The Neurobiology of Mood and Psychotic Disorders

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Disclosures

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%*

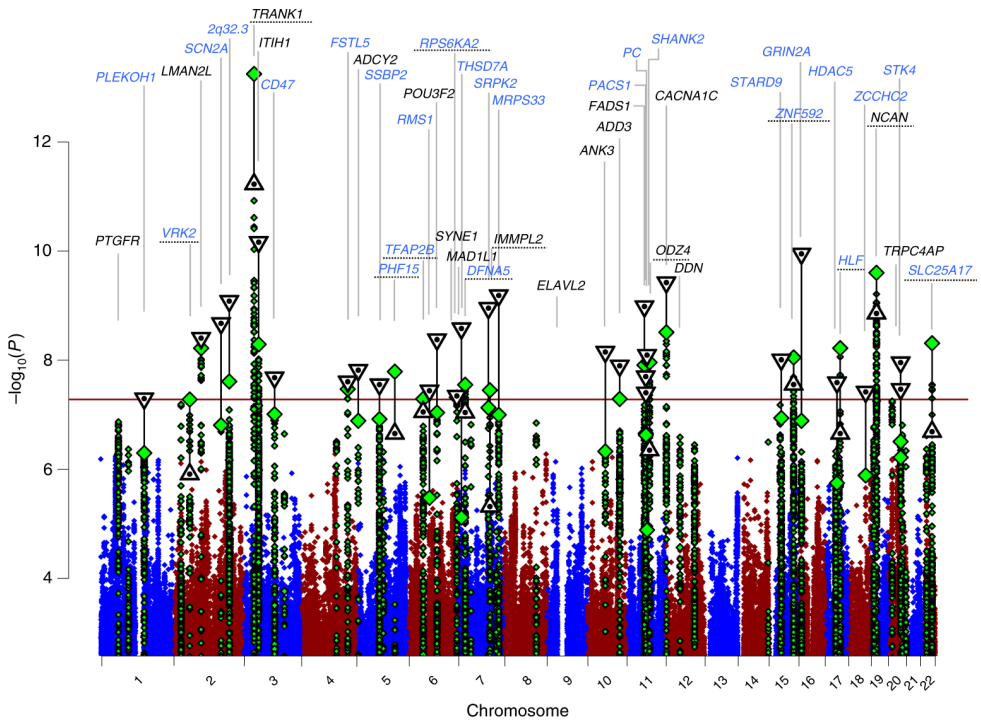
- **Schizophrenia (SZ)**
  Overall lifetime incidence: 0.7%, ~3% defined broadly (with 5+ fold variation in incidence across the world, highlighting the importance of environmental factors)
  Among those with SZ, *lifetime incidence of MDD: 25%*

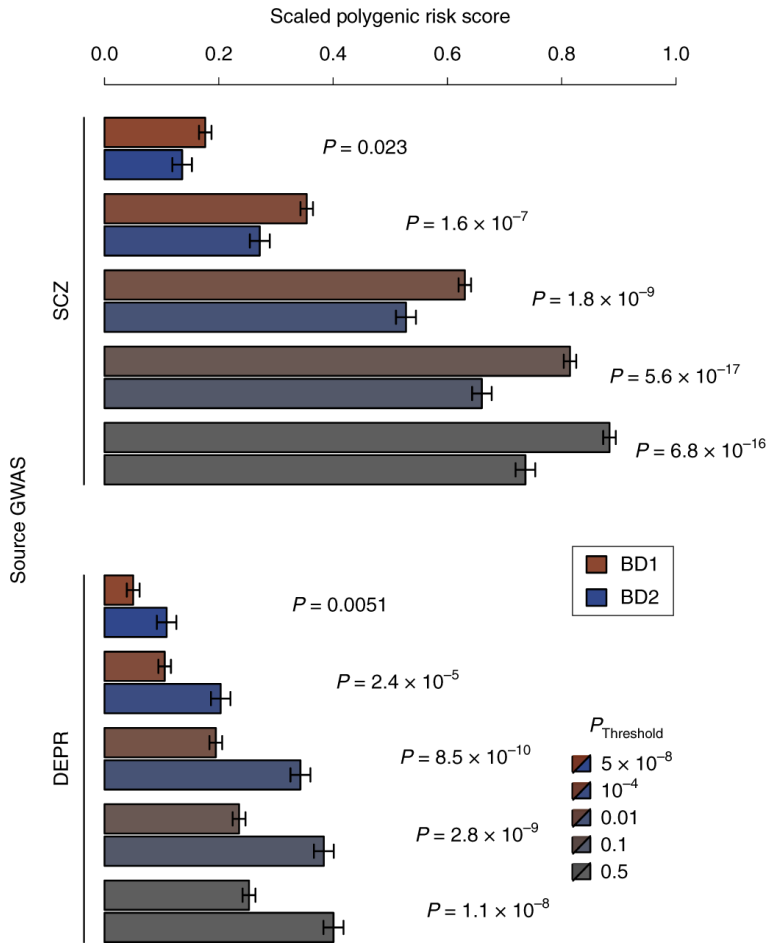
- Genetics and neuroimaging studies show evidence for biological **overlap** and **specificity** (to symptoms or diagnostic category)

Overlap vs. diagnostic specificity:
Bipolar 1–linked genes overlap most with schizophrenia-linked genes,
Bipolar II-linked genes overlap most with depression-linked genes

nature genetics ARTICLES
https://doi.org/10.1038/s41588-019-0397-8

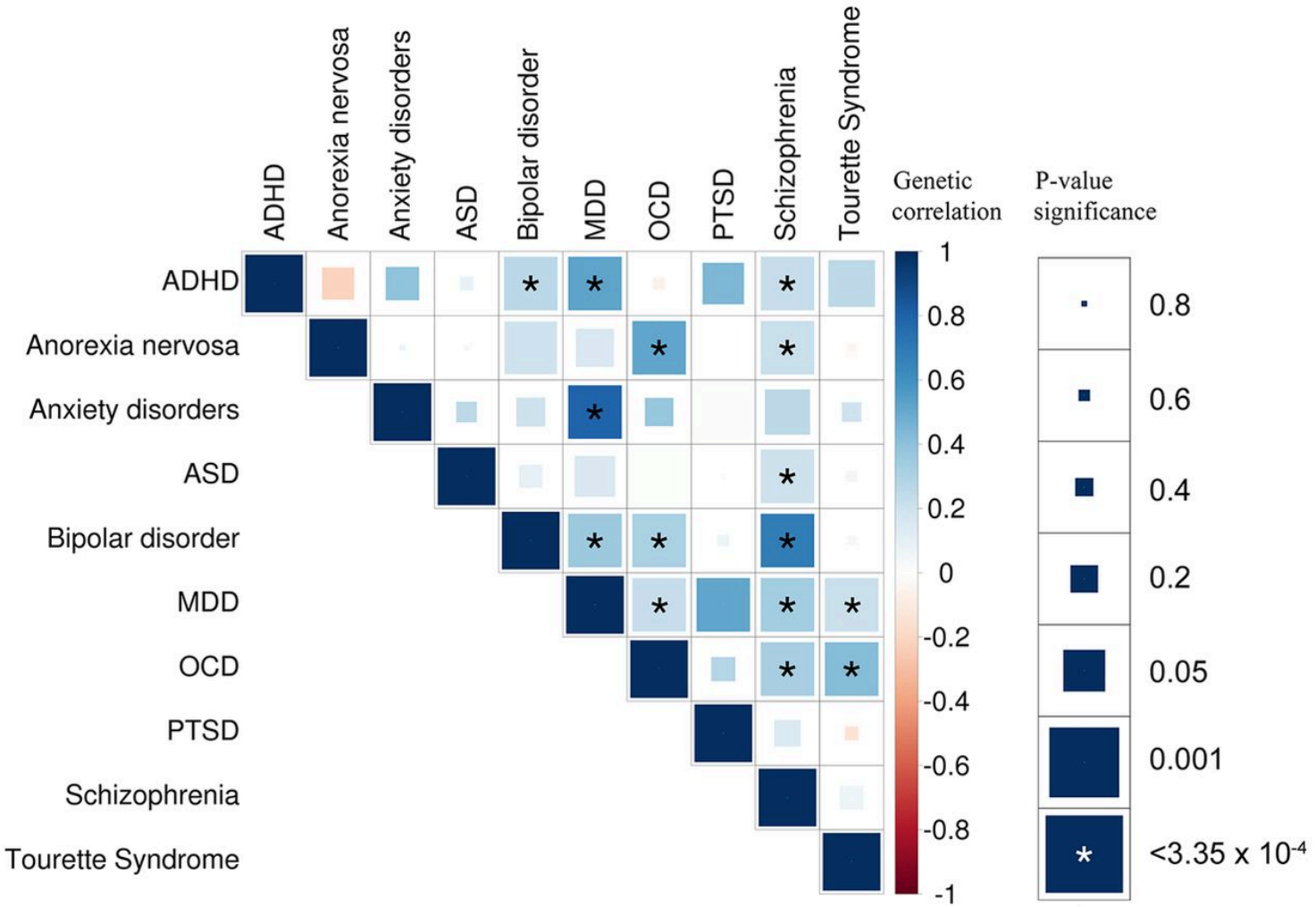
Genome-wide association study identifies 30 loci associated with bipolar disorder





The Bipolar Disorder Working Group of the Psychiatric Genetics Consortium, Nat Gen 2019

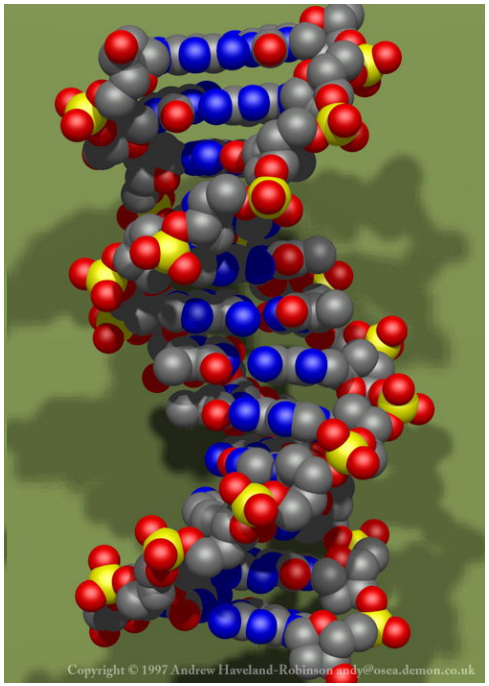
Genetic overlap observed among an increasing number of disorders



The Brainstorm Consortium, Science 2018

G x E

Genes



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

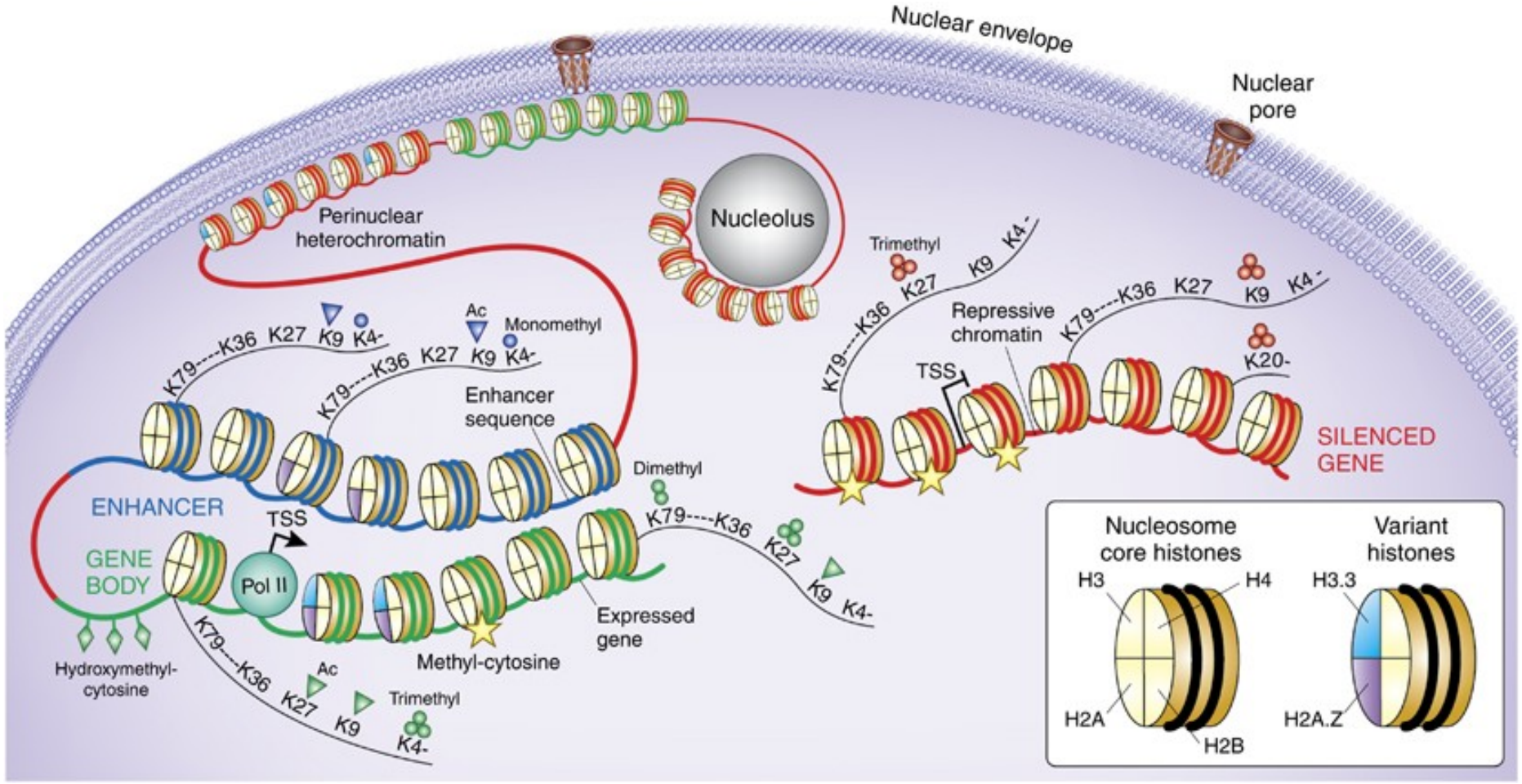
Environment

Mood Disorders: childhood trauma

Schizophrenia:
- -in utero events, such as infections, nutritional deficiencies
- -childhood trauma/bullying
- -urban living
- -minority status/discrimination
- -cannabis use

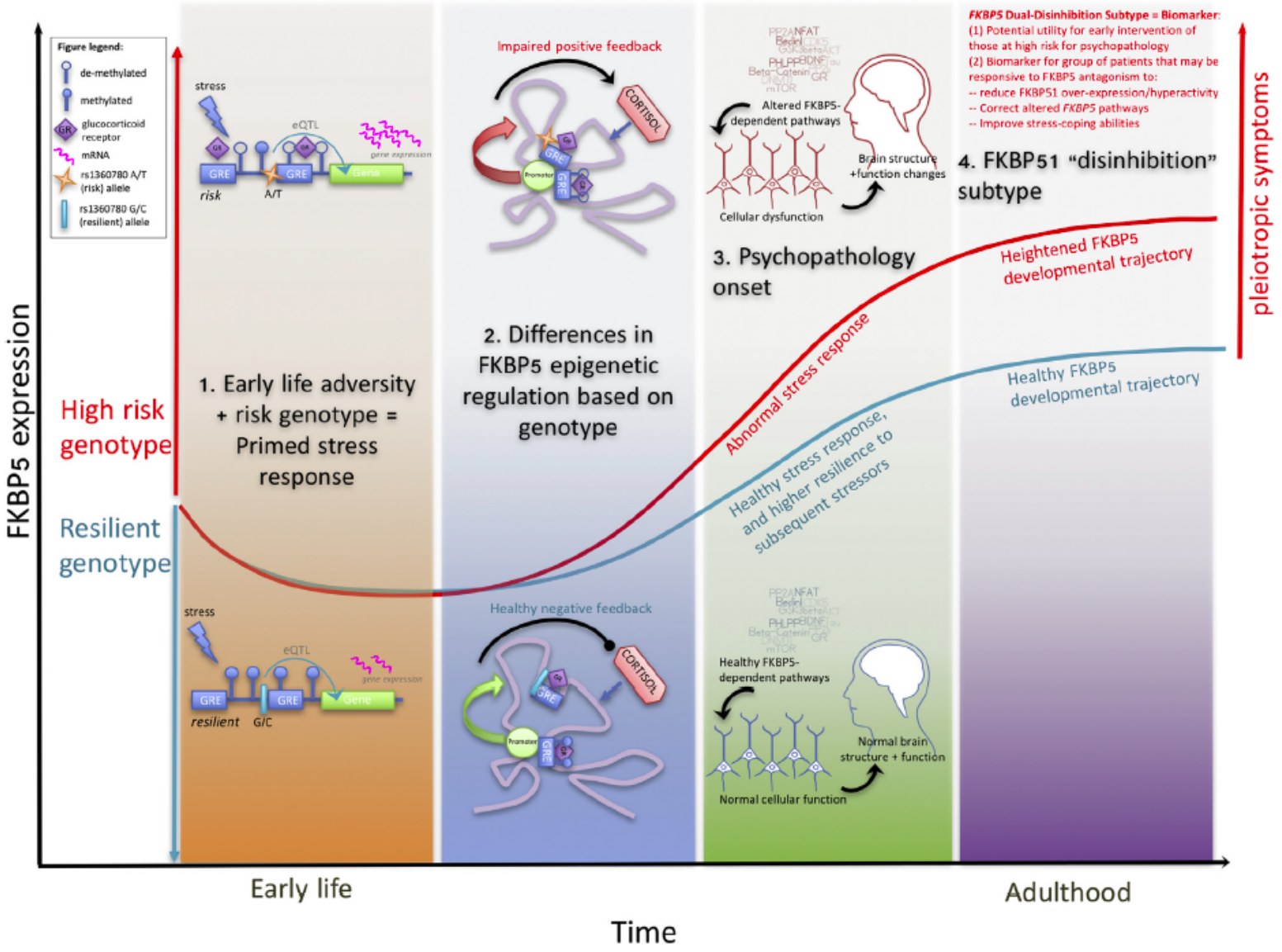
Epigenetic mechanisms

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



Houston et al, Neuropsychopharm Rev 2013

Genetic variation in the FKBP5 gene interacts with early adversity

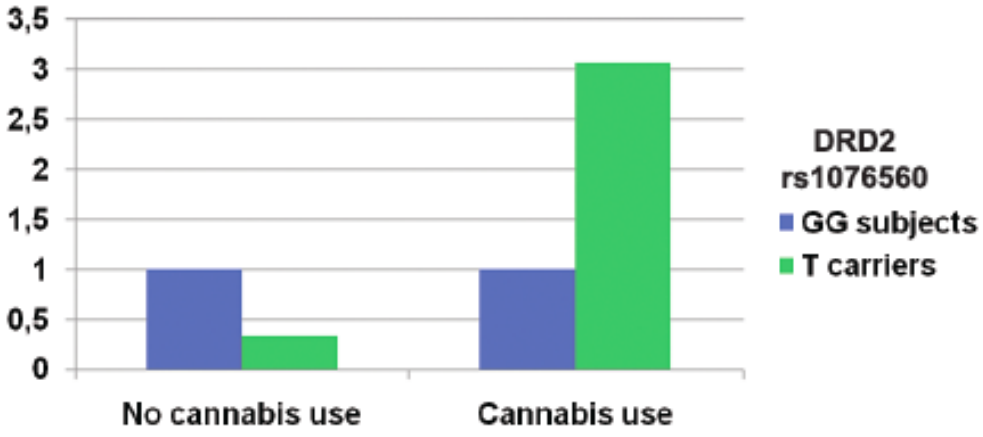


Matosin et al, Biol Psych 2018

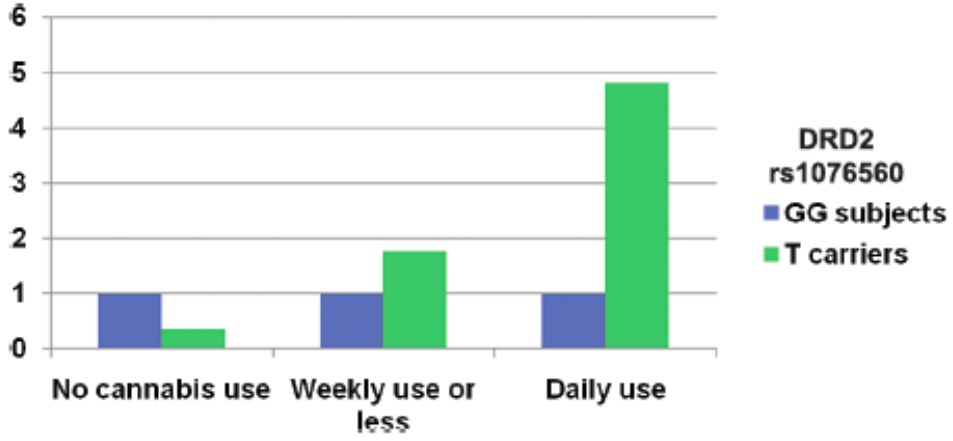
G x E interactions linked with schizophrenia

Example: DRD2 gene x cannabis use

Relative risk
for a psychotic disorder

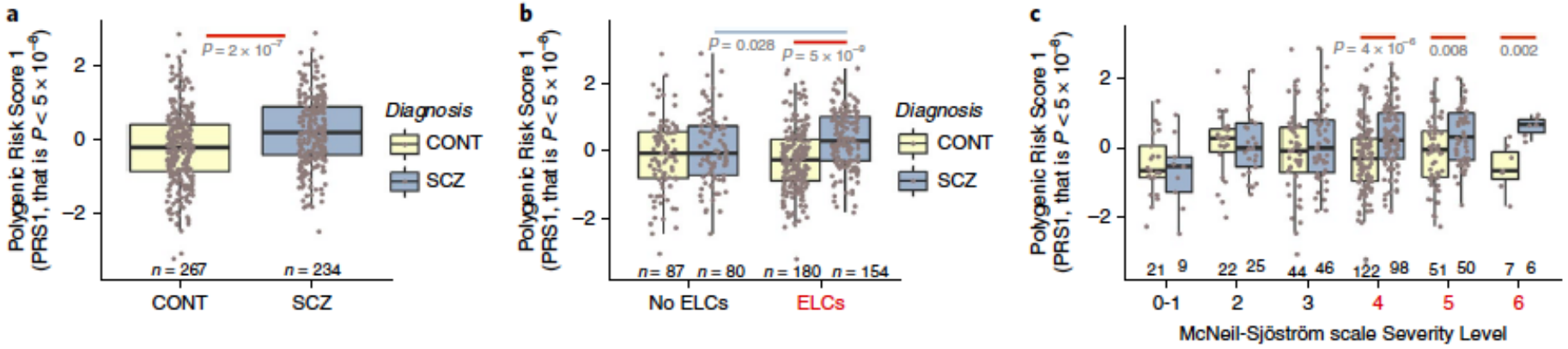


Relative risk
for a psychotic disorder



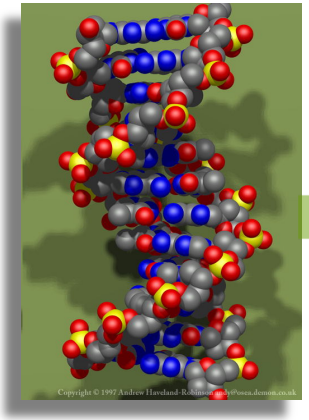
Colizzi et al, Schiz Bull 2015

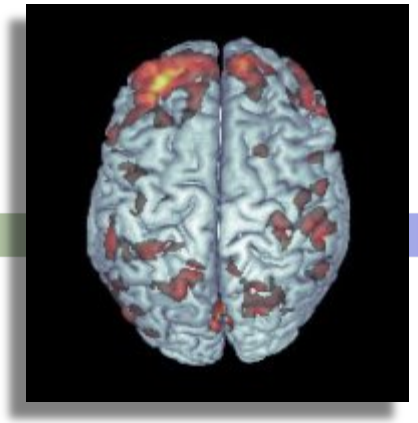
Interaction between increased genetic risk for schizophrenia and obstetric (intra-uterine) complications



Ursini et al, Nat Med 2018

The Overall Model





genetic vulnerability,
present from birth

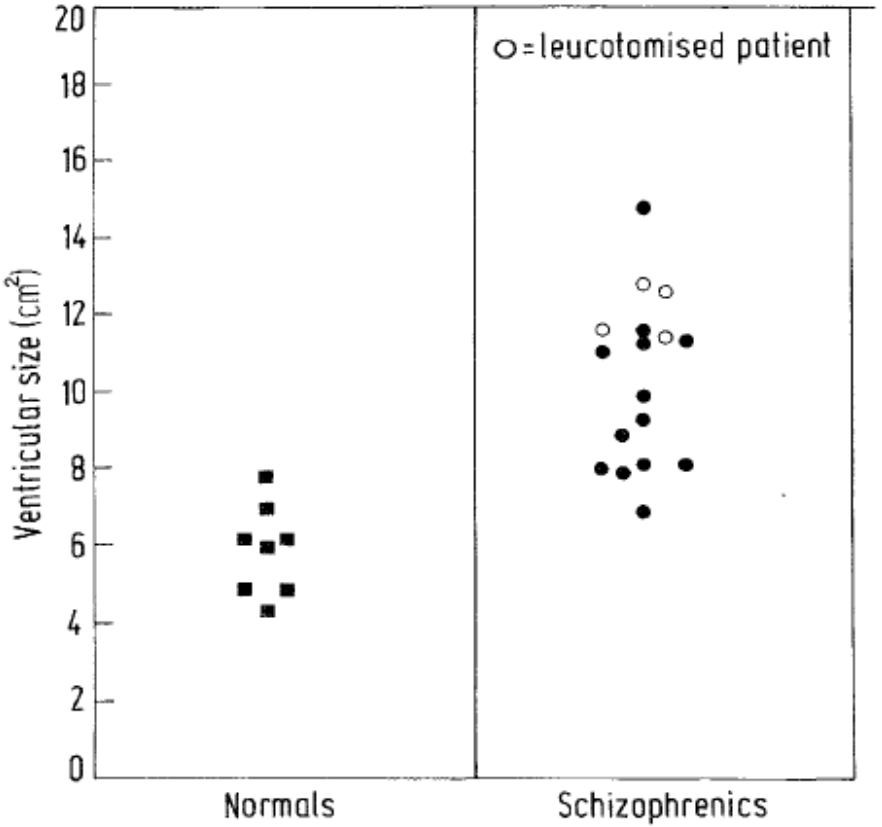
changes in brain
structure/function

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.

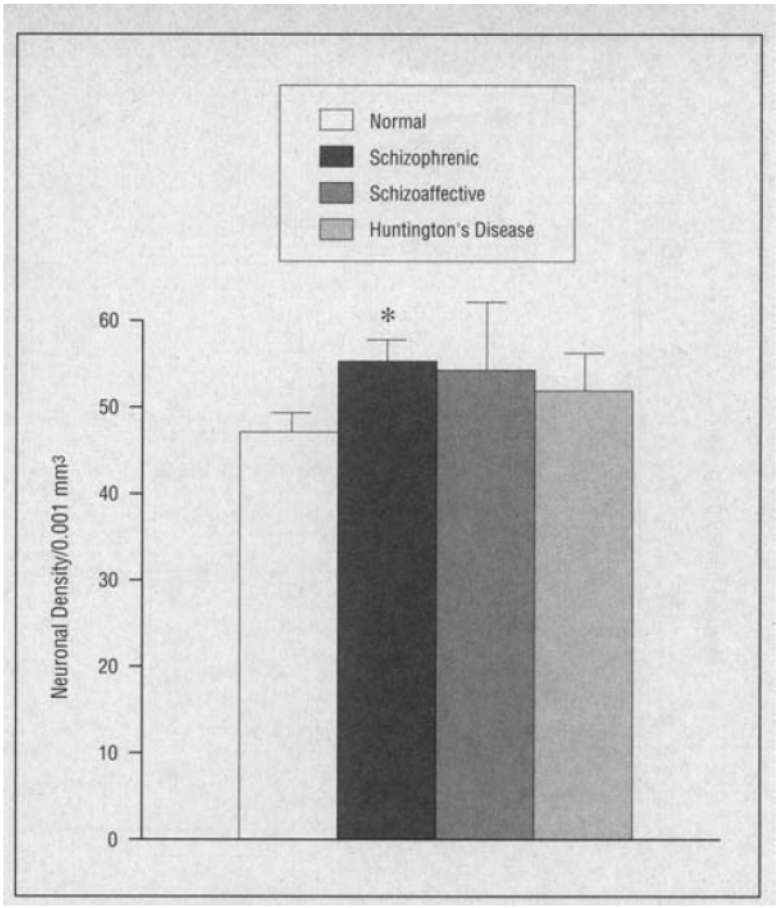
Johnstone et al, Lancet 1976

ORIGINAL ARTICLE

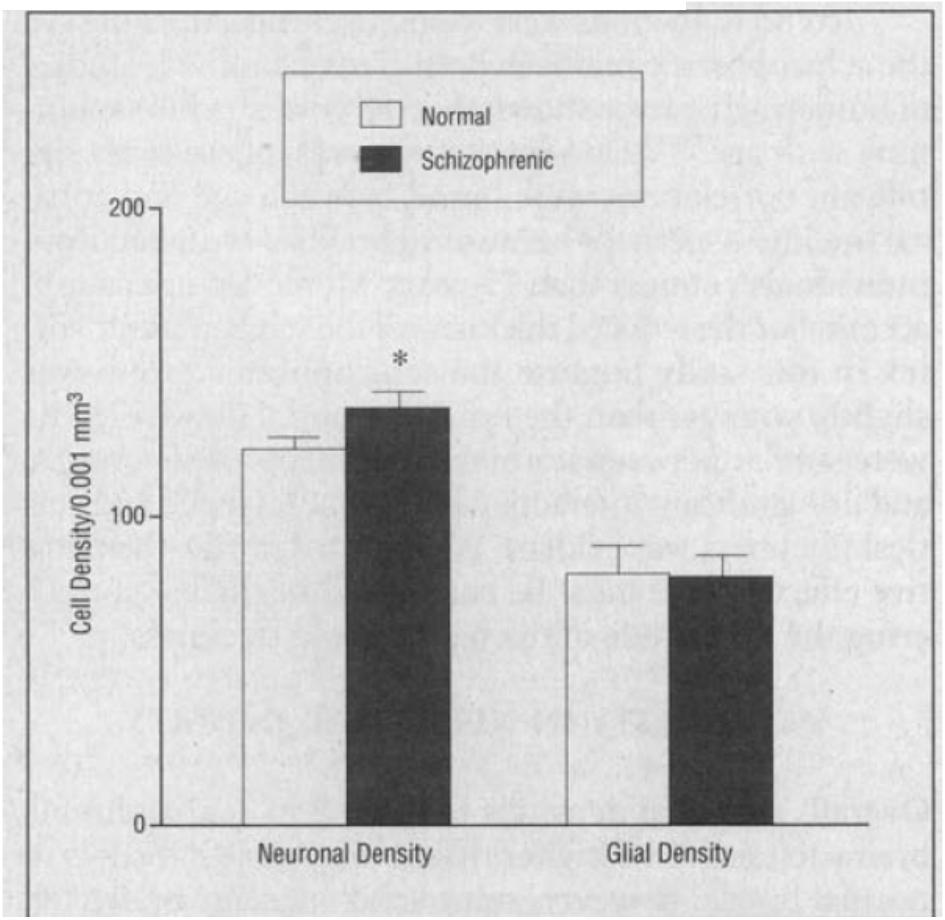
Abnormally High Neuronal Density in the Schizophrenic Cortex

A Morphometric Analysis of Prefrontal Area 9 and Occipital Area 17

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



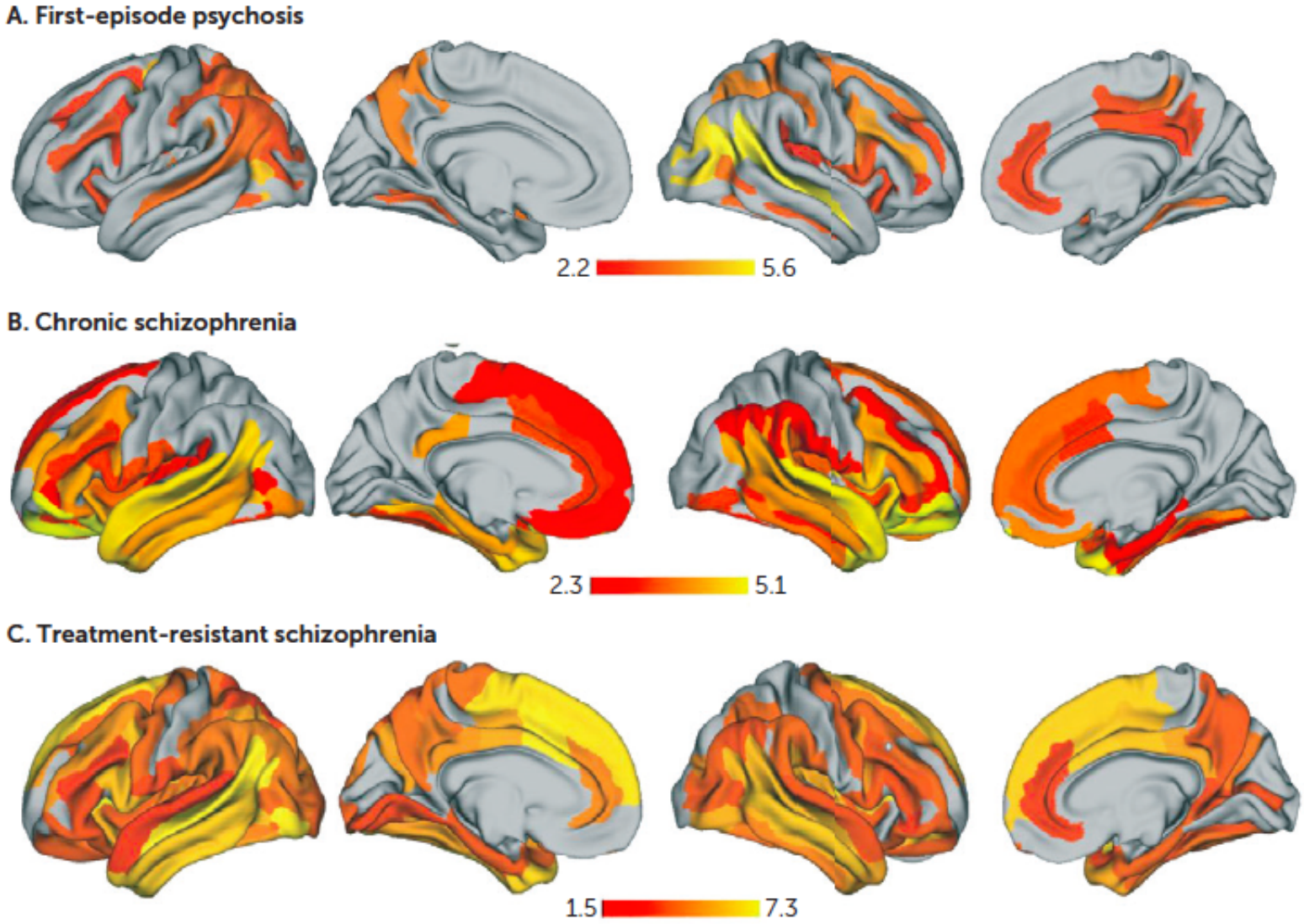
Area 9 (dlPFC)



Area 17 (primary visual cortex)

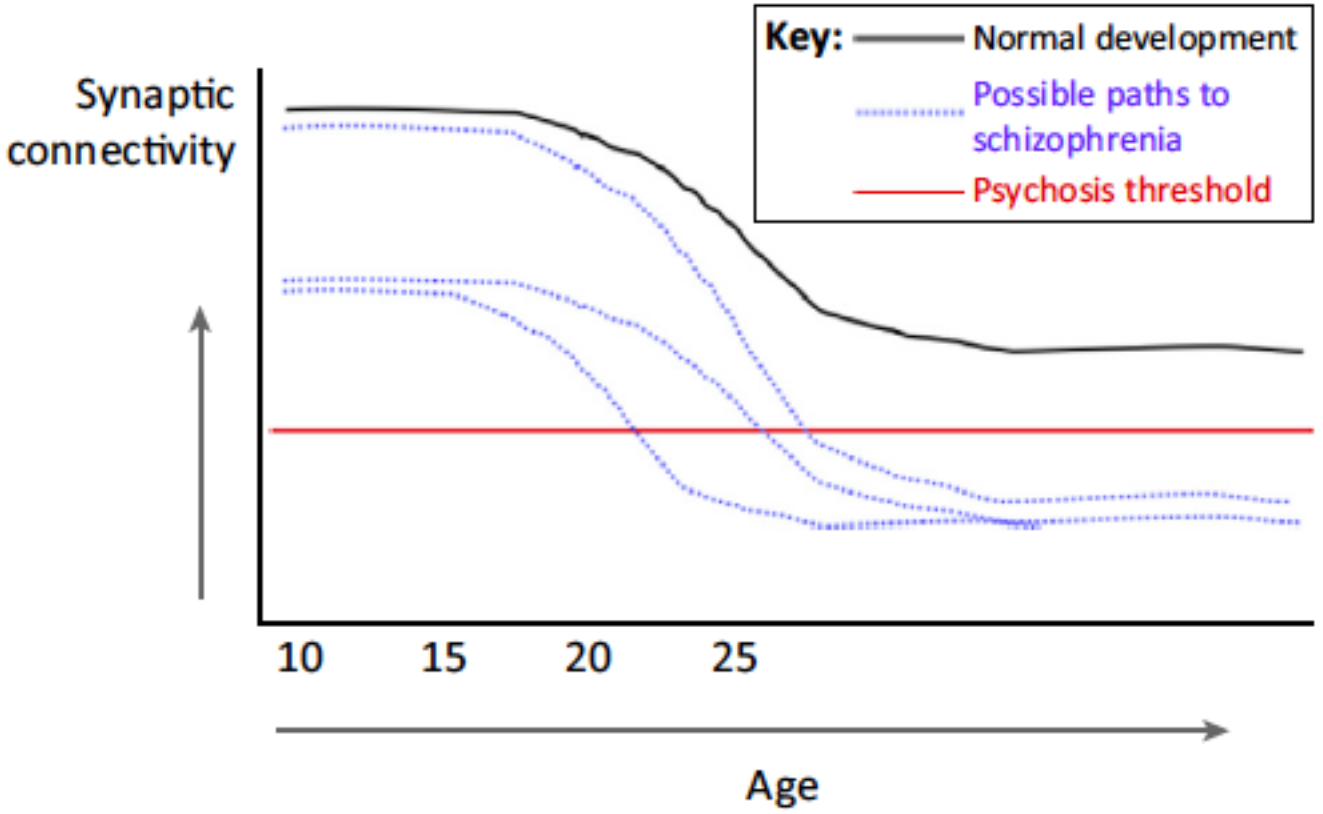
Selemon et al, Arch Gen Psych 1995

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



Wannan et al, AJP 2019

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

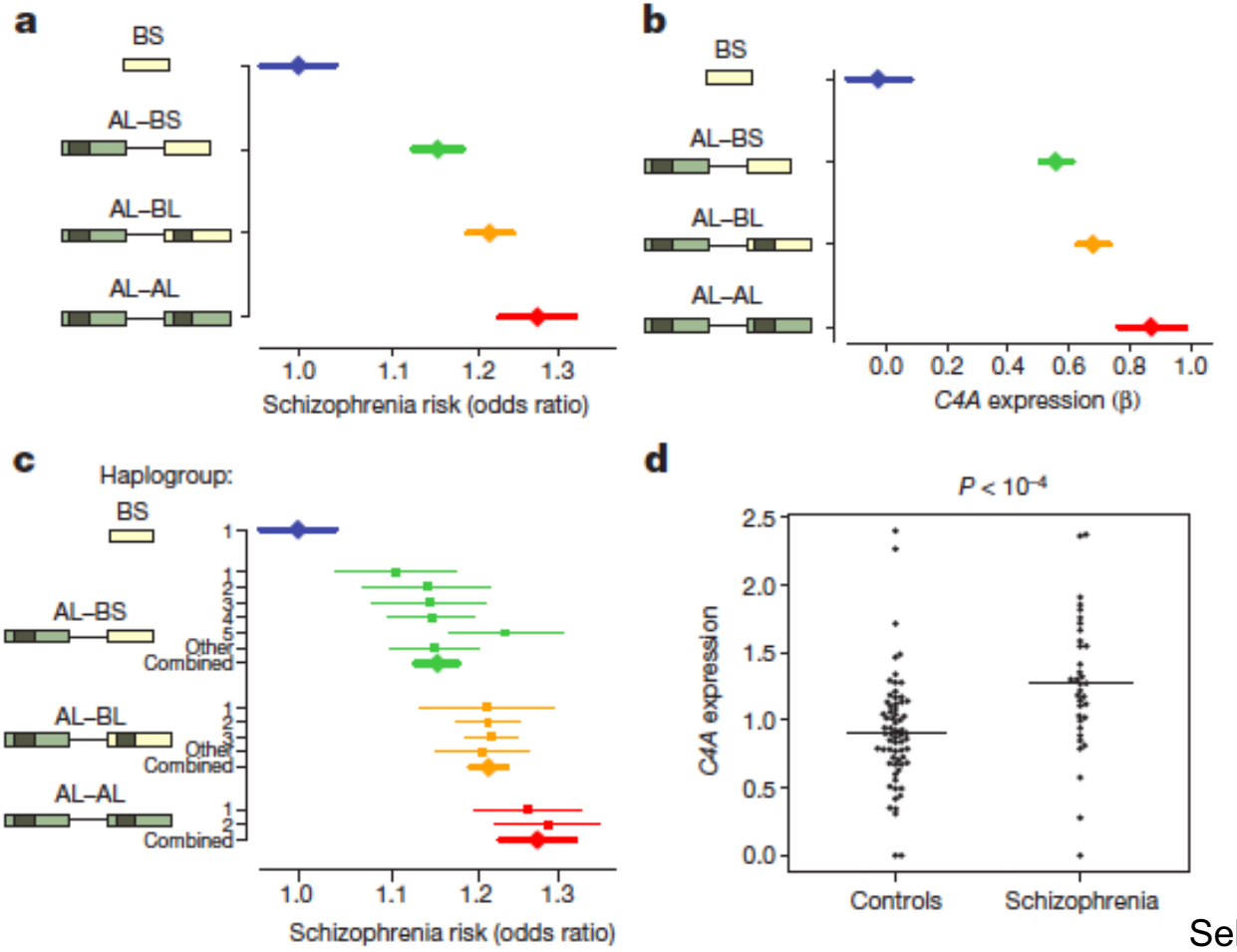


Cannon, TICS 2015

Schizophrenia risk from complex variation of complement component 4

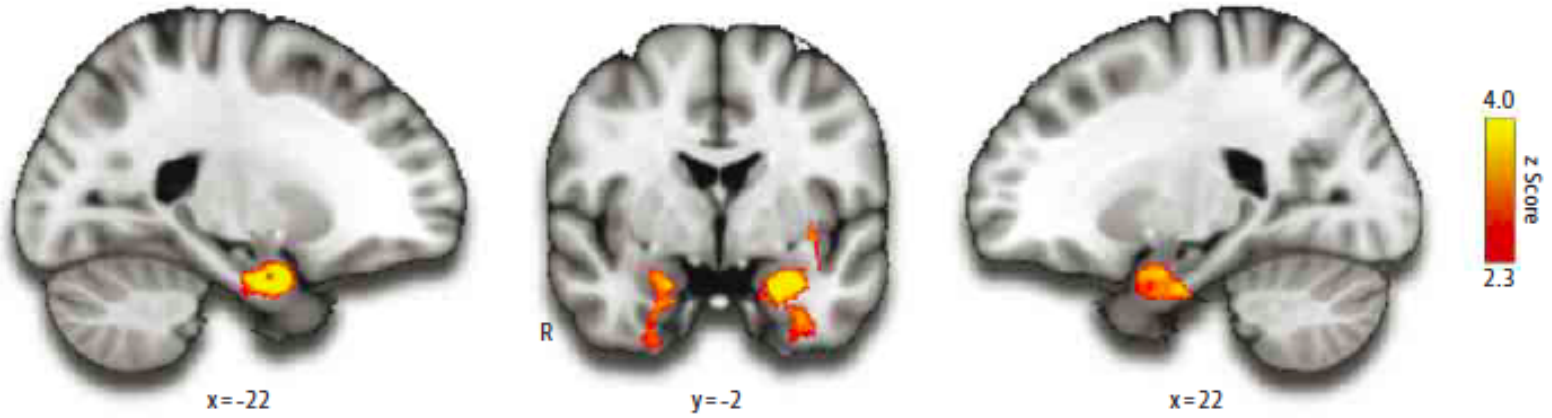
Aswin Sekar[1,2,3], Allison R. Bialas[4,5], Heather de Rivera[1,2], Avery Davis[1,2], Timothy R. Hammond[4], Nolan Kamitaki[1,2], Katherine Tooley[1,2], Jessy Presumey[5], Matthew Baum[1,2,3,4], Vanessa Van Doren[1], Giulio Genovese[1,2], Samuel A. Rose[2], Robert E. Handsaker[1,2], Schizophrenia Working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

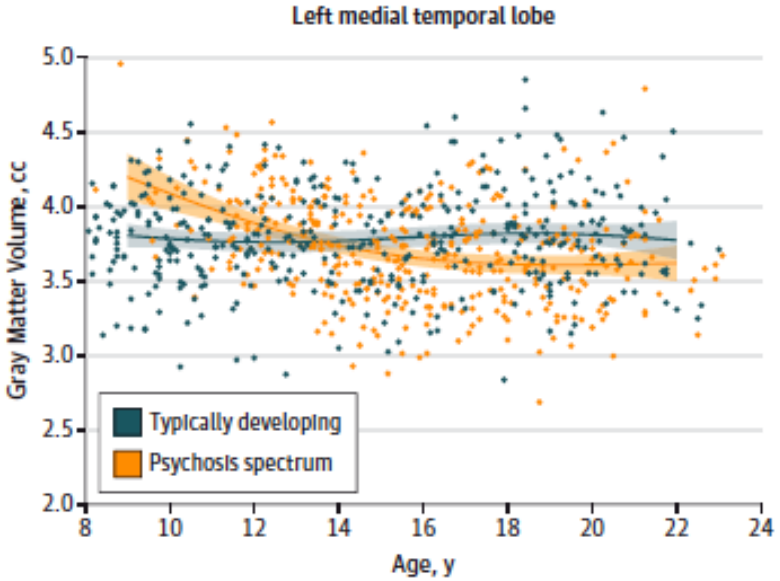
Schizophrenia risk proportional to the C4 allele's tendency to increase C4A expression, which mediates pruning

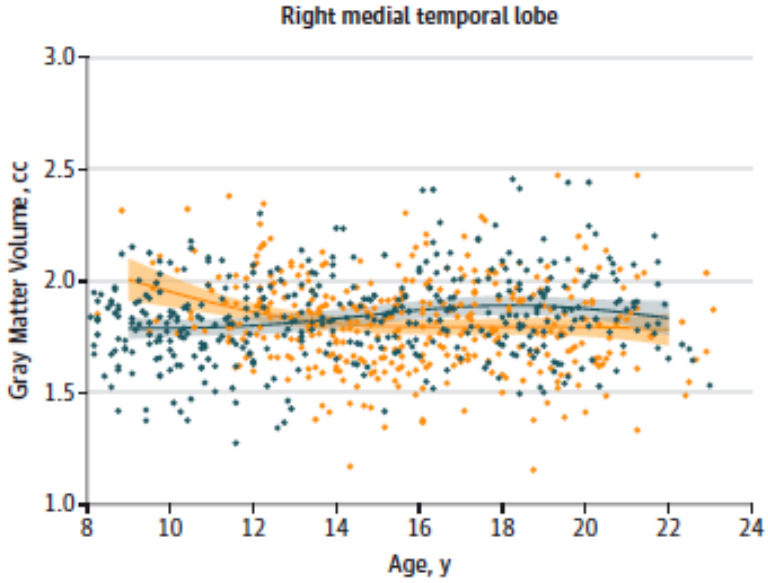


Sekar et al, Nature 2016

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

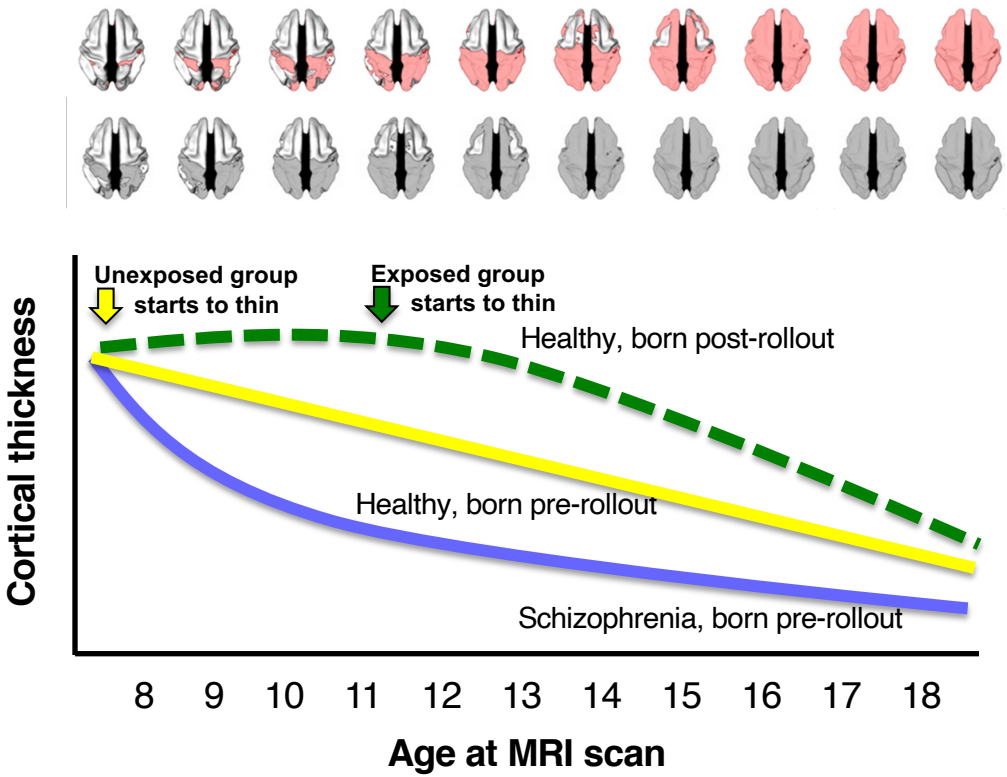






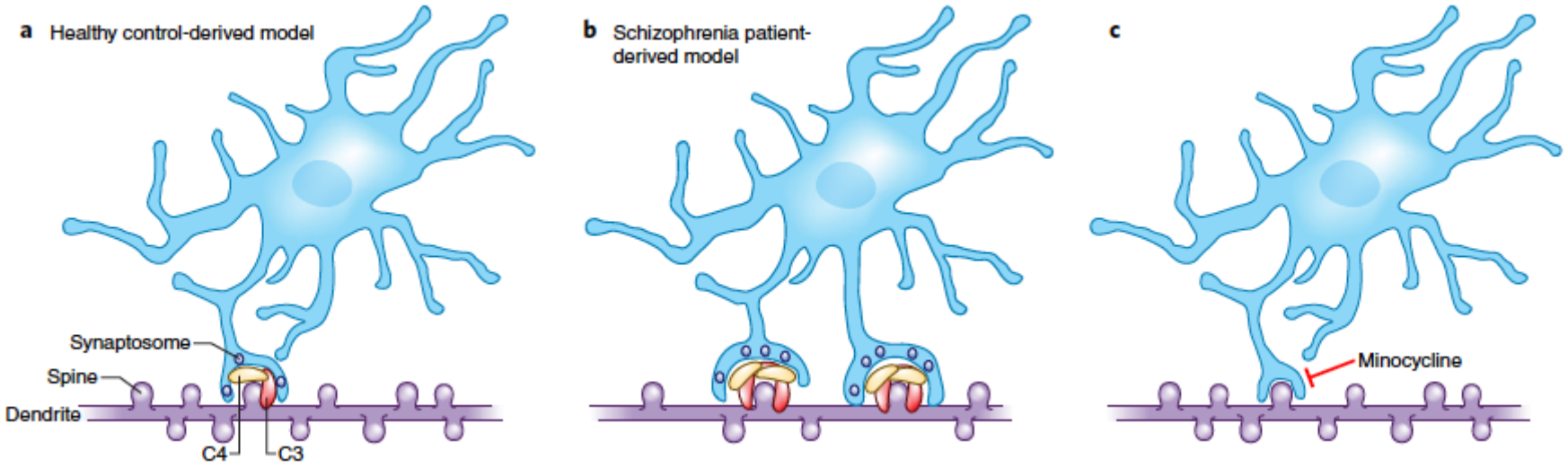
Satterthwaite et al, JAMA Psych 2016

Fetal fortification exposure alters cortical development during adolescence



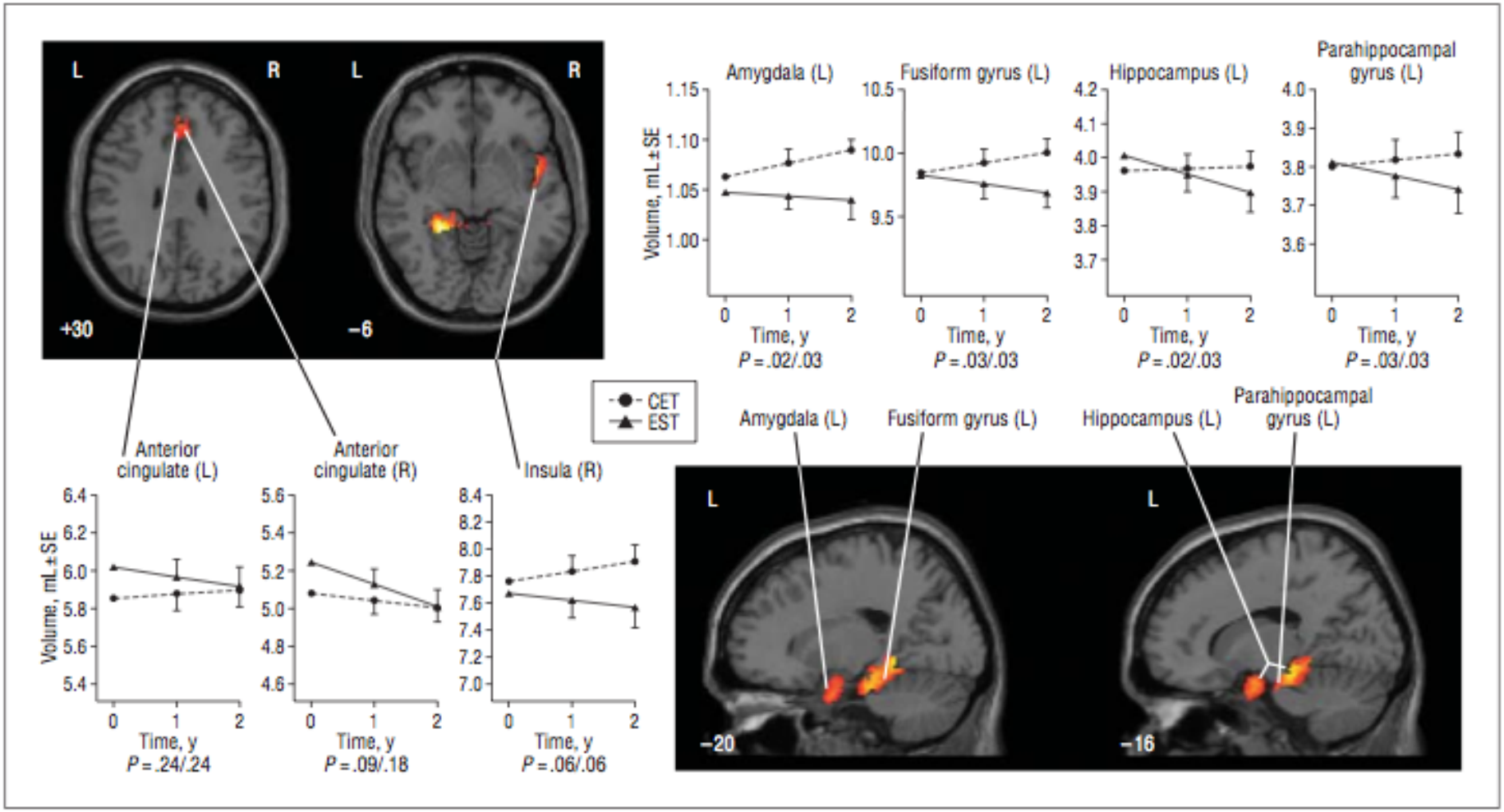
Eryilmaz et al, JAMA Psych 2018

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



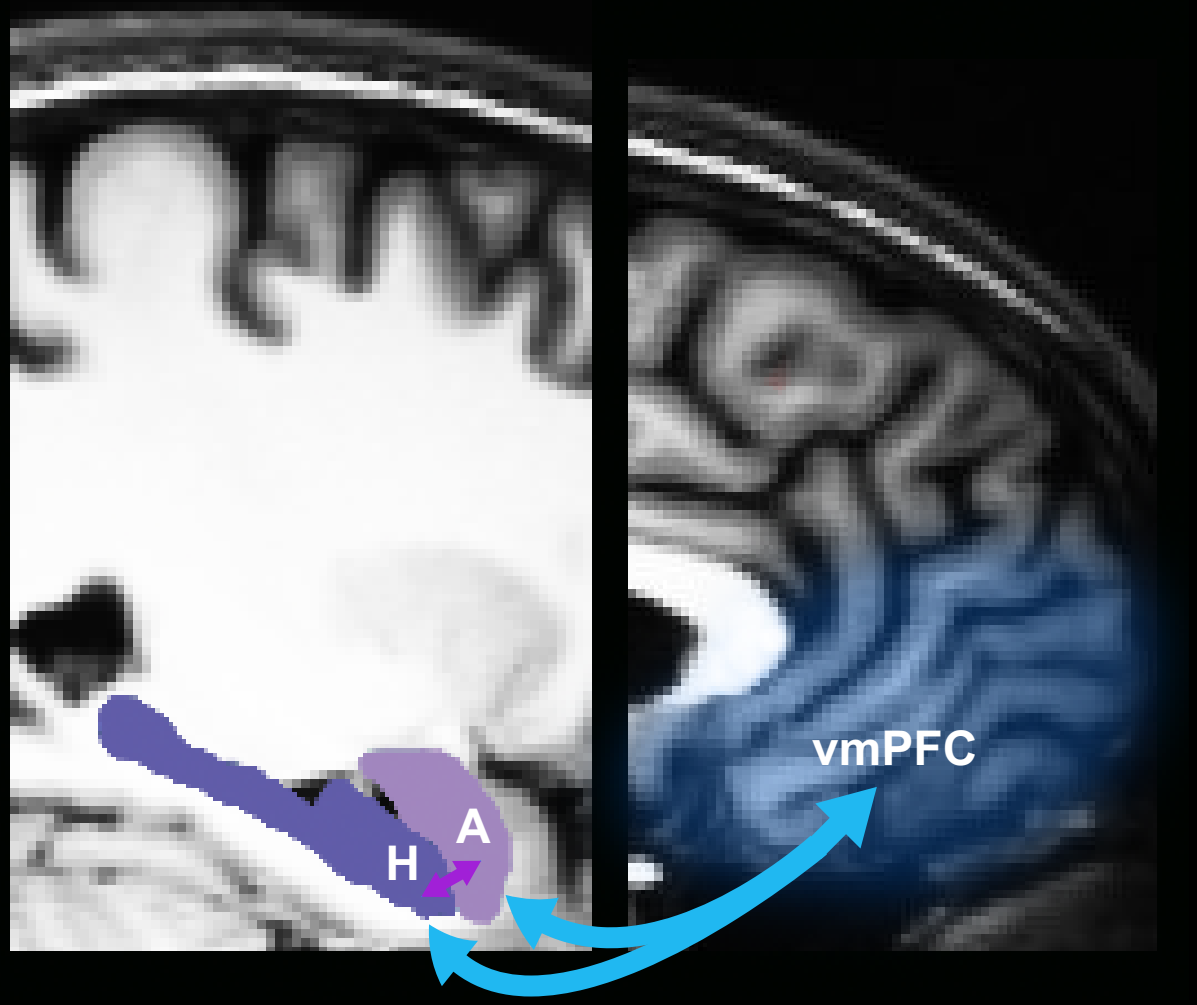
Sellgren et al, Nat Neurosci, 2019;
Wang, Zhang and Gage, Nat Neurosci 2019

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



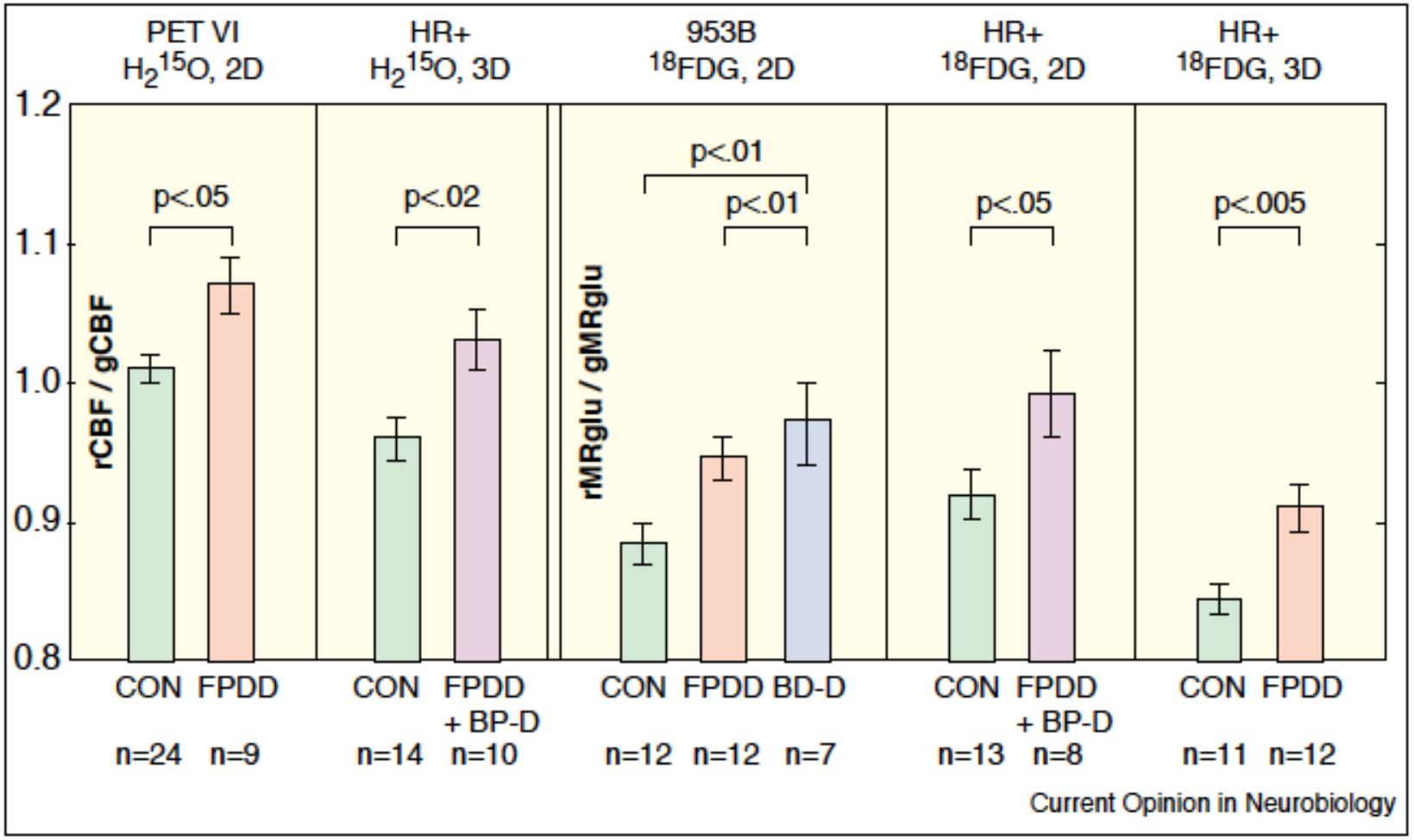
Eack et al, Arch Gen Psych 2010

A key circuit affected in neuropsychiatric disorders



H = hippocampus
A = amygdala

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

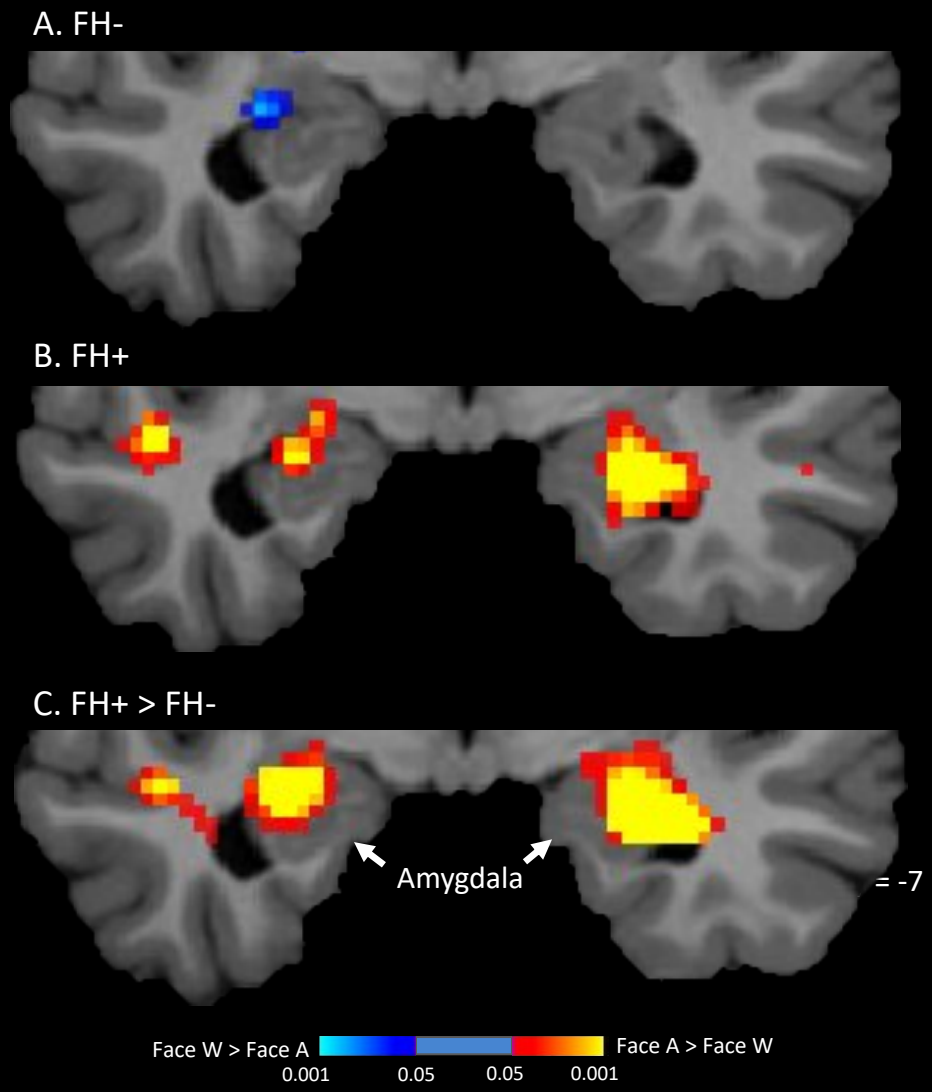


Drevets Curr Opin Neurobio 2001

Overactivity of the amygdala in children of patients with depression has been observed in 3 studies

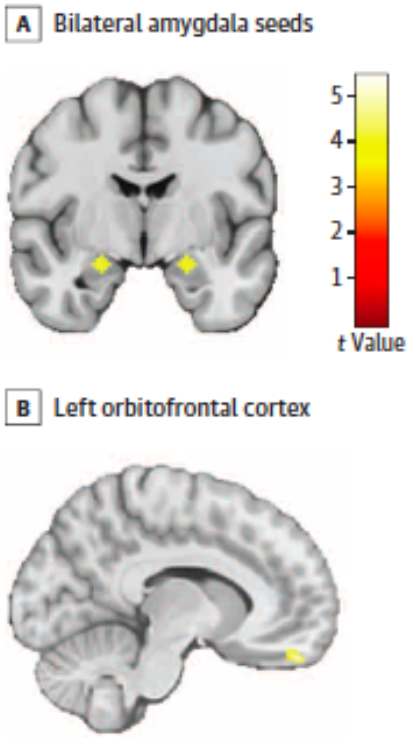
(Monk et al, 2008; Swartz et al, 2014, Chai et al, 2015)

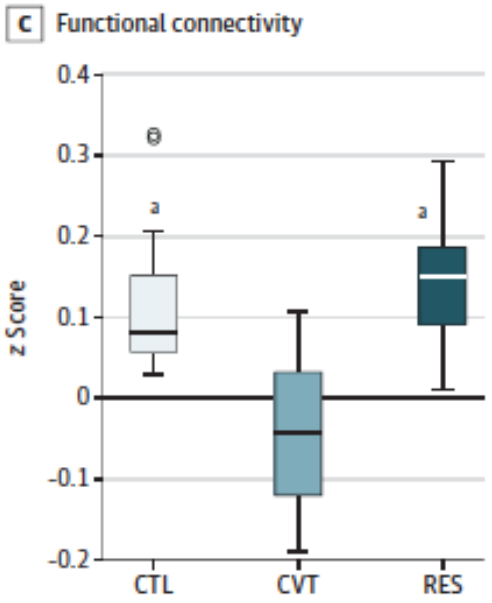
Also found in young adults with a first-degree relative with depression

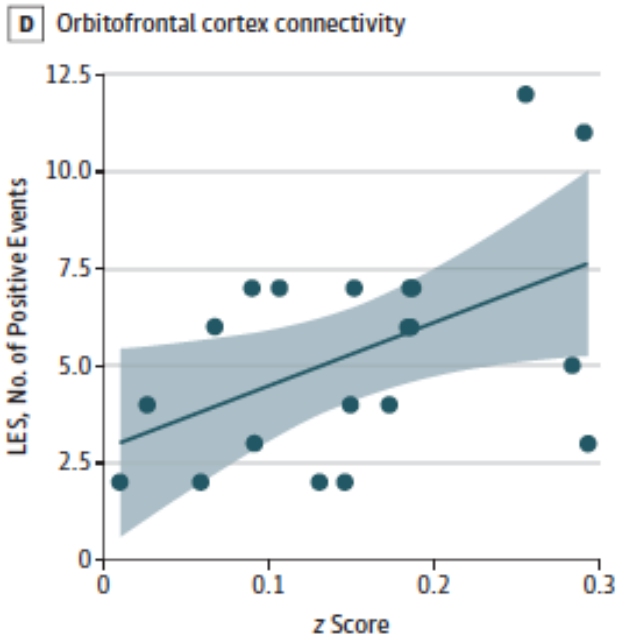


Barbour et al Biol Psych CNNI 2020

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



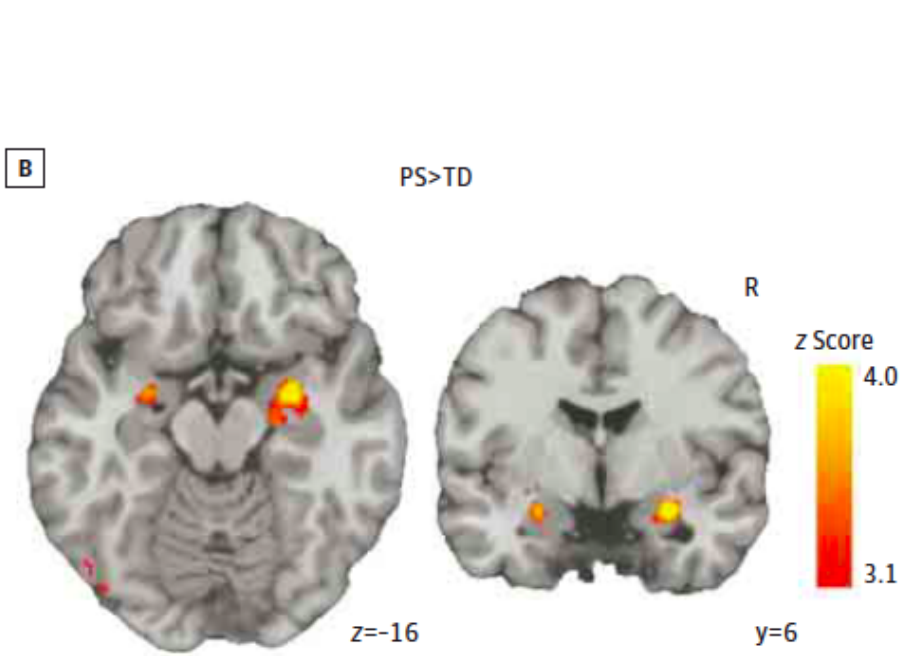


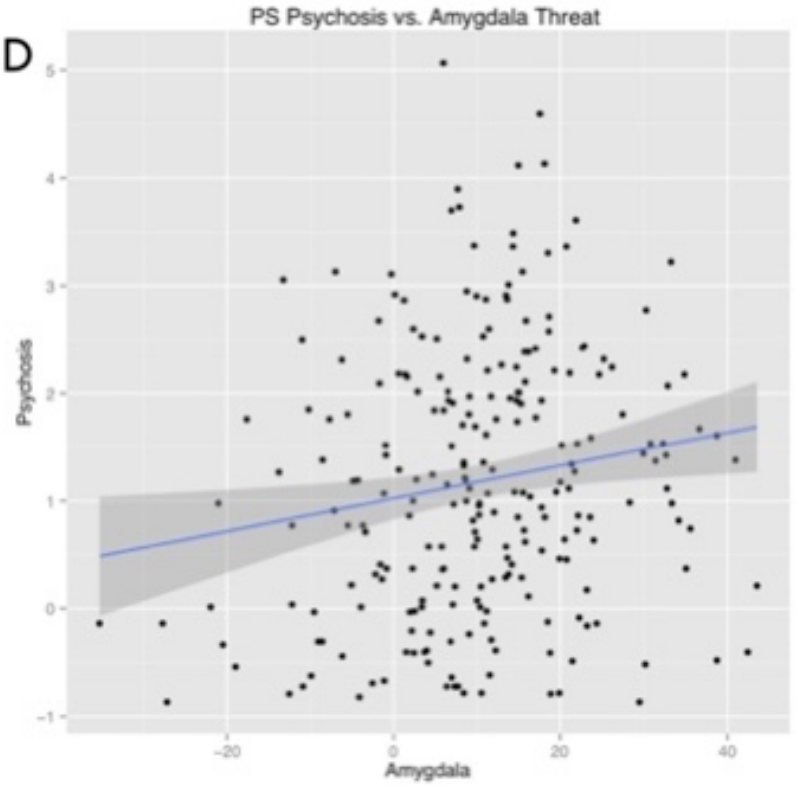


Study population:
40 adolescent females with a mother with recurrent MDD (high risk)
(of whom 20 developed MDD) and 25 control adolescents without such risk

Fischer et al, JAMA Psych 2018

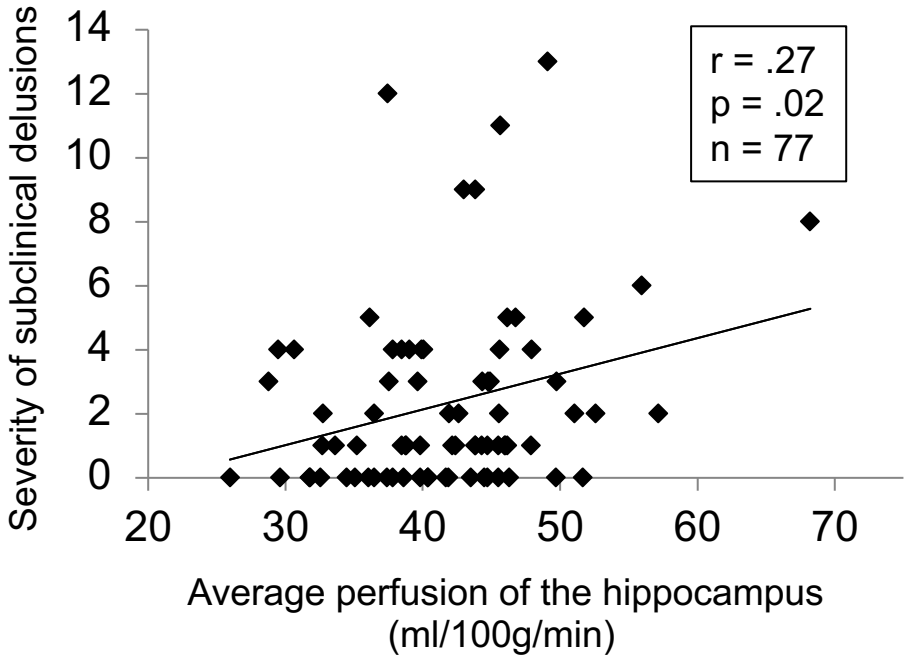
Overactivity of the amygdala in youth with subclinical, psychotic-like symptoms

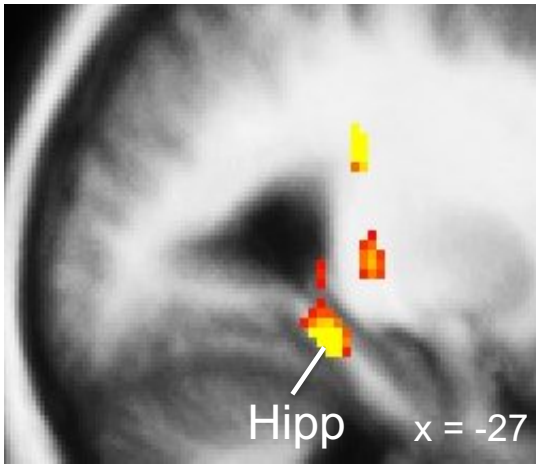




Wolf et al, JAMA Psych 2015

Overactivity of the hippocampus in individuals with subclinical delusions

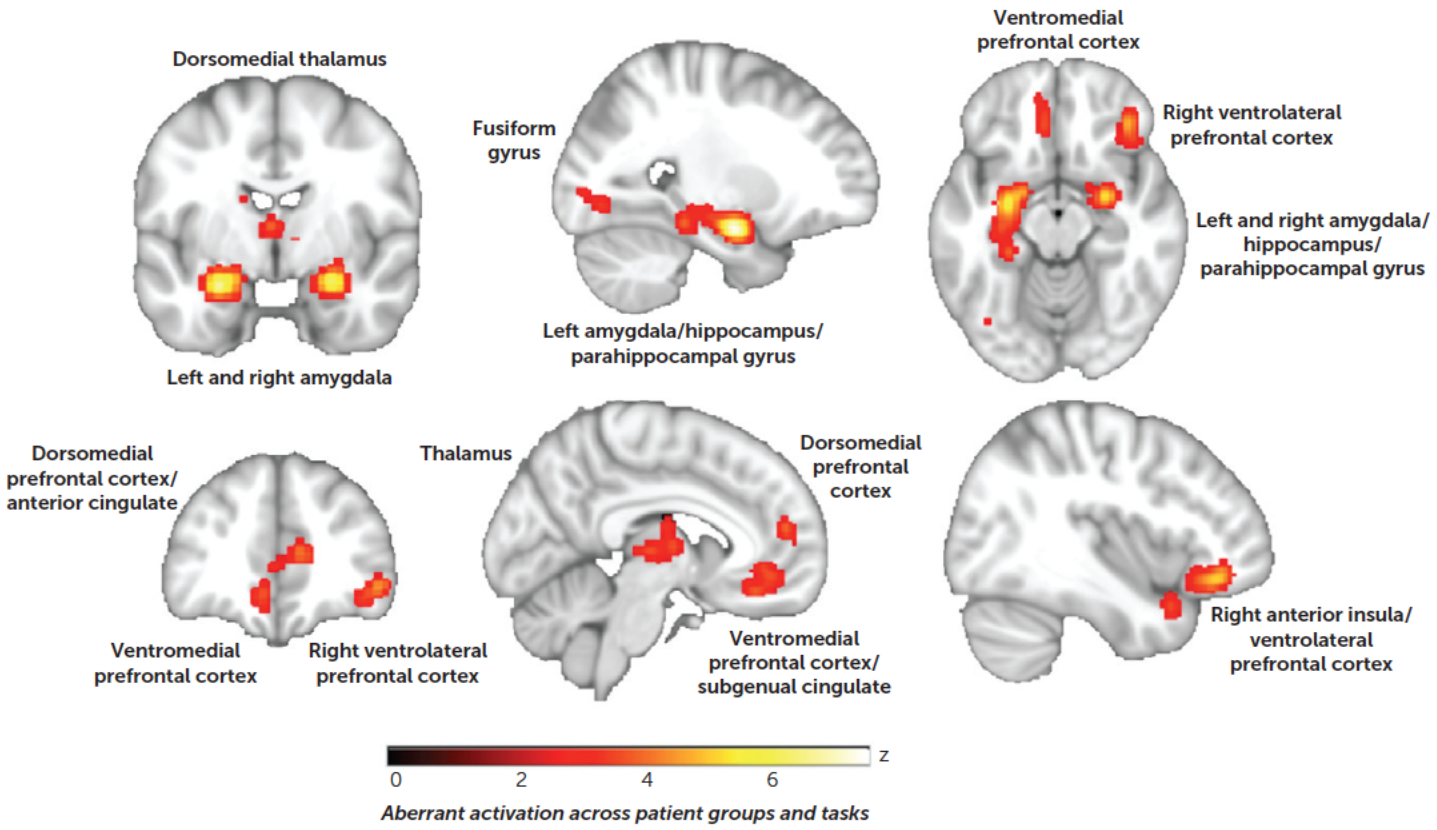




Support for the “continuum model” of psychosis

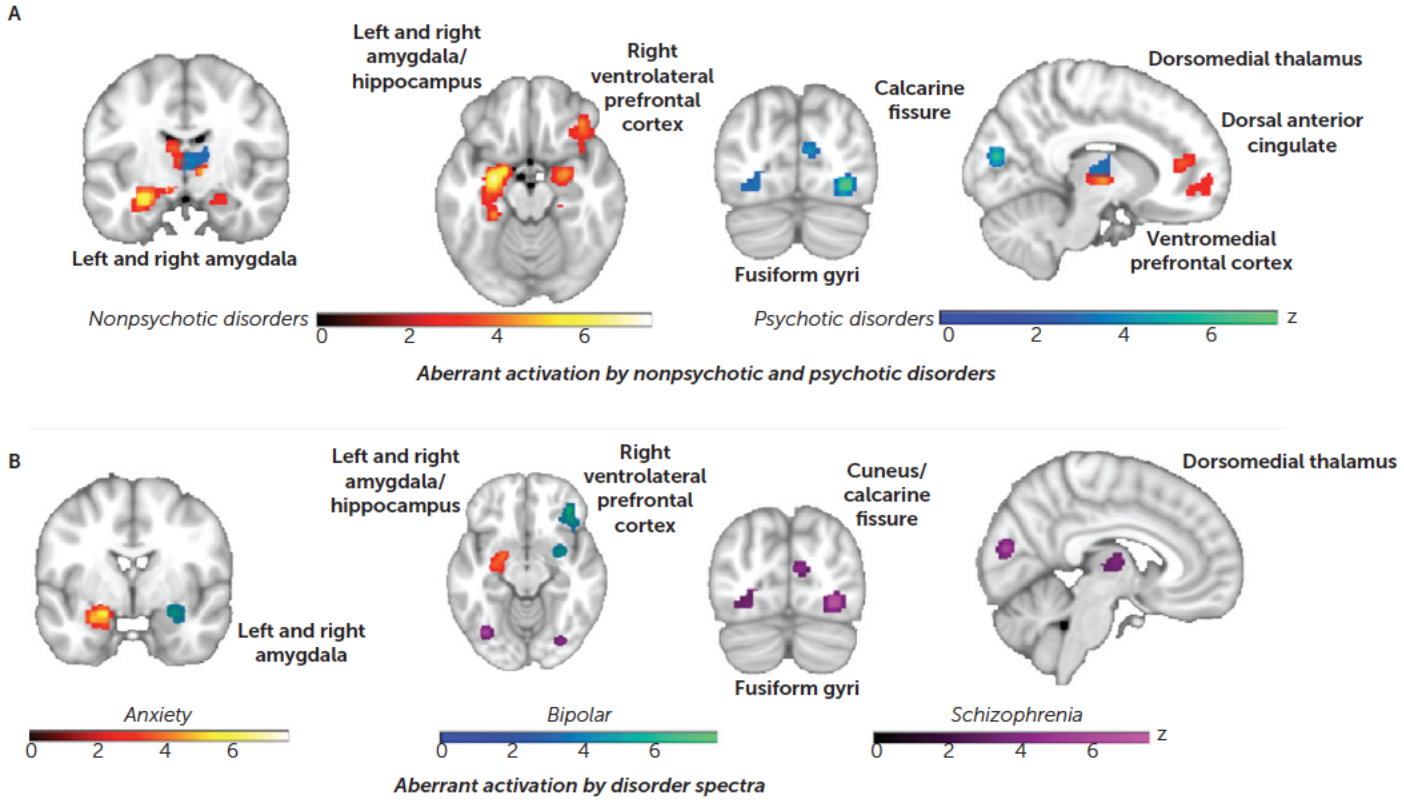
Wolthusen et al, Biol Psych CNNI, 2018

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



McTeague et al, Am J Psych 2020

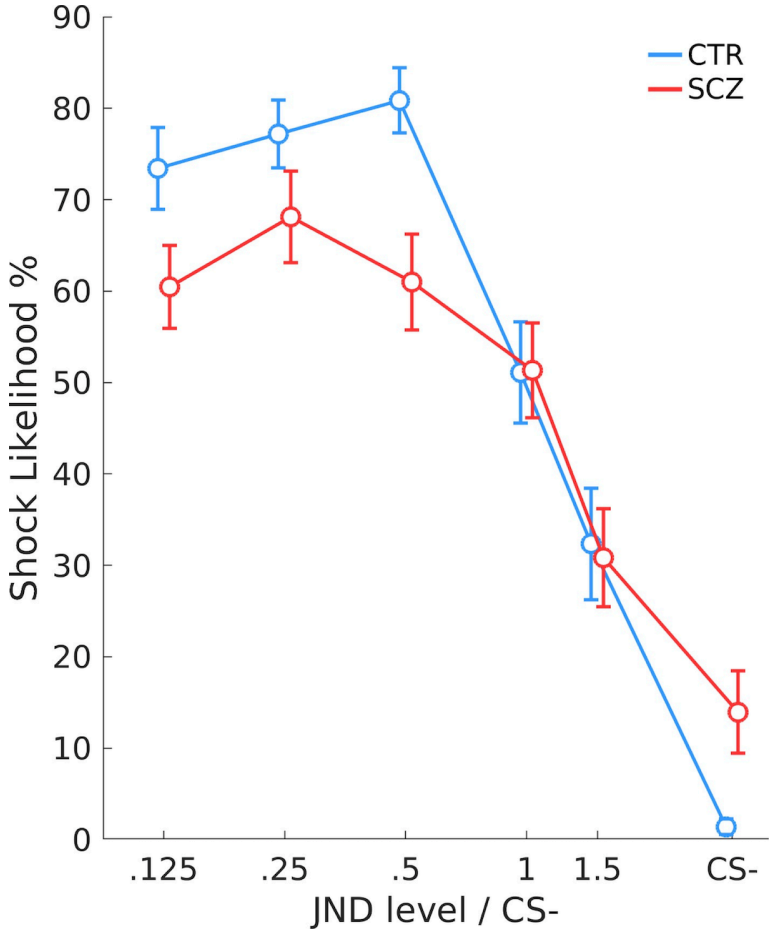
Differences between psychotic and non-psychotic patients

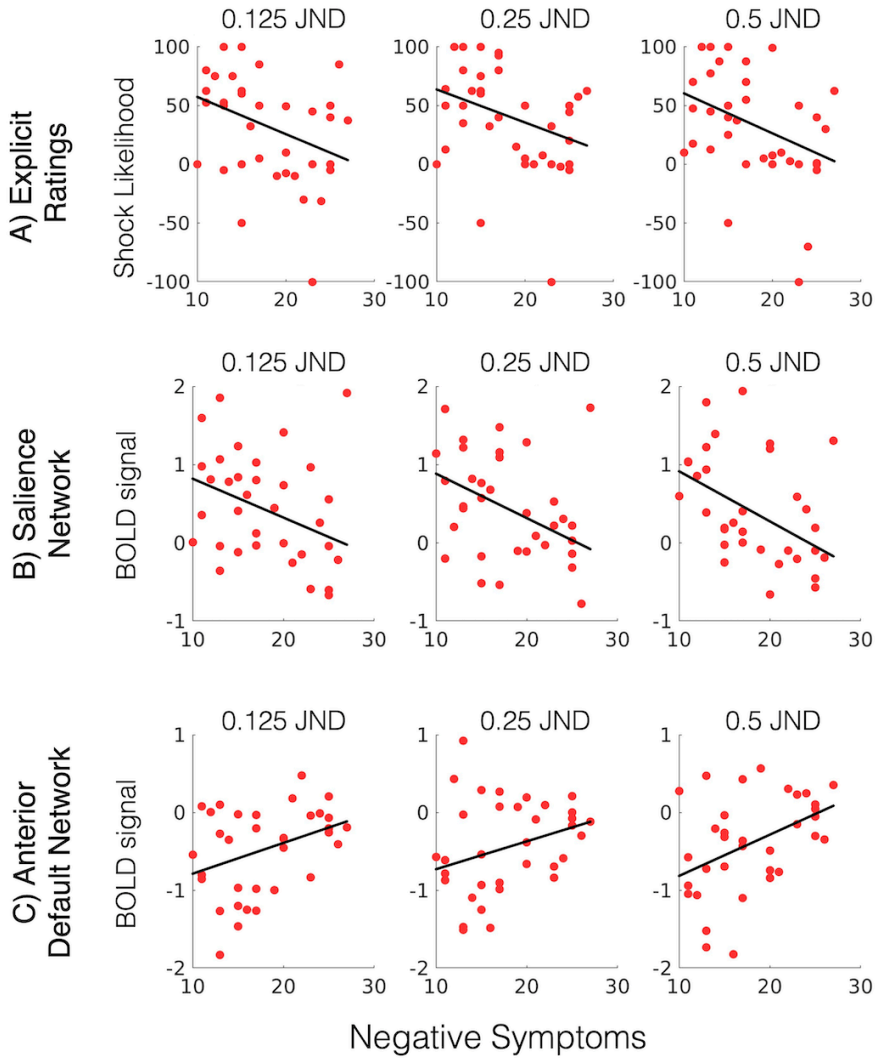


[a] Unipolar depressive and substance use disorder groups did not show convergence.

McTeague et al, Am J Psych 2020

Cognitive neuroscience has shed light on the altered cognitive and affective mechanisms in these illnesses

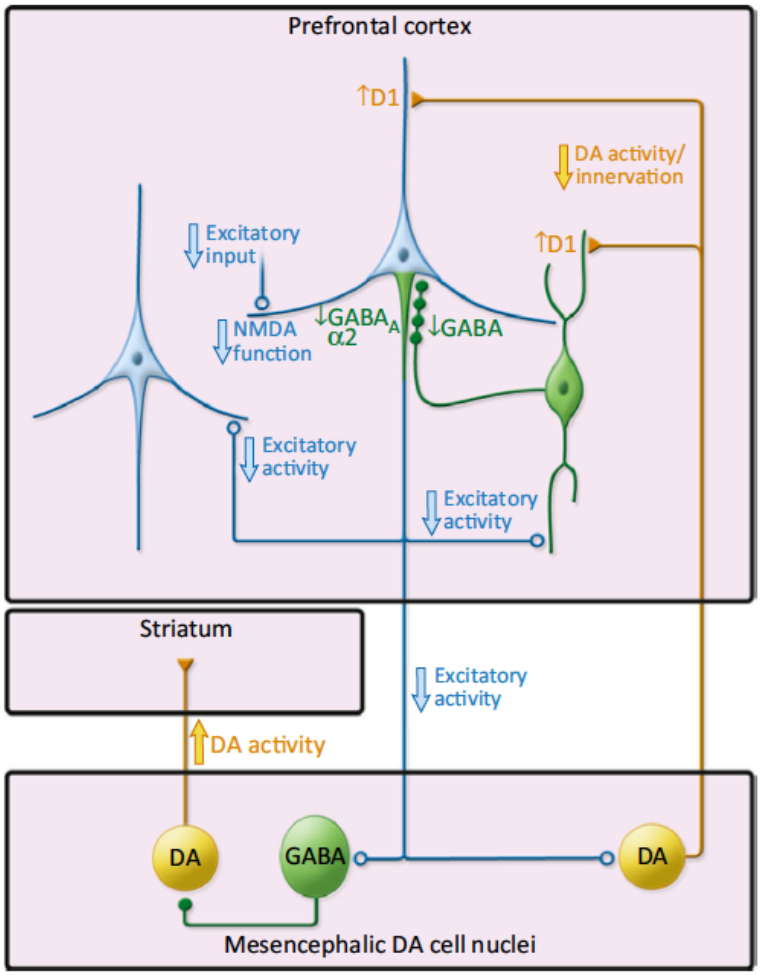




Deficits in fear generalization in schizophrenia are linked to negative symptoms

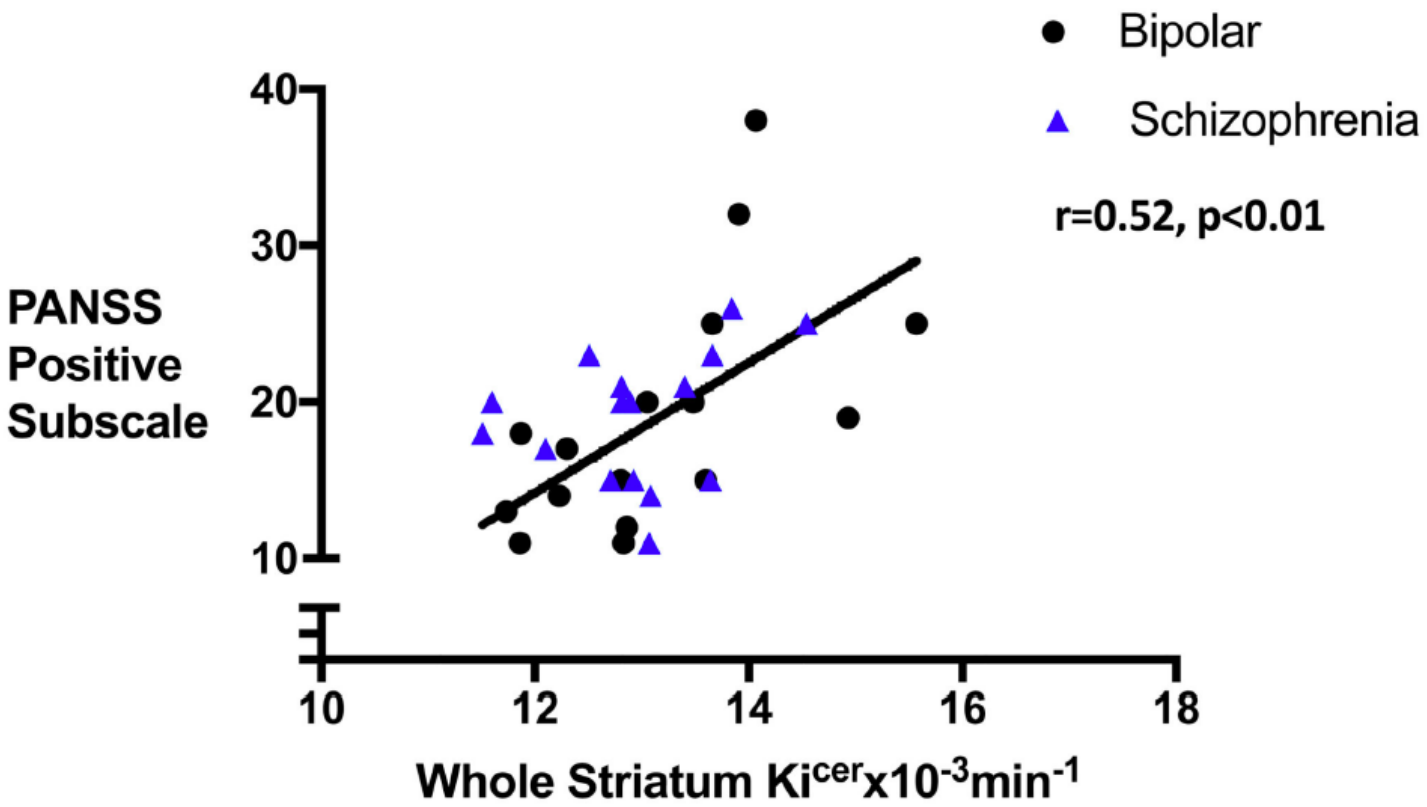
Touminen et al, under review

Cellular model of schizophrenia



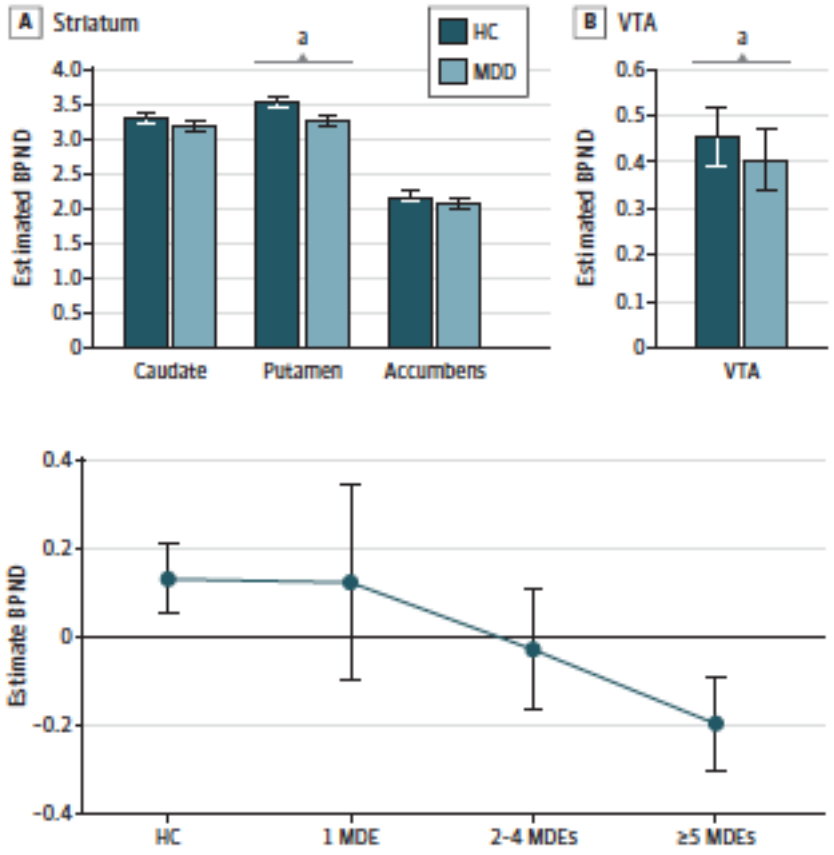
Cannon, TICS 2015

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



Jauhar et al, JAMA Psych 2017

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



Pizzagalli et al, JAMA Psych 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