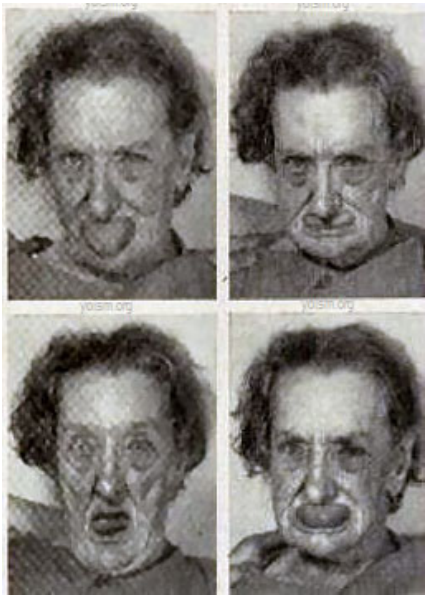
Psychopathology (Ch.16) II

- Schizophrenia
  - The Dopamine Hypothesis, treatment issues and limitations
  - The Glutamate hypothesis of schizophrenia
    - Insights from animal models
  - Prefrontal GABA and cognitive functions: relevance to schizophrenia symptoms

Treatment Issues with Schizophrenia

- Dopamine is involved in motor functions.
  - Long term treatment with antipsychotics (dopamine blockers) can cause movement (a.k.a extrapyramidal) side effects
  - ***Tardive dyskinesia*** occurs in about 1/3 of patients treated with classical antipsychotics
    - grimacing, tongue protrusion, lip smacking, rapid limb/trunk movements; symptoms sometimes continue after discontinuing medication.
  - Drugs that are more selective for dopamine vs other receptors usually cause worst side effects



- Antipsychotic drugs treat ***psychosis*** (delusions, hallucinations). Other negative symptoms rarely improve with typical antipsychotics

Limitations of the Dopamine Hypothesis (I)

- Several findings challenge the dopamine hypothesis

1) Antipsychotics block dopamine receptors right away, yet drug treatment takes ~2 weeks to reach full effect

- If schizophrenia is merely an increase in dopamine, drugs should work right away
- **More recent research suggests that the drugs ***may*** reduce psychotic symptoms relatively quickly, but it takes ~ 2 weeks for treatments to reach full effect.

2) Not all with schizophrenia respond to drugs that block dopamine receptors

- If schizophrenia is merely an increase in dopamine, drugs should work for all patients

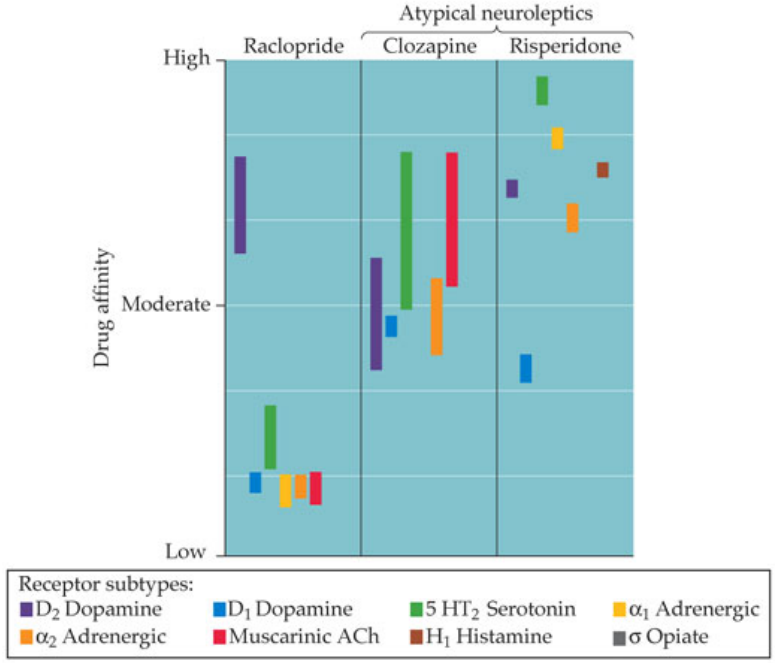
3) Dopamine blockers can alleviate psychosis, but not negative symptoms

- If cognitive deficits are due to an increase in dopamine, these drugs should alleviate the symptoms

Limitations of the Dopamine Hypothesis (II)

4) Some drugs that reduce symptoms do not block D2 receptors that well

- Example: Clozapine (***atypical antipsychotic***)
- Not as effective at blocking D2 receptors as classical antipsychotics
  - Less likely to produce motor side effects
- Has a much higher affinity to other receptors, like serotonin (5 HT)
- Can sometimes improve negative symptoms (possibly via 5 HT blockade)



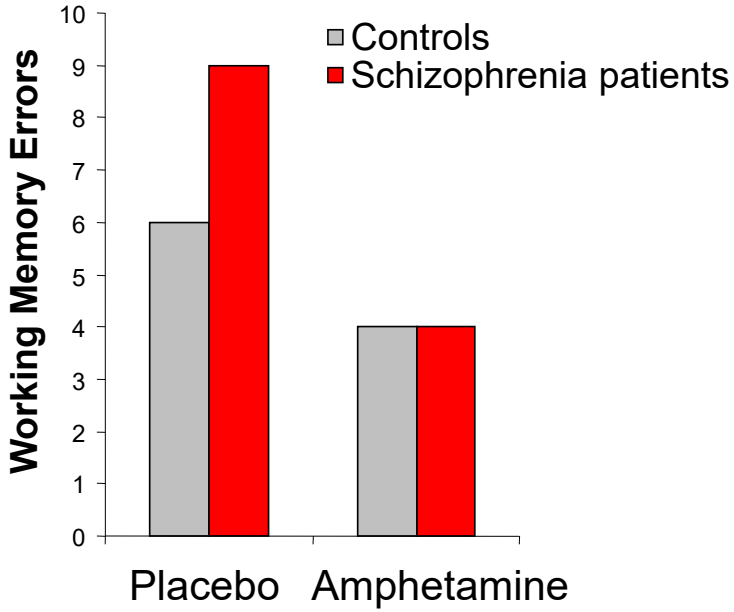
- If positive and negative symptoms are merely due to overstimulation of D2 receptors, atypical antipsychotics shouldn't work as well

- *Treatment issue*: some patients have an adverse blood reaction to clozapine; not all patients can take it safely

Limitations of the Dopamine Hypothesis (III)

5) Drugs that increase dopamine release can *improve* negative symptoms

- **Study**: Schizophrenia patients and healthy controls tested on a working memory task
- Give low dose of amphetamine (that increases dopamine release, but not psychotic symptoms) vs placebo
  - **Note**: higher doses of amphetamine **do** exacerbate symptoms
- Under placebo, schizophrenia patients performed worse than controls
- Amphetamine improved performance in those w/ schizophrenia



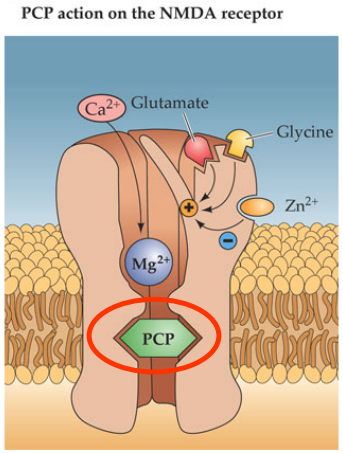
- If schizophrenia is just an increase in dopamine, why should drugs that increases dopamine release ***improve*** cognition?

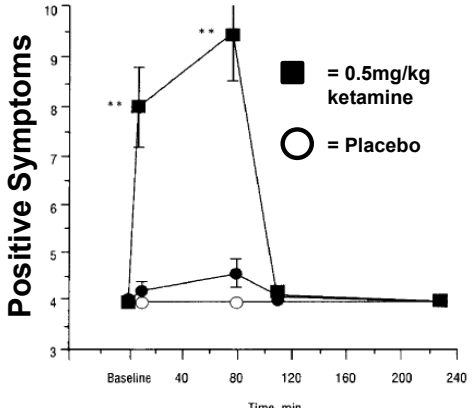
  -Maybe dopamine is not increased in all brain regions in schizophrenia?

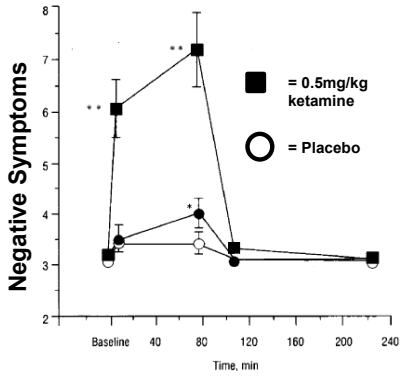
The Glutamate Hypothesis of Schizophrenia

- Abuse of phencyclidine (PCP, *angeldust*) or ketamine (*Special K*) can cause **psychotic symptoms** and **cognitive deficits** resembling schizophrenia

- These drugs block NMDA- glutamate receptors
  - Block the ion channel: glutamate cannot activate receptor

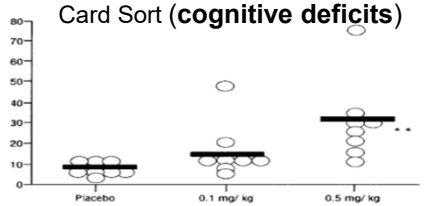






- **Glutamate hypothesis:** Schizophrenia is caused by decreased glutamate transmission
  - PFC/hippocampal neurons use glutamate as transmitter
  - Degeneration of these neurons in schizophrenia disrupts their function, less glutamate released in these areas

Perseverative Errors on Wisconsin Card Sort (**cognitive deficits**)



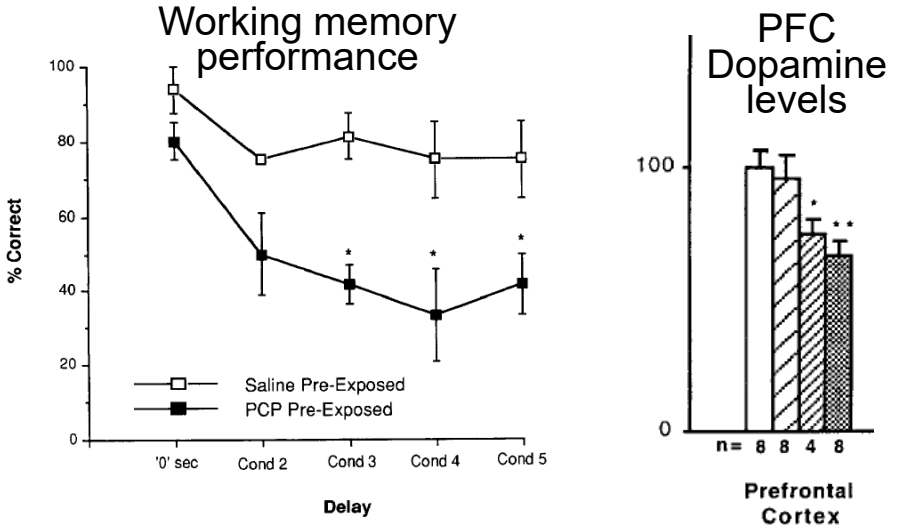
Insight from animal models of schizophrenia

Rat/primate studies show that repeated PCP:

- 1) causes cognitive deficits on PFC-dependent tasks
- 2) decreases PFC dopamine levels

➢ **Schizophrenia is also associated with reduced PFC dopamine activity**

- Different symptoms may be driven by **imbalance of DA transmission in PFC (to little)** and **striatum (too much)**
- May explain why drugs that increase DA (eg-amphetamine) improve cognition in the disorder

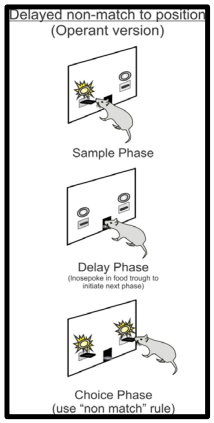


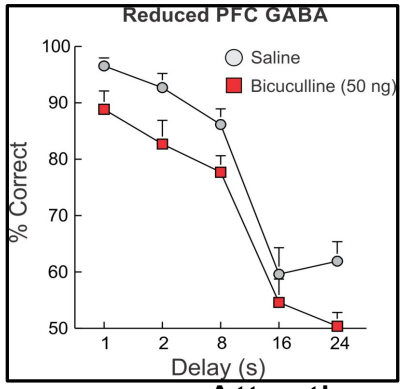
- This model can encompasses some of both the positive and negative symptoms of the disorder

PFC GABA Regulation of Cognition

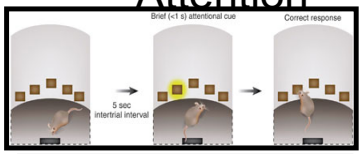
- **Reducing PFC GABA** transmission in animals can also **causes cognitive deficits** that resemble those observed in schizophrenia
  - In these studies, we infuse low doses of a drug that blocks GABA receptors (bicuculline)

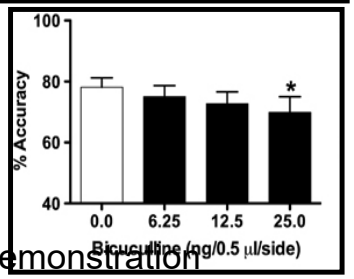
Working Memory



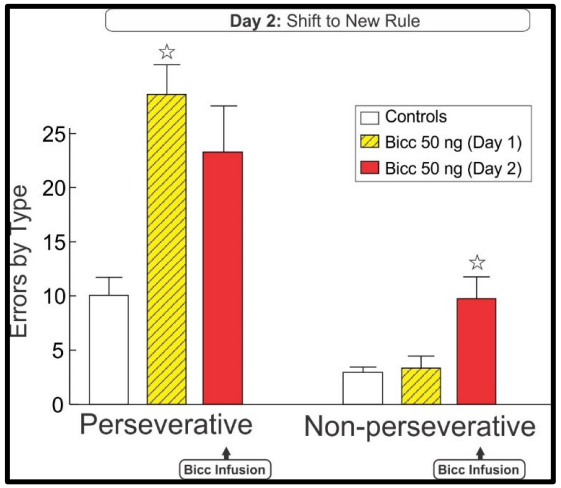


Attention

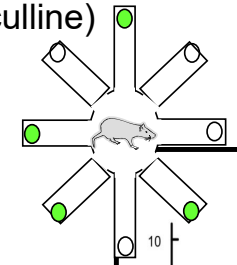


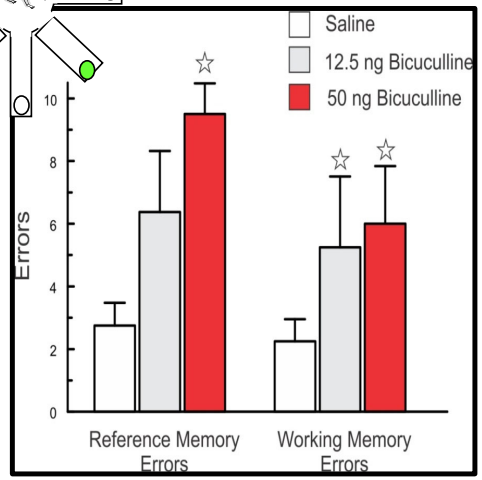


Cognitive Flexibility



Spatial Memory





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Salience Attribution in Schizophrenia- a PFC GABA connection?

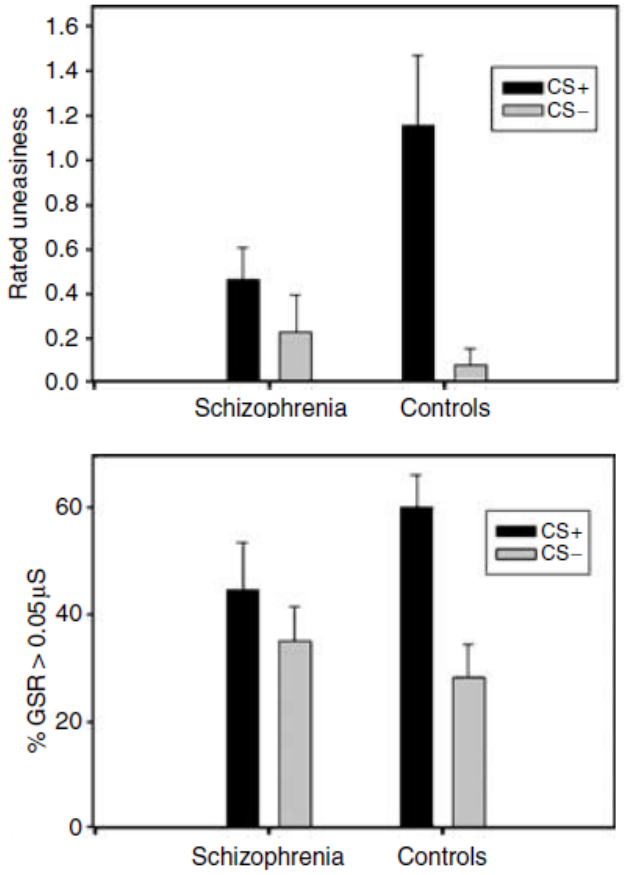
- People with schizophrenia display abnormal fear learning
  - High comorbidity with anxiety disorders
  - Inappropriate *discriminative* fear conditioning:

    ↓ fear to CS that was paired with shock (CS+)

    ↑ fear to CS that was presented alone (CS-)

  - Increased PFC activity when responding to **CS-** in patients with schizophrenia

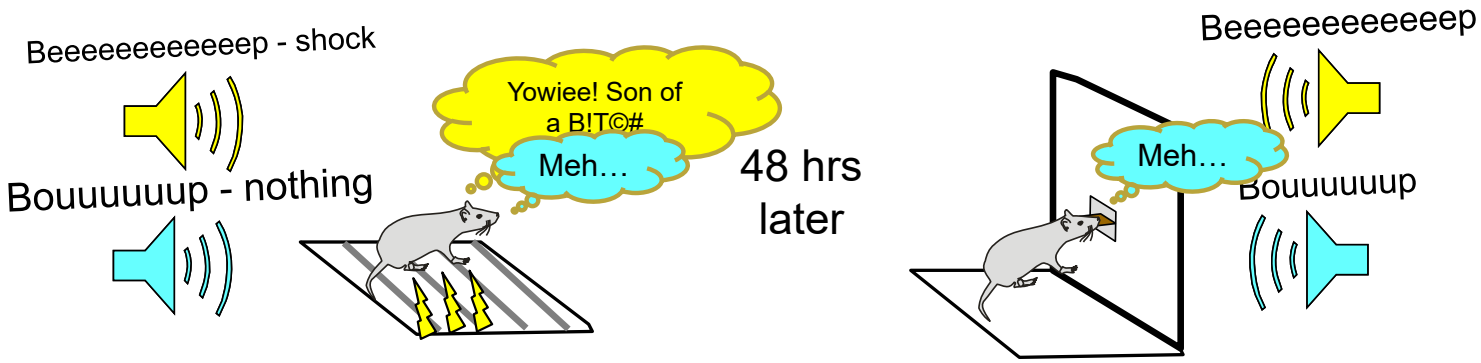
- This aberrant "salience attribution" (identifying which stimuli in the environment are of emotional importance) may contribute to delusions



PFC GABA and Positive Symptoms: Salience Attribution

-Discriminative Fear conditioning: pair ONE tone **(CS+)** with foot shock

-Pair another tone **(CS-)** with no consequence



- During test:

-Present neutral CS- tone: rats display little/no fear (i.e.: continue to lever press for food)

-Present shock-associated CS+: evokes fear response (suppresses ongoing behavior)

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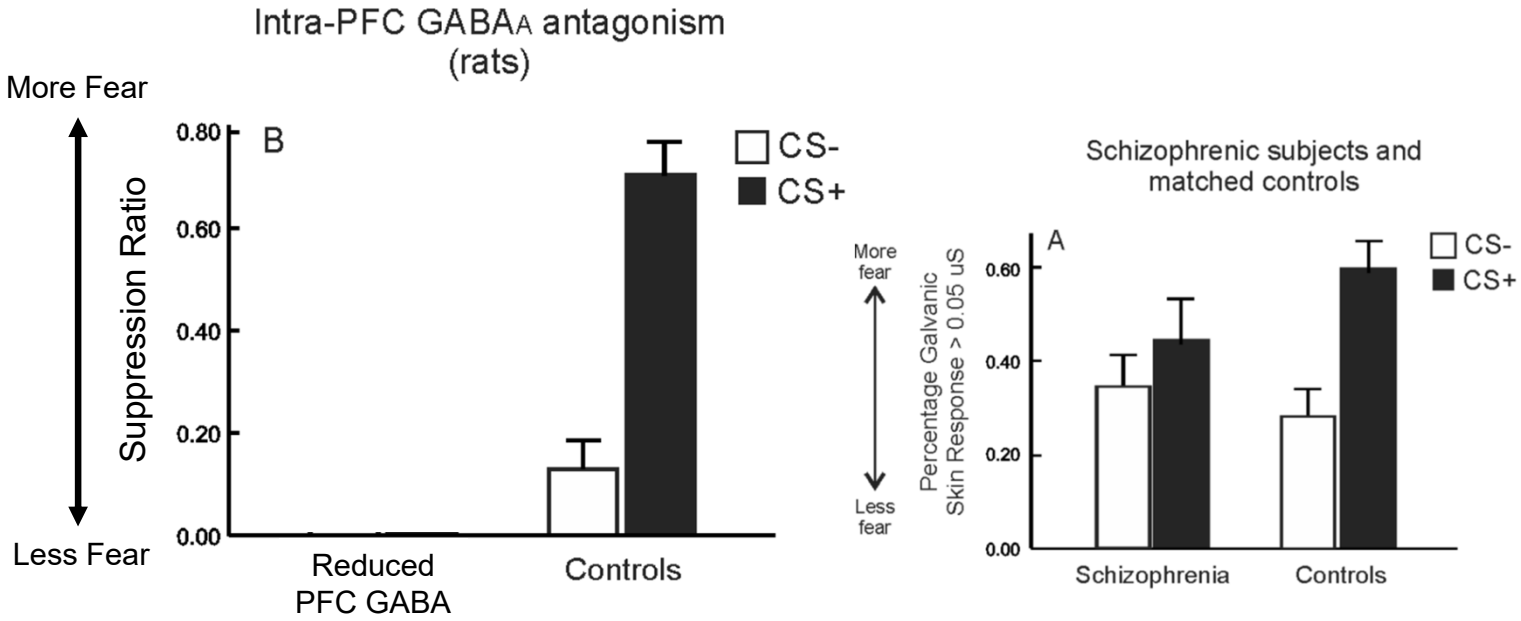
Does GABA-blockade produce similar deficit to schizophrenia?

PFC GABA, fear discrimination and salience attribution (II)



- Reducing PFC GABA:
  - Decreased fear to CS+: Increased fear to CS-
- Patients with schizophrenia **also** show:
  - **Decreased ratings of uneasiness and skin conductance to CS+ (less fear)**
  - **Increased ratings of uneasiness and skin conductance to CS- (more fear)**
- Dysfunctional PFC GABA may also contribute to positive symptoms

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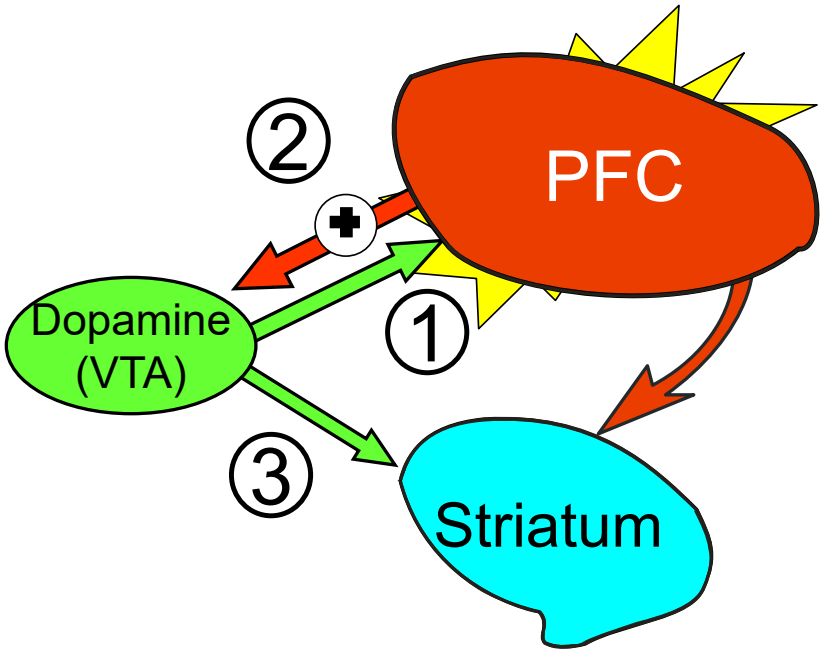
Integrative Hypotheses for Schizophrenia

1) Decreased PFC dopamine/ glutamate reduces activity, **(negative symptoms)**

2) "**Noisy**" PFC (reduced GABA inhibition) may also contribute to cognitive dysfunction

3) Increased subcortical dopamine transmission contributes to **positive symptoms)**



- Schizophrenia is not just a simple increase or decrease in brain dopamine, glutamate or GABA levels
- Subtle changes in the PFC and other regions (occurring over development) can in turn alter subcortical dopamine transmission
- Changes in separate brain regions underlies different symptoms of the disorder