511-11-08-schizophrenia

Rick Gilmore

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Today's Topics

- Schizophrenia

Schizophrenia

Schizophrenia: Gerald, Part 1

Simulating the Experience

Schizophrenia ABC 20-20 Documentary Part 2

Overview

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

"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)

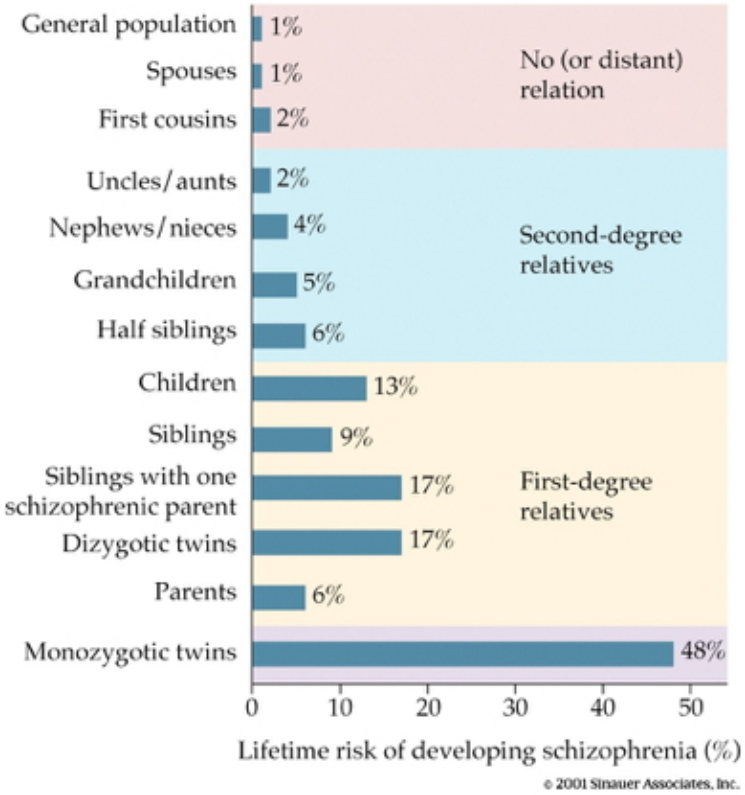
Cognitive symptoms

- 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 [a, b], Richard Border [a, b], Whitney E. Melroy-Greif [d], Christiaan A. de Leeuw [e, f], Marissa A. Ehringer [b, c], Matthew C. Keller [a, b]

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

Genes associated with schizophrenia at higher than chance levels

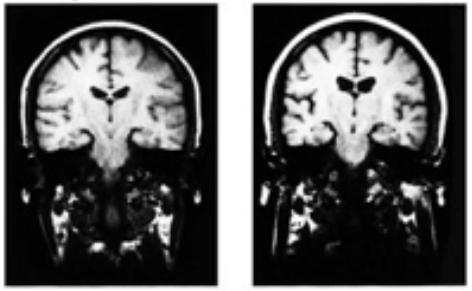
- , :
  - Part of major histocompatibility complex (MHC), cell membrane specializations involved in the immune system
- (dopamine D2 receptor), (Ca+ activated K+ channel), (metabotropic glutatmate receptor)

(Johnson et al. 2017)

Ventricles larger, esp in males

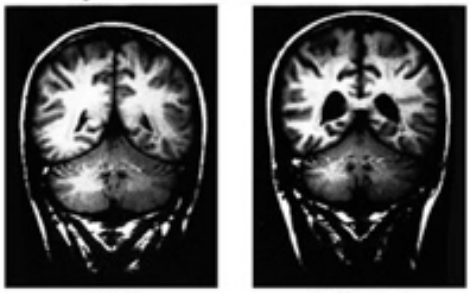
MRI brain images of twins discordant for schizophrenia

35-year-old female identical twins



Well Affected

28-year-old male identical twins

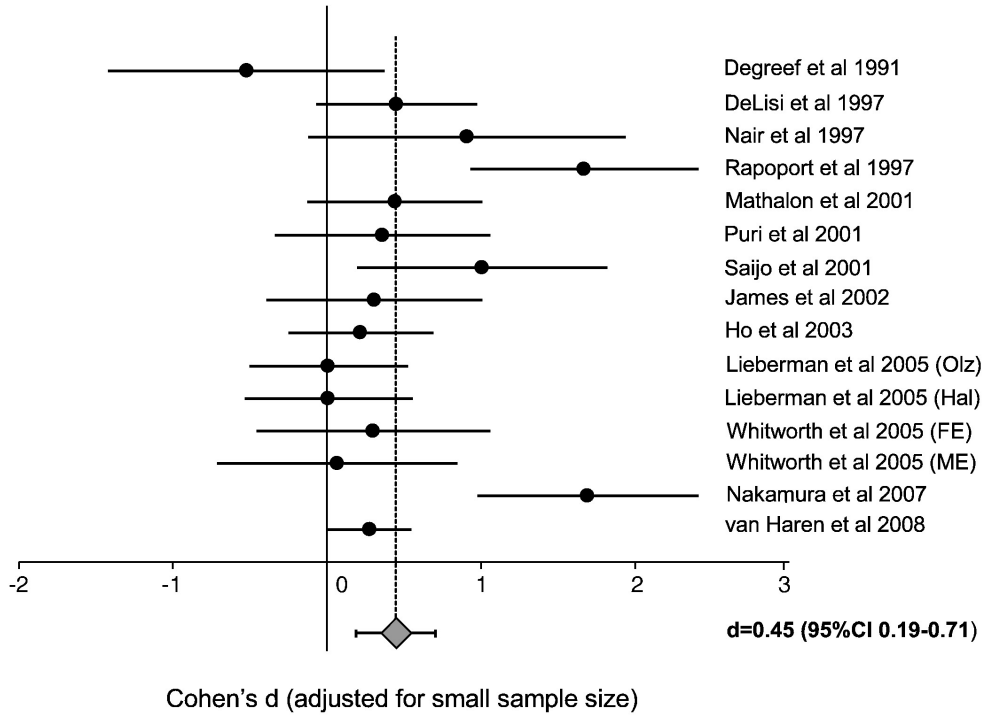


Well Affected

BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 15.4

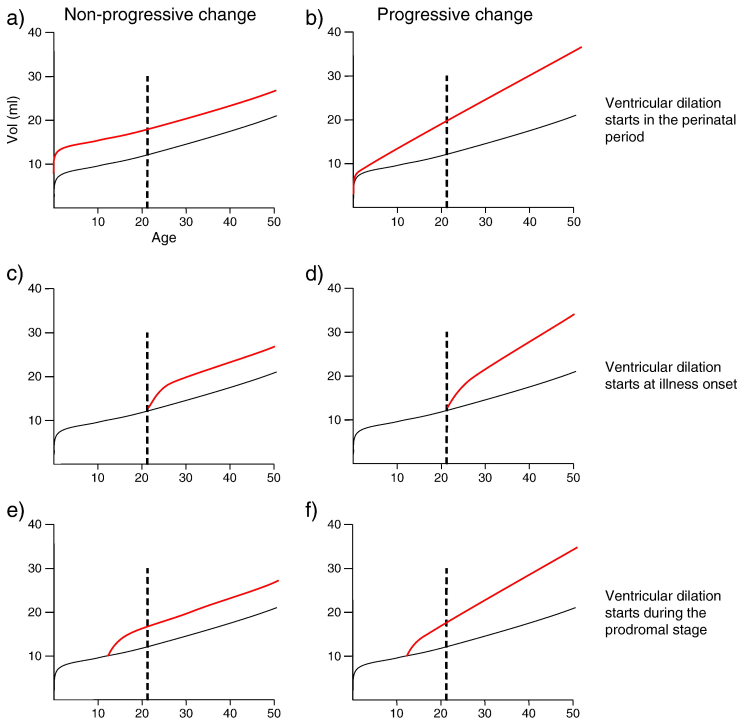
Cause or effect?

Ventricular enlargement increases across time (Kempton et al. 2010)



Enlargement precedes diagnosis?

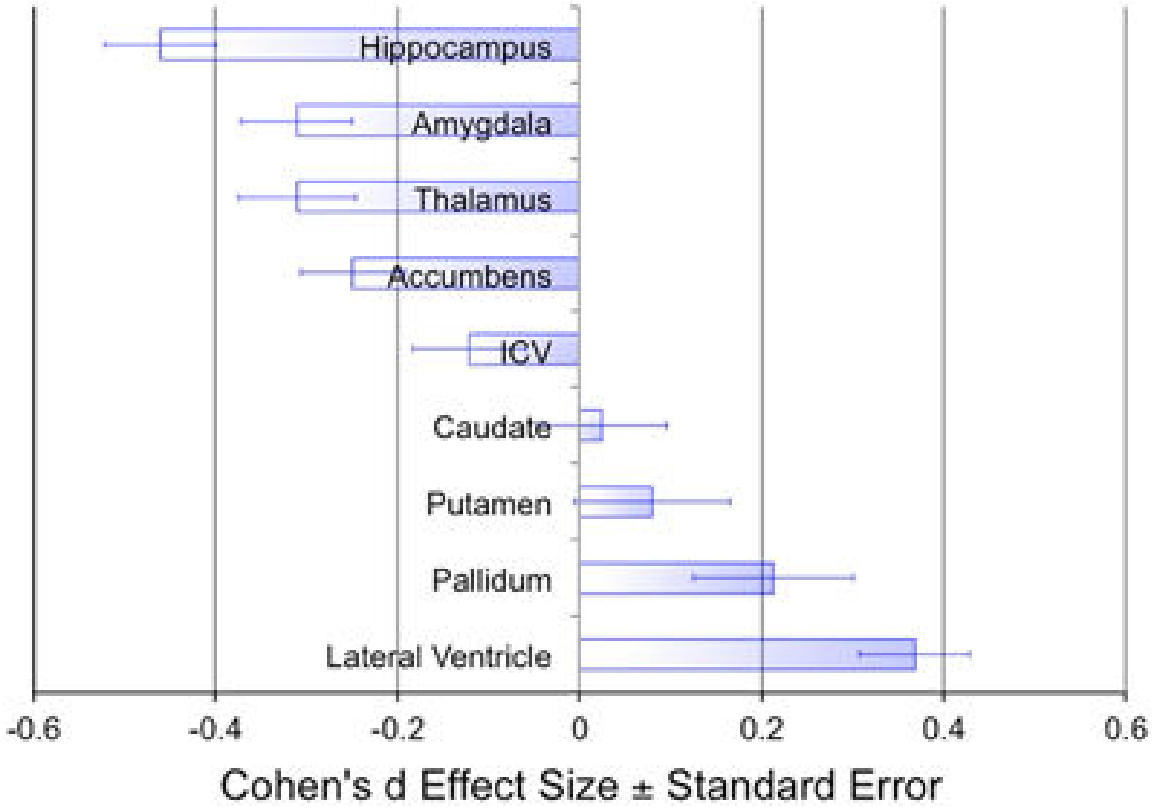
As in trajectories B or F



(Kempton et al. 2010)

Hip and amygdala smaller

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



(Erp et al. 2015)

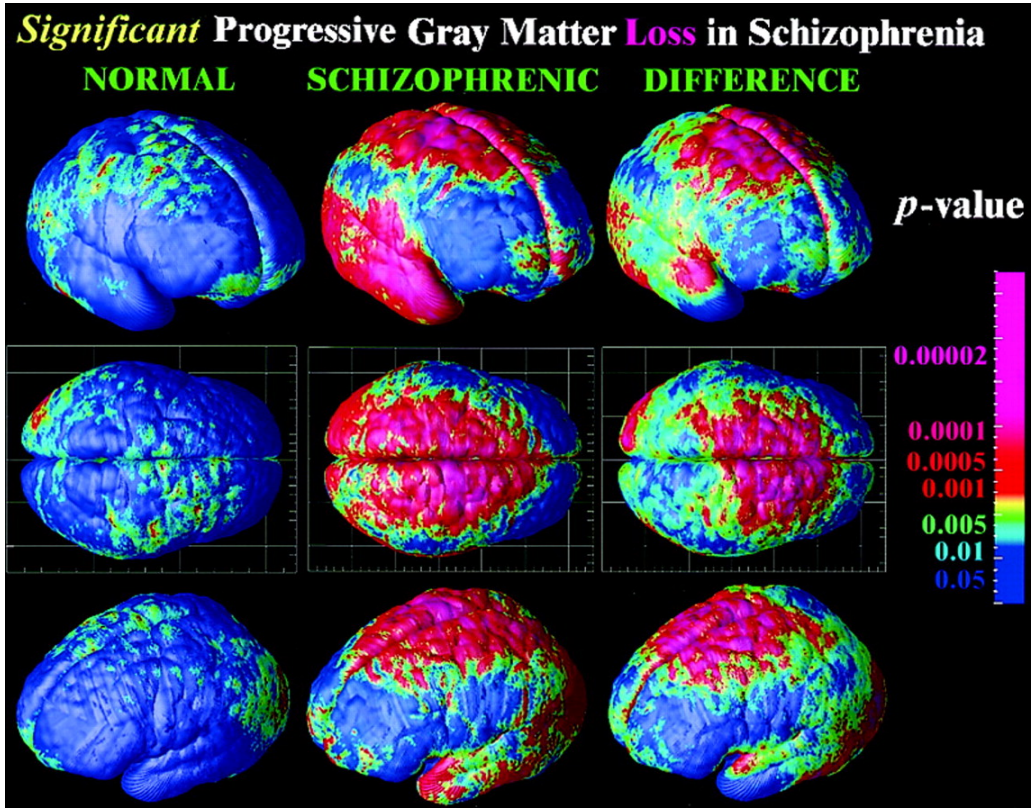
(Jiao et al. 2017)

- Dentate gyrus (DG) in hippocampus critical for spatial coding, learning and memory, and emotion processing.
- DG dysfunction implicated in schizophrenia.
- Gene linked to schizophrenia, Transmembrane protein 108 (Tmem108) enriched in DG granule neurons
- Tmem108 expression increased during postnatal period critical for DG development.

(Jiao et al. 2017)

- Tmem108-deficient neurons form fewer and smaller spines.
- Tmem108-deficient mice display schizophrenia-relevant behavioral deficits.

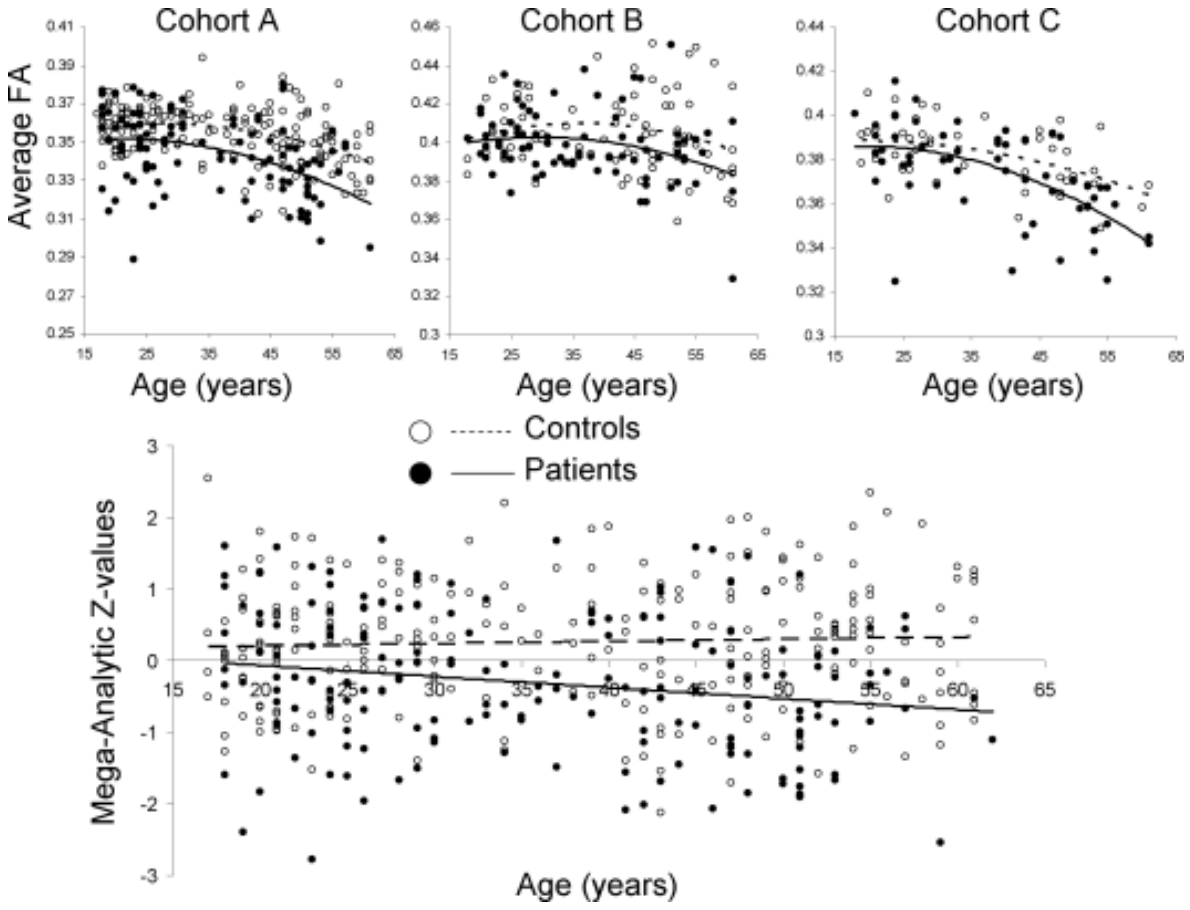
Rapid gray matter loss in adolescents?



(P. M. Thompson et al. 2001)

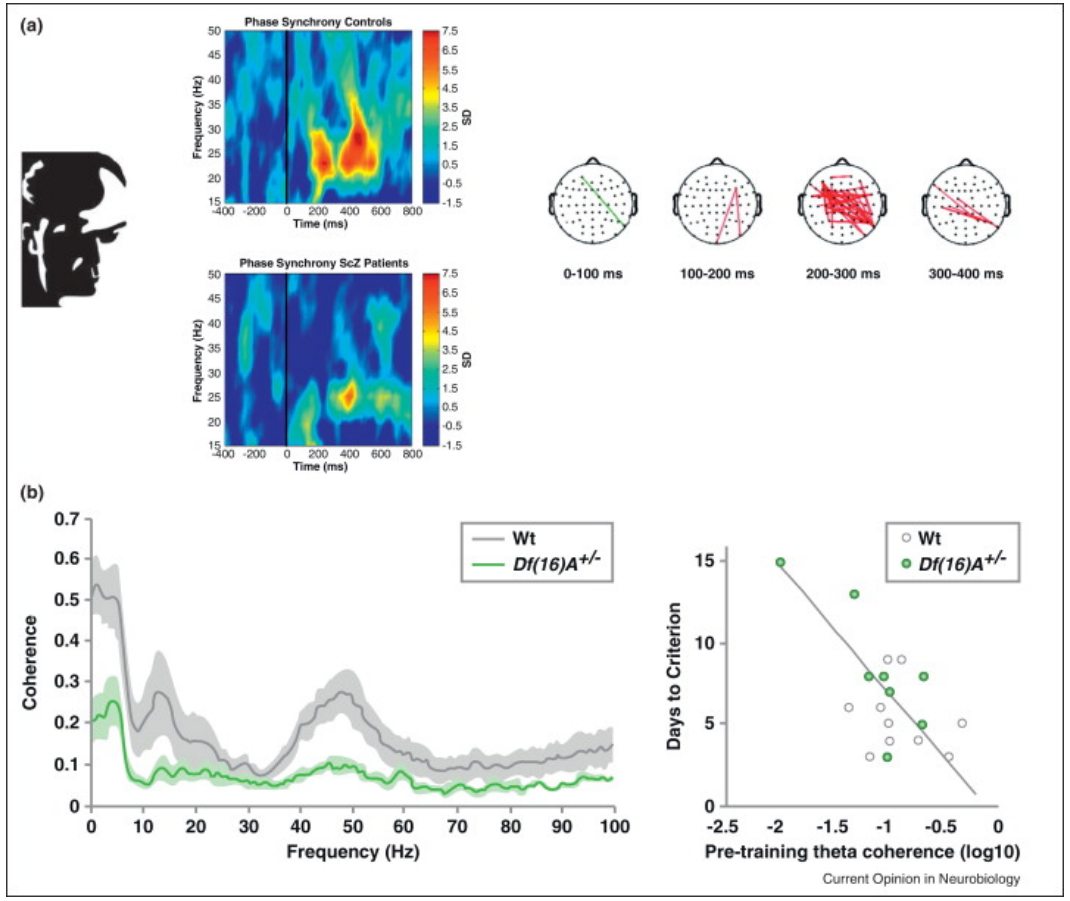
Widespread disruption in white matter connectivity

White matter loss over age



(P. Kochunov et al. 2016)

Dysconnectivity in cortical networks

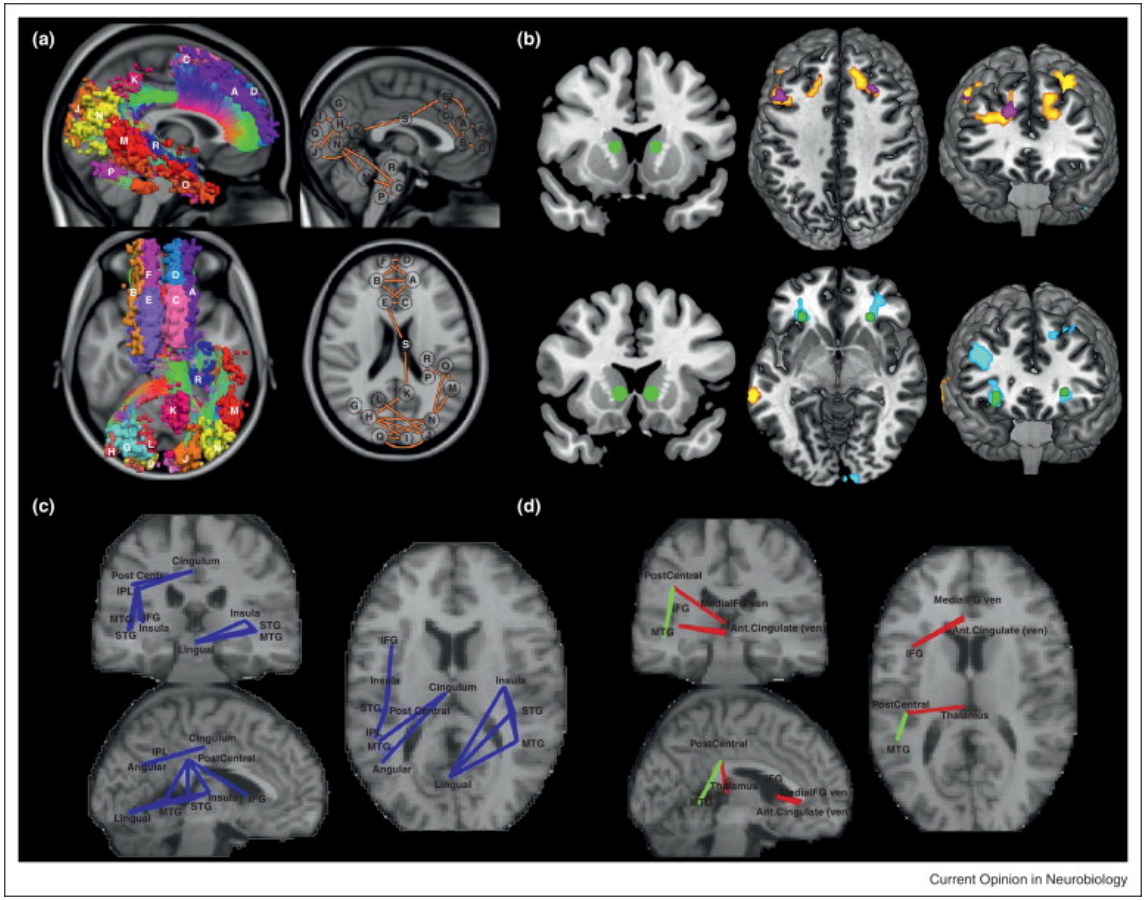


(Uhlhaas 2013)

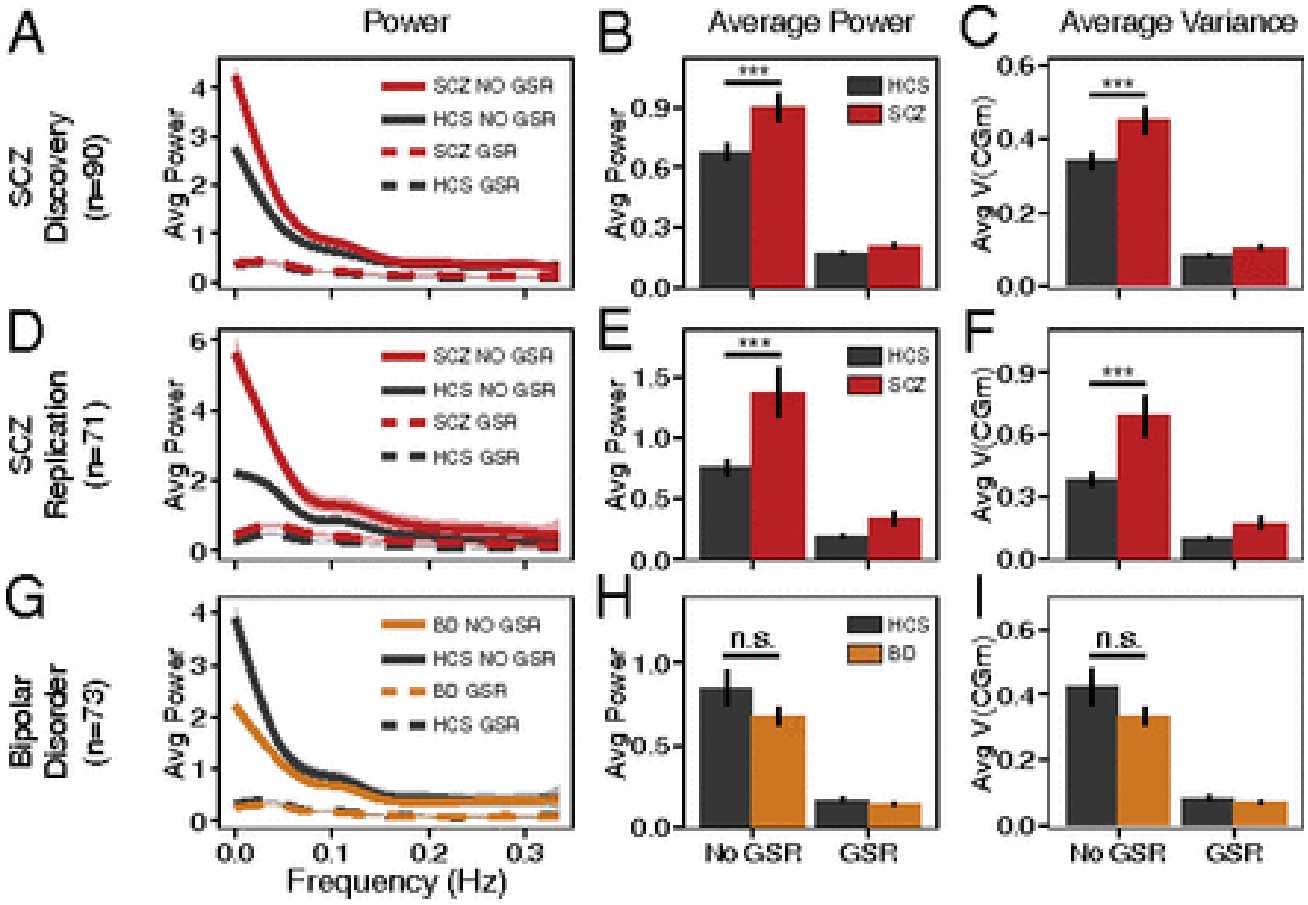
Inconsistent connectivity findings (Fornito and Bullmore 2015)

- Structural connectivity vs.
  - Synaptic, dendritic, axonal connections b/w regions
  - Usually measured via DTI or related diffusion-based MRI technique
- Functional connectivity
  - BOLD, EEG, or MEG covariance
  - Task-free 'resting' state or task-based
- Global signal variations?

(Fornito and Bullmore 2015)

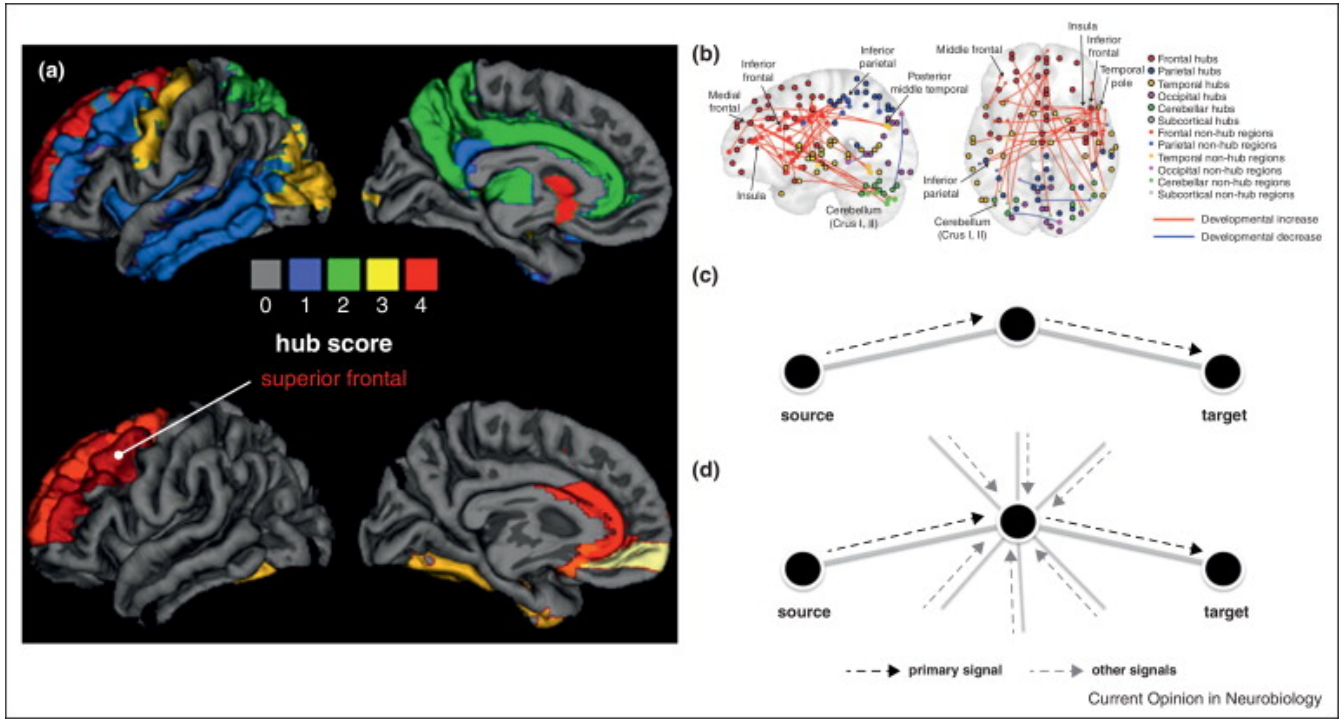


Global signal alterations



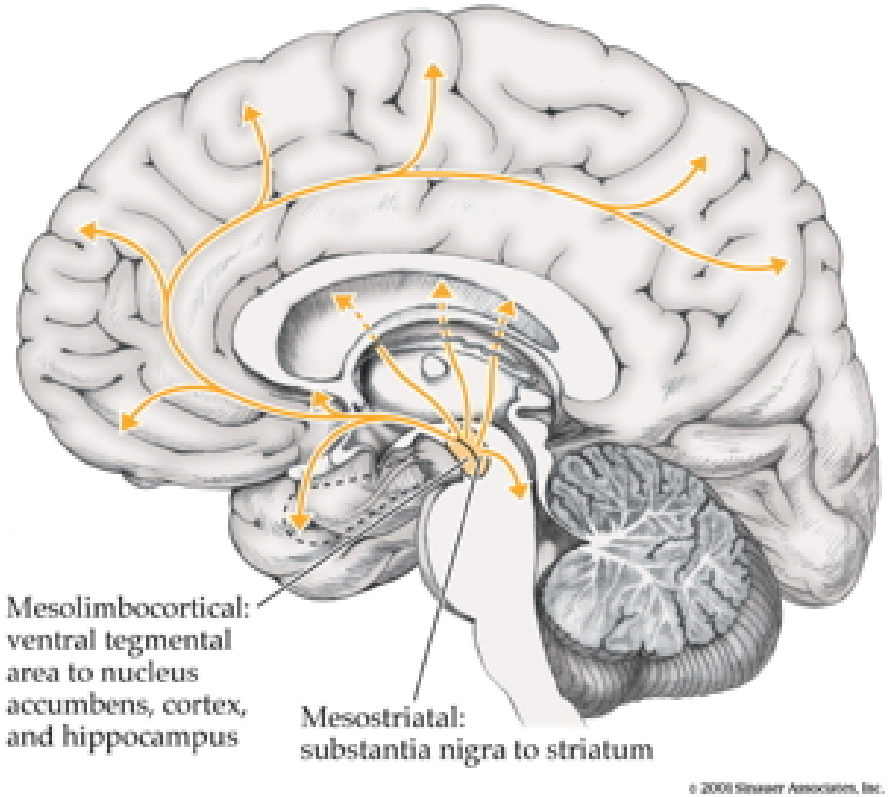
(G. J. Yang et al. 2014)

Dysconnectivity b/w 'hubs' -> higher functional connectivity



(Fornito and Bullmore 2015)

Dopamine hypothesis



Evidence for DA hypothesis

- DA (D_2 receptor) antagonists (e.g. chlorpromazine)
  - improve positive symptoms
- are DA D_2 antagonists
- DA agonists
  - amphetamine, cocaine, L-DOPA
  - mimic or exacerbate symptoms

Evidence against…

- New,
  - (e.g. Clozapine) INCREASE DA in frontal cortex, affect 5-HT
- Mixed evidence for high DA metabolite levels in CSF
- Some DA neurons may release 5-HT, cannabinoids, glutamate (Seutin 2005)

Glutamate/ketamine hypothesis

- drugs induce schizophrenia-like states
  - Phencyclidine (PCP), ketamine
  - NMDA receptor antagonists

Ketamine

- dissociative (secondary) anesthetic
- side effects include hallucinations, blurred vision, delirium, floating sensations, vivid dreams
- binds to serotonin ($5HT_{2a}$) receptor, κ opioid receptor, and σ receptor "chaperone"
- may be dopamine D_2 receptor antagonist

Glutamate/ketamine hypothesis

- Schizophrenia == of NMDA receptors?
  - NMDA receptor role in learning, plasticity
  - DG neurons in (Jiao et al. 2017) were glutamate-releasing.
- NMDAR antagonists -> neurodegeneration, excitotoxicity, & apoptosis

Schizophrenia summed up

- Wide-ranging disturbance of mood, thought, action, perception
- Broad changes in brain structure, function, chemistry, development
- ~~Dopamine hypothesis~~ giving way to glutamate hypothesis
- Genetic (polygenic = multiple genes) risk + environmental factors

Early life stress increases risk

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

(Levine et al. 2016)

- 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 or postnatally
  - Did **not** differ in rates of schizophrenia, but
  - Had higher rehospitalization rates

(Debost et al. 2015)

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

The future of psychiatric research

- The Research Domain Criteria (RDoC) Project
  - Negative valence, positive valence, cognitive systems, social processes, arousal/regulatory systems

The future of psychiatric research

- U.K. Biobank
- Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) Consortium

Next time…

- Affective disorders

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