



# The Neurobiology of Mood and Psychotic Disorders

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# Disclosures

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Neither I nor my spouse has a relevant financial relationship with a commercial interest to disclose.

# Disorder incidence and overlap

- **Major Depressive Disorder (MDD)**

Overall lifetime incidence: 17% in the U.S. (lower in other countries, e.g., in Japan 3%)

Among those with MDD, *lifetime incidence of psychosis: ~18%*

- **Bipolar Disorder (BD)**

Overall lifetime incidence: ~4% (including Bipolar I & II and subthreshold); 1% for Bipolar I

Among those with BD, *lifetime incidence of psychosis: 25%*

- **Schizophrenia (SZ)**

Overall lifetime incidence: 0.7%, ~3% defined broadly (with 5+ fold variation in incidence across the world, highlighting the importance of environmental factors)

Among those with SZ, *lifetime incidence of MDD: 25%*

- Genetics and neuroimaging studies show evidence for biological **overlap** and **specificity** (to symptoms or diagnostic category)

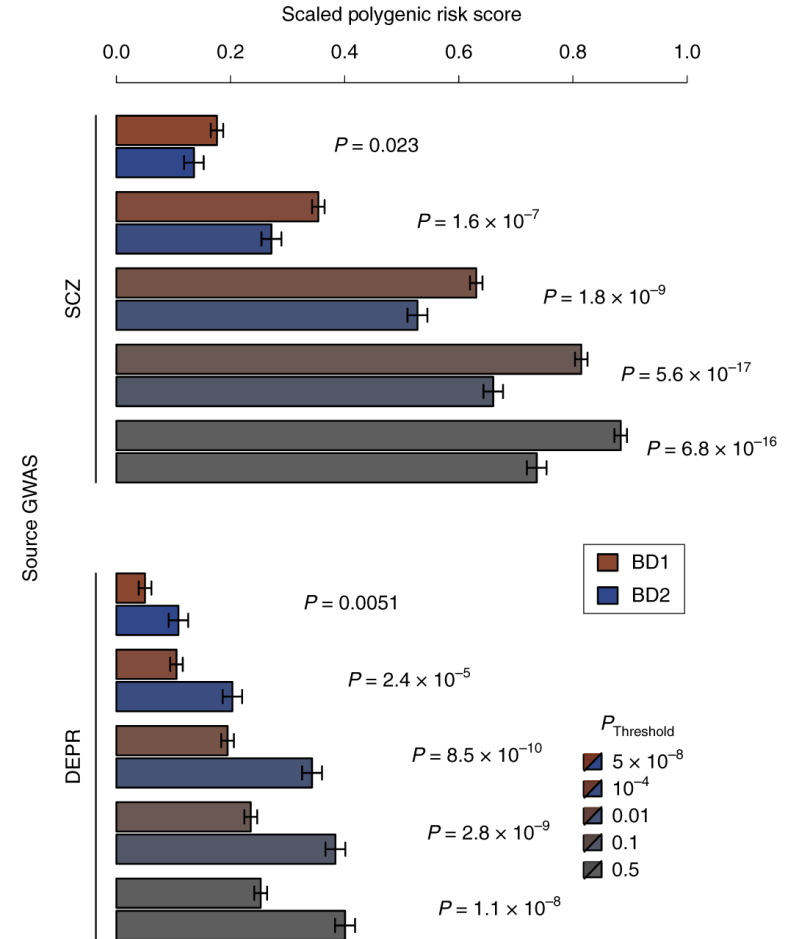
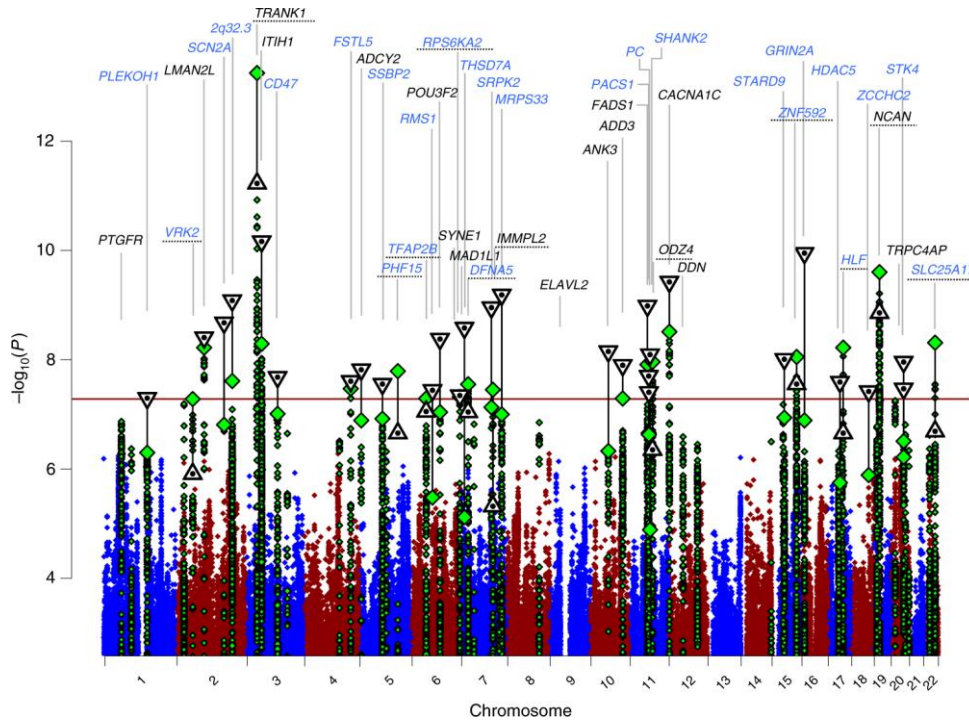
# Overlap vs. diagnostic specificity:

Bipolar 1-linked genes overlap most with schizophrenia-linked genes,

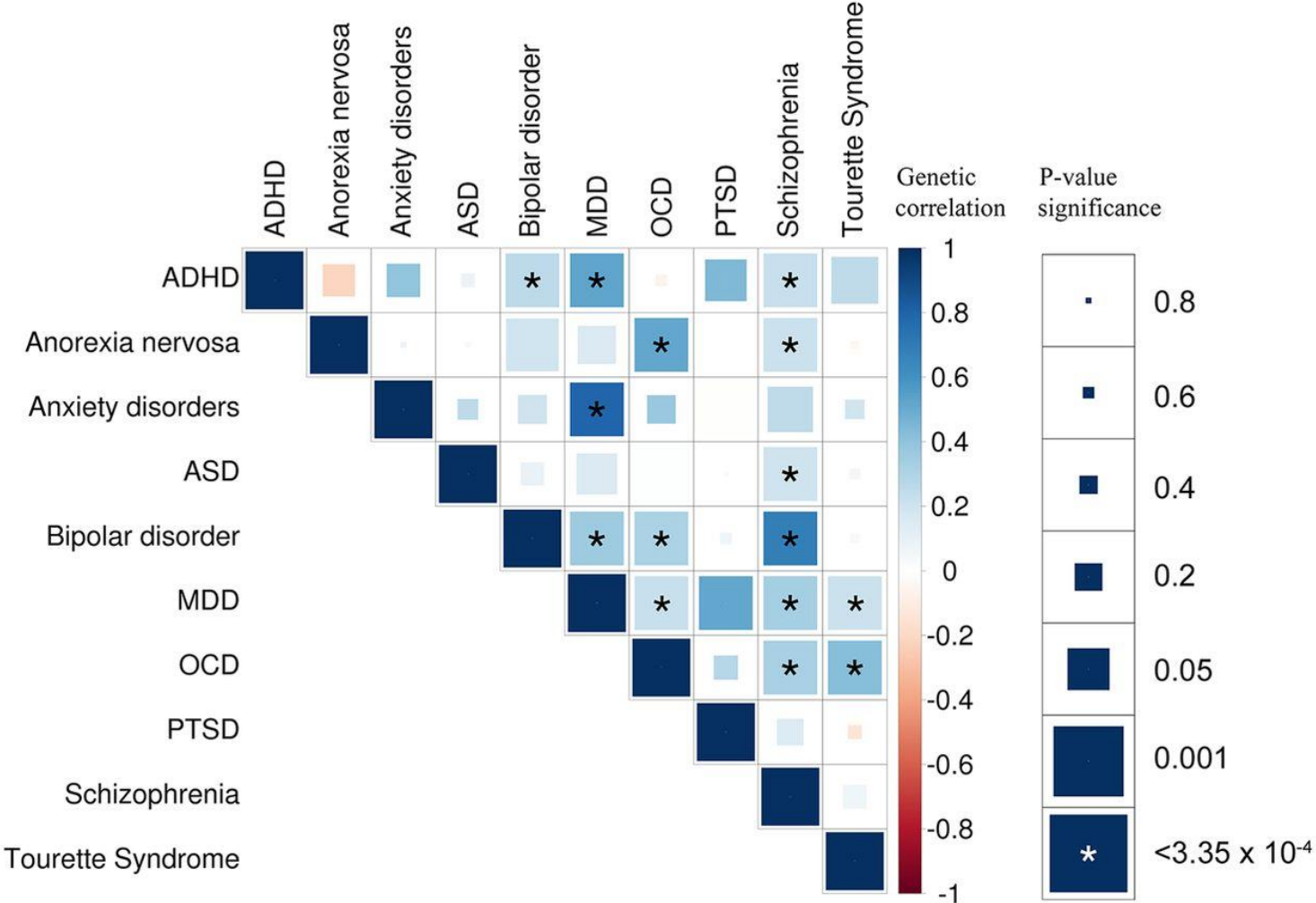
Bipolar II-linked genes overlap most with depression-linked genes



## Genome-wide association study identifies 30 loci associated with bipolar disorder

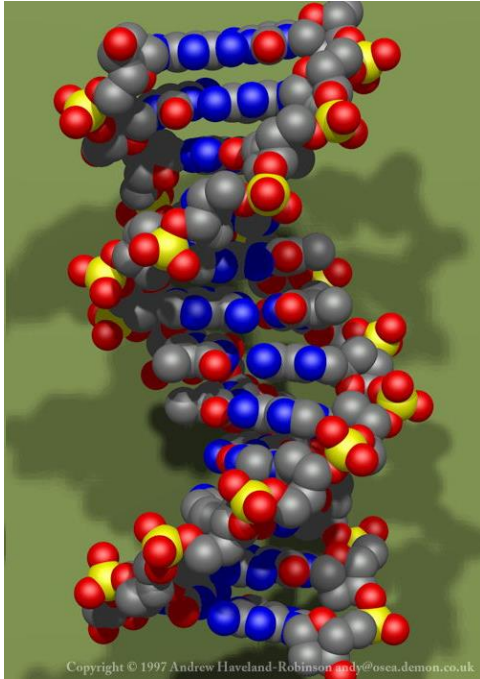


# Genetic overlap observed among an increasing number of disorders



# G x E

## Genes



Heritability of  
Schizophrenia: 80%  
Bipolar Disorder: 90%  
Major Depression: 40%

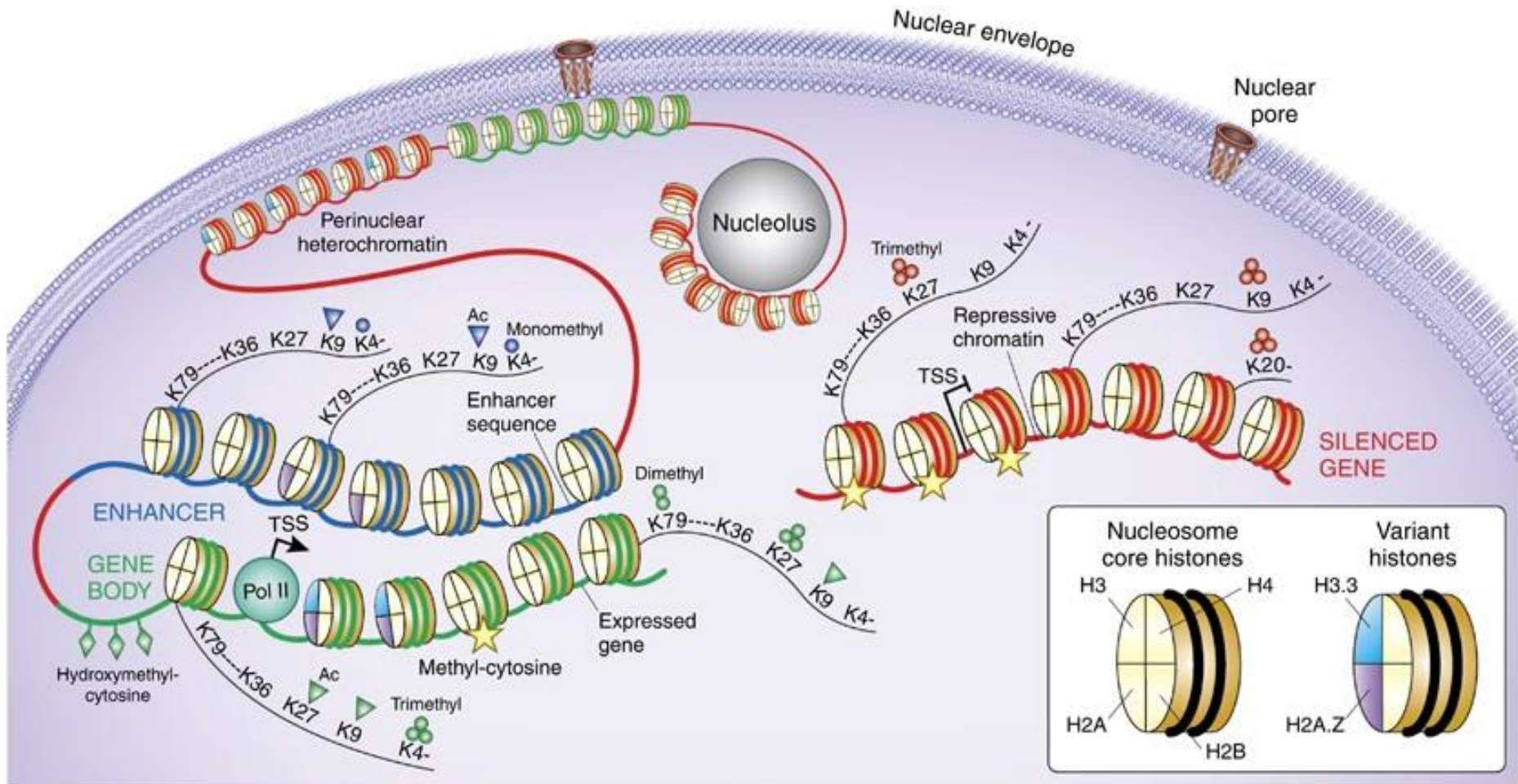
## Environment



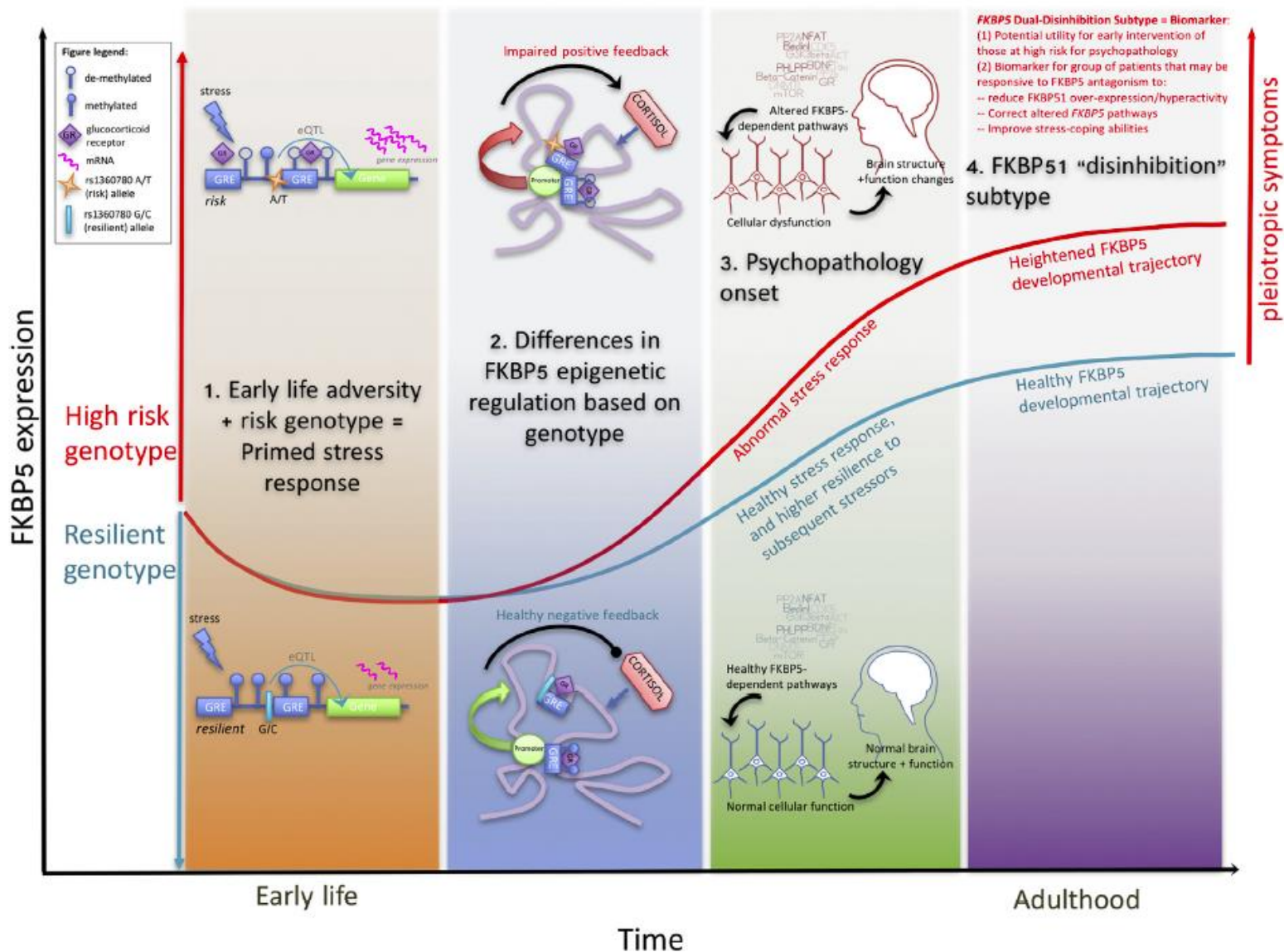
- in utero events
- childhood trauma/bullying
- urban living
- minority status/discrimination
- substance use
- Infections, autoimmune

# Epigenetic mechanisms

- 1) those that alter DNA directly, i.e., via methylation
- 2) histone modification
- 3) non-coding RNAs, e.g., microRNA, that modify gene expression

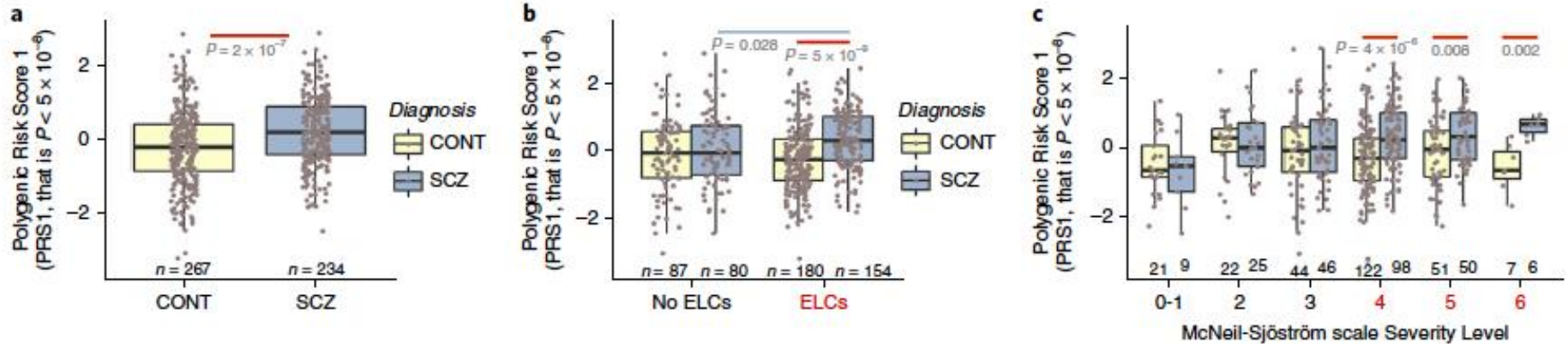


# Genetic variation in the FKBP5 gene interacts with early adversity

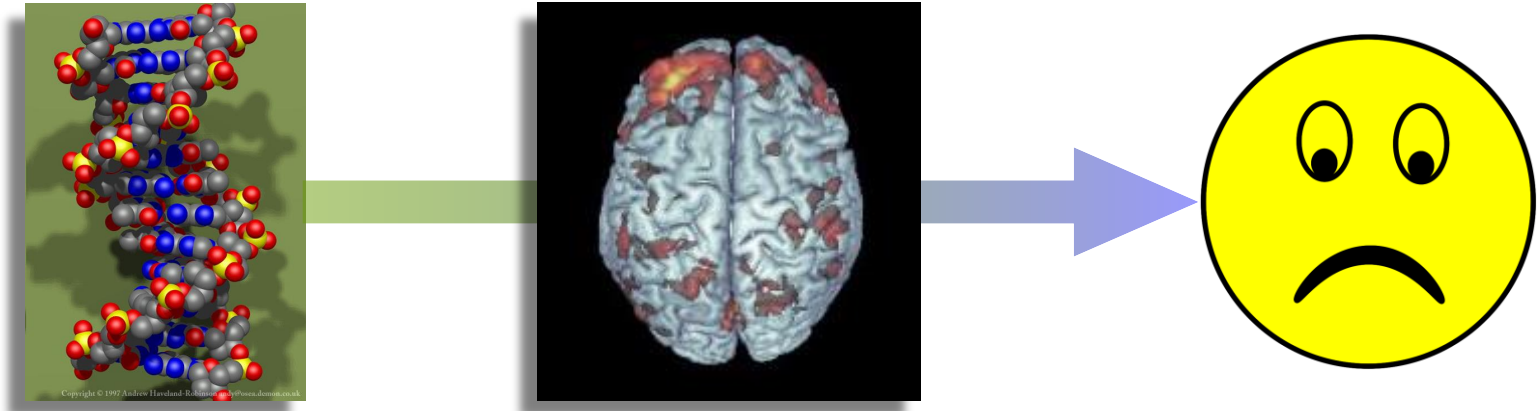




## Interaction between increased genetic risk for schizophrenia and obstetric (intra-uterine) complications



# The Overall Model



genetic vulnerability,  
present from birth

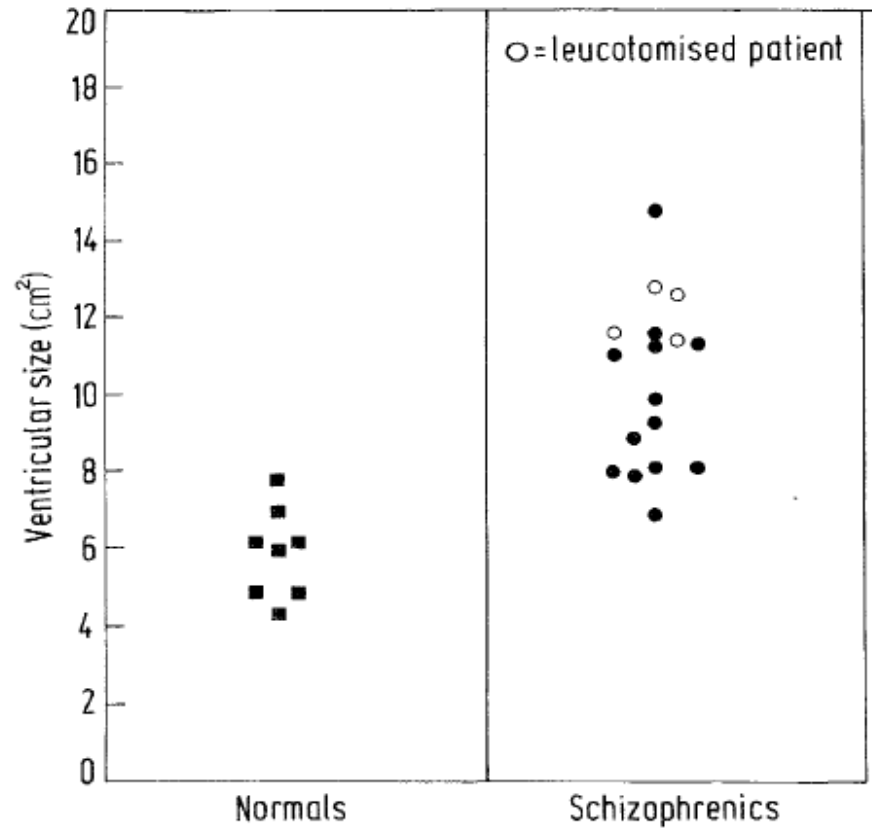
changes in brain  
structure/function

symptoms  
and impaired functioning

E

prenatal or later-in-life events,  
effects depend on developmental stages/critical periods

# Ventricular enlargement and brain volume loss in schizophrenia



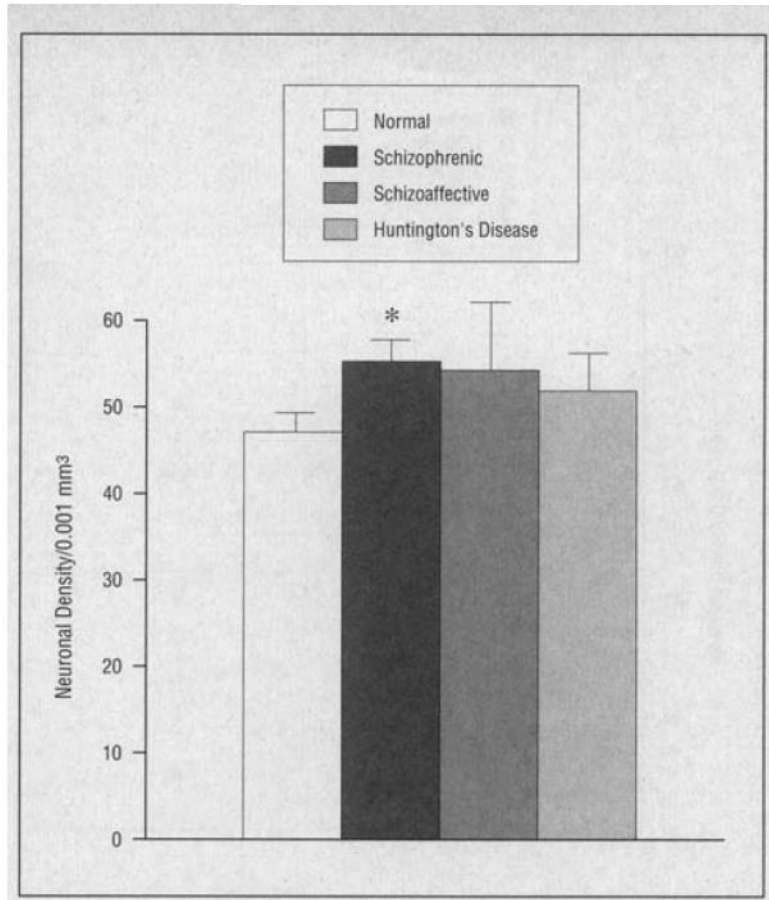
**Ventricular size in patients and controls.**

Each point represents average of four measurements on photographs.

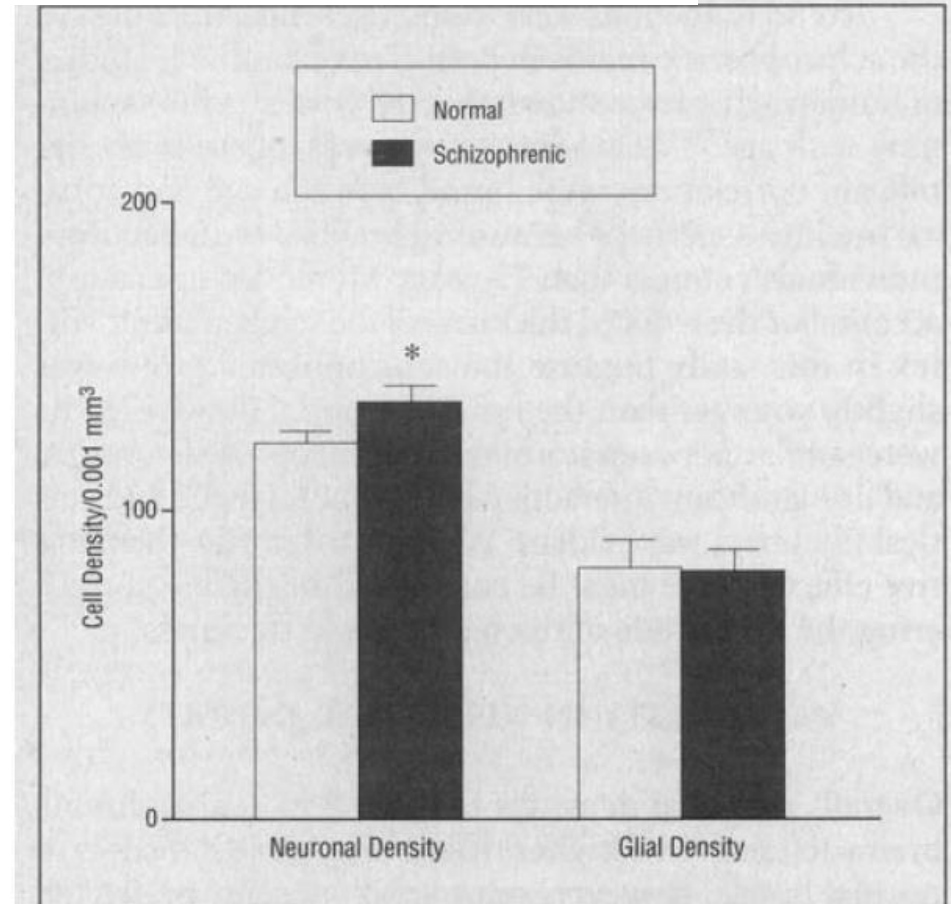
# Abnormally High Neuronal Density in the Schizophrenic Cortex

## *A Morphometric Analysis of Prefrontal Area 9 and Occipital Area 17*

Lynn D. Selemon, PhD; Grazyna Rajkowska, PhD; Patricia S. Goldman-Rakic, PhD



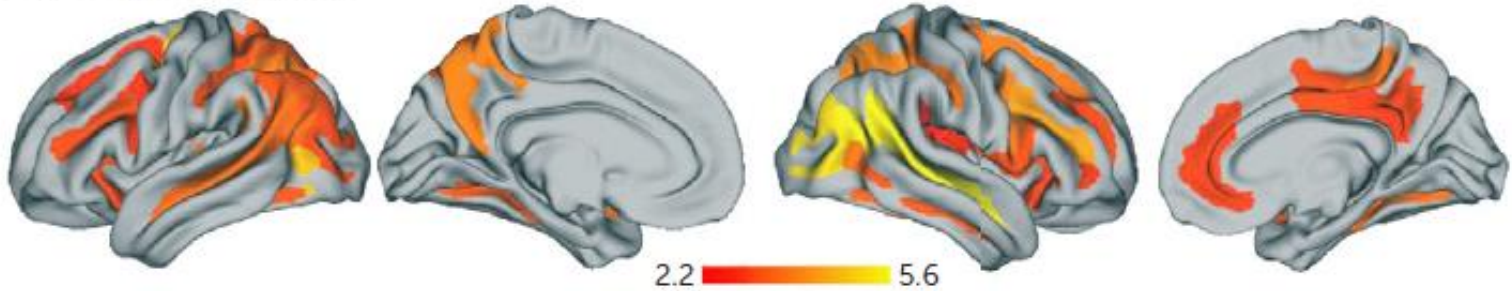
Area 9 (dIPFC)



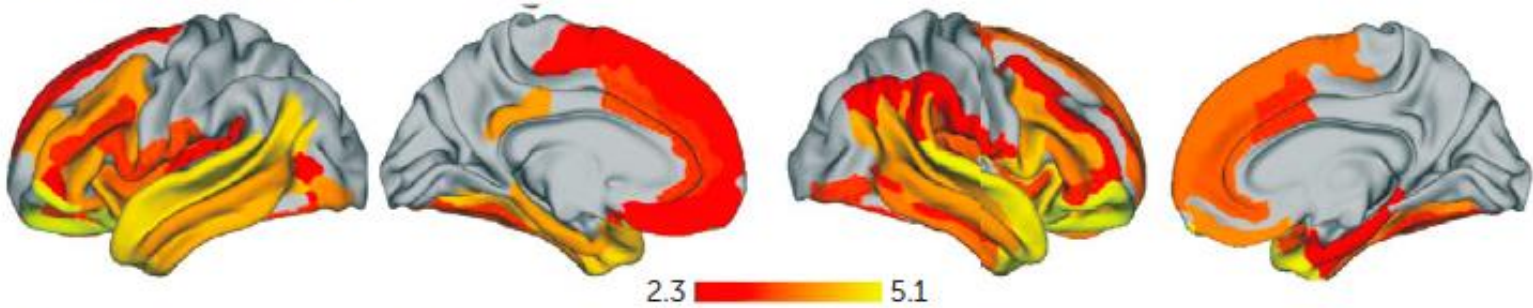
Area 17 (primary visual cortex)

# Consistent patterns of cortical thinning across disease stages, with evidence of progression

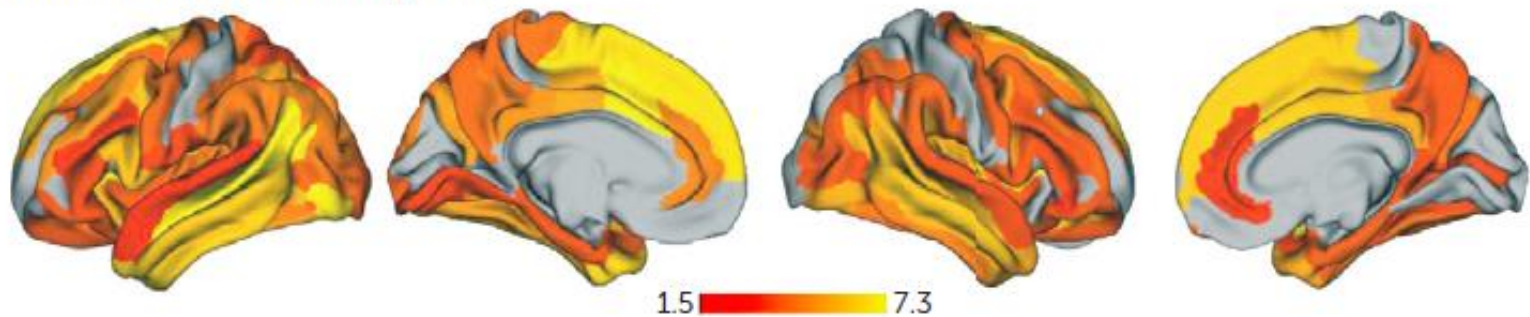
A. First-episode psychosis



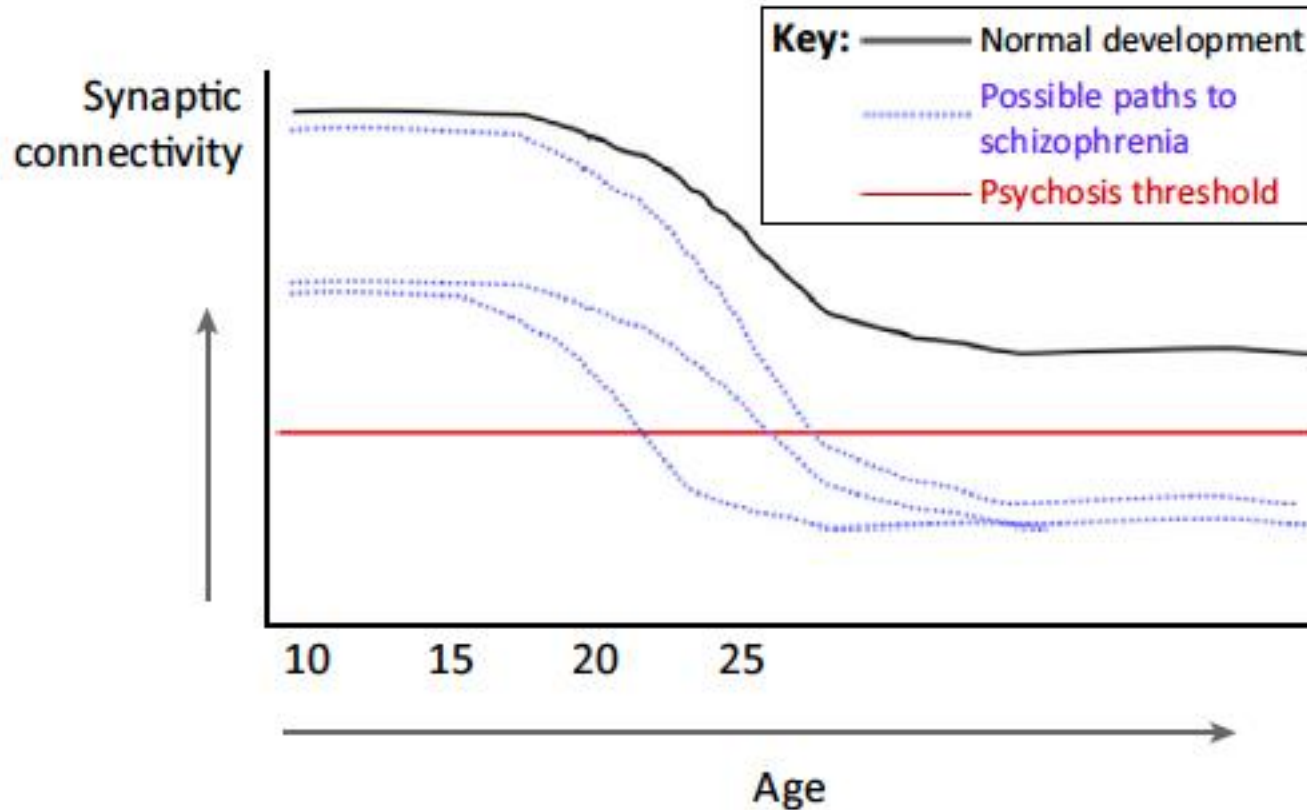
B. Chronic schizophrenia



C. Treatment-resistant schizophrenia



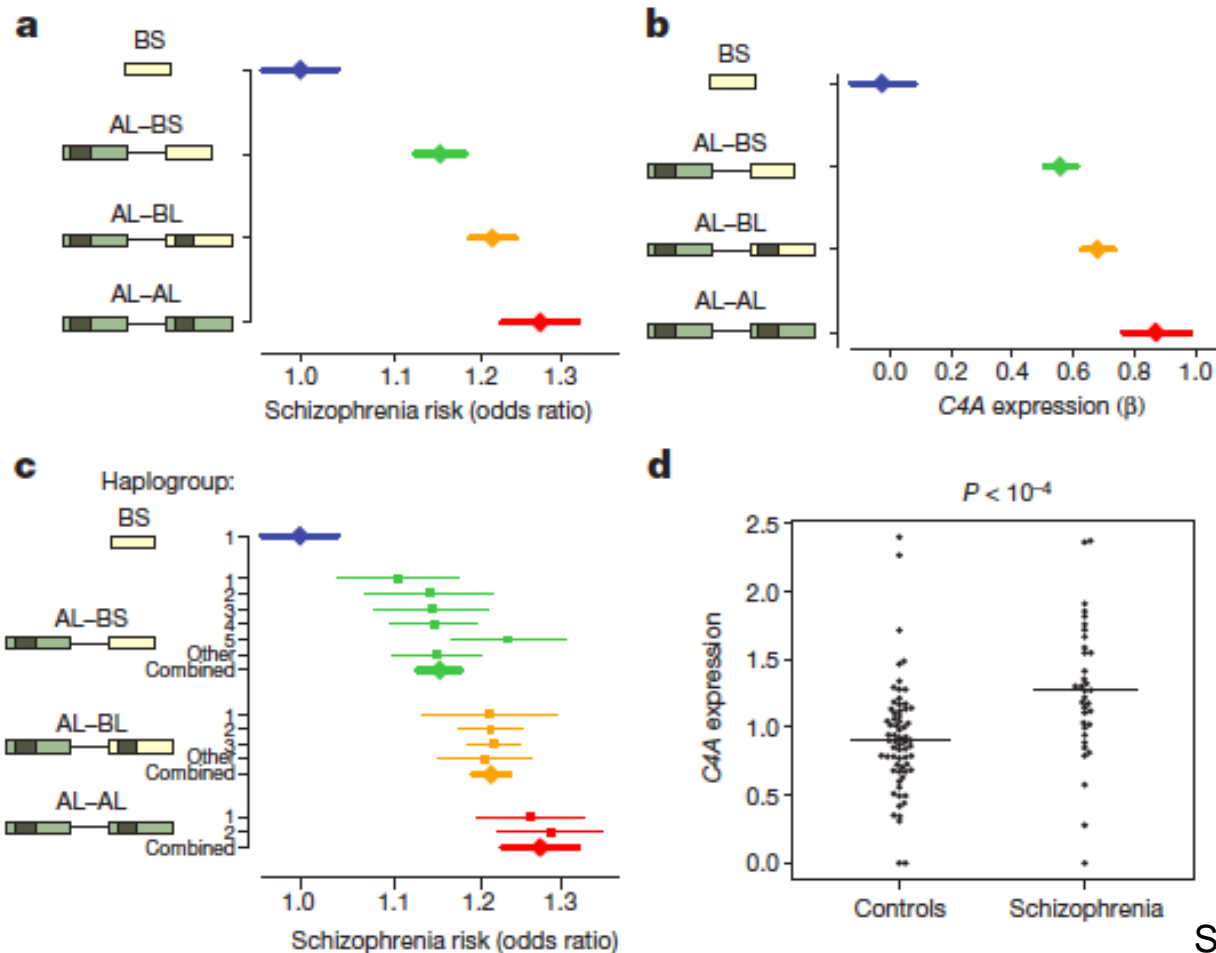
Excessive pruning and loss of cortical connections over time → increased vulnerability to psychosis



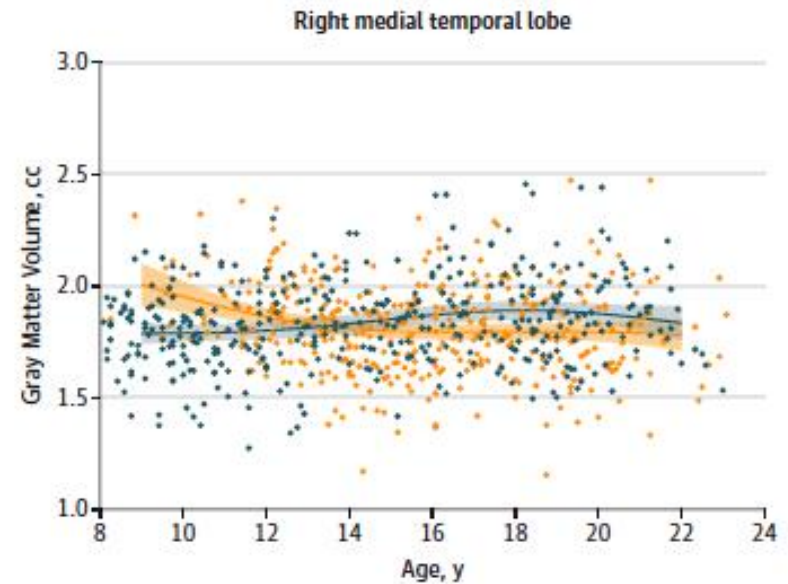
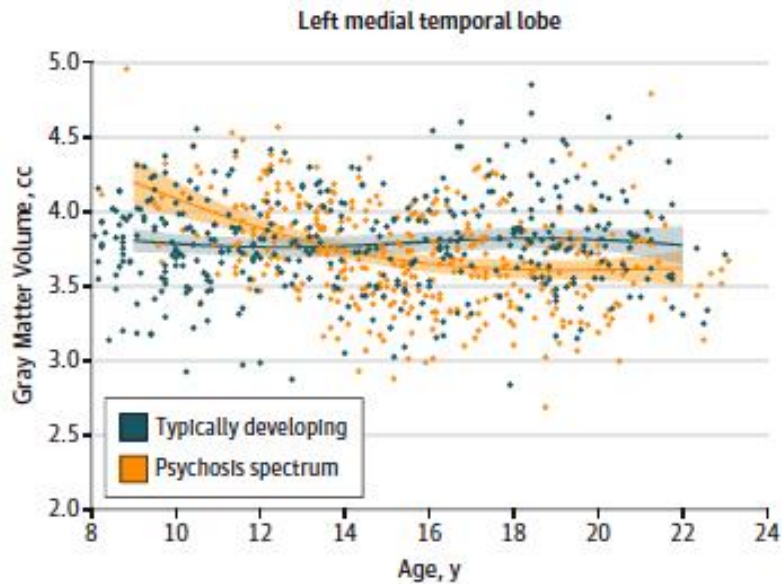
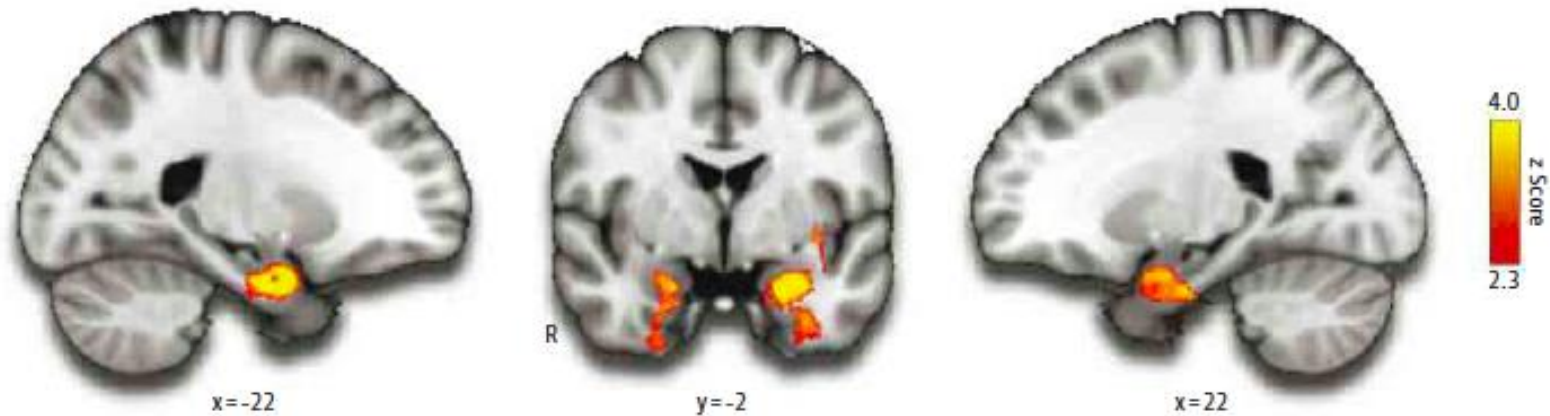
# Schizophrenia risk from complex variation of complement component 4

Aswin Sekar<sup>1,2,3</sup>, Allison R. Bialas<sup>4,5</sup>, Heather de Rivera<sup>1,2</sup>, Avery Davis<sup>1,2</sup>, Timothy R. Hammond<sup>4</sup>, Nolan Kamitaki<sup>1,2</sup>, Katherine Tooley<sup>1,2</sup>, Jessy Presumey<sup>5</sup>, Matthew Baum<sup>1,2,3,4</sup>, Vanessa Van Doren<sup>1</sup>, Giulio Genovese<sup>1,2</sup>, Samuel A. Rose<sup>2</sup>, Robert E. Handsaker<sup>1,2</sup>, Schizophrenia Working Group of the Psychiatric Genomics Consortium\*, Mark J. Daly<sup>2,6</sup>, Michael C. Carroll<sup>5</sup>, Beth Stevens<sup>2,4</sup> & Steven A. McCarroll<sup>1,2</sup>

Schizophrenia risk proportional to the C4 allele's tendency to increase C4A expression, which mediates pruning

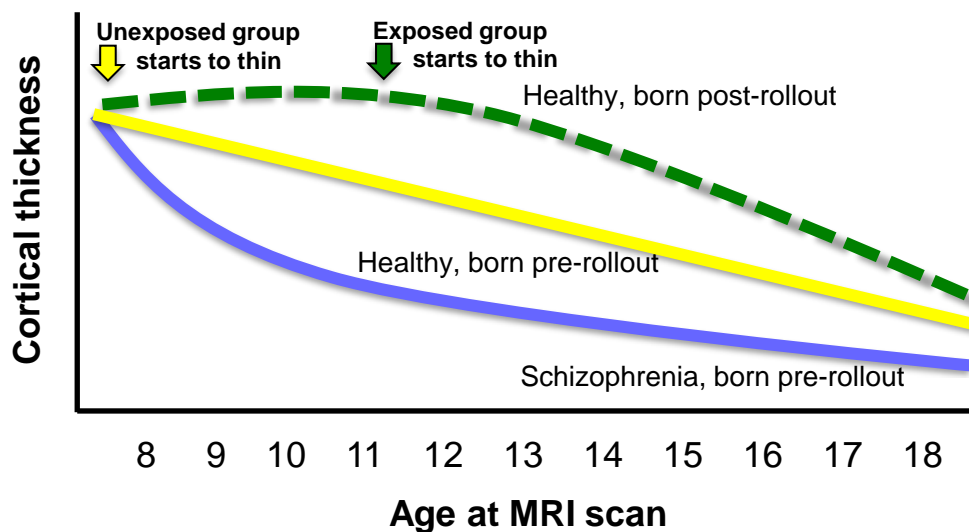
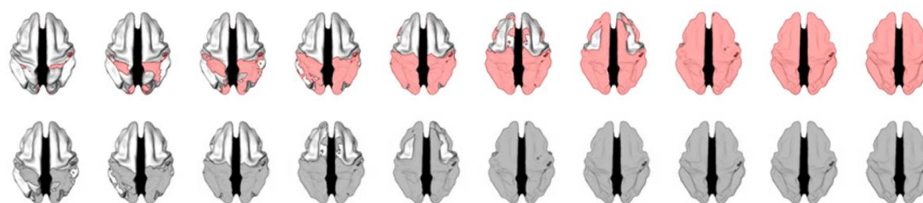


# Similar pattern of “excessive pruning” in adolescents with low level psychotic symptoms

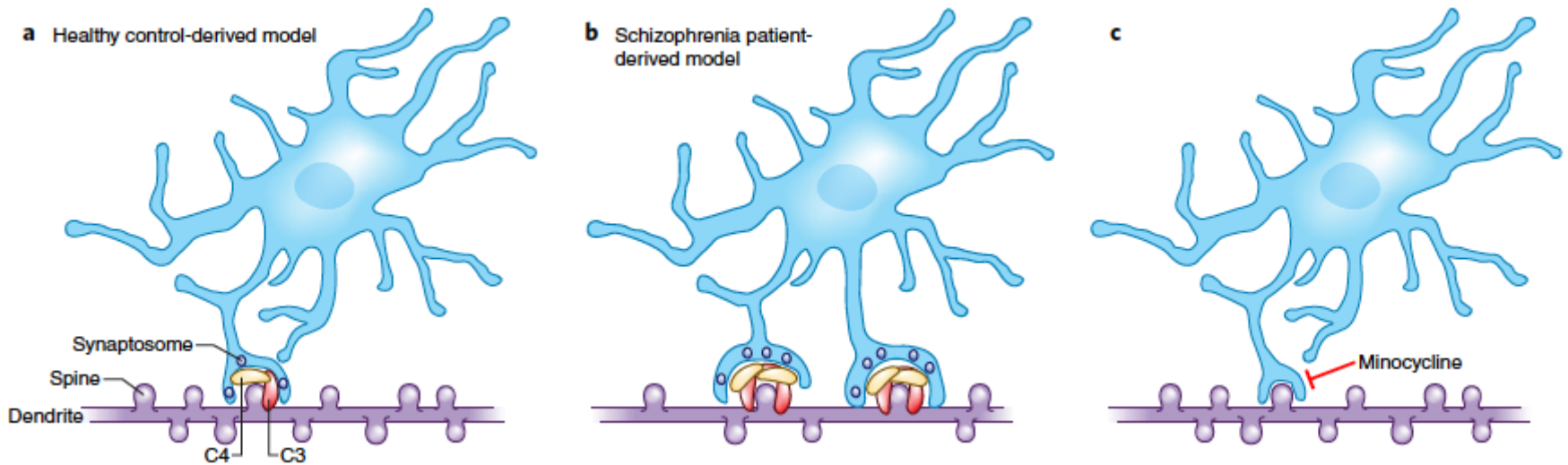




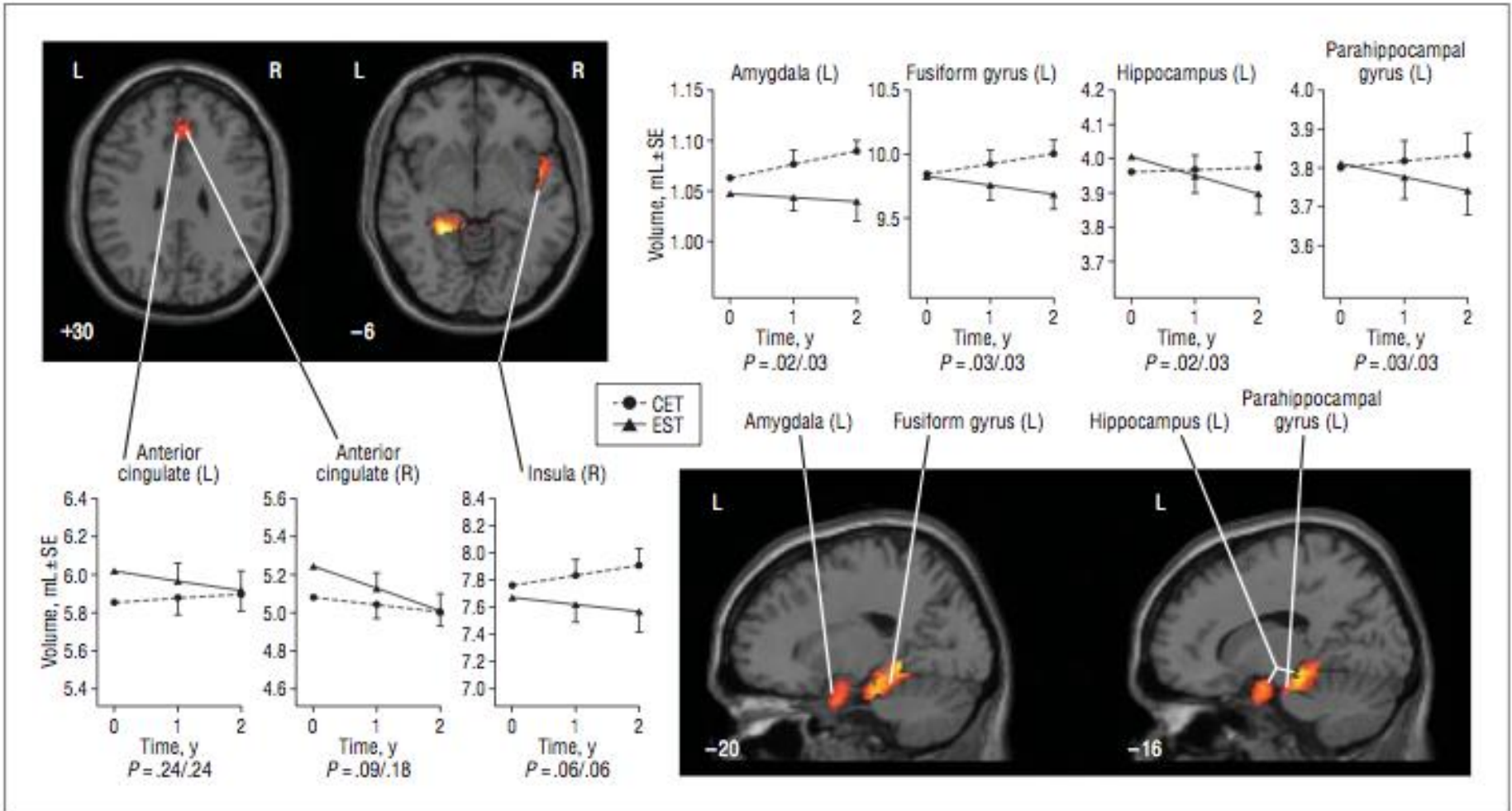
# Fetal fortification exposure alters cortical development during adolescence



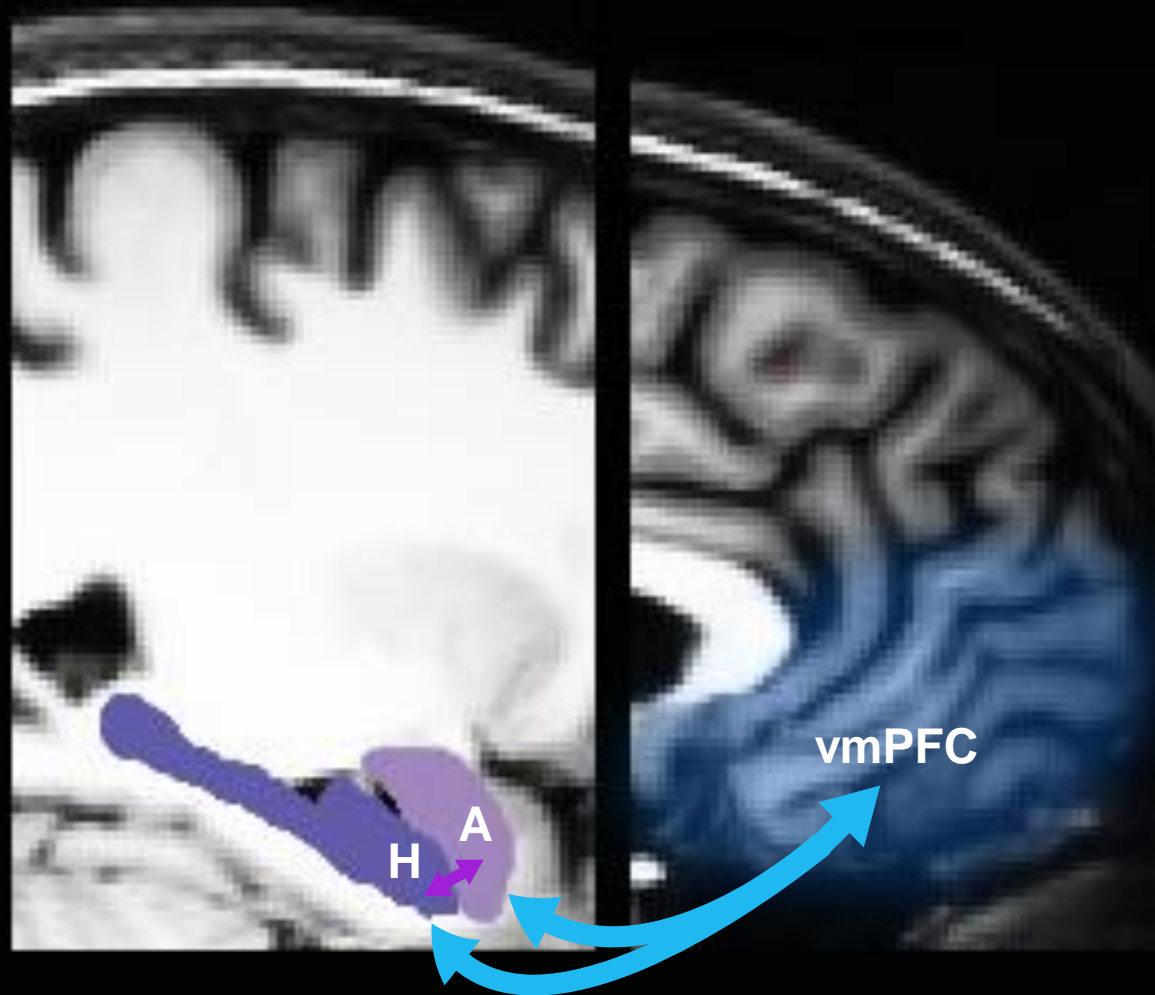
# Induced microglia-like cells derived from patients with schizophrenia display increased synaptic engulfment



Specific types of therapy (e.g., cognitive enhancement treatment) may reverse or prevent progressive changes in the brain during the early stages of schizophrenia

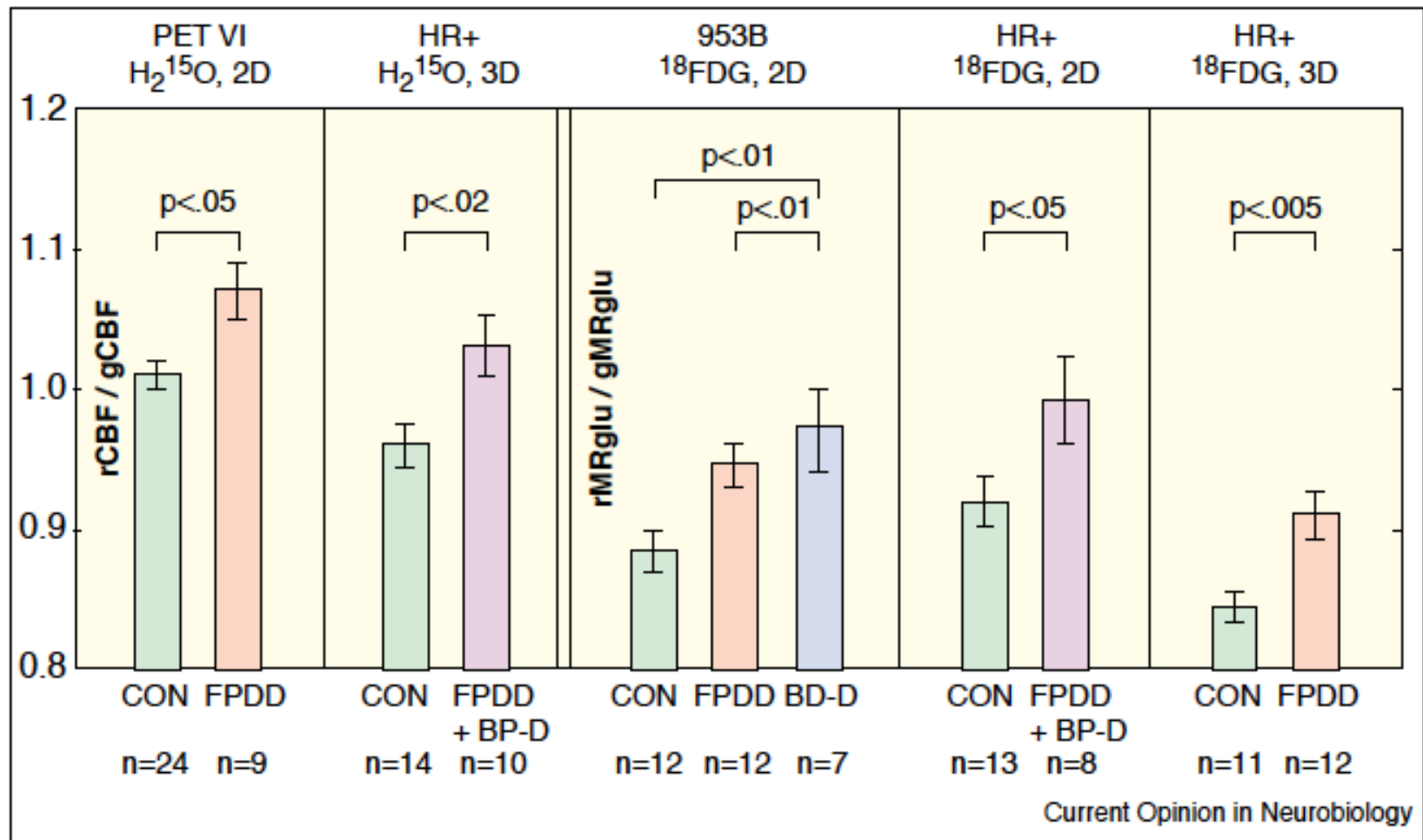


# A key circuit affected in neuropsychiatric disorders



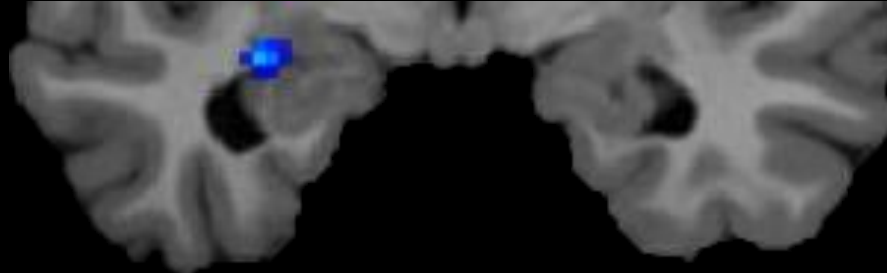
H = hippocampus  
A = amygdala

# Amygdala hyperactivity in unipolar and bipolar depression: **repeatedly replicated**

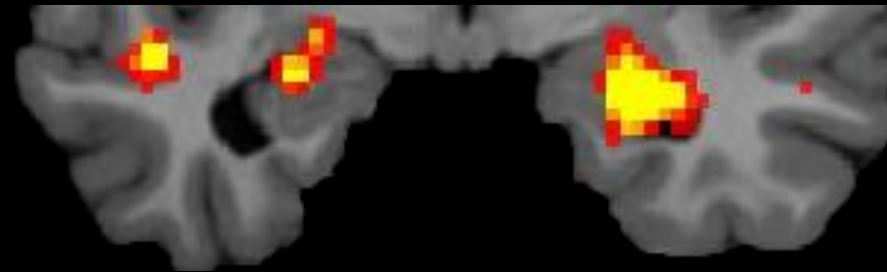


# Overactivity of the amygdala in children of patients with depression has been observed in 3 studies (Monk et al, 2008; Swartz et al, 2014, Chai et al, 2015)

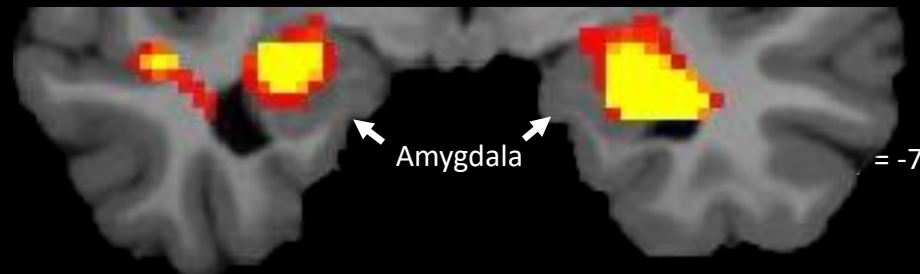
A. FH-



B. FH+



C. FH+ > FH-

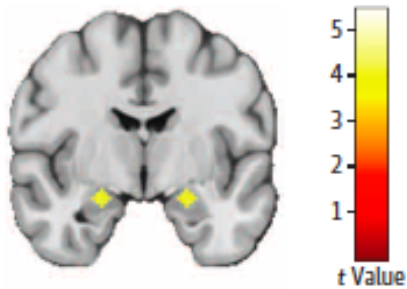


Face W > Face A 0.001 0.05 0.05 0.001 Face A > Face W

Also found in young adults with a first-degree relative with depression

# Greater frontal-amygdala connectivity in resilient (vs. non-resilient) female adolescents

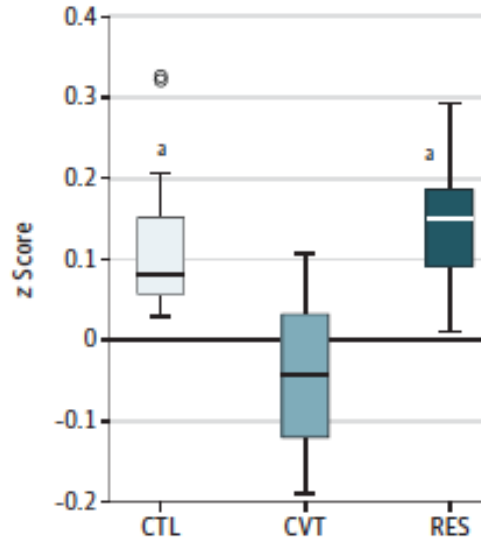
**A** Bilateral amygdala seeds



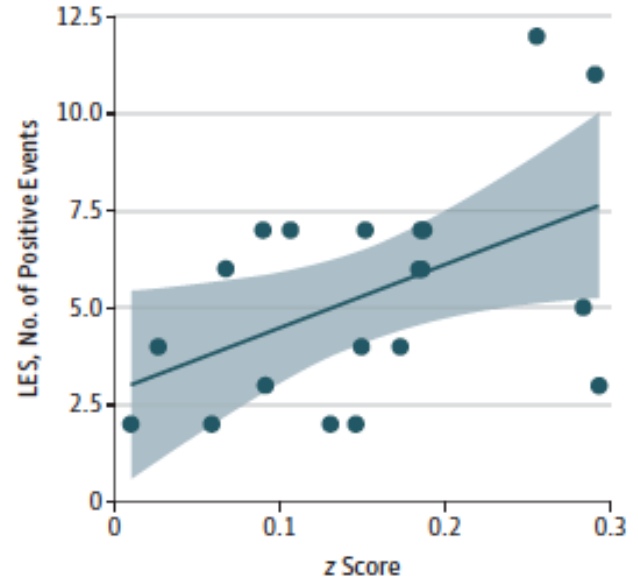
**B** Left orbitofrontal cortex



**C** Functional connectivity



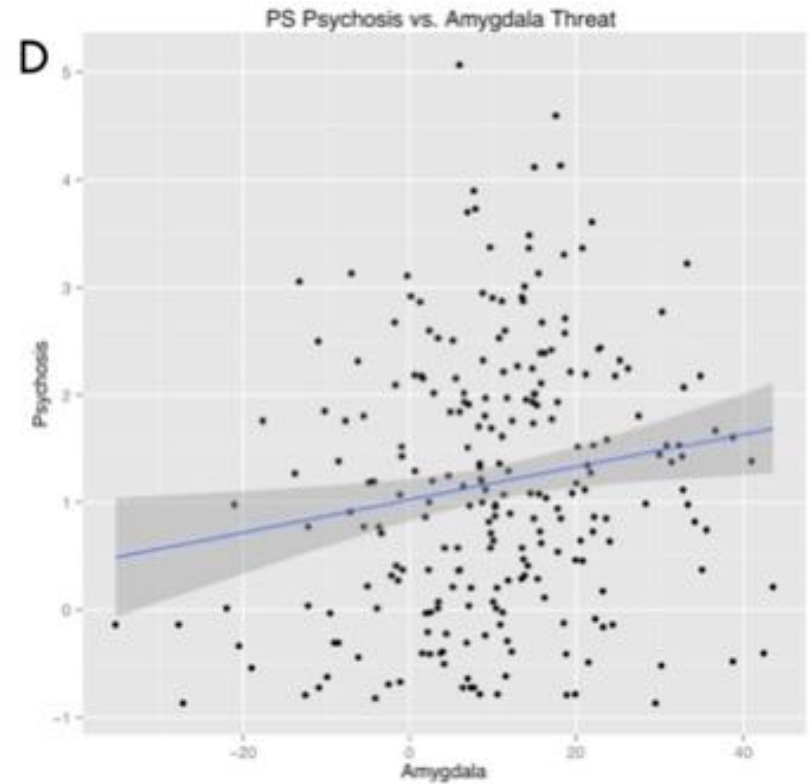
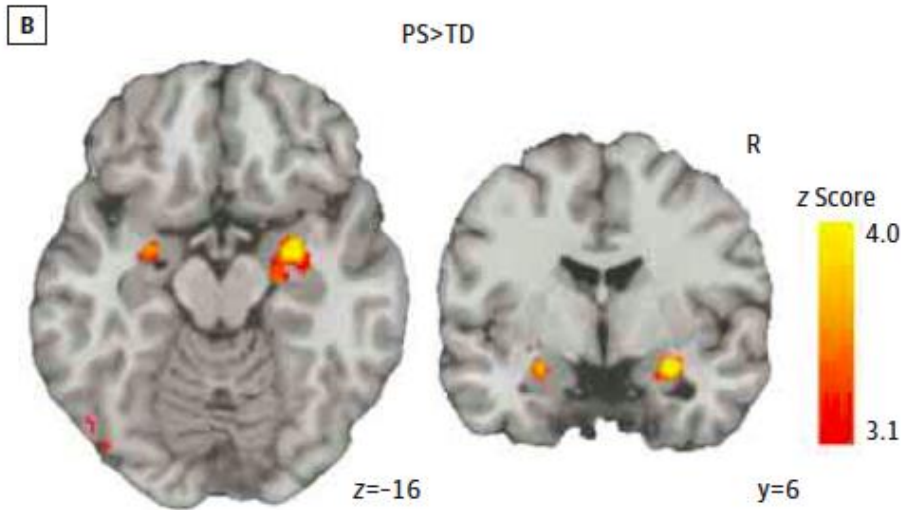
**D** Orbitofrontal cortex connectivity



## Study population:

40 adolescent females with a mother with recurrent MDD (high risk) (of whom 20 developed MDD) and 25 control adolescents without such risk

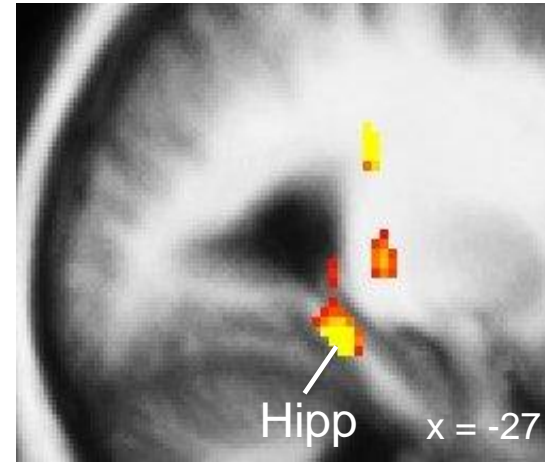
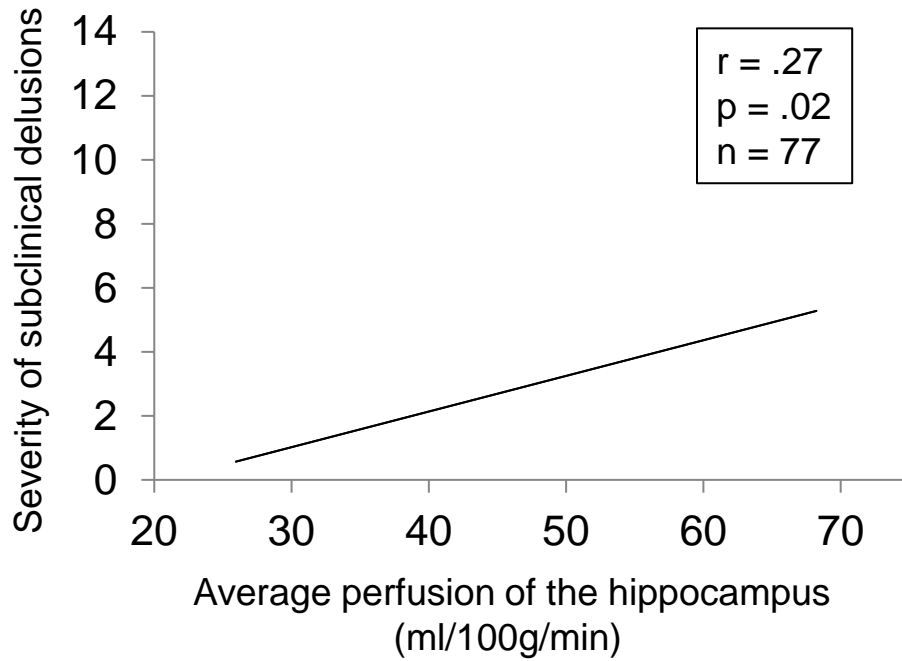
# Overactivity of the amygdala in youth with subclinical, psychotic-like symptoms



Wolf et al, JAMA Psych 2015

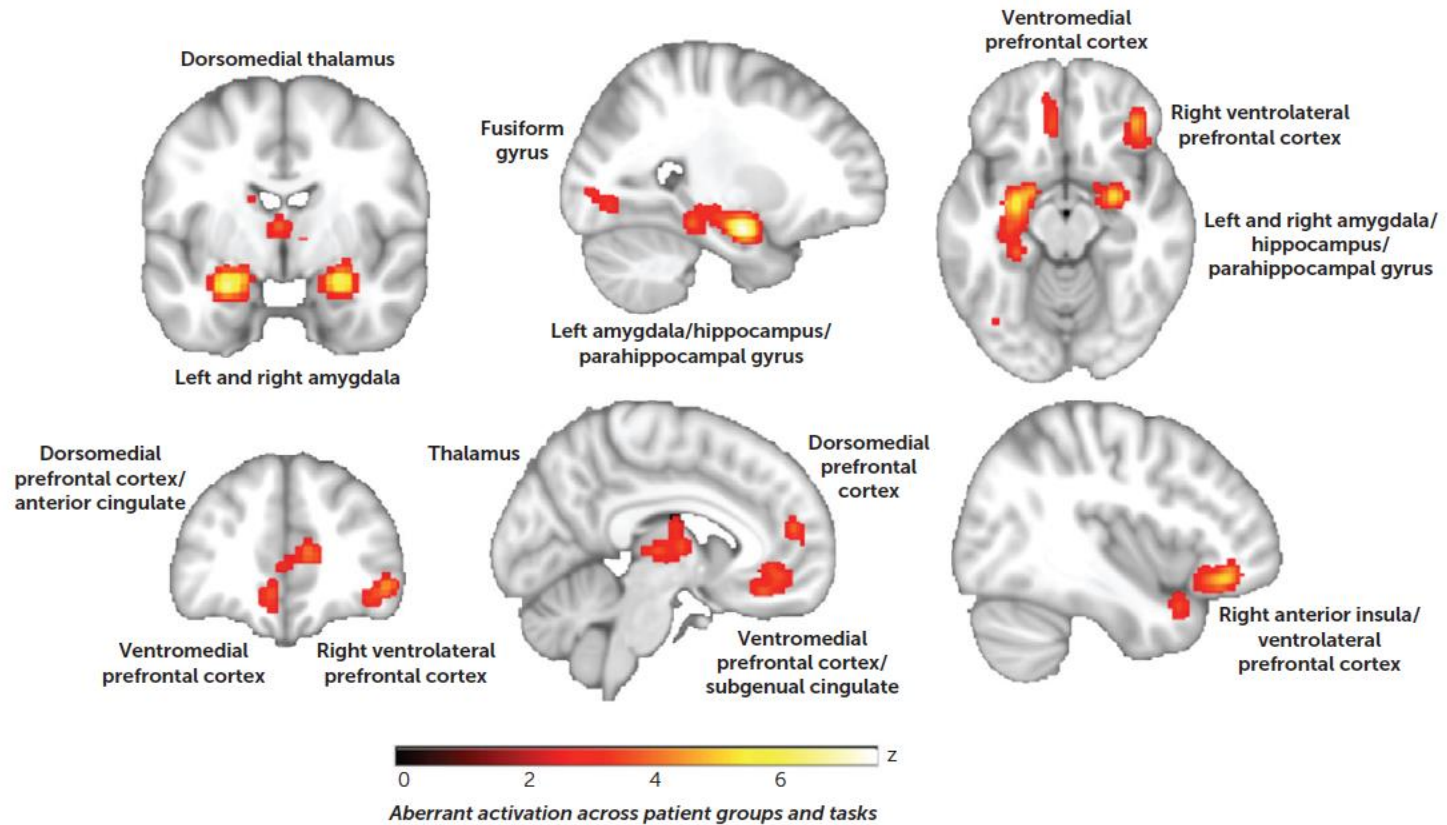


# Overactivity of the hippocampus in individuals with subclinical delusions

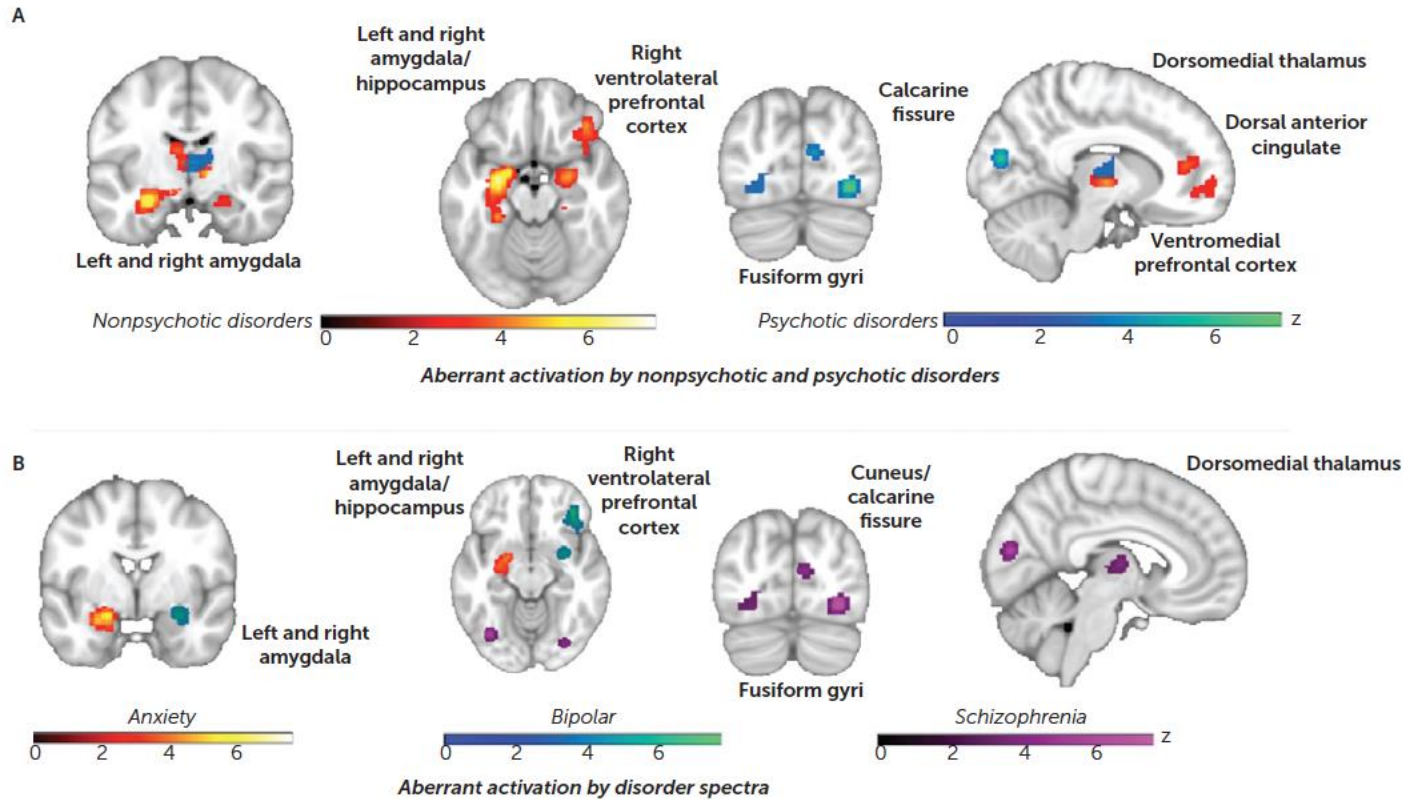


Support for the “continuum model” of psychosis

# Recent meta-analysis of 298 fMRI studies of emotion-related brain responses (N > 10K participants): common brain regions showing aberrant activation across psychiatric disorders

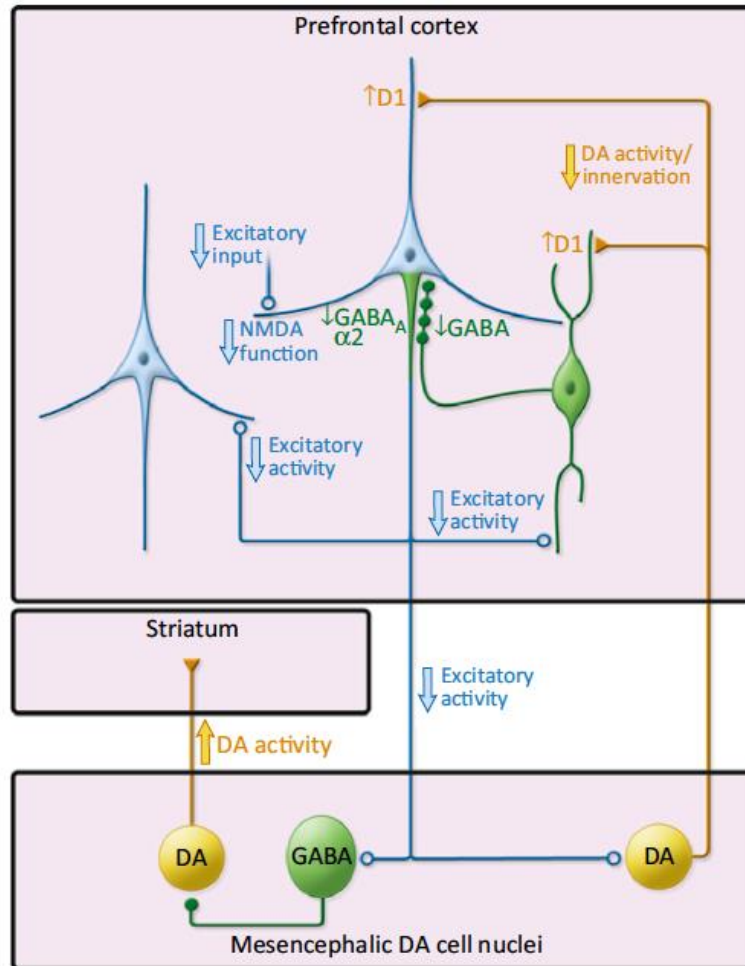


# Differences between psychotic and non-psychotic patients

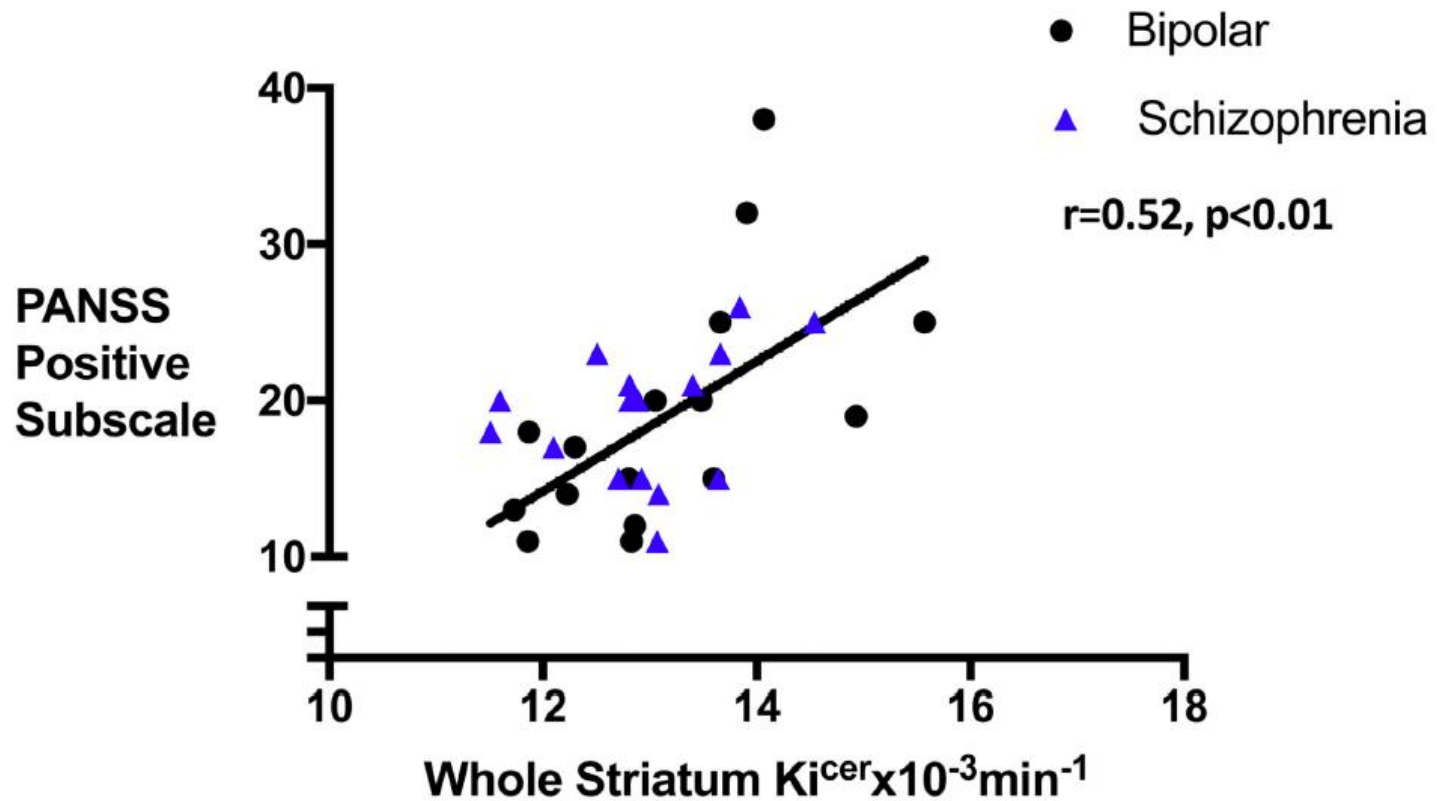


<sup>a</sup> Unipolar depressive and substance use disorder groups did not show convergence.

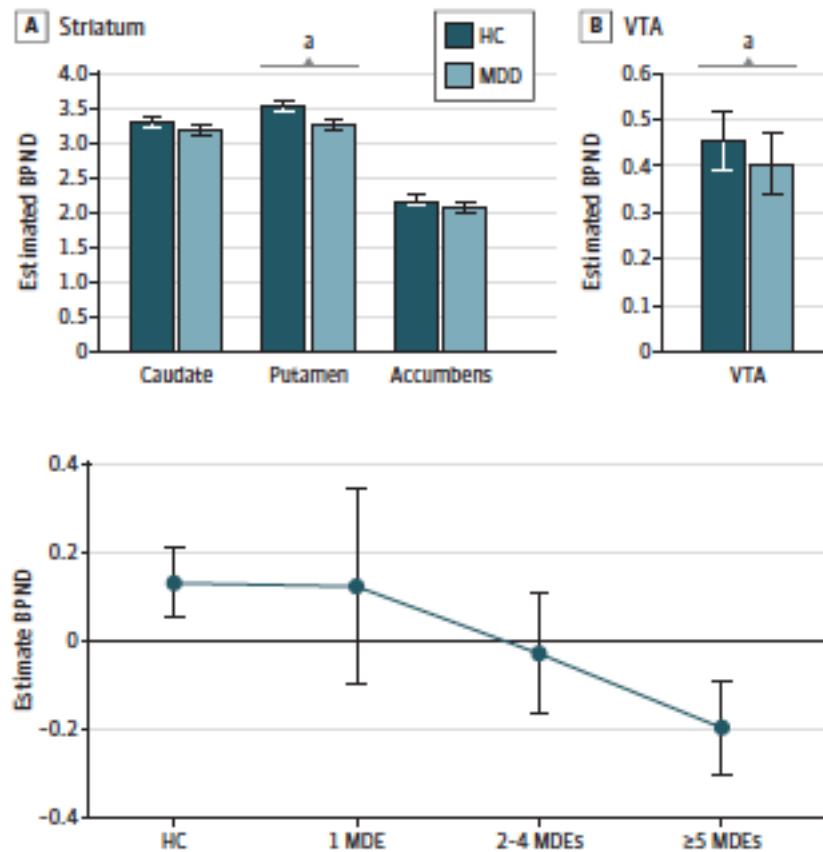
# Cellular model of schizophrenia



Dopamine synthesis is elevated in schizophrenia and bipolar disorder patients in the striatum compared to healthy subjects, and correlates with positive symptom severity

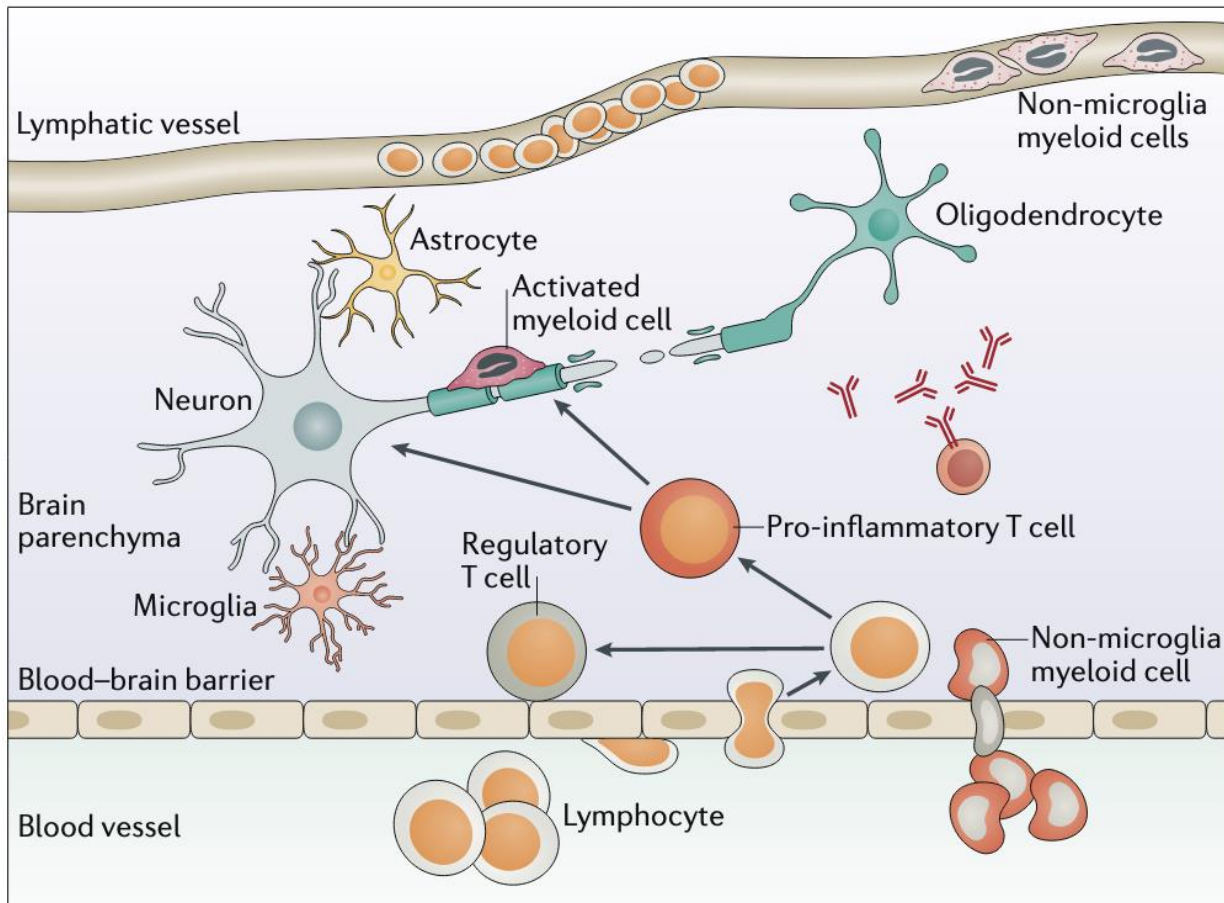


# Lower density of dopamine transporters in the striatum and ventral tegmental area in unmedicated depressed individuals



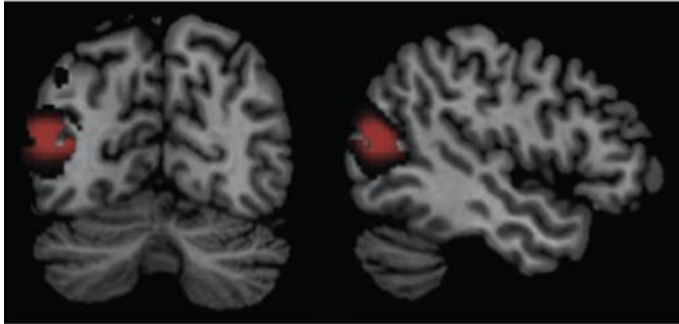
# COVID-19 compared to other respiratory illnesses doubles risk of new-onset mood or psychotic disorder

Taquet et al, Lancet Psychiatry 2021

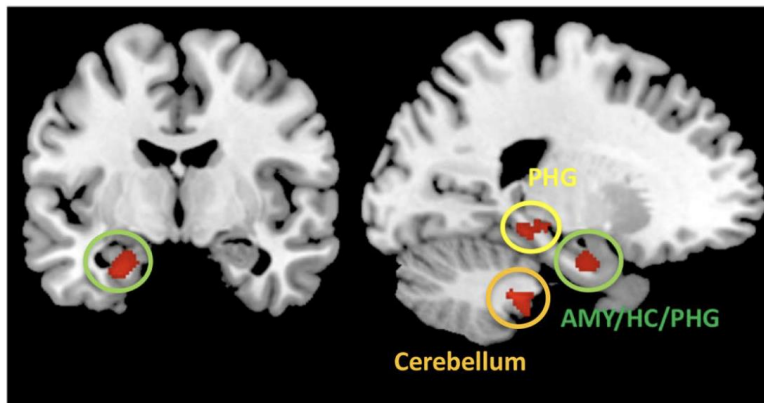
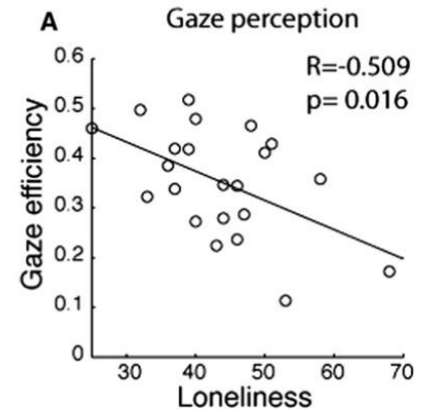
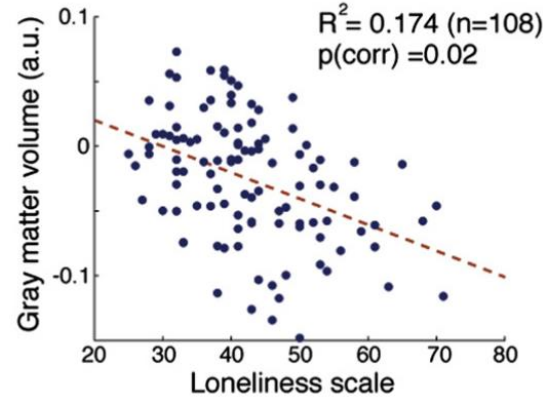


Pape et al, Nature Reviews Neurology 2021

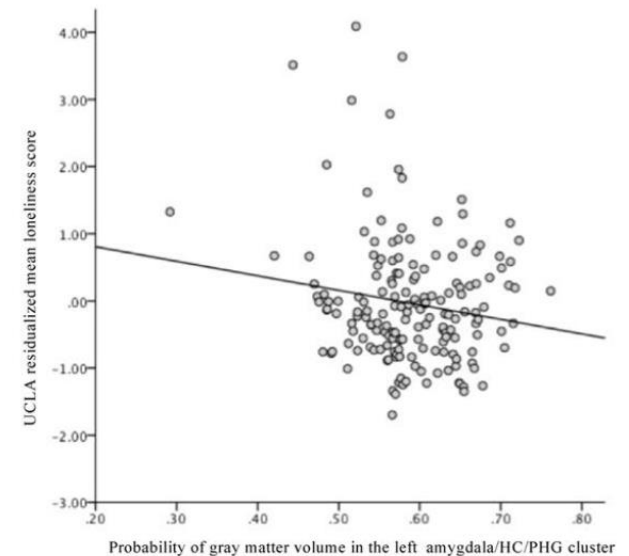
# Loneliness is associated with decreased brain volume in a regions associated with social processing



Cannai et al, Current Biology 2012



Düzel et al, Scientific Reports 2019





# Ongoing/future directions

- **Multi-site, longitudinal studies** aiming to identify the sequence of changes in the brain preceding the onset of clinical symptoms, e.g., the ABCD study, follow-up studies extending the work of the NAPLS study and the Human Connectome Project
- More **large research consortiums** such as ENIGMA, the UK Biobank, the Psychiatric Genetics Consortium
- **Intervention (treatment and preventive) studies focused on modifying mechanisms rather than symptoms** – molecular, neurophysiological and imaging targets
- **Screening and testing of potential novel therapeutics “in the test tube”**, via induced human pluripotent stem cells and related approaches
- **“Transdiagnostic” research** cutting across diagnostic categories to focus on shared genetics, neurophysiology and/or symptoms
- Modulating **immune processes** may reduce risk or improve outcomes for some individuals