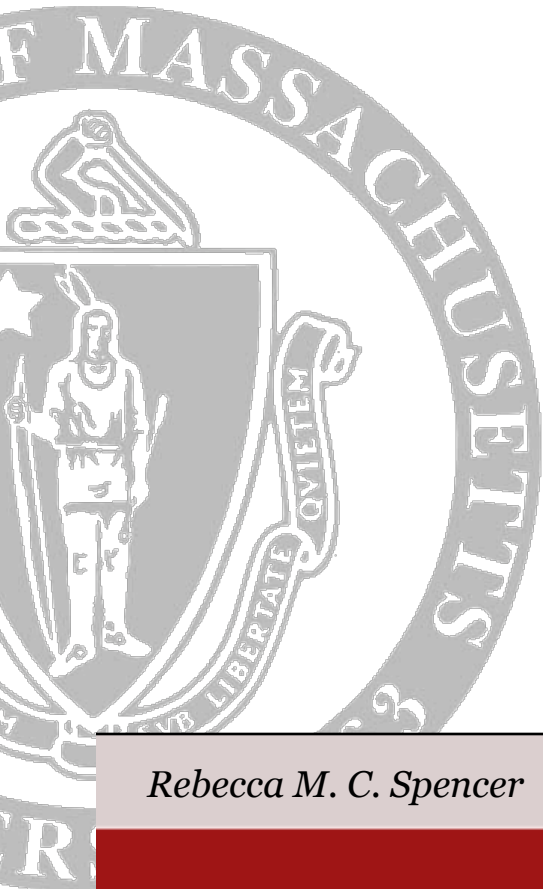


# Neurobiology of brain dysfunction

## *Schizophrenia*



## Schizophrenia – diagnosis

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### **DSM IV criteria for Schizophrenia I:**

- Characteristic symptoms (2 or more): delusions, hallucinations, disorganized speech, grossly disorganized behavior, negative symptoms.
- Social/occupational dysfunction.
- Duration >6 months.
- Not due to a mood disorder.
- Not due to drugs or medical condition.
- Only if hallucinations and/or delusions are prominent and persistent if patient has autism spectrum disorder.

## Schizophrenia – diagnosis

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### **DSM IV criteria for Schizophrenia syndrome:**

#### ■ Positive Symptoms:

- Delusions – false beliefs
- Hallucinations – see, hear\*, smell what no one else does
- Thought disorder – unorganized thoughts; made up words; ‘thought blocking’
- Movement disorder – agitated movements or catatonia (rare now; more common when never medicated)

\*hearing voices is most common

## Schizophrenia – diagnosis

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### **DSM IV criteria for Schizophrenia syndrome:**

- Negative Symptoms:
  - asociality (lacks the ability to form relationships)
  - apathy (indifferent)
  - anhedonia (lacks the ability to experience pleasure)
  - neglect hygiene
  - may speak little
  
- Cognitive Deficits: memory, problem solving, attention

## Schizophrenia – diagnosis

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- Subtypes:
  - Paranoid type: delusions, hallucinations; thought disorder, flattened affect absent
  - Disorganized type (“hebephrenic”): Thought disorder + flat affect
  - Catatonic type: almost immobile; purposeless movement
  - Undifferentiated: Psychotic symptoms present but none of the above types
  - Residual type: Positive symptoms present in low levels
- Spectrum: Schizoid personality disorder, Schizoaffective disorder, Schizophreniform disorder, Schizotypal personality disorder, etc.

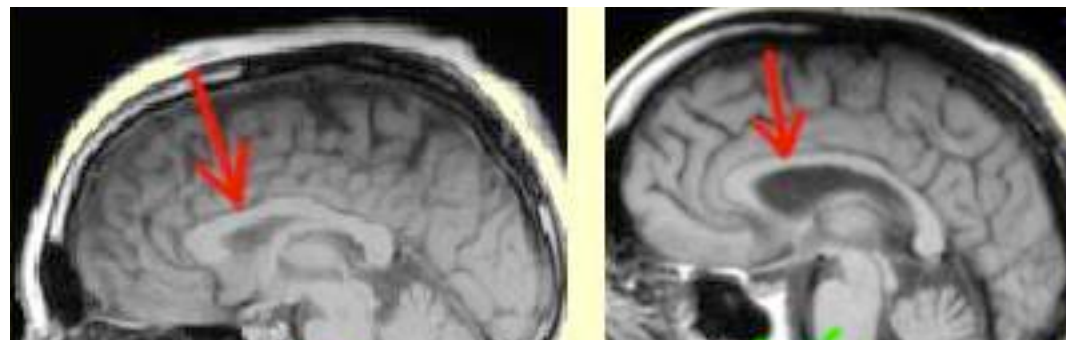
## Schizophrenia – genetic?

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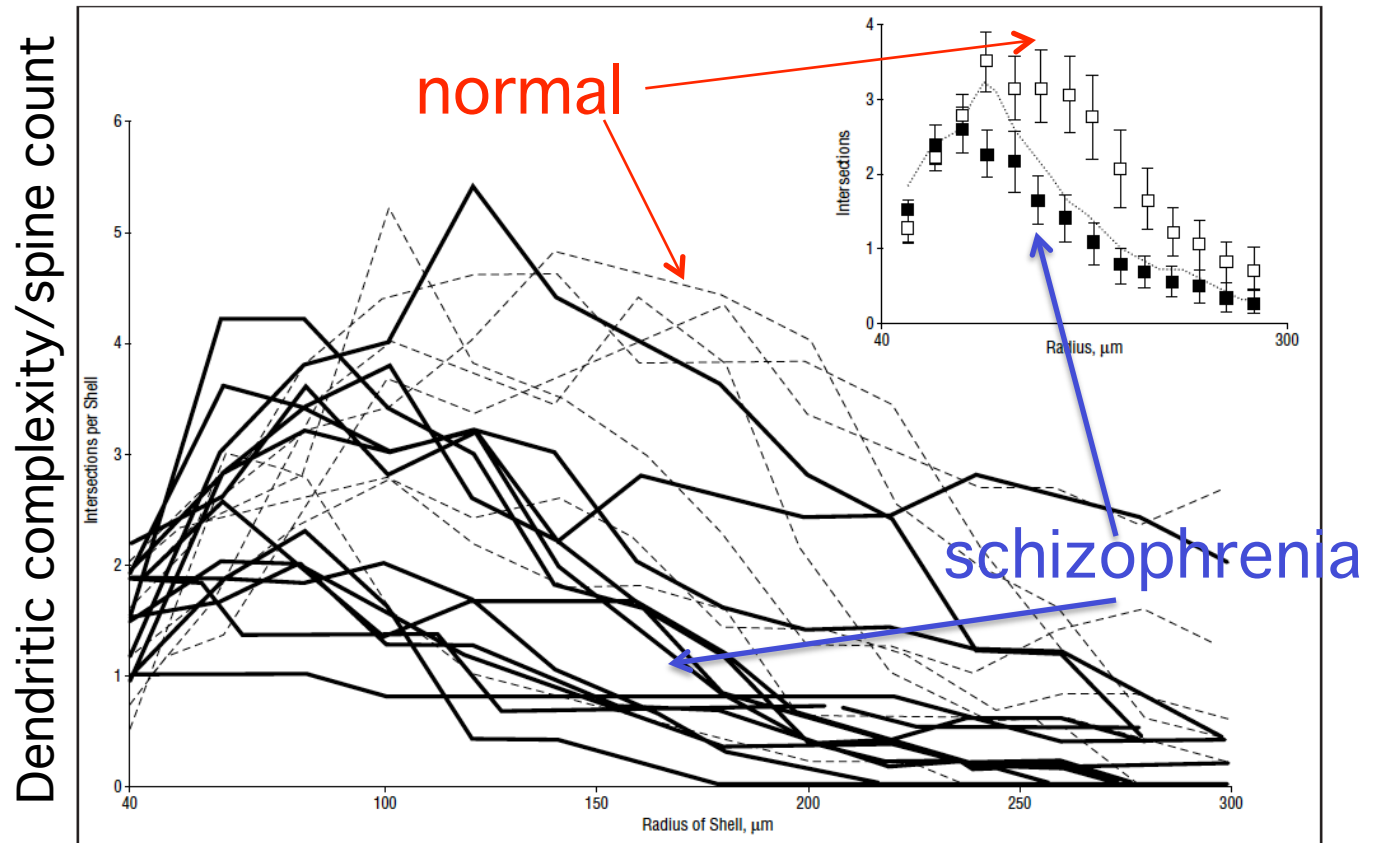
- Life-time prevalence: 1% (0.8 in females, 1.2 in males)
- Concordance rate in identical twins: 40-50%
- Risk in first degree relatives: 6-10%
- Heritability: 80%
- Environmental risk factors: malnutrition and viral infections in second trimester, perinatal insults, urban living
- Linkage/ association studies: DAOA/DAO, GRIN2B, DTNBP1, DISC1, NRG1
- GWAS results: MHC region, MIR137, NRG1, ERBB4, TCF4, ZNF804A

## Schizophrenia – structural?

- Increased ventricular, reduced cortical volume, which affects all subregions but temporal lobe most severely
- Present at first episode but increases over subsequent 5-10 years
- Anti-psychotic treatment exposure correlates with greater cortical volume loss
- Affects subcortical structures like the thalamus but not the basal ganglia



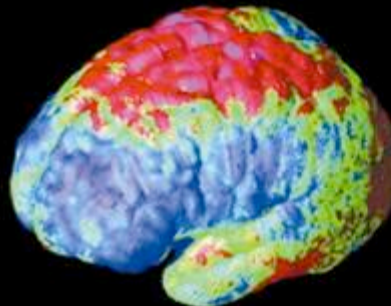
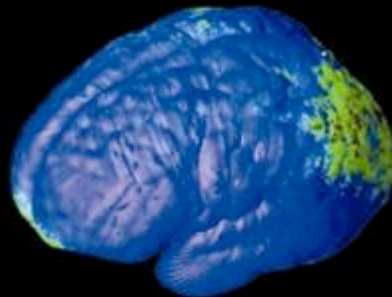
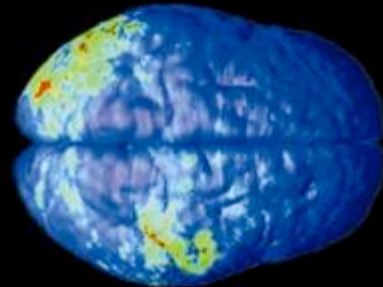
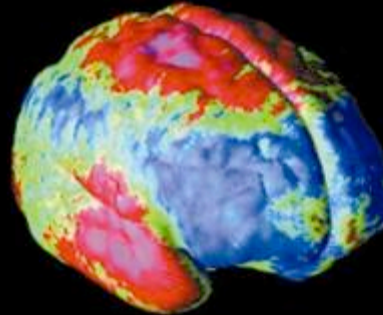
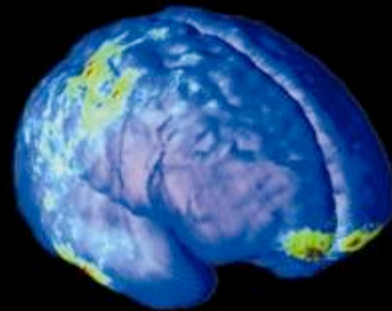
# Schizophrenia – structural?



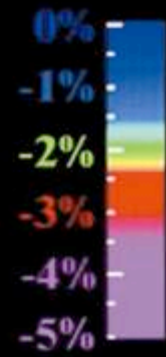
# Rate of gray matter loss

Normal adolescents

Schizophrenic subjects



Average annual loss



## Schizophrenia – structural?

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- Cell loss in schizophrenic patients appears to occur suddenly during late adolescence or early adulthood. Schizophrenia is not a gradual degenerative disease like Parkinson's or Alzheimer's diseases.
- Does not appear to involve cell death and 'gliosis' (replacement of neural tissue by glia).
- The frontal cortex seems to be involved in most cases of schizophrenia (hypofrontality)

## Schizophrenia – brain imaging

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- Hallucinations: Abnormal brain activity in primary and secondary sensory areas but also amygdala and ACC (self monitoring)
- Working memory: Reduced frontal activation (“hypofrontality”)
- Memory: Reduced performance associated with reduced hippocampus activation
- Fusiform gyrus (Brodmann 37) reduced in facial emotion recognition tasks – just like autistics

## Schizophrenia – neurotransmitters?

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Dopamine Theory of Schizophrenia: States that schizophrenia is a disorder of hyperactive dopamine system. Evidence:

- Antipsychotics work by blocking dopamine (D<sub>2</sub>) receptors
- Stimulants (amphetamine, methamphetamine, cocaine) act by releasing dopamine cause psychosis similar to schizophrenia

## Schizophrenia – neurotransmitters?

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Dopamine Theory of Schizophrenia: States that schizophrenia is a disorder of hyperactive dopamine system. Evidence:

- Antipsychotics work by blocking dopamine (D<sub>2</sub>) receptors  
**BUT: block more than just dopamine (also serotonin)**
- Stimulants (amphetamine, methamphetamine, cocaine) act by releasing dopamine cause psychosis similar to schizophrenia  
**AND: drugs bind quickly yet behavior change is slow**

## Schizophrenia – neurotransmitters?

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- GABA – inhibitory neurotransmitter; lots in PFC; receptors are abnormal in schizophrenia
- Serotonin – neurotransmitter basis for classic hallucinogenic drugs; atypical antipsychotics suggest a serotonin mechanism
- NMDA (glutamate receptor) – NMDA antagonists in healthy looks schizophrenic; coagonists reduced schizophrenia symptoms

## Schizophrenia – treatment

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Antipsychotic drugs (block D2 dopamine receptors)

Example: Haloperidol

- PseudoParkinsonism: unintentional tremor, bradykinesia, rigidity, drooling
- Dystonic reactions: axial muscles and tongue, more common in young patients
- Akathesia: sense of inner restlessness, causing agitation
- Neuroleptic malignant syndrome: hyperthermia, rigidity, confusion – high fatality risk
- Tardive Dyskinesia: persistent oral-facial and limb dyskinesia that persists after discontinuing the antipsychotic drugs

## Schizophrenia – treatment

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Atypical (or second generation) antipsychotics:

- Clozaril – treats hallucinations well; can cause loss of white blood cells; blocks D<sub>4</sub> receptors in the nucleus accumbens. Little effect on D2 receptors

- Amblify
- Risperdal
- Invega

Drowsiness  
Blurred vision  
Rapid heartbeat  
Muscle spasms  
Weight gain



# Schizophrenia – multi-factor process

