260-2017-10-20-schizophrenia

Rick Gilmore

2017-10-19 11:19:30

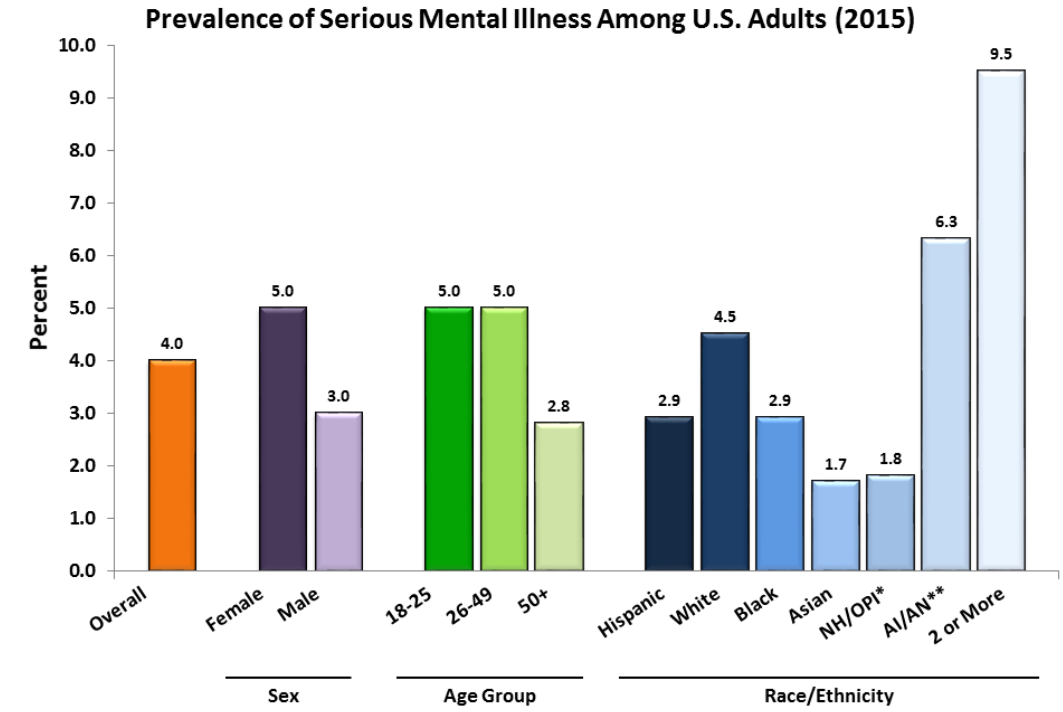
Prelude

the kinks- you really got me

Today's Topics

- Prevalence of mental illness
- Schizophrenia

Mental illness lifetime prevalence



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

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

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
  - Introduced “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)

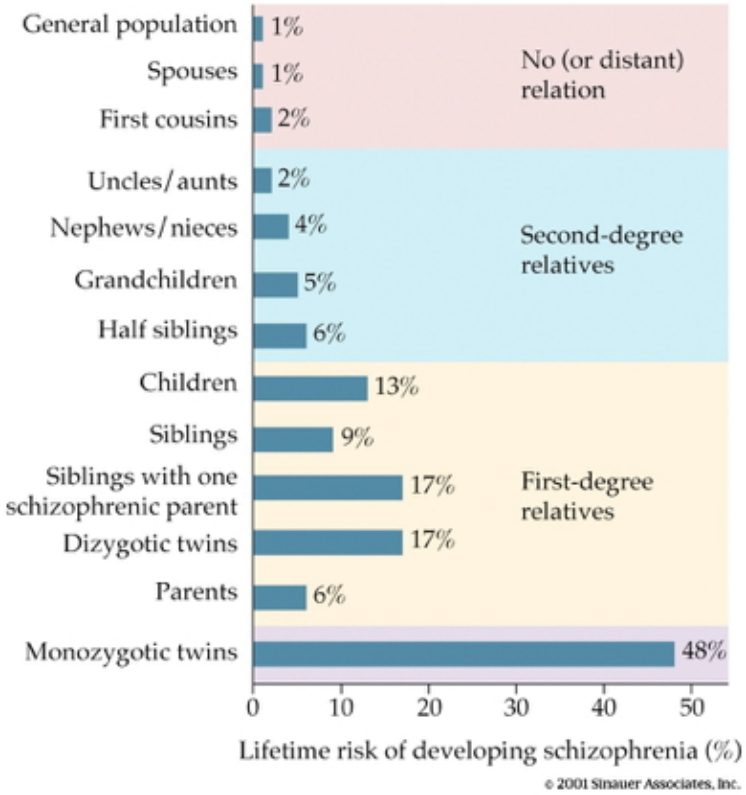
Cognitive symptoms

- 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 [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

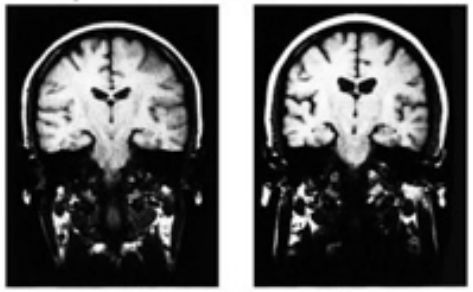
- *NOTCH4*, *TNF*:
    - Part of major histocompatibility complex (MHC), cell membrane specializations involved in the immune system
- *DRD2* (dopamine D2 receptor), *KCNN3* (Ca+ activated K+ channel), *GRM3* (metabotropic glutatmate receptor)

(Johnson et al. 2017)

Ventricles larger, esp in males

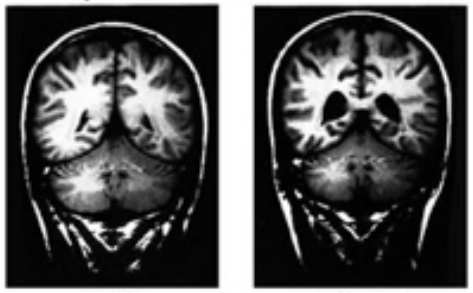
MRI brain images of twins discordant for schizophrenia

35-year-old female identical twins



Well Affected

28-year-old male identical twins

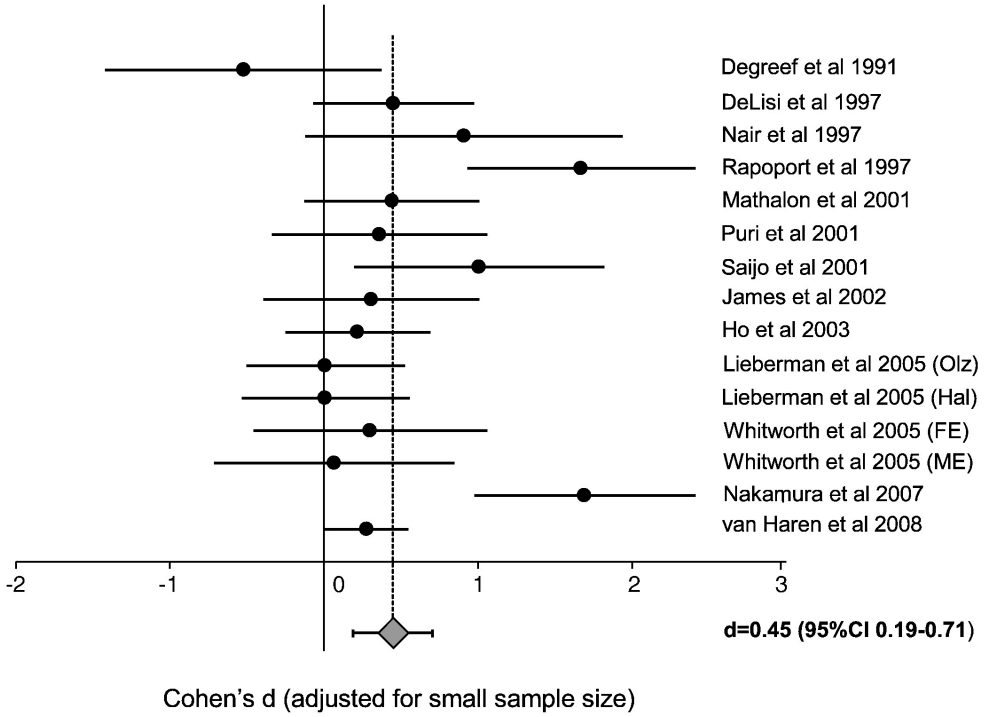


Well Affected

BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 15.4 © 2004 Sinauer Associates, Inc.

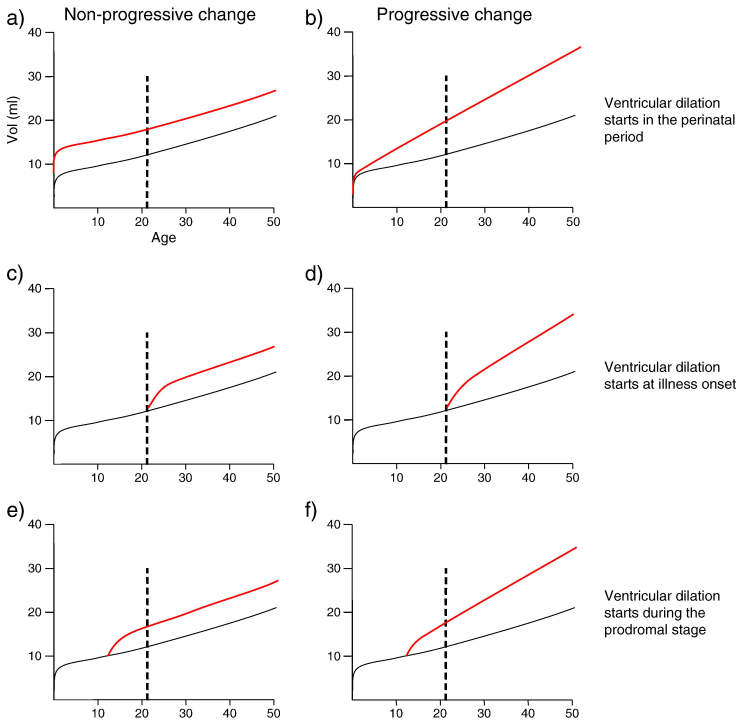
Cause or effect?

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



Enlargement precedes diagnosis?

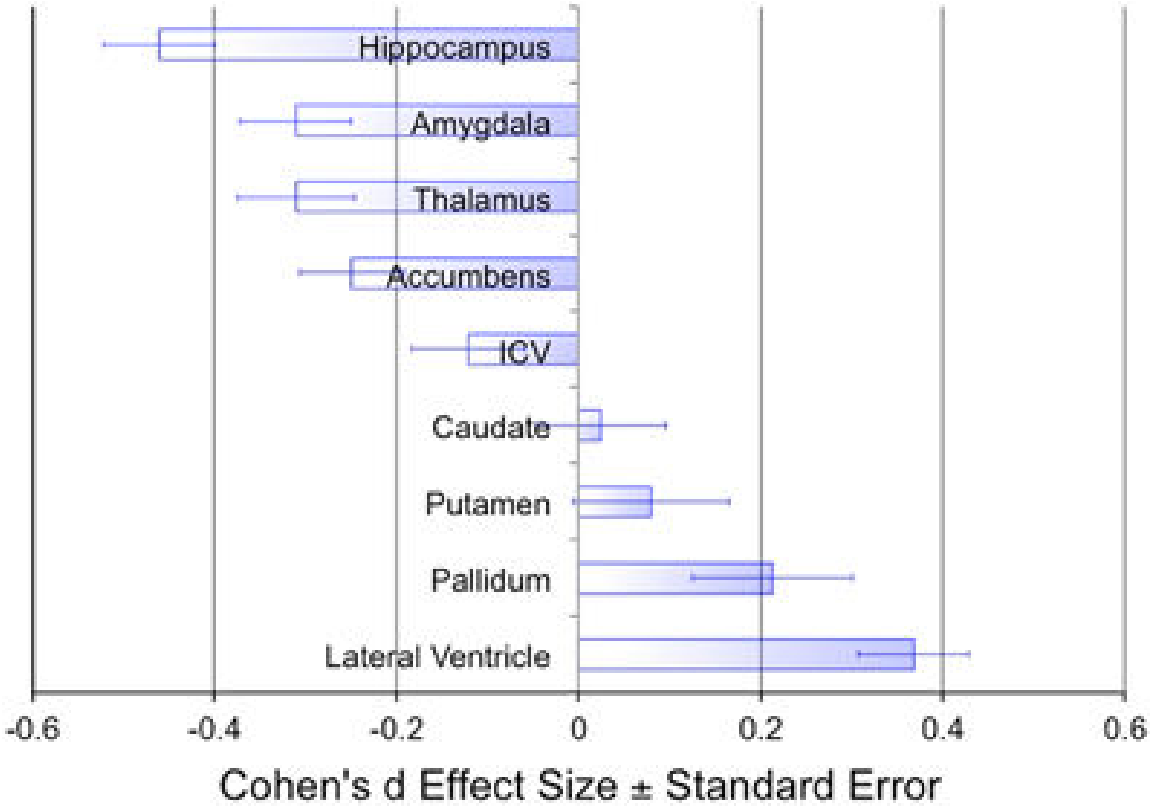
As in trajectories B or F



(Kempton et al. 2010)

Hip and amygdala smaller

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



(Erp et al. 2015)

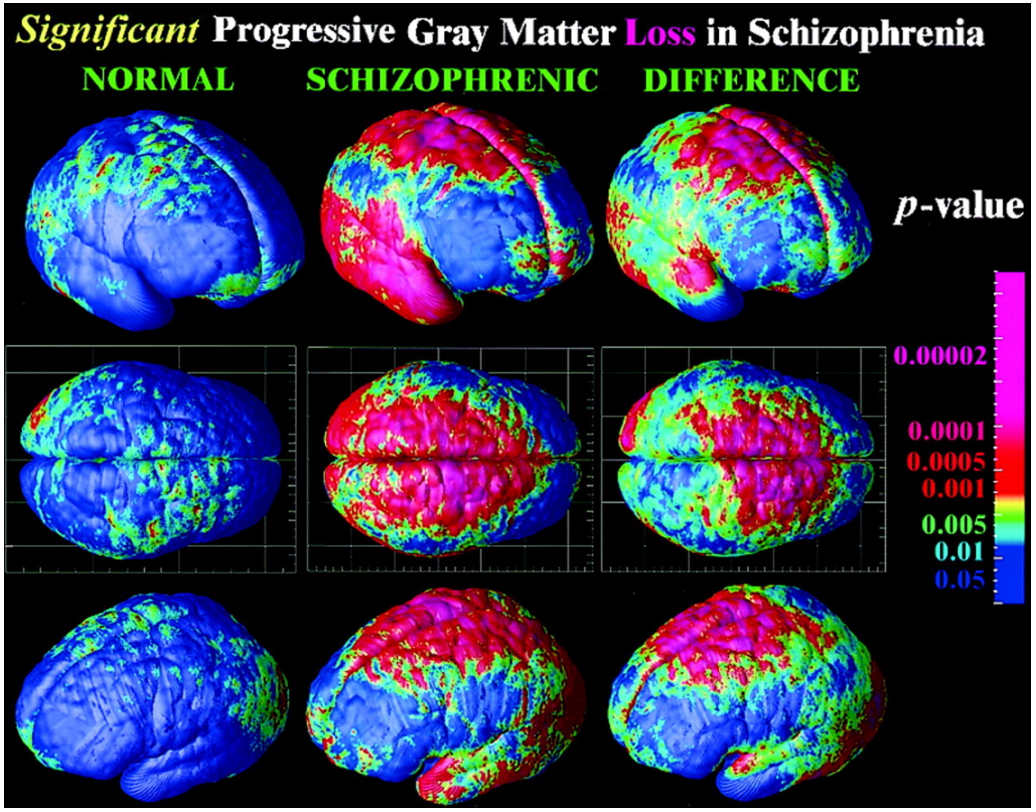
(Jiao et al. 2017)

- 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)

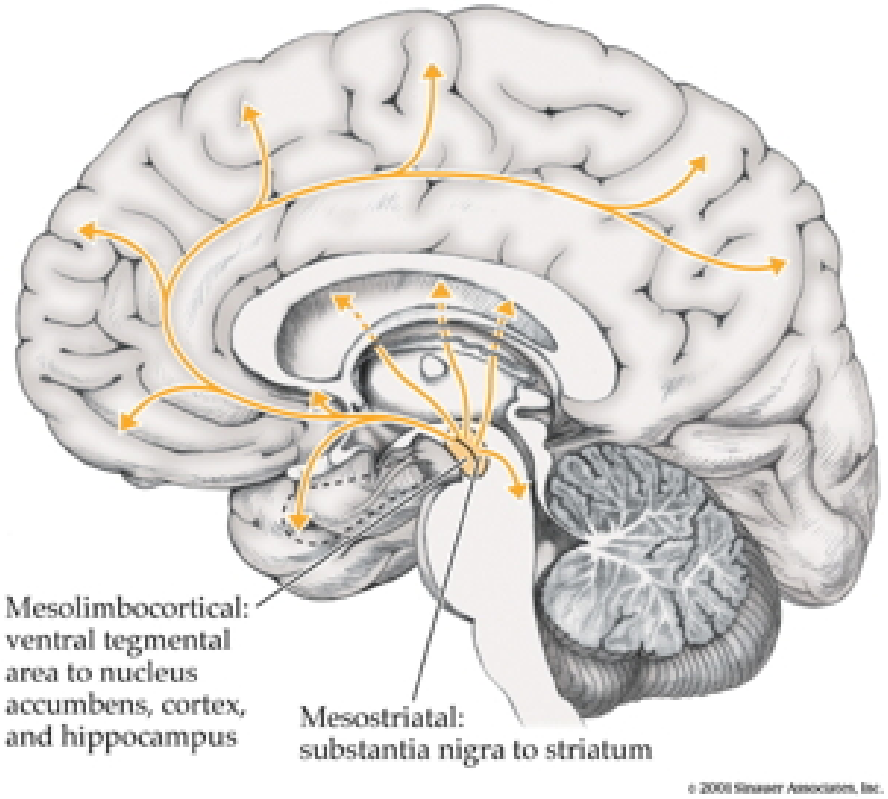
- Tmem108-deficient neurons form fewer and smaller spines.
- Tmem108-deficient mice display schizophrenia-relevant behavioral deficits.

Rapid gray matter loss in adolescents?



(P. M. Thompson et al. 2001)

Dopamine hypothesis



Evidence for DA hypothesis

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

Tardive Dyskinesia a side effect of DA antagonists

https://2e.mindsmachine.com/ch/12/av/mm2e_1203_tardiv

Evidence against…

- 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 induce schizophrenia-like states
  - Phencyclidine (PCP), ketamine
  - NMDA receptor antagonists
- Schizophrenia == *underactivation* of NMDA receptors?
  - NMDA receptor role in learning, plasticity
  - DG neurons in (Jiao et al. 2017) were glutamate-releasing.

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 *in utero*, 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 *in utero* 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
  - *in utero* did **not** increase risk of schizophrenia, but
  - during 0-2 years increased risk
- Increased risk associated with an allele of a cortisol-related gene

Next time…

- Emotion, happiness, and reward

References

Debost, Jean-Christophe, Liselotte Petersen, Jakob Grove, Anne Hedemand, Ali Khashan, Tine Henriksen, Ole Mors, et al. 2015. “Investigating Interactions Between Early Life Stress and Two Single Nucleotide Polymorphisms in HSD11B2 on the Risk of Schizophrenia.” *Psychoneuroendocrinology* 60 (October): 18–27. doi:10.1016/j.psyneuen.2015.05.013.

Erp, T G M van, D P Hibar, J M Rasmussen, D C Glahn, G D Pearlson, O A Andreassen, I Agartz, et al. 2015. “Subcortical Brain Volume Abnormalities in 2028 Individuals with Schizophrenia and 2540 Healthy Controls via the ENIGMA Consortium.” *Mol. Psychiatry*, June. doi:10.1038/mp.2015.63.

Jiao, Hui-Feng, Xiang-Dong Sun, Ryan Bates, Lei Xiong, Lei Zhang, Fang Liu, Lei Li, et al. 2017. “Transmembrane Protein 108 Is Required for Glutamatergic Transmission in Dentate Gyrus.” *Proceedings of the National Academy of Sciences* 114 (5): 1177–82. doi:10.1073/pnas.1618213114.

Johnson, Emma C, Richard Border, Whitney E Melroy-Greif, Christiaan A de Leeuw, Marissa A Ehringer, and Matthew C Keller. 2017. “No Evidence That Schizophrenia Candidate Genes Are More Associated with Schizophrenia Than Noncandidate Genes.” *Biol. Psychiatry* 82 (10): 702–8. doi:10.1016/j.biopsych.2017.06.033.

Kempton, Matthew J, Daniel Stahl, Steven C R Williams, and Lynn E DeLisi. 2010. “Progressive Lateral Ventricular Enlargement in Schizophrenia: A Meta-Analysis of Longitudinal MRI Studies.” *Schizophr. Res.* 120 (1-3): 54–62. doi:10.1016/j.schres.2010.03.036.

Levine, Stephen Z., Itzhak Levav, Inna Pugachova, Rinat Yoffe, and Yifat Becher. 2016. “Transgenerational Effects of Genocide Exposure on the Risk and Course of Schizophrenia: A Population-Based Study.” *Schizophrenia Research* 176 (2): 540–45. doi:10.1016/j.schres.2016.06.019.

Thompson, Paul M., Christine Vidal, Jay N. Giedd, Peter Gochman, Jonathan Blumenthal, Robert Nicolson, Arthur W. Toga, and Judith L. Rapoport. 2001. “Mapping Adolescent Brain Change Reveals Dynamic Wave