First Episode Psychosis

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Learning Objectives

Understand

- biological and genetic factors associated with risk of schizophrenia
- how comprehensive treatment may impact the course of illness
- conventional and alternative/complimentary treatment approaches

Case: Jim
October, 2005

- Above average high school student, on tennis team, small group of close friends.
- Did well Freshman year at University
- Early fall Sophomore year Jim's parents are called by hospital social worker, with "bad news", Jim has schizophrenia.
- Parents fly out, meet with Jim on the unit. Jim is convinced he has a chip in his head, communicating with aliens, when he meets with his parents he accuses them of being "imposters".
- The unit social worker meets with parents, informing them that Jim has schizophrenia, that they should be prepared for the fact that he will be disabled by this illness

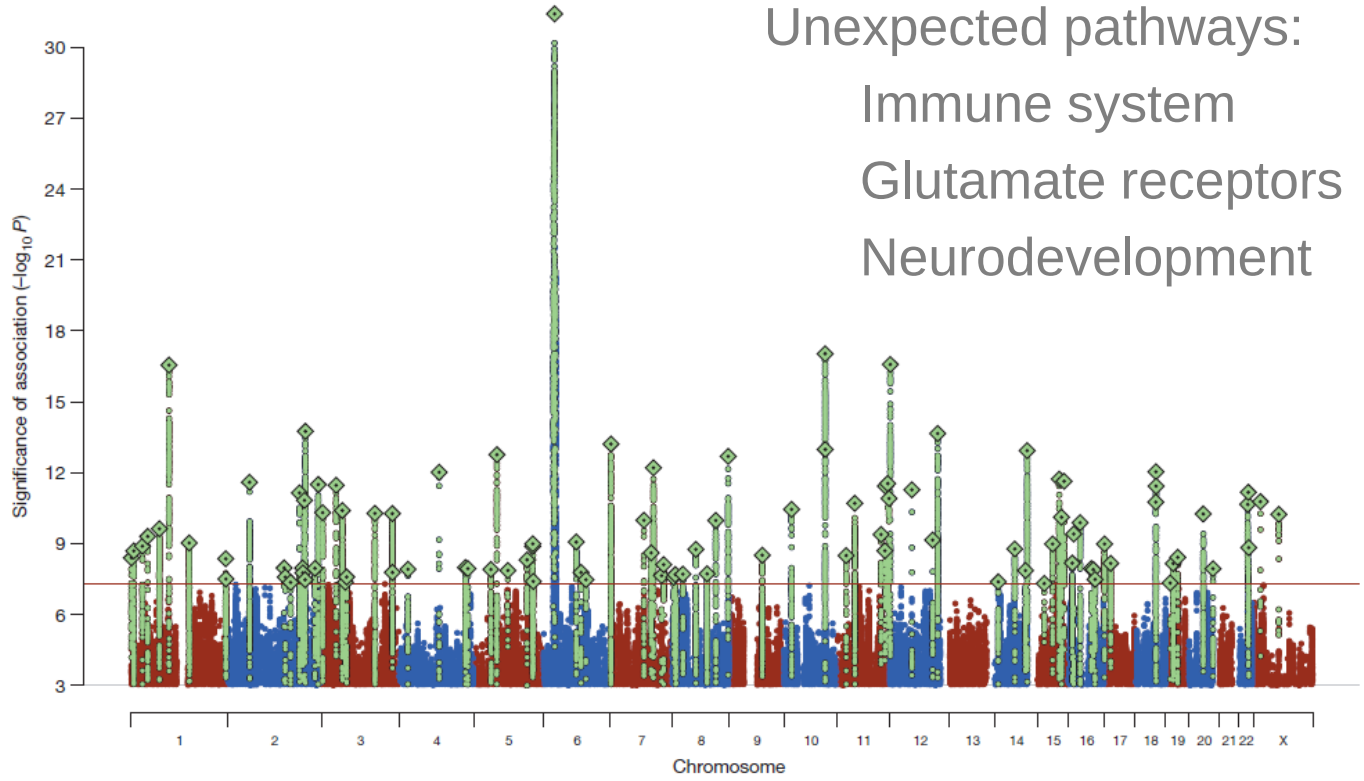
WHAT WE KNOW ABOUT CAUSE AND COURSE

"You made that diagnosis just to be mean."

http://www.condenaststore.com/-sp/You-made-that-diagnosis-just-to-be-mean-New-Yorker-Cartoon-Prints_i8545822_.htm

Genetics

- Schizophrenia runs in families, but…
- 70% of persons have no close relative with schizophrenia
- Multiple common genetic variants that increase schizophrenia risk by ~5-10%.



Unexpected pathways:

Immune system

Glutamate receptors

Neurodevelopment

1. International HapMap Consortium. Nature 2003;426(6968):789–796;
2. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014;511(7510):421–427

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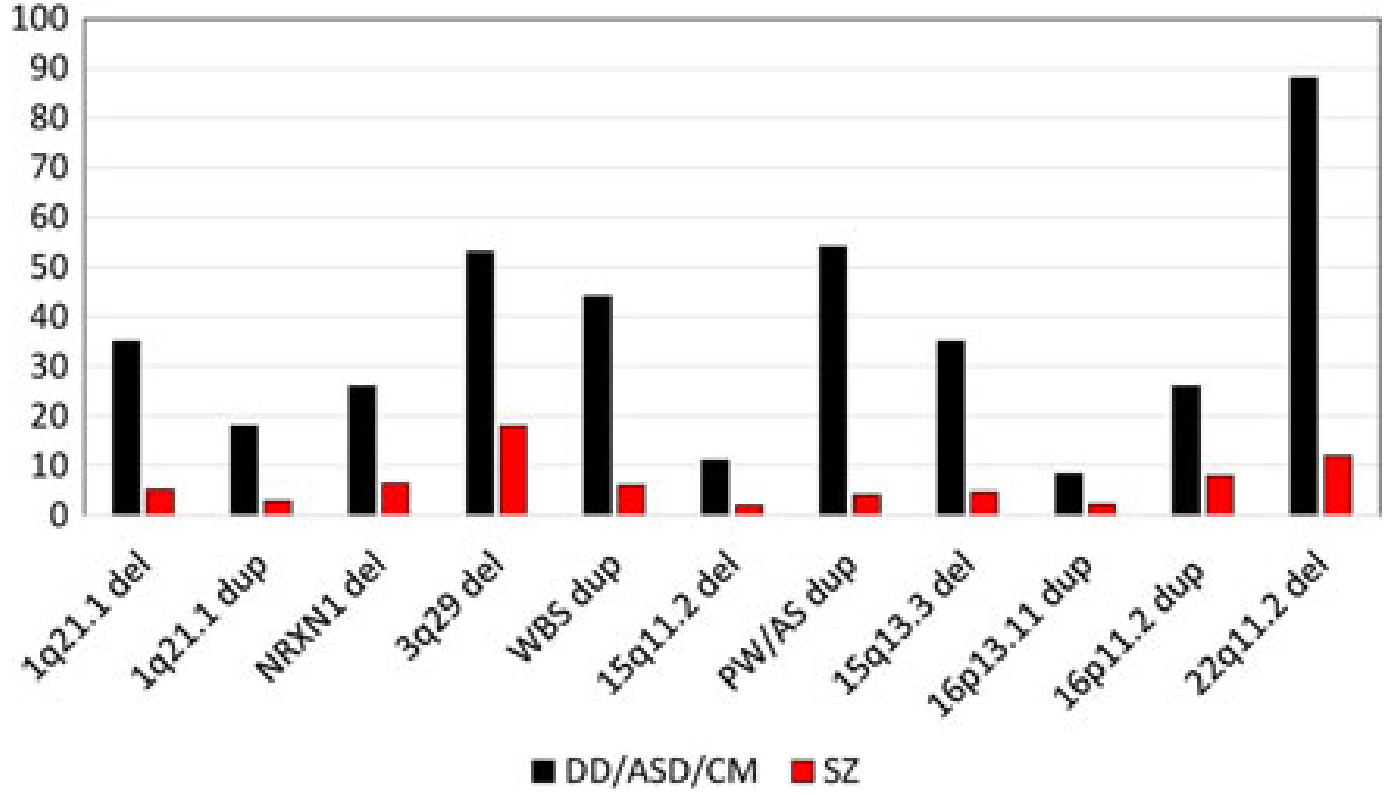
Genetics

- Rare “copy number” variants
  - Found in ~ 2.4% of schizophrenia and 0.5% of unaffected persons
  - Associated with elevated paternal age
  - Penetrance:



Kirov. CNVs in neuropsychiatric disorders Hum Mol Genetics 2015 Jun 30. pii: ddv253. [Epub ahead of print]

In utero environmental factors influencing schizophrenia vulnerability

- Maternal infection: ~2–7-fold increase in risk[1,2]
  - Increased incidence following epidemic (esp. influenza) patterns
  - Maternal cytokine levels associated with subsequent risk
- Maternal stress: ~1.5-fold increase in risk[1,3]
- Maternal nutrition
  - Maternal starvation: 2-fold increase in risk[1,4]
  - Micronutrients:[1]
    - Vitamin D deficiency[5] (and the further away from the equator a person lives, the greater the risk)
    - Maternal folate deficiency (elevated homocysteine)
    - Maternal low iron
- Maternal diabetes: ~3-fold increase[6]
- Hypoxic injury at birth: ~2-fold increase[1,7]

1. Meli et al. J Matern Fetal Neonatal Med 2012;25(12):2559–2563;
2. Brown & Derkits. Am J Psychiatry 2010;167(3):261–280; 3. Khashan et al. Arch Gen Psychiatry 2008;65(2):146–152;
4. Xu et al. Schizophr Bull 2009;35(3):568–576; 5. McGrath et al. Schizophr Res 2003;63(1-2):73–78;
6. Cannon et al. Arch Gen Psychiatry 2002;59:35–41; 7. Dalman et al. Br J Psychiatry 2001;179:403–408

Developmental factors in childhood influencing psychosis risk

- Childhood encephalitis:[1] 7–8-fold
- Childhood emotional trauma:[2] 2–3-fold
- Status as immigrant: 2.7-fold increase in risk[3]
  - Offspring of first degree relatives: 4.5-fold increase[3]
- Urban environment: 1.9-fold increase in risk[4]; 4-fold risk of hospitalisation for schizophrenia[5]
- Marijuana use (early/heavy): 4-fold increase in risk[6]

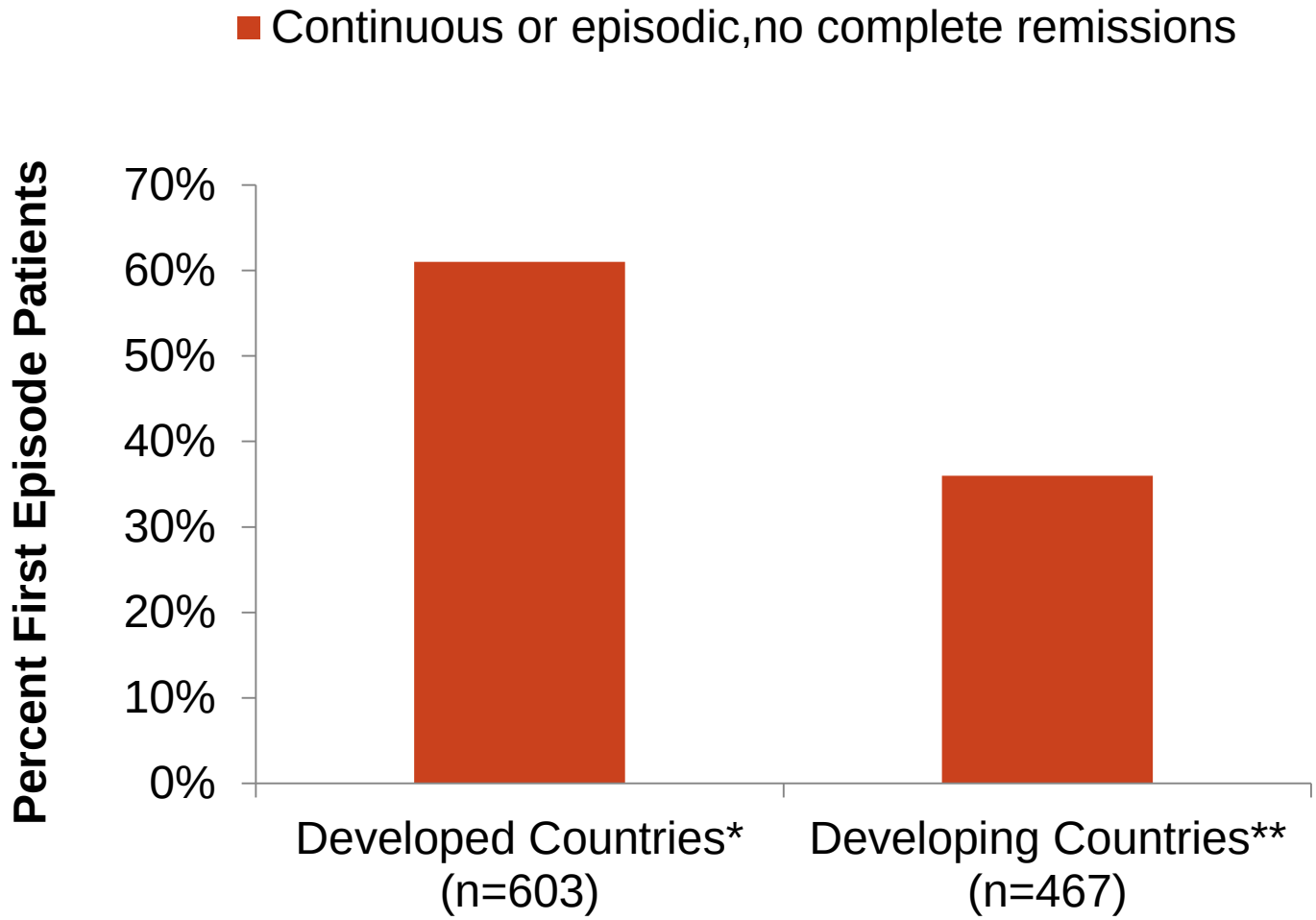
1. Hirsch & Weinberger. Schizophrenia 2nd edition 2003; 2. van Os et al. Nature 2010;468(7321):203–212;
3. Cantor-Graae & Selten. Am J Psychiatry 2005;162(1):12–24; 4. Kelly et al. Schizophr Res 2010;116(1):75–89;
5. Eaton et al. Schizophr Res 2000;43(2-3):117–123; 6. Moore et al. Lancet 2007;370(9584):319–328

Marijuana and Psychosis Risk

- Use in early adolescence or heavy use later in life increases risk of a psychotic illness 4-fold
  - ~ 4% of marijuana users develop schizophrenia
  - ~ 10–14% of schizophrenia may be related to marijuana use
- “Kind” of schizophrenia related to marijuana use associated with less severe negative symptoms and cognitive impairments
- Continued use once psychosis develops associated with relapse and worse functional outcomes

Environment Impacts Prognosis

Symptomatic and Functional Prognosis at Two Years After a First Episode Schizophrenia



*Czech Repubic, Denmark, Ireland, Japan, Russia, UK, USA

**Columbia, India, Nigeria

Jablensky 2000

Environment Impacts Prognosis

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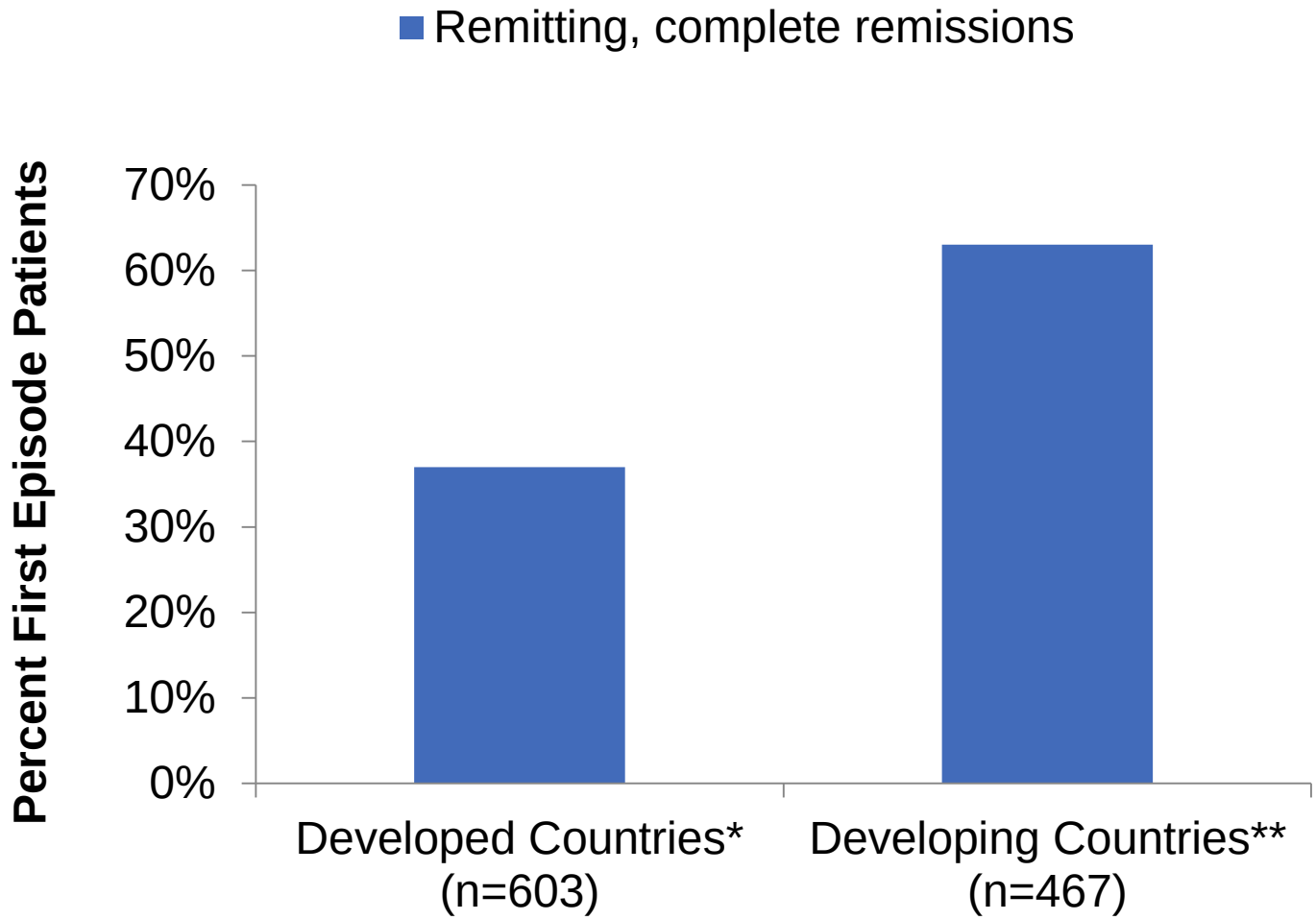

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**Columbia, India, Nigeria

Jablensky 2000

Time from Onset of Psychosis to Onset of Treatment

- Treatment Delays Are Common
  - On average, 1 year or more elapses from onset of psychosis to onset of treatment
  - Why the delay?
    - Early stage of psychosis clinically different
      - Patients look more “more normal”
      - Less severe negative symptoms
      - Substance use, school failure, behavioral problems may obscure underlying psychosis
    - Symptoms recognized but misinterpreted
    - Stigma

•Hales RE, et al. (Eds). *Textbook of Psychiatry.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2008;
•Franz L. *Early Interv Psychiatry*. 2010;4(1):47-56.

The Longer the Treatment Delay, the Worse the Prognosis

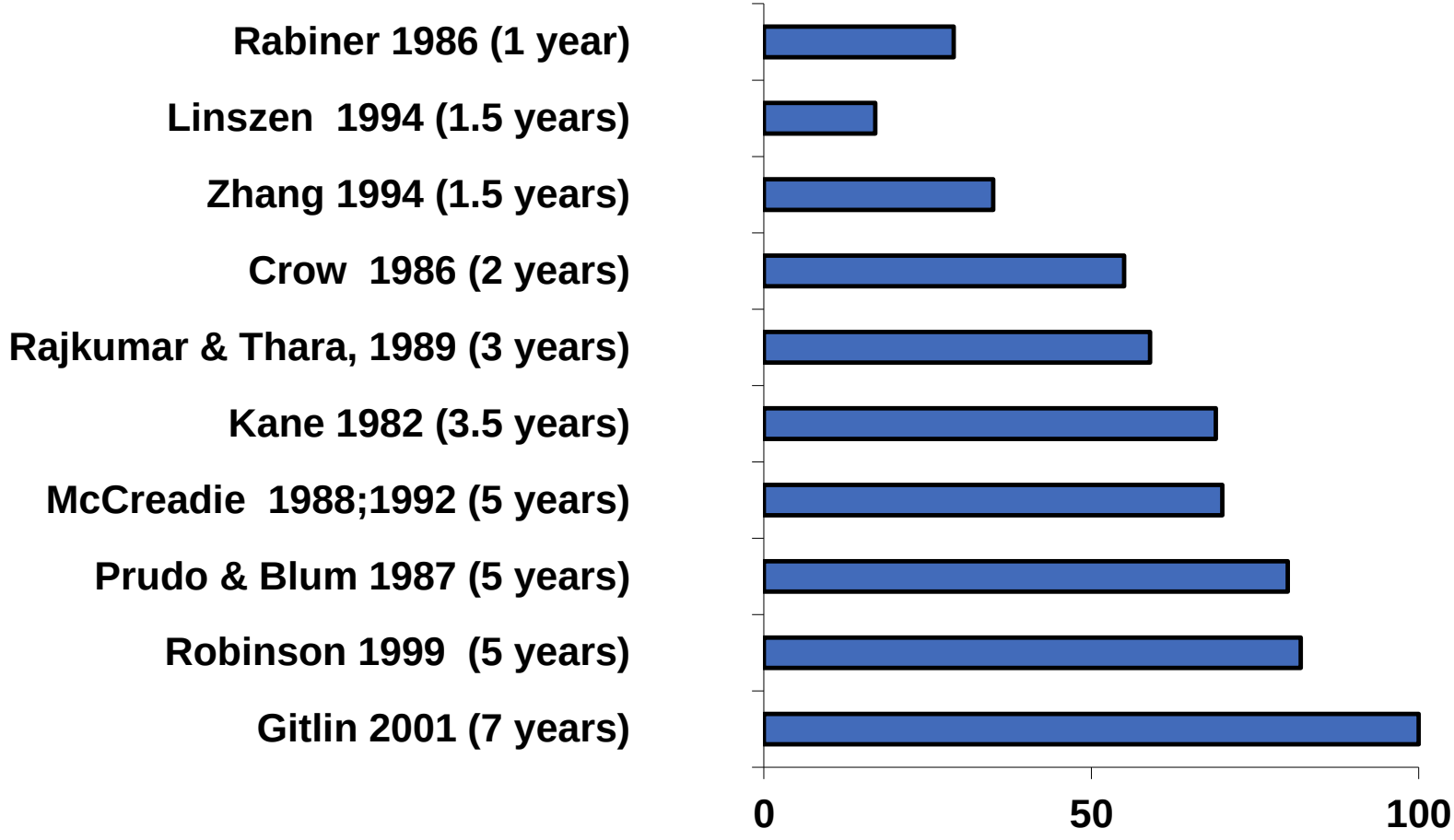
- Greater the chance of aggression and violence prior to first treatment contact
- Social and role function derailment
- Longer time to recovery
- Less likely to recover from first episode
- Chronic symptoms more severe and worse social and role function
- Greater risk of brain tissue loss

•**Franz L. *Early Interv Psychiatry*. 2010;4(1):47-56.**

Variable Outcomes in Schizophrenia

- After a first episode, positive symptoms usually remit
- Without maintenance antipsychotic medication, most relapse

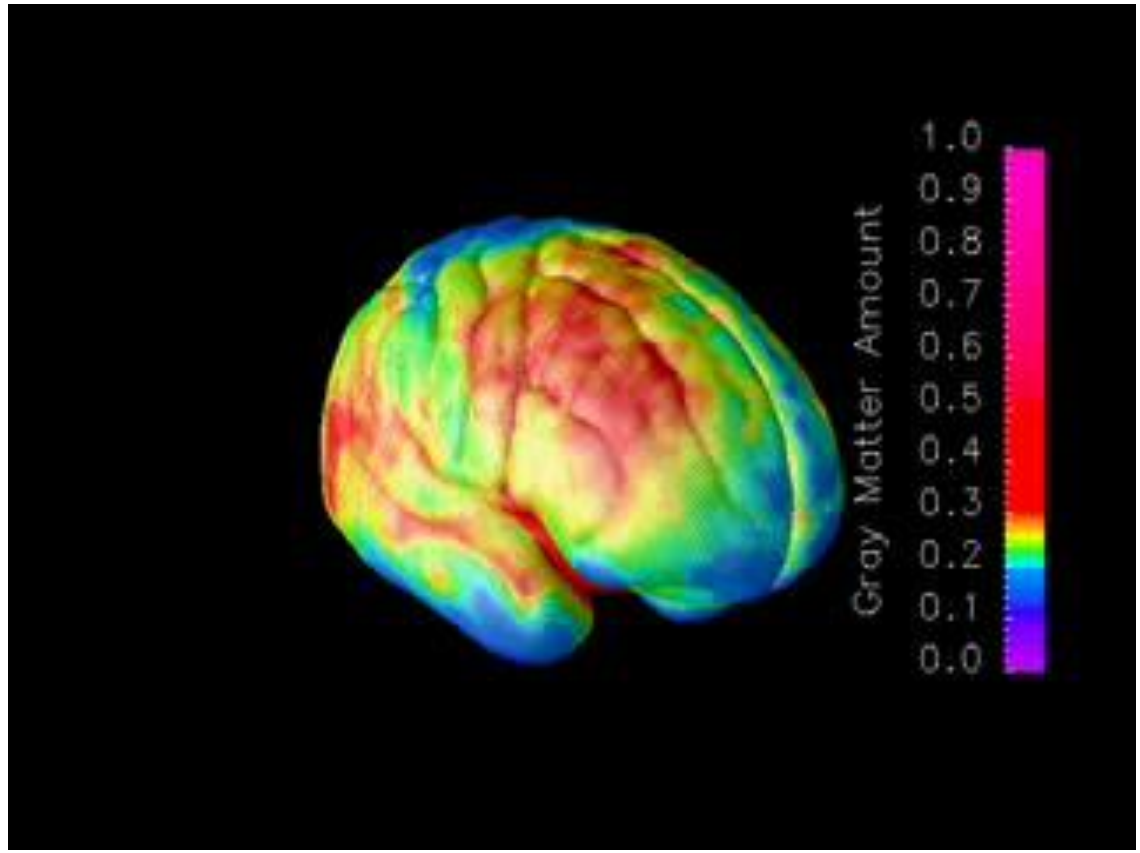
Relapse after Treatment of a First Psychosis Episode: Naturalistic Studies



Variable Outcomes

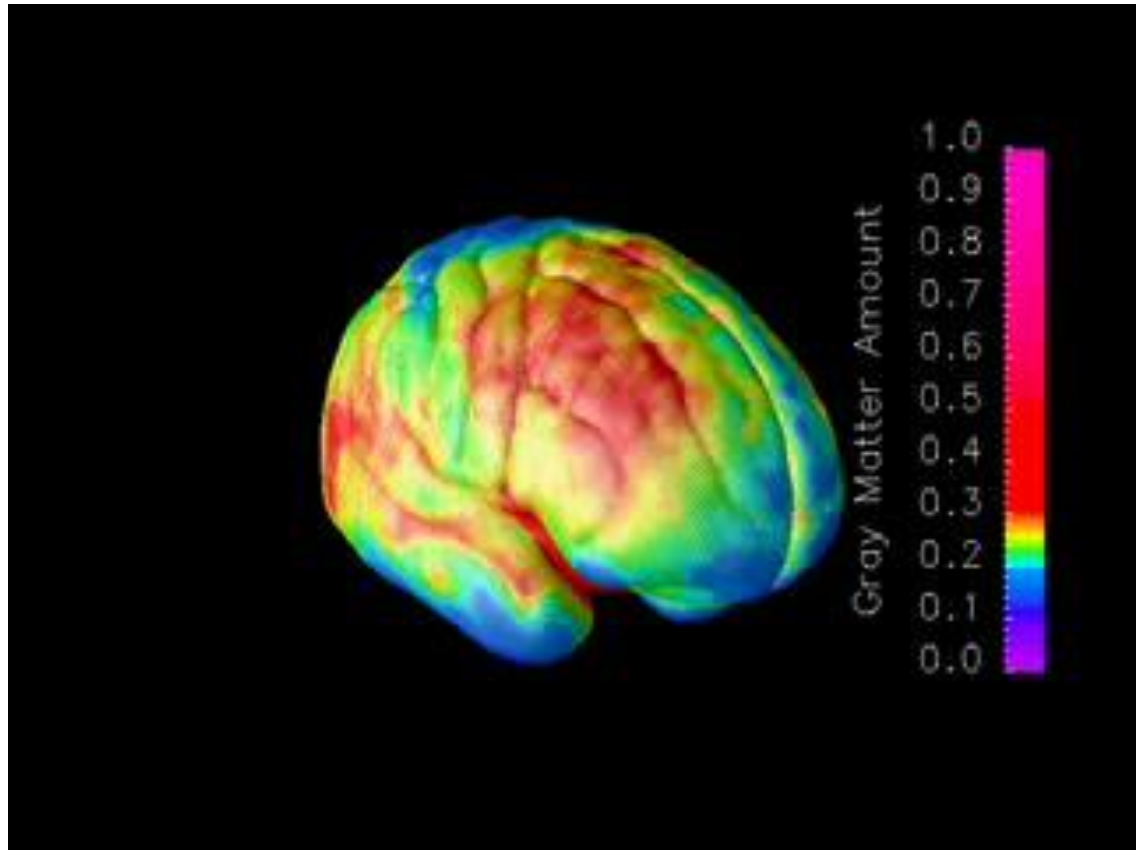
- Most patients experience positive symptom remission after a first episode
- Without maintenance antipsychotic medication, most relapse
- Relapse is associated with symptomatic, functional, and brain progression

Normal brain maturation



Gogtay et al. PNAS 2004;101(21):8174–8179

Normal brain maturation



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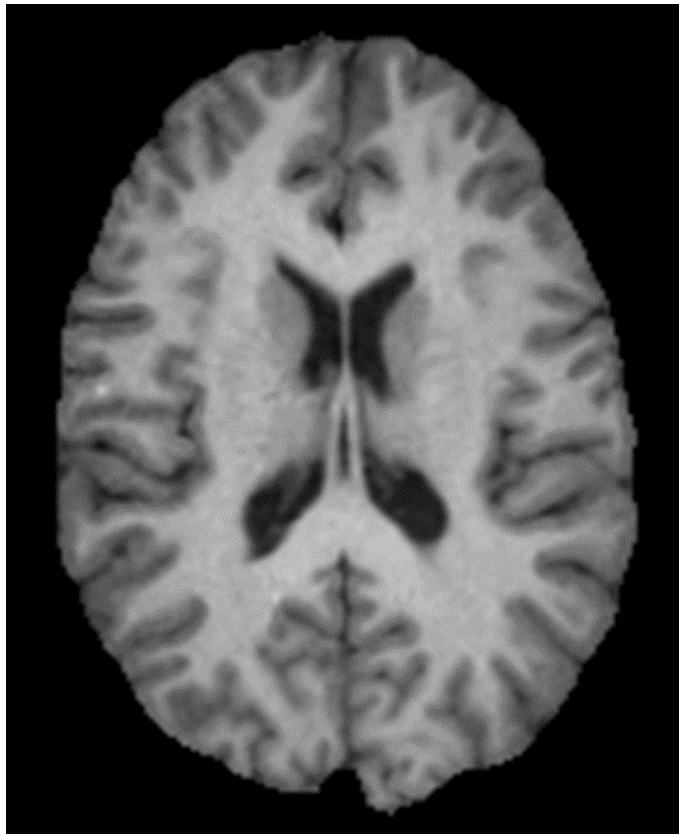
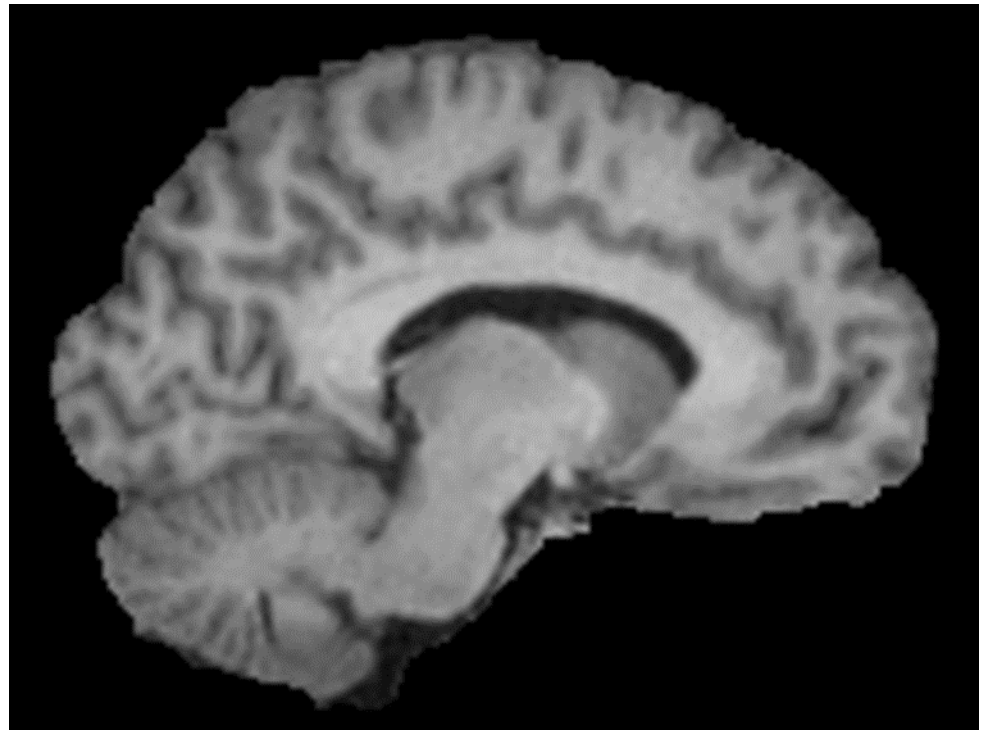
FE Schizophrenia: Change in brain volume over 6 months



axial slice



midsagittal

Sarang Joshi, Matthieu Jomier, Guido Gerig,
Fluid Warping baseline-follow-up after
Intensity Calibration

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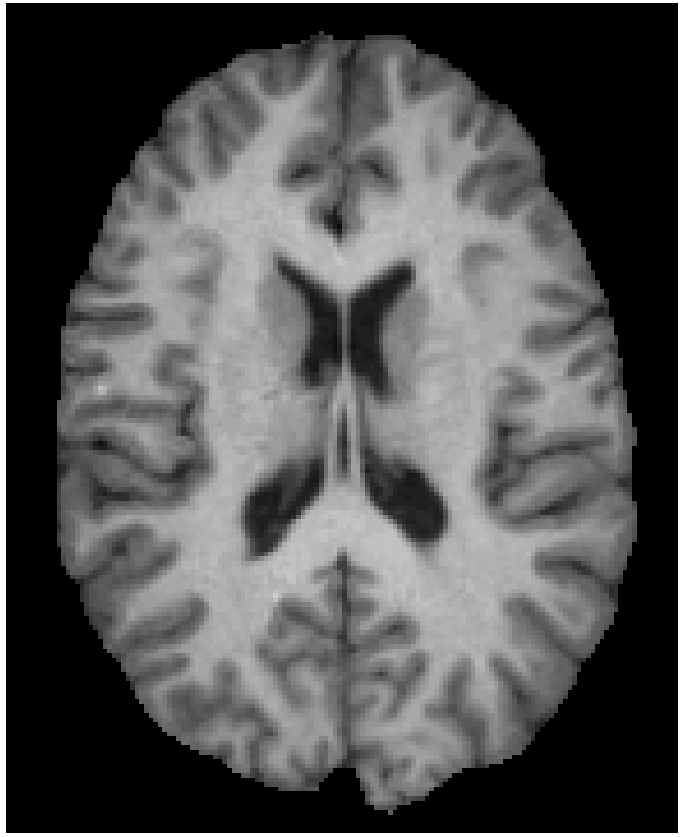

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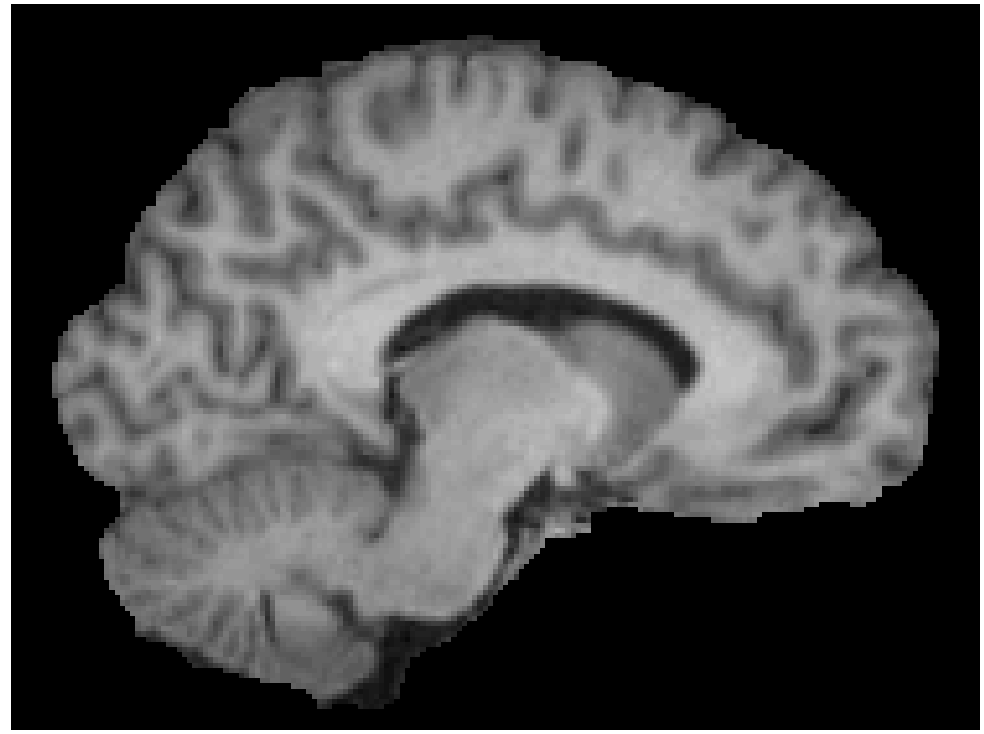

midsagittal

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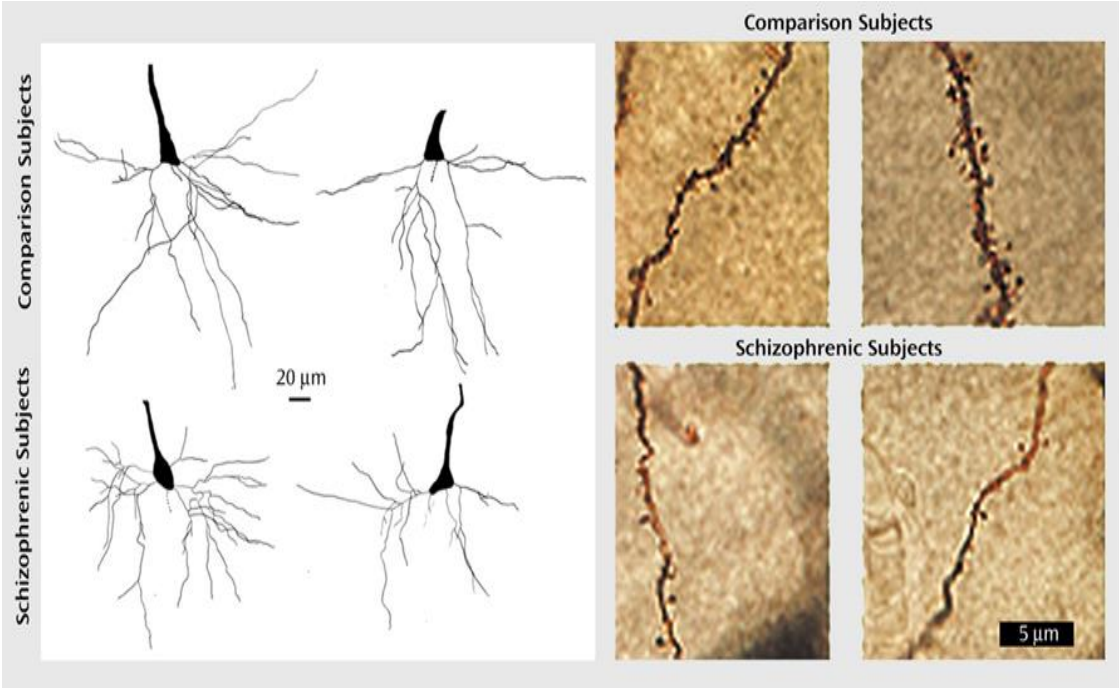
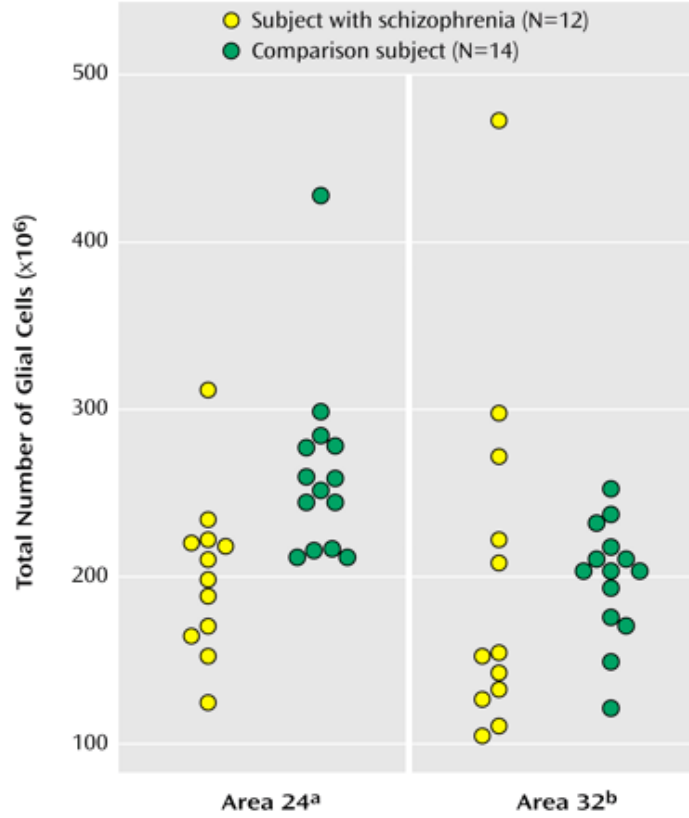
Why Does the Brain "Shrink"?

- Disordered synaptic plasticity

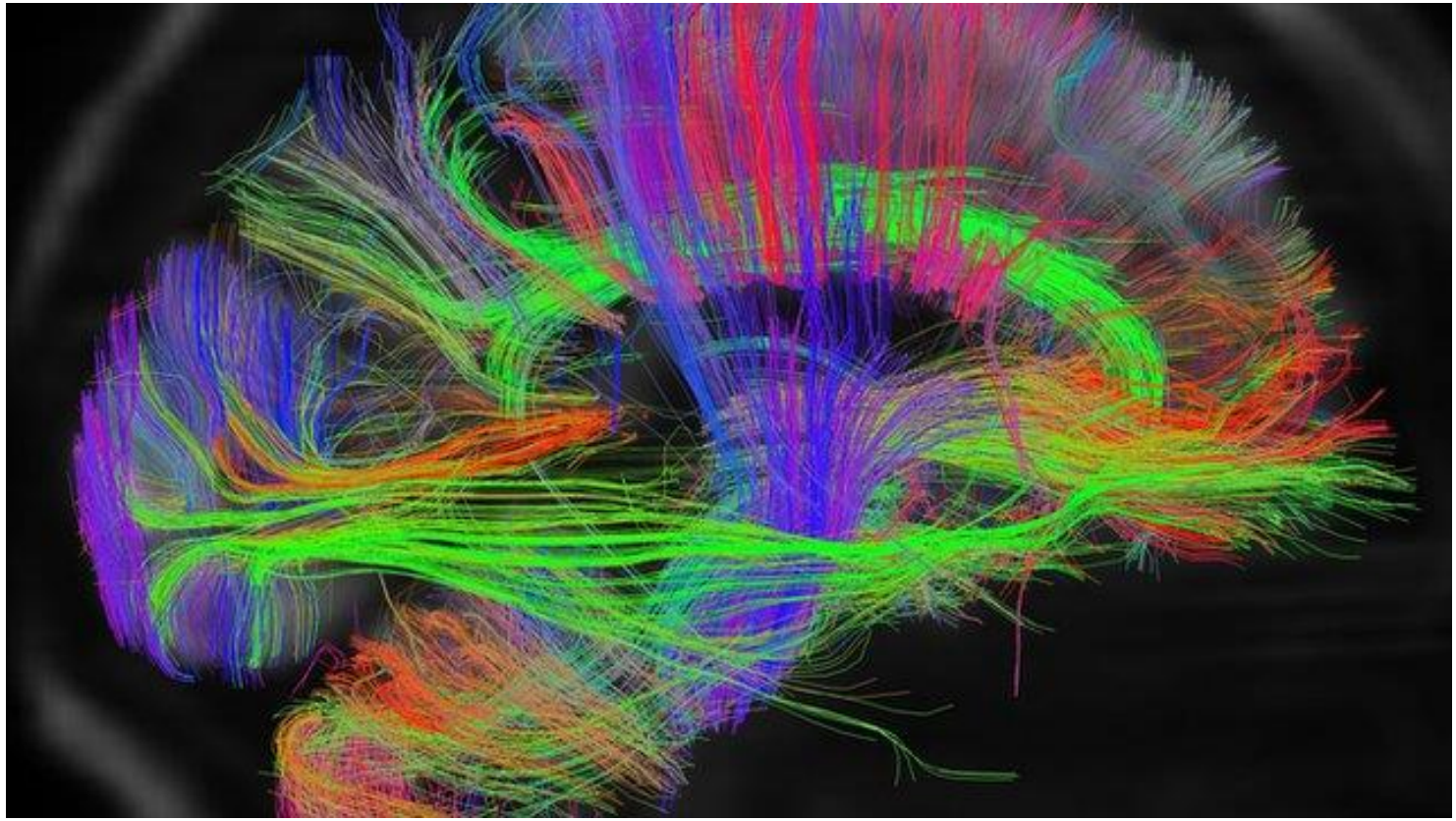


- Loss of glia



•Stark AK, et al. *Am J Psychiatry*. 2004;161:882-888.

Disrupted integrity of white matter



Associated with trauma history

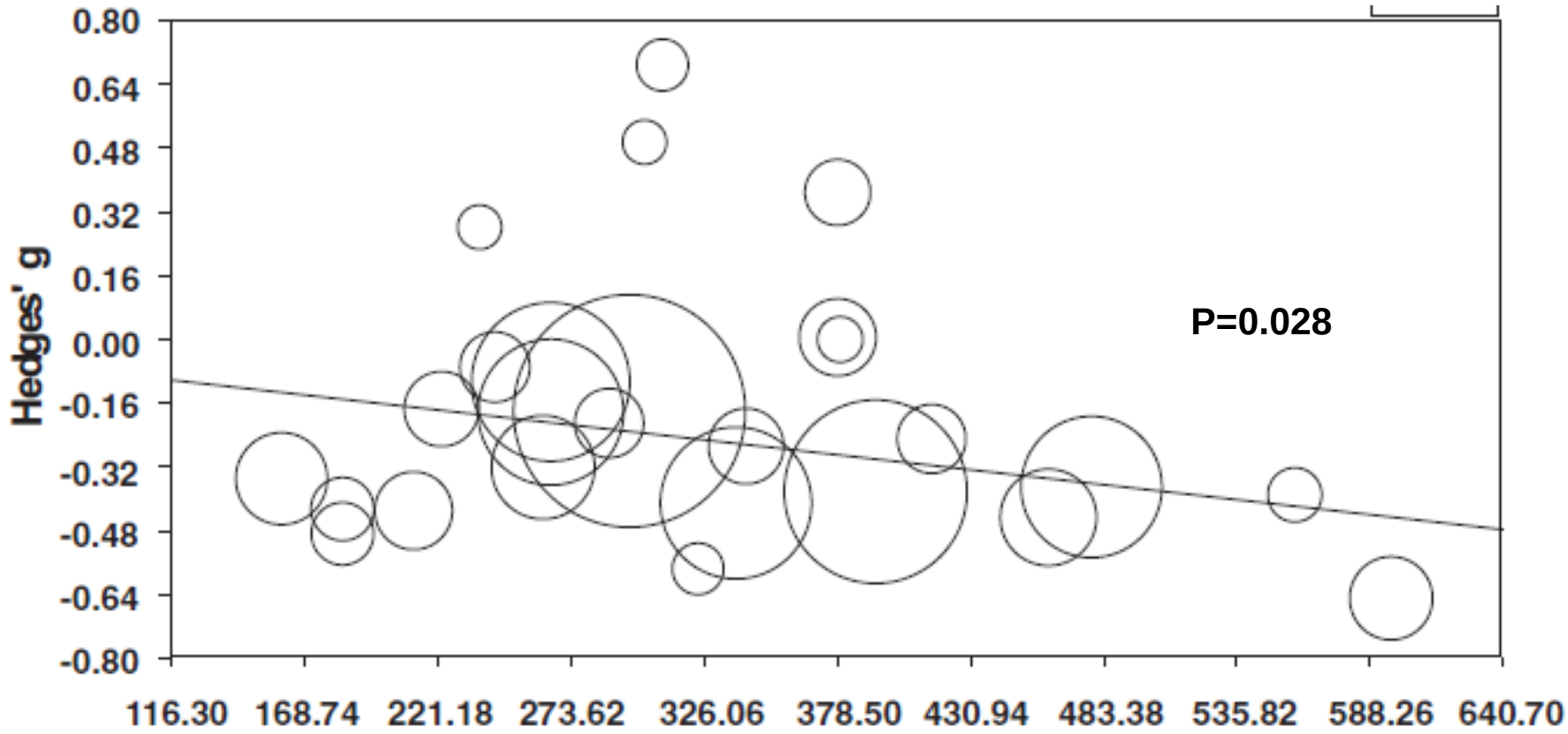
and impaired stress reactivity

Nugent, et al. *Psychosomatic Medicine*. 2015;77:733-742;

Poletti et al. *Psychiatry Res* 2015 Aug 14. pii: S0925-4927(15)30055-X. doi: 10.1016/j.pscychresns.2015.08.003. [Epub ahead of print].

Do Antipsychotics Contribute to Gray Matter Loss?

All Antipsychotics, size of circle reflects relative sample size in study.

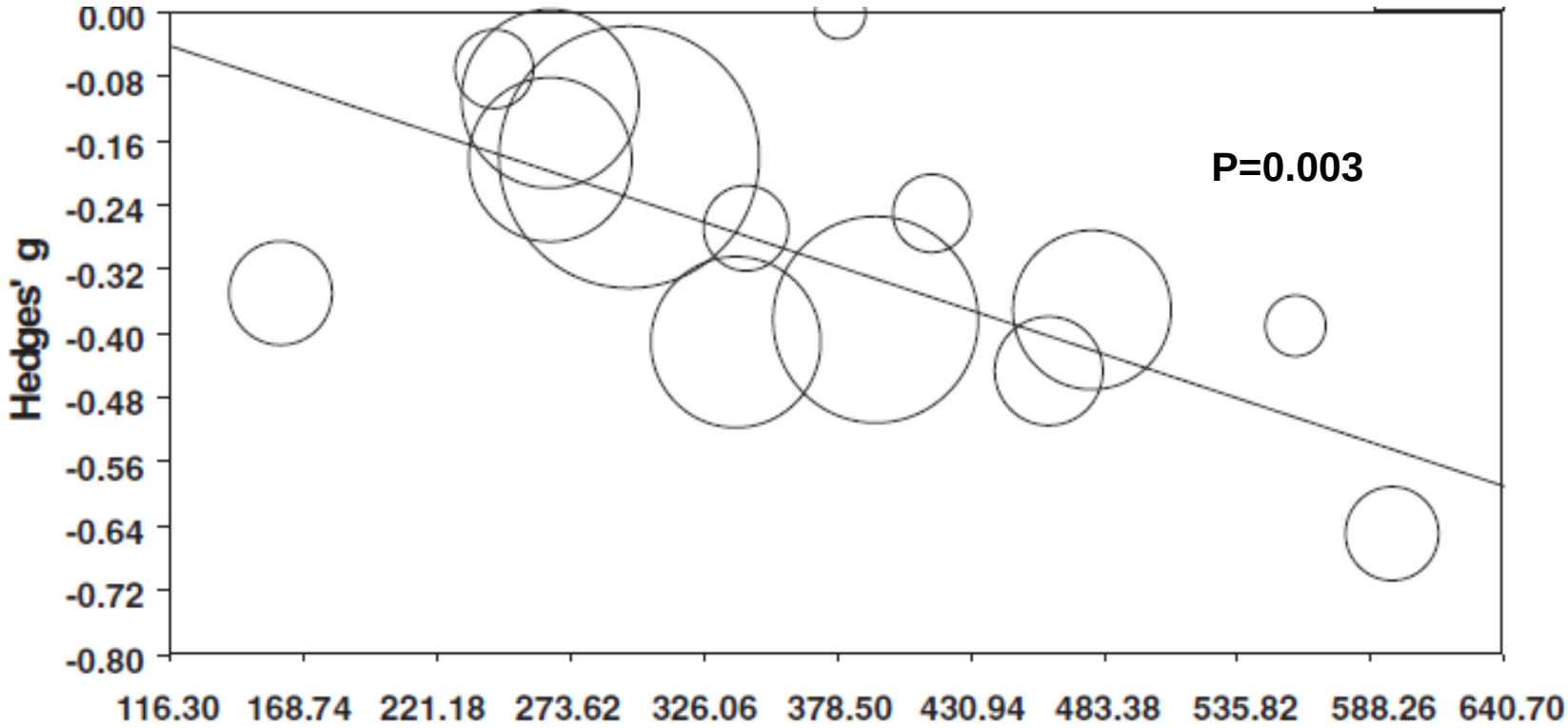


Mean Daily Antipsychotic Dose Administered During Scan Interval (chlorpromazine equivalents)

Vita et al. 2015 Biological Psychiatry

Do Antipsychotics Contribute to Gray Matter Loss?

Any treatment with "typical" antipsychotics, size of circle reflects relative sample size in study.



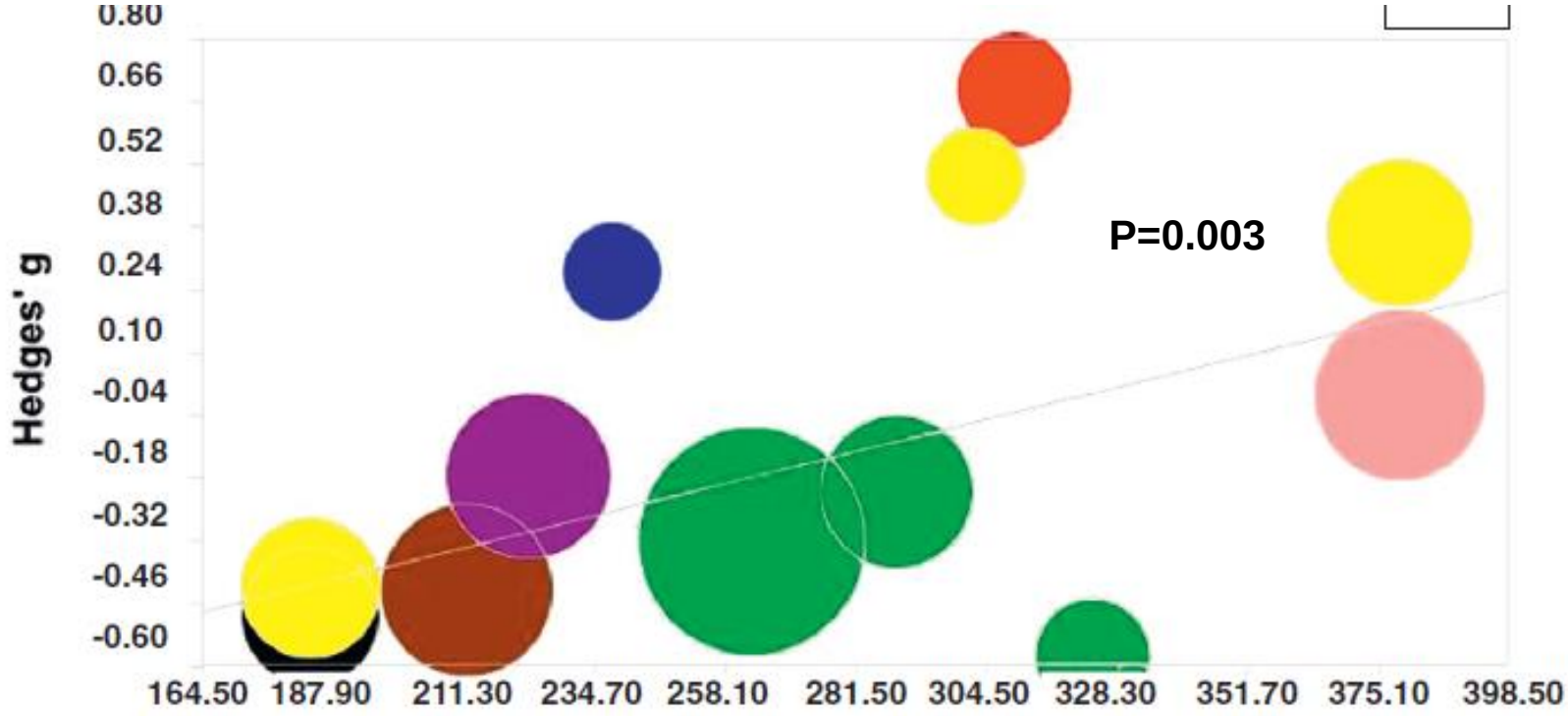
Mean Daily Antipsychotic Dose Administered During Scan Interval (chlorpromazine equivalents)

Vita et al. 2015 Biological Psychiatry

Do Antipsychotics Contribute to Gray Matter Loss?

Only treated with "atypical" antipsychotics, size of circle reflects relative sample size in study.

clozapine olanzapine quetiapine risperidone ziprasidone multiple-atypicals



Mean Daily Antipsychotic Dose Administered During Scan Interval (chlorpromazine equivalents)

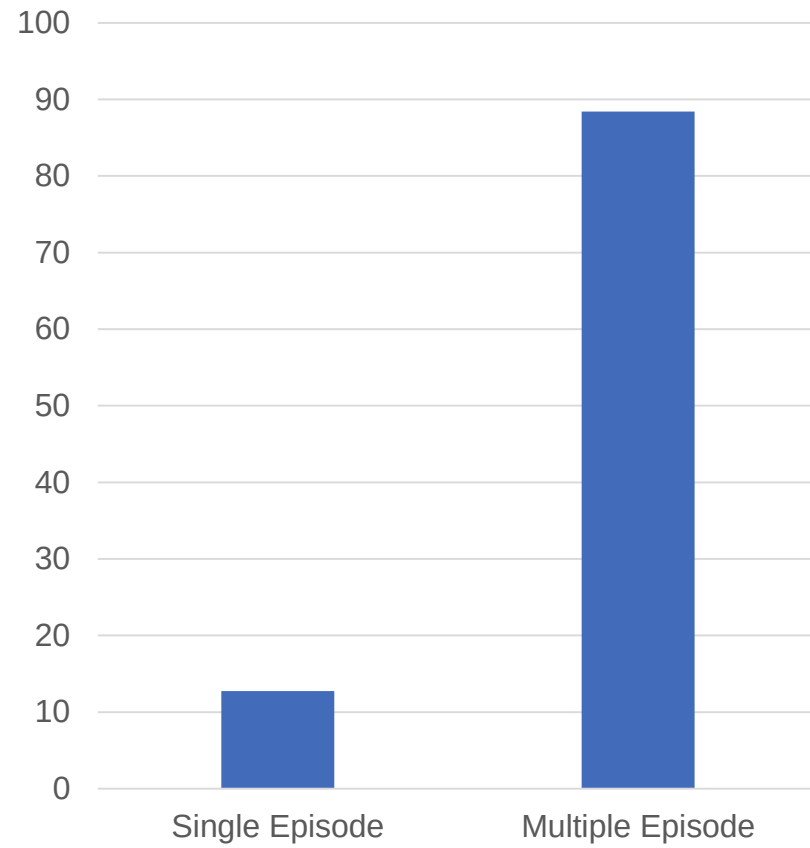
Vita et al. 2015 Biological Psychiatry

Variable Outcomes

- Relapse
  - Most patients will relapse if antipsychotics are discontinued
  - Interferes with normal psychosocial development
  - Interferes with educational and vocational achievements
  - Risk of harm to self, others, or property higher during active psychosis
  - Risk of involuntary hospitalization increases
  - Prognosis may be negatively impacted
- Some people have worse schizophrenia than others
  - 10-15% highly treatment resistant
  - 10-15% benign course

Most but not all patients have a recurrent illness

- 207 persons with first episode schizophrenia
- 24 had only a single episode in 7.5 years
- Predictors* of a single episode included shorter duration of untreated psychosis and more rapid time to response to medication
- Single episode patients all stopped taking antipsychotic medication during follow-up period**



*Including only predictors that survived adjustment for multiple testing; **Personal communication Alvarez-Jimenez

Alvarez-Jimenez et al. Schizophrenia Research (2011) 125:236-246

What we knew in 2005
Variable Outcomes

- Most patients will have symptomatic recovery from a first episode.
- Most patients elect for a trial off of antipsychotics, most experience multiple relapses
  - Interferes with normal psychosocial development
  - Interferes with educational and vocational achievements
  - Risk of harm to self, others, or property higher during active psychosis
  - Risk of involuntary hospitalization increases
  - Prognosis may be negatively impacted
- Some people have worse schizophrenia than others
  - 10-15% highly treatment resistant
  - 10-15% benign course
- Long-term outcomes: variable, but most show less than 20% have full recovery
  - Almost all VA schizophrenia patients are disabled
- Risk of suicide is high (~5-6%)

Palmer et al.The lifetime risk of suicide in schizophrenia: a reexamination.
Archives of General Psychiatry. 2005;62(3):247–53

Harvey et al. Functional impairment in people with Schizophrenia: Focus on employability and eligibility for disability compensation

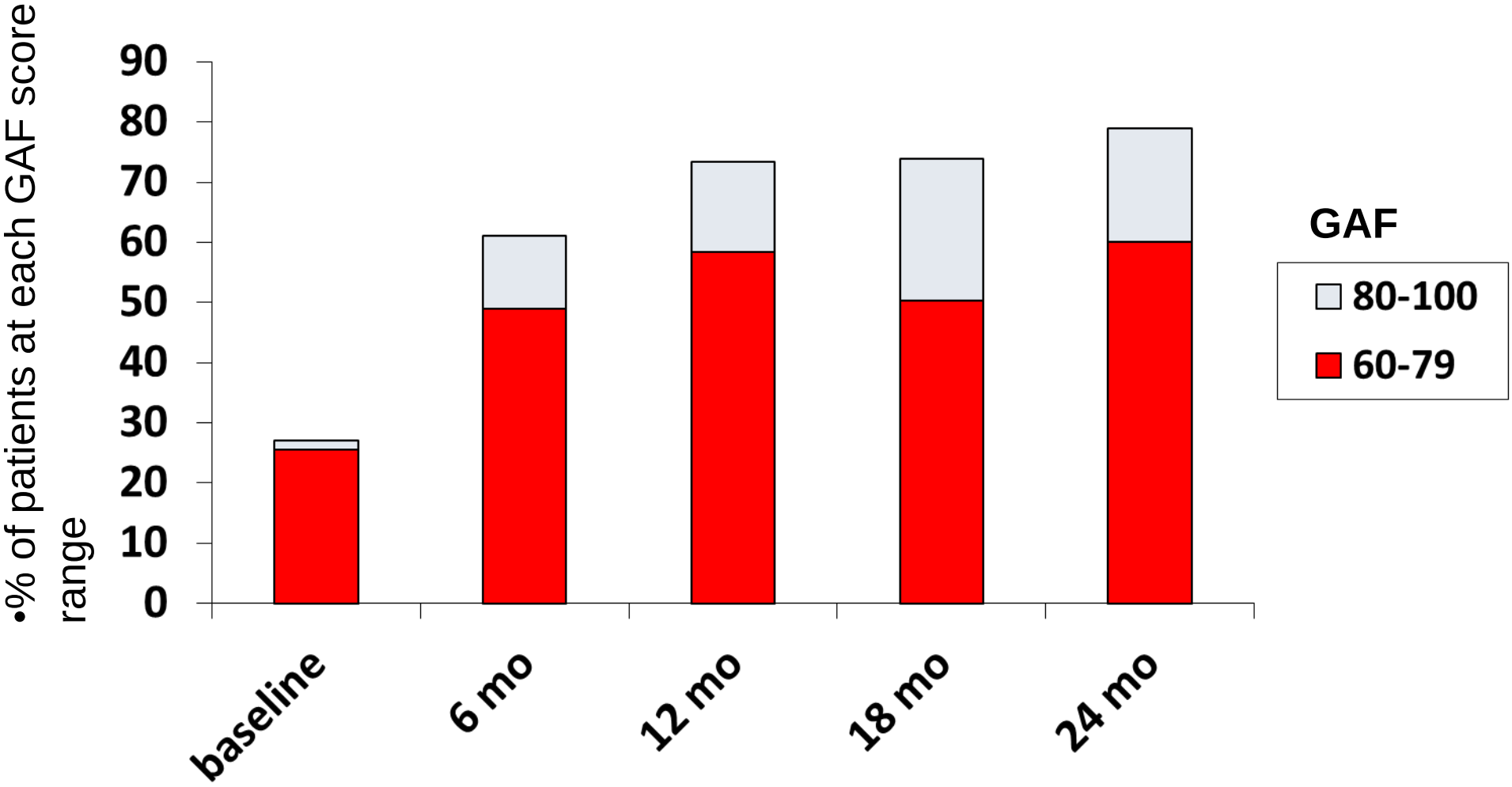
University of North Carolina at Chapel Hill Outreach and Support Intervention Services (OASIS)

- In operation since 2005*
- Foster sustained recovery from early psychosis
  - Translate science to practice
  - Translate practice to science
- Increase public understanding of psychotic disorders
- Promote early identification of psychosis

*Funded by the KB Reynolds and Duke Endowment Foundations;

*Supported by the citizens of North Carolina

% of OASIS patients with good and excellent functioning as measured by the GAF score



OASIS Patient Outcomes

- 23% on Disability & Medicaid
  - 41% of those on disability are working or in college
  - Over half applied for disability to qualify for Medicaid
- Two persons committed suicide

Treatment Philosophy

- “Psychosis” and Schizophrenia-spectrum disorders are heterogeneous
  - Symptom characteristics
  - Etiology
  - Course
- People who develop “psychosis” and schizophrenia-spectrum disorders are heterogeneous
  - Experience (especially with the illness)
  - Personality
  - Culture
  - Resources

Treatment Philosophy

- Treatment interventions must be individualized
  - Stage of illness
  - Stage of person
- Treatment interventions must be multimodal
  - Address symptoms
  - Address function
  - Address meaning

Interventions

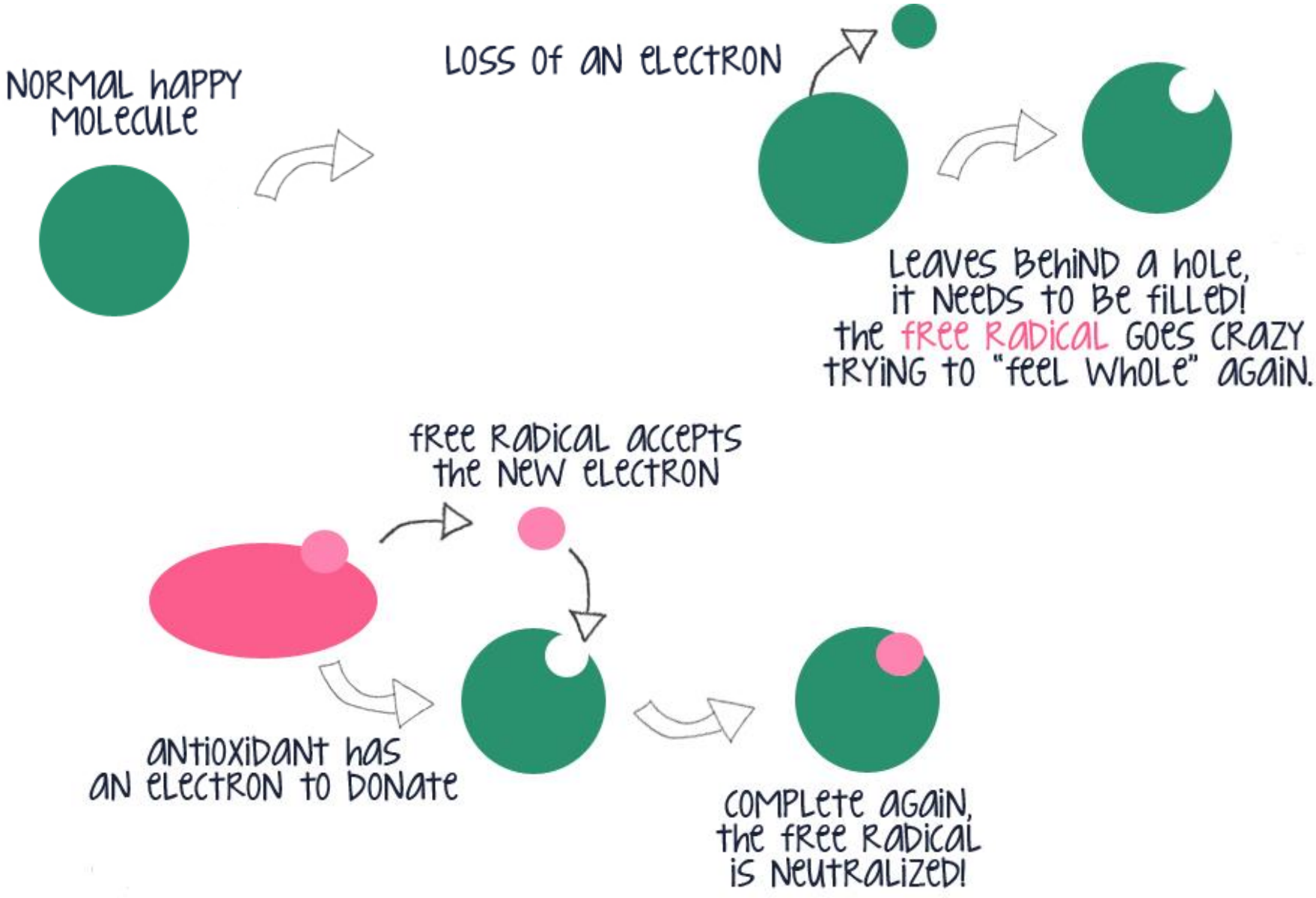
- Multidisciplinary Team Approach
  - Medication Management
    - Collaborative model
    - Adherence/insight addressed with motivational interviewing
    - Long-acting injectable first choice
    - Clozapine option after 2-3 medication failures
    - Treat-to-Target
    - Alternative/complimentary treatments

Redox and Free Radicals

- Includes reactive oxidative species and nitric oxide free radicals[1,2]
- Highly reactive molecules generated during normal metabolic processes[3]
- Generated during metabolism of neurotransmitters[3]
  - Dopamine
  - Glutamate
- Neutralized in the body by a host of antioxidants[4,5]
  - Endogenous (eg, **glutathione**)
    - Dietary supplements that increase glutathione levels: n-acetylcysteine, S-adenosylmethionine, alpha lipoic acid, vitamin D)
  - Exogenous (eg, vitamins E and C, flavonoids, niacin, lipoic acid, carotenoids)

•[1]Pompella A et al. *Biochem Pharmacol.* 2003;66(8):1499-1503. [2]Clementi E et al. *The Plant Cell.* 1999;11(6):1153-1164. [3]http://www.drugs.com/pdr/immunocal-powder-sachets.html. Accessed October 8, 2012. [4]Scholz RW et al. *Ann NY Acad Sci.* 1989;570:514-517. [5]Hughes RE. *Nature.* 1964;203:1068.1069.

Oxidative Stress



By-product normal metabolism

Sun/Radiation

Stress

Poor nutrition

Smoking/Pollution

Heart Disease

Diabetes

Aging

Schizophrenia

Other diseases

Antioxidants And Oxidative Stress

- Oxidants are neutralized in the body by a host of antioxidants[4,5]
  - Produced by our body (eg, **glutathione, uric acid, melatonin, etc.**)
  - From food and supplements (eg, vitamins E and C, flavonoids, niacin, lipoic acid, carotenoids)

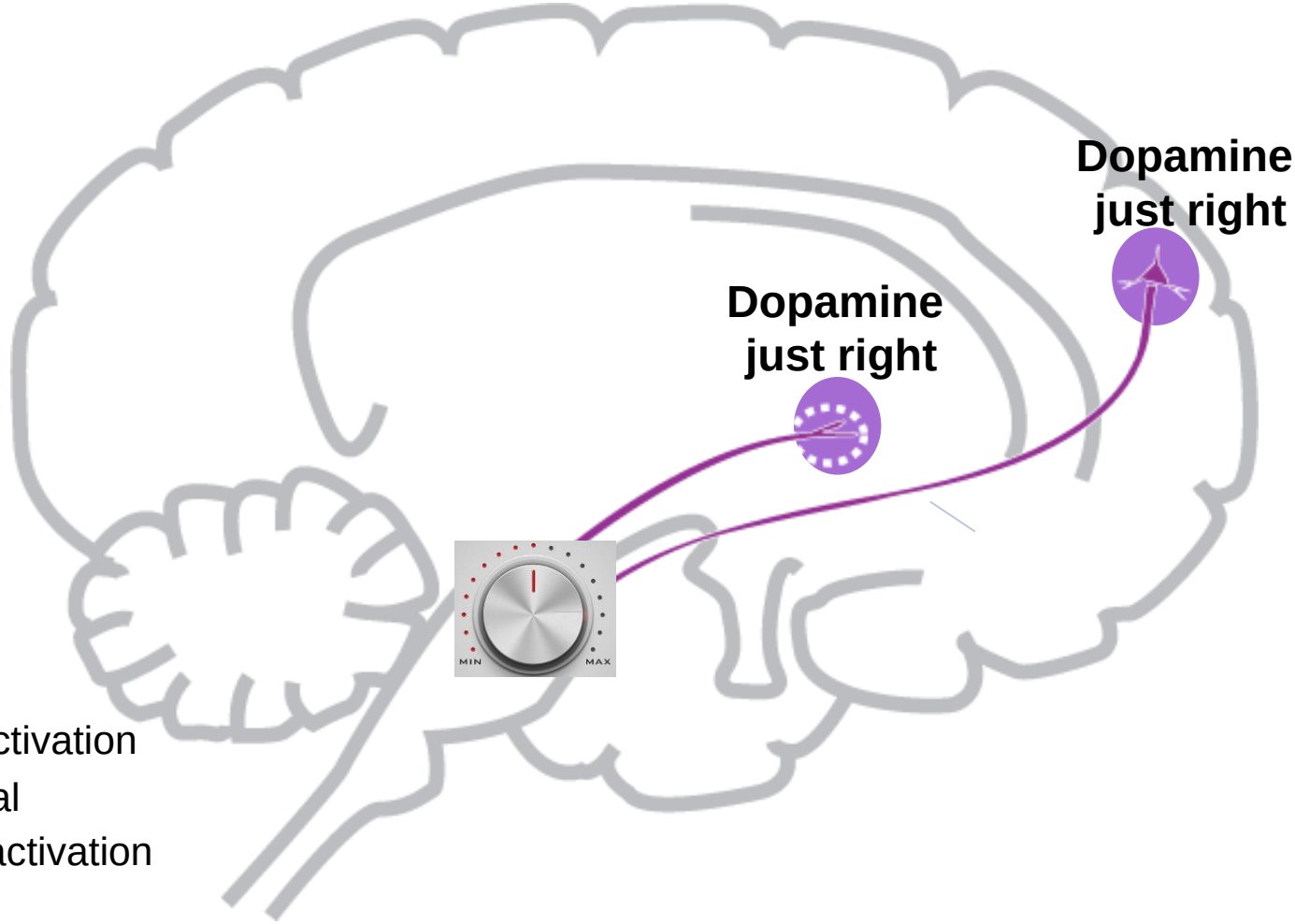
•[1]Pompella A et al. *Biochem Pharmacol.* 2003;66(8):1499-1503. [2]Clementi E et al. *The Plant Cell.* 1999;11(6):1153-1164. [3]http://www.drugs.com/pdr/immunocal-powder-sachets.html. Accessed October 8, 2012. [4]Scholz RW et al. *Ann NY Acad Sci.* 1989;570:514-517. [5]Hughes RE. *Nature.* 1964;203:1068.1069.

High Oxidative Stress in Schizophrenia

- Levels of endogenous antioxidants, especially glutathione, are low[1]
- Levels of free radicals are high[1]
- Mitochondrial function is impaired[1]
- High dopamine levels lower endogenous antioxidants[1]
- Animal models suggest oxidative stress can cause many of the abnormalities found in schizophrenia[2]
- Glutathione depletion results in NMDA receptor hypofunction[2]

•[1]**Bitanihirwe et al. *Neurosci Biobehav Rev.* 2011;35(5):878-893. [2]Steullet P et al. *Neuroscience*. 2006;137(3):807-819.**

NMDA Tunes Dopamine Tone in Brain



•Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 3rd Edition.* New York, NY: Cambridge University Press; 2008.

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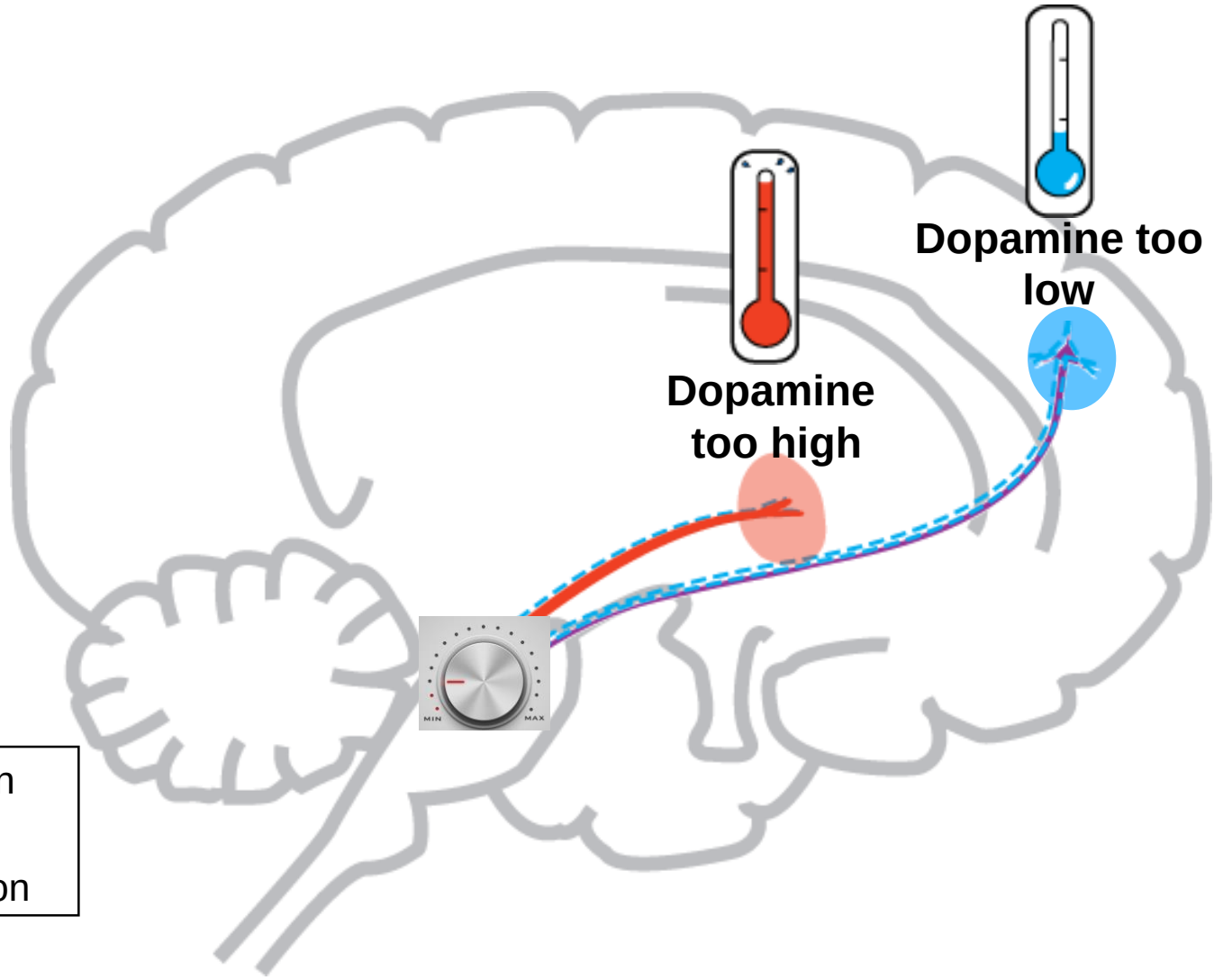
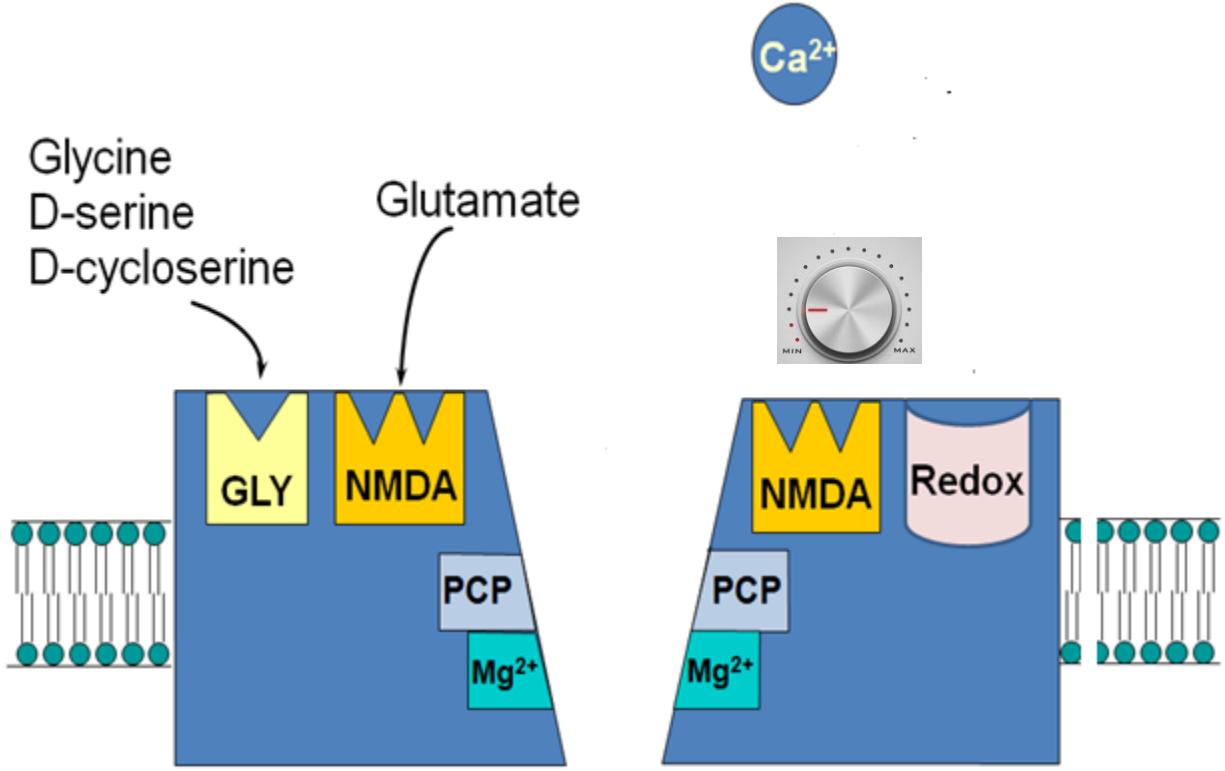


•Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 3rd Edition.* New York, NY: Cambridge University Press; 2008.

Glutathione tunes the NMDA receptor “up”



Javitt & Zukin, Am J Psyc iatry, 1991

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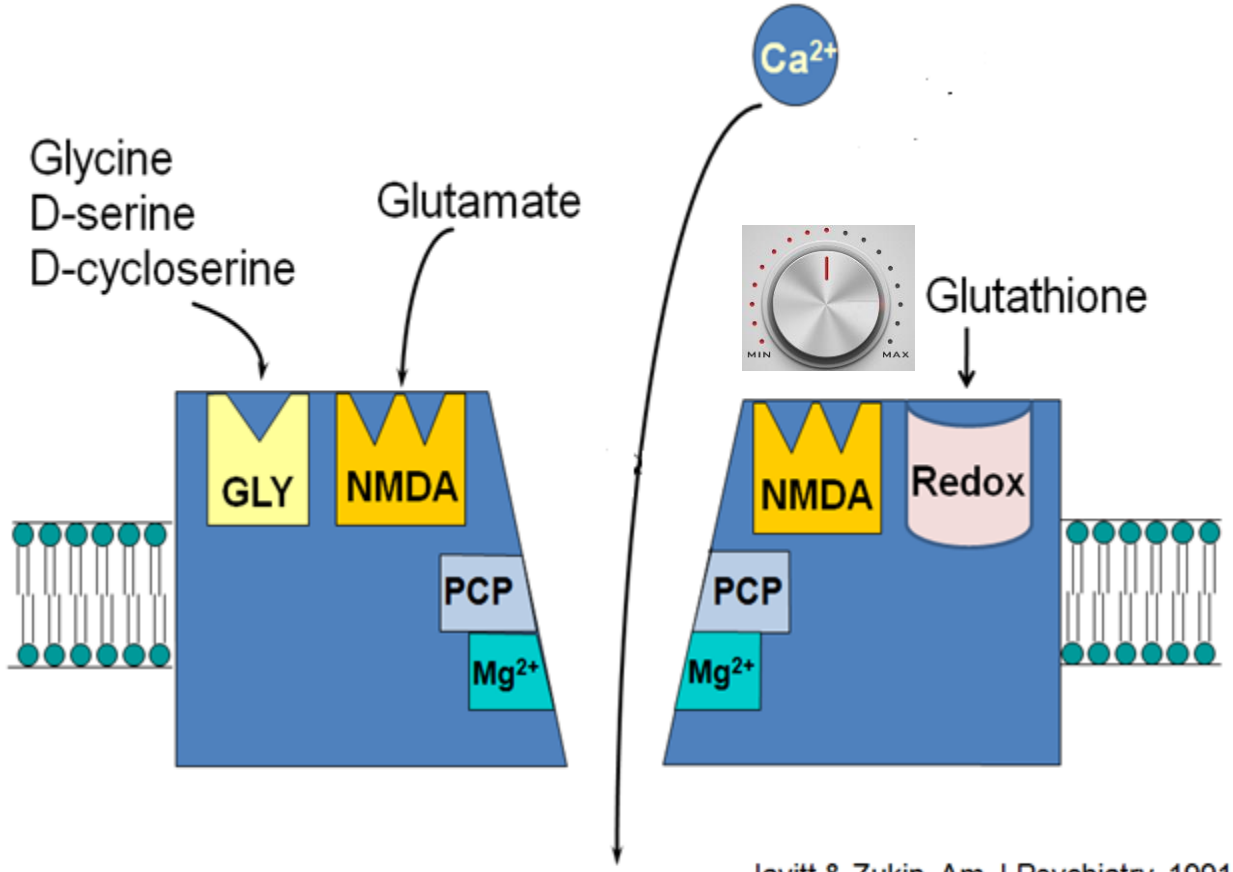
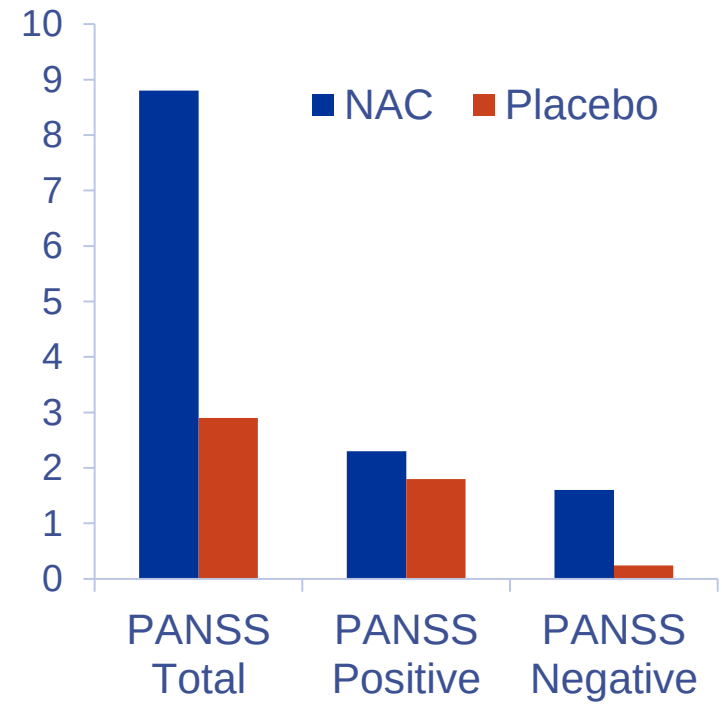


Javitt & Zukin, Am J Psychiatry, 1991

N-Acetyl Cysteine: Clinical Trial

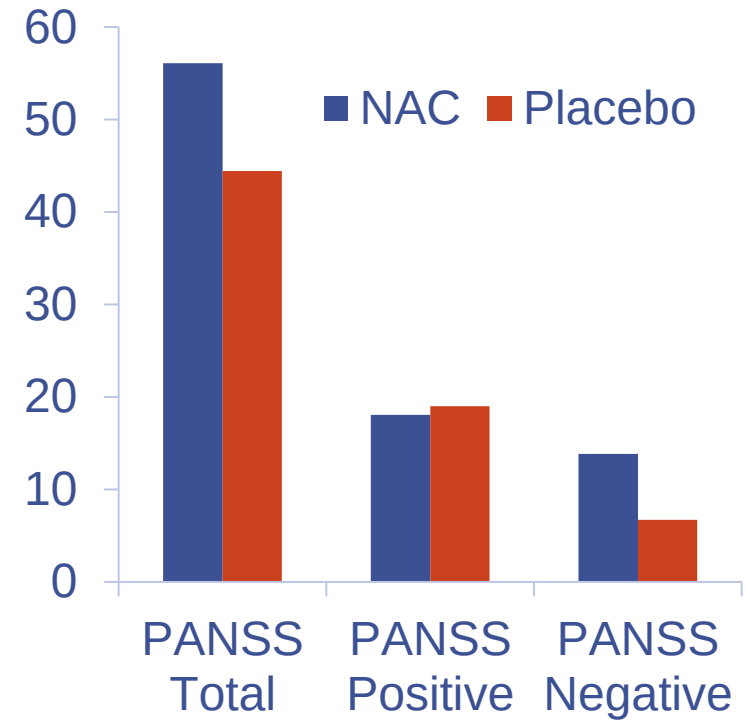
- Rationale
  - N-acetyl cysteine is a glutathione precursor, oral administration increases glutathione levels
- Subjects: 140 subjects with schizophrenia
- Design: 24-week, randomized, double-blind, placebo-controlled augmentation on current antipsychotic
- Treatment: 1000 mg BID N-acetyl cysteine
- Outcomes: N-acetyl cysteine augmentation is associated with reduced total (*P* = .009), negative (*P* = .028), and general psychopathology



Berk et al. *Biological Psychiatry*. 2008;64(5):361-8.

N-Acetyl Cysteine: Clinical Trial

- Rationale
  - N-acetyl cysteine is a glutathione precursor, oral administration increases glutathione levels
- Subjects: 42 subjects with schizophrenia, acutely psychotic
- Design: 8-week, randomized, double-blind, placebo-controlled augmentation on current antipsychotic
- Treatment: 1000 mg BID N-acetyl cysteine
- Outcomes: N-acetyl cysteine augmentation is associated with reduced total (*P* = .006), negative (*P* = .001), and general psychopathology (*P* =.005), not for positive symptoms (p=.42)
  - No adverse effects were reported

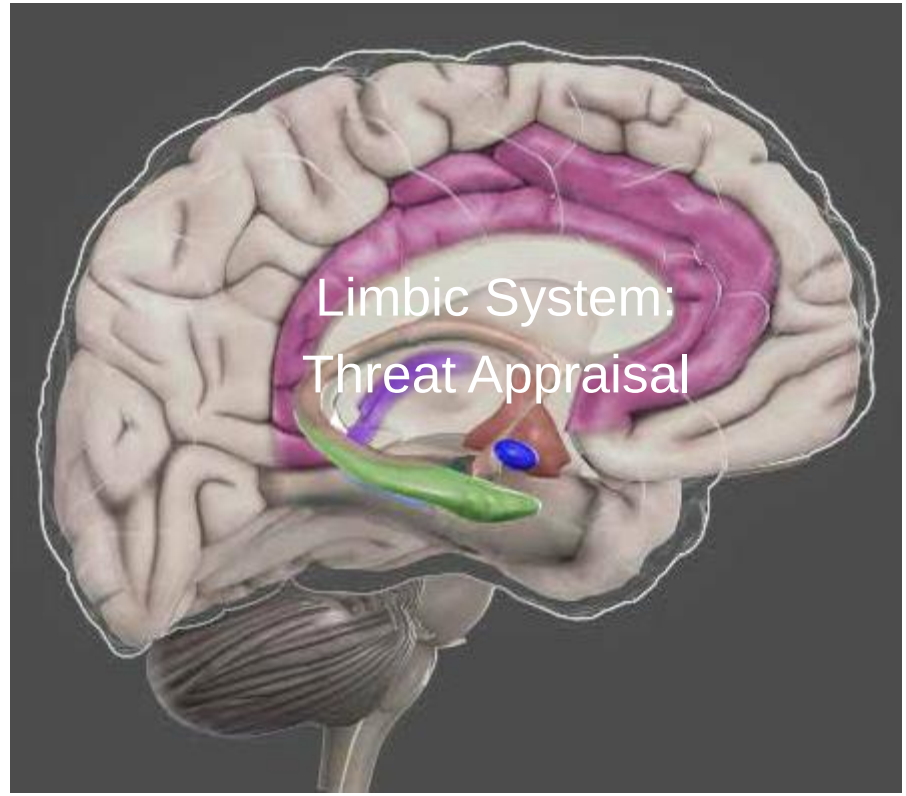


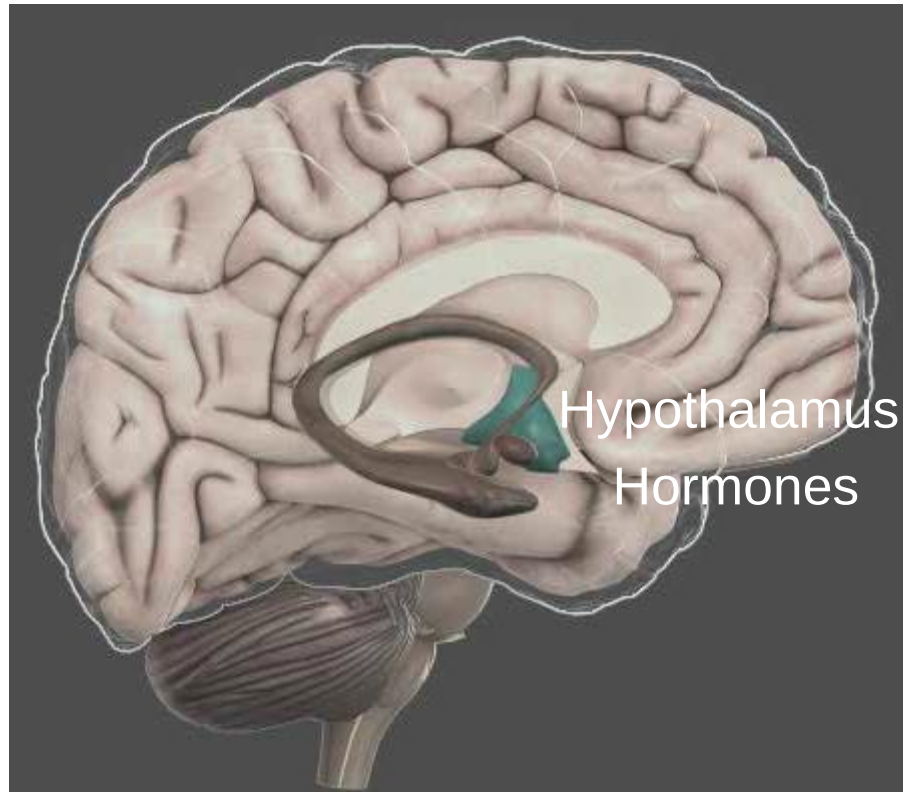
Farokhnia et al. *Clinical Neuropharmacology* 2013;36:185-192

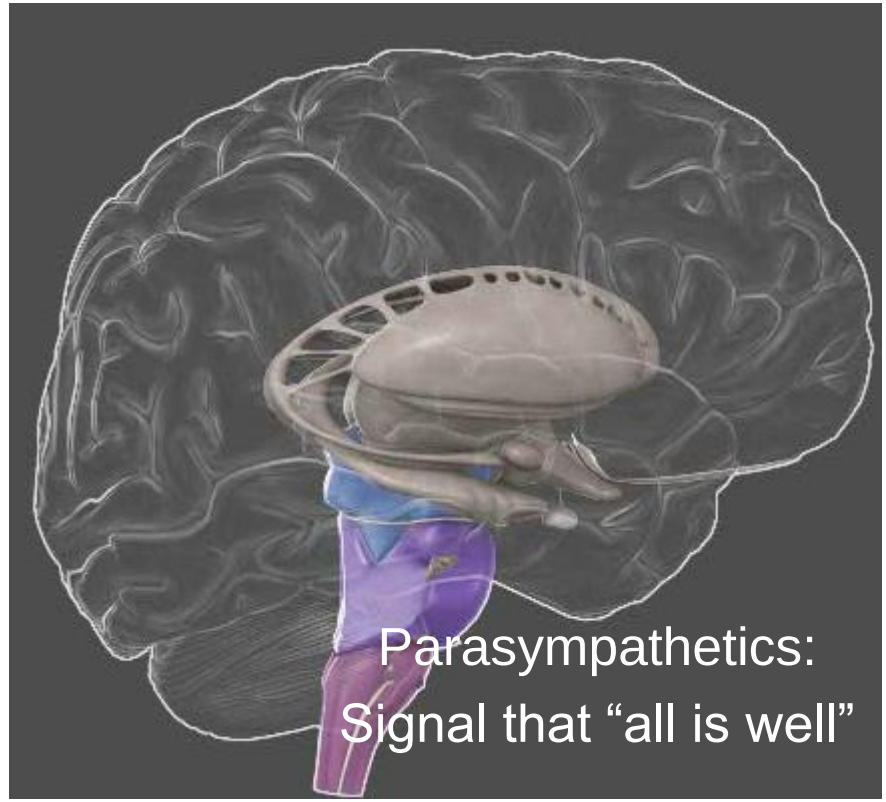
Interventions

- Multidisciplinary Team Approach
  - Medication Management
    - Collaborative model
    - Adherence/insight addressed with motivational interviewing
    - Long-acting injectable first choice
    - Clozapine option after 2-3 medication failures
    - Treat-to-Target
    - Alternative/complimentary treatments discussed
  - Individual therapy
    - Engagement in treatment
    - Disease management/education
    - Address meaning of psychosis to individual
    - Substance use
    - Stress reactivity

STRESS REACTIVITY, RESILIENCE, AND PSYCHOSIS

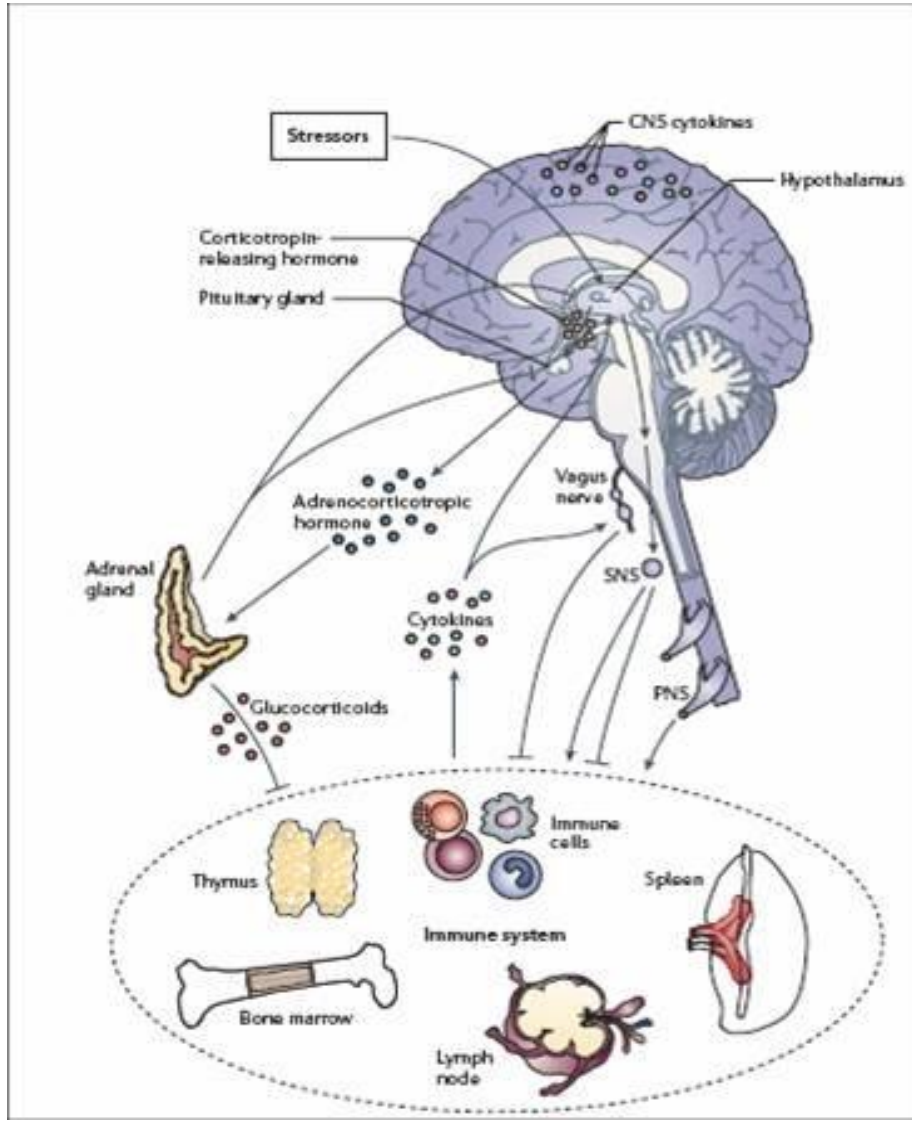

Limbic System:
Threat Appraisal


Hypothalamus
Hormones


Parasympathetics:
Signal that “all is well”

Mobilizing Our Bodies for a Challenge

- Threat/Stress
  - Essential body functions prioritized
  - Energy systems mobilized
  - Immune system prepared for inury and infection
  - Brain on “auto-pilot”
- All is well
  - Repair/restoration prioritized
  - Immune system in surveillance mode
  - Brain on social engagement, thinking things through
- Chronic threat/stress
  - Repair/restoration neglected
  - Immune system: In a pro-inflammatory state
  - Metabolism dysregulated
  - Brain dysregulated



Chronic stress is bad for the brain!

- Cognitive function is impaired (foggy brain)
- Brain “shrinks”
- Aging accelerated!
- Related to:
  - Hormonal imbalance (like cortisol)
  - Chronic inflammation
  - Oxidative stress
  - Impaired vagal tone

Well-Regulated Immune System Required for Normal Brain Function

- Bidirectional regulation:
  - Brain regulates immune and hormonal systems
    - Hypothalamus Hormones
    - Vagus Immune Reflex
  - Body regulates brain;
    - Immune cell signals (cytokines)
    - Vagus nerve transmits signals from organs
  - Influence behavior (e.g. sickness syndrome)
  - Regulate the brain's immune cells, microglia, level of activation, that influence brain plasticity

Dantzer et. al. (2008). Nat Rev Neurosci 9:46–56.

Well-Regulated Immune System Required for Normal Brain Function

- Immune-deficient mice:

  - cognitive impairments that are improved with immune cell transplantation
  - impaired resilience to stress that is improved with immune cell transplantation
  - Impaired neurogenesis that is improved with immune cell transplantation

- Offspring of mothers  that were immune-activated during pregnancy:
  - altered immune cell populations
  - behavioral abnormalities
  - brain plasticity impairments
  - brain structure changes
  - **Behavior, brain and immune alterations <u>reversed</u> with bone marrow transplantation from normal mice**

Filiano et al. 2014 Brain Research, in press, Hsiao et al. 2012 PNAS 109:12776-12781
Villeda eta al Nat Med 2014 20:659-663, Villeda eta l. Nature 2011 477:90-94

Well-Regulated Immune System Required for Normal Brain Function

- Better neurocognitive test performance in healthy seniors associated with a well-regulated immune system
- Healthy humans exposed to endotoxin had transient impairments in social cognition (ToM)
  - Impairments were not associated with magnitude of cytokines response

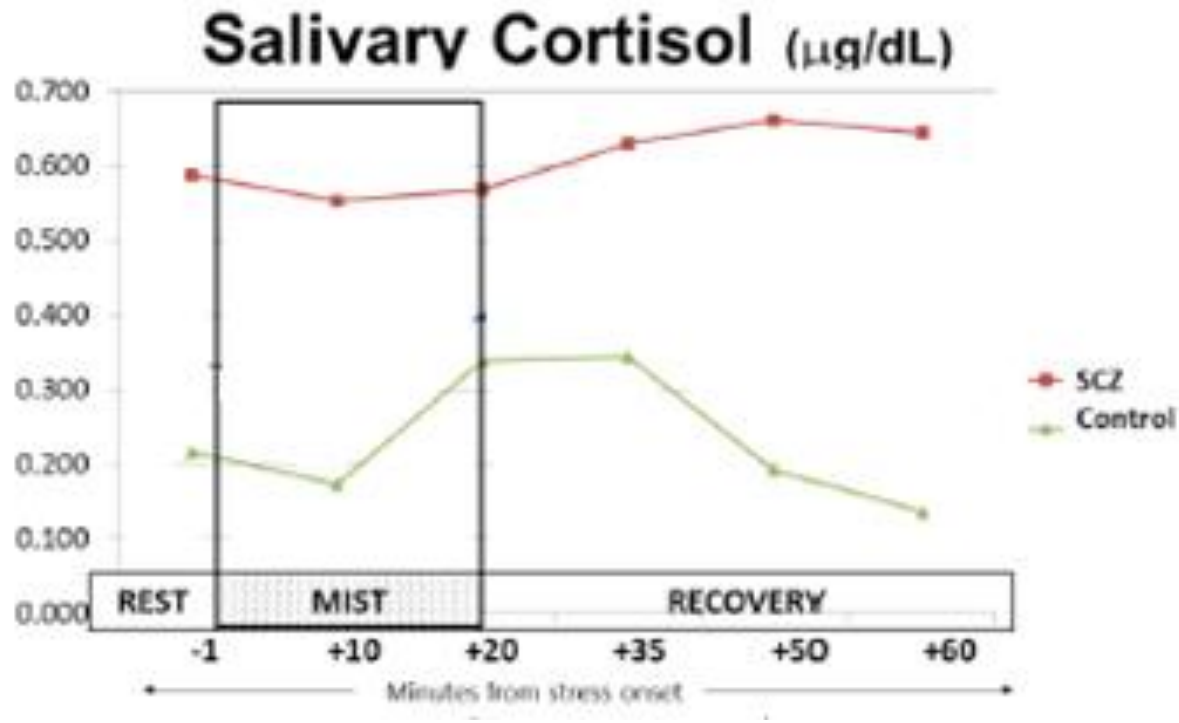
Sierre-Miranda 2015 Neurology: Neuroimmunology & Neuroinflammation in press,
Hodes et al. 2014 PNAS111:18799-16141,de Vellejo et al 2013 The Journal of Immunology 190:

Immune Cell Populations Altered in Schizophrenia

- Schizophrenia associated with peripheral "pro-inflammatory" state
  - Elevated inflammatory cytokines
  - Immune cell populations shifted towards inflammation

Miller et al. 2013 Biological Psychiatry 73:993-999
Dalmau et al. 2008 Lancet Neurol 7:1091-1098

Stress Response Dysregulated in Persons with Schizophrenia



- Impaired stress response found in persons recovered from a first episode of schizophrenia
  - Resting stress level is high
  - Poor ability to mount a robust stress response to acute stress
  - Difficulty engaging relaxation response

Interventions

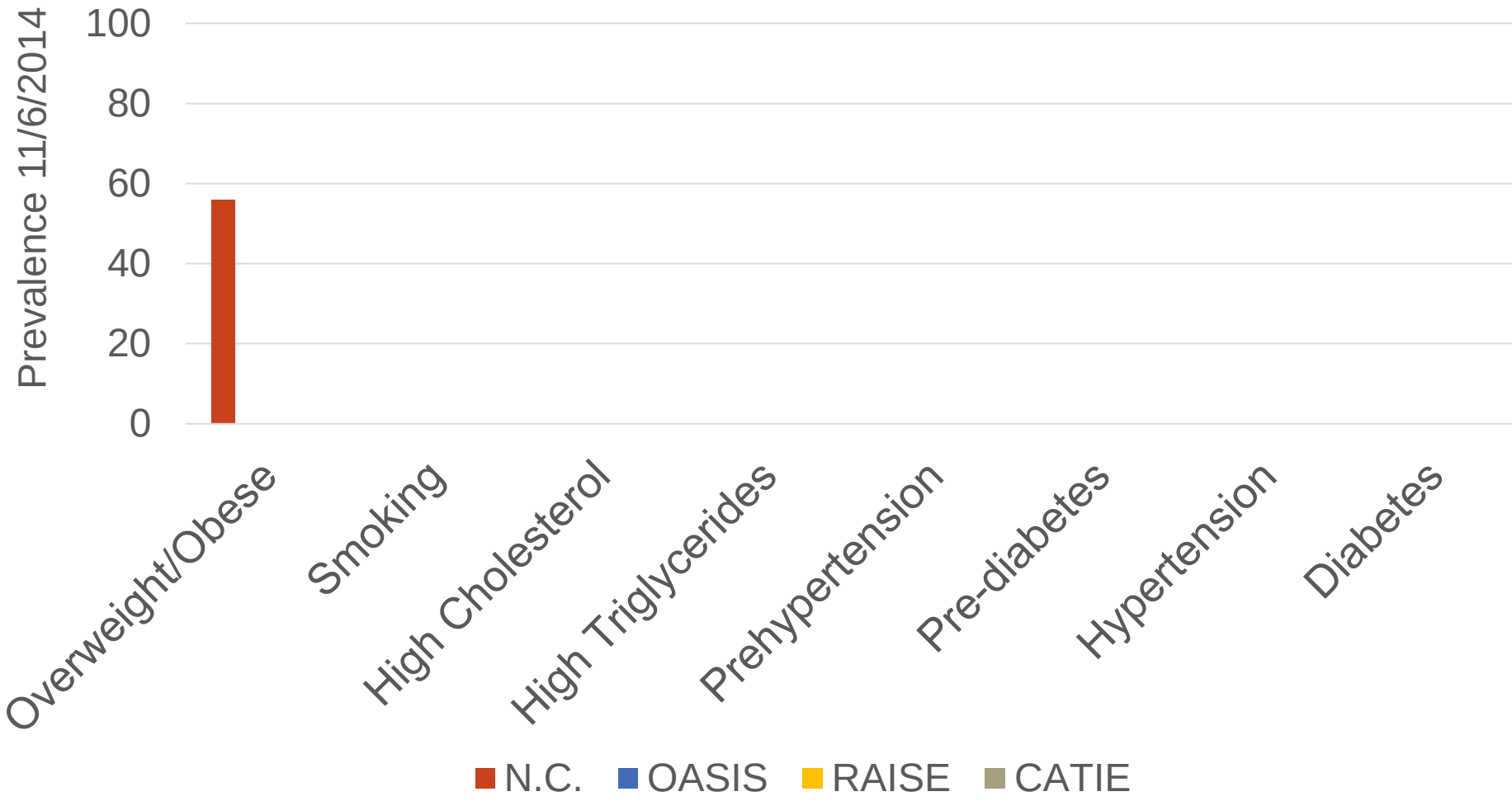
- Multidisciplinary Team Approach
  - Medication Management
    - Collaborative model
    - Adherence/insight addressed with motivational interviewing
    - Long-acting injectable first choice
    - Clozapine option after 2-3 medication failures
    - Treat-to-Target approach
  - Individual therapy
    - Engagement in treatment
    - Disease management/education
    - Address meaning of psychosis to individual
    - Substance use
    - Stress reactivity
  - Family therapy
    - Multifamily group
    - Individual family therapy
  - Group interventions
    - Social skills/social cognition
    - Monthly recreation activity
    - Quarterly workshops
  - Heath and Wellness

Health and Wellness

- Patients with schizophrenia die early from cardiovascular disease, lung and breast cancers, and respiratory diseases
- Emphasis on monitoring and prevention
- 100% of patients receive health and wellness counseling
  - Daily exercise
  - Healthy diet
  - Smoking cessation
- Weight gain prevention
  - Monitor closely (weekly intervals)
  - Pharmacological interventions: e.g. metformin

Dutla et al. 2012 Mortality in first-contact psychosis patients in the U.K.: a cohort study. Psychol Med 42:1649-61

Cardiometabolic Risk Factors

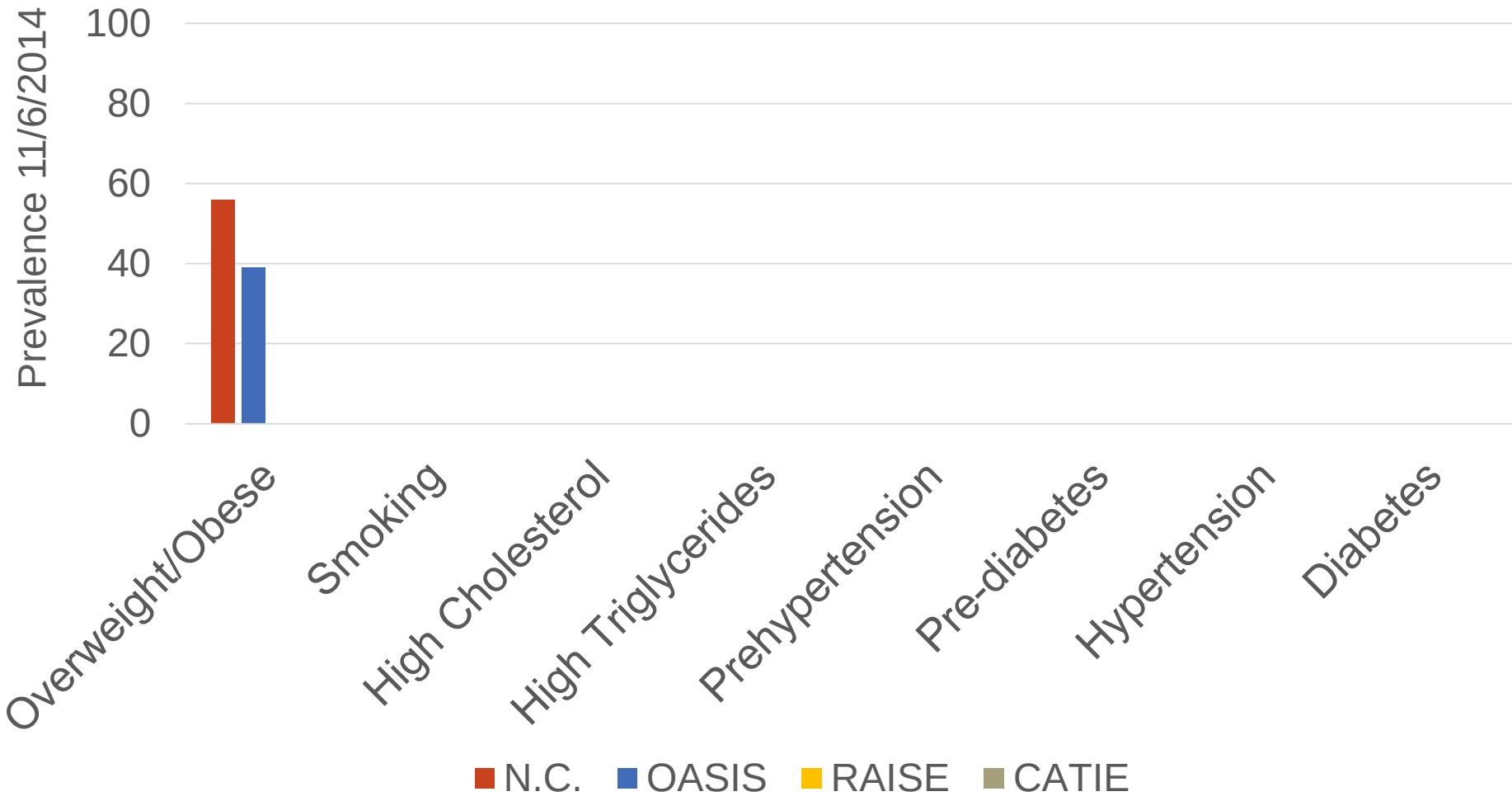


NC data from http://www.eatsmartmovemorenc.com/ObesityInNC/ObesityInNC.html;

Correll et al., JAMA Psychiatry, in press

OASIS data “snapshot” as of 6 November 2014

Cardiometabolic Risk Factors



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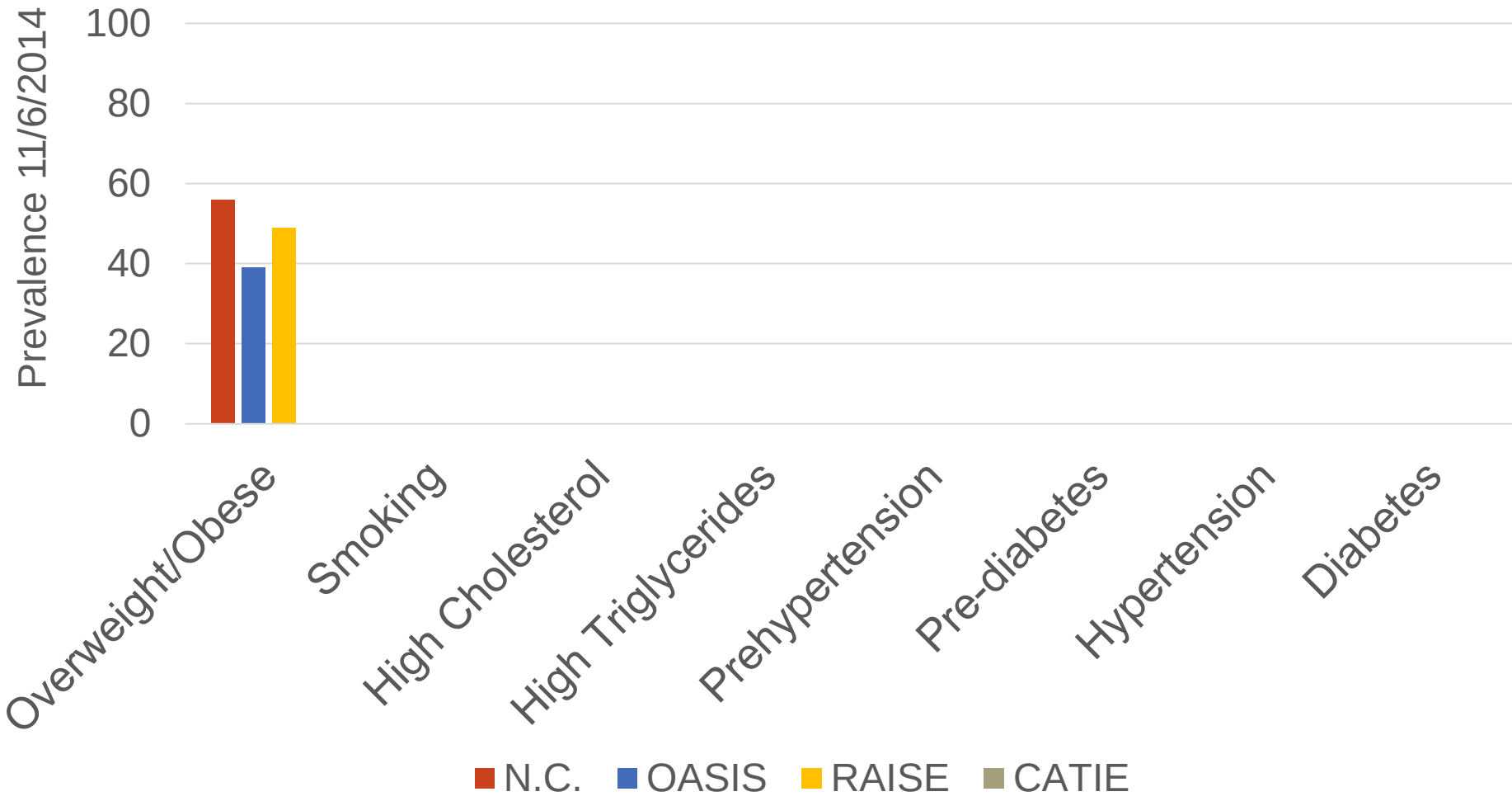

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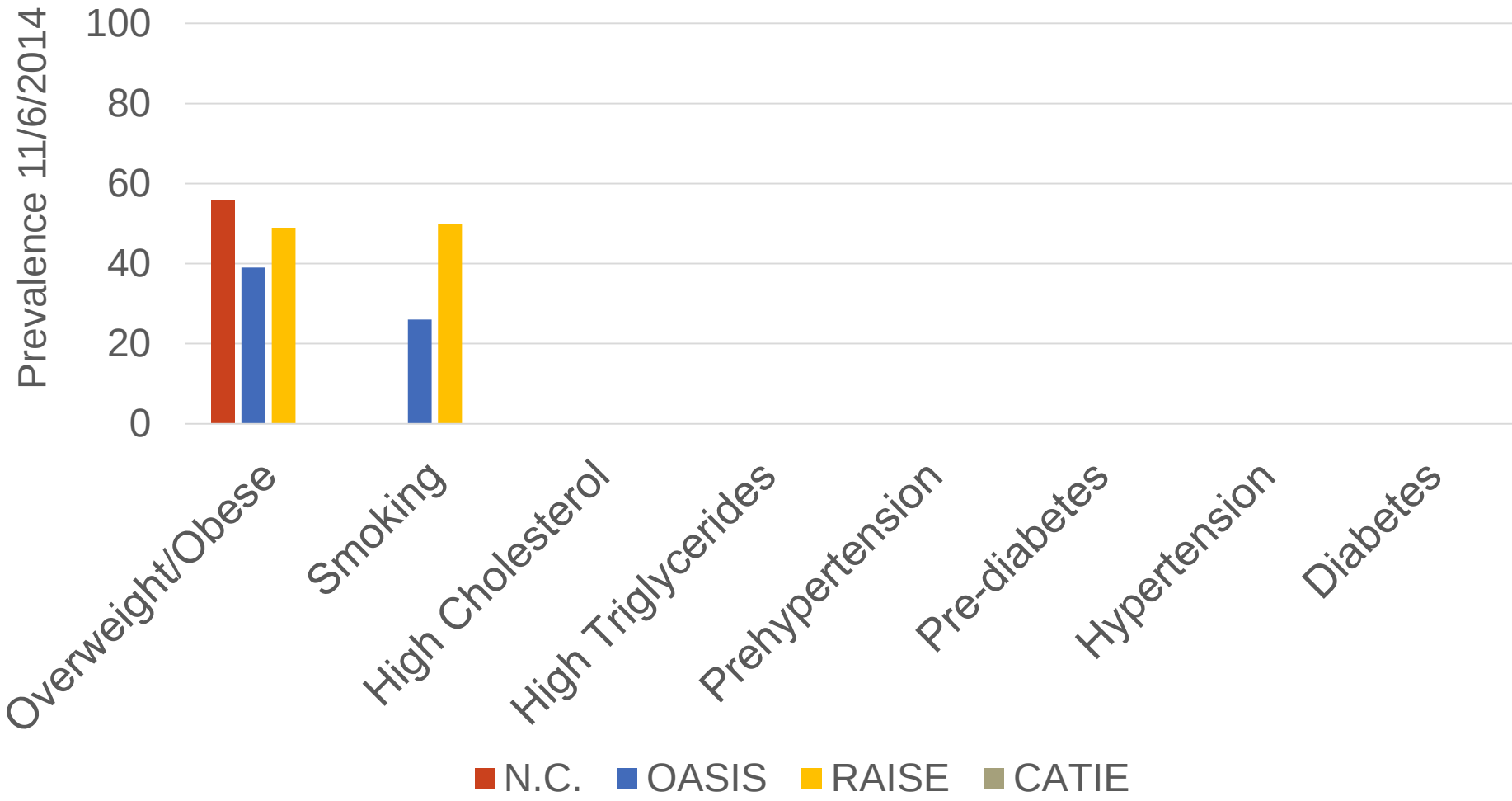

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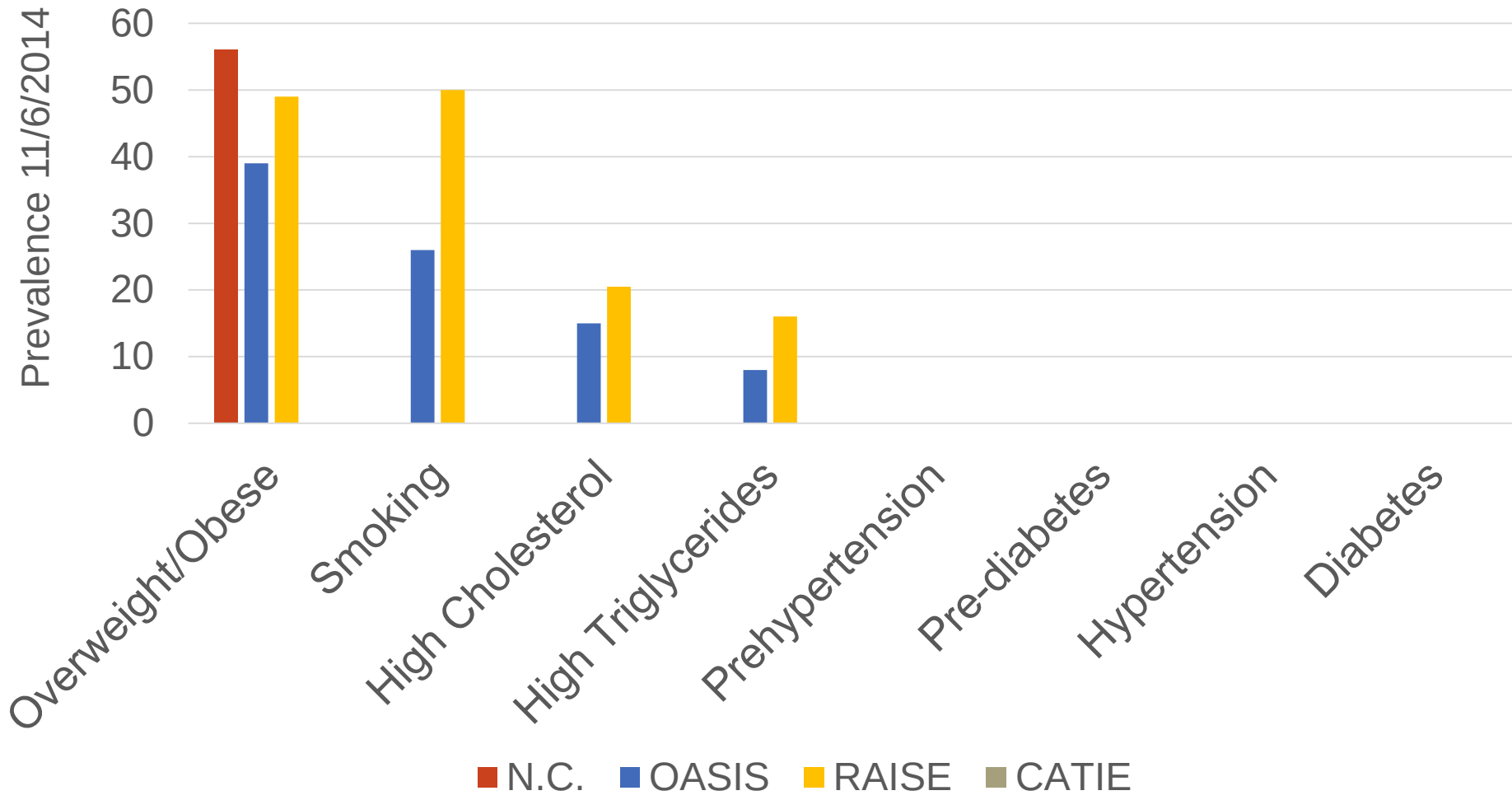

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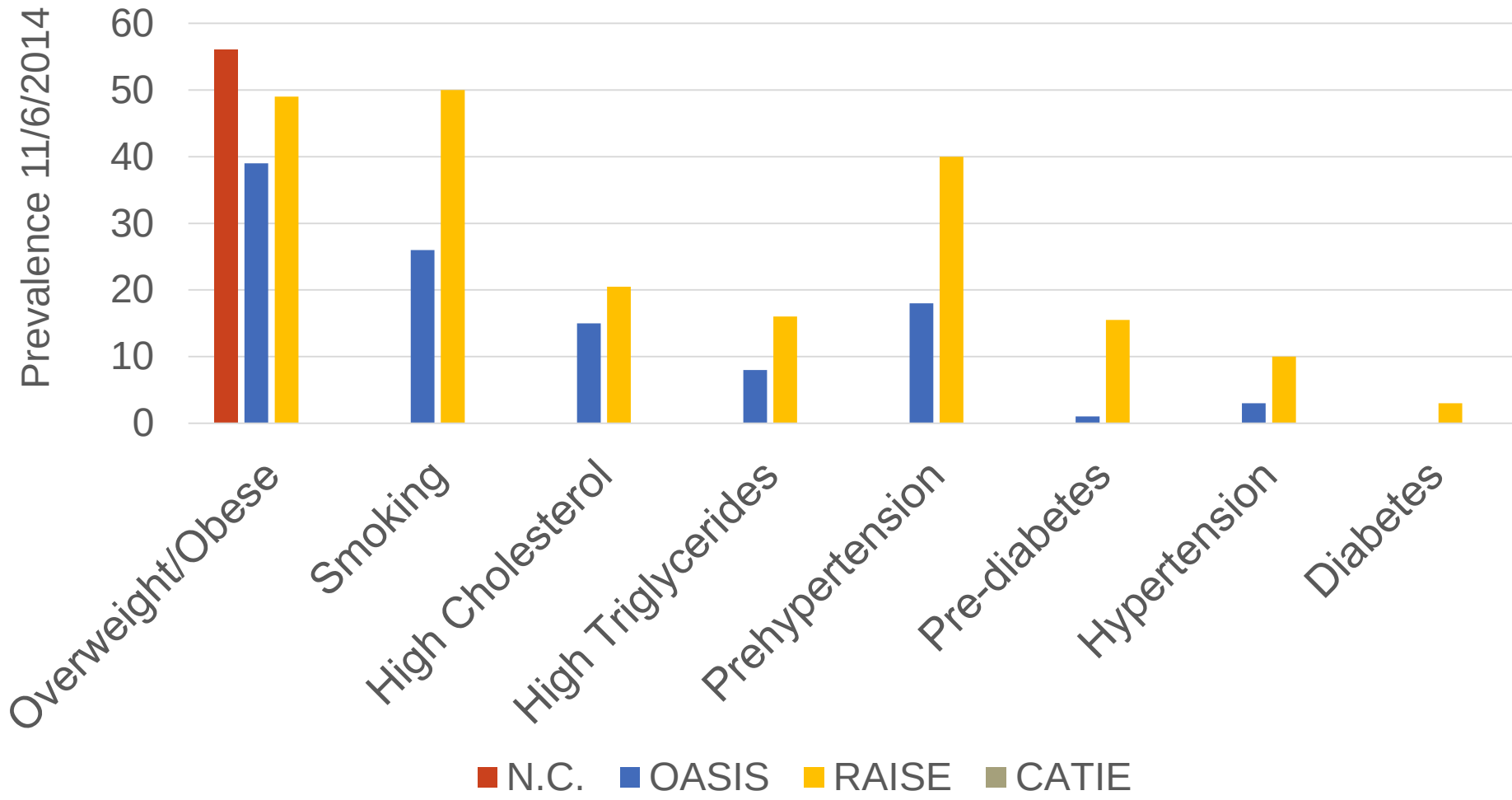

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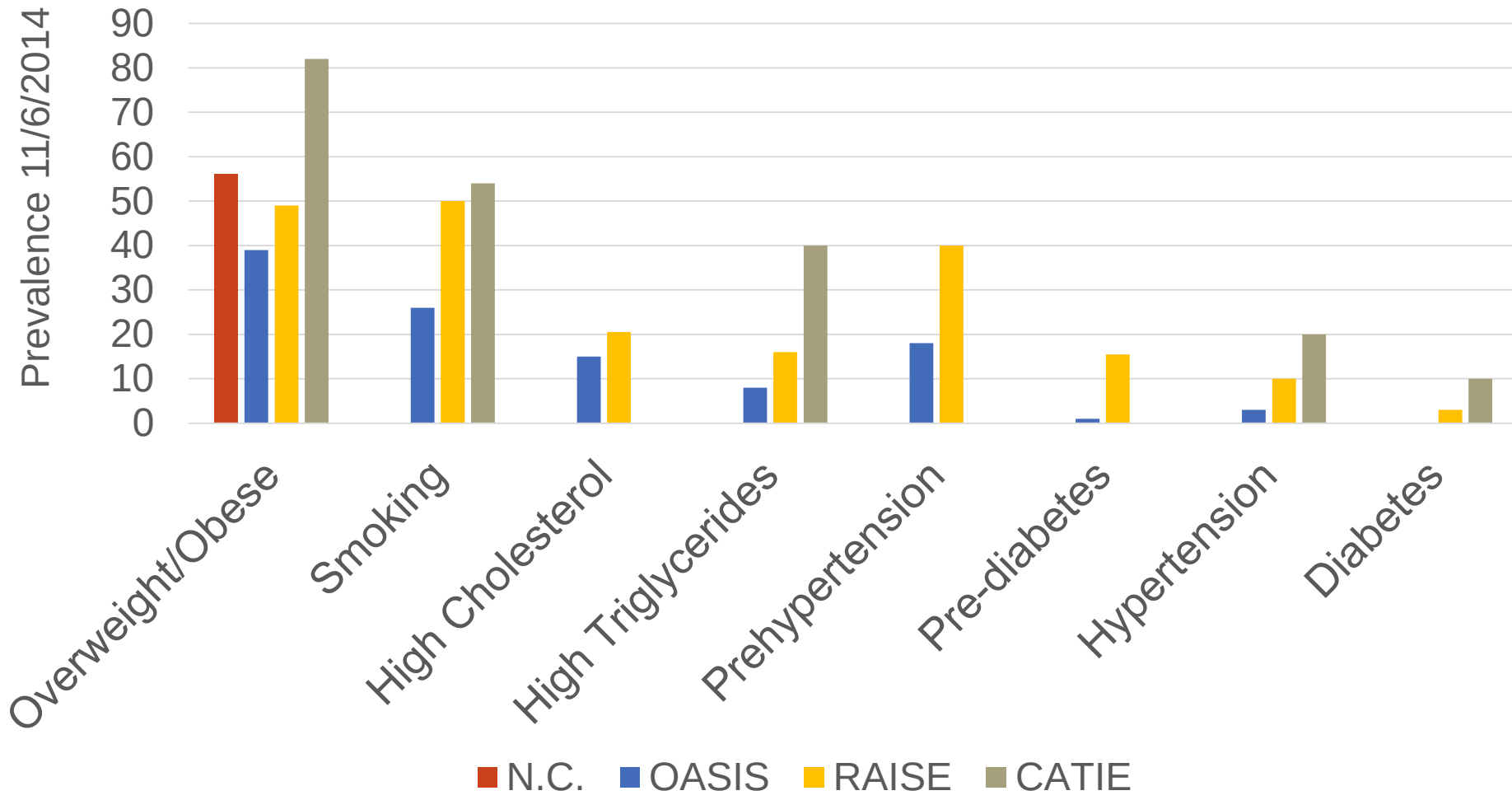

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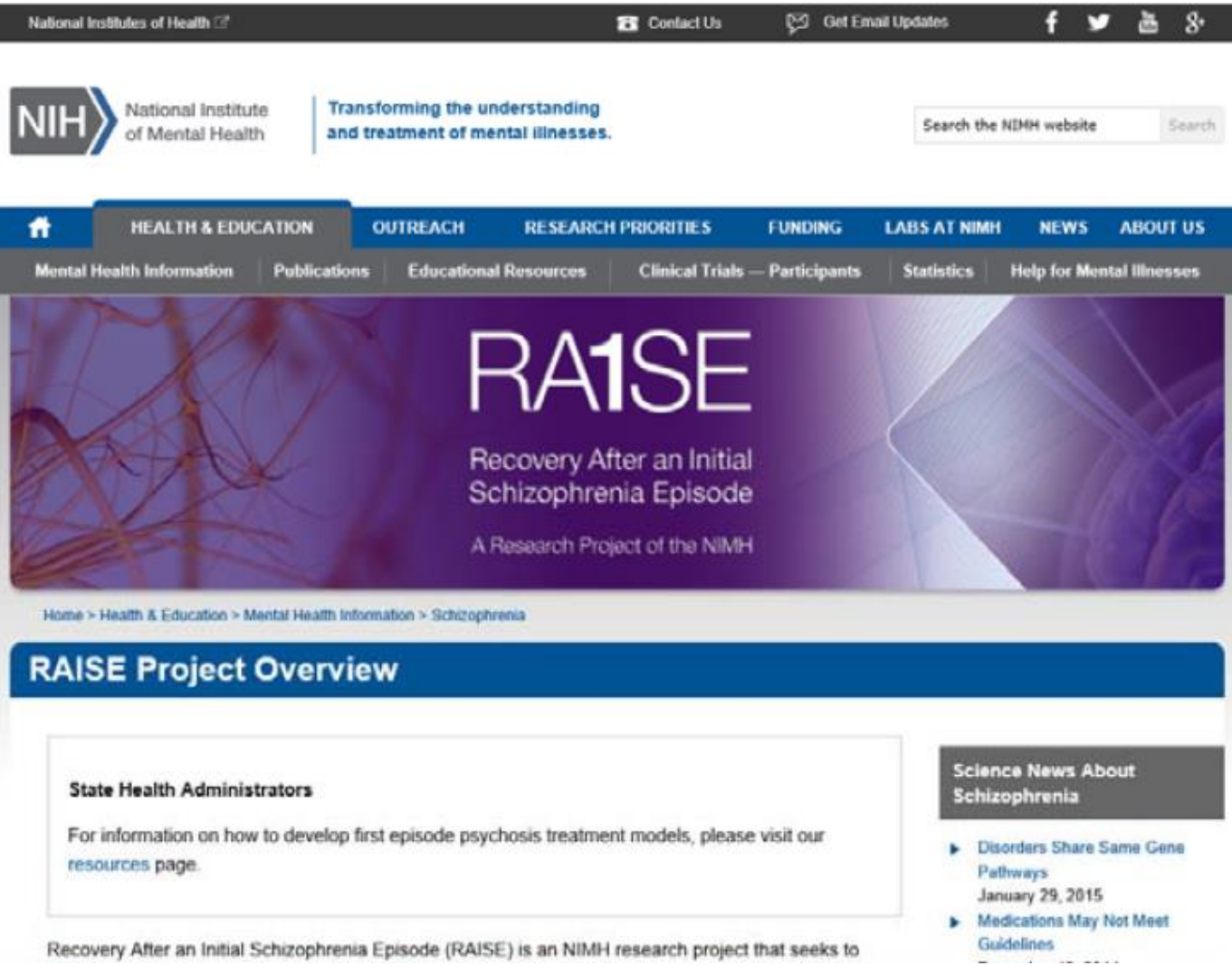

http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml (accessed 9/16/2015)