Psychosis Schizophrenia and the neural pathways of dopamine

Disorders in which psychosis is a defining feature:

- Schizophrenia
- Substance include medication induced psychotic disorders
- Schizophreniform disorder
- Schizoaffective disorder
- Delusional disorder
- Brief psychotic disorder
- Shared psychotic disorder
- Psychotic disorder due to general medical condition
- Childhood psychotic disorder

Disorders in which psychosis is an associated feature

- Mania
- Depression
- Cognitive disorders
- Alzheimer's disease and other dementias
- Parkinson's disease

Symptom dimensions is schizophrenia

- Positive symptoms
    - Delusions: false beliefs that are not emendable to logical convincing. The product of distorted reality
    - Hallucinations: usually auditory but could be any type of sensory hallucinations
    - Distortions or exaggerations in language and communication
    - Disorganized speech
    - Disorganized behavior
    - Catatonic behavior: mutism, or catatonic excitement
    - Agitation
- Negative symptoms
    - Apathy: don't care believed to be related to insufficient information processing through the PFC and the hypothalamic centers (regulated by norepinephrine and dopamine neurons), and the nucleus accumbens (Regulated by dopamine)
    - Anhedonia: lack of pleasure
    - Cognitive blunting
    - Neuroleptic dysphoria
    - Blunted affect
    - Emotional withdrawal
    - Poor rapport
    - Passivity
    - Social withdrawal
    - Difficulty in abstract thinking
    - Lack of spontaneity
    - Stereotyped thinking
    - Alogia: restrictions in fluency and productivity of thought and speech
    - Avolition: restrictions in initiative of goal-directed behavior
    - Attentional impairment

Domain	Descriptive term	Translation
Dysfunction of communication	Alogia	Poverty of speech; e.g., talks little; uses few words
Dysfunction of affect	Blunted affect	Reduced range of emotions (perception, experience, and expression); e.g., feels numb or empty inside; recalls few emotional experiences, good or bad
Dysfunction of socialization	Asociality	Reduced social drive and interaction; e.g., little sexual interest; few friends; little interest in spending time with (or little time spent with) friends
Dysfunction of capacity for pleasure	Anhedonia	Reduced ability to experience pleasure; e.g., finds previous hobbies or interests unpleasurable
Dysfunction of motivation	Avolition	Reduced desire, motivation, or persistence; e.g., reduced ability to undertake and complete everyday tasks; may have poor personal hygiene

Key Negative Symptoms Identified Solely on Observation

Reduced speech: Patient has restricted speech quantity, uses few words and nonverbal responses. May also have impoverished content of speech, when words convey little meaning*

Poor grooming: Patient has poor grooming and hygiene, clothes are dirty or stained, or subject has an odor*

Limited eye contact: Patient rarely makes eye contact with the interviewer*

Reduced emotional responsiveness: Patient exhibits few emotions or changes in facial expression, and when questioned can recall few occasions of emotional experience*

Reduced interest: Reduced interests and hobbies, little or nothing stimulates interest, limited life goals and inability to proceed with them*

Reduced social drive: Patient has reduced desire to initiate social contacts and may have few or no friends or close relationships*

A symptom is in a circuit

- Positive symptoms
  - Mesolimbic and nucleus accumbens: dopamine excess
  - Nucleus accumbens reward circuit
- Negative symptoms
  - Mesocortical/prefrontal cortex
  - Dopamine deficit in the cerebral cortex
- Affective symptoms
  - Ventromedial prefrontal cortex
- Aggressive symptoms
  - Brain location: Orbitofrontal cortex & amygdala
- Cognitive symptoms
  - Brain Location: Dorsolateral prefrontal cortex
  - Cognitive symptoms of schizophrenia
    - Problems representing and maintaining goals
    - Problems allocating attentional resources
    - Problems with focusing attention
    - Problems sustaining attention
    - Problems evaluating functions
    - Problem's monitoring performance
    - Problem's prioritizing
    - Problems modulating behaviors based on social cues
    - Problems with serial learning
    - Impaired verbal fluency
    - Difficulty with problem solving (executive functioning= putting things together, analyze it and solve a problem with it) in schizophrenia we see executive dysfunction

Types of Violence:

- Psychotic: 17%
  - associated with positive symptoms of psychosis, orbital frontal cortex association
  - typically command hallucinations and or delusions
- Impulsive 54%
  - Characterized by high levels of autonomic arousal
  - Precipitated by provocation
  - Associated with negative emotions such as anger or fear
  - Usually represents response to perceived stress
  - Also called reactive, affective, or hostile
- Organized 29% - usually seen in prison, not in schizophrenia
  - Planned behavior not typically associated with frustration or response to immediate threat
  - Might not be accompanied by autonomic arousal
  - Planned with clear goals in mind
  - Also called predatory, instrumental, proactive, or premeditated aggression

Three major hypotheses of psychosis and their neurotransmitters & Two others

- Dopmaine Theory
  - Hyperactive dopamine at D2 receptors in the mesolimbic pathway
- Gluatmate Theory

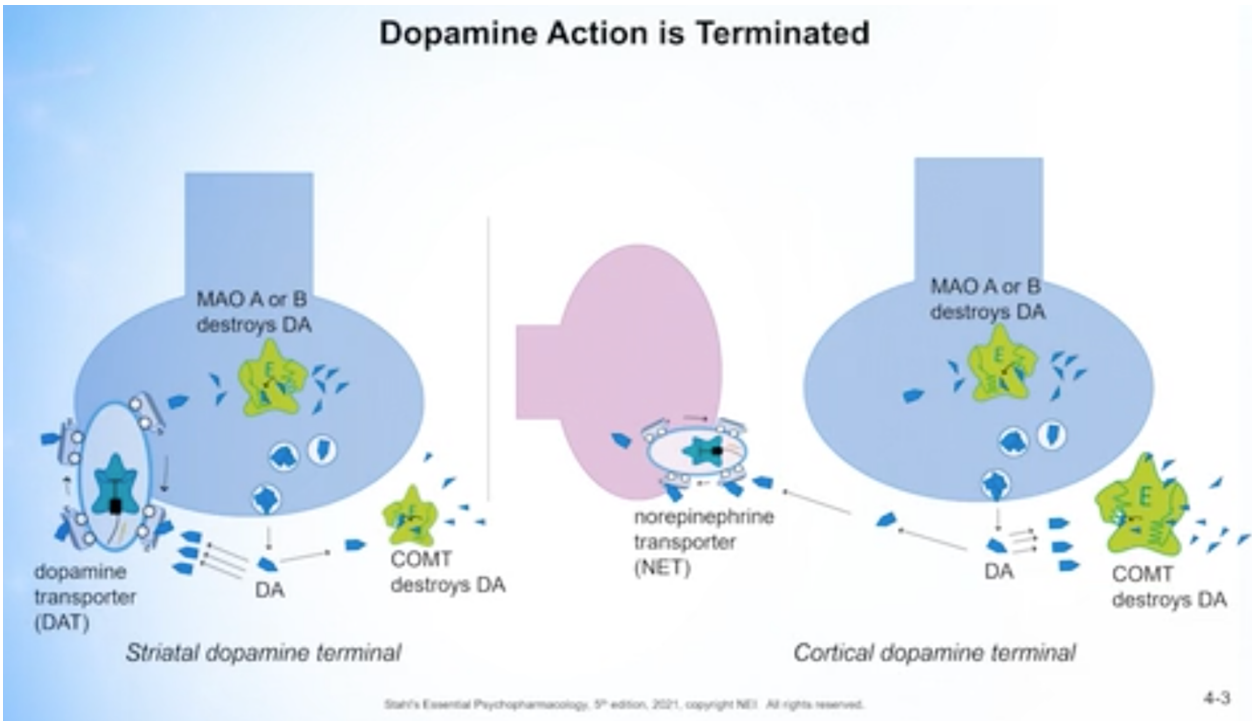
    - NMDA receptor hypofunction
- Serotonin Theory
    - 5HT2A receptor hyperfunction in the cortex
- Trace Amine Theory
- Colinergic Theory

Pharmacological models link dopamine, serotonin, and glutamate to psychosis

	Psychostimulants (cocaine, amphetamine)	Dissociative anesthetics (PCP, ketamine)	Psychedelics (LSD, psilocybin)
Proposed mechanism	Dopamine D2 agonist	NMDA antagonist	Serotonin 5HT2A agonist (and to a lesser extent 5HT2C)
Main type of hallucinations	Auditory	Visual	Visual
Most frequently associated delusions	Paranoid	Paranoid	Mystical
Insightfulness	No	No	Yes

<u>Dopamine Theory</u>

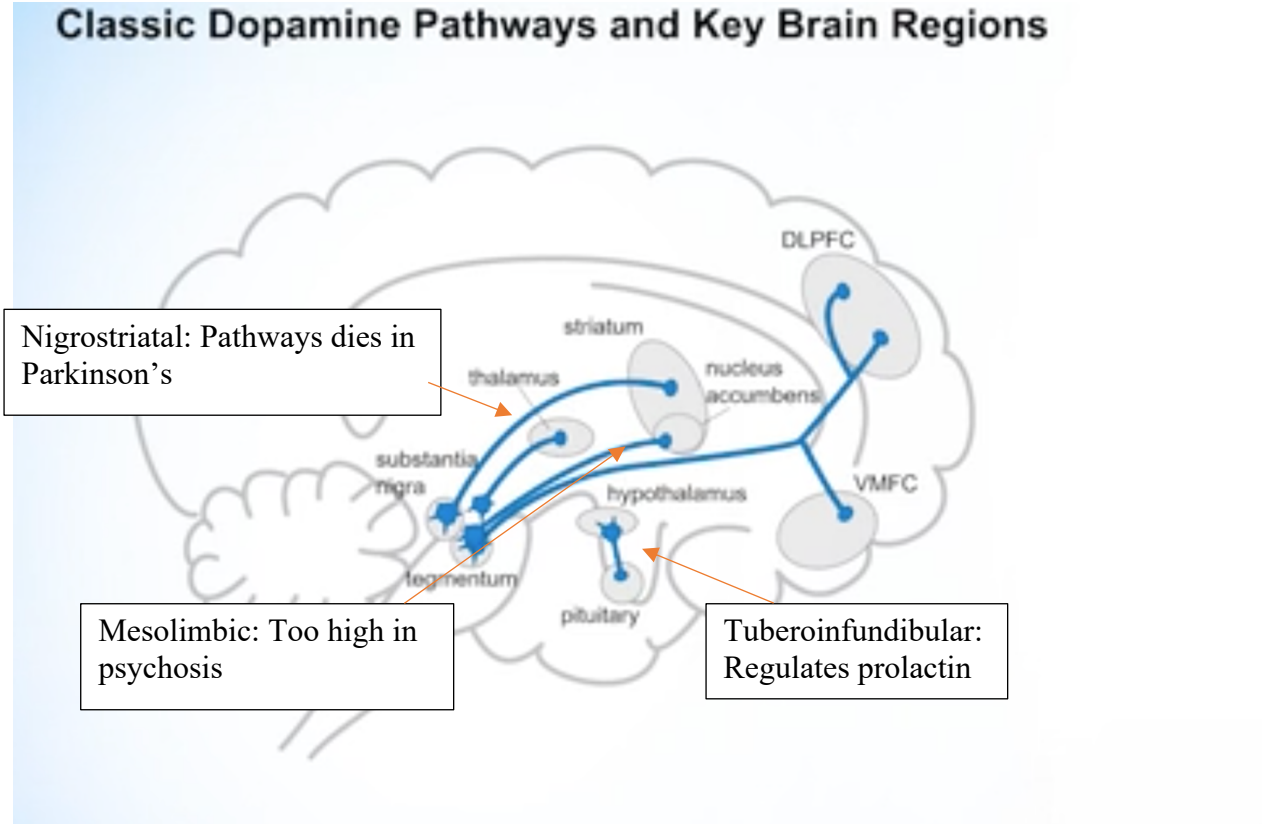
How Dopamine is Produced
Amino acid transporter Tyrasine Precursor of Dopamine (Tyrasine) and pumps it into the presynaptic neuron, passes it off to TOH which turns it into L-dopa, hands off to DDC which takes carboxyl group off, makes into dopamine and stores it into the synaptic vesicles, it gets into that from VMAT2.



Norepinephrine transporter has a higher affinity for dopamine

Presynaptic dopamine receptors

- D1: excitatory, stimulate
  - D1-like (D1 and D5 receptors)
- D2: Inhibitory, stop stimulation:
  - D2-like (D2, D3, and D4 receptors)
  - Targets of drug treatments
  - Role: detects dopamine in the synapse, and when it gets to a certain level it shuts off dopamine release
  - There are gatekeepers (D2 or D3), which stop presynaptic dopamine release (presynaptic dopamine inhibition)
    - Somatodendric autoreceptor (D2 or D3)
- D3: very sensitive to dopamine
  - There are gatekeepers (D2 or D3), which stop presynaptic dopamine release (presynaptic dopamine inhibition)
    - Somatodendric autoreceptor (D2 or D3)
- D4
- D5



Classic CSTC (Cortico-striato-thalamo-cortical) loop

Dopamine regulation of:

- Direct (D1)
  - Go pathway, if you activate the GP pathway it will release GABA and it will stop the neuron from firing, which causes the cortex to fire away.
  - Says "go"

- Indirect (D2)
    - Go pathway, if you activate the GP pathway it will release GABA and it will stop the neuron from firing, which causes the next one to fire, and causes the next one not to fire, which causes the cortex to fire away. = More steps.
    - Says “don’t stop”

Mesolimbic pathway

- Pathway for motivation & reward
- Too high
    - Simulant, or drug induced
    - Positive symptoms of psychosis
        - Too high because of a problem in the pathway
        - Can see on a PET scan
    - Mesolimbic overactivity
        - Impulsivity
        - Agitation
        - Violence or aggression
        - Hostility
        - Positive symptoms
- New concept: Integrative hub mesostriatal hyperdopaminergia: Too high in the associative striatum and sensorimotor. Neurons are too close in humans. (rat studies shows previous theory of classic mesolimbic hyperdopaminergia not the same in humans)

Classic Mesocortical pathway to DLPFC

- Too low
    - Negative and cognitive symptoms

Classical mesocortical pathway to VMPFC

- Too low
    - Negative and affective symptoms

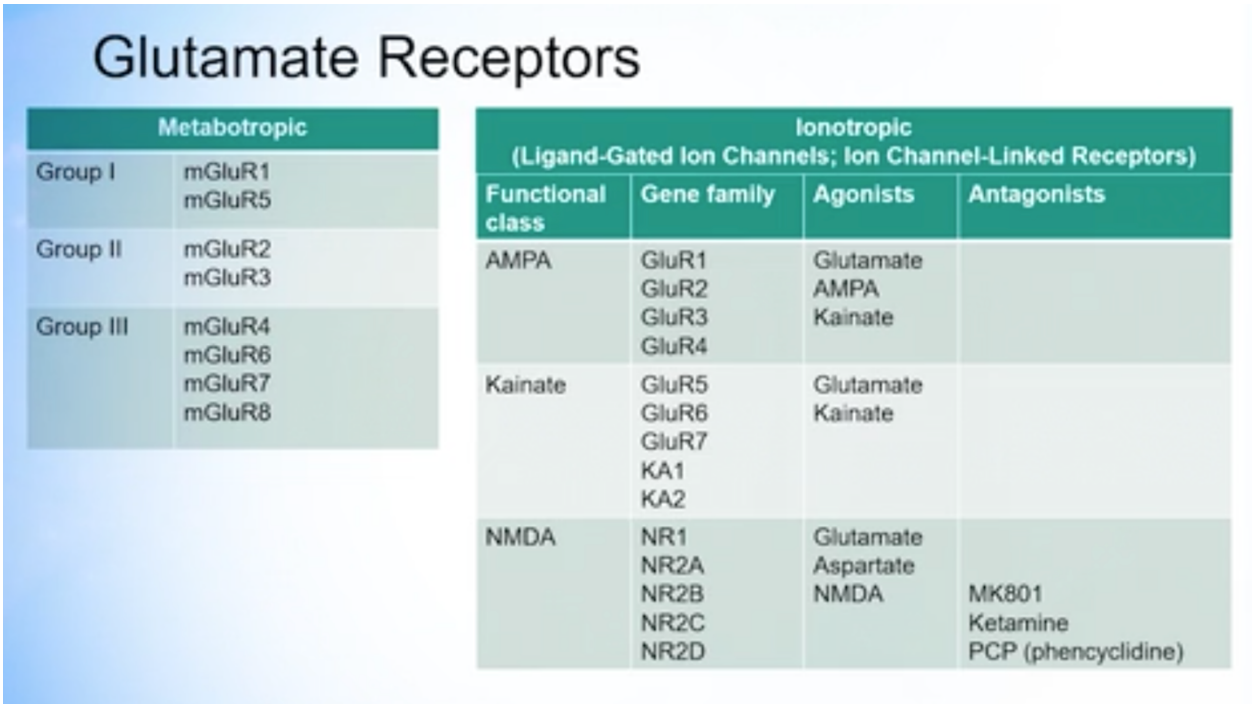
How to fix: want to boost dopamine for cognitive, negative, and affective symptoms

NMDA Antagonist Theory

Glutamate neurotransmitter pathway: next to glutamate neurons are glial cells which have the EAAT transporters which pulls the glutamate into the cell and transforms it to glutamine, transports the glutamine out of the cell with a SNAT transporter to another SNAT transporter which puts the glutamine into the neuron. Then confronts glutaminase and it transforms the glutamine into glutamate. The process starts over.

NMDA receptor works with glutamate and glycine, needs both in the receptor.

L—serine is pulled into the glial cell by L-SER.T transporter. SHMT converts to glycine and it is transported out of the cell by GLYT1



For NMDA receptor action three things must happen

1. Pop magnesium off the receptor : Glutamate goes to the AMPA receptor which leads to activation and depolarization, the nerve fires and the magnesium pops off
2. Glutamine in place
3. Glycine in place

Leads to calcium channel open and calcium comes in and you get your long-term potential (neuroplasticity, memory, and synapse formation)

Key glutamate pathways

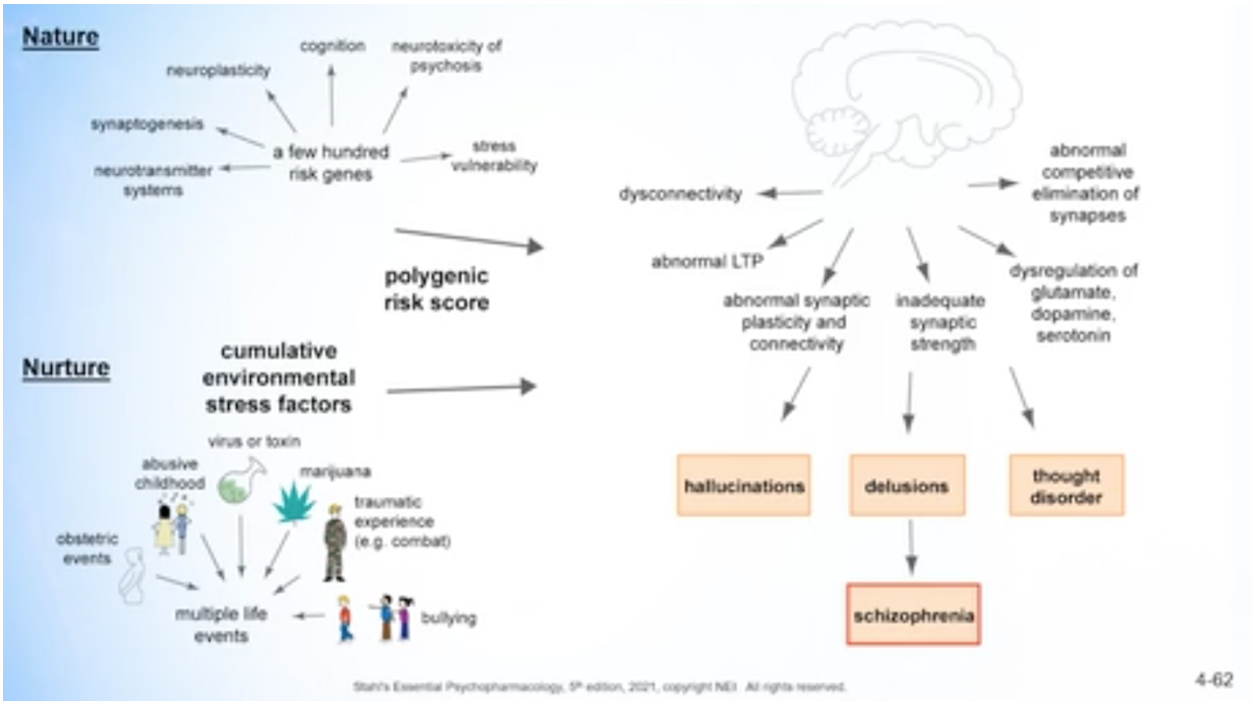
- Cortex to striatum to the brain stem
- Hippocampus to striatum
- Thalamic cortico (CSTC loop)
- Cortical striatal
- Thalamic cortical
- Corical thalamic
- Some neurons don’t leave the cortex

Glutamate hypothesis of schizophrenia

- Neurodevelopmental abnormalities causes downstream dopamine to be too high.
- Normally a parametrial neuron communicates to GABA neuron which communicates with another parametrial neuron. If GABA neuron gets excited, it releases GABA which activates the next parametrial neuron which inhibits it and causes less glutamate to be released
- Hypofunctional NMDA receptor and synapse after ketamine or in schizophrenia does not activate GABA neuron then the next parametrial neuron is not activated then it is not inhibited, a lot of glutamate comes out. Increases dopamine and glutamate.
- PCP site (in the ion channel) if it is blocked calcium can’t go through and the neuron cant be activated

The cause of schizophrenia

- Classic Theory: genes cause mental illness – not true genes code for proteins and epigenetics
- Nature:
    - Neuroplasticity, cognition, synaptogenesis, neurotoxicity, stress
- Nurture
    - Obstetric events, abusive childhood, virus or toxin, marijuana, traumatic experience such as combat, bullying



Neurodevelopment

Stem cell transforms to immature neurons, then the brain gets rid of 90% of neurons keeps 10% (Could possibly select wrong neurons). These neurons move around and the connections wire when you are young. Age 6 wire most of your connections, Age 14-60 you rewire your connections (the thought is there may be something wrong with which neurons and connections are selected).

Could be neurodegenerative
Course of schizophrenia

- Prodrome related to restructuring of neuro connections. During this prodrome you become odd, IQ may drop, may hear some voices in head
- First episode: Brain looks normal but fully psychotic
- Second episode: not taking medications: now brain is degenerating
- Third episode: ventricles are getting more degenerating.
- Each episode creates more brain deterioration.
- As progressive brain tissue is lost, you become unresponsive to medications leading to chronic residual symptoms.

Serotonin Theory (5HT2A receptor)

How serotonin is produced

Tryptophan is taken out of plasma and spinal fluid by the tryptophan transporter. Which brings it into the neuron where tryptophase is converted by TRY-OH to 5HTP is converted by AADC to serotonin. Then sent out into the synapse by VMAT2.

Serotonin is destroyed (action terminated) by the Serotonin reuptake uptake pump (SERT), which pulls it out of the synapse and pulls it into synaptic vesicles. MAO-B destroys serotonin before it reaches the vesicles.

Serotonin receptor subtypes currently at 14 changes often.
Presynaptic

- B/D: this Occupies serotonin and shuts it off which decreases serotonin release.
- 1A

Postsynaptic

- 1A:
- 2B: many drugs bind here. It increases the action which increases serotonin postsynaptic.

When serotonin is added presynaptically it slows down the release of serotonin postsynaptic.

5HT receptors regulate glutamate release directly and indirectly through GABA.
5HT interacts in a neuronal network that regulates all major neurotransmitters systems.

- At 1A receptors 5HT is inhibitory: so 1A receptor will inhibit GABA, but will increase norepinephrine, dopamine, and acetylcholine.
- At 1B receptors 5HT is disinhibitory so 1B receptors disinhibit GABA and decrease norepinephrine, dopamine, and acetylcholine (don't want) so will need 1B Antagonist
- 2A receptor 5HT can increase GABA and decrease glutamate or 2A decreases glutamate depends on the pathway.
- 2C activates GABA inhibits dopamine neuron so decreases NE and DA in prefrontal cortex. (we do not want this) so the drugs we have are 2C antagonists.
- T3 always excitatory, increase GABA so it will inhibit Ach/NE (and serotonin) (which we do not want) so we have medications T3 Antagonist.
- T7 inhibits glutamate so we have T7 antagonists

The serotonin hypothesis of psychosis

- Hallucinogen (LSD, psilocybin, mescaline) stimulates 5HT2A receptors and excite glutamate receptors = visual hallucinations
- Parkinson's disease psychosis: normal or low 5HT release now overstimulates upregulated 5HT2A receptors causing glutamate excitation, mesolimbic DA hyperactivity, and psychosis= delusions, visual hallucinations
- Psychosis in dementia: plaque, tangle, stroke, Lewy body leads to loss of GABA inhibition by neurodegeneration leads to sustained 5HT2A excitation no longer balance by GABA inhibition causing glutamate excitation, mesolimbic DA hyperactivity and psychosis. To fix you are going to block with a 5HT2A antagonist.