STANLEY CENTER
FOR PSYCHIATRIC RESEARCH

Unmet Medical Need for Nervous System Disorders

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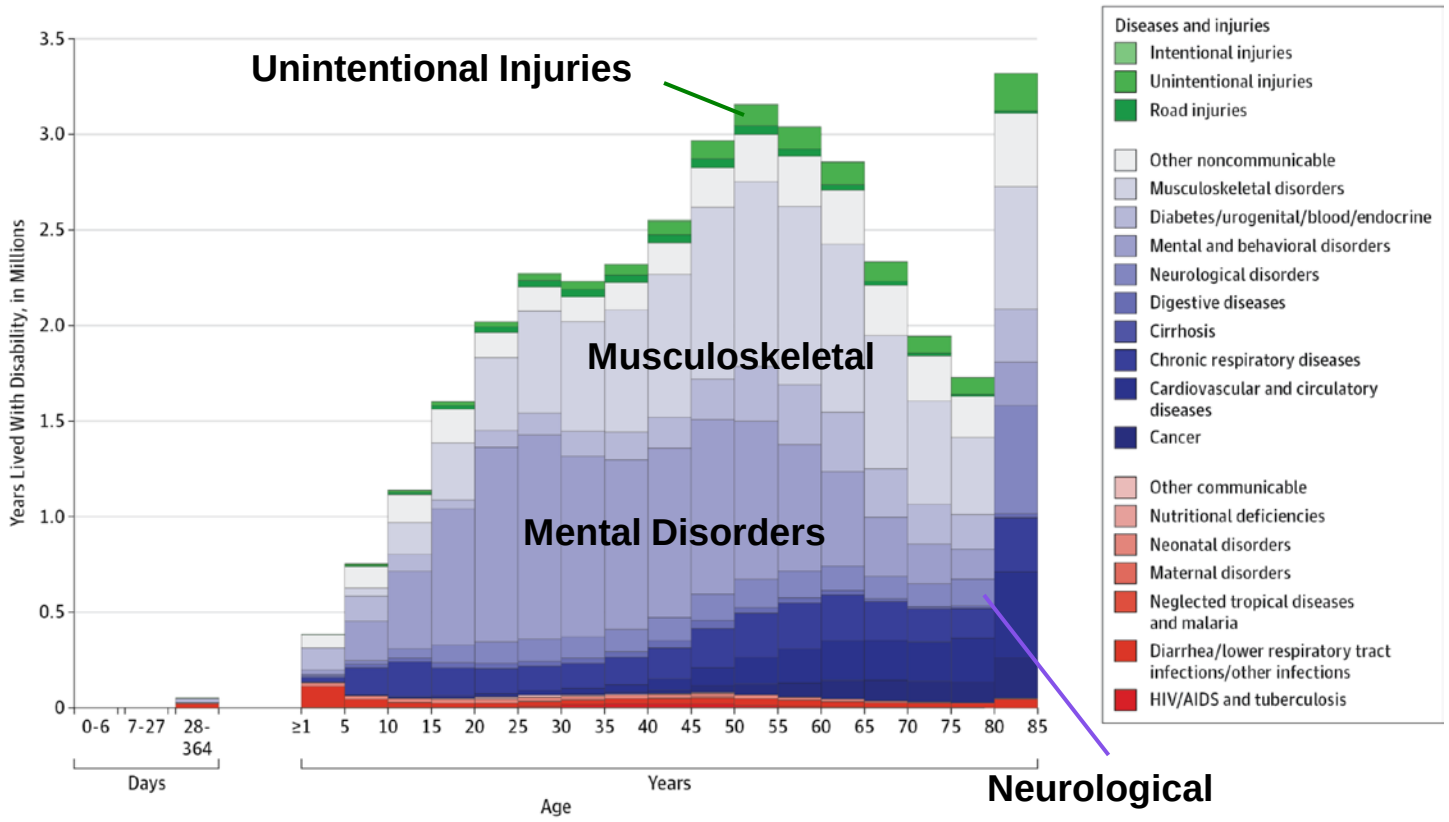
Brain Disorders are Common and Disabling

Burden of Diseases, Injuries, and Risk Factors, U.S.1990-2010:
Years lived with *disability* by age and disease class



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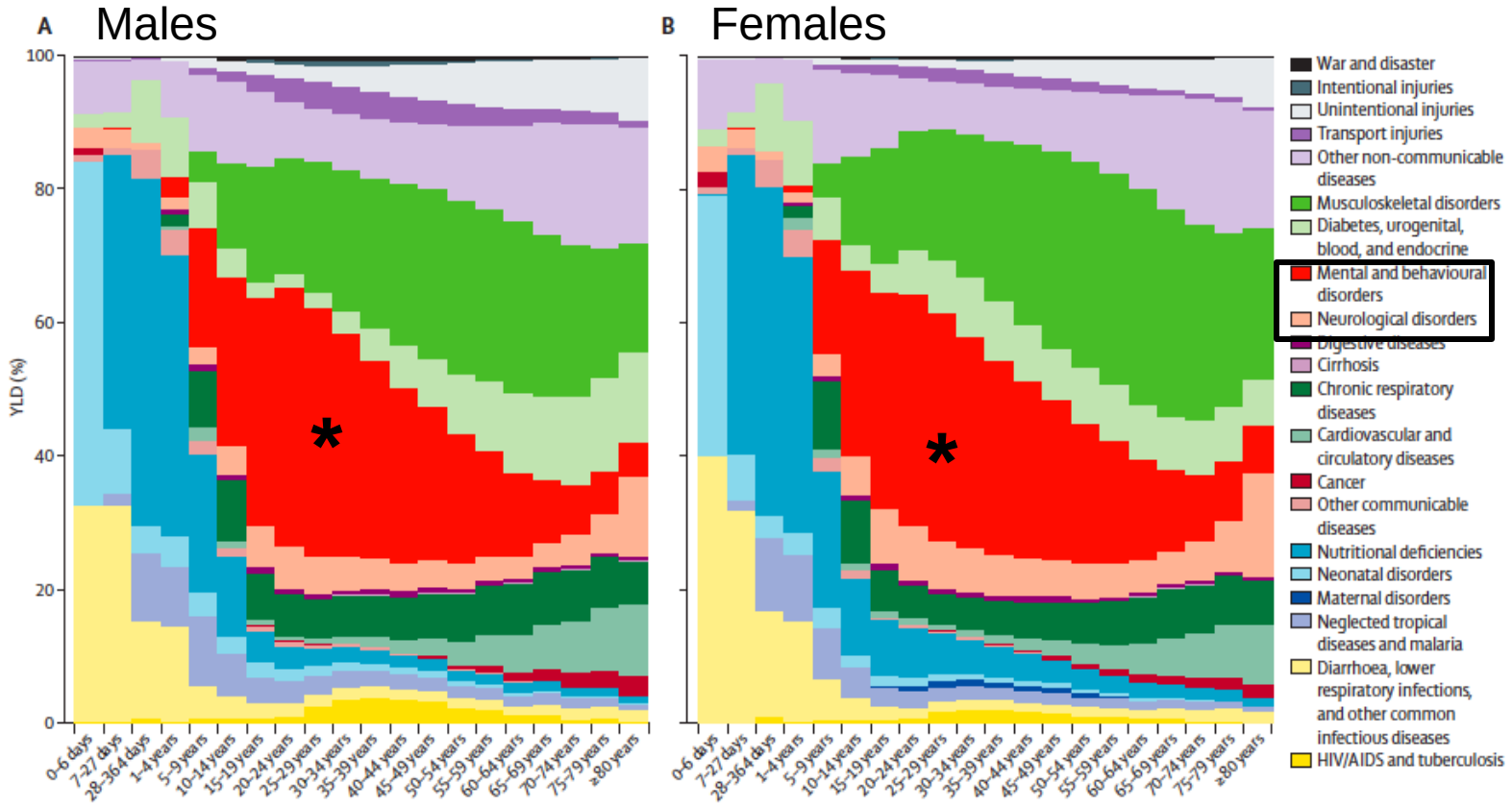
Source: JAMA 2013 doi:10.1001/jama2013.13805

Percentage of years lived with disability by cause and age:

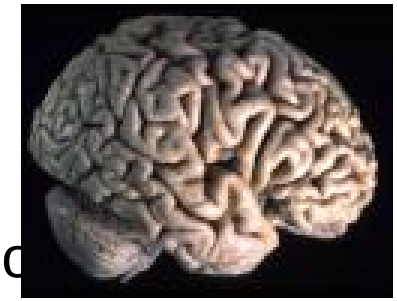
Mental disorders account for 22.7% of YLDs in 2010



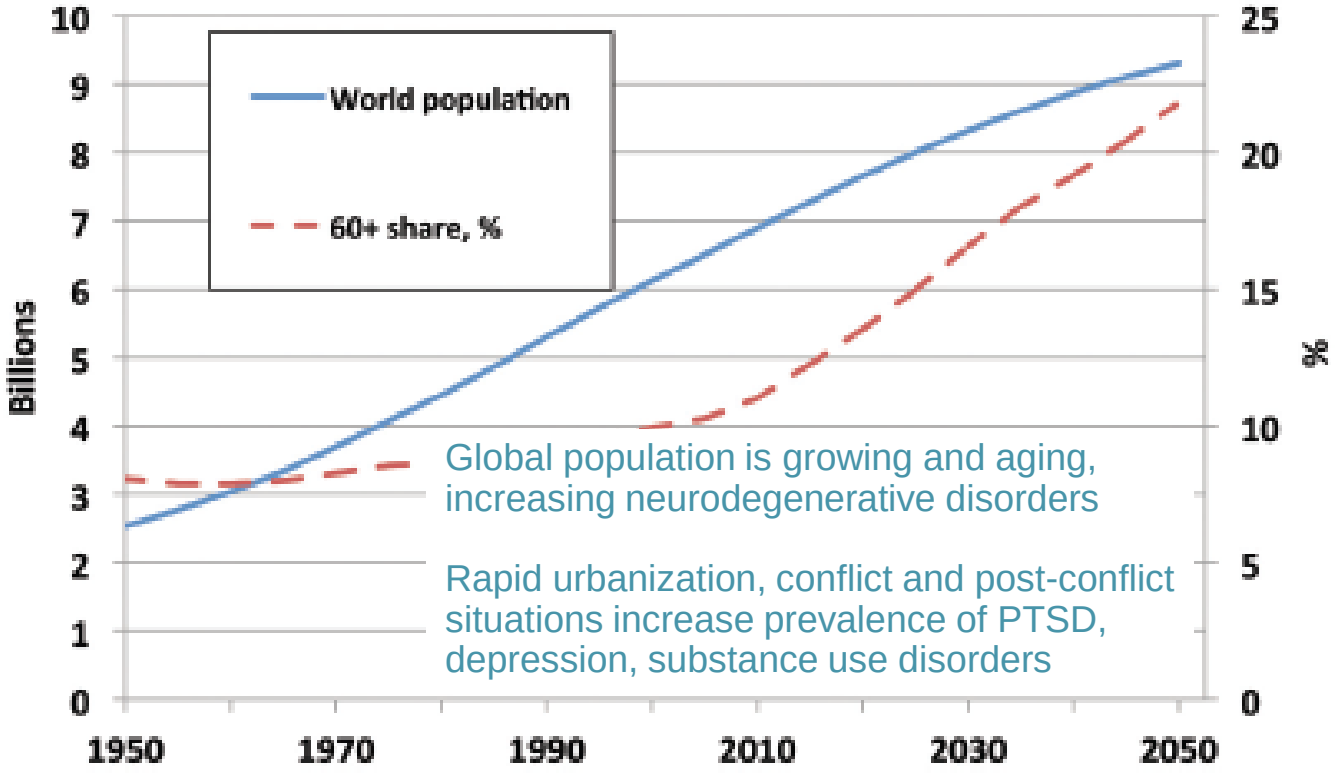
* Mental and Behavioral Disorders

Brain Disorders exert an outsized effect on disease burden worldwide

- Burden: Disability Adjusted Life Years (YLDs) sum of years lost to premature mortality and years of healthy life lost to disability (YLD)
- Brain disorders influence mortality (stroke, suicide), but greatest effects are on disability:
  - High aggregate prevalence
  - Early onsets for many disorders; chronic or recurrent course
  - Brain is the organ of cognition, emotion regulatio executive function



The Prevalence of Brain Disorders is Growing



Source: UN Population Division, 2011

Current and Projected Costs of Dementia (US)

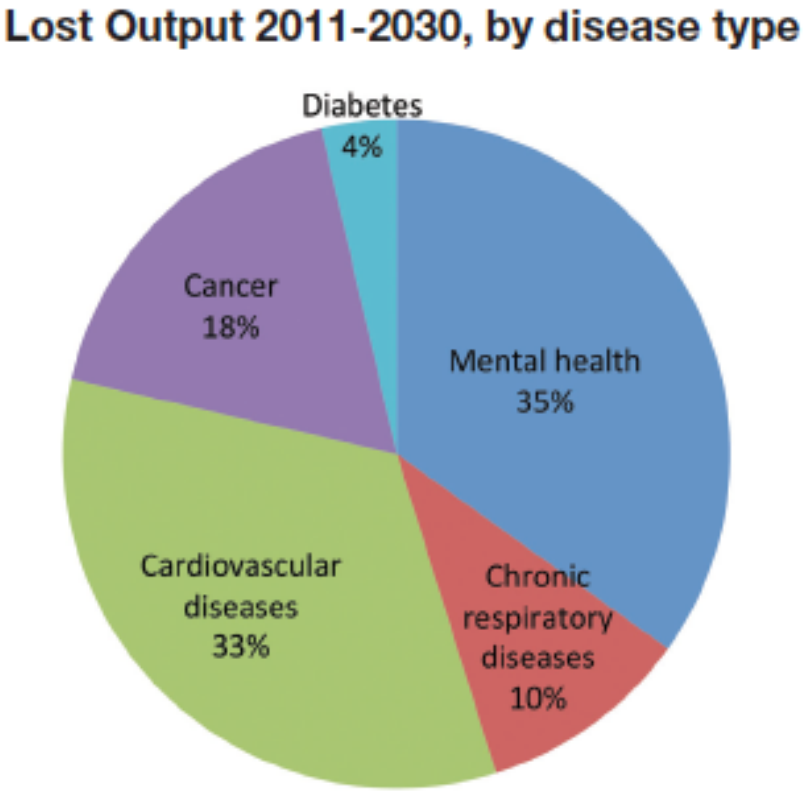
Table 3. Projected Total and Per-Person Annual Monetary Costs of Dementia in the United States, in 2010 Dollars.*

Cost and Year	Care Purchased in Marketplace	Total Cost According to Valuation of Cost of Informal Care	
		Replacement Cost (95% CI)	Cost of Forgone Wages (95% CI)
Total cost (billions of $)			
2010	109 (86–132)	215 (171–259)	159 (126–192)
2020	129 (102–156)	255 (204–306)	189 (150–228)
2030	183 (145–221)	361 (289–434)	267 (212–322)
2040	259 (204–314)	511 (408–615)	379 (300–457)
Total per-person cost ($)			
2010	464 (416–511)	915 (825–1006)	678 (610–746)
2020	498 (445–550)	983 (882–1083)	728 (652–804)
2030	640 (569–712)	1,264 (1,128–1,400)	936 (833–1,039)
2040	831 (733–929)	1,641 (1,455–1,826)	1,215 (1,074–1,356)

* Confidence intervals, estimated with the use of bootstrapping, account for the sampling error in estimates of the effect of dementia on spending and in the prevalence of dementia but treat population projections as nonrandom. Per-person costs are total population costs divided by the number of persons 18 years of age or older.

Source: Hurd et al. N Engl J Med 368:1326, 2013

Projected global loss of economic output due to non-communicable disease



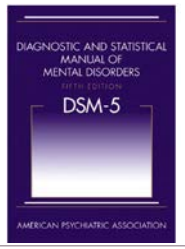
Source: Report of World Economic forum and Harvard School of Public Health,

Despite vast unmet need industry disinvesting in brain disorders, especially psychiatric

- Dearth of new molecular targets
- Difficulties in validating targets
  - Current animal models/assays do not predict efficacy

  - Human brain inaccessible to direct study in

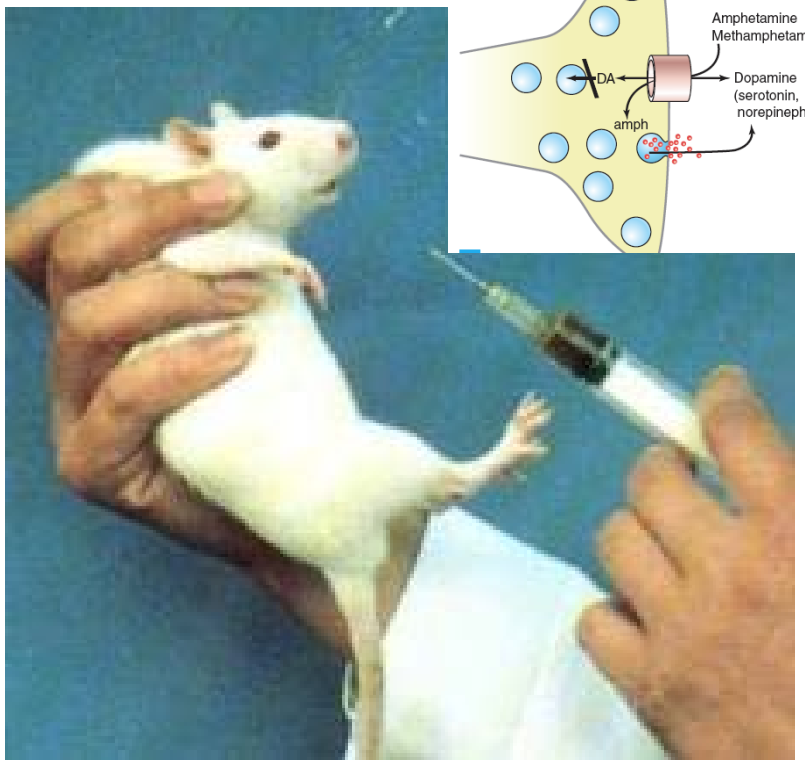
  - Lack of validated biomarkers



How did we get here?

Antipsychotic drugs. Not anti-schizophrenia drugs

Rotarod test: detected motor side effects



Amphetamine injection

Current drugs for neuropsychiatric disorders have the same targets as 1950's prototypes

Table 2. Major classes of drugs developed to treat psychiatric disorders. NE, norepinephrine; 5-HT, 5-hydroxytryptamine (serotonin); GABA, γ-aminobutyric acid.

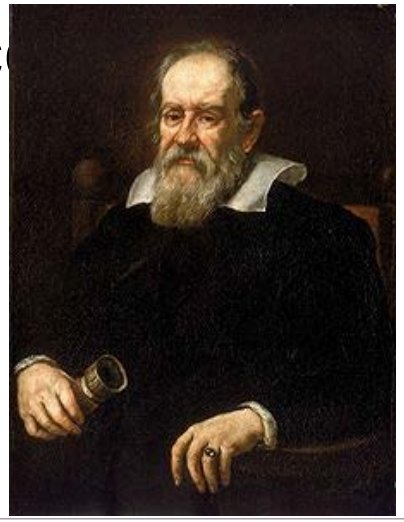
Drug class	Prototype compound	Molecular target(s)
Mood stabilizer	Lithium (Li^+)	GSK3β, inositol 1-phosphatase*
Antipsychotic drugs	Chlorpromazine	Dopamine D_2 receptor
Antidepressants	Iproniazid, Imipramine	Monoamine oxidase, NE, and 5-HT transporters
Benzodiazepine receptor agonists	Chlordiazepoxide	$GABA_A$ receptor, benzodiazepine site

*Although much research favors GSK3β (glycogen synthase kinase β) as the relevant target of Li^+, the drug's mechanism of action remains uncertain.

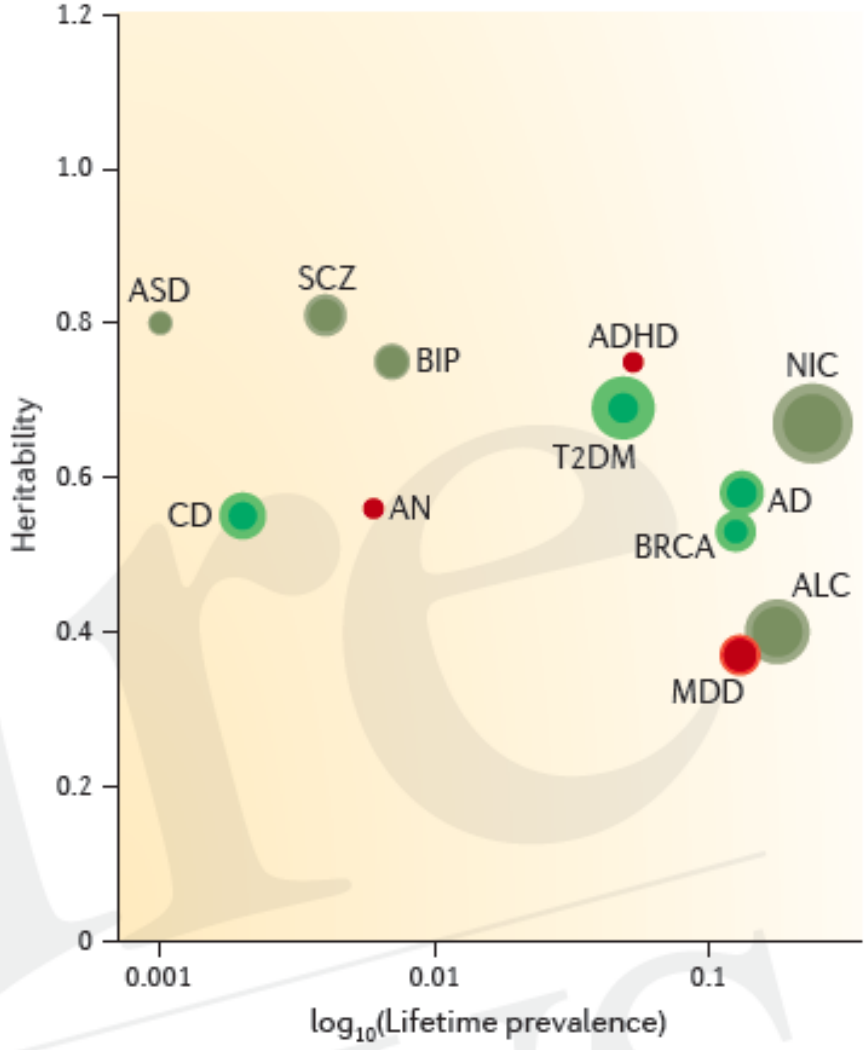
There are no pharmacologic treatments for the core symptoms of autism or for the deficit or cognitive symptoms of schizophrenia

Why make the case for investment now?

- Recent emergence of revolutionary technologies
  - Genomic and computational technologies
  - Stem cell technologies
  - Genome engineering technologies
  - Tools for systems-level neurobiology
- New forms of organization for scienc
  - Durable consortia for genetic studies
  - Increased data sharing
  - Biobanks
  - Interdisciplinary neuroscience



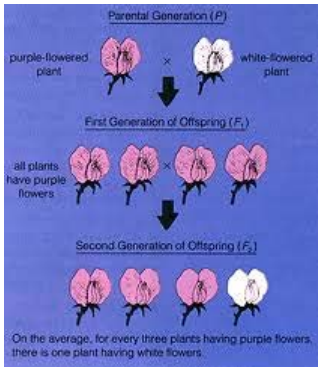
Example: Molecular clues to pathogenesis lie within in our genomes

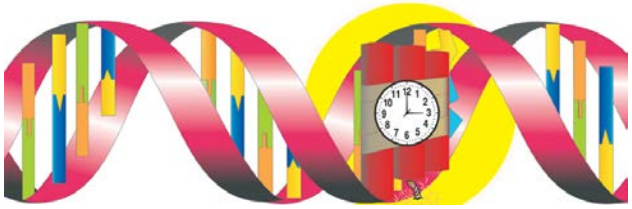


Heritabilities derived from twin studies

Source: Sullivan, Daly, O'Donovan 2012

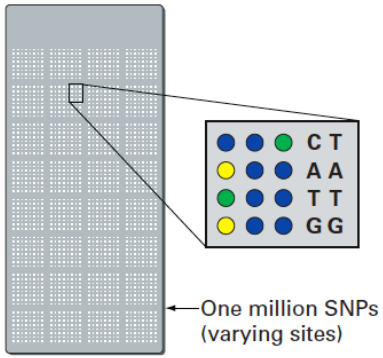
But we could not access these clues for common disorders: our brains are not like Mendel's Peas



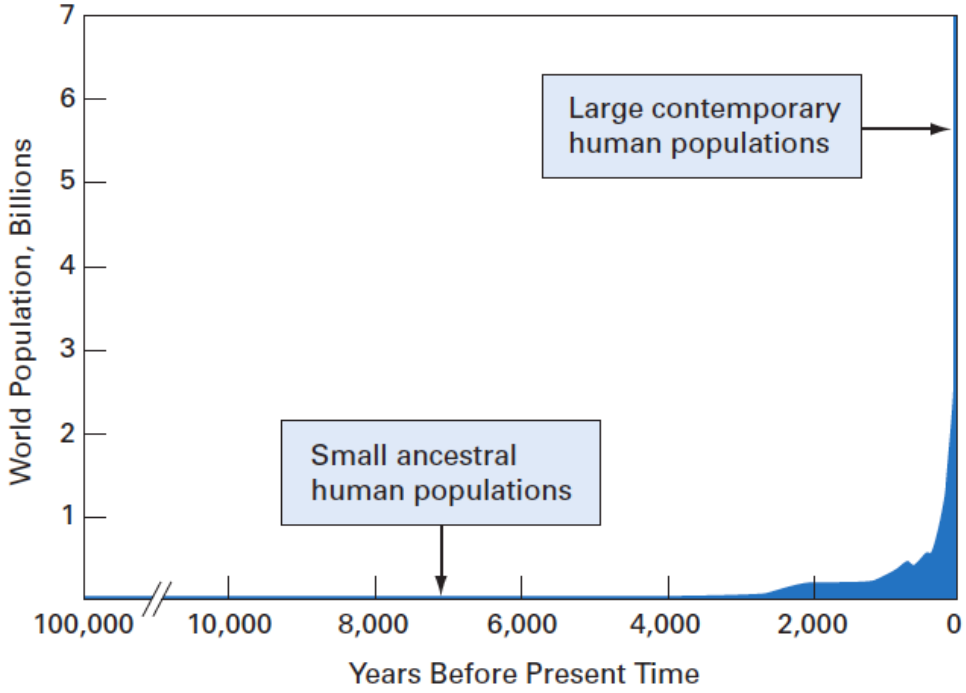


Mendelian disorder

Technology makes it possible to address both common and rare variation at the needed scale

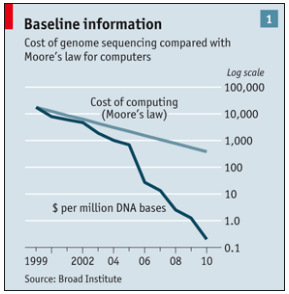


Inexpensive microarrays for ancient common variants

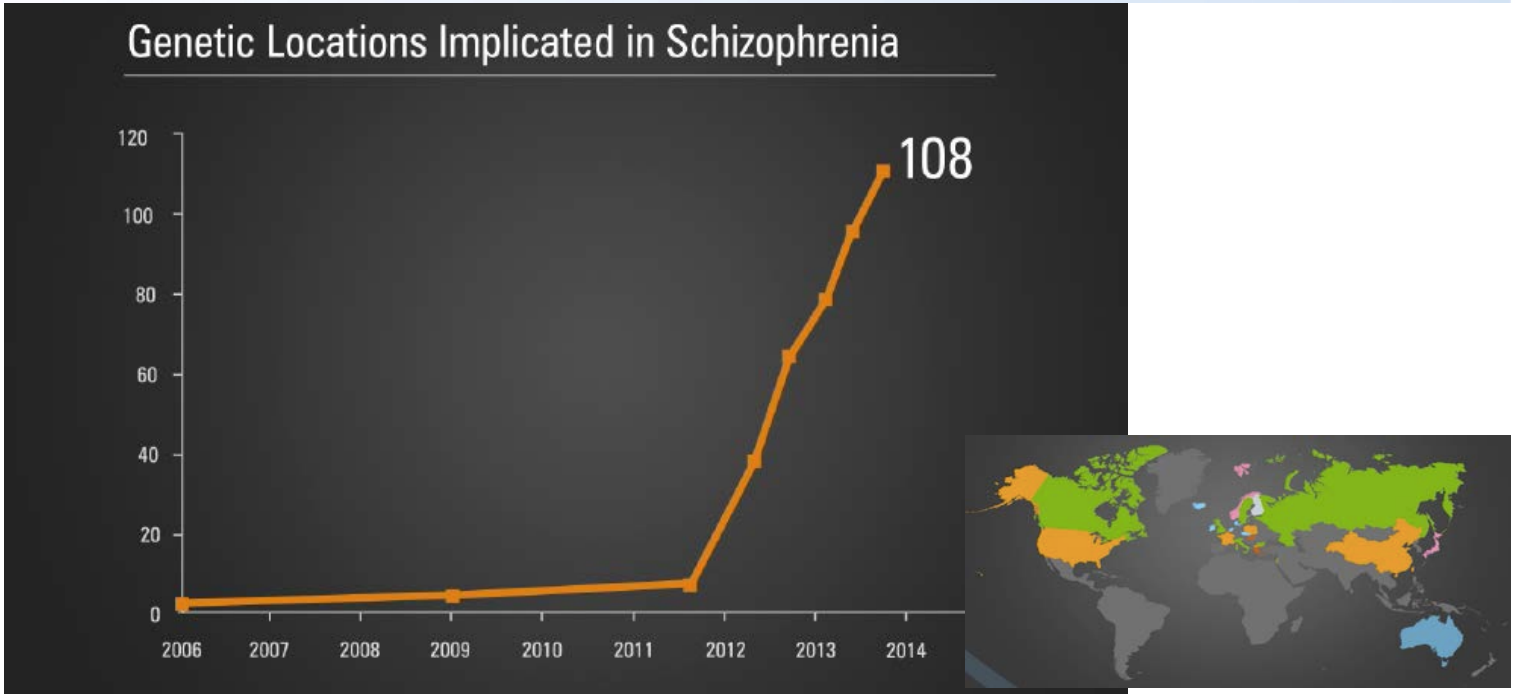


Ancient variation that is common across populations

Sequencing for rare variants less subjected to natural selection

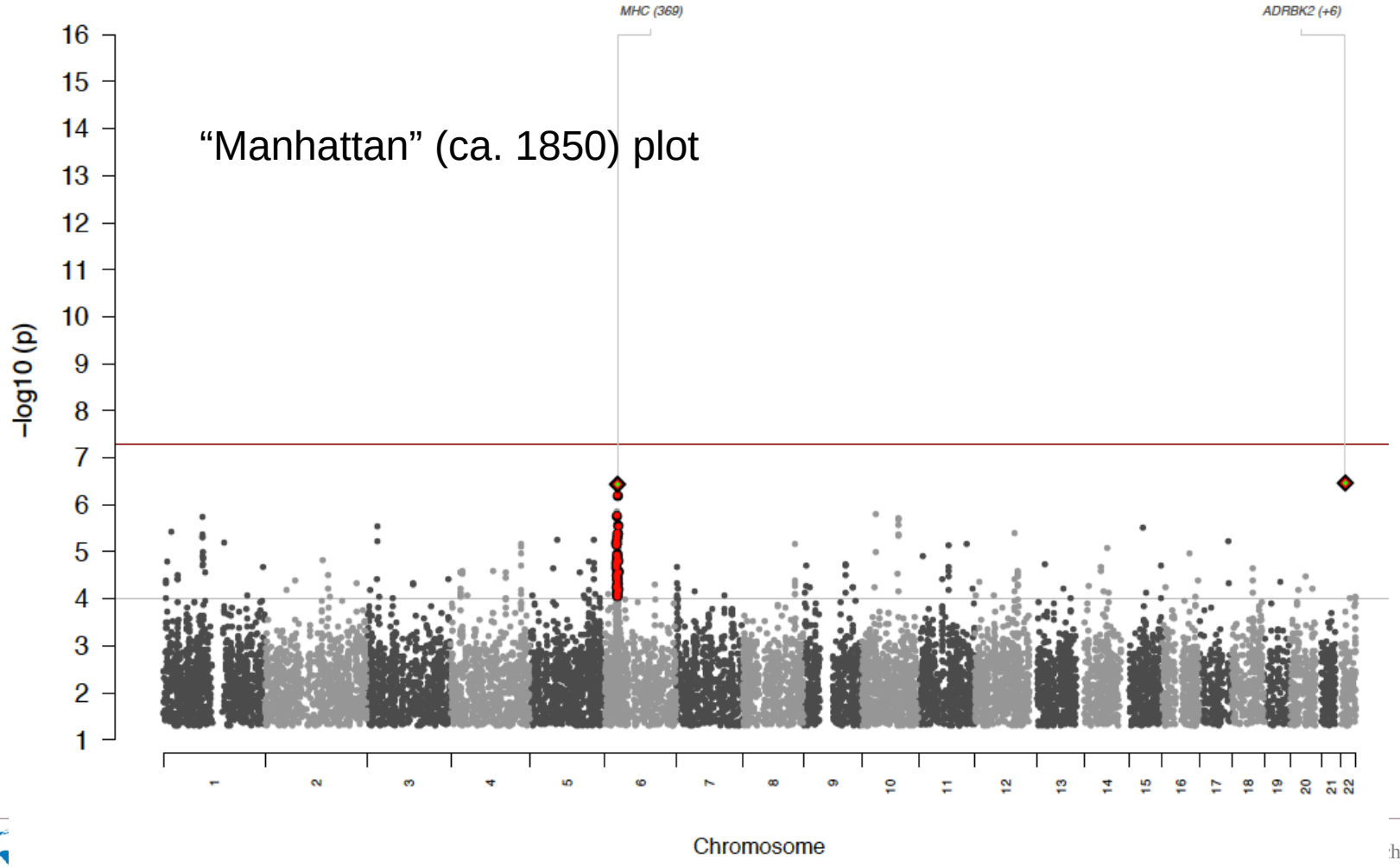


Large-scale, unbiased approaches yield results where underpowered and hypothesis-driven approaches failed

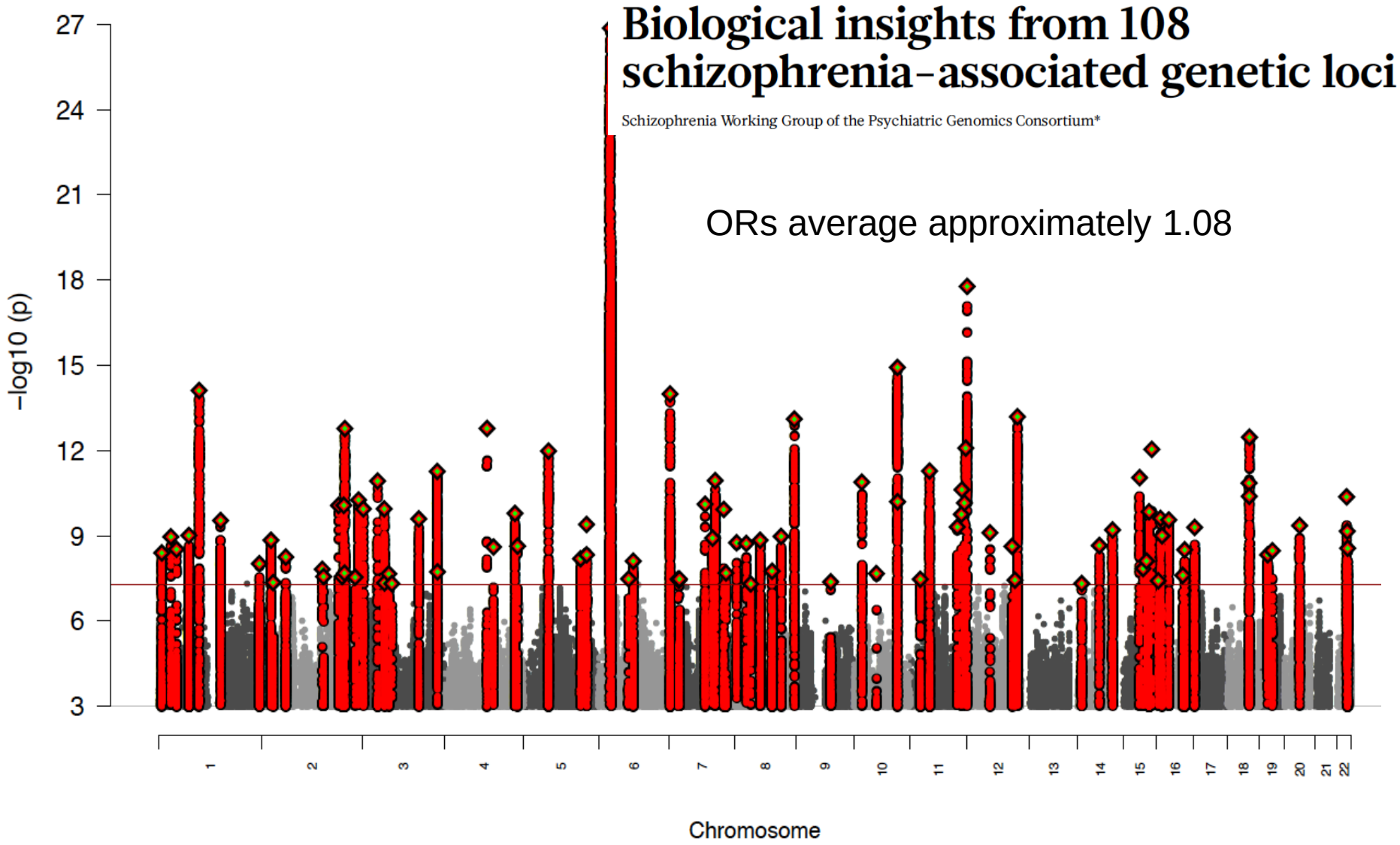


Do we have the will to collaboratively push the genetics of highly heritable neuropsychiatric disorders to diminishing returns across human populations?

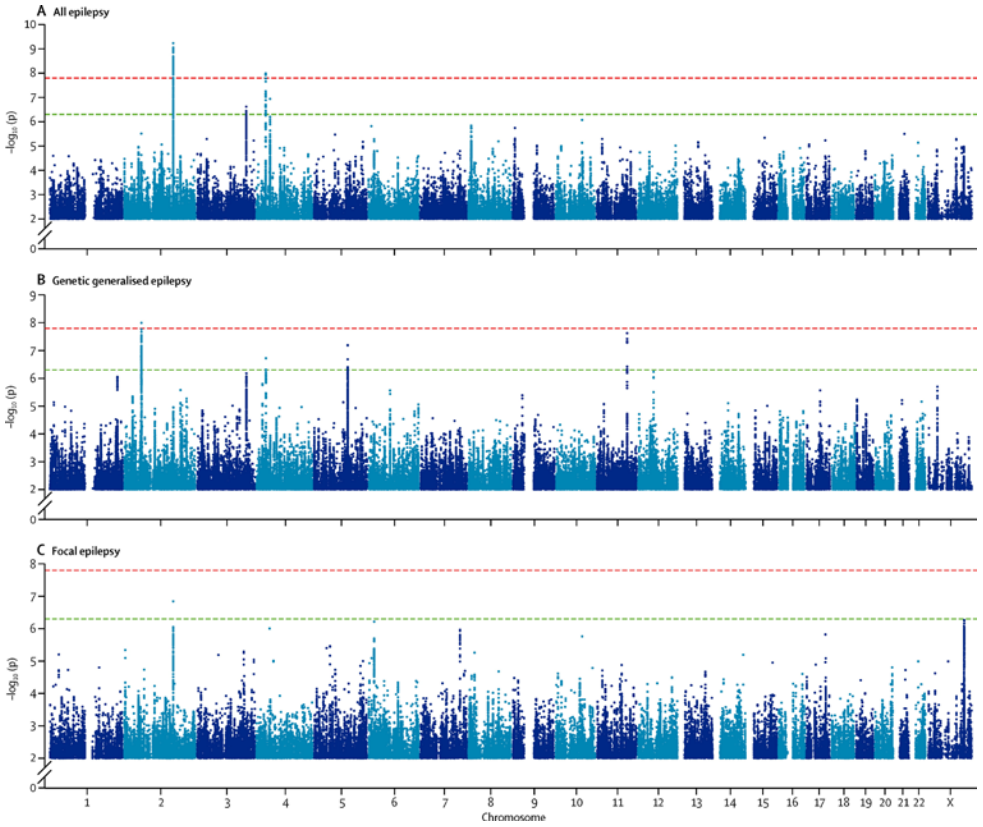
Genome-wide *common variant association* in schizophrenia in 2009 (4,000 cases)



PGC schizophrenia Common Variant Association; 37,000 cases



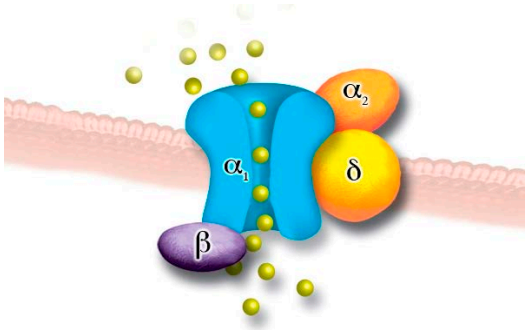
Epilepsy: ILAE Consortium Meta-Analysis 2014



Source: Lancet Neurology 2014

An initial ‘parts list’ for schizophrenia

Voltage-gated calcium channels
- *CACNA1C*
- *CACNA1D*
- *CACNA1I*
- *CACNB2*
- *CACNB3*

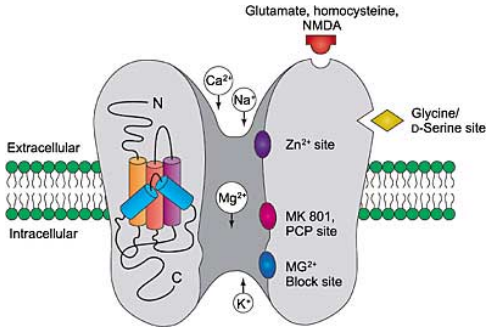


Selective protein degradation
- *KCTD13*
- *UBE3A*

Cytoskeleton and synapse assembly
- *GIT1*
- *SYNGAP1*
- *ITSN1*

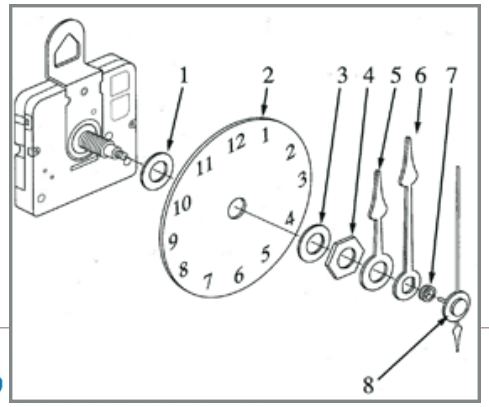
Immune system related proteins
Complement components

Glutamate/NMDA signaling
- *GRIA1*
- *GRIN2A*
- *GRIN2B*
- *GRM3*
- *NRGN*



Utilizing the molecular “parts lists”

CACNA1C
CACNA1D
CANCA1I
CACNB2
GRIA1
GRIA2
GRIN2A
GRIN2B
GRM3
… 106 genes in schizophrenia
… 15 genes in bipolar disorder

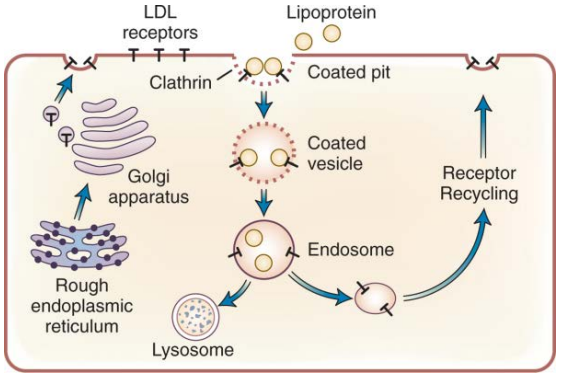


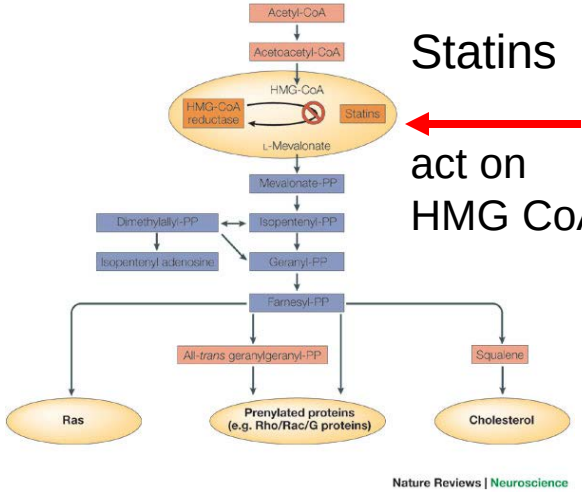
Newly possible: Understand how the parts fit together

Will yield targets and directionality

Why do we care about alleles of small effect? They are our *best* tools to glean biological clues

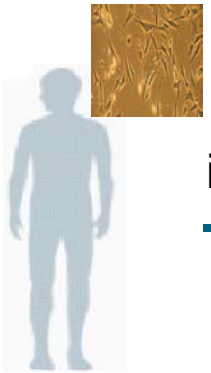
- Risk alleles identify disease-relevant genes
- Genes identify pathways and protein networks
- These illuminate disease mechanisms and suggest drug targets





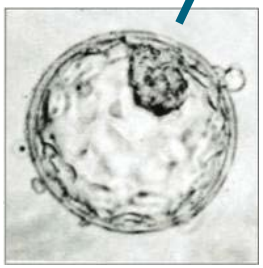
Statins act on HMG CoA-reductase

Stem cell technology enables *high throughput* systems expressing *human transcriptional networks*

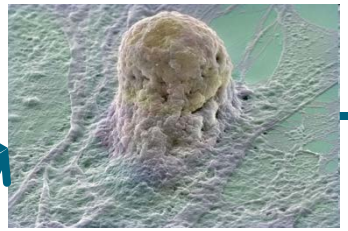


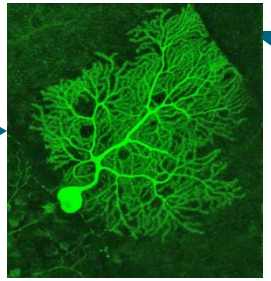
iPSCs

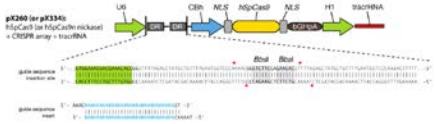
hESCs



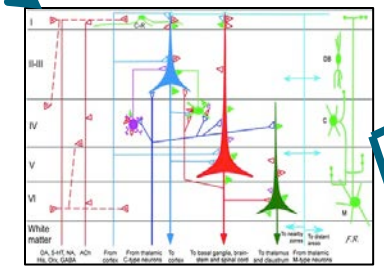
Differentiate



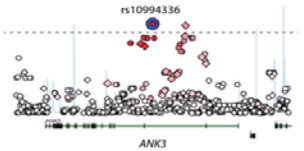




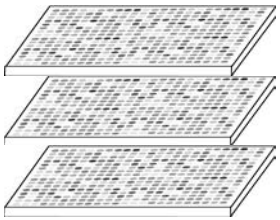
CRISPR: add risk variants
or rescue patient cells



Build circuits



phenotype

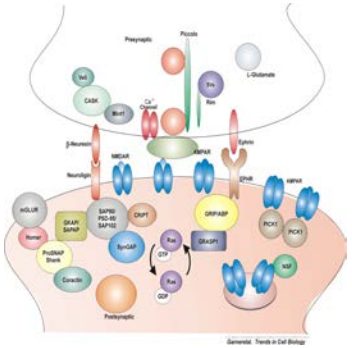


Small molecule
Screens

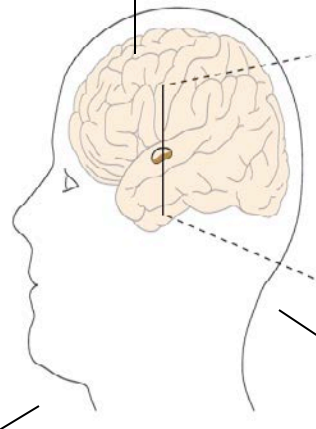
Compare genetic rescue
to small molecule effects

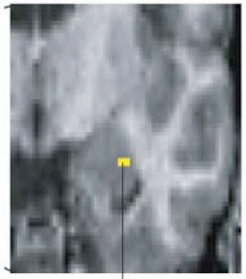
Challenge of target validation

Need for translatable phenotypes

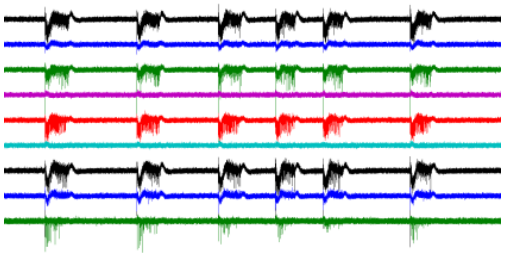


90 myr





Ventral amygdala
(basolateral nucleus)



40 myr

The human model for the human

- Assuming that *toxicity* has been tested in animals, can we take a central nervous system (CNS) drug into humans that has only been tested in cellular models?
- The issues are both ethical and pragmatic (will companies invest without animal 'efficacy gate'?)

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Forum on Neuroscience and Nervous System Disorders

Accelerating Therapeutic Development for Nervous System Disorders towards First-in-Human Trials: A Workshop

April 8 and 9, 2013

National Academy of Sciences Building, Lecture Room
2101 Constitution Ave., N.W., Washington, DC