MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Research on the neural basis of schizophrenia “then” and “now”

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Schizophrenia Education Day
December 9th, 2022

MASSACHUSETTS GENERAL HOSPITAL

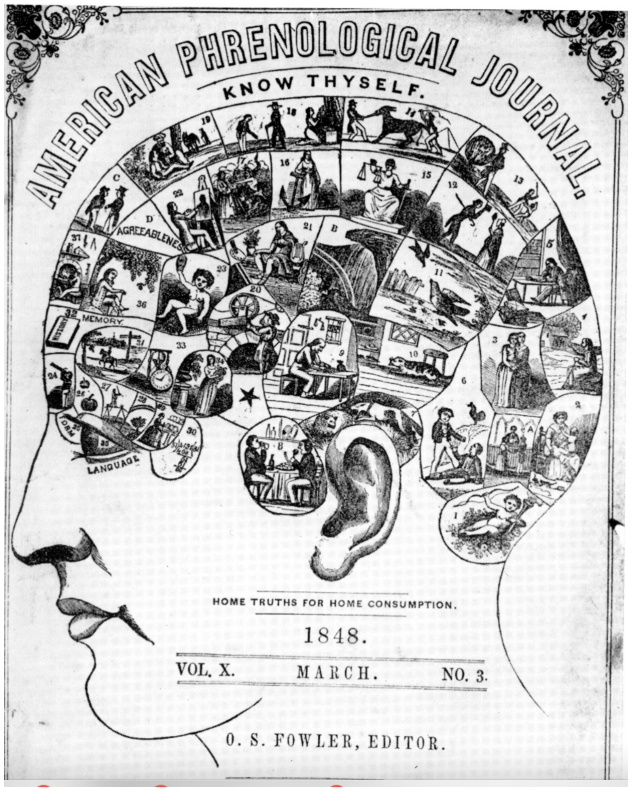
Athinoula A. Martinos Center For Biomedical Imaging

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

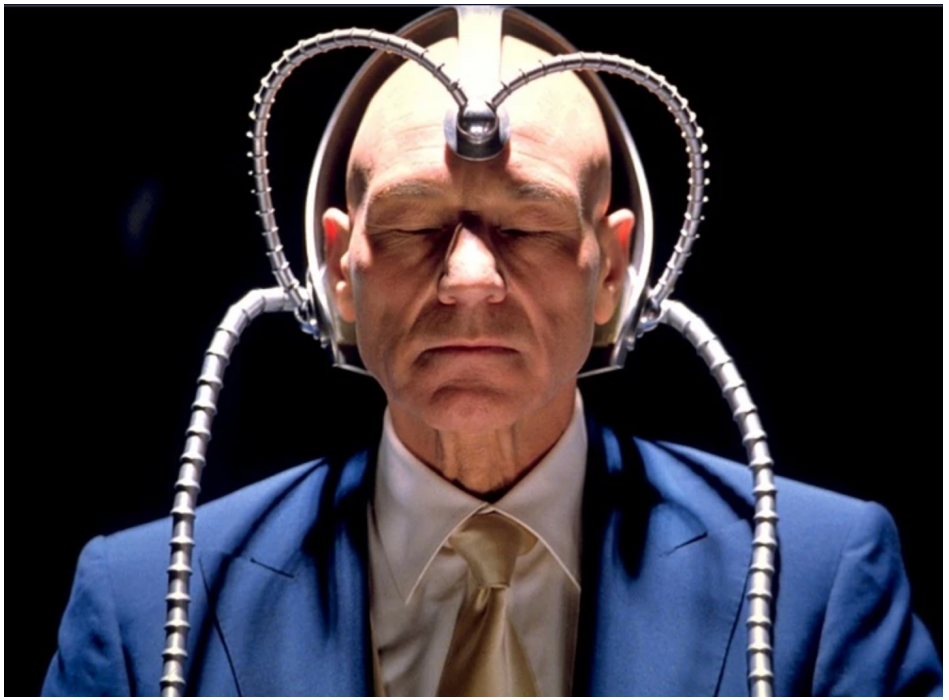
Disclosures

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

“Then” (2002) versus “Now” (2022)?



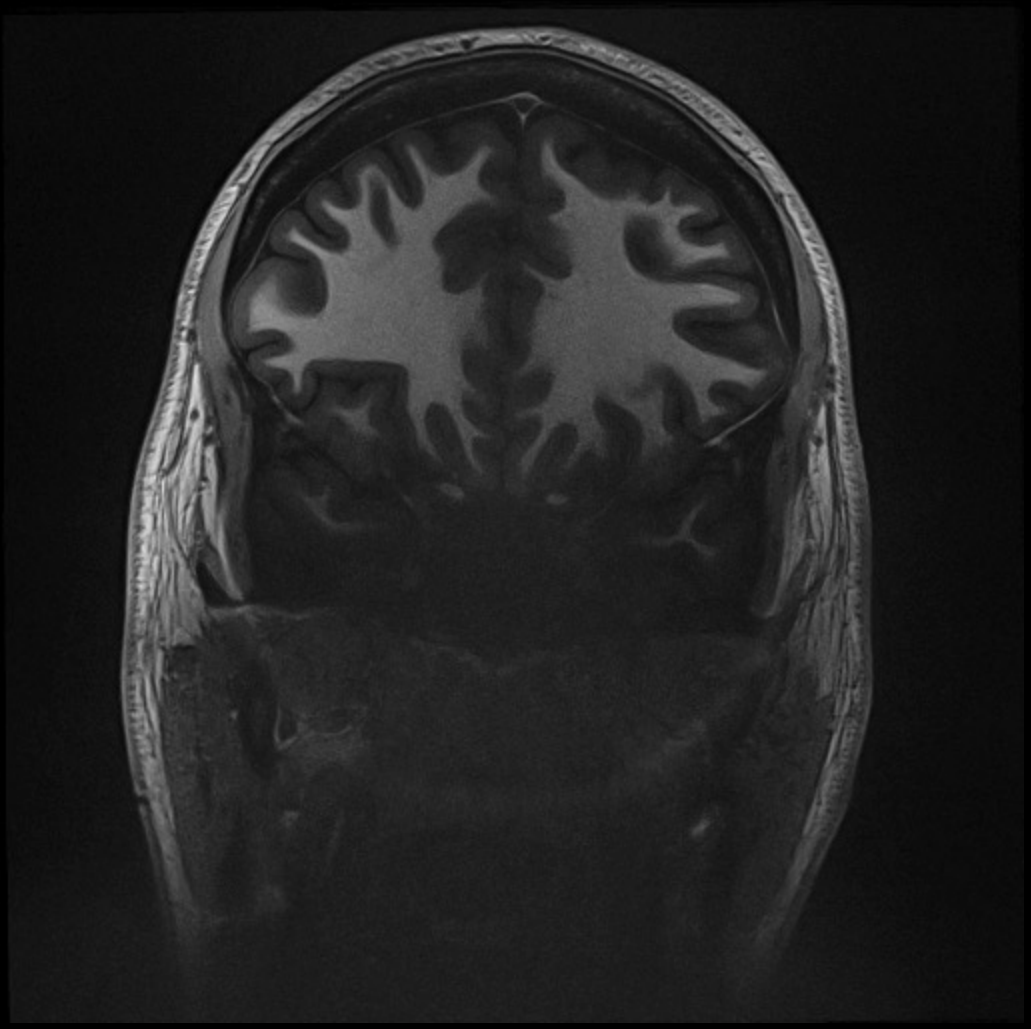
Phrenology?



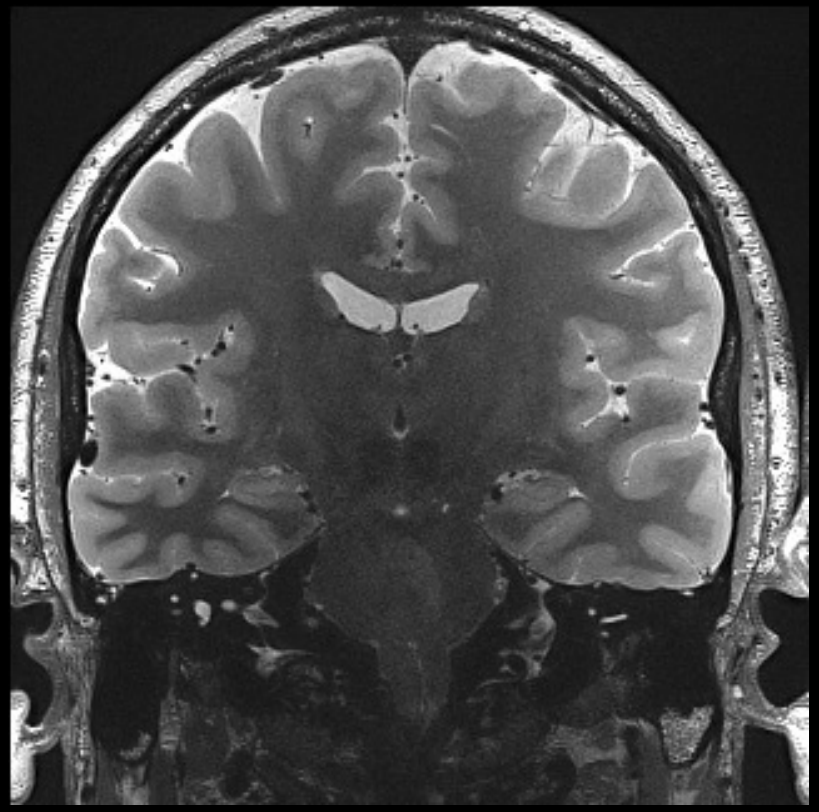
Mind reading?

?

High Resolution 3T MRI imaging



MPRAGE at 3T
.375 x .375 x 1mm



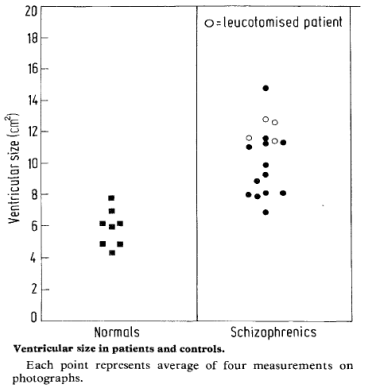
TSE .5mm isotropic
TR / TE = 3200 / 456

When did brain imaging research on schizophrenia begin?

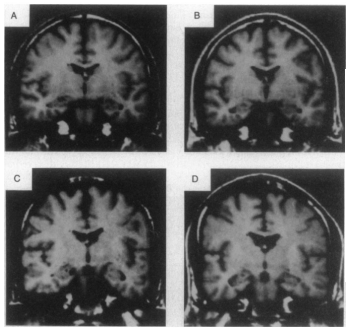
CT scans → PET and structural MRI scans → functional MRI… and now: DTI, MEG, EEG, TMS

Johnstone et al, Lancet 1976: first brain imaging study of people with schizophrenia, using CT scans

1976 — Late 1980s — Early 1990s — 1999-2002



Ventricular size in patients and controls.
Each point represents average of four measurements on photographs.



Weinberger, Berman PET and structural MRI studies of the prefrontal cortex and hippocampus

Invention of functional MRI at MGH (Belliveau, Kwong, Rosen)

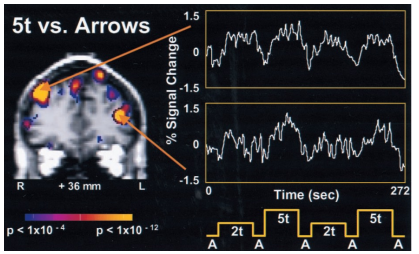
Functional Cerebral Imaging by Susceptibility-Contrast NMR

JOHN W. BELLIVEAU,* BRUCE R. ROSEN, HOWARD L. KANTOR, RICHARD R. RZEDZIAN,† DAVID N. KENNEDY, ROBERT C. MCKINSTRY, JAMES M. VEVEA, MARK S. COHEN,† IAN L. PYKETT,† AND THOMAS J. BRADY

Massachusetts General Hospital NMR Center, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114; and †Advanced NMR Systems, Inc., Woburn, Massachusetts 01801

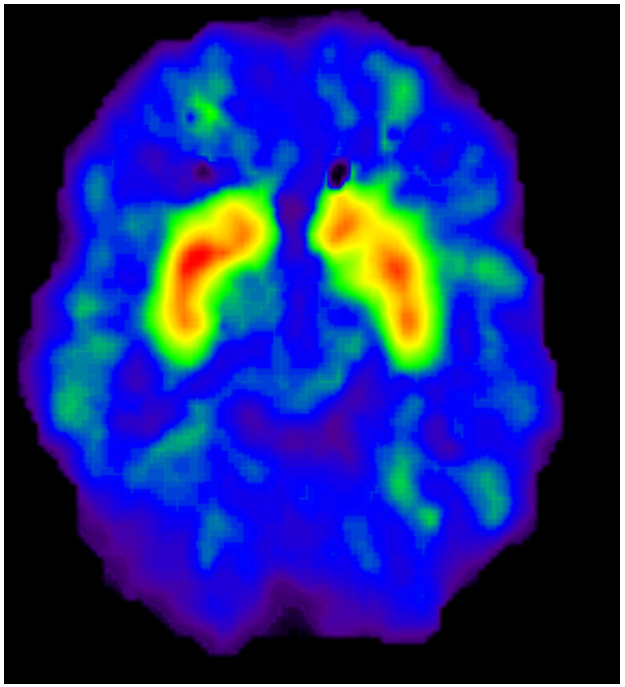
Received December 7, 1989; revised March 6, 1990

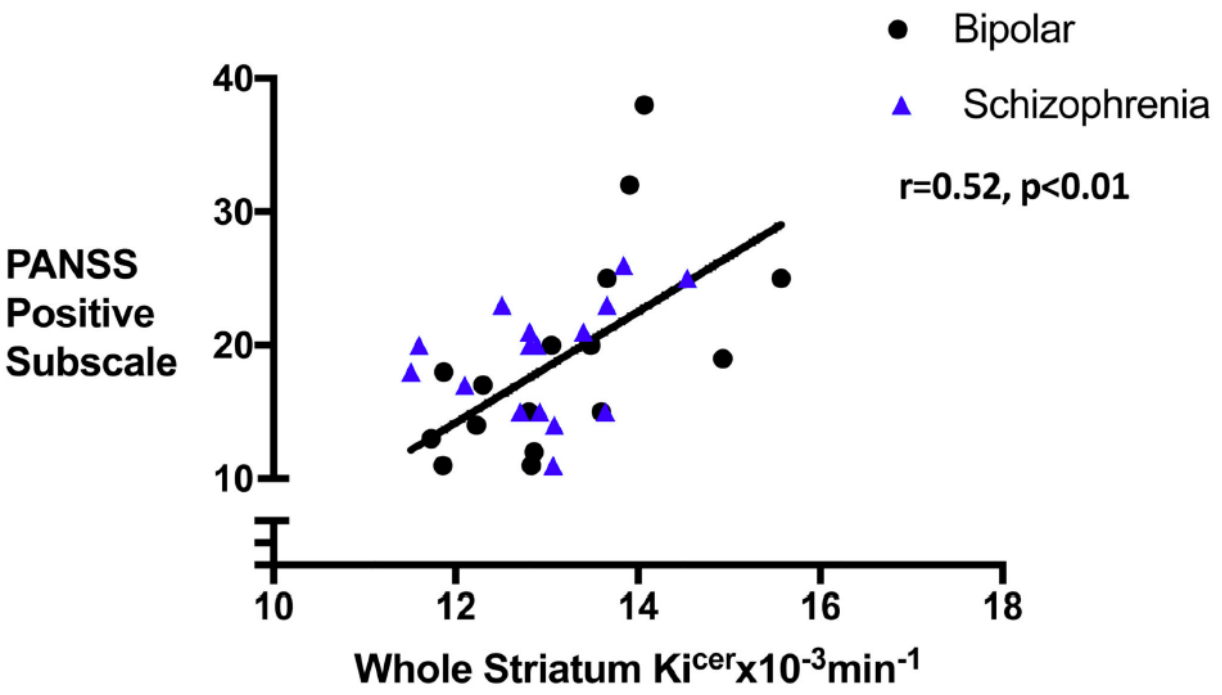
First functional MRI studies of schizophrenia



PET Imaging beginning in the 1980s: dopamine elevations in schizophrenia

Dopamine synthesis is elevated in schizophrenia and bipolar disorder and correlates with psychotic (positive) symptom severity





Jauhar et al, 2017

The MGH Psychosis Clinical and Research Program – Neuroimaging and Cognitive Neuroscience Research

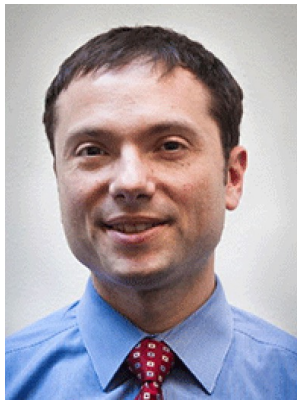
In 2002:

Stephan Heckers, MD

Dara Manoach, PhD

Gina Kuperberg, MD, PhD

Daphne Holt, MD, PhD

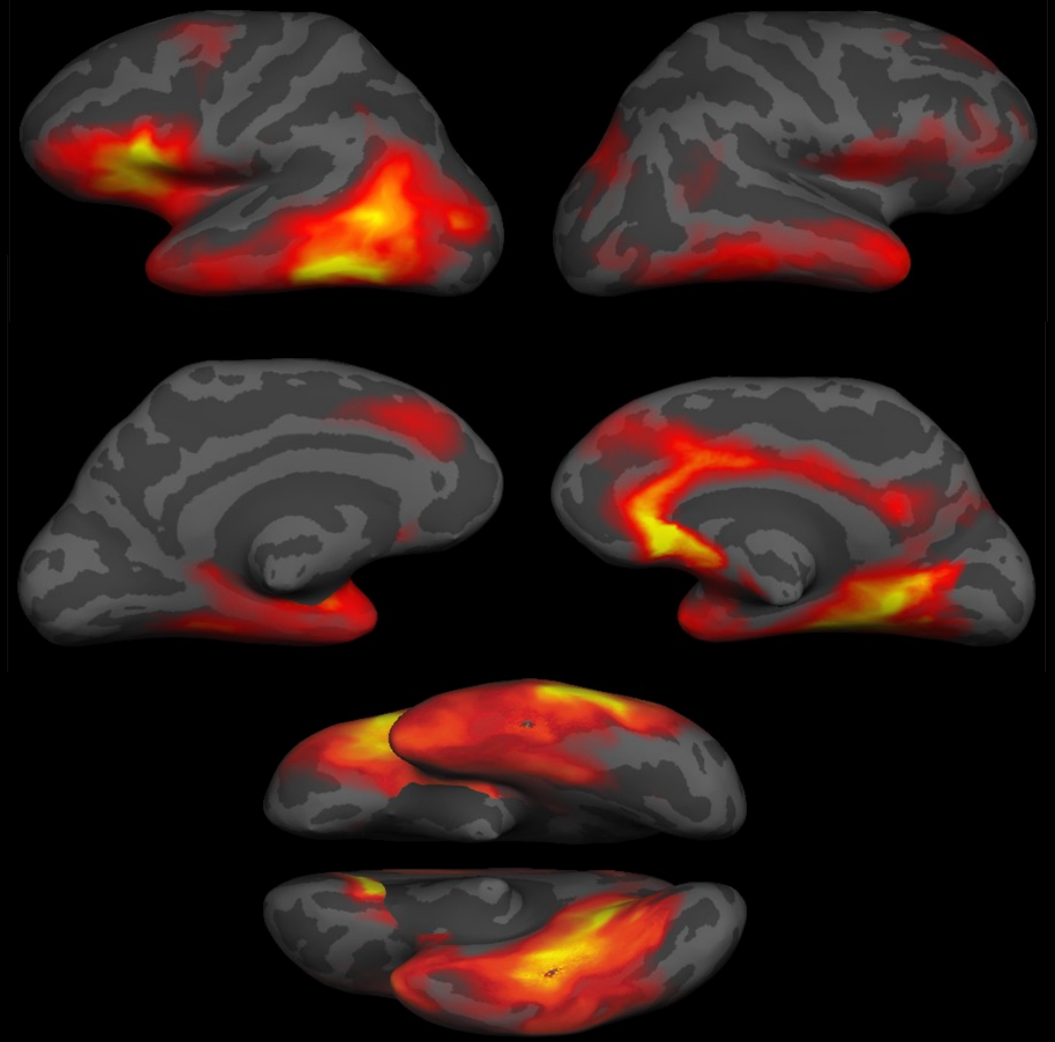


Joshua Roffman, MD

MGH East, Charlestown Navy Yard

Hamdi Erylimaz, PhD

Cortical thinning is observed in some people with schizophrenia



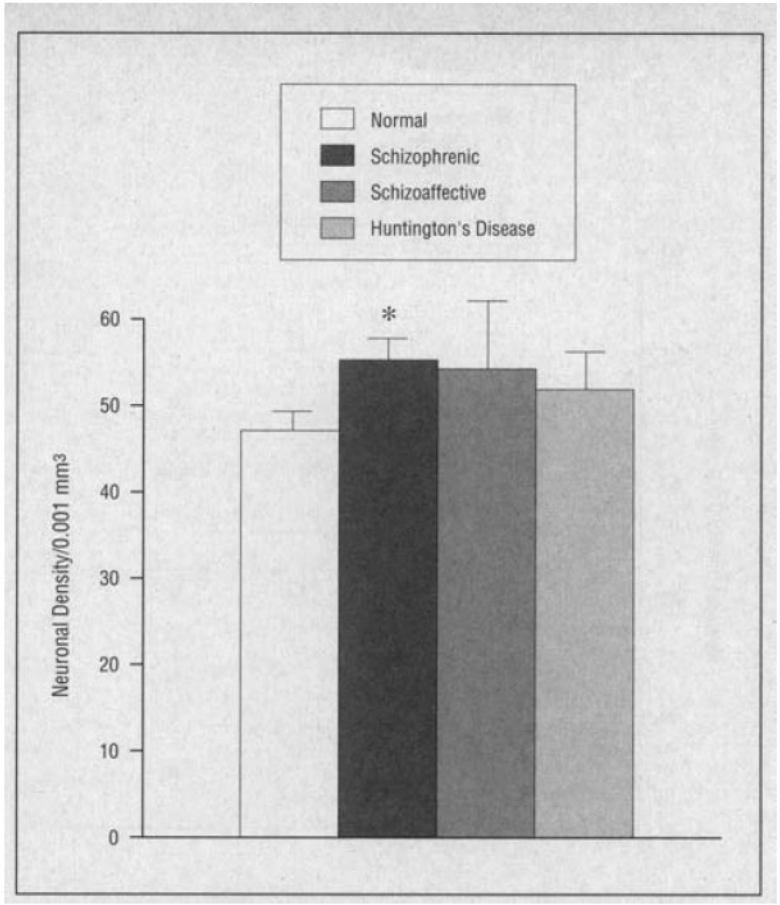
Kuperberg et al, 2003

ORIGINAL ARTICLE

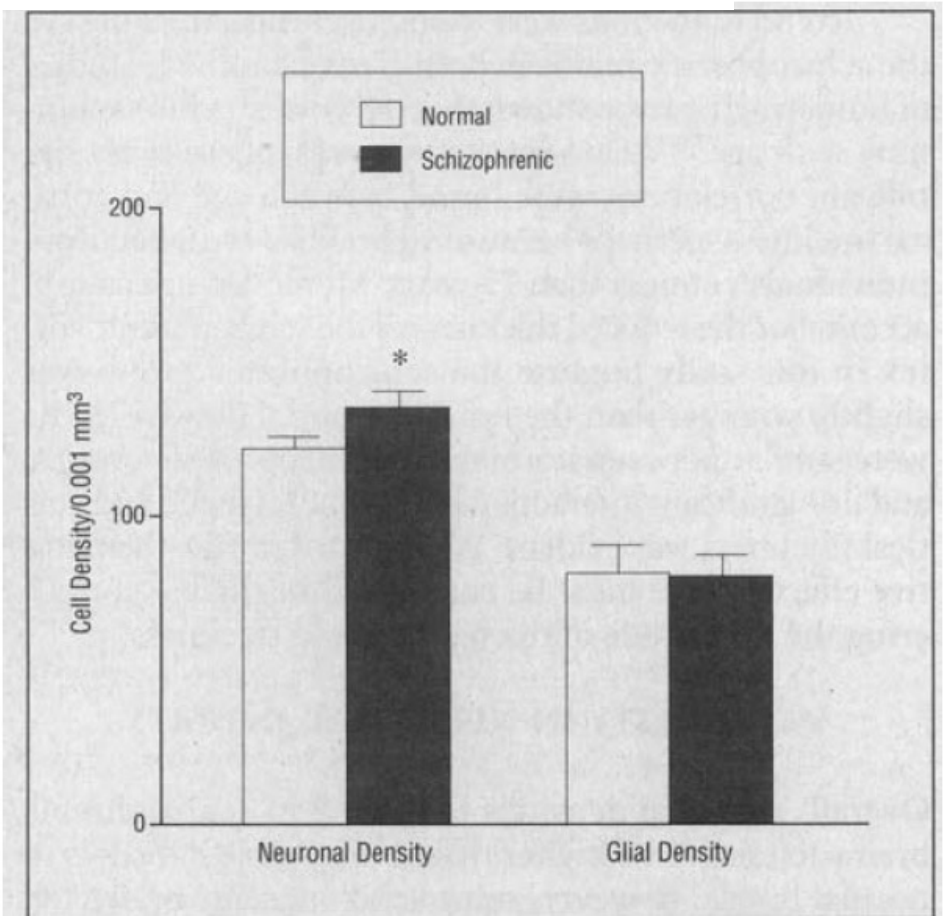
Abnormally High Neuronal Density in the Schizophrenic Cortex

A Morphometric Analysis of Prefrontal Area 9 and Occipital Area 17

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



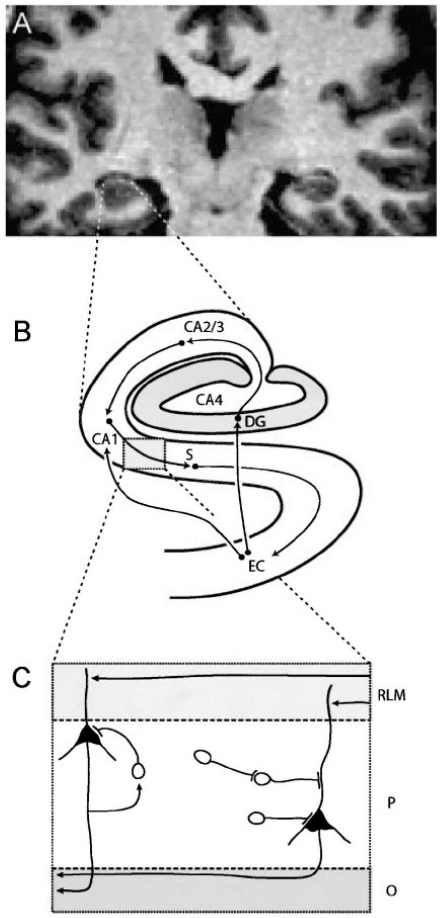
Area 9 (Frontal Cortex)

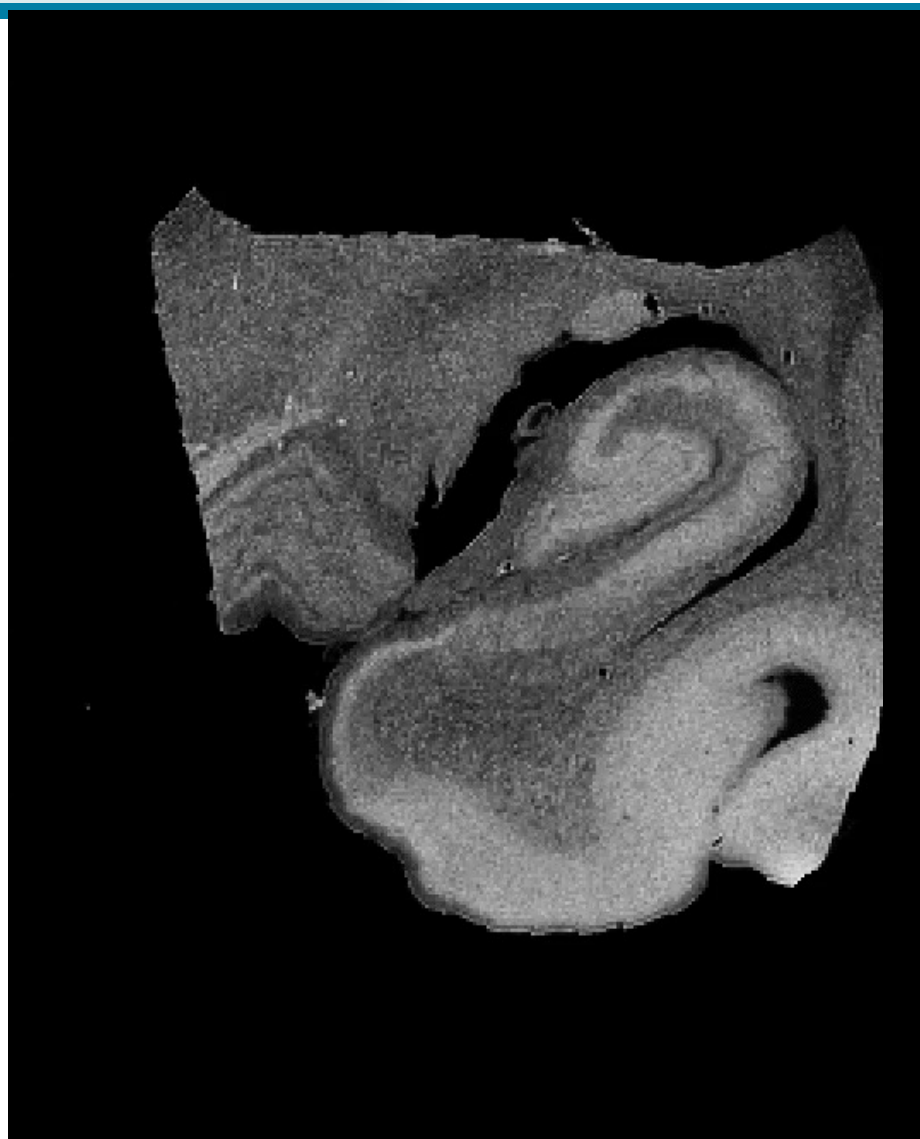


Area 17 (Visual Cortex)

Selemon et al, 1995

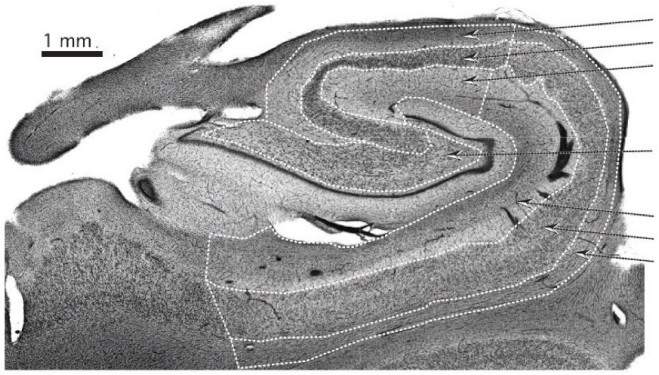
A smaller hippocampus

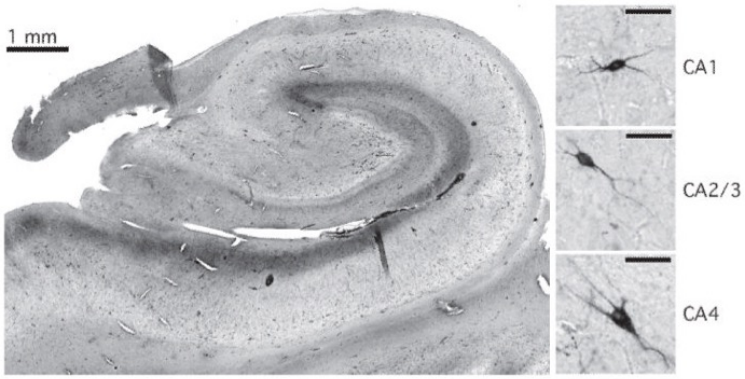


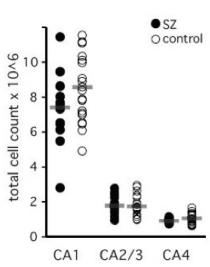


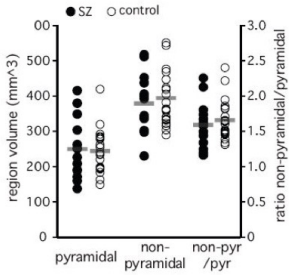
Heckers and Konradi, 2002

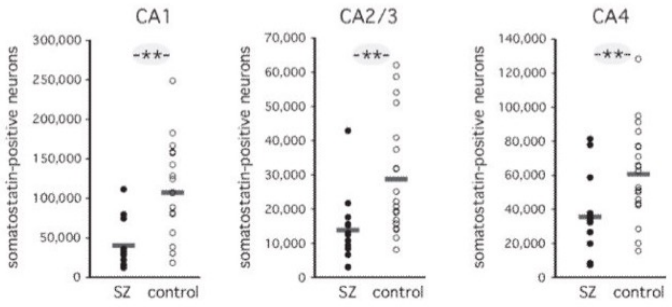
Changes in hippocampal interneurons







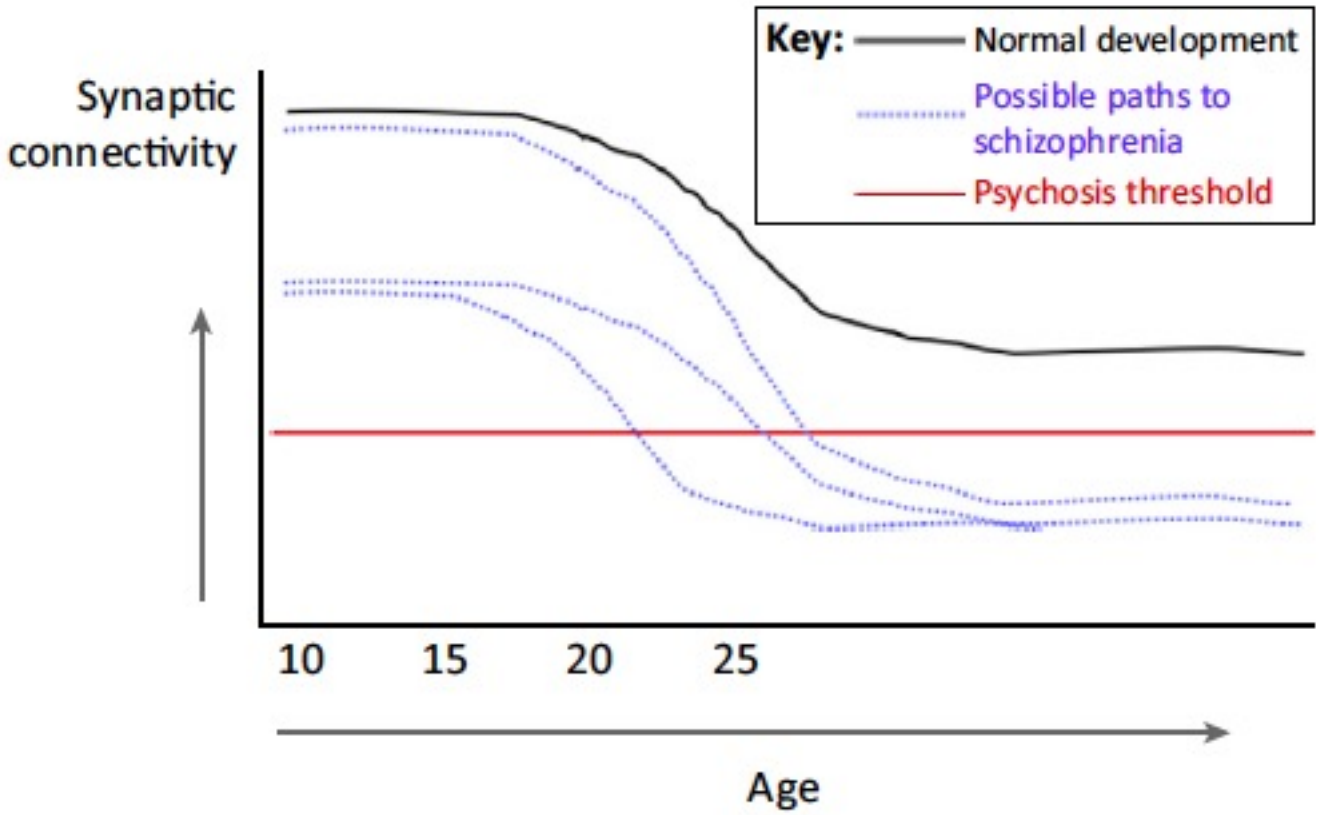




Konradi et al, 2011

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

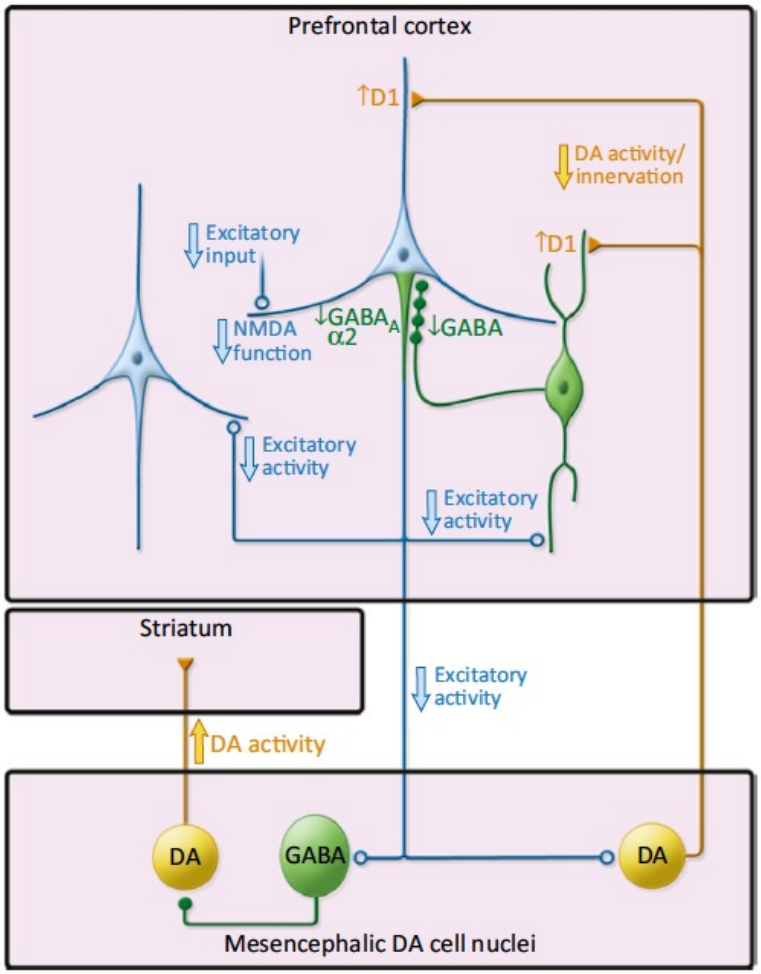
One (still unproven) model:

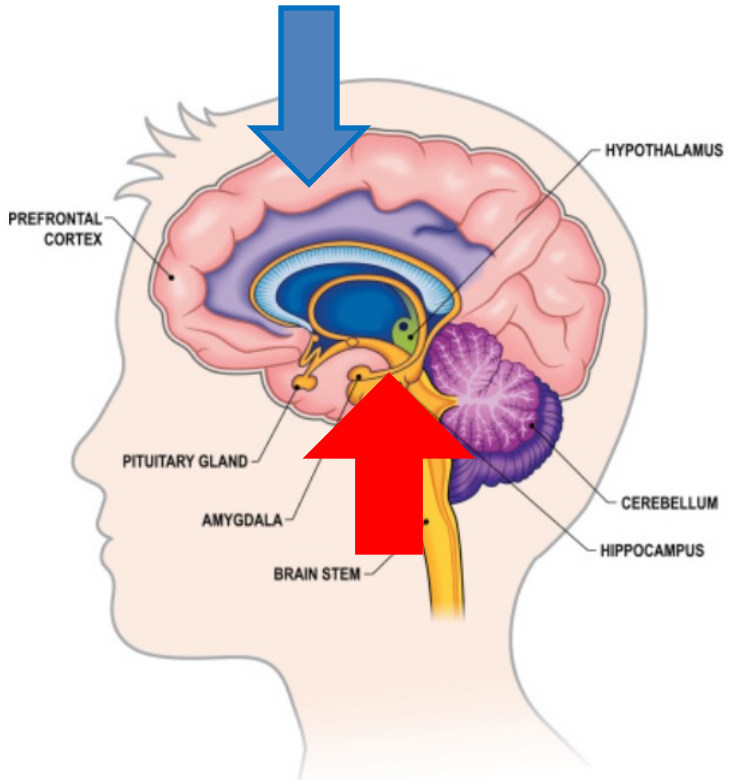


Cannon 2015

One model:
Cortical *hypo*activity → Subcortical *hyper*activity

Cellular model of schizophrenia





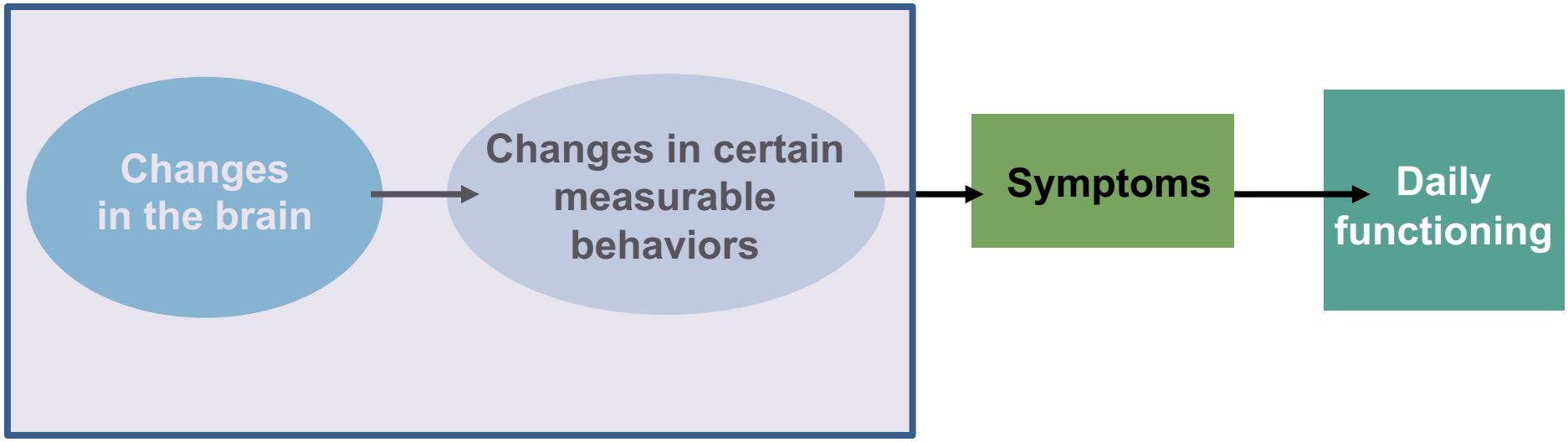
Cannon 2015

One model:
Cortical *hypo*activity → Subcortical *hyper*activity

Eugene Bleuler: "When the faculty of logical reasoning is weakened, the influence of the affects increases in strength…The distortion can eventually reach the proportions of delusional ideas..."

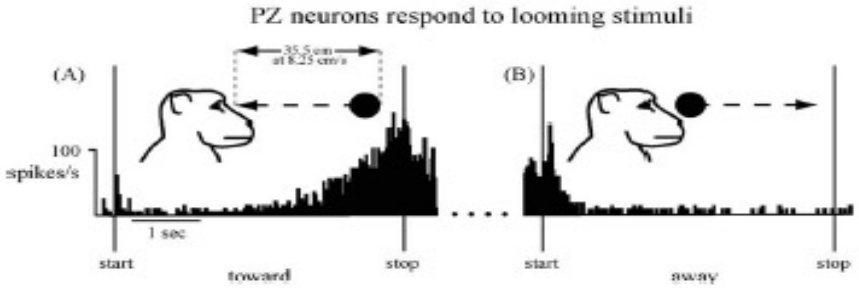
Eugen Bleuler, 1857-1939

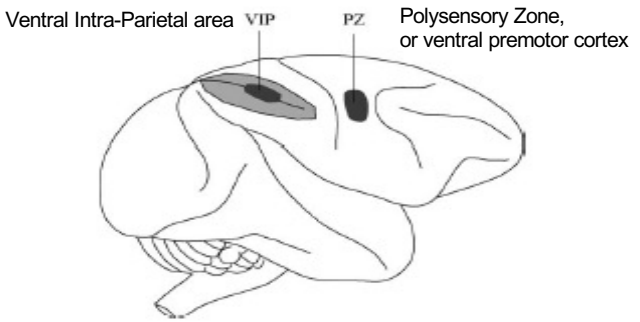
What are the links between the changes in the **brain** and **symptoms** and **quality of life**?



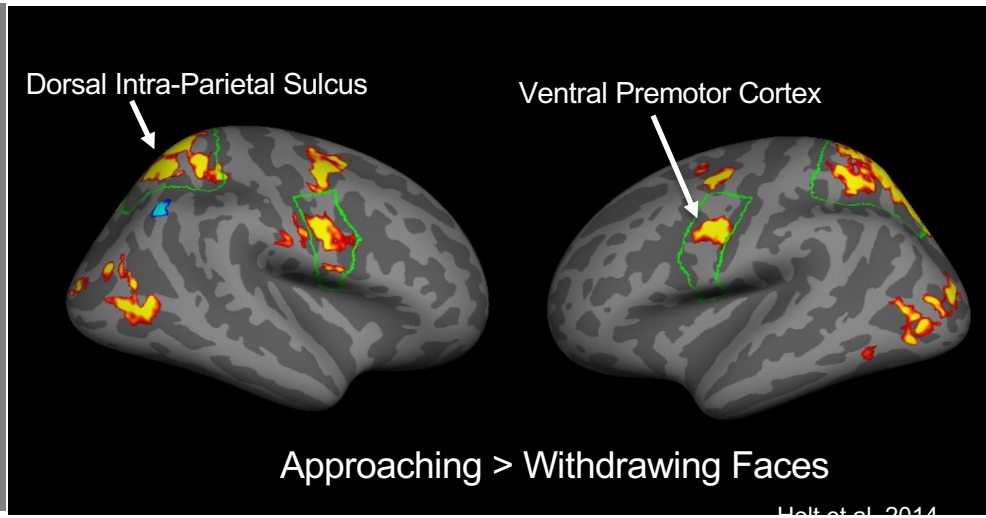
Cognitive neuroscience & neuroimaging research can shed light on this

Functional, task-based neuroimaging: How does it work?



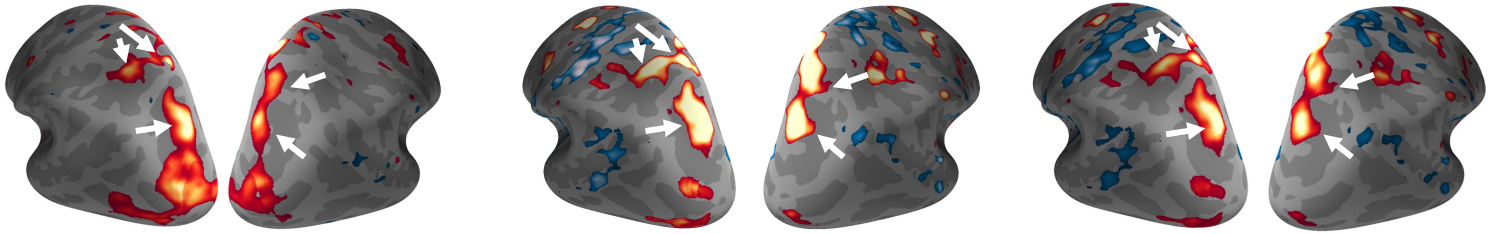


Graziano and Cooke, 2006



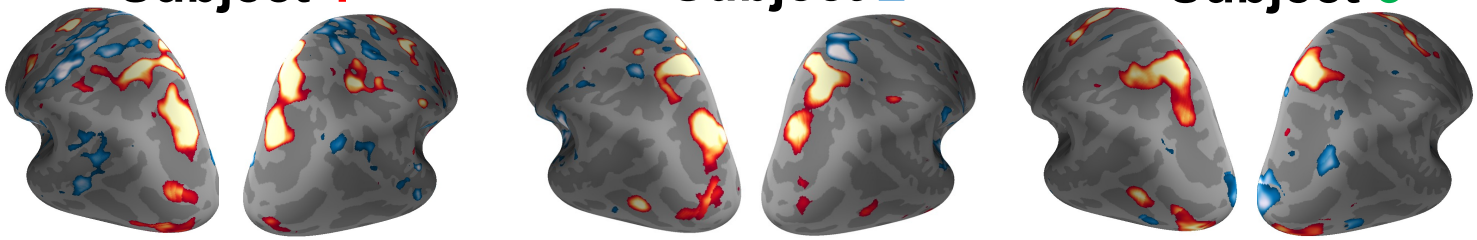
Functional, task-based neuroimaging: How does it work?

Subject 1: Scan 1 **Subject 1**: Scan 2 **Subject 1**: Scan 3



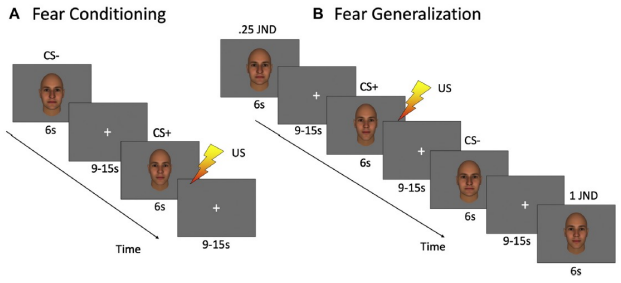
Approach vs. Withdrawal Contrast

Subject 1 **Subject 2** **Subject 3**

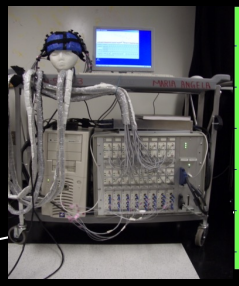


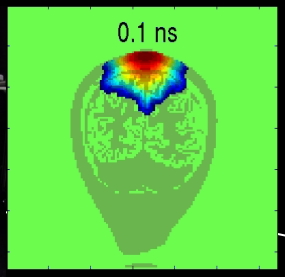
Approach vs. Withdrawal Contrast

Examples of tasks performed inside the scanner:
Perceptual: Checkerboard patterns (contrast), depth perception, motion detection
Cognitive: working memory, episodic memory, attention, language processing
Emotion: fearful faces, looming faces, unpleasant and pleasant pictures
Social cognition: Theory-of-Mind, self vs. other reference task

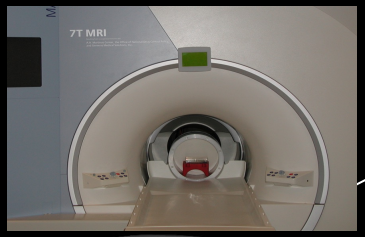


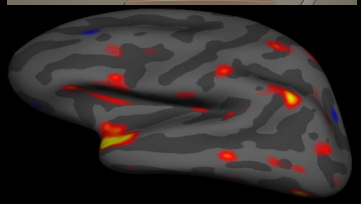
Brain Imaging: Across Space and Time
Anatomy, Physiology, Metabolism, Electrophysiology, Neurochemistry



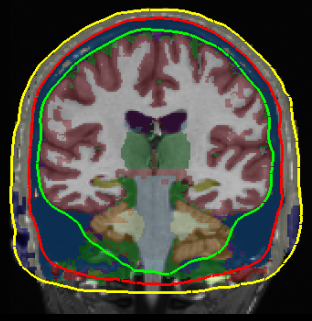


Optical Imaging

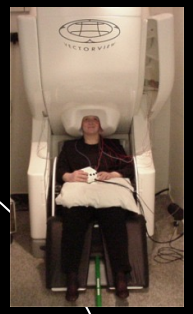




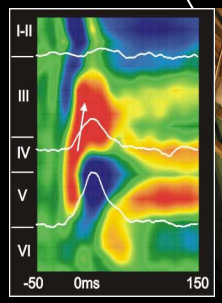
High-Field fMRI

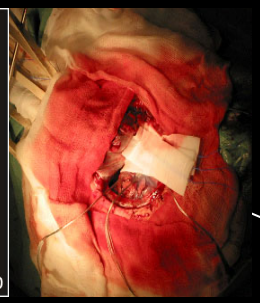


Anatomic MR

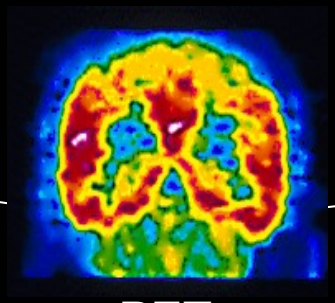


MEG/EEG

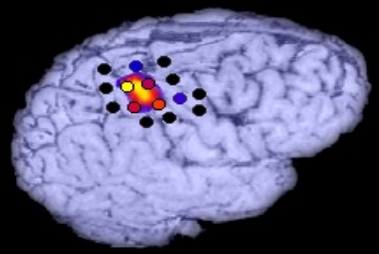




Cortical Stim



PET

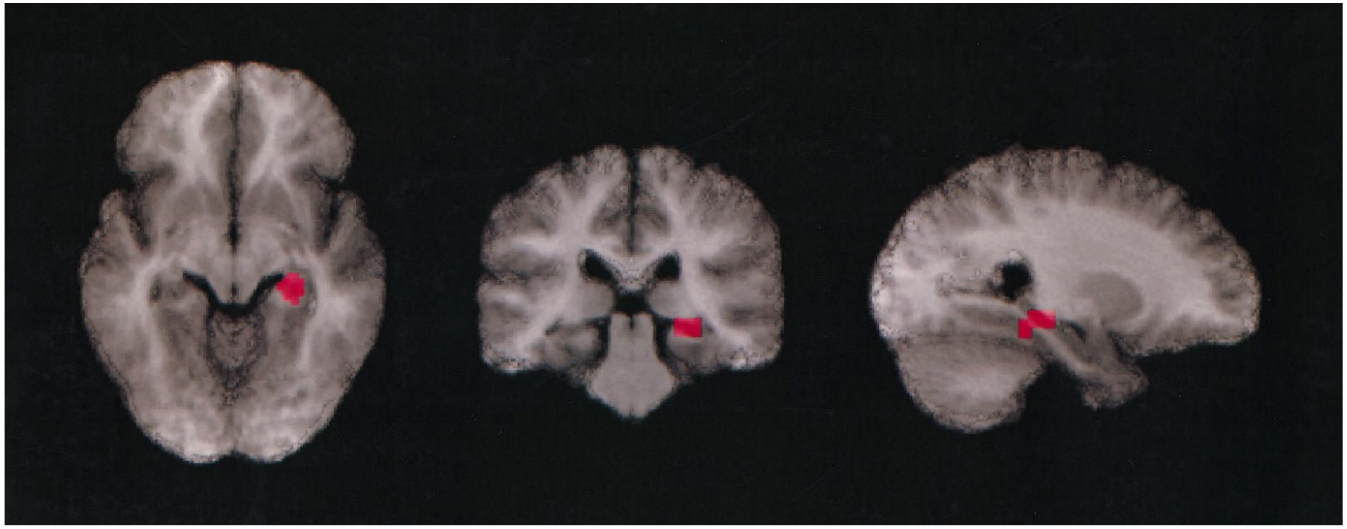


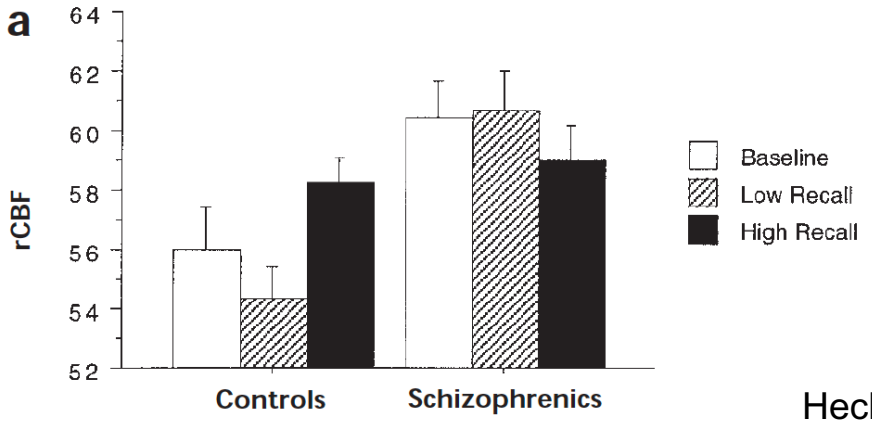
TMS

Courtesy of Bruce Rosen

The hippocampus: episodic/declarative memory (conscious recollection)

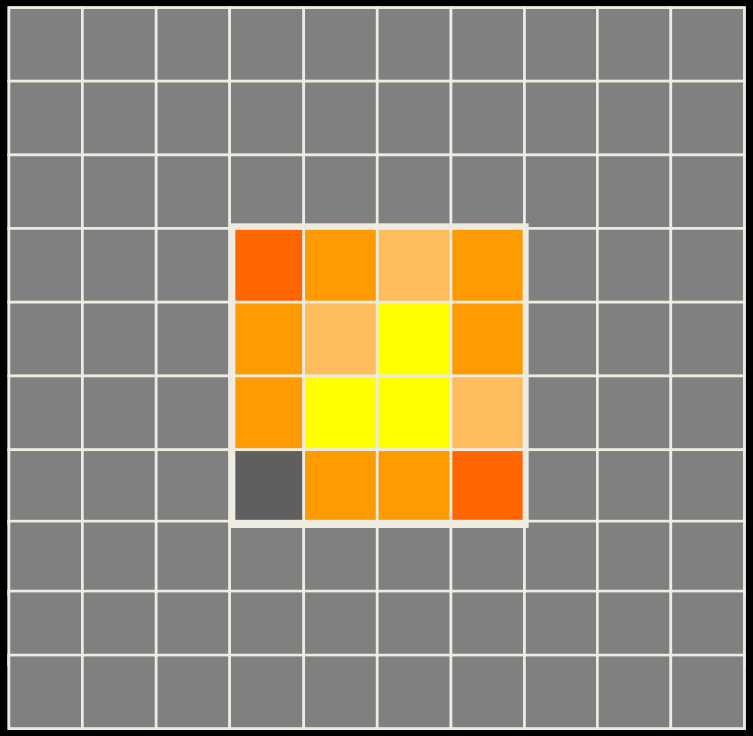
Less hippocampal activation during episodic memory recall in people with schizophrenia, compared to control subjects



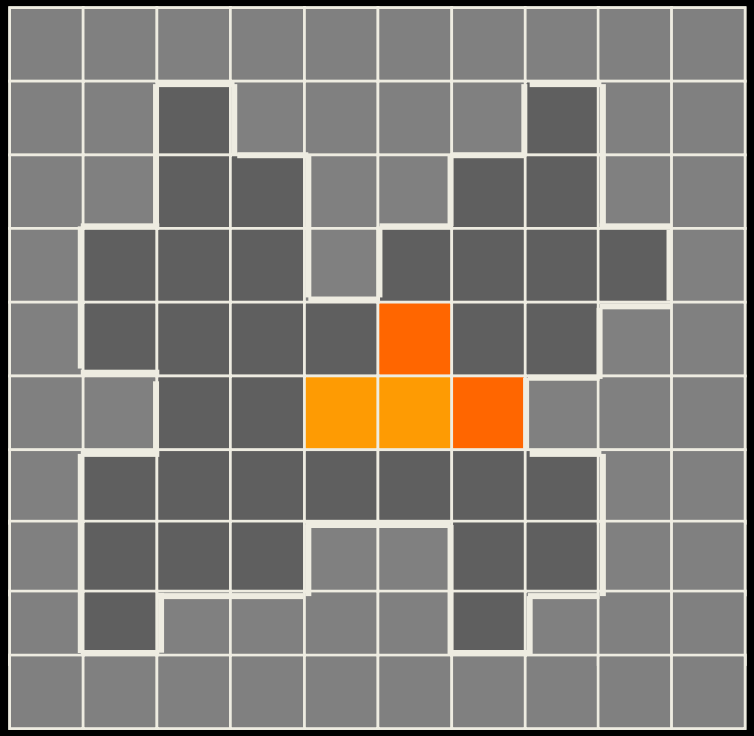


Heckers et al, 1998

Control Group



Schizophrenia Group



Number of Subjects

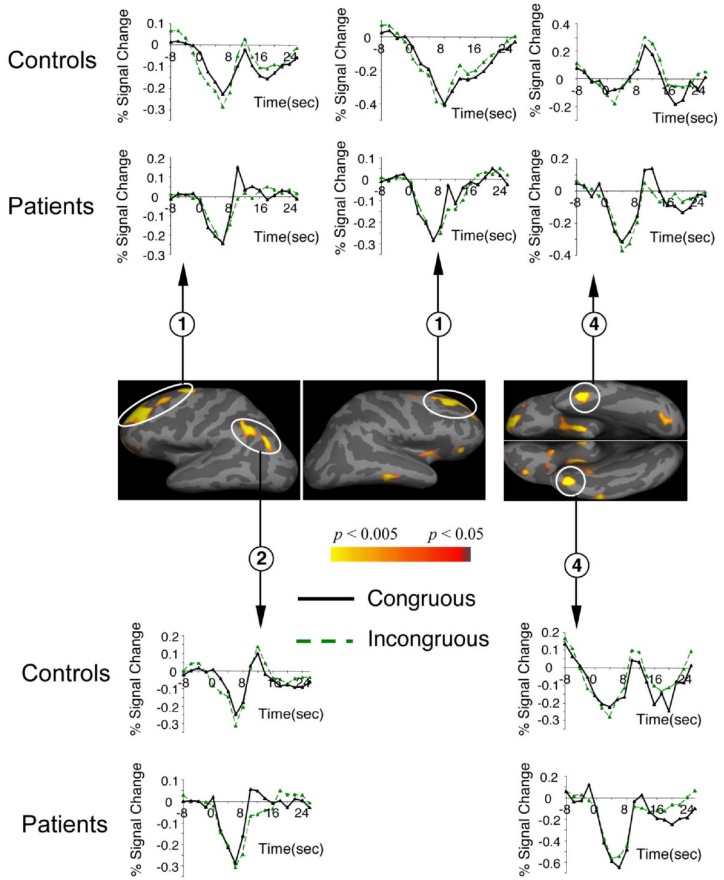
Manoach et al, 2000, 2002

Frontal and parietal cortex: understanding and producing language

Sentence types:

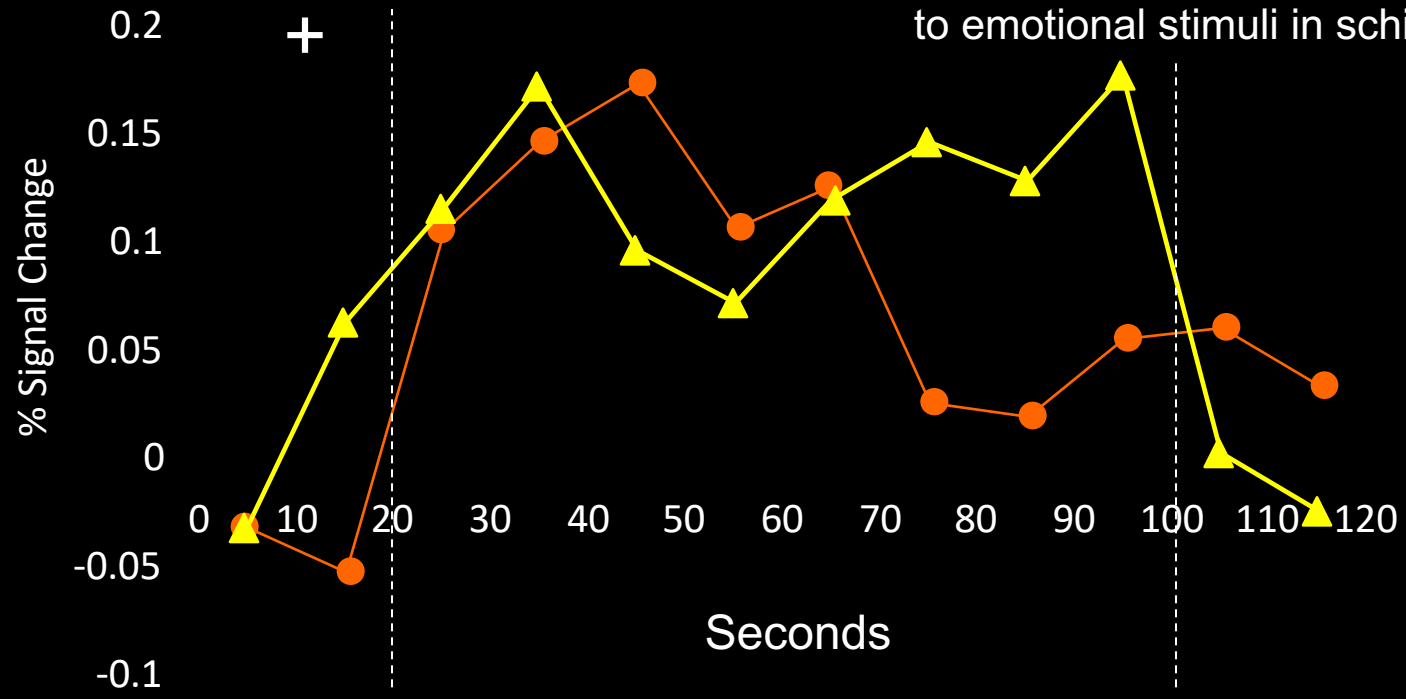
Concrete*Congruous:* During the rain storm he carried a large golf umbrella.
Incongruous: The twenty dairy cows are kept in the red bench.

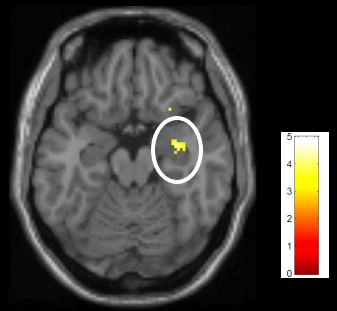
Abstract:
Congruous:
Although she strove for perfection she continued to make mistakes.
Incongruous:
Her outer expressions were completely blank and revealed no equality.



Kuperberg et al, 2008

The midline cortex and limbic system: emotion and social cognition





Holt et al, 2005

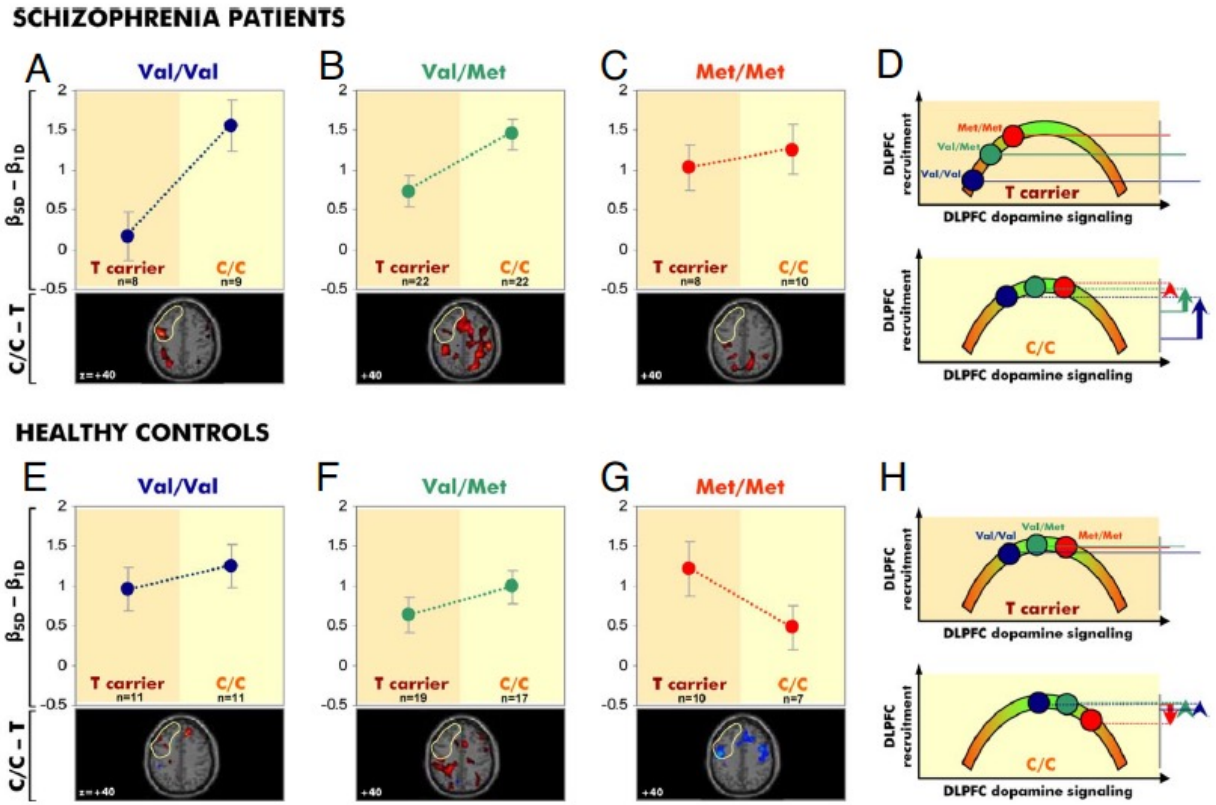
Why does this happen?

We have made **observations** about what might be different in the brain in schizophrenia

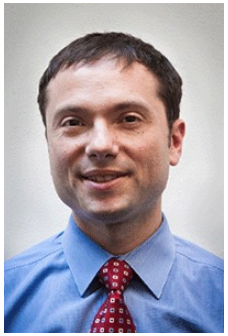
Can we now “look under the hood” and figure out what is causing the changes?

Understanding **the underlying causes or mechanisms** will help us come up with better treatments

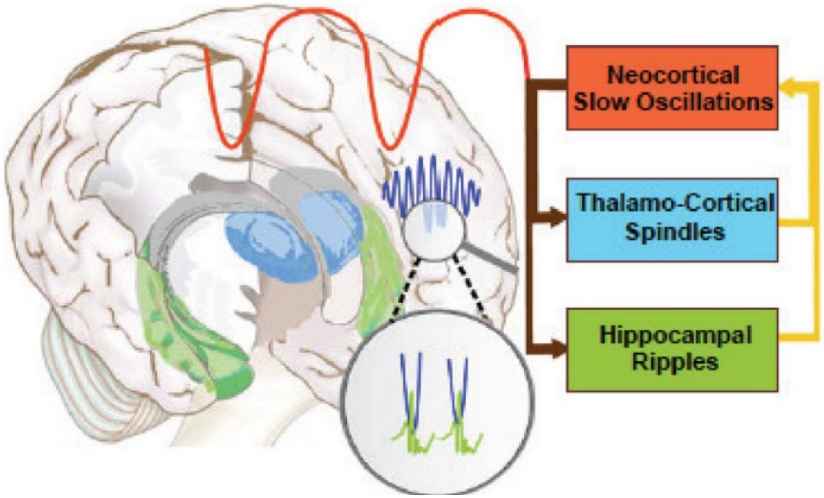
Why does this happen?

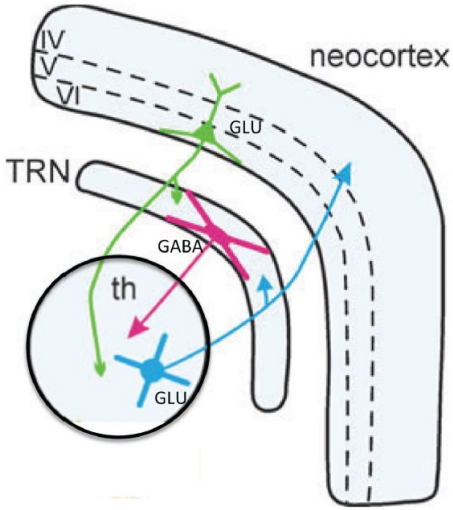


Roffman et al, 2008

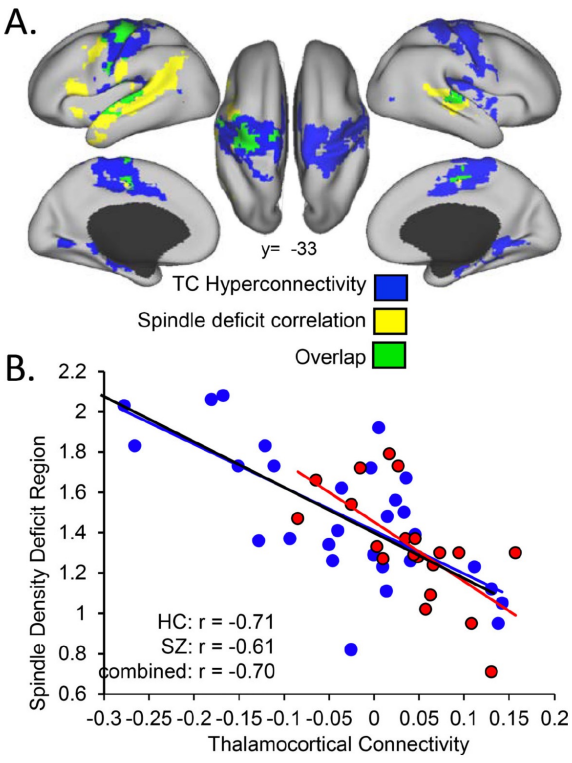


Why does this happen?





Manoach et al, 2016

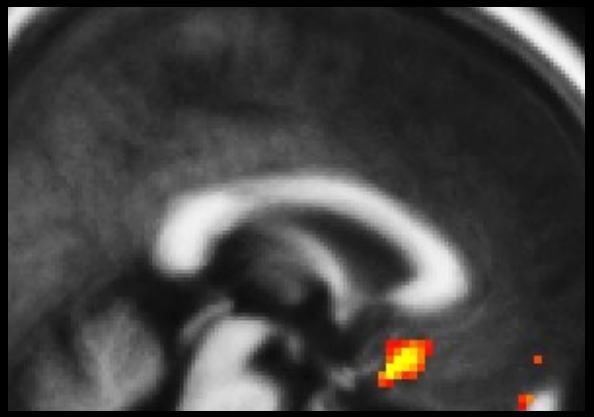


Manoach & Stickgold, 2019

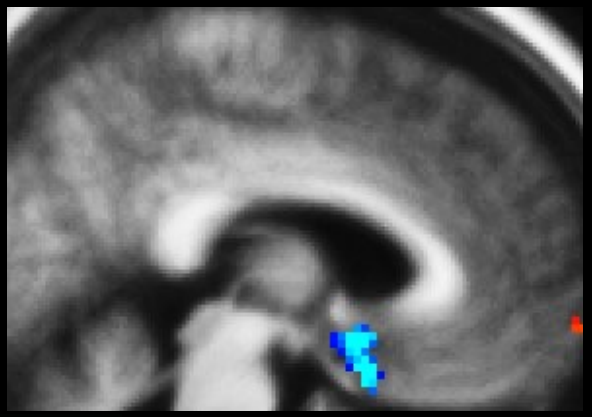
Why does this happen?

Extinction Recall

A. CON



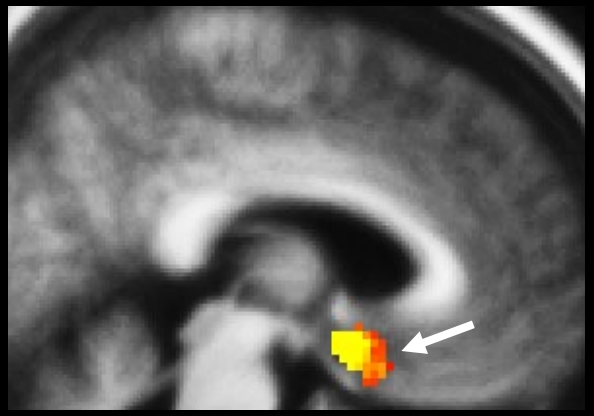
B. SCZ



CS+E > CS+U, p < .05

CS+U > CS+E, p < .05

C. CON vs. SCZ

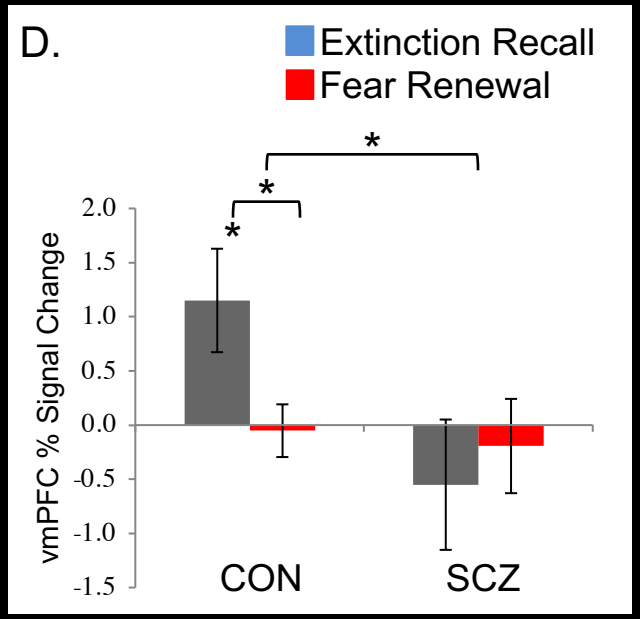


CON > SCZ

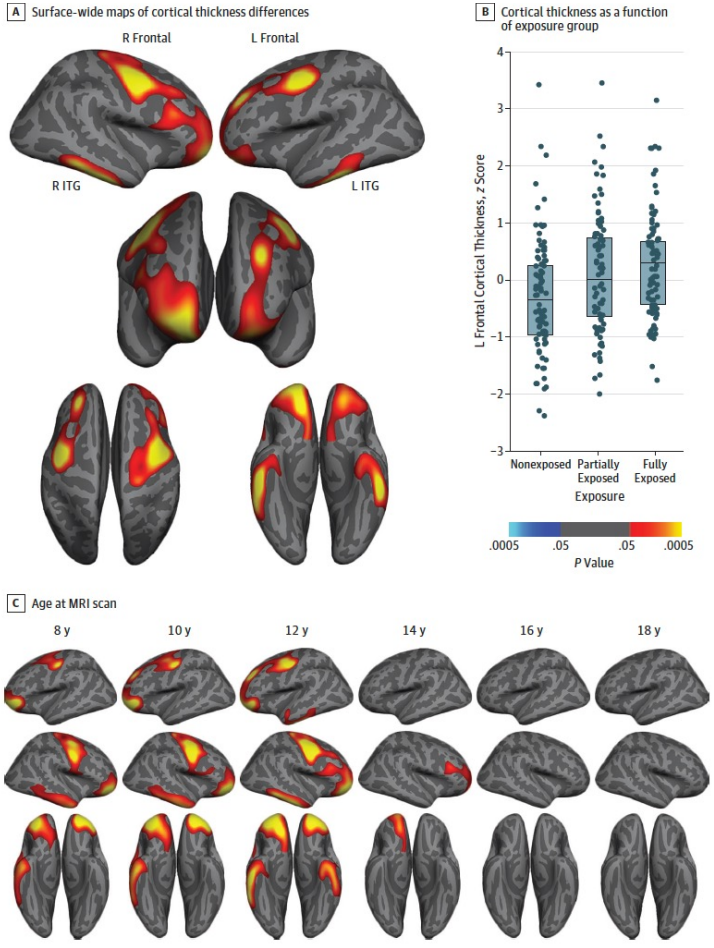
SCZ > CON

Peak vmPFC between-group difference: $p < 10^{-4}$

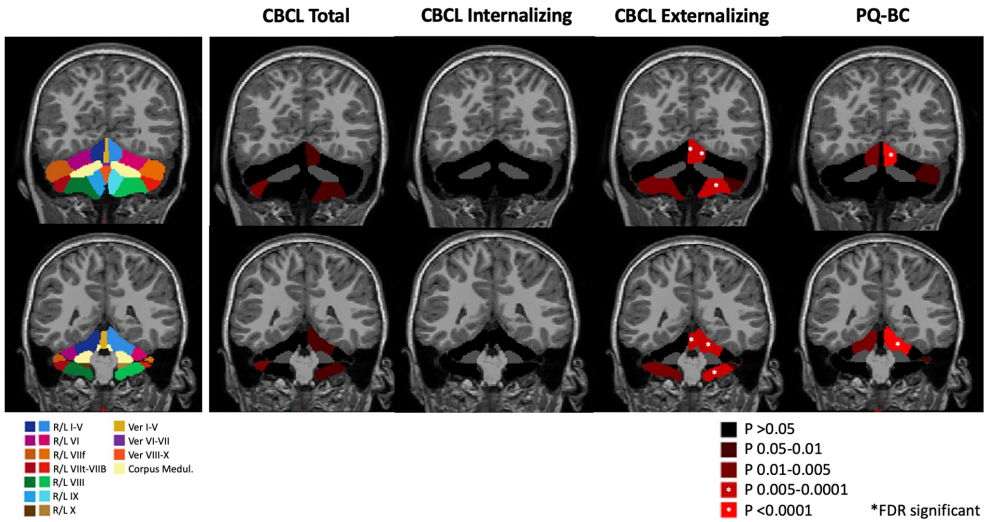
D.



When does all of this happen? Clues from neurodevelopment and genetics



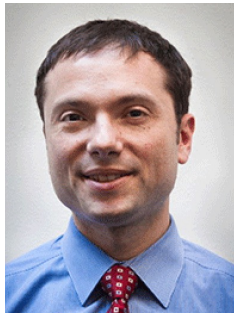
Eryilmaz et al, 2018



Hughes et al, under review

Hamdi Erylimaz, PhD

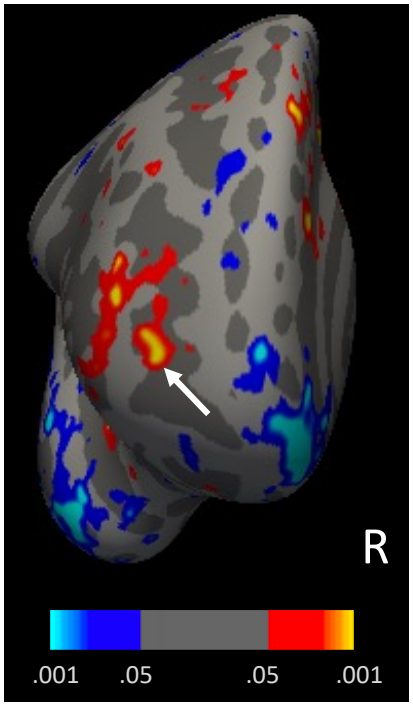
Dylan Hughes, BS



Joshua Roffman, MD

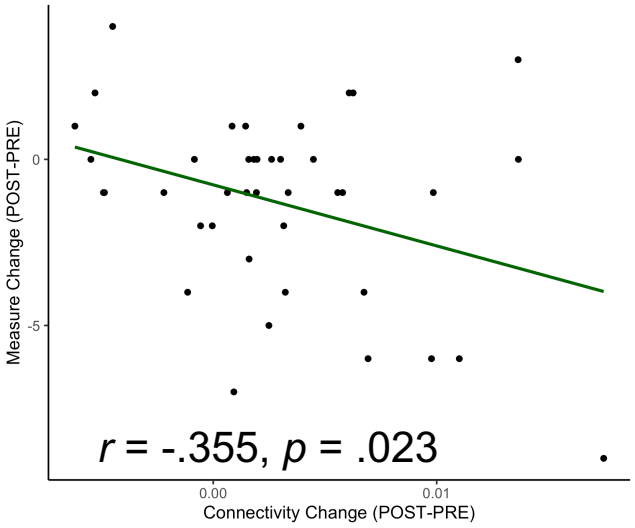
Can we change this? Evidence from a study of Resilience Training (RT)

Post-RT change in frontohippocampal connectivity

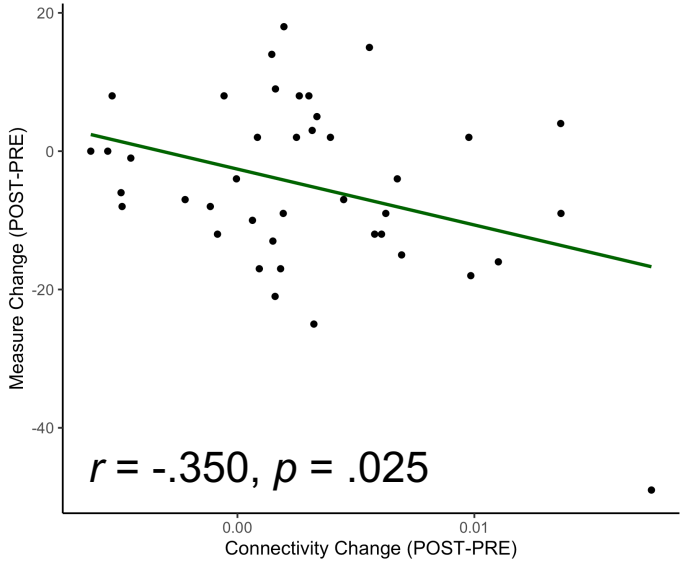


Post-RT change in delusional thinking and emotional dysregulation vs. post-RT change in frontohippocampal connectivity

Delusional thinking



Emotional dysregulation



The greater the increase in frontohippocampal connectivity, the greater the decrease in delusional thinking and emotional dysregulation following Resilience Training

Holt, DeTore, Sussman, Vinke, Burke et al, unpublished data

The Present and Future…

Louis Vinke, PhD

Faye McKenna, PhD

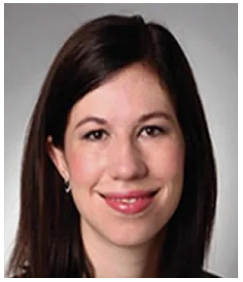
Keiko Kunitoki, PhD

Paige Hickey, PhD

Victoria Grunberg, PhD

Martin Sjøgård, PhD

Baktash Babadi, MD, PhD



Jacci Clauss, MD, PhD

Nicole DeTore, PhD

The Present and Future…