



# PSYCH 260/BBH 203

## Schizophrenia

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# Prelude



2:55

# Today's Topics

- Quiz 3 next Tuesday (after class)
- Wrap-up on bipolar disorder
- Schizophrenia

# Schizophrenia



# Simulating the Experience



# Overview

- Lifetime prevalence ~ 1/100
- ~1/3 chronic & severe
- Onset post-puberty, early adulthood
- Pervasive disturbance in mood, thinking, movement, action, memory, perception

# Screening (Yale PRIME test)

1. I think that I have felt that there are odd or unusual things going on that I can't explain.
2. I think that I might be able to predict the future.
3. I may have felt that there could possibly be something interrupting or controlling my thoughts, feelings, or actions.

<http://www.schizophrenia.com/sztest/primetest.pdf>

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# Screening (continued)

1. I get confused at times whether something I experience or perceive may be real or may be just part of my imagination or dreams.
2. I have thought that it might be possible that other people can read my mind, or that I can read other's minds.
3. I wonder if people may be planning to hurt me or even may be about to hurt me.

# Historical background

- Bleuler
  - Coined term “schizophrenia” or “split mind”
  - NOT multiple personality disorder
- Kraeplin
  - Dementia Praecox and Paraphrenia (1919)
  - Emphasized developmental and hereditary origins

# “Positive” symptoms

- “Additions” to behavior
- Disordered thought
- Delusions of grandeur, persecution
- Hallucinations (usually auditory)
- Bizarre behavior

# “Negative” symptoms

- “Reductions” in behavior
- Poverty of speech
- Flat affect
- Social withdrawal
- Impaired executive function
- Anhedonia (loss of pleasure)
- Catatonia (reduced movement)

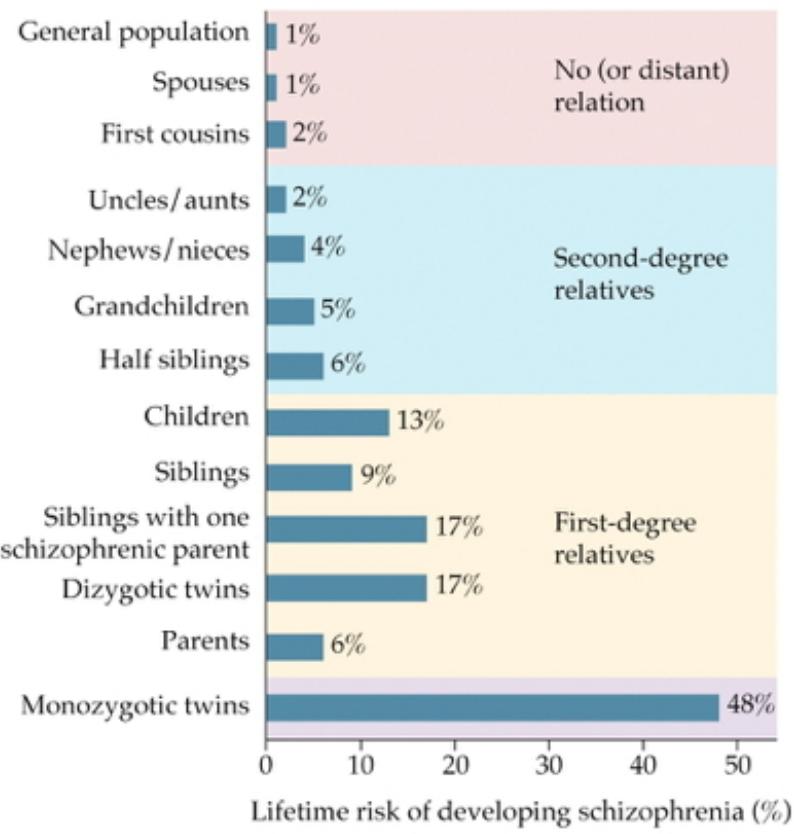
# Cognitive symptoms

- Memory
- Attention
- Planning, decision-making
- Social cognition
- Movement

# Biological bases

- Genetic disposition
- Brain abnormalities
- Developmental origins

# Genetic disposition



# But, no single gene...

Archival Report

## No Evidence That Schizophrenia Candidate Genes Are More Associated With Schizophrenia Than Noncandidate Genes

Emma C. Johnson <sup>a, b</sup>  , Richard Border <sup>a, b</sup>, Whitney E. Melroy-Greif <sup>d</sup>, Christiaan A. de Leeuw <sup>e, f</sup>, Marissa A. Ehringer <sup>b, c</sup>, Matthew C. Keller <sup>a, b</sup>

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<https://doi.org/10.1016/j.biopsych.2017.06.033>

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[\(Johnson et al., 2017\)](#)

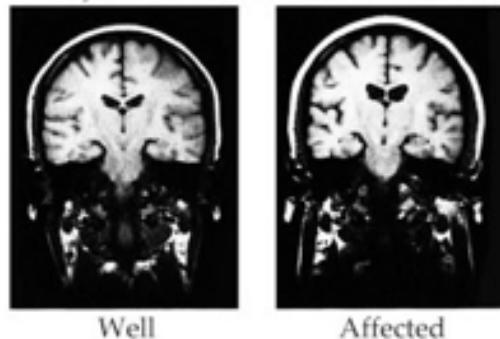
# Genes associated with schizophrenia at higher than chance levels

- *NOTCH4, TNF*:
  - Part of major histocompatibility complex (MHC), cell membrane specializations involved in the immune system
- *DRD2* (dopamine D2 receptor), *KCNN3* (Ca<sup>+</sup> activated K<sup>+</sup> channel), *GRM3* (metabotropic glutamate receptor)

(Johnson et al., 2017)

# Ventricles larger, esp in males

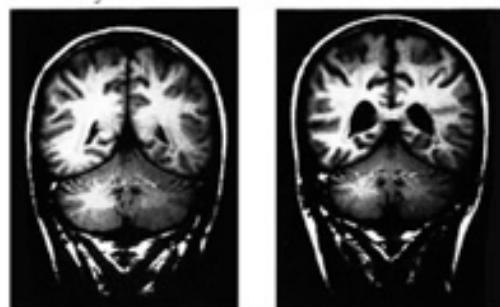
MRI brain images of twins discordant for schizophrenia  
35-year-old female identical twins



Well

Affected

28-year-old male identical twins



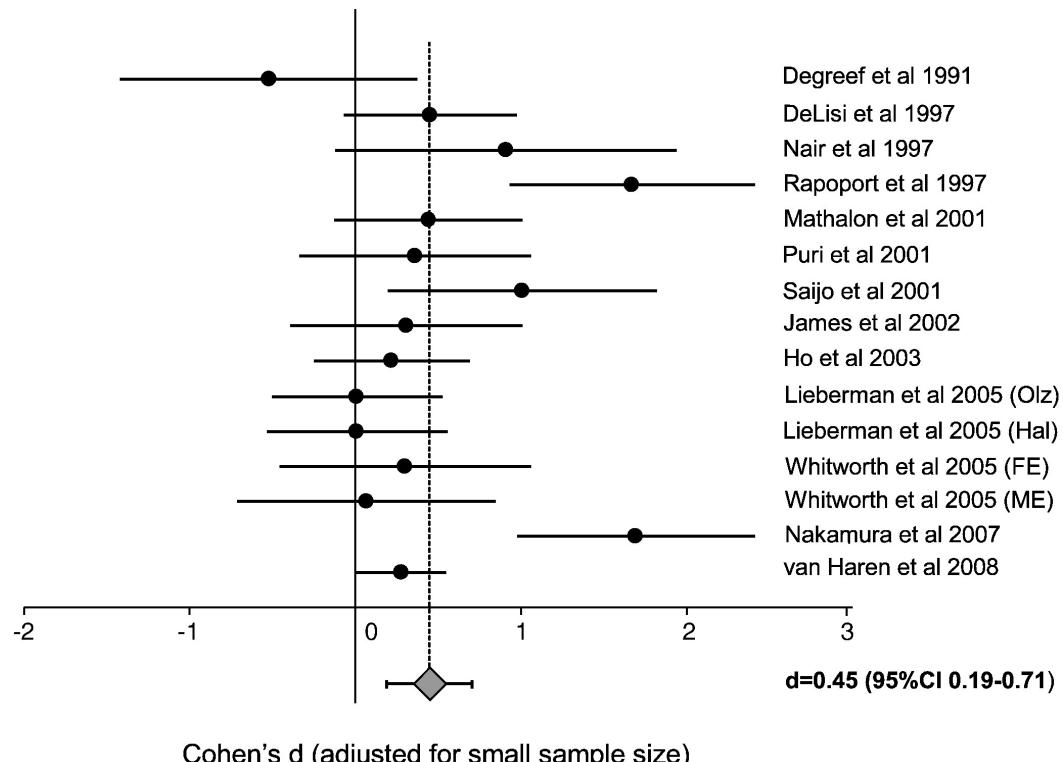
Well

Affected

BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 18.4 © 2004 Sinauer Associates, Inc.

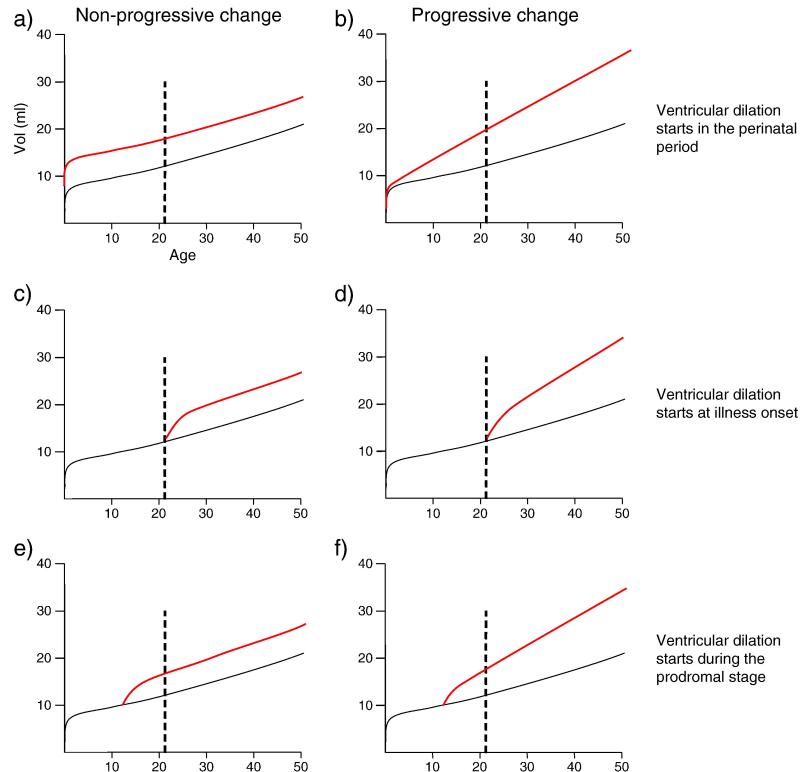
# Cause or effect?

Ventricular enlargement increases across time ([Kempton, Stahl, Williams, & DeLisi, 2010](#))



# Enlargement precedes diagnosis?

As in trajectories B or F

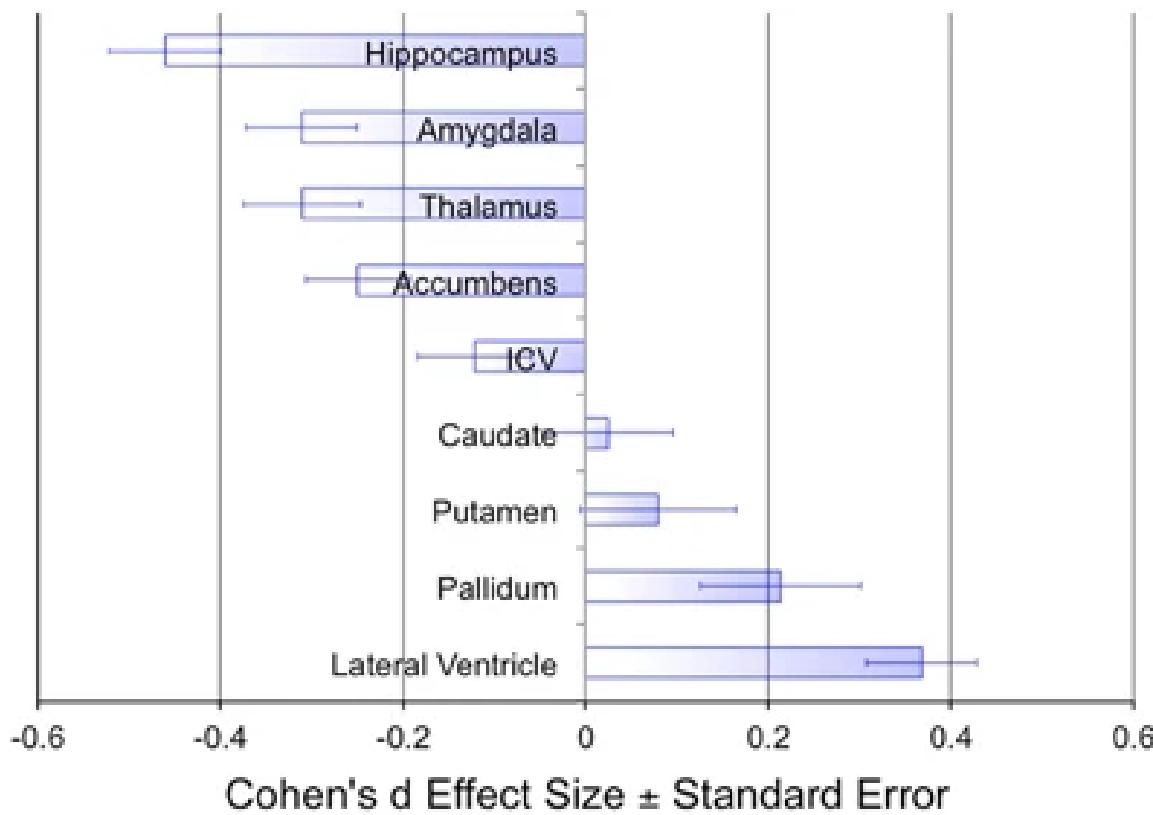


(Kempton et al., 2010)

# Hippocampus, amygdala, thalamus, nucleus accumbens smaller

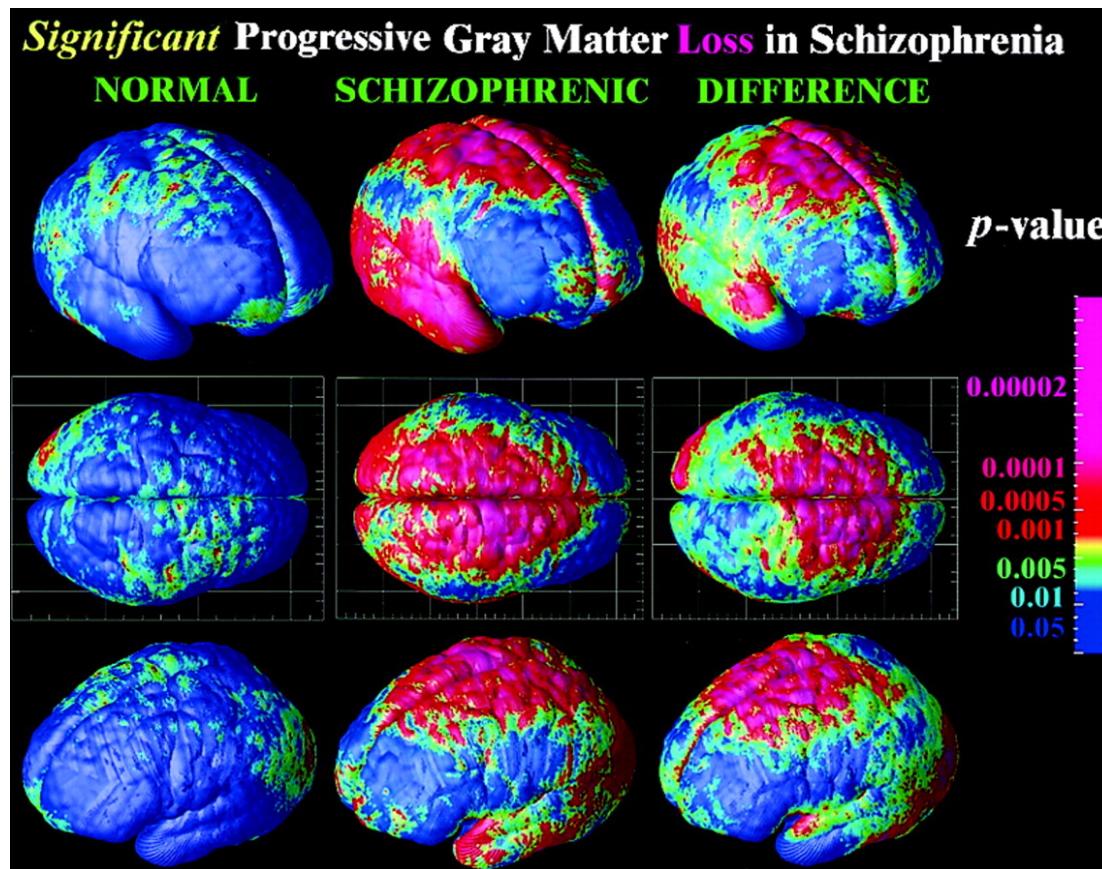
- Related to ventricular enlargement?
- Early disturbance in brain development?

# (Erp et al., 2015)



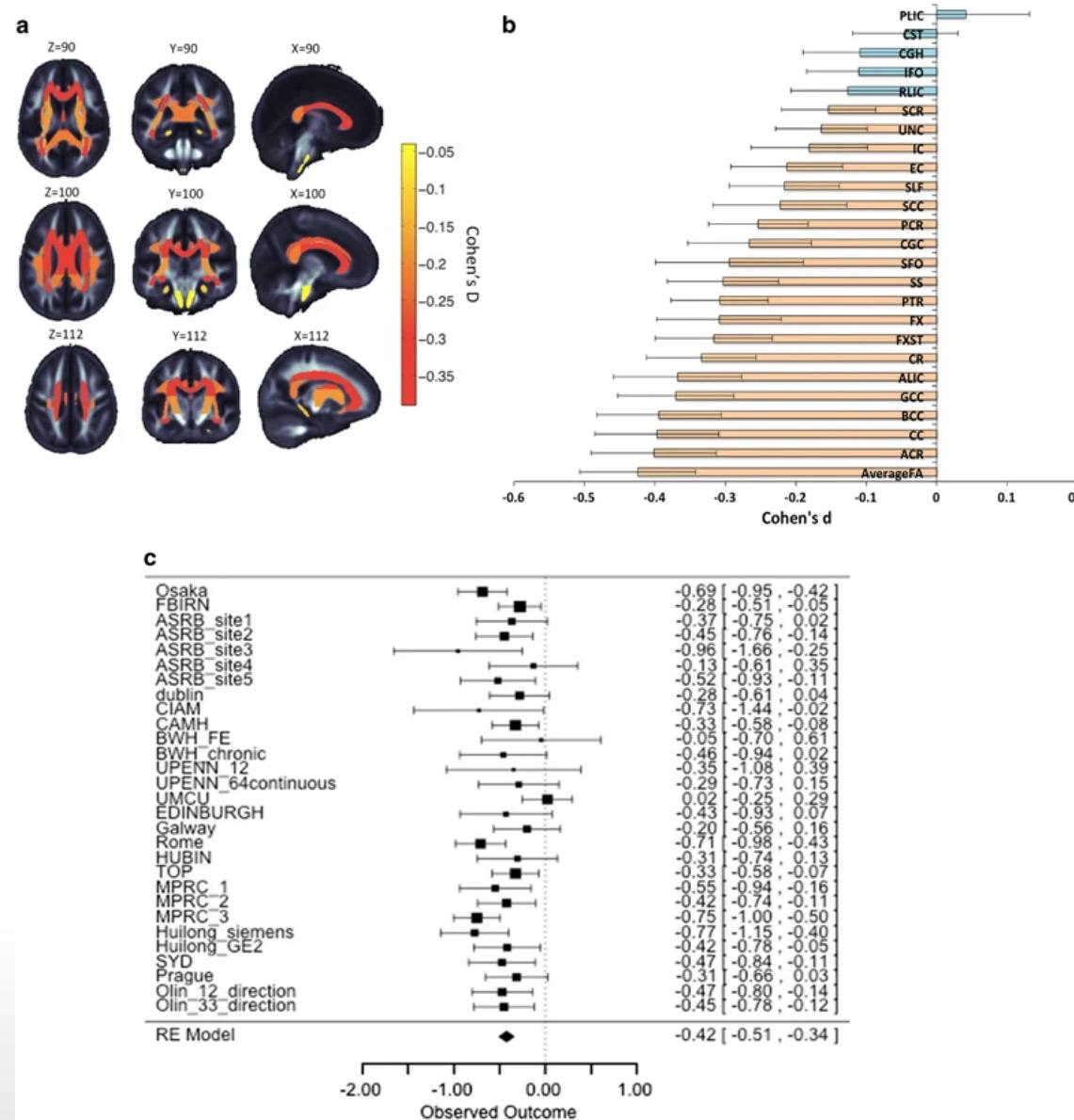
<https://www.nature.com/articles/mp201563/figures/1>

# Rapid gray matter loss in adolescents?

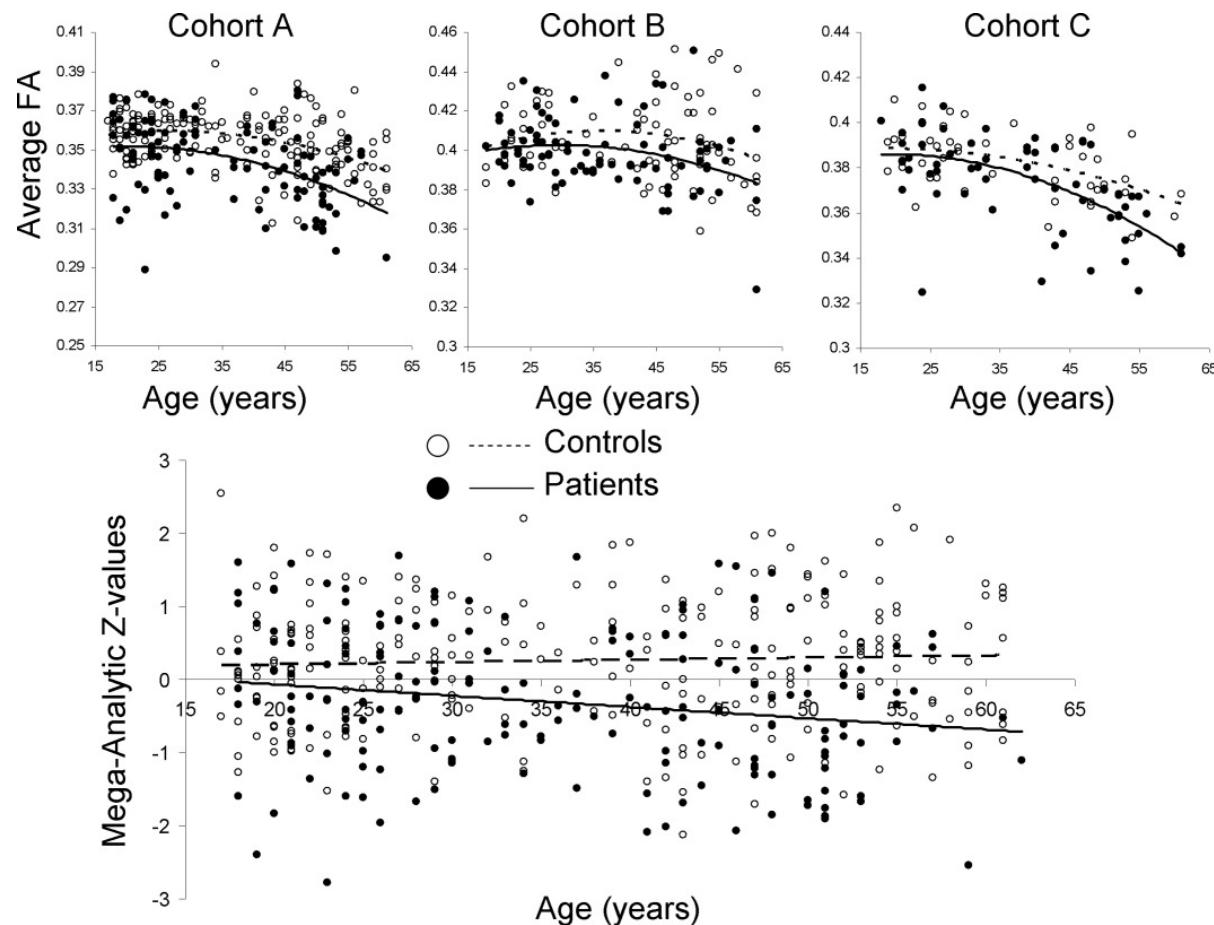


(Thompson et al., 2001)

# Widespread disruption in white matter connectivity (Kelly et al., 2017)

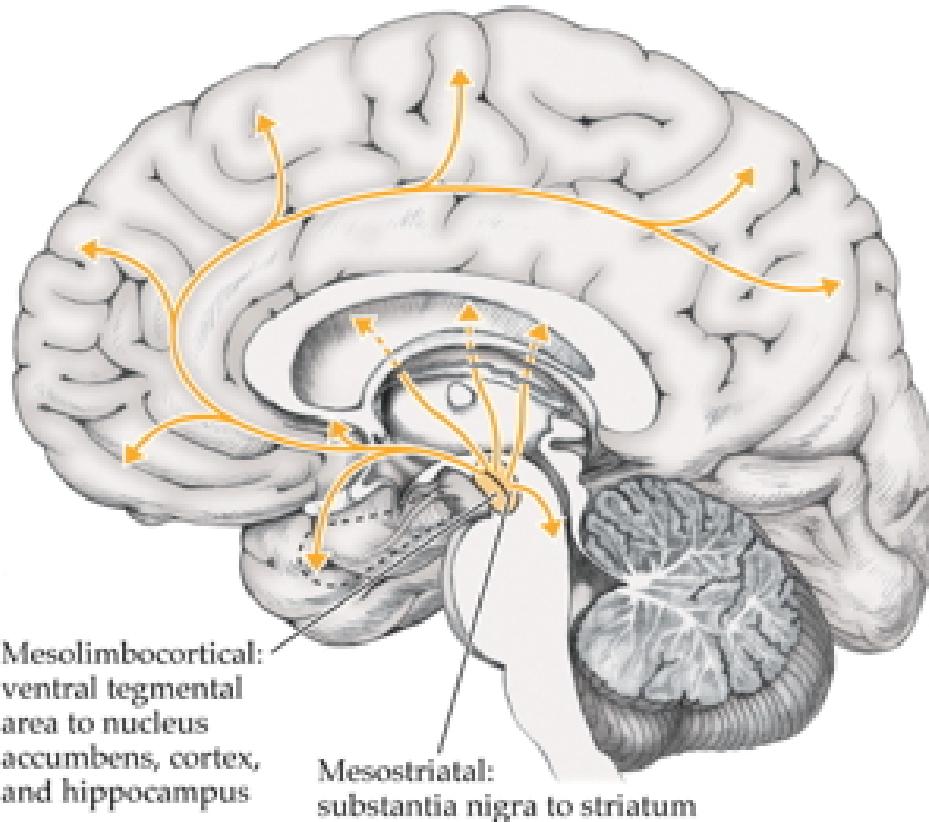


# White matter loss over age



(Kochunov et al., 2016)

# Dopamine hypothesis



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# Evidence for DA hypothesis

- DA (D2 receptor) antagonists (e.g. chlorpromazine)
  - improve positive symptoms
- *Typical antipsychotics* are DA D2 receptor antagonists
- DA agonists
  - amphetamine, cocaine, L-DOPA
  - mimic or exacerbate symptoms

# Tardive Dyskinesia a side effect of DA antagonists



[https://www.youtube.com/watch?v=\\_UCaWSMddwA](https://www.youtube.com/watch?v=_UCaWSMddwA)

# Evidence against DA hypothesis...

- New, *atypical antipsychotics*
  - (e.g. Clozapine) INCREASE DA in frontal cortex, affect 5-HT
- Mixed evidence for high DA metabolite levels in CSF

# Glutamate hypothesis

- *Psychomimetic* drugs...
  - Phencyclidine (PCP), ketamine
  - NMDA receptor antagonists
- ...can induce schizophrenia-like states
- Schizophrenia == *underactivation* of NMDA receptors?
  - NMDA receptor role in learning, plasticity
  - Dentate gyrus neurons in [Jiao et al., 2017](#) were glutamate-releasing.

# Early life stress increases risk

- Urban vs. rural living
- Exposure to infection *in utero*, other birth complications

# (Levine, Levav, Pugachova, Yoffe, & Becher, 2016)

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- Children (N=51,233) of parents who born during Nazi era (1922-1945)
- Emigrated before (indirect exposure) or after (direct exposure) to Nazi era
- Children exposed to direct stress of Nazi era *in utero* or postnatally
  - Did not differ in rates of schizophrenia, but
  - Had higher rehospitalization rates

## **(Debost et al., 2015)**

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- Danish cohort (n=1,141,447)
- Exposure to early life stress
  - *in utero* did not increase risk of schizophrenia, but
  - but *exposure during infancy (0-2 years) increased risk*
- Increased risk associated with an allele of a cortisol-related gene

# Schizophrenia summed up

- Wide-ranging disturbance of mood, thought, action, perception
- Broad changes in brain structure, function, chemistry, development
- ~~Dopamine hypothesis~~ -> glutamate hypothesis
- Genetic (polygenic = multiple genes) risk + environmental factors
- One disorder or many?

# Next time...

- Emotion, happiness, and reward
- Quiz 3 (after class)

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