511-2018-11-07-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 ~ 0.3-0.7%
  - Broader definitions suggest 2-3 or 3-5%
- ~1/3 chronic & severe
- Onset post-puberty, early adulthood
- Males earlier onset & greater severity
- Pervasive disturbance in mood, thinking, movement, action, memory, perception
- Increased (early) mortality

"Positive" symptoms

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

"Negative" symptoms

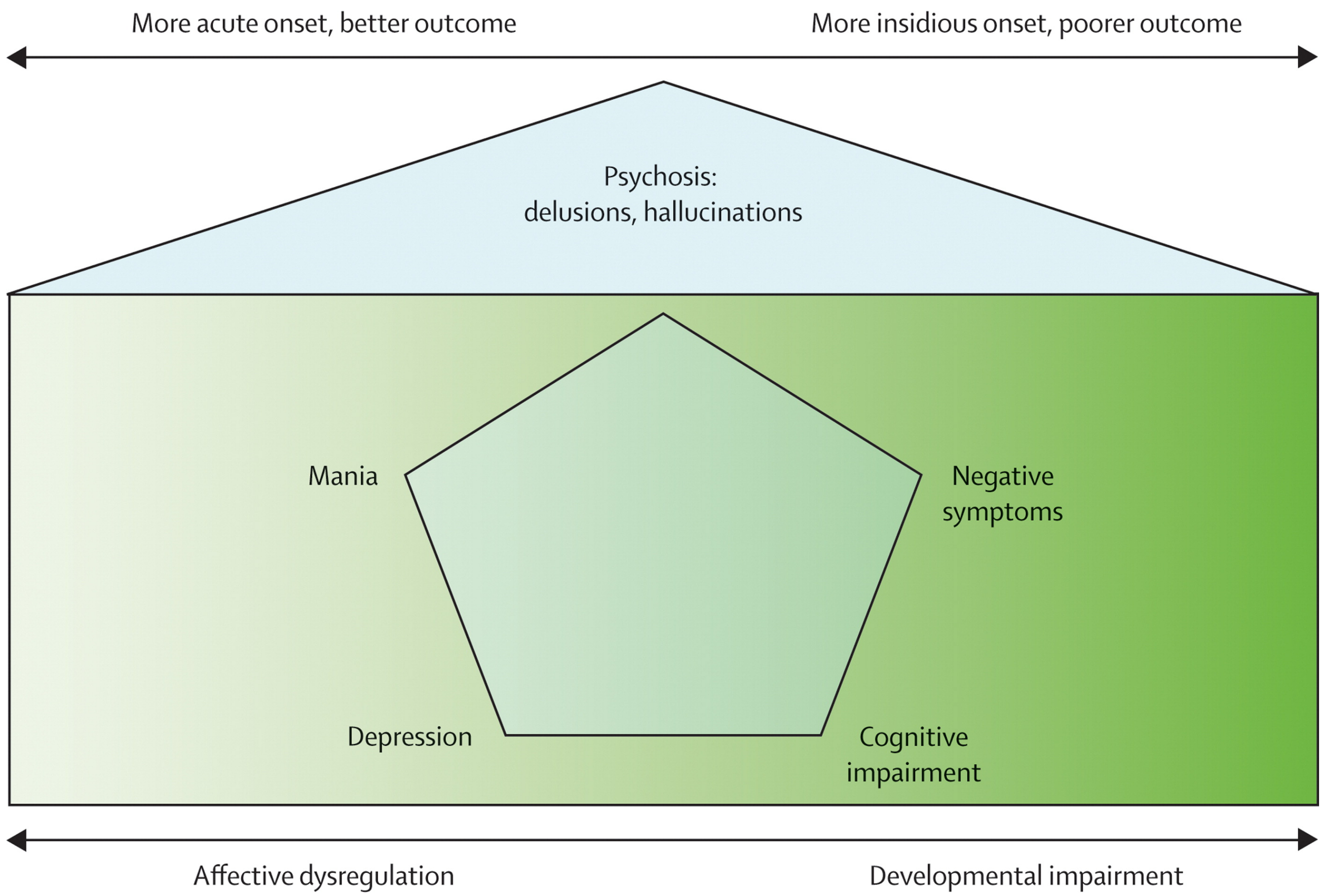
- “Reductions” in behavior
- Poverty of speech
- Flat affect
- Social withdrawal
- Impaired executive function
- Anhedonia (loss of pleasure)
- Catatonia (reduced movement)

Cognitive symptoms

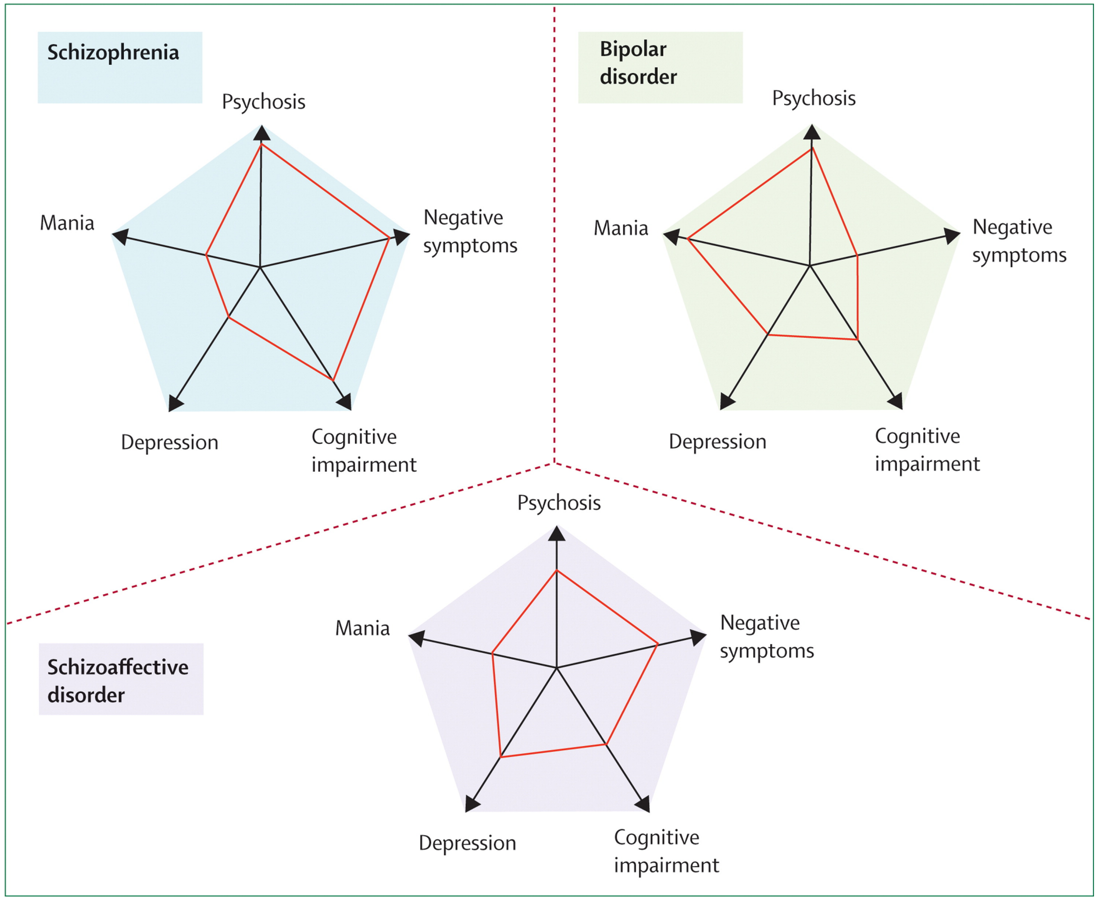
- Memory
- Attention
- Planning, decision-making
- Social cognition
- Movement

Affective dysregulation

- Depressive, manic states



(Os & Kapur, 2009)

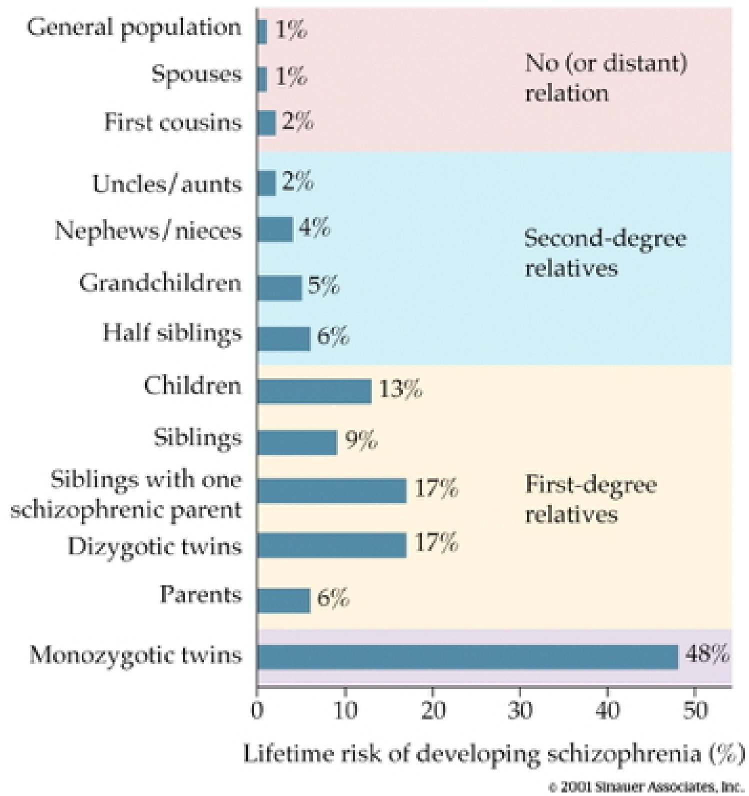


(Os & Kapur, 2009)

Biological bases

- Genetic predisposition
- Brain abnormalities
- Developmental origins

Genetic disposition



Heritability

- 80%
- vs. 60% for osteoarthritis
- 30-50% for hypertension (Os & Kapur, 2009)

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

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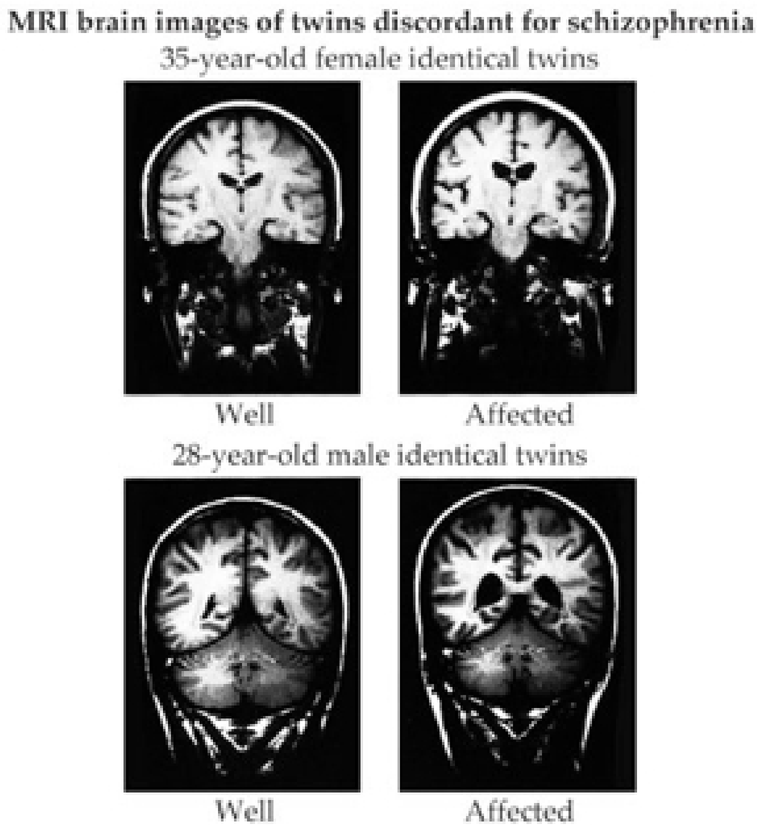
(Johnson et al., 2017)

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 glutamate receptor)

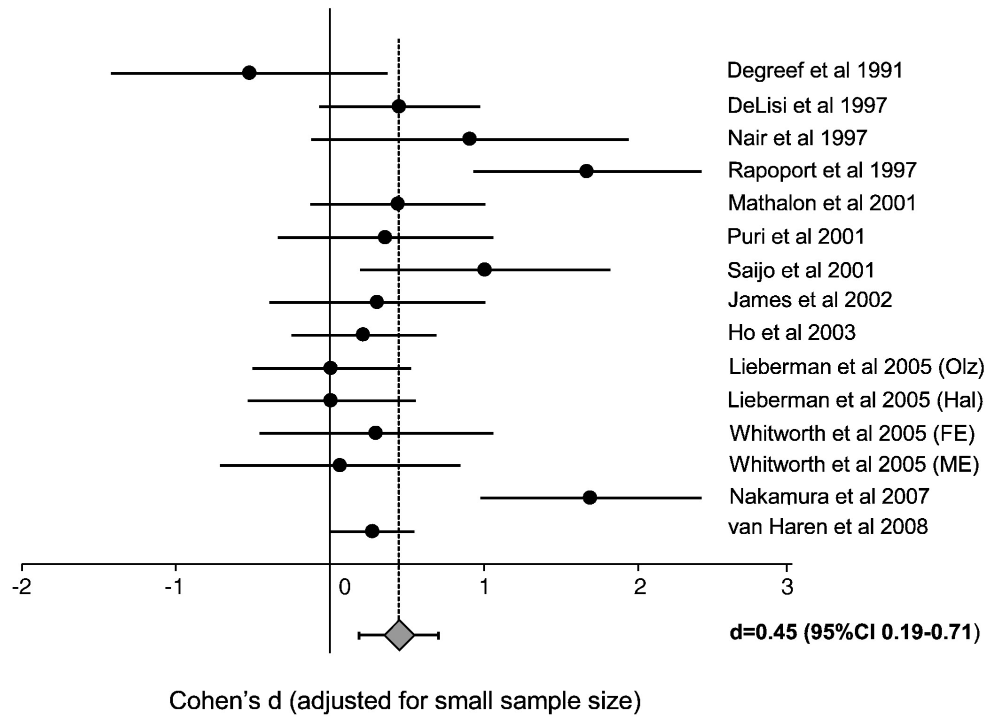
(Johnson et al., 2017)

Ventricles larger, esp in males



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

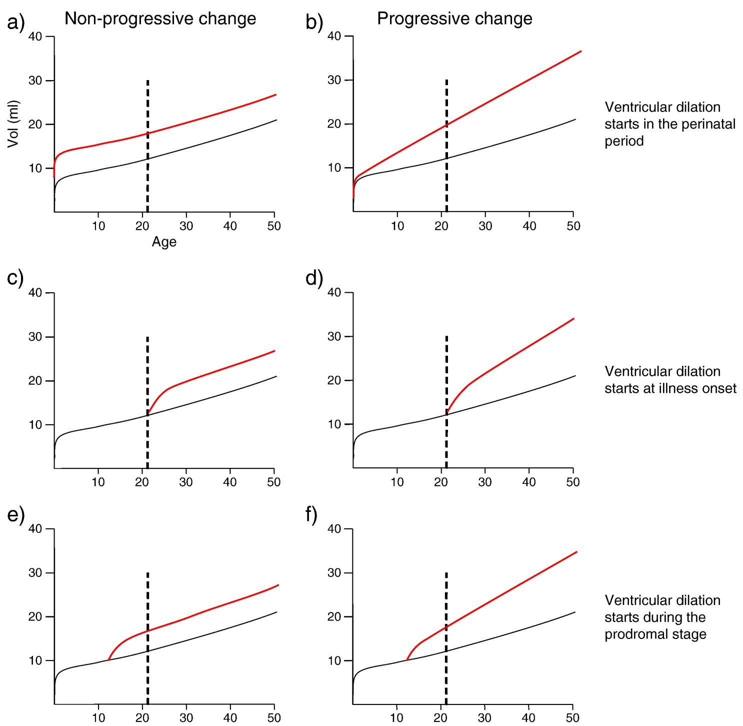
Ventricular enlargement increases across time



(Kempton, Stahl, Williams, & DeLisi, 2010)

Enlargement precedes diagnosis?

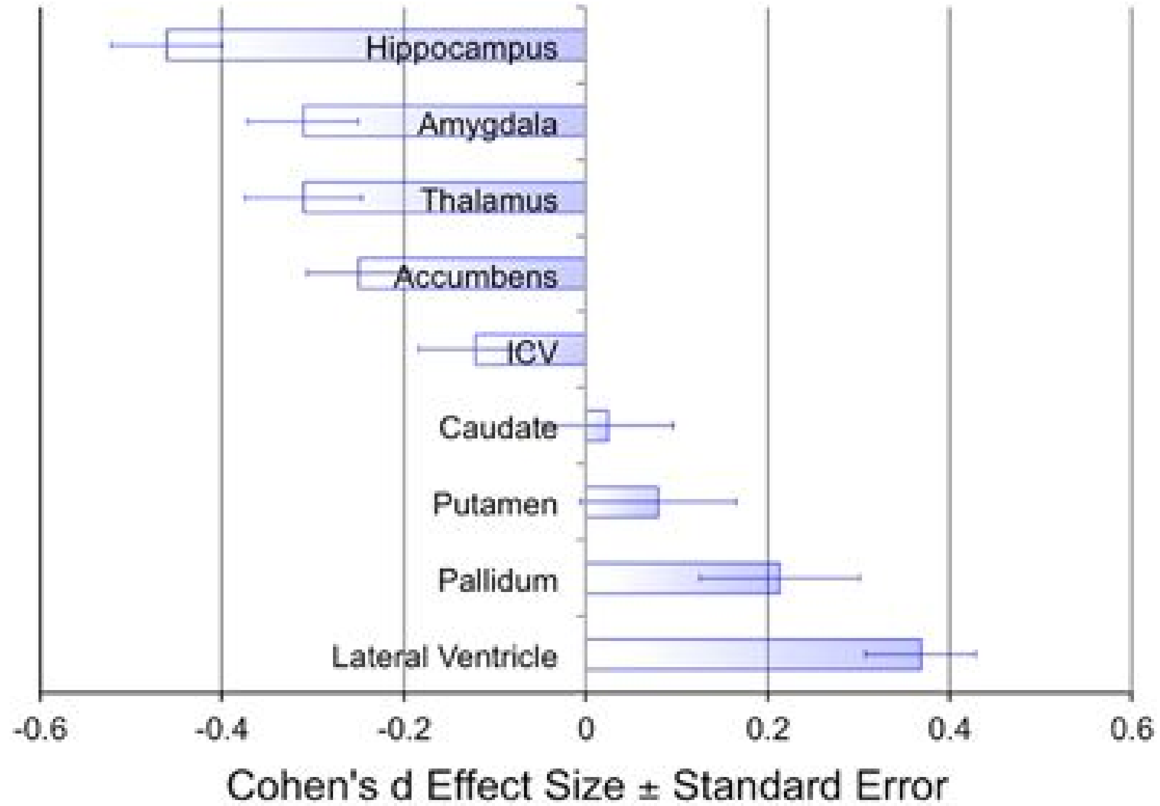
As in trajectories B or F



(Kempton et al., 2010)

Hip, amyg, thal, NA smaller

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



(Erp et al., 2015)

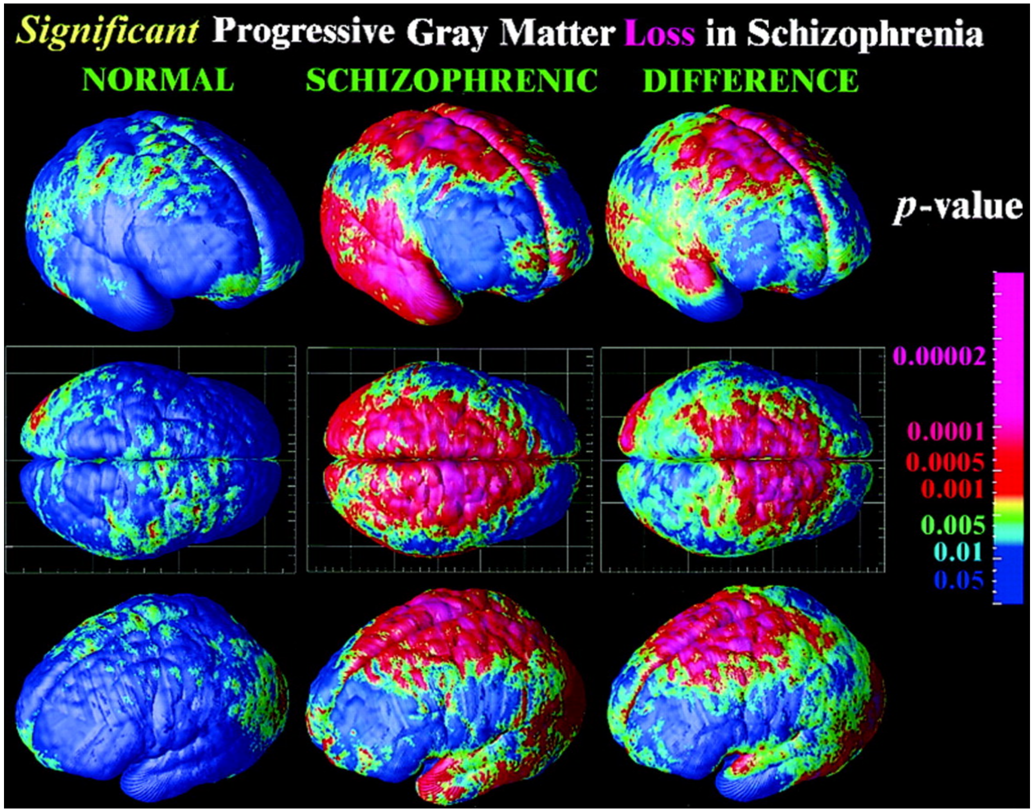
(Jiao et al., 2017)

- Dentate gyrus (DG) in hippocampus
  - spatial coding, learning & memory, 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)

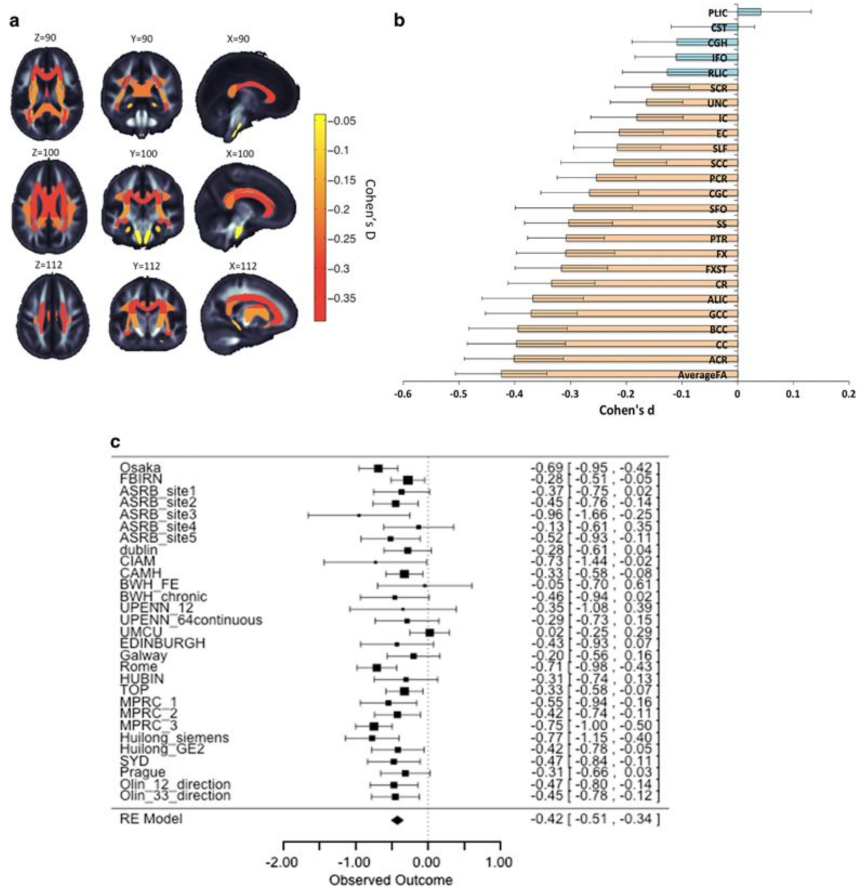
- Tmem108-deficient neurons form fewer and smaller spines.
- Tmem108-deficient mice display schizophrenia-relevant behavioral deficits.

Rapid gray matter loss in adolescents?



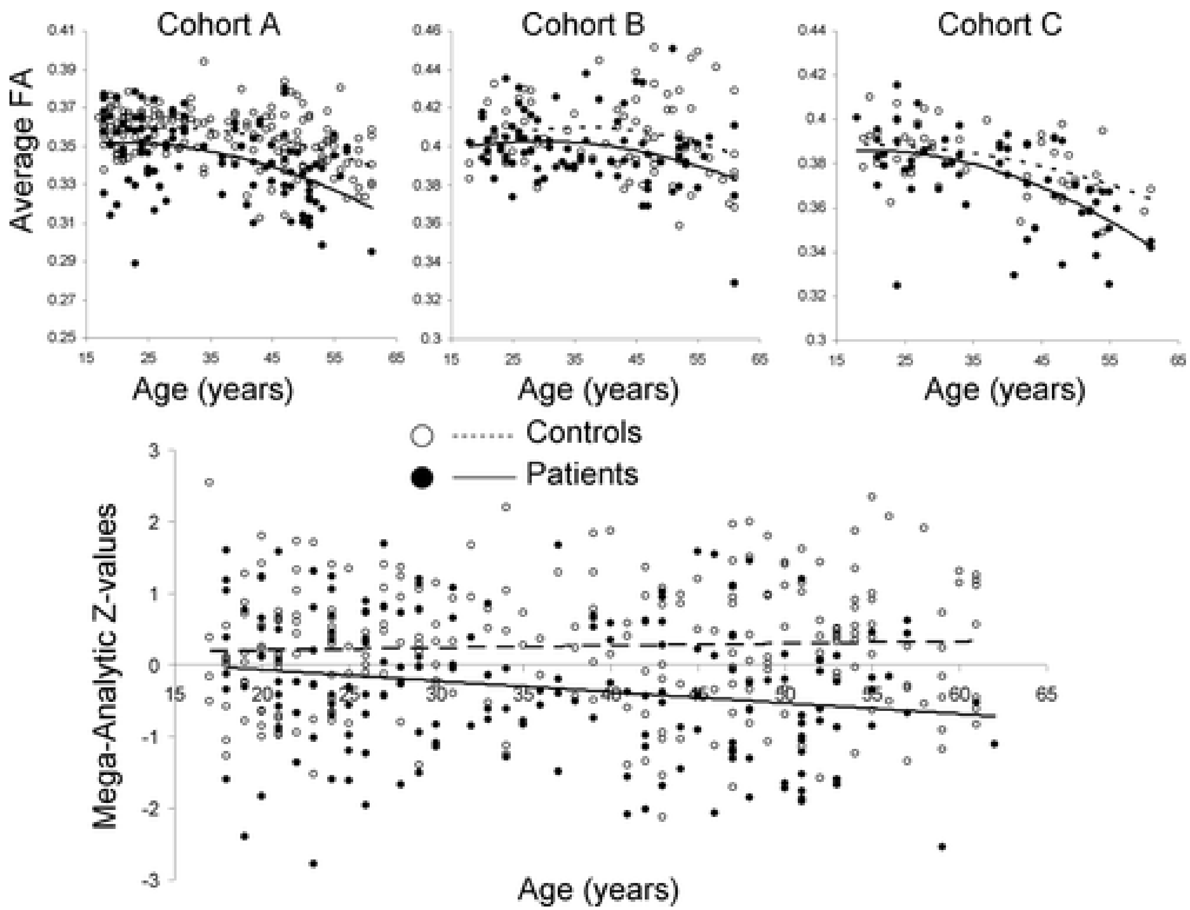
(P. M. Thompson et al., 2001)

Widespread white matter disruption



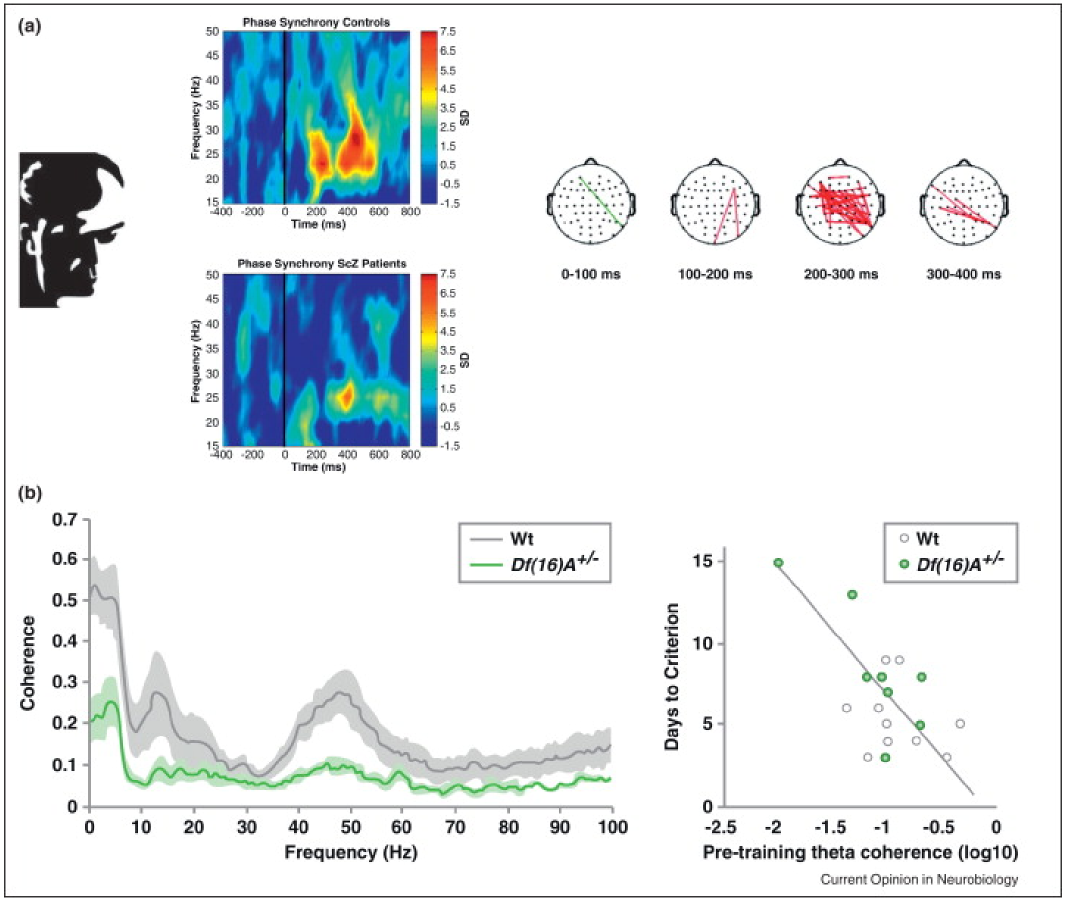
(Kelly et al., 2017)

White matter loss over age



(P. Kochunov et al., 2016)

Dysconnectivity in cortical networks

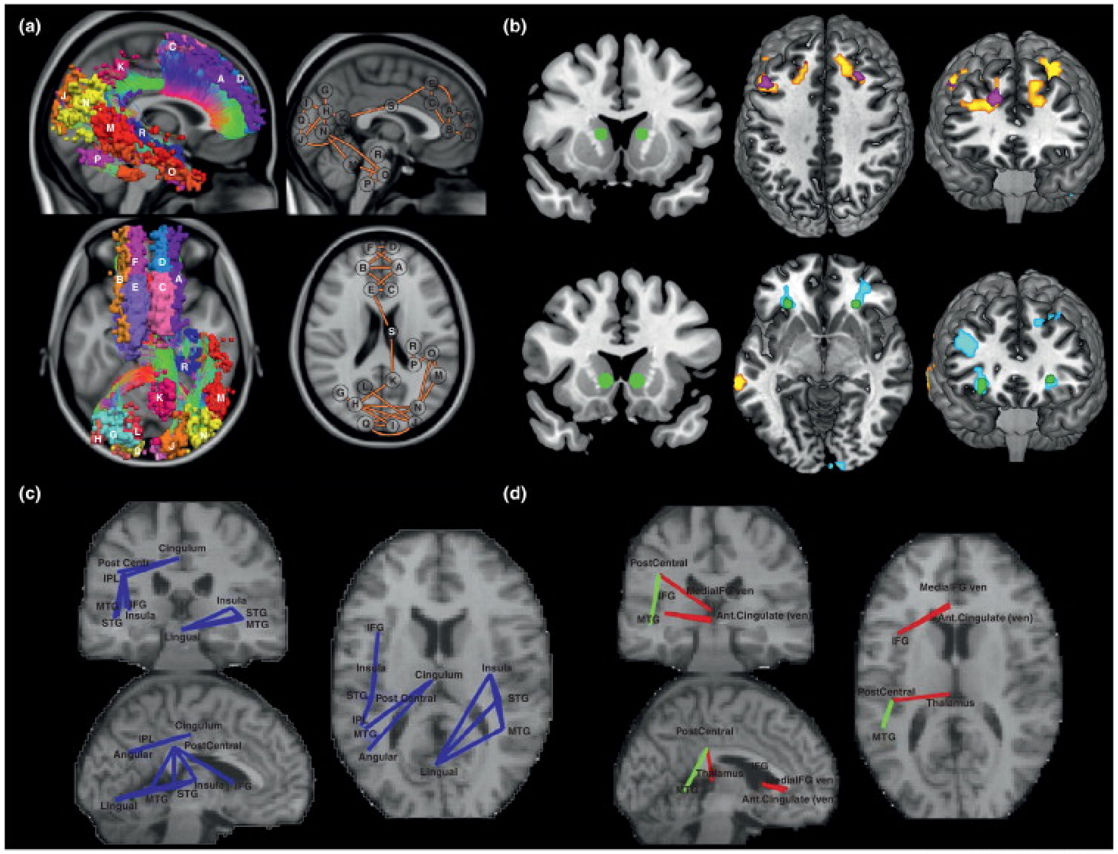


(Uhlhaas, 2013)

Inconsistent connectivity findings (Fornito & Bullmore, 2015)

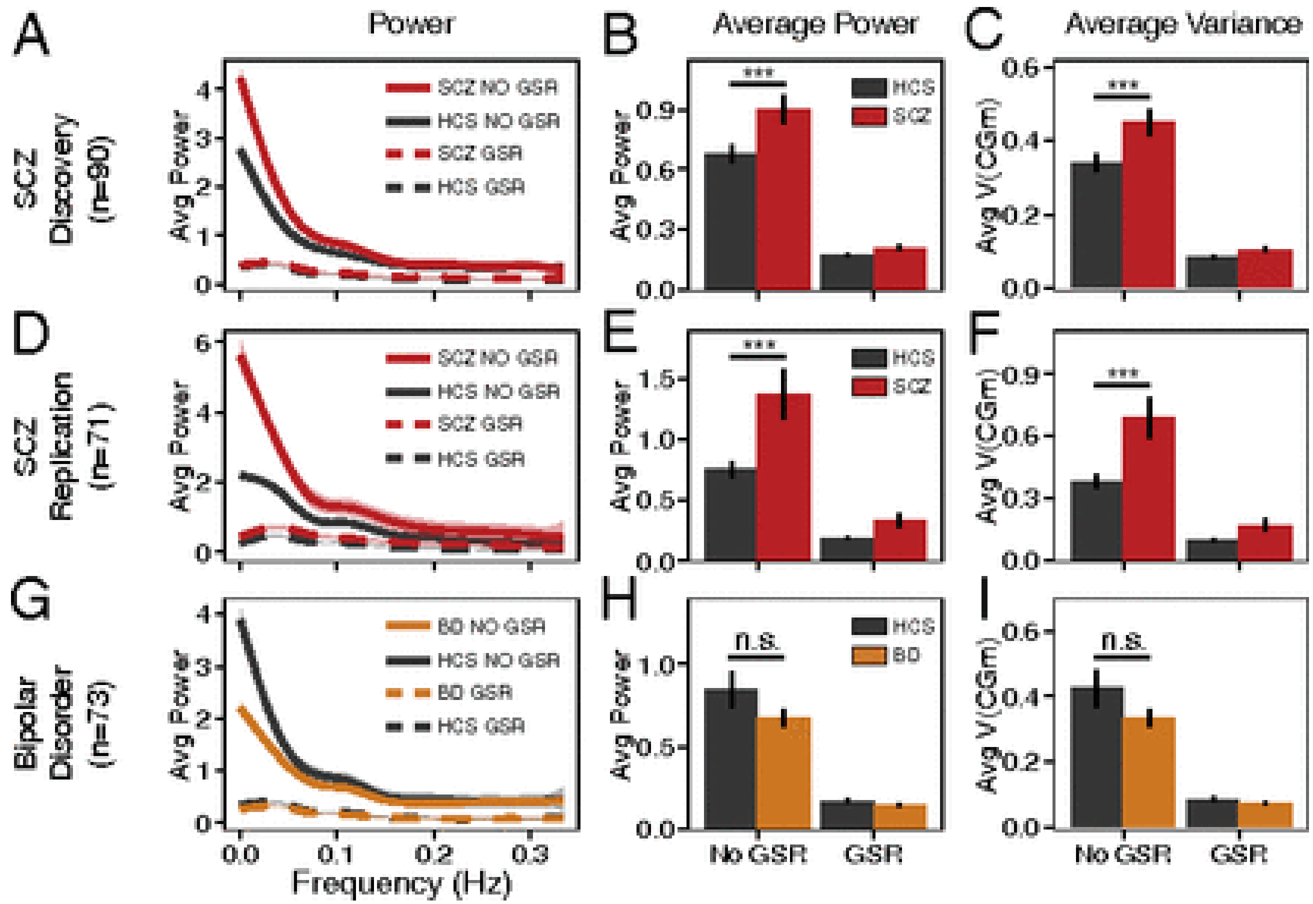
- Structural connectivity vs.
  - Synaptic, dendritic, axonal connections b/w regions
  - Usually measured via DTI or related diffusion-based MRI technique
- Functional connectivity
  - BOLD, EEG, or MEG covariance
  - Task-free 'resting' state or task-based
- Global signal variations?

(Fornito & Bullmore, 2015)



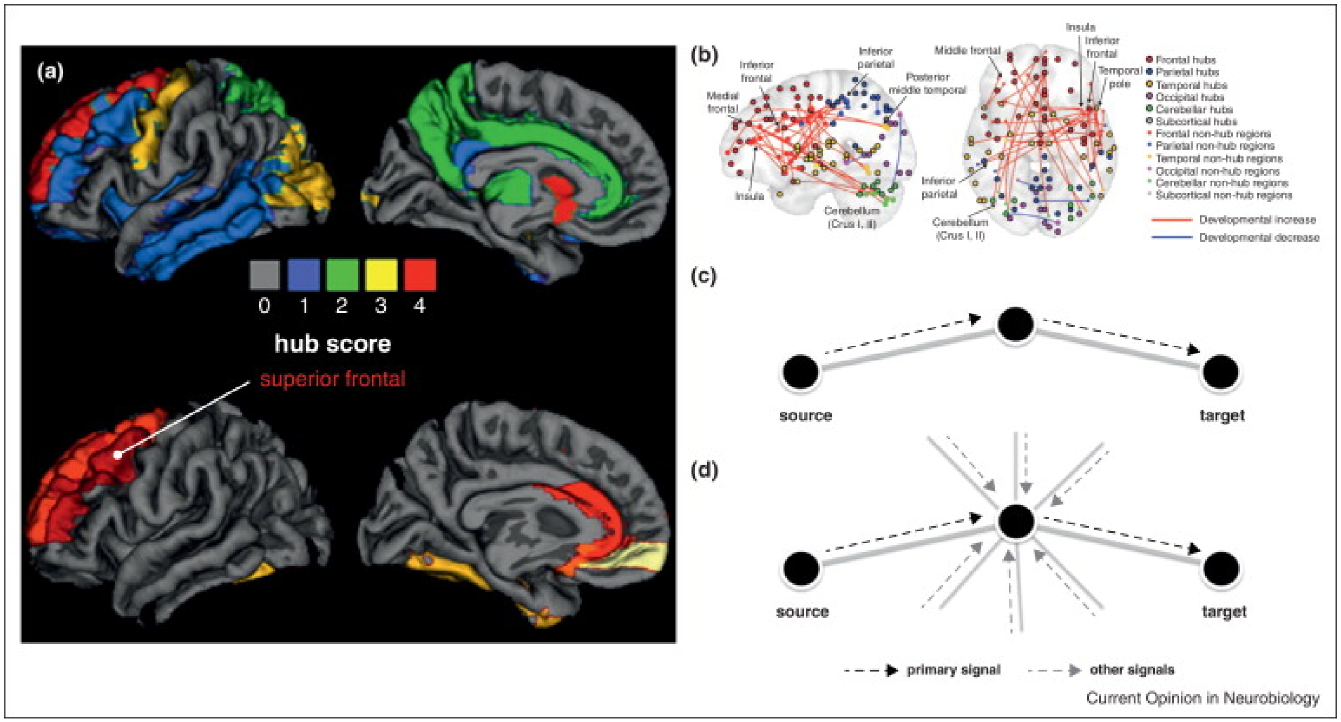
Current Opinion in Neurobiology

Global signal alterations



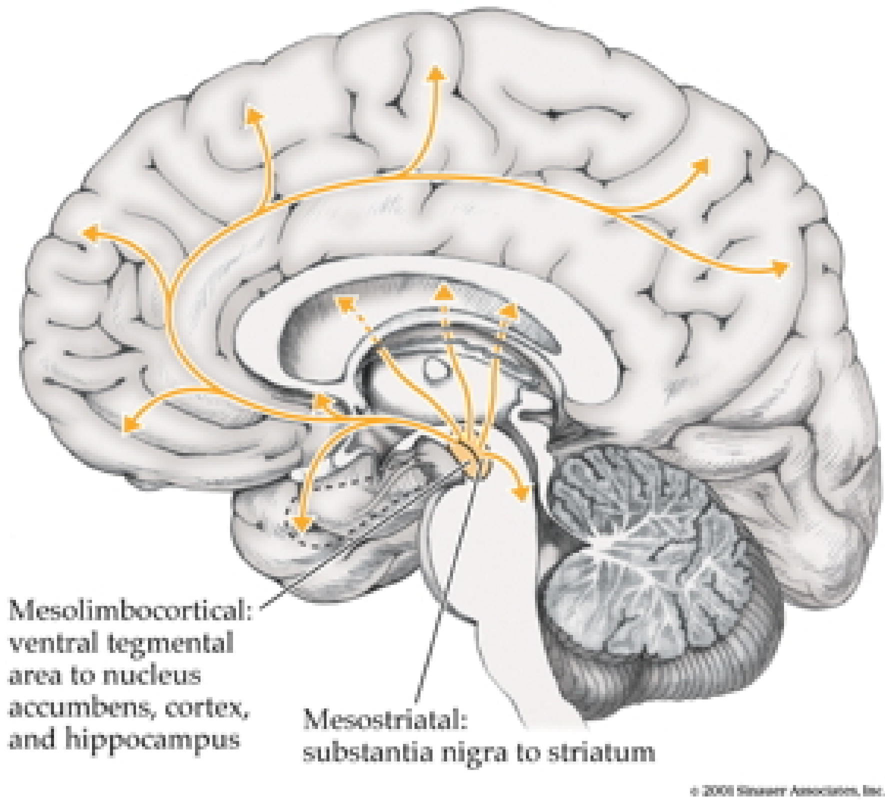
(G. J. Yang et al., 2014)

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



(Fornito & 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

- 2x greater odds for children in urban environments
- Higher risk among migrant populations (Cantor-Graae & Selten, 2005)
- Exposure to infection , other birth complications
- Exposure to cannibis
- Paternal age > 40

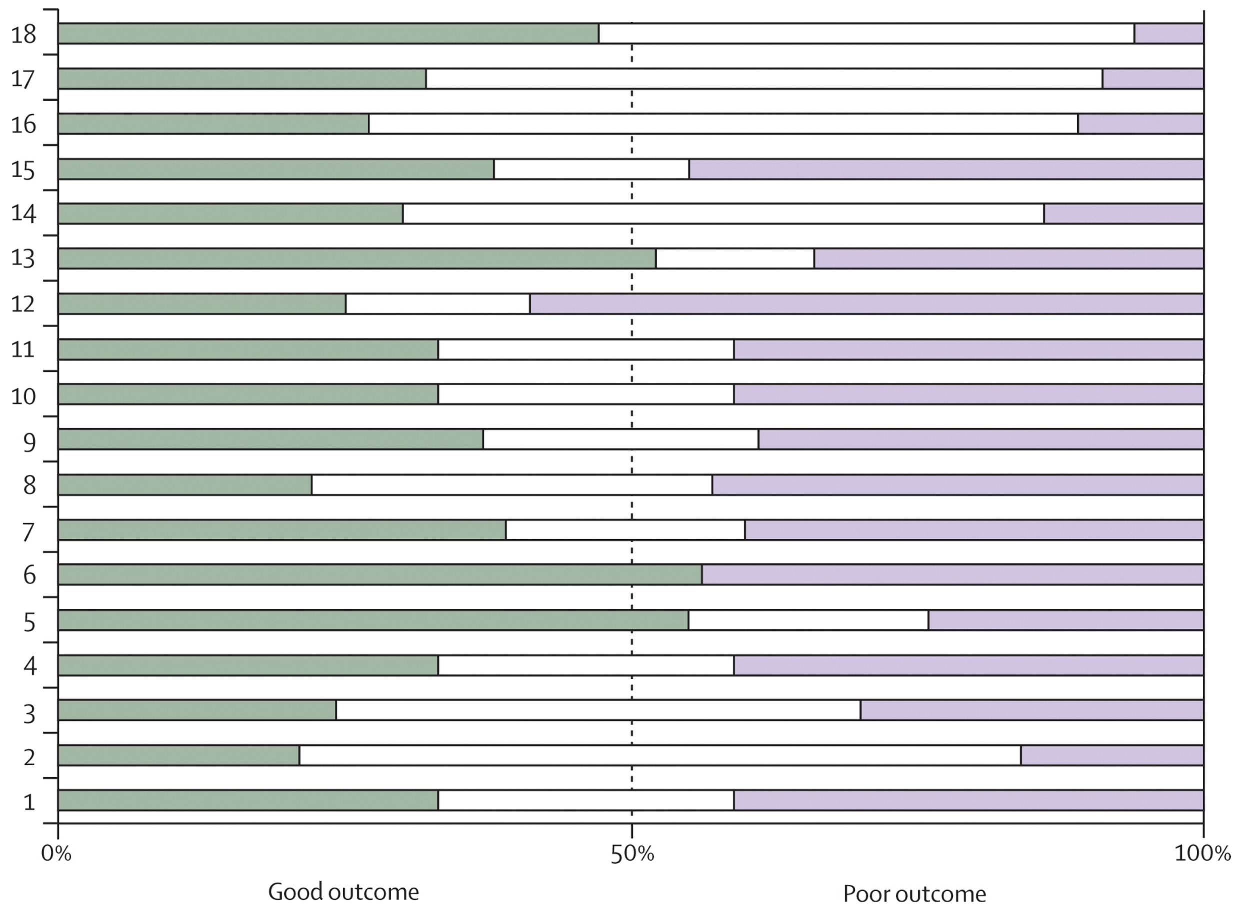
(Levine, Levav, Pugachova, Yoffe, & Becher, 2016)

- 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: Outcomes following hospitalization



(Os & Kapur, 2009)

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

References

Cantor-Graae, E., & Selten, J.-P. (2005). Schizophrenia and migration: A meta-analysis and review. , (1), 12–24. https://doi.org/10.1176/appi.ajp.162.1.12

Debost, J.-C., Petersen, L., Grove, J., Hedemand, A., Khashan, A., Henriksen, T., … Mortensen, P. B. (2015). Investigating interactions between early life stress and two single nucleotide polymorphisms in HSD11B2 on the risk of schizophrenia. , , 18–27. https://doi.org/10.1016/j.psyneuen.2015.05.013

Erp, T. G. M. van, Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., … Turner, J. A. (2015). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. . https://doi.org/10.1038/mp.2015.63

Fornito, A., & Bullmore, E. T. (2015). Reconciling abnormalities of brain network structure and function in schizophrenia. , , 44–50. https://doi.org/10.1016/j.conb.2014.08.006

Jiao, H.-F., Sun, X.-D., Bates, R., Xiong, L., Zhang, L., Liu, F., … Mei, L. (2017). Transmembrane protein 108 is required for glutamatergic transmission in dentate gyrus. , (5), 1177–1182. https://doi.org/10.1073/pnas.1618213114

Johnson, E. C., Border, R., Melroy-Greif, W. E., Leeuw, C. A. de, Ehringer, M. A., & Keller, M. C. (2017). No evidence that schizophrenia candidate genes are more associated with schizophrenia than noncandidate genes. , (10), 702–708. https://doi.org/10.1016/j.biopsych.2017.06.033

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., … Donohoe, G. (2017). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA schizophrenia DTI working group. . https://doi.org/10.1038/mp.2017.170