (early dementia), and later by Bleuler as *schizophrenia* (split mind)
- Best viewed as a **family of disorders**, characterized by at least a few distinct symptoms





- ***Positive Symptoms****:* abnormal behaviours that have been gained
  - Hallucinations (typically auditory), Delusions (paranoia), thought disorder = PSYCHOSIS
- **Negative Symptoms**: normal functions that have been lost
  - Blunted emotional responses, poverty of speech, social withdrawal, anhedonia, Lack of insight, COGNITIVE DEFICITS

Diversity of Symptoms in Schizophrenia

- At least (1) of (3) core symptoms is required for diagnosis (DSM-5) – although presentation vary greatly

➢ ***Hallucinations***, ***delusions*** or ***disorganized speech***

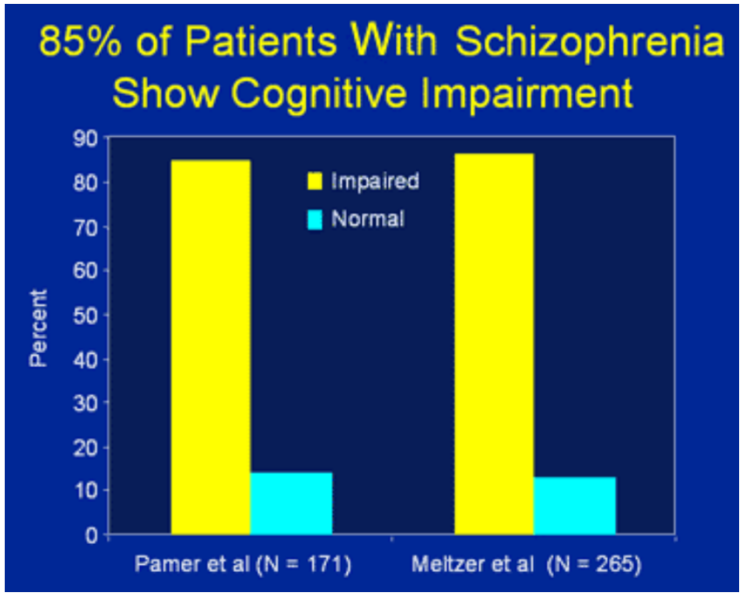
- These symptoms also present in other conditions that need to be ruled out before schizophrenia is diagnosed

– Lack of insight into illness	97%	Auditory hallucinations	74%
– Delusions of reference	70%	Verbal hallucinations	70%
– Suspiciousness	65%	Flatness of affect	65%
– Paranoid state	64%		

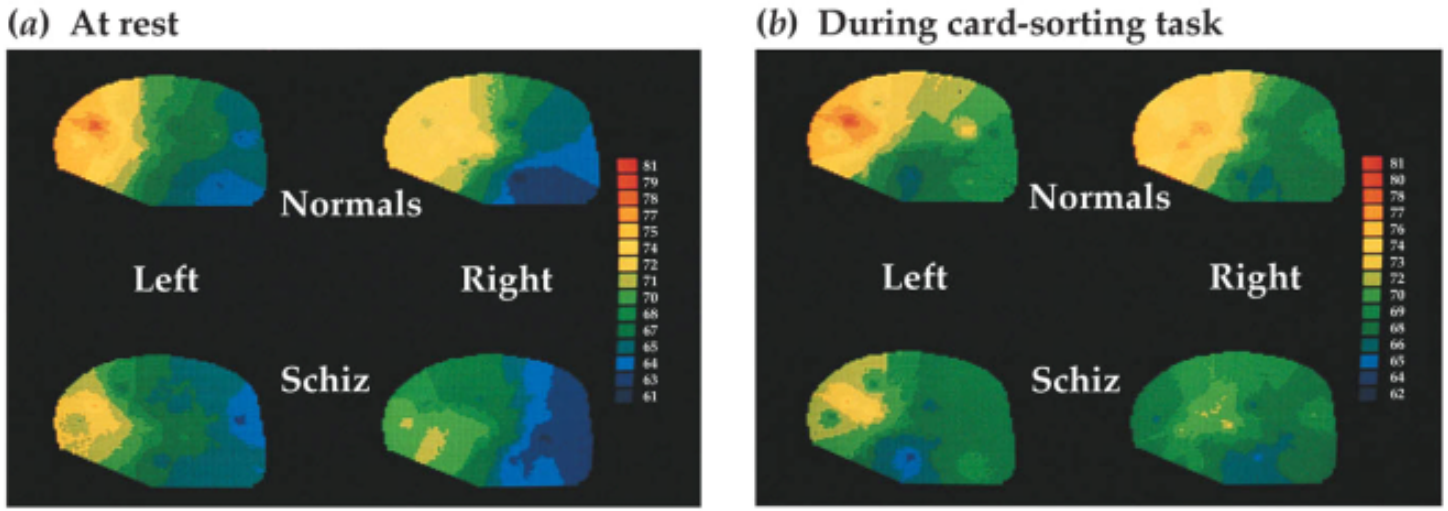
- ~ 1% of population suffer from schizophrenia at any given time
  - Onset is typically after puberty (18 yrs).
  - Typically does not onset after 30 in men, small number of women develop symptoms after menopause (+45 yrs)

Cognitive Abnormalities in Schizophrenia (I)

- Cognitive deficits in schizophrenia are less dramatic than psychotic symptoms: however, these deficits may be a core component of the disorder (i.e.: *dementia praecox*)
  - Cognitive functioning is the #1 predictor of long term outcome (better function = better prognosis)
  - Severity of psychotic symptoms not related to severity of cognitive deficits
  - Many of the functions impaired in schizophrenia are mediated by the prefrontal cortex and/or hippocampus



Cognitive Abnormalities in Schizophrenia (II)



- **Brain activation studies:** schizophrenia patients and discordant identical twin controls performed Wisconsin Card Sort
- Schizophrenia patients showed minimal increase in PFC activity when performing task, unlike controls
- Other brain regions were activated similarly in both groups
- Schizophrenia is associated w/ disruption in PFC function, but not as much for other cortical regions

Genetics of Schizophrenia

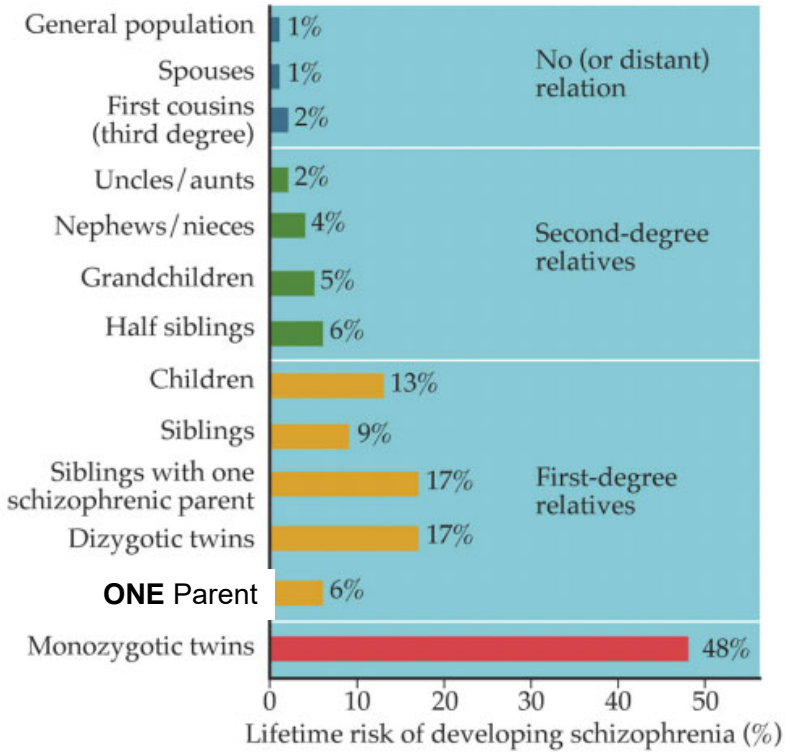
- Odds of developing disorder increases if one has a relative diagnosed with schizophrenia
  - Highest concordance in identical twins, or if both parents have schizophrenia (~50%)
- Adoption studies also indicate that there is a heritability component.

These findings indicate:

1) there is a strong genetic component to schizophrenia, but

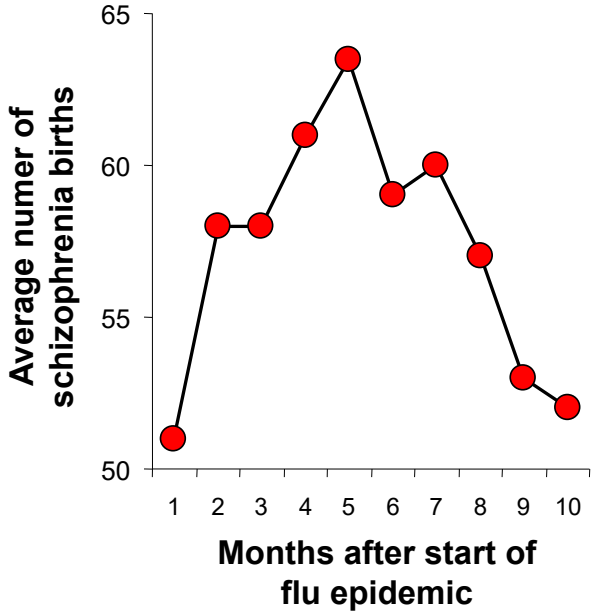
2) altered genes are NOT the only cause of the disease

- Genetic component not linked to just one gene, there are likely dozens that may be altered.



Neural Developmental and Schizophrenia

- Alterations during development are thought to be major contributing factor to the disorder
- *In utero* influences include:
  - Poor nutrition during pregnancy
  - Premature birth/low birth weight
  - Physical/immune stressors during pregnancy



- Early developmental insults lead to brain abnormalities in adulthood
- Stressors later in life (after puberty) can trigger onset
- Genetics ↑ sensitivity to stressors by mother or child, either *in utero* or later in life
  - Some people may have a genetic susceptibility to acquiring the disease, but certain types of stressors needed to trigger it

Neural Abnormalities in Schizophrenia (I)

- **Hippocampus:** Some individuals w/ schizophrenia have enlarged lateral ventricles, due to smaller hippocampus and other temporal lobe regions

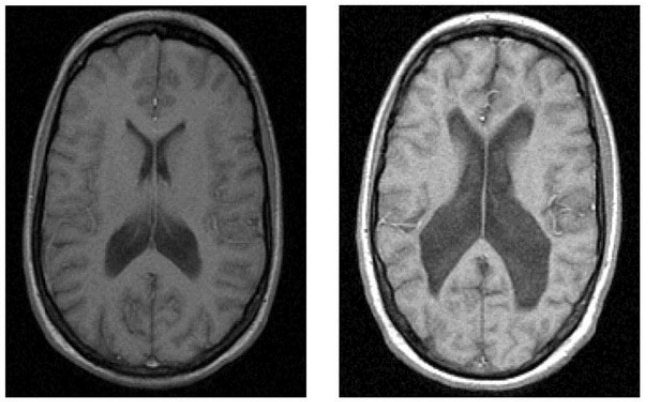
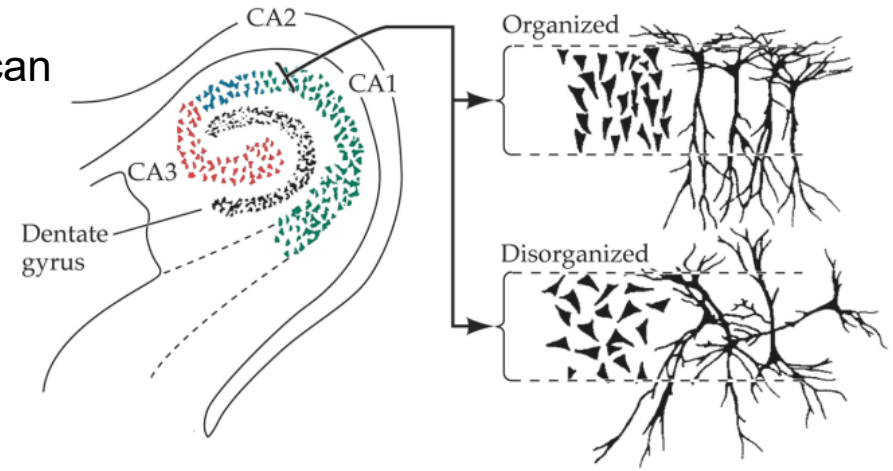


Fig. 1 Ventriculomegaly in discordant monozygotic twins seen on T_2-weighted MRI scans. Healthy twin (left) compared with twin with schizophrenia (right). With permission of Dr M. Picchioni.

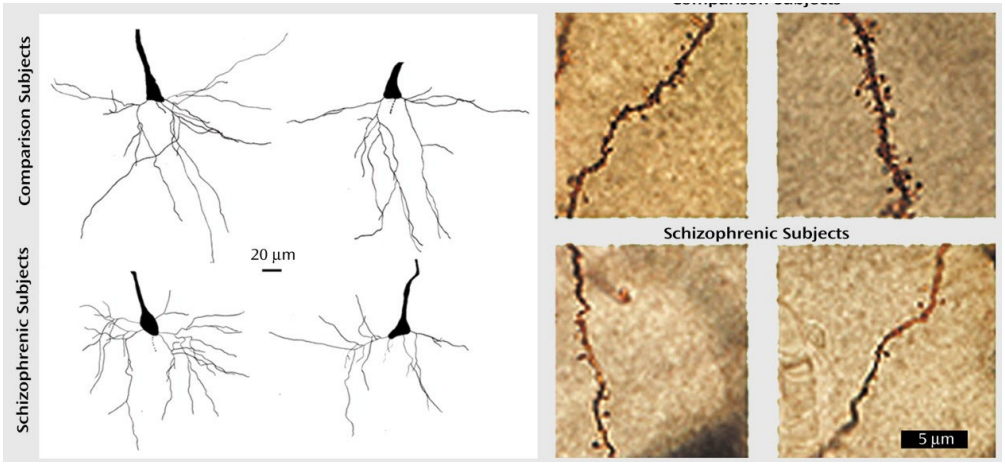
- Closer inspection reveals altered organization of hippocampal neurons in brains of those w/schizophrenia

- Not brain damage *per se*: changes in neural organization (occurring **during development**) can disrupt how brain regions process information

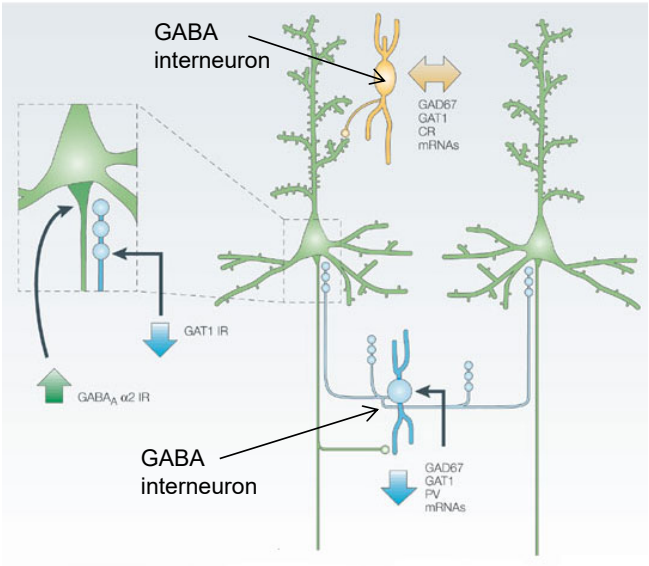


Neural Abnormalities in Schizophrenia (II)

- **Prefrontal Cortex** pyramidal neurons have reduced #of dendrites; reduces processing power of these cells.
- ***Hypofrontality*** (reduced PFC function) is a characteristic negative symptom of schizophrenia

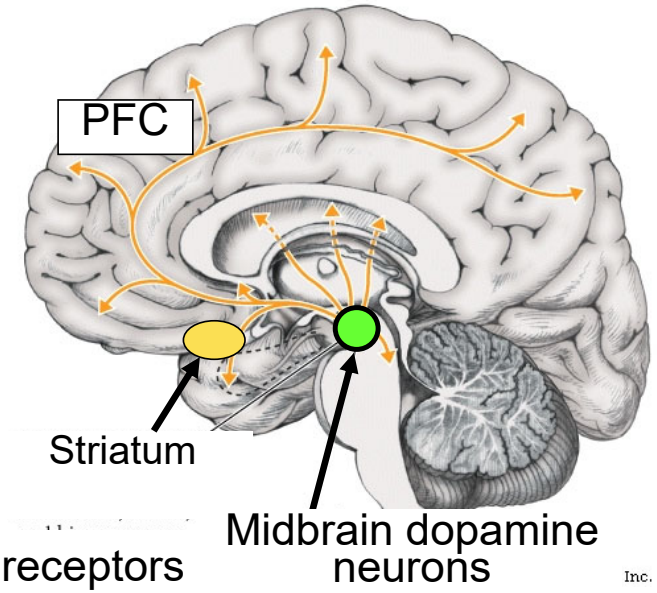


- **GABAergic interneurons:** serve as a major information filter for PFC (and other regions like hippocampus**)**
- Schizophrenics have reduced GABAergic interneurons in these regions
- This may lead to a “noisy” cortex, reducing information filtering and impairing functioning of these regions



The Dopamine Hypothesis of Schizophrenia

- Most of the dopamine in the brain is produced in small nuclei in the midbrain
- **1950s:** Chlorpromazine found to be antipsychotic; causes Parkinson's symptoms in healthy individuals
- Brains of Parkinson's patients found to be depleted of dopamine
- **1960s:** Drugs that increase dopamine release (e.g.; amphetamine) could induce psychotic symptoms



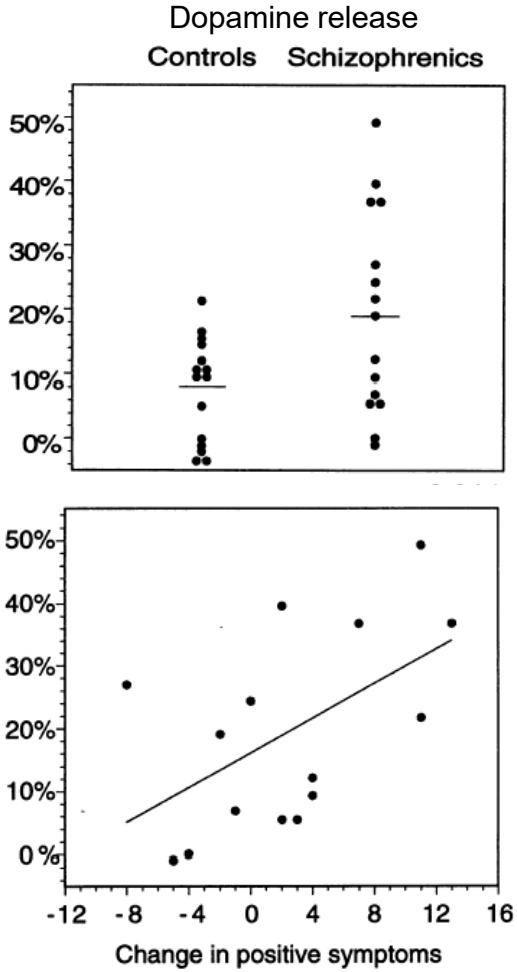
- Chlorpromazine, other antipsychotics found to block dopamine receptors
- **1970s:** Dopamine receptor subtypes discovered; antipsychotic potency of a drug correlated with binding to D2 receptors (not D1)
- THUS, The dopamine ***hypothesis*** was born:
- **Schizophrenia is caused by an abnormal increase in dopamine transmission, leading to overstimulation of D2 receptors**

Support for the Dopamine Hypothesis

- **ALL** drugs are effective in treating *psychosis* block D2 receptors to some degree
  - How are D2 receptors being overstimulated?

➢ More D2 receptors?
  - **Unlikely**: Some post mortem studies report ↑ D2 receptors in schizophrenia brains, others failed to find this effect
  - Changes may be due to chronic antipsychotic medication ***upregulating*** dopamine receptors

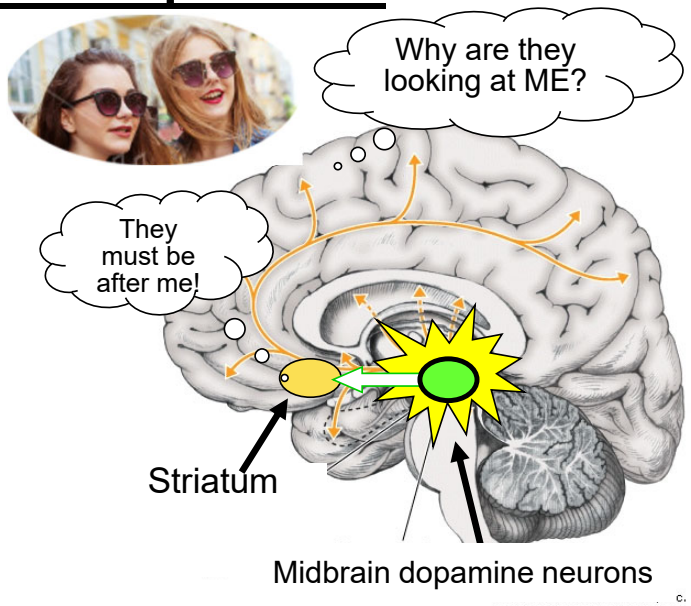
➢ More dopamine being released?
  - **Study:** imaging allows for non-invasive measure of dopamine release in human brain
  - Give amphetamine to those with schizophrenia or controls
  - **Greater dopamine release in striatum in those w/ schizophrenia**
  - More dopamine release correlated with more positive symptoms induced by amphetamine



•Dopamine release may be hypersensitive in schizophrenia

What is Dopamine Doing in Schizophrenia?

- DA neurons show increased activity to highly salient/novel stimuli
  - This increase in activity (and dopamine release in striatum) may serve as a signal the brain uses to determine what's important or relevant
- A hyperactive DA system may "tag" normally irrelevant stimuli as important, and impair filtering out of irrelevant stimuli



- This leads to "aberrant salience attribution" that may contribute to delusions
  - Eg: instead of disregarding them, you start thinking they out to get YOU and working for the CIA, who are controlled by aliens etc…
- Antipsychotic medications are thought to reduce this aberrant salience by reducing DA activity
- **Note:** often, people w/schizophrenia still report hearing the "voices" when they're on medication, but they are no longer bothered by them