KING'S College LONDON

INSTITUTE OF PSYCHIATRY,
PSYCHOLOGY & NEUROSCIENCE

Module:
Biological Foundations of Mental Health

Week 3:
Synaptic transmission and neurotransmitter systems

Dr Anthony Vernon

Topic 3:

Neurotransmission defects and mental health: Focus on schizophrenia

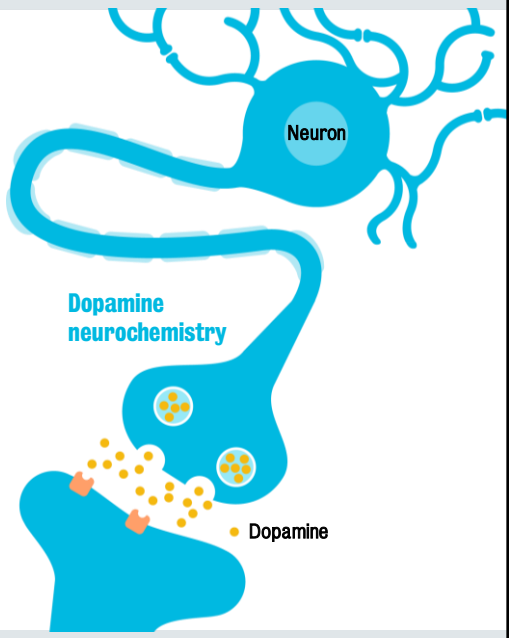
Part 2 of 3

Part 2

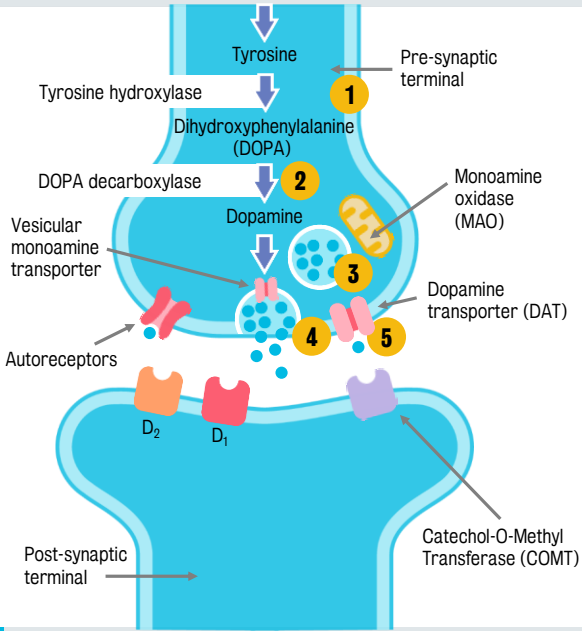
Dopamine neurochemistry

In this section, we will consider how **deficits in neurotransmission underpin the symptoms of schizophrenia**.

Dopamine hypothesis of schizophrenia

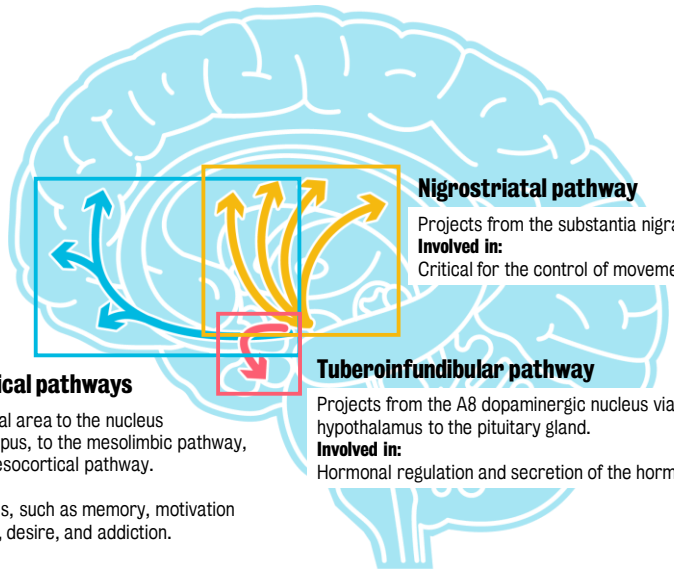


Dopamine neurochemistry



1. **Uptake**
2. **Synthesis**
3. **Storage**
4. **Release**
5. **Re-uptake**

Dopaminergic pathways in the brain



Nigrostriatal pathway

Projects from the substantia nigra to the striatum.
Involved in:
Critical for the control of movement.

Tuberoinfundibular pathway

Projects from the A8 dopaminergic nucleus via the hypothalamus to the pituitary gland.
Involved in:
Hormonal regulation and secretion of the hormone prolactin.

Mesolimbic and mesocortical pathways

Project from the ventral tegmental area to the nucleus accumbens, amygdala, hippocampus, to the mesolimbic pathway, and the prefrontal cortex, the mesocortical pathway.
Involved in:
Both limbic and cognitive functions, such as memory, motivation and emotional response, reward, desire, and addiction.

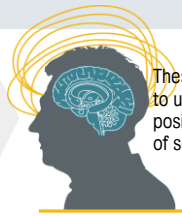
Medlibes, Online Medical Library. (n.d.)

The dopamine hypothesis of schizophrenia

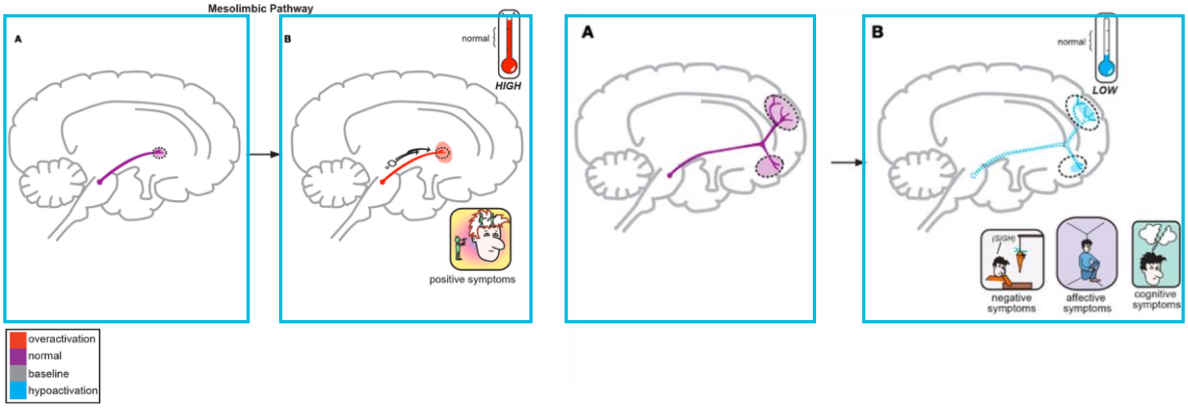
Dopamine hypothesis of schizophrenia

An increase in dopaminergic neurotransmission in the mesolimbic pathway

Leads to abnormally high levels of dopamine in the nucleus accumbens and the striatum



These are thought to underlie the positive symptoms of schizophrenia



Schwartz et al. (2012)

Evidence base for the dopamine hypothesis

What is the evidence for the dopamine hypothesis?

1950s

Doctors observed that chlorpromazine **decreased the positive symptoms** of schizophrenia.

Antipsychotic drugs:
- Chlorpromazine
- Phenothiazines
- Haloperidol
- Risperidone
- Olanzapine

1963

Carlsson and Lindquist showed that these drugs **increased the amount of dopamine metabolites** in the cerebral spinal fluid of patients.

Hypothesis:
The blockade of dopamine receptors may lead the brain to compensate by increasing the amount of dopamine being made.

1980s 1990s 2000s

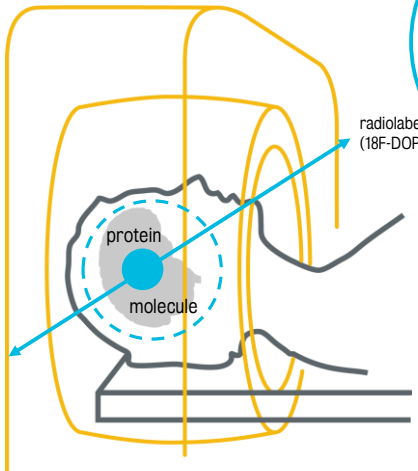
PET scans were carried out on healthy people and patients with a diagnosis of schizophrenia who had been prescribed amphetamines.

Finding:
Amphetamines increased dopamine neurotransmission and consequently induced schizophrenia-like symptoms in otherwise healthy people. Amphetamines also increased the severity of symptoms in patients with a diagnosis of schizophrenia.

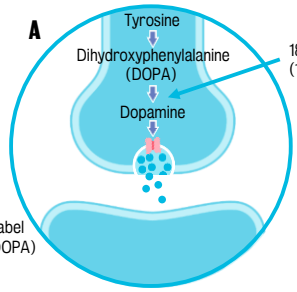
Stahl (2007, 2008[1,2])

Neuroimaging evidence for the dopamine hypothesis

Positron emission tomography (PET)



A



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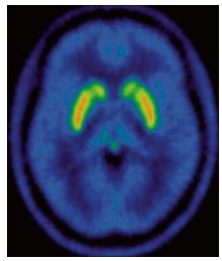
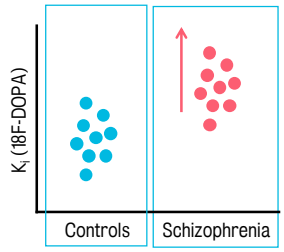


PET image

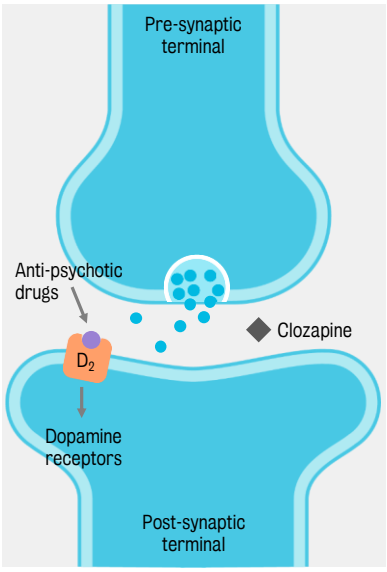
Striatal 6-fluoro–L-dopa F 18–dopa summation image showing highest signal intensity (yellow and red areas) in the striatum (indicating the synthesis and accumulation of dopamine in the striatum during positron emission tomography).



Comparison of the uptake of 18F-DOPA in the striatum of patients with schizophrenia and healthy controls.

Howes et al. (2009)

Antipsychotics and dopamine D2 receptors (1)

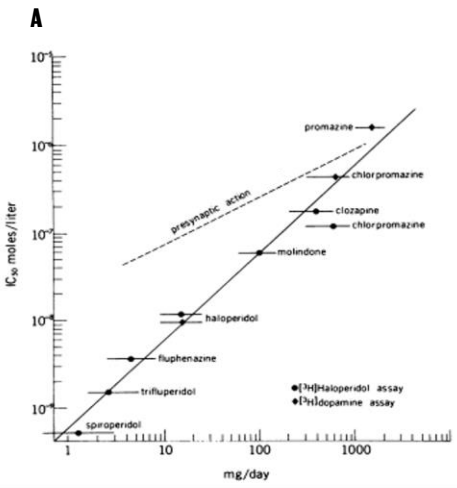


Further evidence for the dopamine hypothesis comes from **studies of anti-psychotic drugs** and their **binding to dopamine D2 receptors**.

The finding of drugs such as chlorpromazine led to the coining of the term **anti-psychotic drugs.**

The importance of the role that dopamine plays in schizophrenia was strengthened by the finding that **all anti-psychotic drugs bind to the dopamine D2 receptor**.

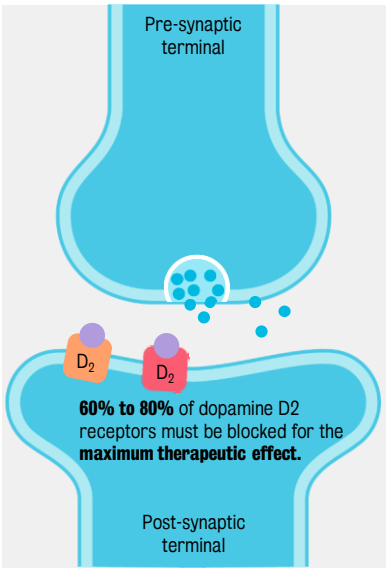
An exception to this, however, is **clozapine**, which has a low affinity for the D2 receptor, but is one of the most effective anti-psychotic drugs.



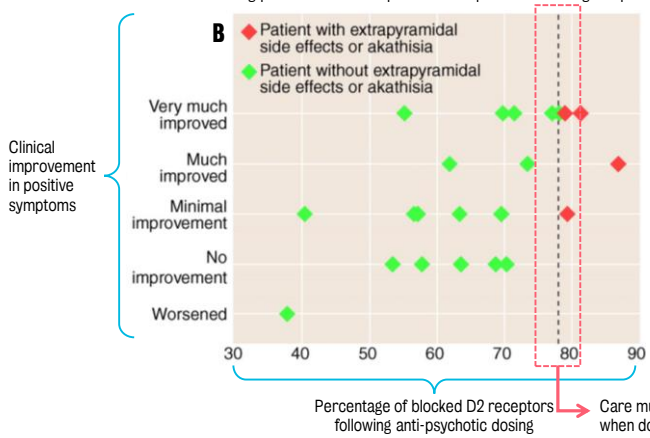
The efficacy of antipsychotics is closely correlated to the potency with which a particular antipsychotic binds to the D2 receptor

Creese et al. (1976); Seeman et al. (1976)

Antipsychotics and dopamine D2 receptors (2)



Relation of dopamine D2 occupancy to CGI-rated clinical response among patients with first-episode schizophrenia receiving haloperidol



Extrapyramidal symptoms: Reflect the action of anti-psychotics on dopamine D2 receptors in other dopamine pathways, such as the nigrostriatal pathway, responsible for the control of movement.

Kapur et al. (2000)

Where does the excess dopamine come from?

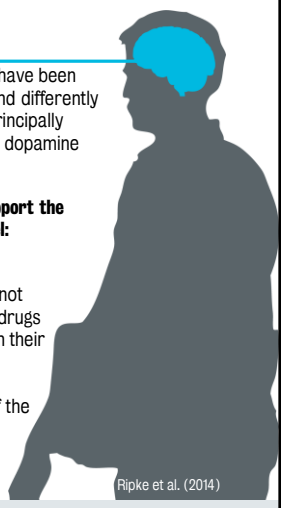
Where does the excess dopamine activity come from?

Different possibilities include:

Produce too much dopamine

Not metabolise excess dopamine quickly enough

Has D2 receptors that have been modified so they respond differently to dopamine binding, principally being more sensitive to dopamine



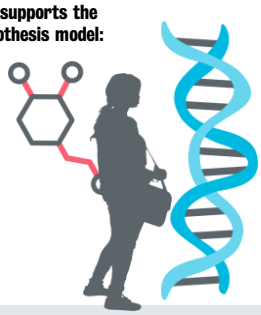
Stress – diathesis model:

Suggests that an individual inherits several genes that encode for abnormal proteins, leading to defective dopamine function in the mesolimbic pathway and positive symptoms consequently.

Evidence that supports the dopamine hypothesis model:

Genetic risk

Environmental stresses



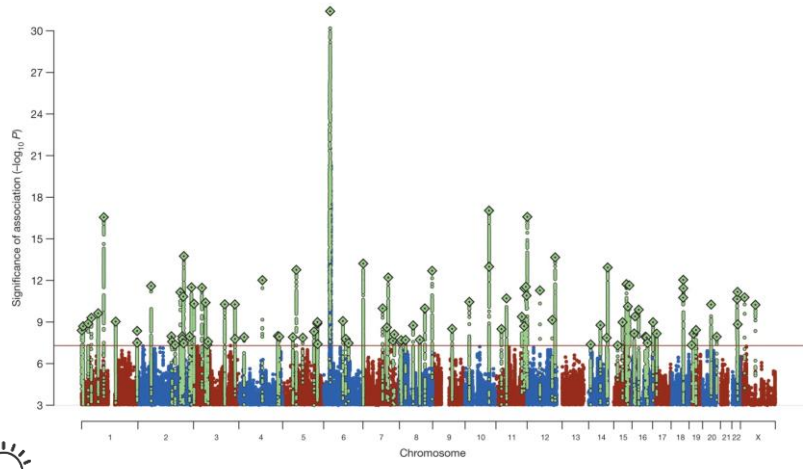
Evidence that does not support the dopamine hypothesis model:

A significant proportion of schizophrenia patients do not respond to anti-psychotic drugs and see no improvement in their positive symptoms, in turn suggesting that dopamine hyperactivity is only one of the causes for the onset of schizophrenia.

Ripke et al. (2014)

Schizophrenia associations plot

Manhattan plot showing schizophrenia associations



Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The *x* axis is chromosomal position and the *y* axis is the significance ($-\log_{10} P$; 2-tailed) of association derived by logistic regression. The red line shows the genome-wide significance level (5×10^{-8}). SNPs in green are in linkage disequilibrium with the index SNPs (diamonds) which represent independent genome-wide significant associations.

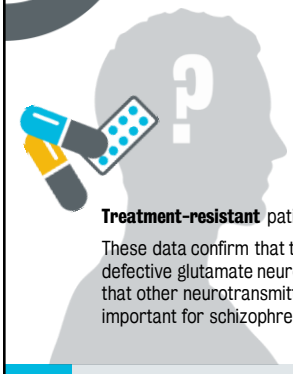
Take a moment to study this graph and the association between different factors and schizophrenia.

Click **Next** to continue

Ripke et al. (2014)

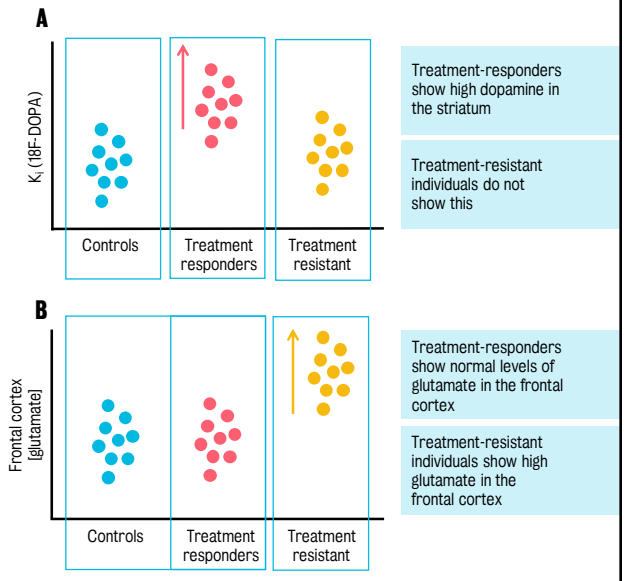
Dopamine and antipsychotic treatment response

In about **30% of cases**, the positive symptoms of schizophrenia patients do not improve following treatment with anti-psychotic drugs.



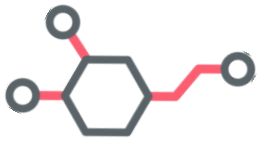
Treatment-resistant patients

These data confirm that treatment-resistant patients may have defective glutamate neurotransmission, therefore suggesting that other neurotransmitters, particularly glutamate, are important for schizophrenia symptoms.

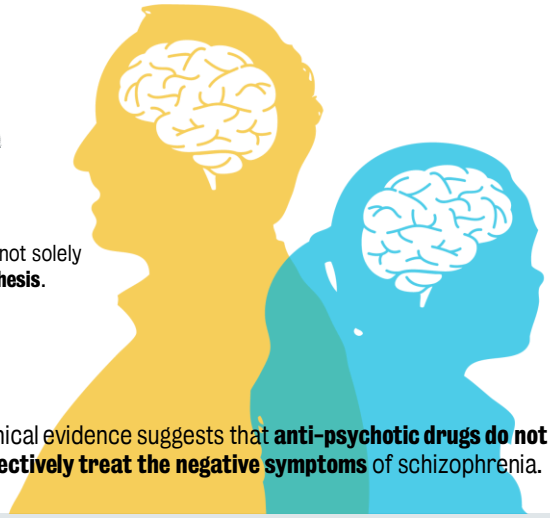


Reflections

There might be **two sub-types of schizophrenia**: one based on dopamine, one not.



The symptoms of schizophrenia cannot solely be explained by the **dopamine hypothesis**.



In the next section, we will look at the **glutamate hypothesis**.

Clinical evidence suggests that **anti-psychotic drugs do not effectively treat the negative symptoms** of schizophrenia.

End of part 2