

# *Biomarkers for Psychiatric Drug Toxicity*

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Oct 24, 2008

Thomas R. Insel, M.D.

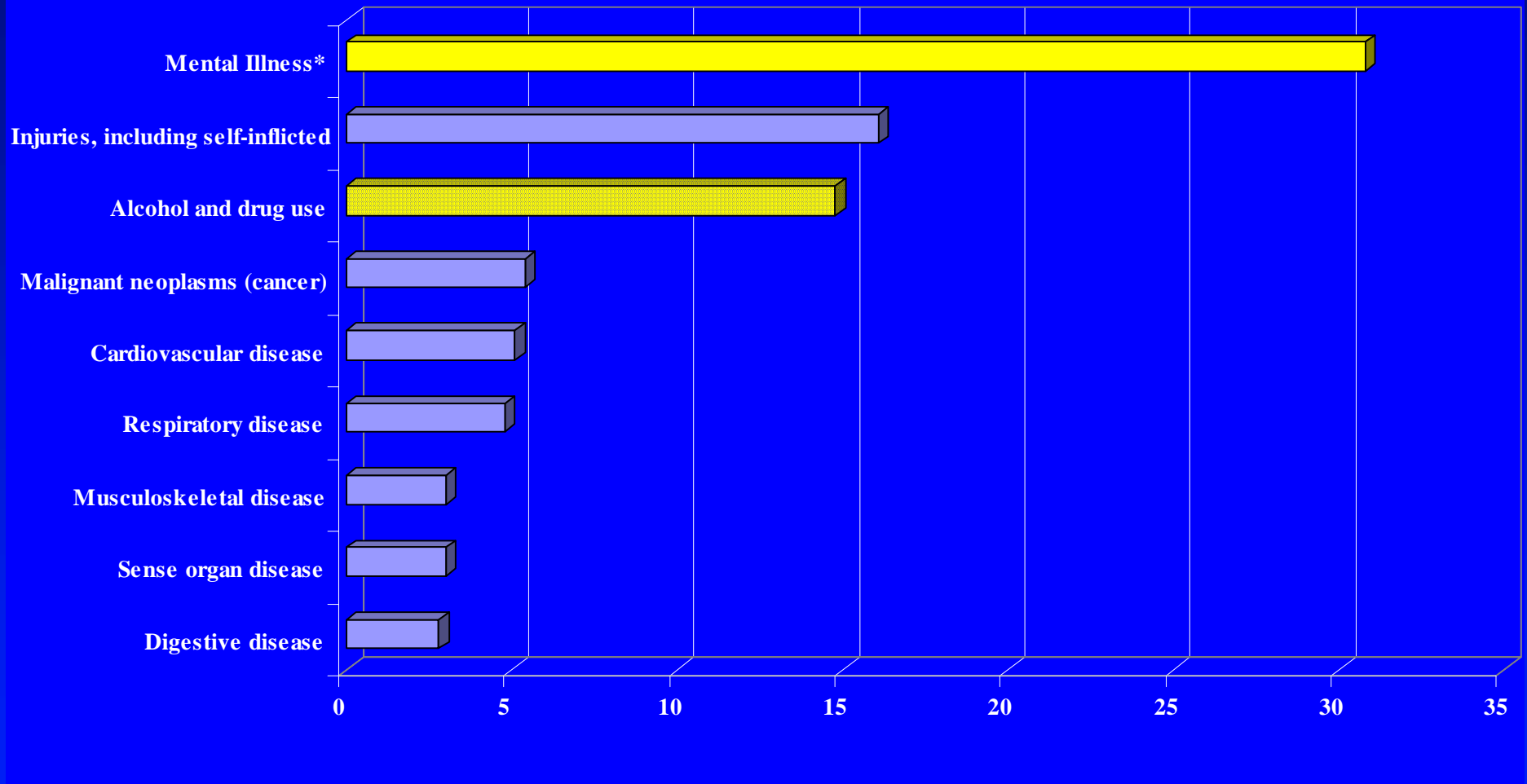
Director, NIMH



**NIMH**  
National Institute  
of Mental Health

# Burden of Disease (DALYs)

U.S., Canada, and Western Europe *15-44 years old*

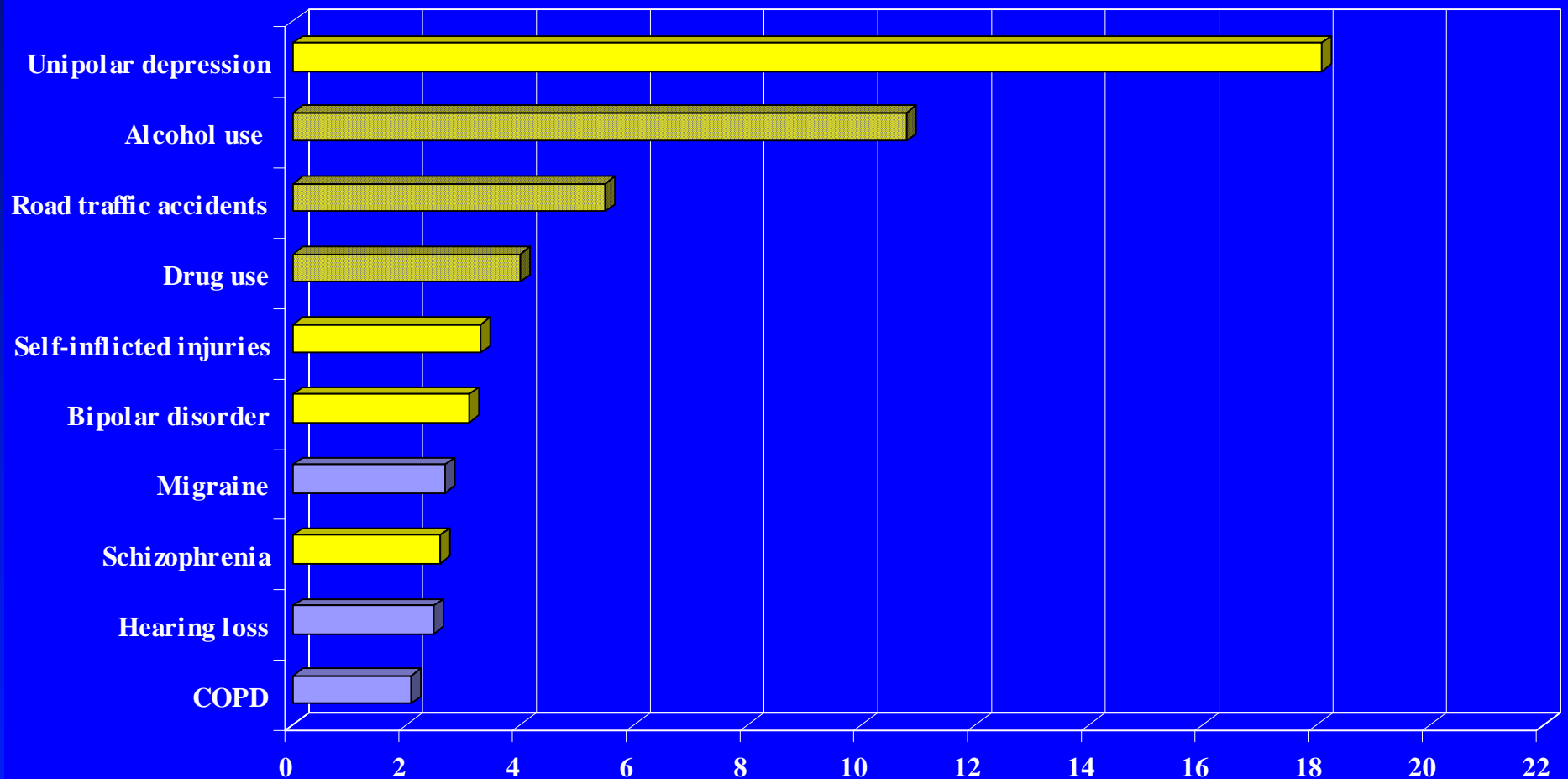


Source: WHO World Health Report 2002

# Burden of Disease by Specific Illness – DALYs

## United States, Canada, and Western Europe

### 15-44 years old



Source: WHO World Health Report 2002

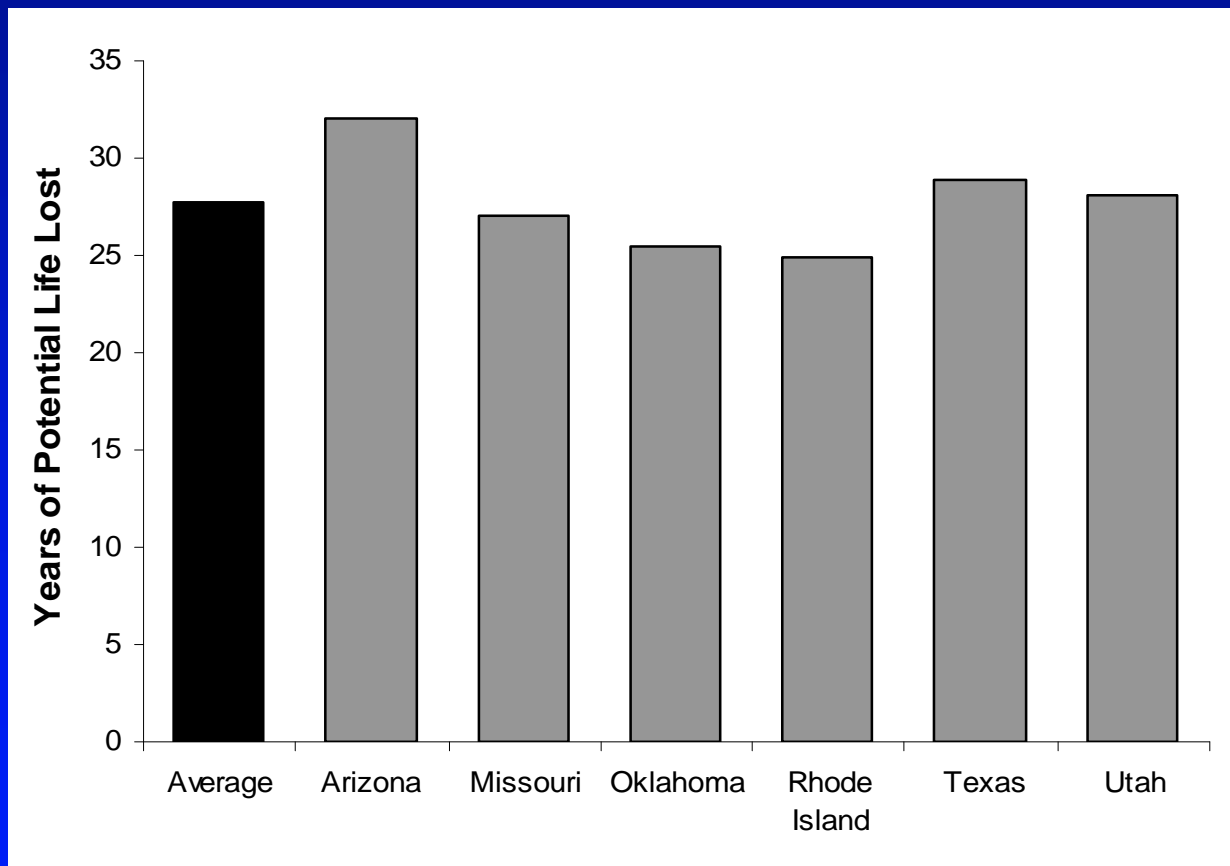
# Mental Disorders: Mortality

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- **Over 30,000 suicides per year (in the U.S.)**
  - **90% related to mental illness**
- **For context:**
  - **18,000 homicides**
  - **20,000 AIDS deaths**
  - **only 3 forms of cancer > 30,000**

# Public Health Impact: Early Mortality in Individuals with Major Mental Illness (MMI)

- Data from outpatient and inpatient clients diagnosed with MMI
- Average age at time of death : **56 years**
- Increased likelihood of dying from suicide
- Decreased likelihood of dying from cancer



Adapted from Colton and Manderscheid, 2006, Prev Chronic Dis

## **“Average Medicine”**

- Assumes homogeneity
- Classic RCT
- Results based on group means
- Recommendations are generic

## **Personalized Medicine**

- Assumes heterogeneity
- Moderator trials
- Results focus on variance and individual patterns
- Recommendations are specific

**Implications: Clinical research based on individual risk and response**

# Personalized Medicine for Mental Disorders

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- Mental disorders can be understood as developmental brain disorders: chronic, early onset, heterogeneous.
- Current treatments, at best, ameliorate symptoms, but there is variation in response, adverse events, adherence, and access.

# Personalized Medicine: Where is the need?

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- Depression:

Highest burden of illness ages 15-44 (WHO, 2002)

50 - 70% of pts respond to SSRIs or CBT

Side-effects of medication reduce effectiveness

Which treatment for which patient?

- Schizophrenia:

Deficits precede psychosis

Rx's have serious side effects, poor adherence

Identifying individual risk, preemptive Rx's.

Which treatment for which patient?

# Personalized Medicine: Where is the need?

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- PTSD:

Increasing prevalence (“failure of recovery”)

Rx helpful

Identifying individual risk, preemptive Rx's  
Which treatment for which patient?

- Bipolar Disorder:

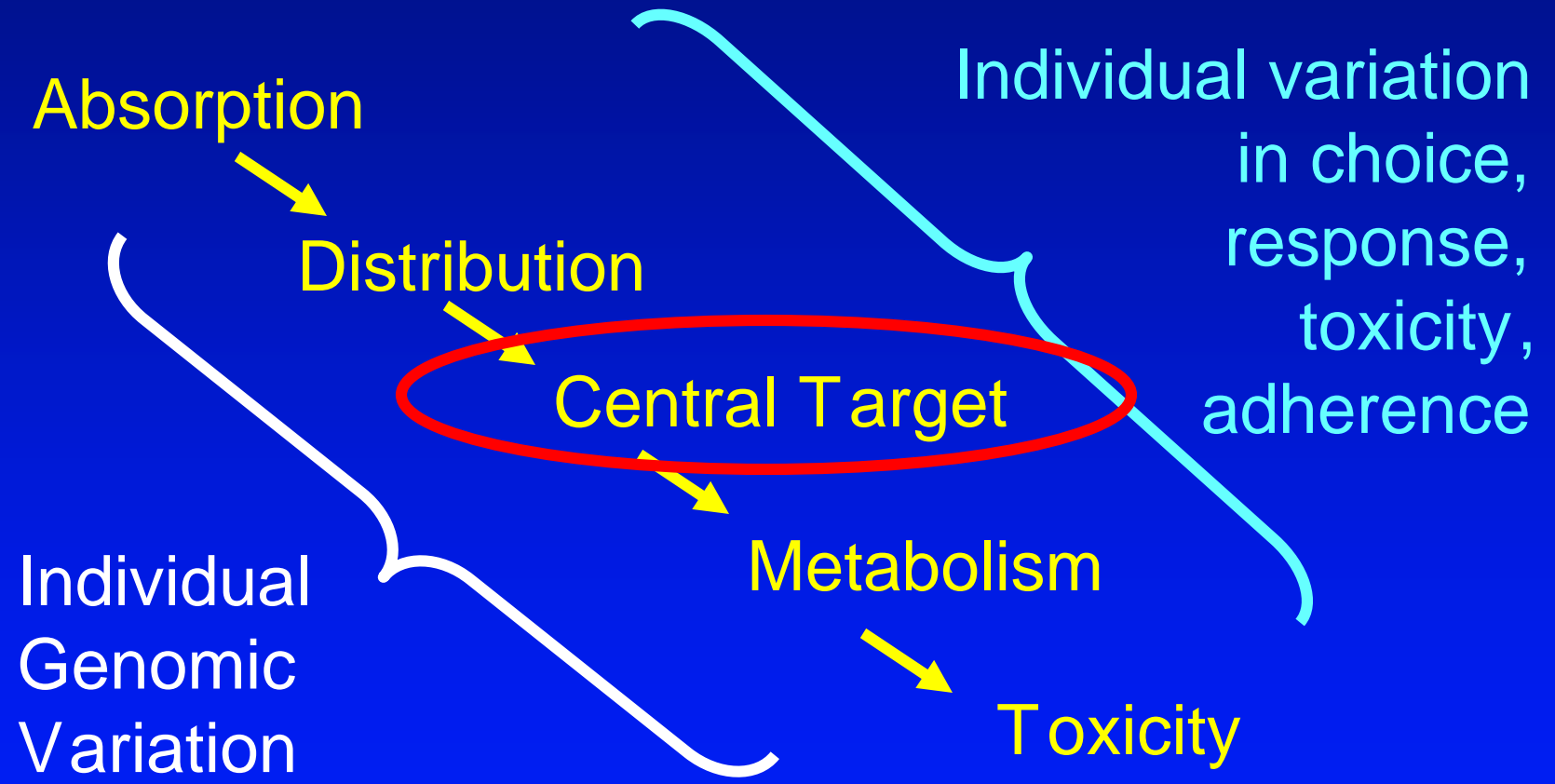
Medical and psychiatric co-morbidities

Lithium effective for some but underutilized

Which treatment for which patient?

# Approaches to Pharmacogenomics of Psychiatric Medications

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# Genomics of SSRI Response

- Absorption and distribution

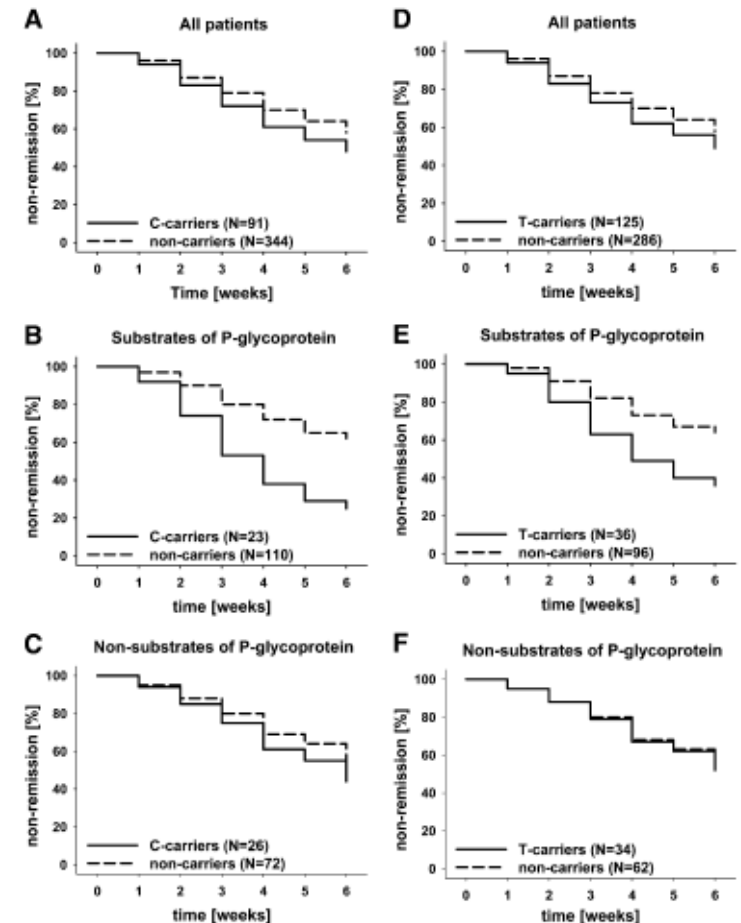
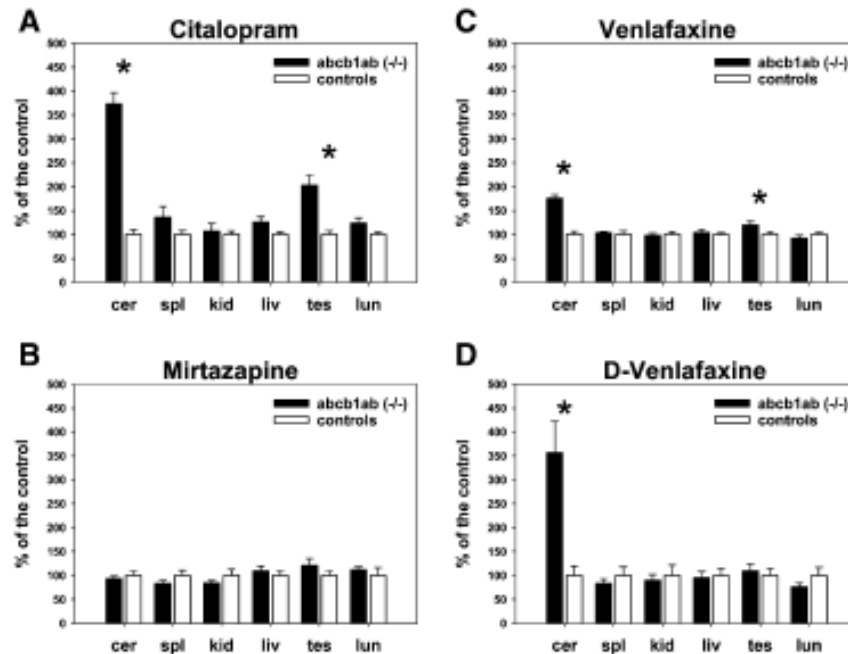
## Polymorphisms in the Drug Transporter Gene *ABCB1* Predict Antidepressant Treatment Response in Depression

Manfred Uhr,<sup>1,\*</sup> Alina Tontsch,<sup>1</sup> Christian Namendorf,<sup>1</sup> Stephan Ripke,<sup>1</sup> Susanne Lucae,<sup>1</sup> Marcus Ising,<sup>1</sup> Tatjana I Martin Ebinger,<sup>1</sup> Marcus Rosenhagen,<sup>1</sup> Martin Kohli,<sup>1</sup> Stefan Kloiber,<sup>1</sup> Daria Salyakina,<sup>1</sup> Thomas Bettecken,<sup>1</sup> Michael Specht,<sup>1</sup> Benno Pütz,<sup>1</sup> Elisabeth B. Binder,<sup>1</sup> Bertram Müller-Myhsok,<sup>1</sup> and Florian Holsboer<sup>1</sup>

<sup>1</sup>Max Planck Institute of Psychiatry, Kraepelinstr. 10, 80804 Munich, Germany

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DOI 10.1016/j.neuron.2007.11.017

Neuron, 2007



# Genomics of SSRI Response

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- CNS Targets

SLC6A4, 5HT2a, 5HT3a, Glutamate Rec Complex

**Association Between a Functional Serotonin Transporter Promoter Polymorphism and Citalopram Treatment in Adult Outpatients With Major Depression**

Arch Gen Psych  
2007

Xian-Zhang Hu, MD, PhD; A. John Rush, MD; Dennis Charney, MD; Alexander F. Wilson, PhD; Alexa J. M. Sorant, MA; George J. Papanicolaou, PhD; Maurizio Fava, MD; Madhukar H. Trivedi, MD; Stephen R. Wisniewski, PhD; Gonzalo Laje, MD; Silvia Paddock, PhD; Francis J. McMahon, MD; Hussein Manji, MD; Robert H. Lipsky, PhD

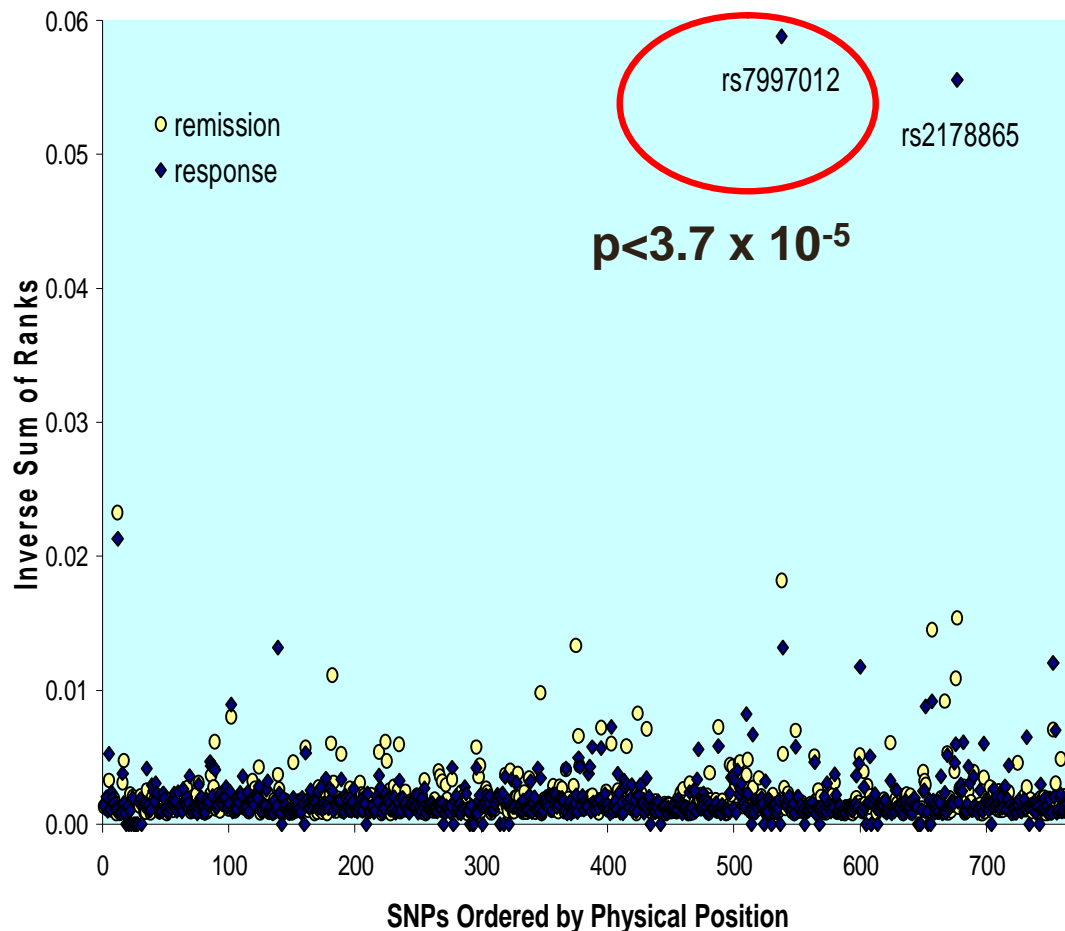
The American Journal of Human Genetics Volume 78 May 2006

**Variation in the Gene Encoding the Serotonin 2A Receptor Is Associated with Outcome of Antidepressant Treatment**

Francis J. McMahon,<sup>1,\*</sup> Silvia Buervenich,<sup>1,\*</sup> Dennis Charney,<sup>3</sup> Robert Lipsky,<sup>4</sup> A. John Rush,<sup>5</sup> Alexander F. Wilson,<sup>6</sup> Alexa J. M. Sorant,<sup>6</sup> George J. Papanicolaou,<sup>6</sup> Gonzalo Laje,<sup>1</sup> Maurizio Fava,<sup>7</sup> Madhukar H. Trivedi,<sup>5</sup> Stephen R. Wisniewski,<sup>8</sup> and Hussein Manji<sup>2</sup>

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§The allele associated with better outcome was ~7 times more common in whites than blacks

§Afr-Am. also had a less favorable outcome, overall, than Cauc. in this sample

# Genomics of SSRI Response

- Metabolism

CYP450: CYP2D6, CYP2C19, CYP3A4,

OPEN ACCESS Freely available online



## Pharmacokinetic Genes Do Not Influence Response or Tolerance to Citalopram in the STAR\*D Sample

Eric J. Peters<sup>1\*</sup>, Susan L. Slager<sup>2</sup>, Jeffrey B. Kraft<sup>1</sup>, Greg D. Jenkins<sup>2</sup>, Megan S. Reinalda<sup>2</sup>, Patrick J. McGrath<sup>3</sup>, Steven P. Hamilton<sup>1\*</sup>

STAR\*D data:

Discovery sample: 831

Validation sample: 1,046

**Table 3.** Effect of subject metabolizer status on final citalopram dose.

Metabolizer Status	Mean Final Dose (s.d.)	p-value
CYP2C19 EM	45.3 (15.7)	0.13
CYP2C19 PM	40.7 (16.4)	
CYP2D6 EM	45.4 (15.8)	0.25
CYP2D6 PM	43.2 (16.8)	

Mean final dose (mg) for each metabolizer group is shown, along with the standard deviation (S.D.) and significance level assessed using student's t-test. Results are shown for the Caucasian subgroup, similar non-significant results were obtained in the African-American subset.

doi:10.1371/journal.pone.0001872.t003

# Treatment-Emergent Suicidal Ideation

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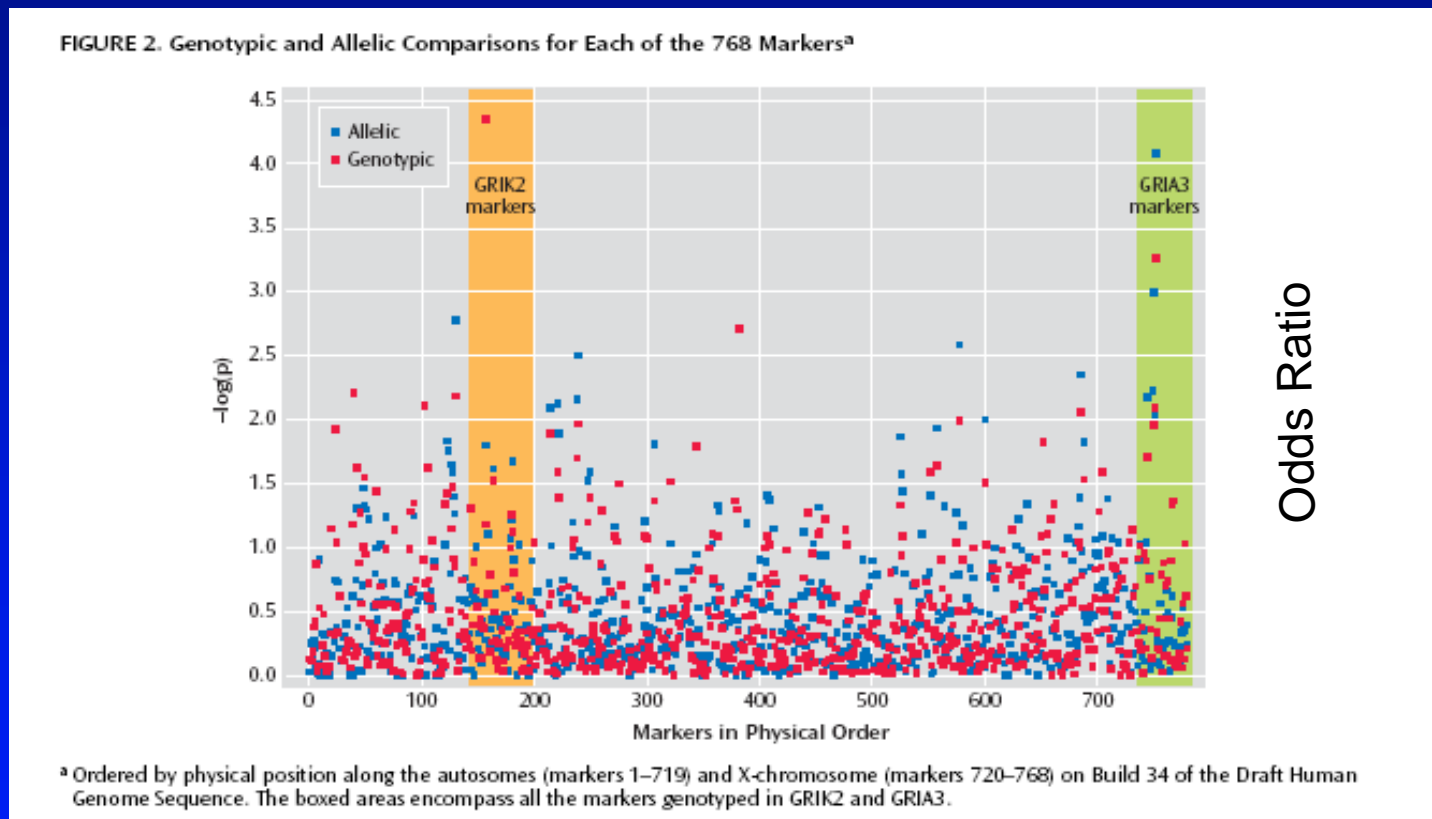
- Worrisome phenomenon that occurs in ~5% of people receiving SSRIs
- Led to a “Black Box” warning on all antidepressants in adolescents

## Design in STAR\*D:

- Participants who scored “0” at baseline (before citalopram treatment) and later scored 1, 2 or 3 on the same item at least once while on citalopram (n=120)
- Comparison group (n=1742): all participants who denied suicidal ideation emerging during treatment

# Genomics of SSRI Response

- Adverse events: Treatment-emergent suicidal ideation

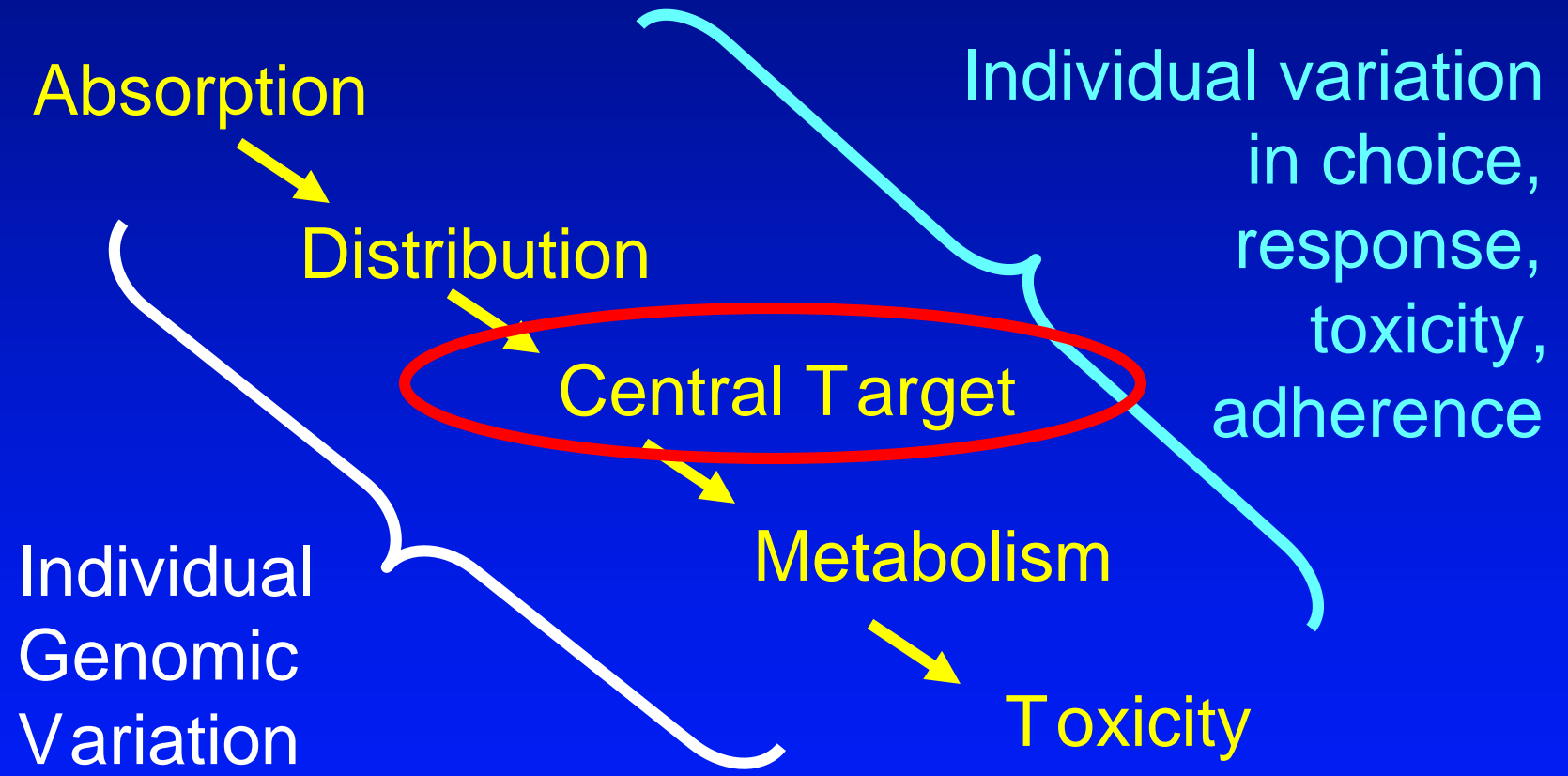


**Out of 1915 patients with depression treated with citalopram, 120 developed suicidal ideation.**

Lahe et al, AJP, 2007

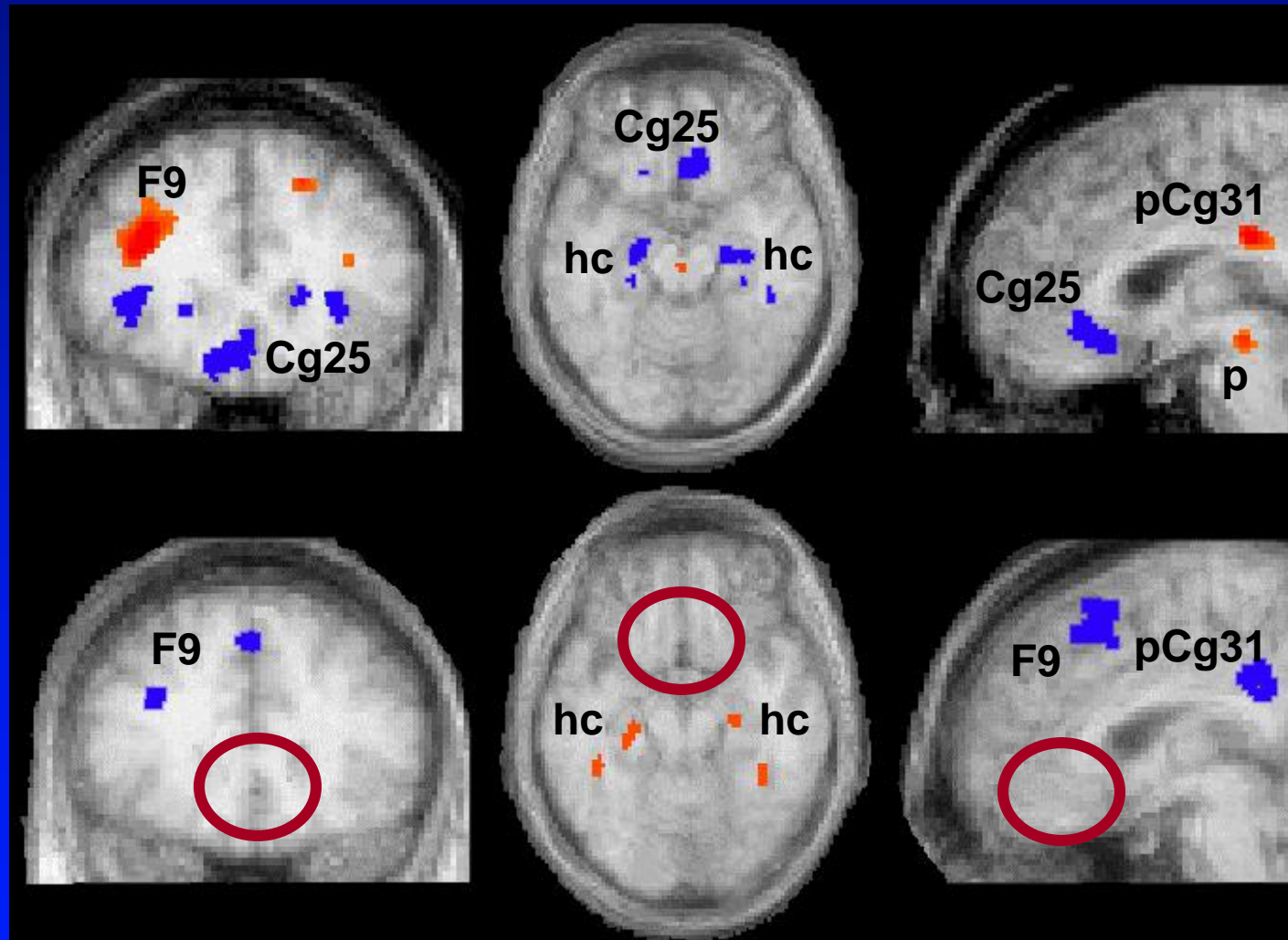
# Approaches to Pharmacogenomics of Psychiatric Medications

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# Neuroimaging: A Predictive Biomarker?

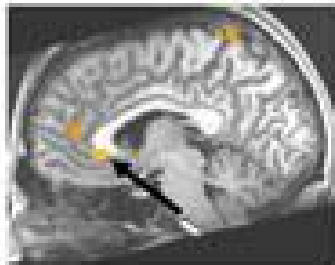
**Fluoxetine  
Responders**



**Non-  
Responders**

Mayberg, 2006

# MEG: A Predictive Biomarker?

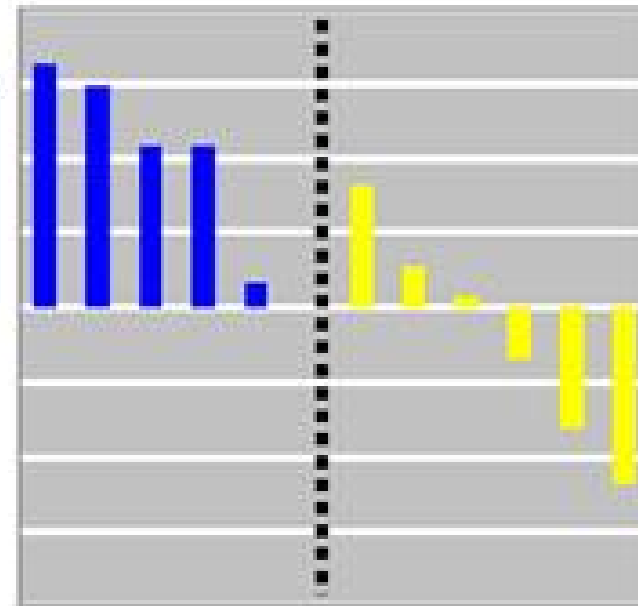


Anterior cingulate cortex (ACC)  
responds to fearful face

ACC activity increases  
as face is repeated



Responders      Non-Responders

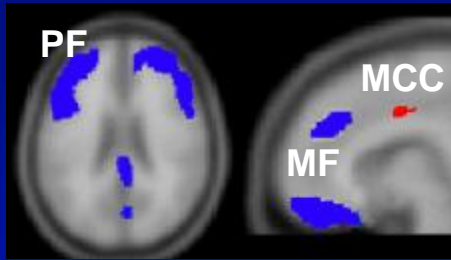


ACC activity decreases  
as face is repeated



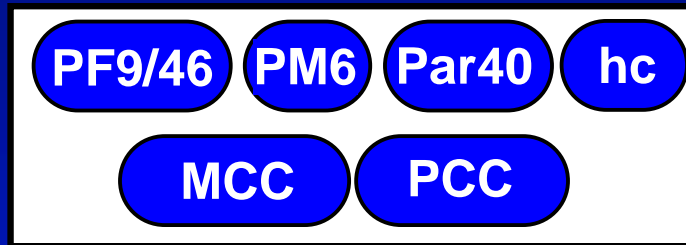
Zarate et al, Biol Psych, 2008

# Defining Depression Circuits Response Pathways

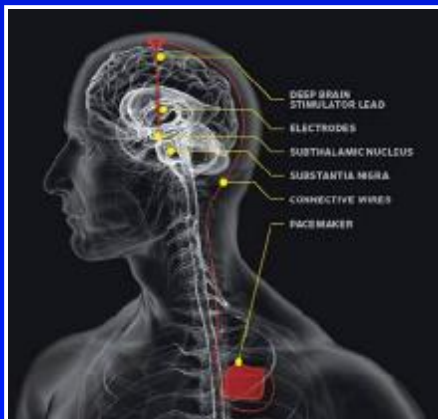


**CBT**

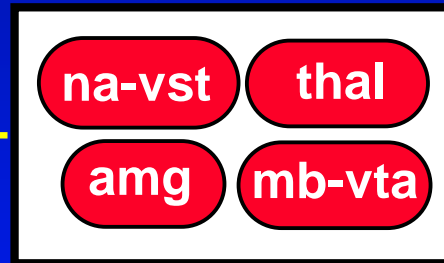
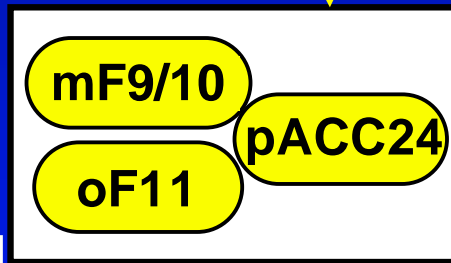
**Cognition**  
(attention-appraisal-action)



**Self-awareness insight**



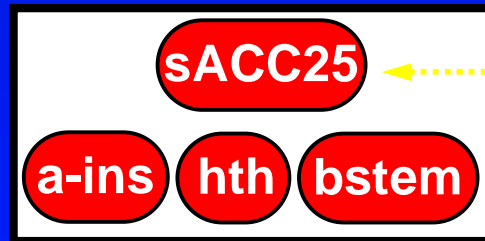
Br Med Bul 65:193-207, 2003  
Arch Gen Psych 61:34-41-2004



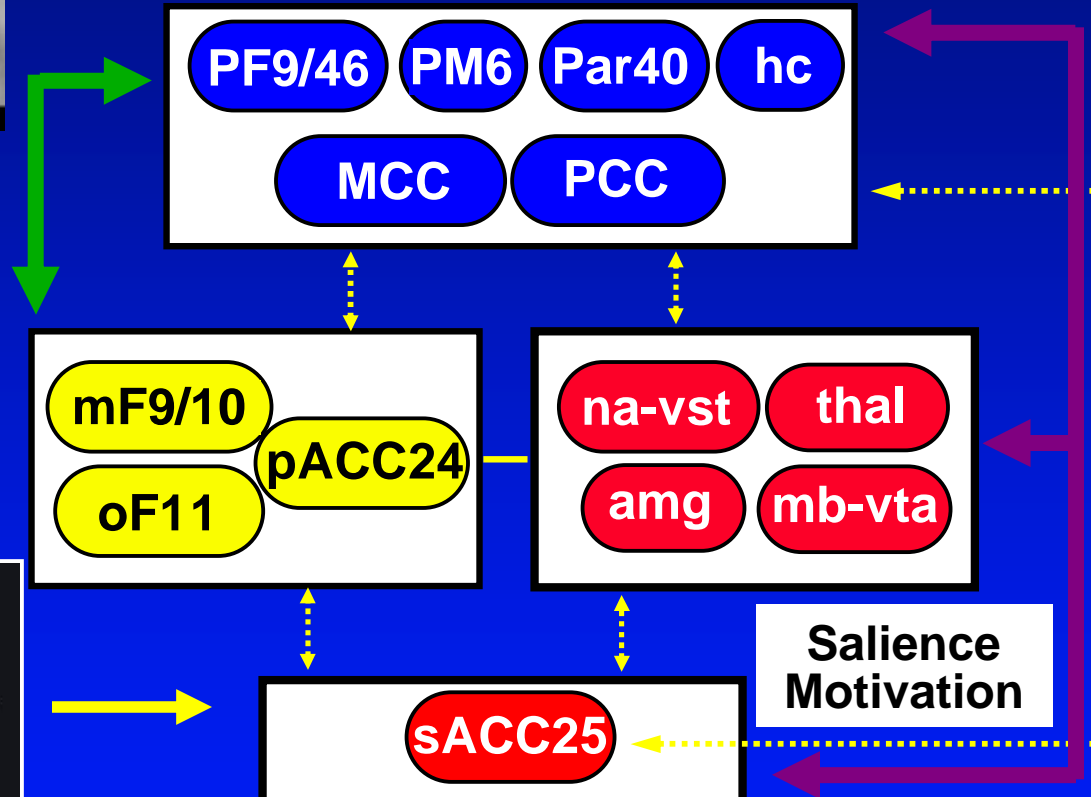
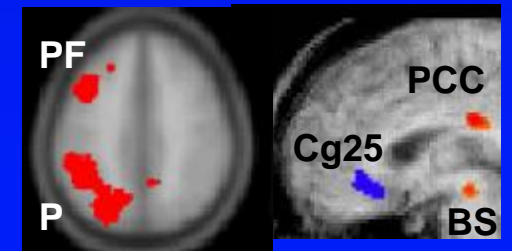
**Mood state**

**Salience Motivation**

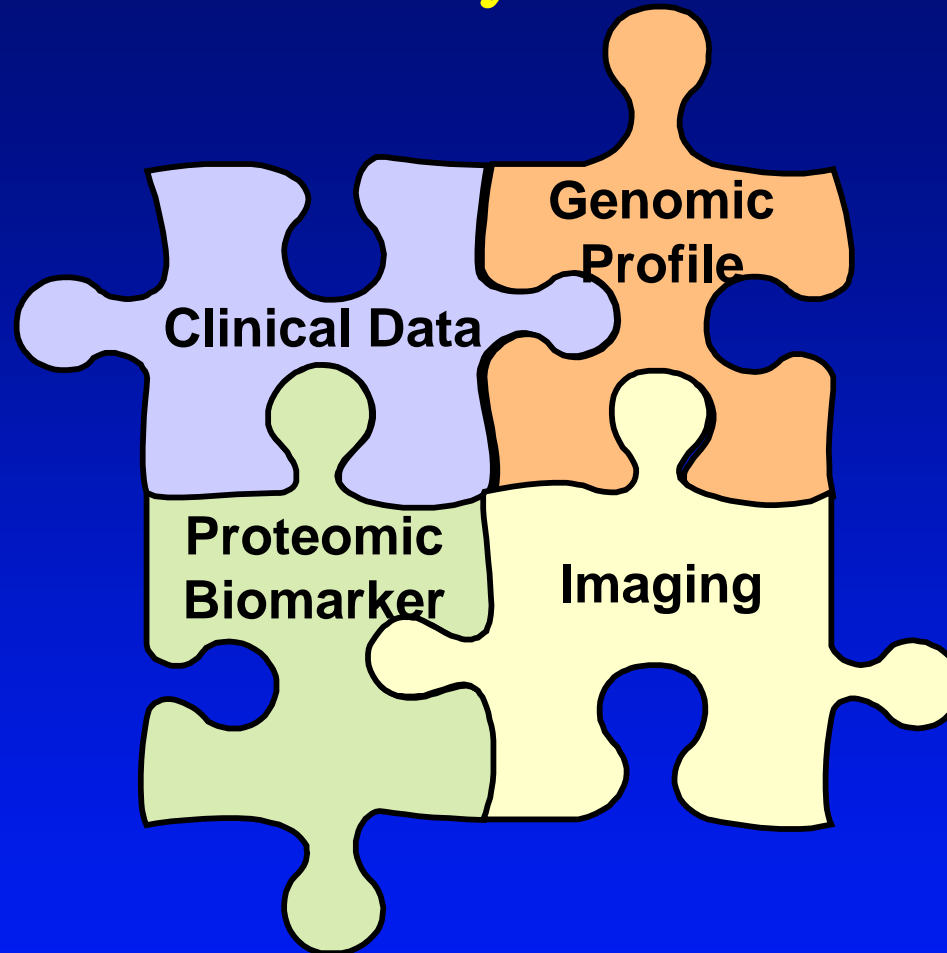
**MEDS**



**Interoception**  
(drive-autonomic-circadian)

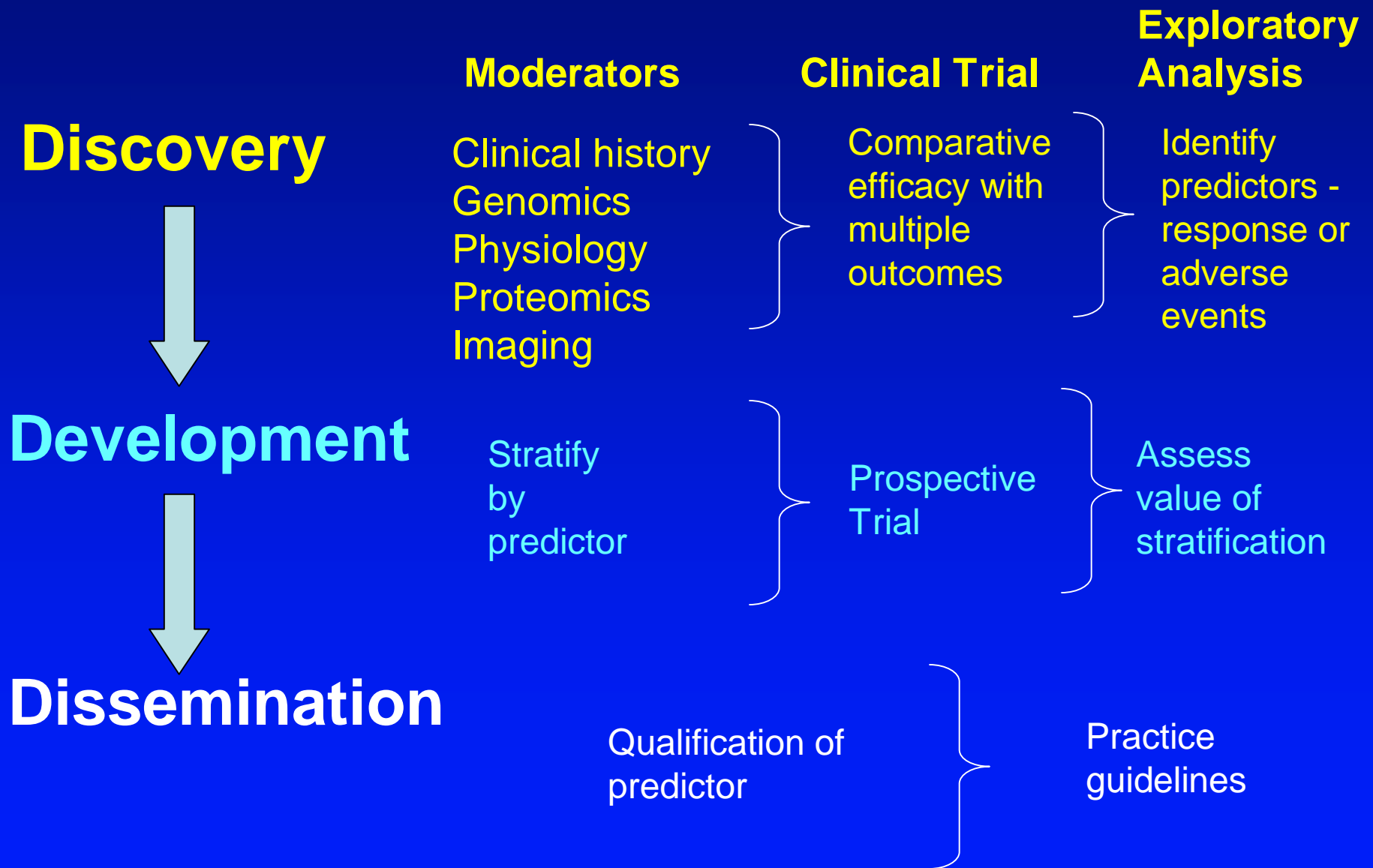


# Predictors of efficacy or adverse events



Biomarker  $\longrightarrow$  Biosignature

# Pathways to Personalized Medicine



**NIMH**

National Institute  
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**[www.nimh.nih.gov](http://www.nimh.nih.gov)**