Genes and environment:

The complex etiology of psychiatric disorders

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Outline

- The issue of Gene-Environment Interactions: Why are they important?
- Methods in psychiatric genetics
- Psychiatry in a nutshell: Dementia, Schizophrenia, Depression, Bipolar Disorder, Personality disorders.
- Implementation of genetic results: Pharmacogenetics, drug development, prevention.

Case presentation

- 23 year old female patient presents herself at the Department after a family debate.
- Chief complaints: „I am treated brutally by my family… I think people on the street mean bad to me…”
- Following examination: symptoms of anxiety, paranoid and religious delusions, acoustic hallucinations (I heard the voice of Jesus.)

Question: What is the cause of her psychiatric problems according to the patient? According to you?

Questions

- How do we call the decribed condition?
- What is the most probable diagnosis?
- What other diagnoses should we think of?
- What is the cause of her psychiatric problems according to the patient?
- According to you?
- The fundamental question of etiology: What causes the disorder? Environmental or genetic factors?

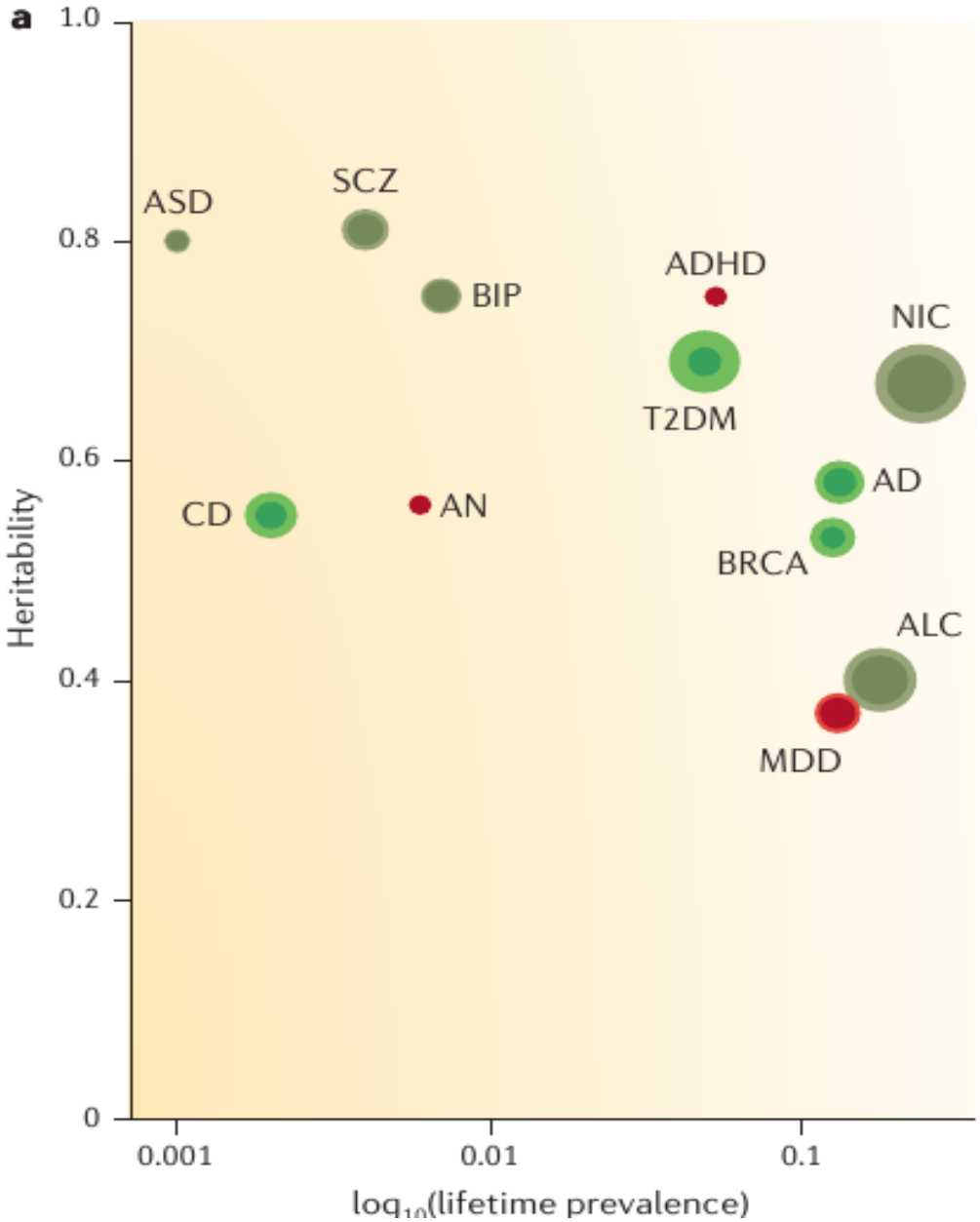
Psychiatric disorders

- Mental disorders: significant dysfunction in an individual's cognitions, emotions, or behaviors

- Diagnoses based on behavioral assessment, no lab tests or biomarkers are available (except for organic psychosyndromes)

- Why do we think that they have anything to do with genes?

Heritability of psychiatric disorders



ASD: autism spectrum disorders
AD: Alzheimer dementia
ADHD: attention-deficit hyperactivity disorder
AN: anorexia nervosa
ALC: alcohol dependence
BIP: bipolar disorder
BRCA: breast cancer
CD: Crohn disorder
MDD: major depressive disorder
NIC: nicotine dependence
SCZ: schizophrenia
T2DM: type 2 diabetes mellitus

From: Sullivan et al, 2012. Genetic architectures of psychiatric disorders: the emerging picture and implications. *Nature*

Genetic studies

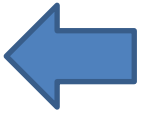
- Population genetics:
  - Family studies
  - Twin studies
  - Adoption studies
- Epidemiologic studies:
  - Genetic cohorts
- Molecular methods
  - Linkage studies
  - Association studies
  - Expression studies
  - (epigenetic analyses)
- Animal models

A typical genetic analysis workflow

Population studies

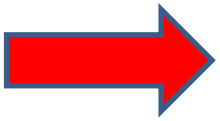
Molecular methods

Candidate genes
(polymorphisms)



biological hypotheses

Epidemiologic analyses

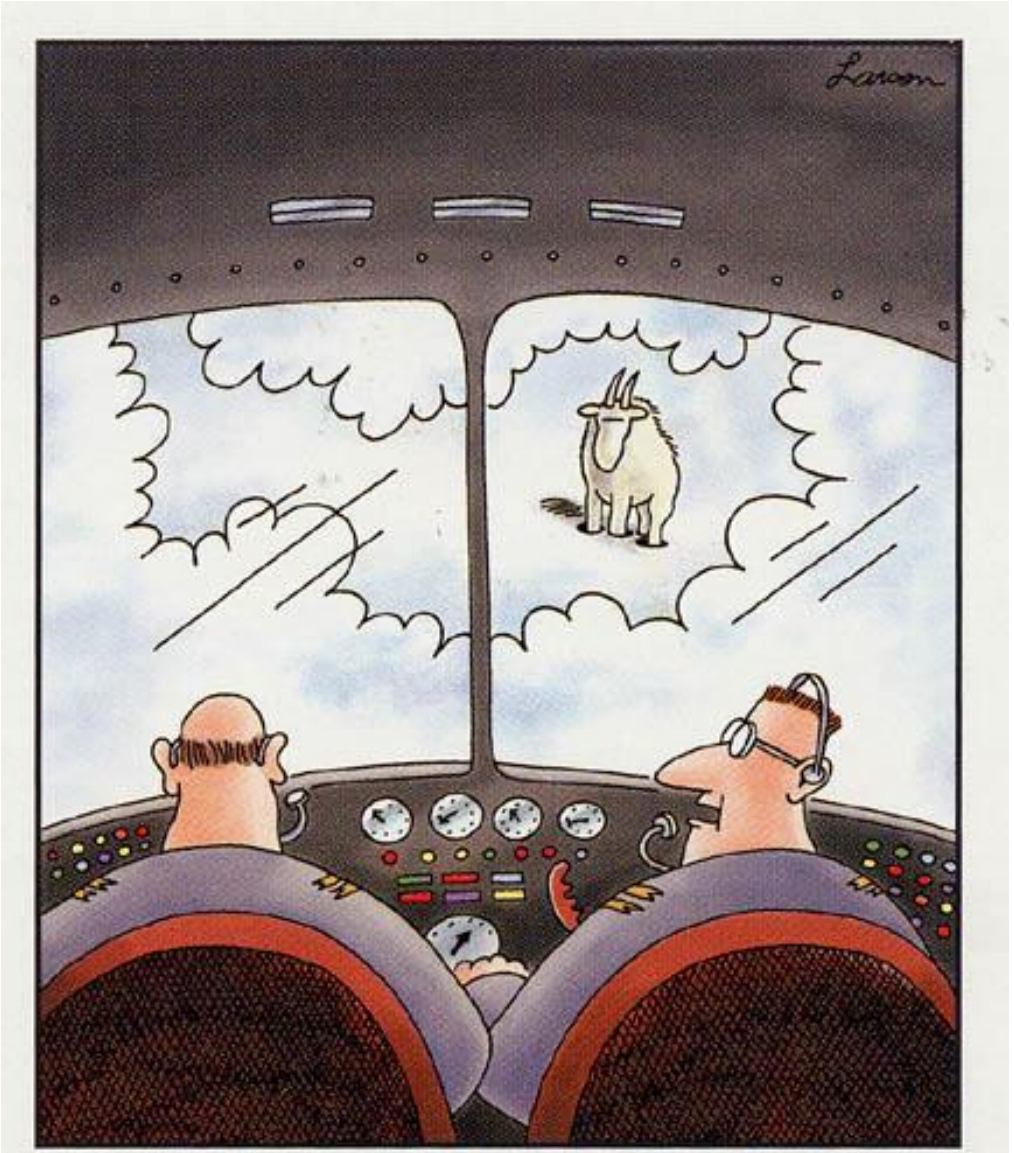


Genetic Risk

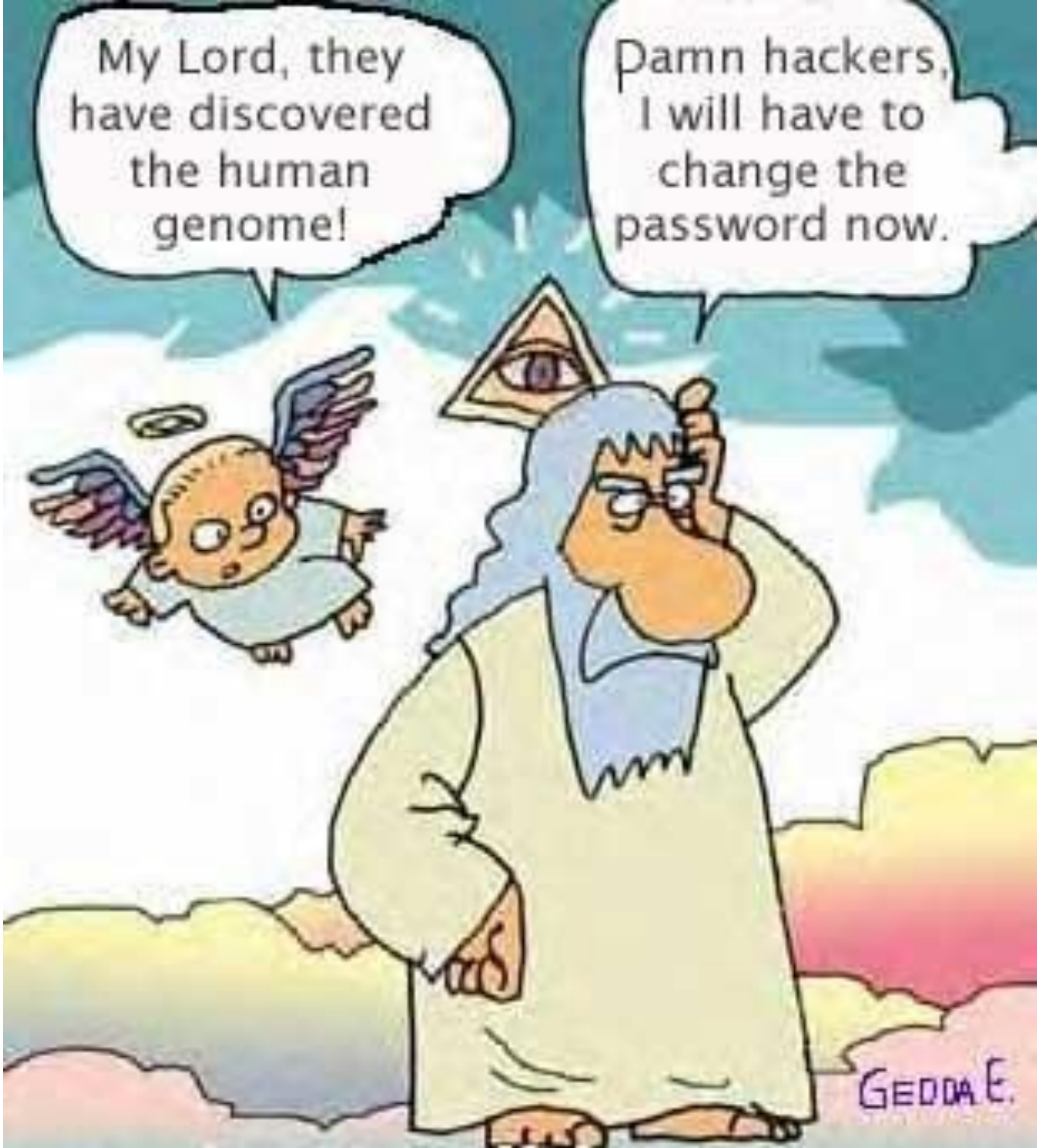
Results of Psychiatric GWAS Studies

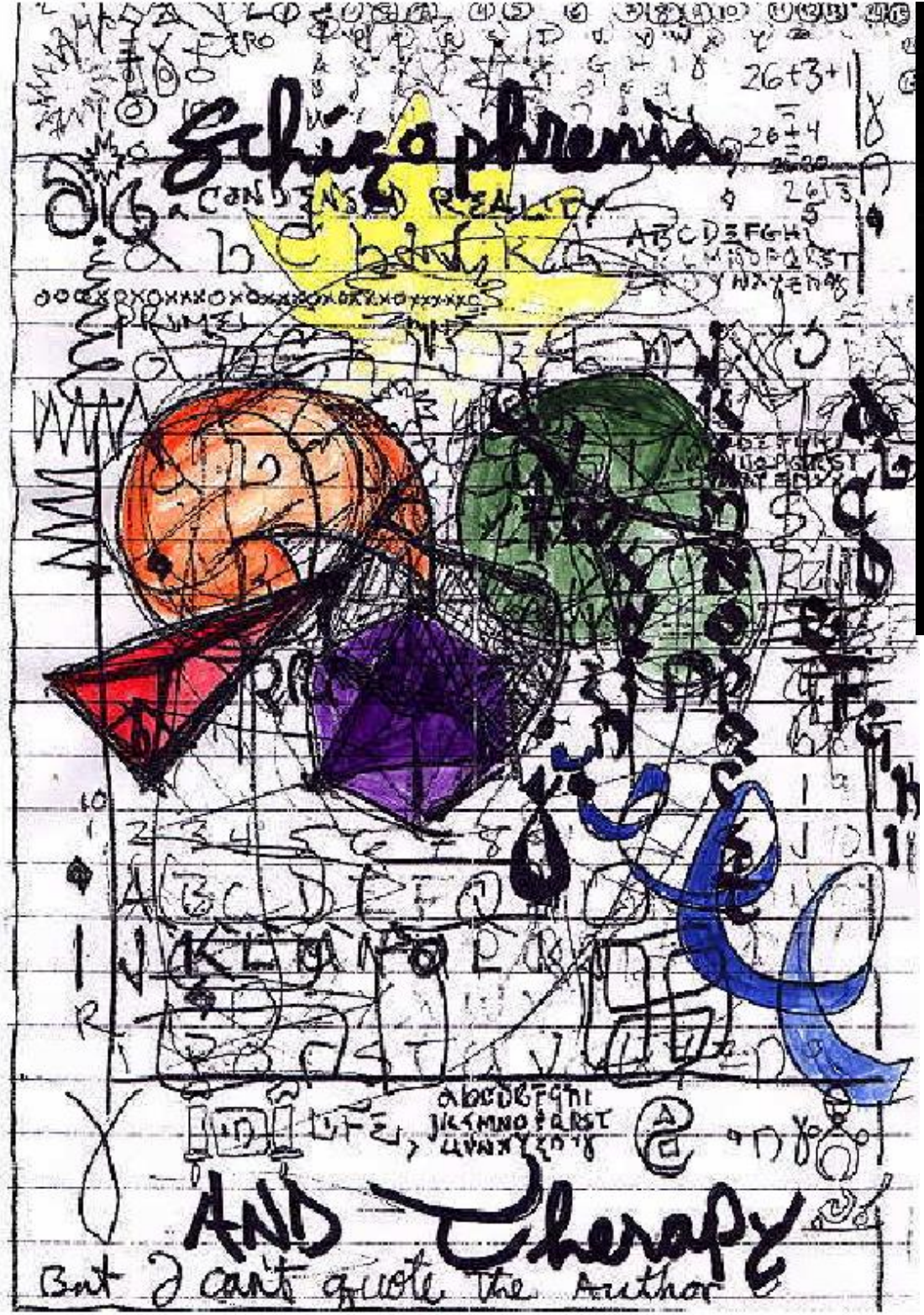
Phenotype	SNP	Location	Discovery GWAS (cases/controls)	Largest meta-analysis (cases/controls)	*P* value	Odds ratio	Nearest gene
Alzheimer's disease	rs3818361	chr1:207784968	2,018/5,324 (REF. 34)	<19,870/39,846 (REF. 35)	3.7×10^{-14}	1.18	*CR1*
	rs744373	chr2:127894615	3,006/14,642 (REF. 193)	<19,870/39,846 (REF. 35)	2.6×10^{-14}	1.17	*BIN1*
	rs9349407	chr6:47453378	8,309/7,366 (REF. 36)	18,762/29,827 (REF. 36)	8.6×10^{-9}	1.11	*CD2AP*
	rs11767557	chr7:143109139	8,309/7,366 (REF. 36)	18,762/35,597 (REF. 36)	6.0×10^{-10}	1.11	*EPHA1*
	rs11136000	chr8:27464519	3,941/7,848 (REF. 33)	8,371/26,965 (REF. 193)	1.6×10^{-16}	1.18	*CLU*
	rs610932	chr11:59939307	6,688/13,251 (REF. 35)	>19,000/38,000 (REF. 35)	1.2×10^{-16}	1.10	*MS4A* cluster
	rs3851179	chr11:85868640	3,941/7,849 (REF. 33)	8,371/26,966 (REF. 193)	3.2×10^{-12}	1.15	*PICALM*
	rs3764650	chr19:1046520	5,509/11,531 (REF. 35)	>17,000/34,000 (REF. 35)	5.0×10^{-21}	1.23	*ABCA7*
	rs2075650	chr19:45395619		8,371/26,966 (REF. 193)	1×10^{-295}	2.53	*APOE, TOMM40*
	rs3865444	chr19:51727962	8,309/7,366 (REF. 36)	18,762/29,827 (REF. 36)	1.6×10^{-9}	1.10	*CD33*
Alcohol consumption	rs1229984	chr4:100239319	REF. 102		1.3×10^{-11}		*ADH1B*
	rs6943555	chr7:69806023	REF. 101		4.1×10^{-9}		*AUTS2*
	rs671	chr12:112241766	REF. 100		3×10^{-211}		*ALDH2*
Bipolar disorder	rs12576775	chr11:79077193	7,481/9,251 (REF. 60)	11,974/51,793 (REF. 60)	4.4×10^{-8}	1.14	*ODZ4*
	rs4765913	chr12:2419896	7,481/9,250 (REF. 60)	11,974/51,792 (REF. 60)	1.5×10^{-8}	1.14	*CACNA1C*
	rs1064395	chr19:19361735	682/1300 (REF. 194)	8,441/35,362 (REF. 194)	2.1×10^{-9}	1.17	*NCAN*
Nicotine consumption	rs1329650	chr10:93348120	38,181 (REF. 93)	73,853 (REF. 93)	5.7×10^{-10}		*LOC100188947*
	rs1051730	chr15:78894339	38,181 (REF. 93)	73,853 (REF. 93)	2.8×10^{-73}		*CHRNA3*
	rs3733829	chr19:41310571	38,181 (REF. 93)	73,853 (REF. 93)	1.0×10^{-8}		*EGLN2, CYP2A6*
Smoking cessation	rs3025343	chr9:136478355	41,278 (REF. 93)	64,924 (REF. 93)	3.6×10^{-8}	1.13	*DBH*
Smoking initiation	rs6265	chr11:27679916	74,035 (REF. 93)	143,023 (REF. 93)	1.8×10^{-8}	0.94	*BDNF*
Schizophrenia	rs1625579	chr1:98502934	9,394/12,462 (REF. 59)	17,839/33,859 (REF. 59)	1.6×10^{-11}	1.12	*MIR137*
	rs2312147	chr2:58222928		18,206/42,536 (REF. 195)	1.9×10^{-9}	1.09	*VRK2*
	rs1344706	chr2:185778428	479/2,937 (REF. 174)	18,945/38,675 (REF. 196)	2.5×10^{-11}	1.10	*ZNF804A*
	rs17662626	chr2:193984621	9,394/12,463 (REF. 59)	17,839/33,860 (REF. 59)	4.6×10^{-8}	1.20	*PCGEM1*
	rs13211507	chr6:28257377	3,322/3,587 (REF. 70)	18,206/42,536 (REF. 195)	1.4×10^{-13}	1.22	*MHC*
	rs7004635	chr8:3360967	9,394/12,465 (REF. 59)	17,839/33,862 (REF. 59)	2.7×10^{-8}	1.10	*MMP16*
	rs10503253	chr8:4180844	9,394/12,464 (REF. 59)	17,839/33,861 (REF. 59)	4.1×10^{-8}	1.11	*CSMD1*
	rs16887244	chr8:38031345	3,750/6,468 (REF. 68)	8,133/11,007 (REF. 68)	1.3×10^{-10}	1.19	*LSM1*
	rs7914558	chr10:104775908	9,394/12,466 (REF. 59)	17,839/33,863 (REF. 59)	1.8×10^{-9}	1.10	*CNNM2*
	rs11191580	chr10:104906211	9,394/12,467 (REF. 59)	17,839/33,864 (REF. 59)	1.1×10^{-8}	1.15	*NT5C2*
	rs11819869	chr11:46560680	1,169/3,714 (REF. 197)	3,738/7,802 (REF. 197)	3.9×10^{-9}	1.25	*AMBRA1*
	rs12807809	chr11:124606285		18,206/42,536 (REF. 195)	2.8×10^{-9}	1.12	*NRGN*
	rs12966547	chr18:52752017	9,394/12,468 (REF. 59)	17,839/33,865 (REF. 59)	2.6×10^{-10}	1.09	*CCDC68*
	rs9960767	chr18:53155002		18,206/42,537 (REF. 195)	4.2×10^{-9}	1.20	*TCF4*

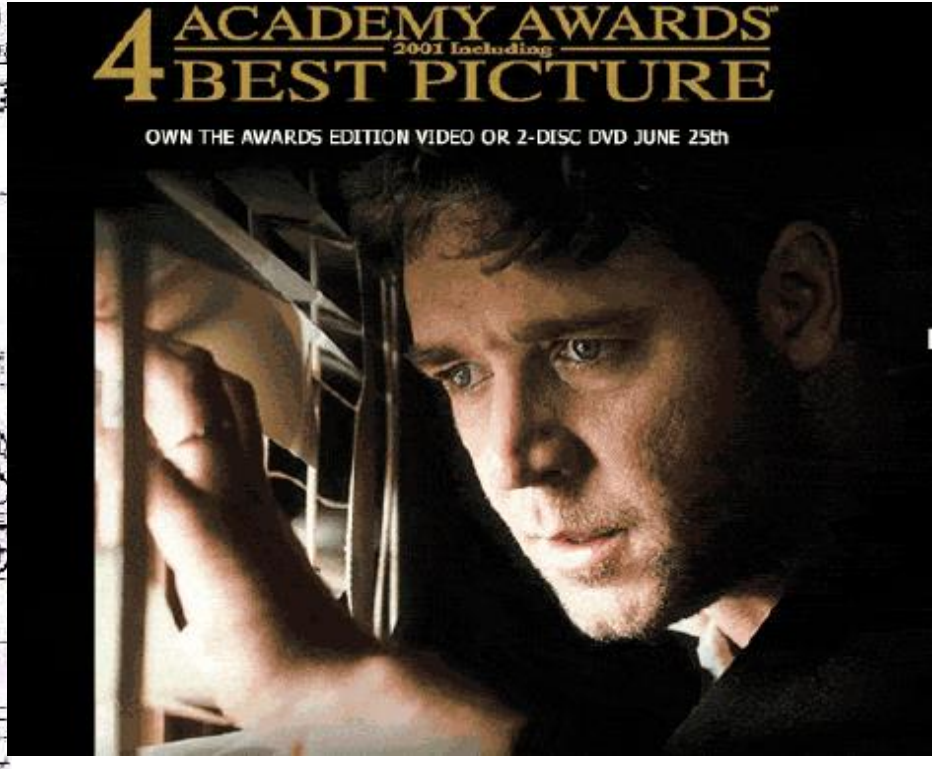
…the interpretation

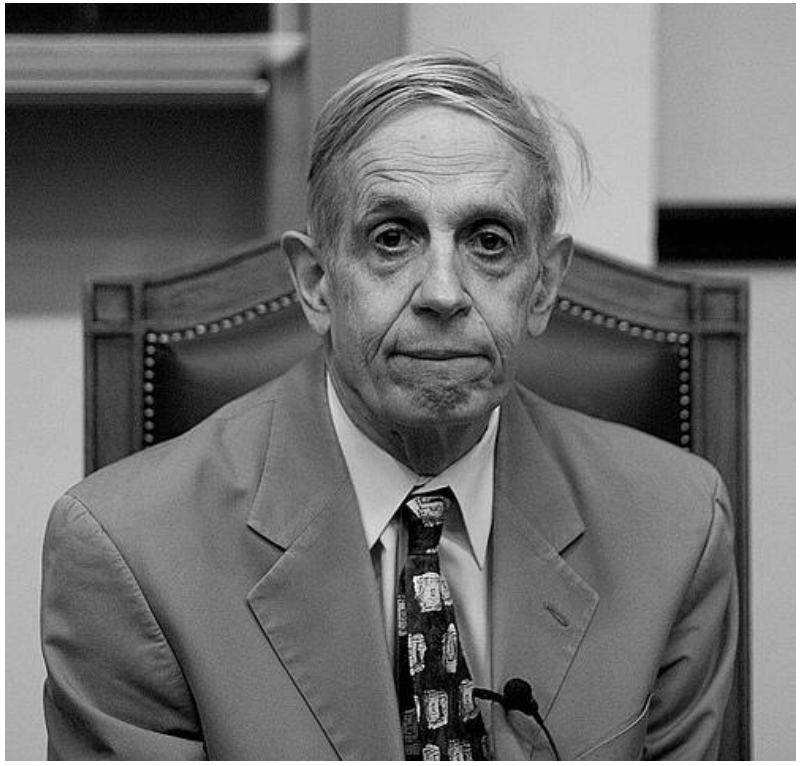


"Say … what's a mountain goat doing
way up here in a cloud bank?"


My Lord, they have discovered the human genome!
Damn hackers, I will have to change the password now.
GEDDA E.


Schizophrenia
AND Therapy
But I can't quote the Author


4 ACADEMY AWARDS
2001 Including
BEST PICTURE
OWN THE AWARDS EDITION VIDEO OR 2-DISC DVD JUNE 25th



Schizophrenia

- Main symptoms: delusions, hallucinations, disorganized thoughts and behavior
- Familial transmission is straightforward (heritability: 0.8, MZ twins: 48-59%, DZ twins: 16% concordance)
- Referred to as the totally unsuccessful example of linkage and association studies
- GWAS studies did not replicate previously implicated candidate genes, and significant markers only explain 3% of the heritability -> “missing heritability”

Candidate genes in schizophrenia

Gene[1]	Description	OMIM[2]	Cytogenetic Band	Cytogenetic Abnormalities	Genome Scan Meta-Analysis[3]	Linkage Evidence[4]	Association Study Support[5]	Expression in PFC[6]	Functional Studies: Plausibility?
AKT1	V-AKT murine thymoma viral oncogene homolog 1	164730	14q32.33	No	No	No	2+ & 1– studies	++	Yes
COMT	Catechol-O-methyltransferase	116790	22q11.21	Yes	Yes	Yes	Some studies +	++	Yes
DISC1	**Disrupted in schizophrenia 1**	605210	1q42.2	Yes	No	Yes	Multiple studies +	+	Yes
DRD3	Dopamine receptor D3	126451	3q13.31	No	No	Inconsistent	Meta-analysis +	–	Yes
DTNBP1	**Dystrobrevin binding protein 1**	607145	6p22.3	No	Yes	Yes	Multiple studies +	++	Yes
G30/G72	Putative proteins LG30 & G72	607415	13q33.2	No	No	Inconsistent	Multiple studies +		Insufficient data
HTR2A	Serotonin receptor 2A	182135	13q14.2	No	No	Inconsistent	Meta-analysis +	++	Yes
NRG1	**Neuregulin 1**	142445	8p12	No	Nearby	Yes	Multiple studies +	+	Yes
PRODH	Proline dehydrogenase 1	606810	22q11.21	Yes	Yes	Yes	-	++	Yes
RGS4	**Regulator of G-protein signaling 4**	602516	1q23.3	No	Yes	Yes	Multiple studies +	++	Yes
SLC6A4	Serotonin transporter	182138	17q11.2	No	Nearby	Inconsistent	Meta-analysis +	+	Yes
ZDHHC8	Zinc finger/DHHC domain protein 8	608784	22q11.21	Yes	Yes	Yes	2+ & 1– studies	++	Yes

Question

Which character suffers from schizophrenia in one of Shakespeare's dramas?

John William Waterhouse:
Ophelia

Edgar - Tom O’Bedlam
(King Lear)

Origins of magic: review of genetic and epigenetic effects

BMJ 2007;335:1299-301
doi:10.1136/bmj.39414.582639.BE
Accepted: 16 November 2007

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ABSTRACT

Objective To assess the evidence for a genetic basis to magic.

Design Literature review.

Setting Harry Potter novels of J K Rowling.

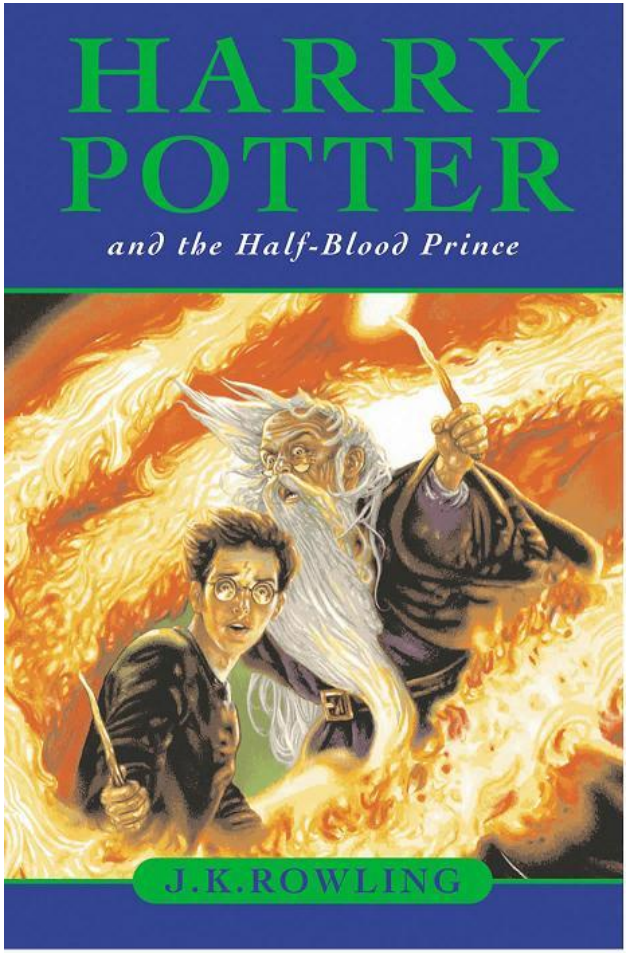
Participants Muggles, witches, wizards, and squibs.

Interventions Limited.

Main outcome measures Family and twin studies, magical ability, and specific magical skills.

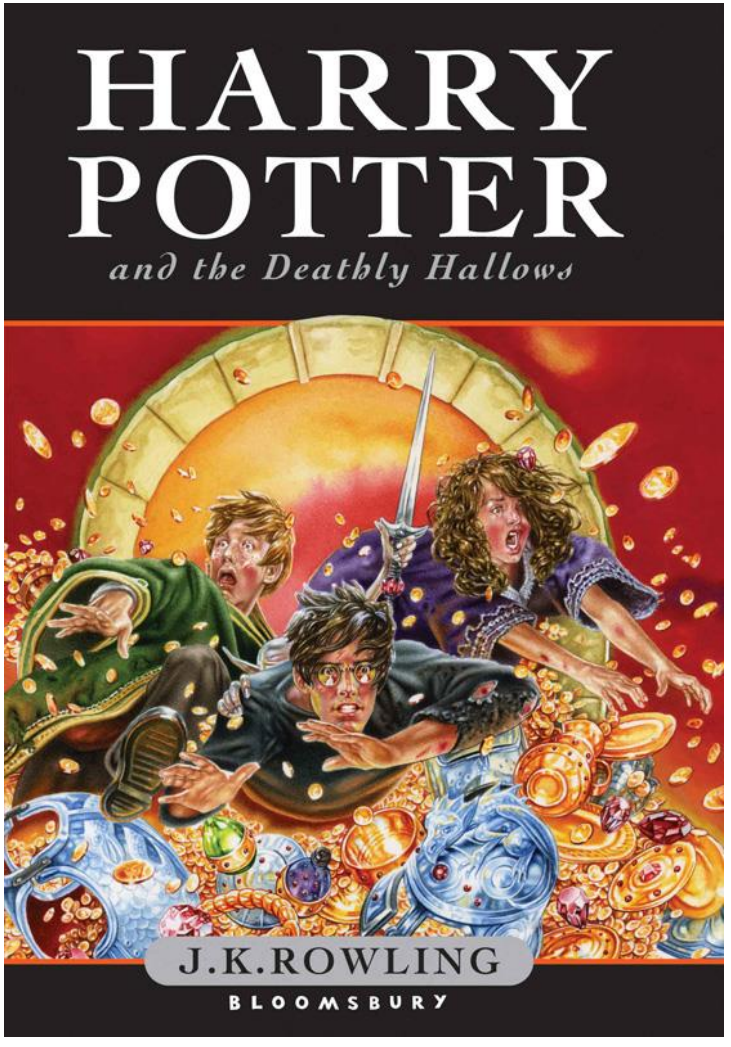
Results Magic shows strong evidence of heritability, with familial aggregation and concordance in twins. Evidence suggests magical ability to be a quantitative trait. Specific magical skills, notably being able to speak to snakes, predict the future, and change hair colour, all seem heritable.

Conclusions A multilocus model with a dominant gene for magic might exist, controlled epistatically by one or more loci, possibly recessive in nature. Magical enhancers regulating gene expression may be involved, combined with mutations at specific genes implicated in speech and hair colour such as FOXP2 and MCR1.



Without population based studies to confirm our points these findings should be treated with caution, but using the information available we can be certain that some aspects of magical ability are heritable. We await with bated breath the results of a genome wide association study for magic.

We thank the three underage witches who gave specialist advice on more technical aspects of the Harry Potter novels and David Dyment, Blanca Herrera, Emma Walton, and Claire Vandiedonck for helpful comments.



GLOSSARY

Assortative mating—people tending to mate with others like themselves

Chromatin—complex of DNA and protein that constitute chromosomes

Epigenetics—heritable changes in gene function not involving changes in DNA sequence

Epistasis—action of one gene modified by another

Founder effect—increase in gene frequency when a population has only a small number of original settlers (founders), one or more of whom had that gene

HapMap project—haplotype (series of correlated alleles) map of the human genome, currently being analysed in populations of African, Asian, and European ancestry

Histones—main protein components of chromatin

House elves—human-like creatures with distinctive magical abilities who are bound to, and act as servants for, several magical families

Metamorphmagus—someone with the ability to change their physical appearance

Muggle—someone with no magical abilities

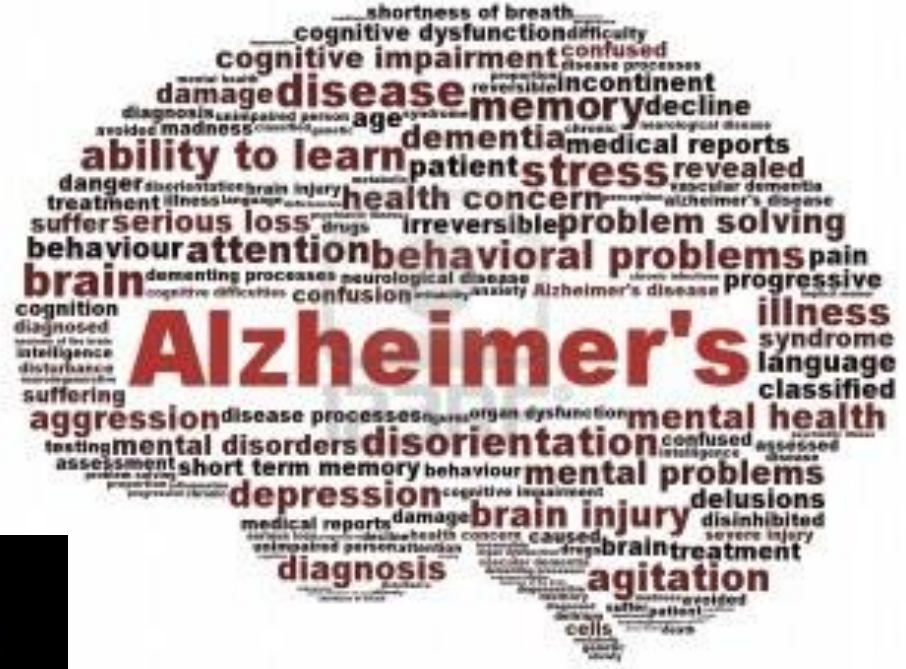
Parseltongue—ability to talk to snakes

Pureblood—someone whose ancestors all possess magical abilities

Seer—someone who can predict the future

Squib—someone with virtually no magical abilities who comes from a magical family


Science Photo Lib


Alzheimer's
shortness of breath
cognitive dysfunction
cognitive impairment
confused
damage
disease
memory
incontinent
decline
diagnosis
age
madness
dementia
medical reports
ability to learn
patient
stress
revealed
danger
health concern
treatment
suffer
serious loss
irreversible
problem solving
behaviour
attention
behavioral problems
pain
brain
progressive
confusion
cognition
diagnosed
illness
syndrome
language
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suffering
aggression
disease processes
mental health
mental disorders
disorientation
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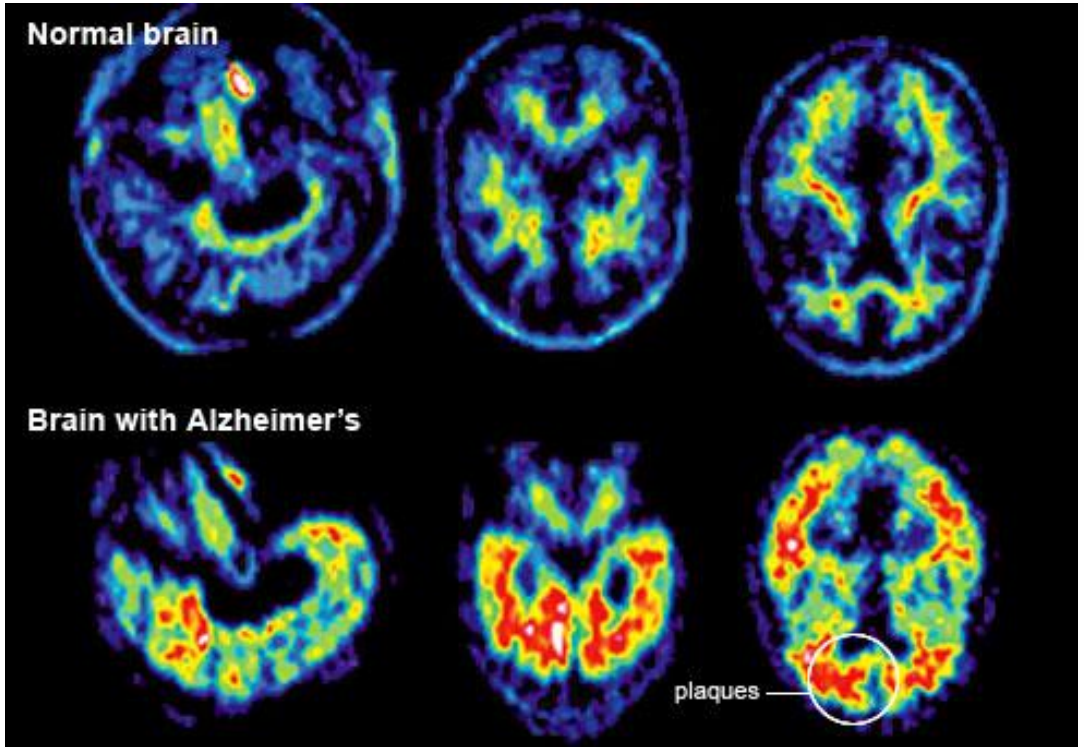
agitation
cells

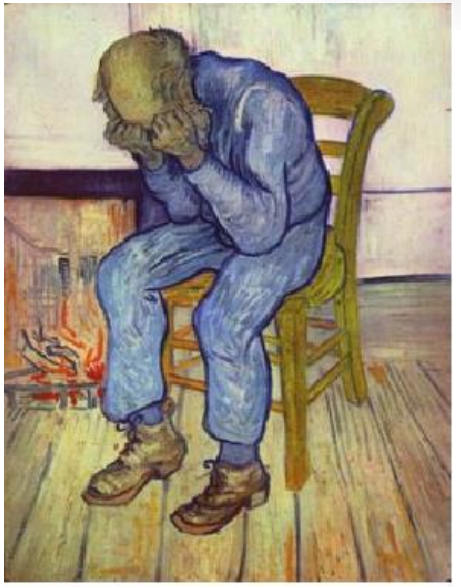

Normal brain
Brain with Alzheimer's
plaques

Alzheimer dementia

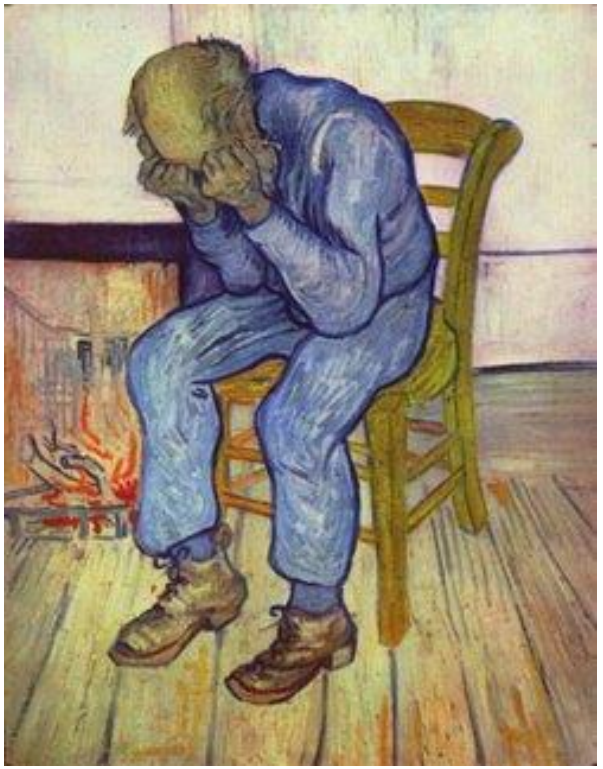
- Main symptoms: Progressive deterioration of cognitive abilities, agitation, hallucinations.
- Neurodegenerative disease, EC: neuritic plaque, IC: neurofibrillar filaments, beta-amiloyd
- Familial AD (5%): mendelian transmission, dominant, early manifestation: APP (amyloid precursor protein), presenilin1, presenilin 2
- Sporadic AD (95%): polygenic, late-onset: apolipoprotein E e4 allele risk factor, GWAS replicated
- APP gene on chromosome 21- association with Down-trisomy

Mood disorders

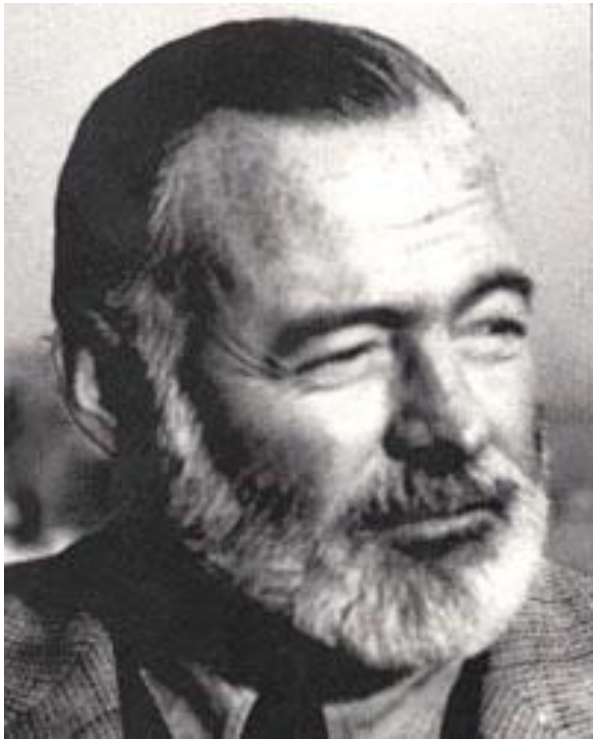
- Depression: depressed mood, performance problems, somatic symptoms (loss of appetite, sleep problems)
- Mania: elevated mood, hyperactivity, decreased critical insight
- Bipolar disorder: cycles of depression and mania, social disability, family problems, high suicide risk



DEPRESSION: abnormal sadness, loss of joy and motivation, decreased energy, desperation, and suicide



Van Gogh



Hemingway

Genetics of mood disorders

- Highly prevalent disorders (MDD~15%, BD~6%)
- Familial transmission straightforward in BD (h2: 0.8, MZ: 65%, DZ: 14%), moderate in MDD (h2: 0.39, MZ:50%, DZ:18%)
- GWAS studies yielded a few significant markers in BD with only 1 gene in concert with linkage results (CACNA1C, OR=1.14), again explaining only 2% of heritability variance
- No markers reached significance in MDD, and the main candidate gene (SLC6A4) association was dismissed by recent meta-analyses

What is the explanation? Why can’t we find the genes for schizophrenia, dementia, or depression?

- Although psychiatric disorders have a high heitability we couldn’t identify individual genes or polygenic models.

- Gene-gene interactions? Epistatic and other regulatory mechanisms?

- Is there any other factor that we should consider?

Health Tip

Obesity doesn't run in family. The main problem is nobody runs in the family.

Gene-Environment Interactions

- Refers to the phenomenon where genetic and environmental factors both play a role in the etiology of a disease and possibly strengthen each others effect.
- Especially important in chronic non-communicable diseases and psychiatry.
- Elucidating GxE interactions can lead to better
- prevention and therapeutic measures.
- The field is connected closely to psychiatric
- genetics.

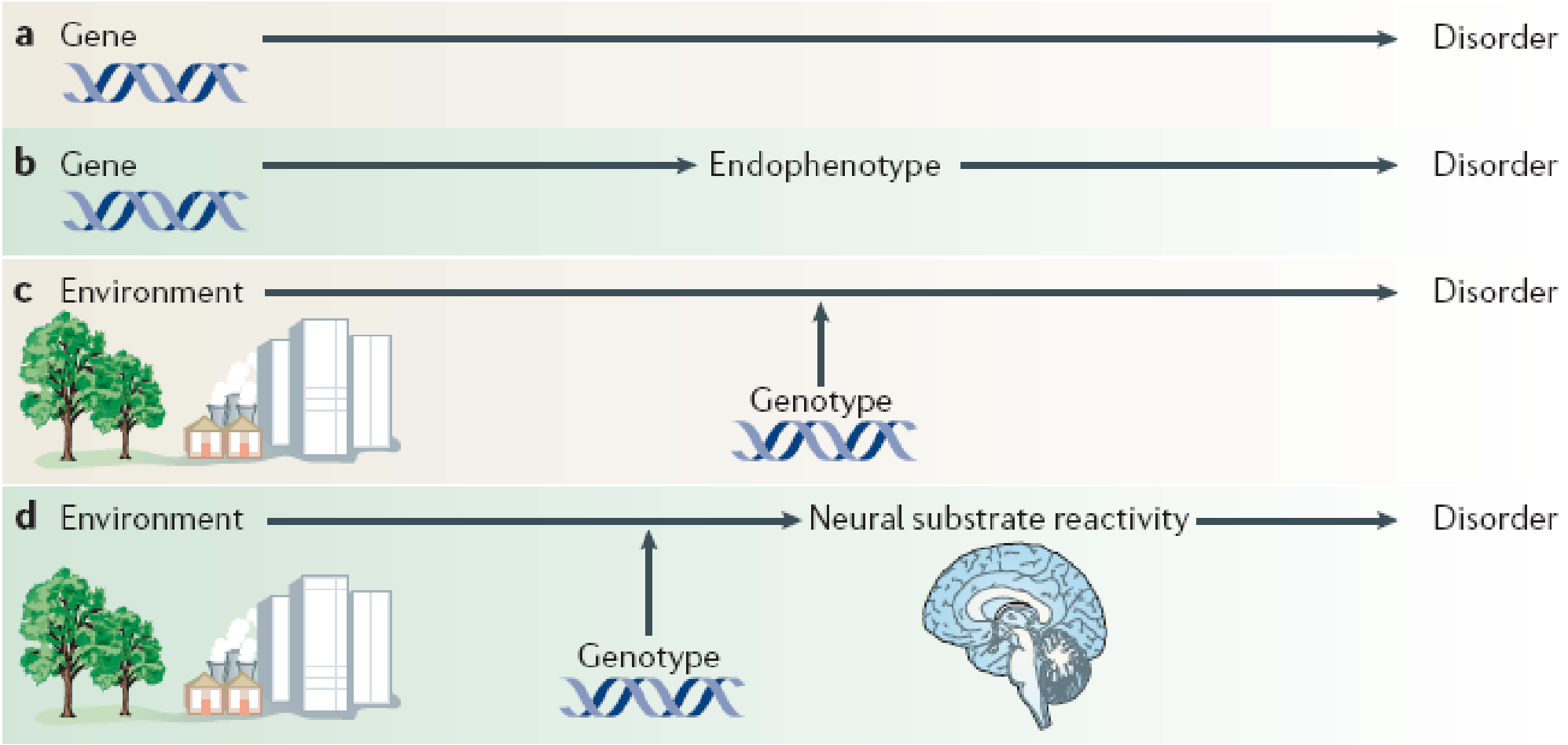


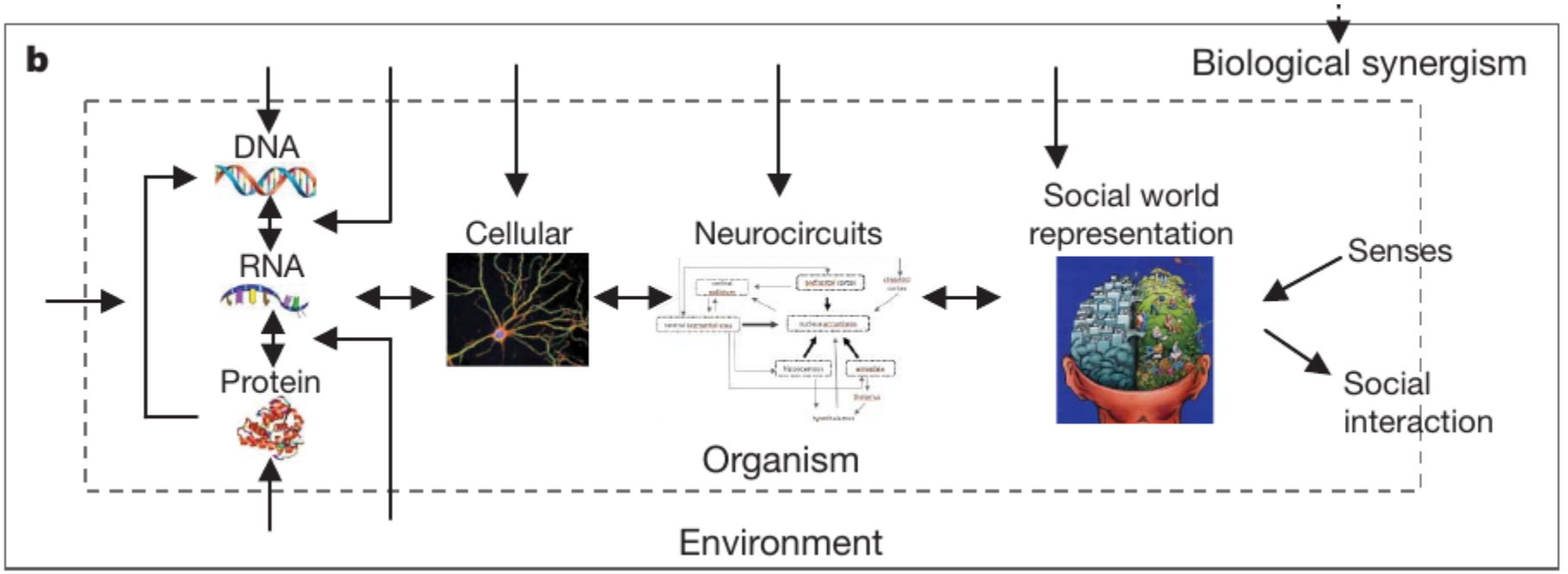
Figure 1 | **Approaches to psychiatric genetics research. a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder. **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. **c** | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. **d** | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.

Gene-Environment Interactions

- Synergistic: G and E factors enhancing each others' effect
- Antagonistic: G and E suppress each other

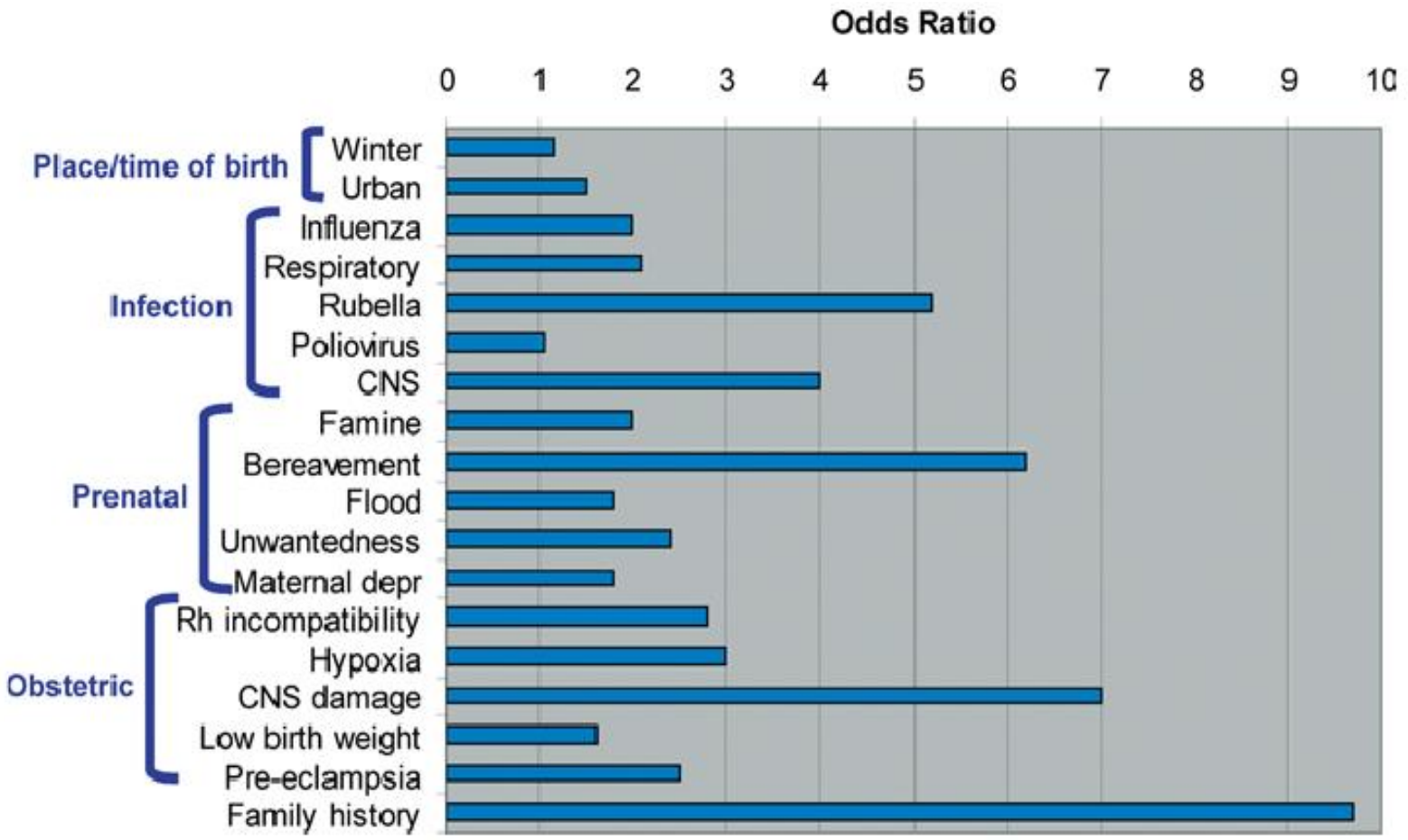
- Vulnerability model: G predispose a sensitivity towards E stressors
- Plasticity model: G may confer susceptibility, but can be beneficial in optimal E

Gene-Environment Interactions



From: van Os et al., 2010. The environment and schizophrenia. *Nature*

Environmental risk factors in schizophrenia



From: Sullivan, 2005. The Genetics of Schizophrenia. *PloS Medicine*

Environmental risk factors in schizophrenia

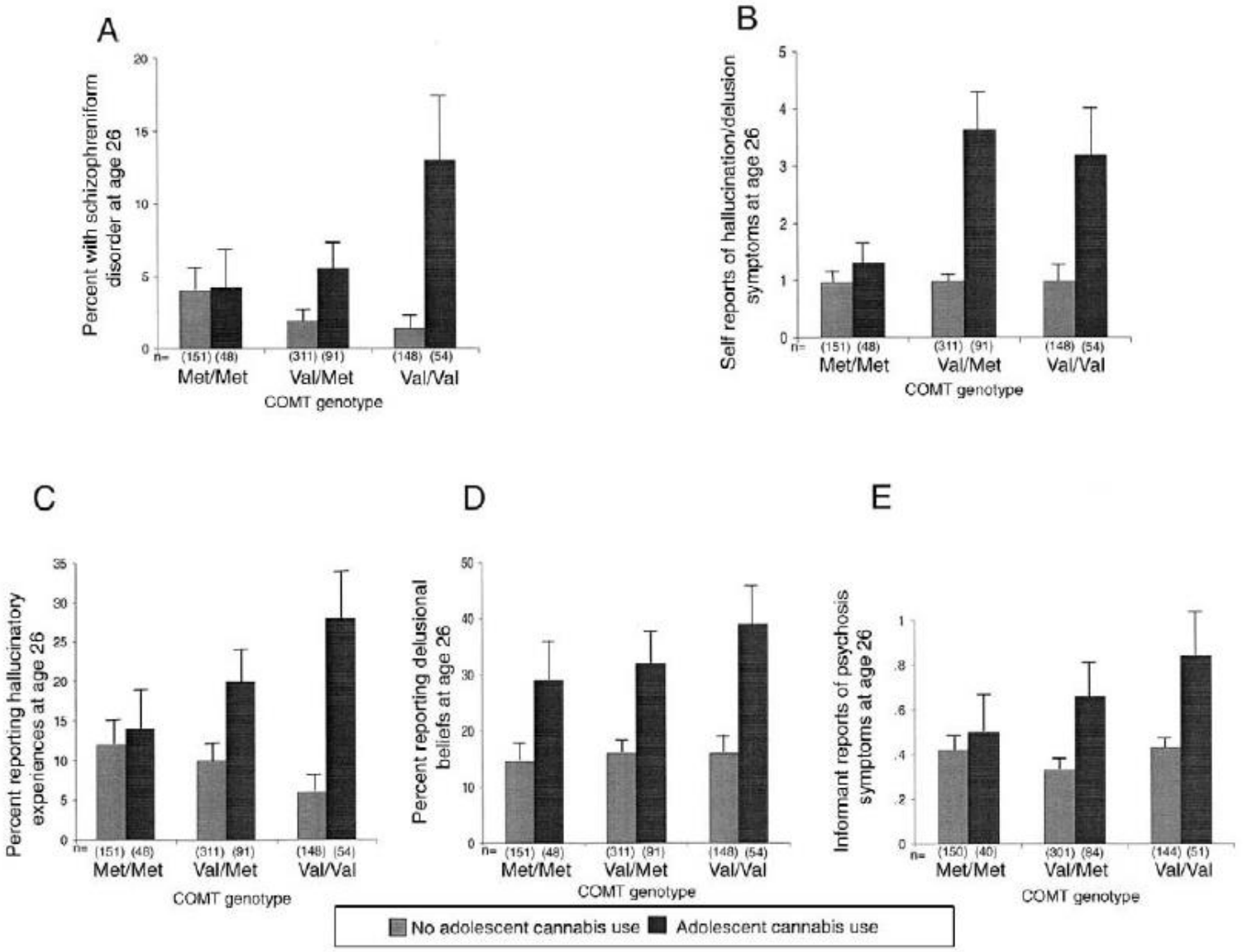
From: van Os et al., 2010. The environment and schizophrenia. *Nature*

Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction

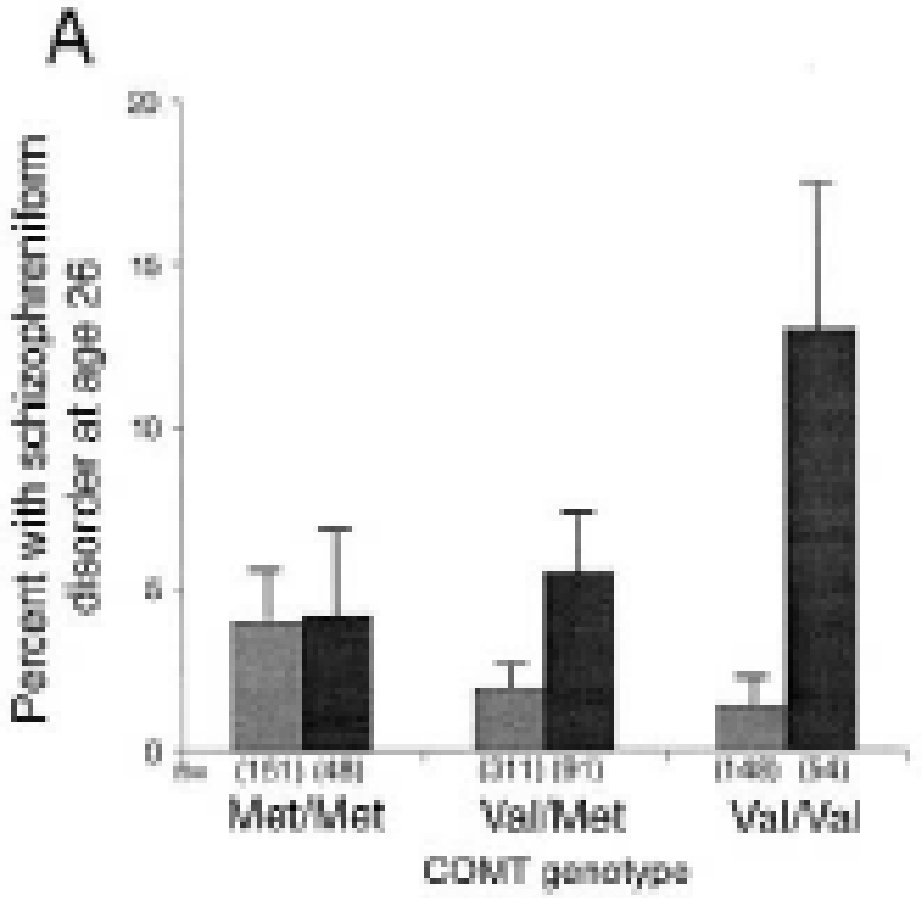
- Epidemiological cohort study: Dunedin (New-Zeeland)
- Catecholamin-O-methyltransferase: role in the break-down of dopamine
- missense mutation that generates a valine (Val) to methionine (Met) substitution at codon 158 ($Val^{158}Met$),

Caspi et al, 2005

The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene



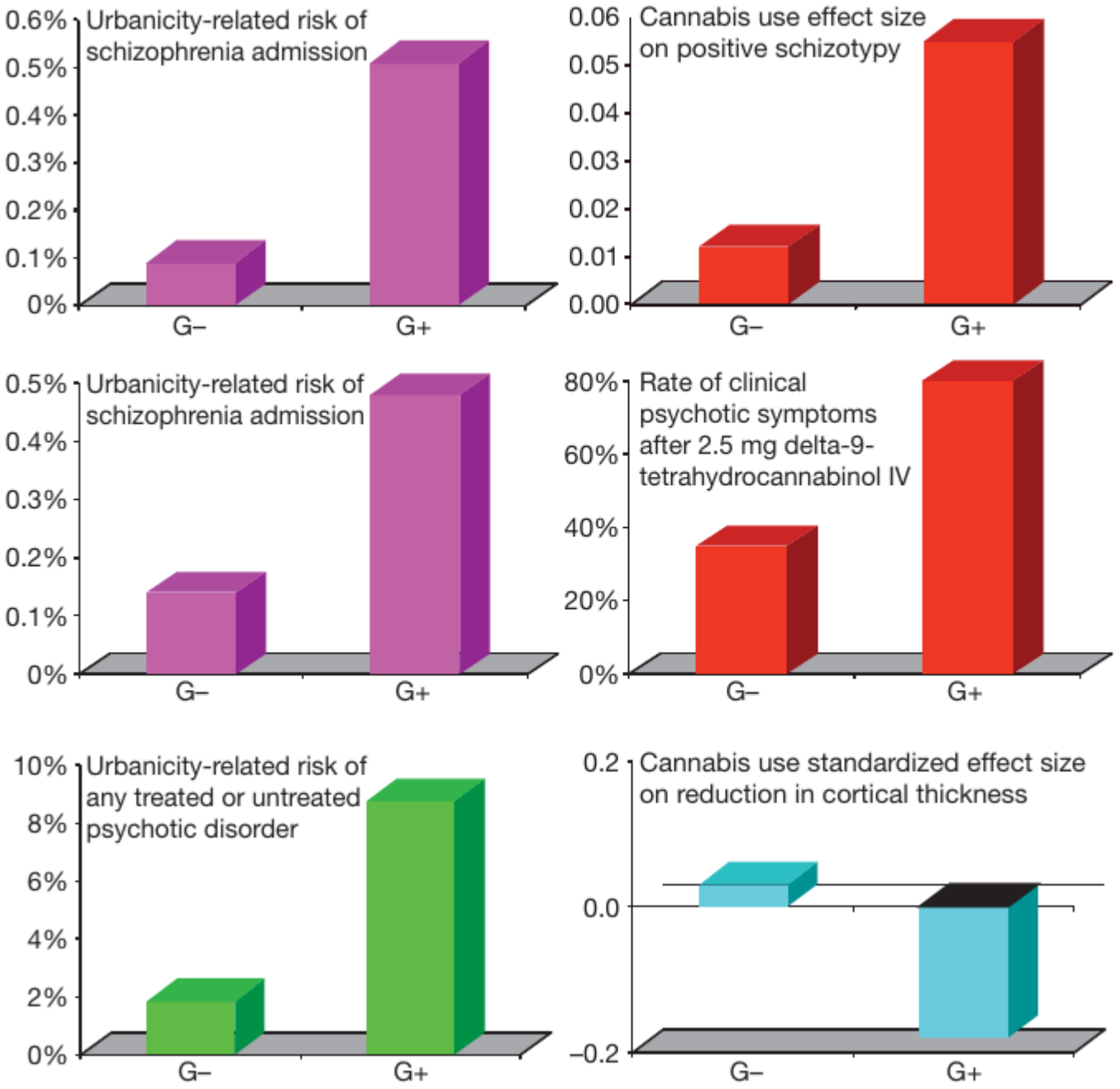
Caspi et al, 2005.



13% of individuals carrying the Val/Val genotype and using cannabis had schizophreniform disoder

Good idea to genotype yourself before you fly to Amsterdam.

GxE effect on psychotic outcomes



From: van Os et al., 2010. The environment and schizophrenia. *Nature*

The „multiple-hit” neurobiological model of schizophrenia

„First hit”

Genetic risk, prenatal risk

„Second hit”

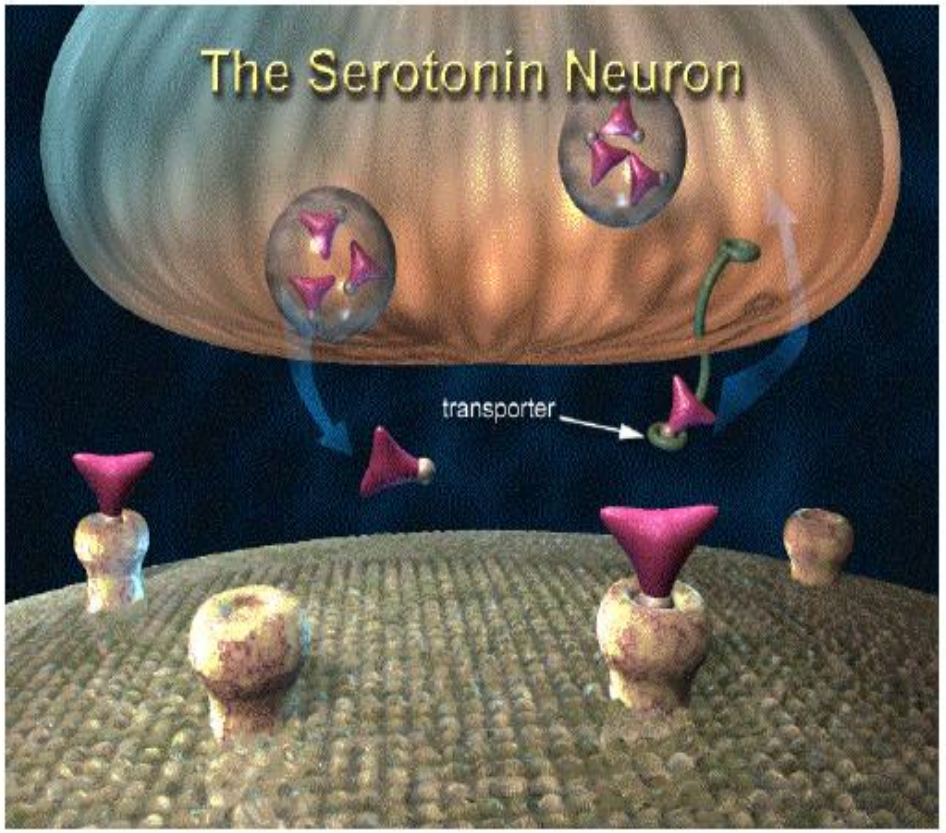
Manifestation of the disease

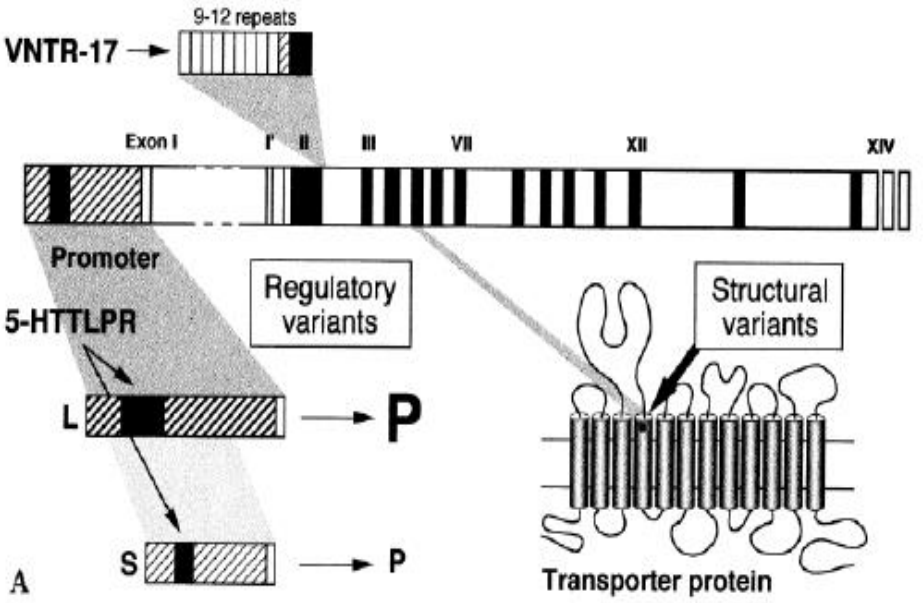
„Third hit”

Deficit-schizophrenia

Non Deficit-schizophrenia

Serotonin transporter (SLC6A4, 5-HTT)

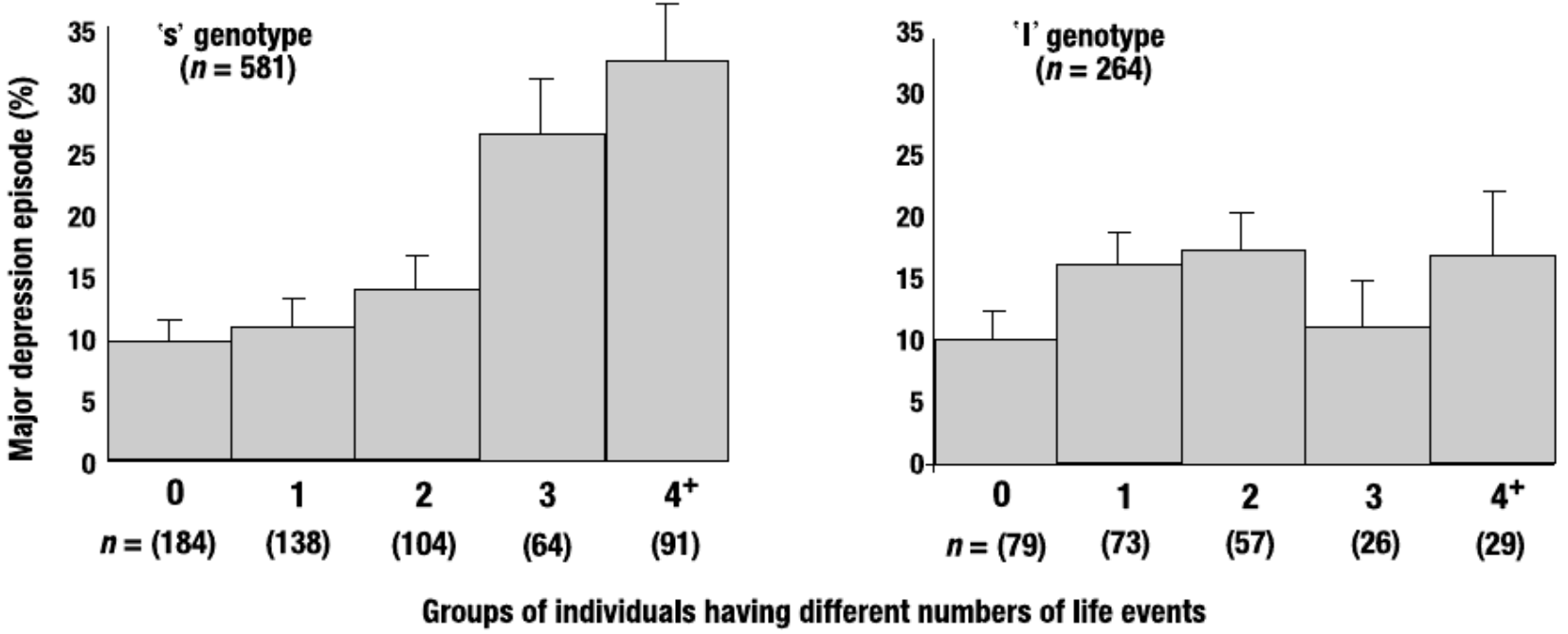




Lesch et al, 1998

Location: 17q11.2
Major regulatory element in the serotonin transmission and primary target of antidepressant (SSRI) medications
S allele (14 repeats) -> reduced expression level and slower serotonin turnover
L allele (16 repeats) -> normal expression level and serotonin turnover

Influence of Life Stress on Depression: Moderation by 5-HTTLPR



From: Caspi et al, 2003. Science

Influence of 5-HTTLPR on Depression: Moderation by Environmental Risk

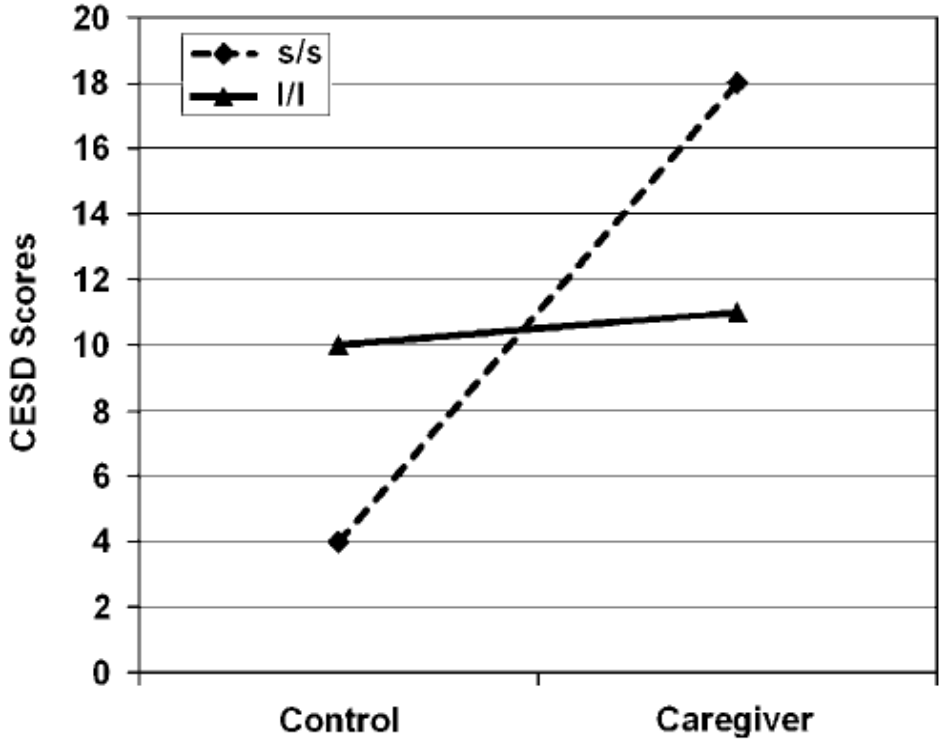


Figure 1 Center for Epidemiological Studies-Depression (CESD) scores for female caregivers and non-caregiver controls by 5-HTTLPR genotype (Brummett *et al.*[27]).

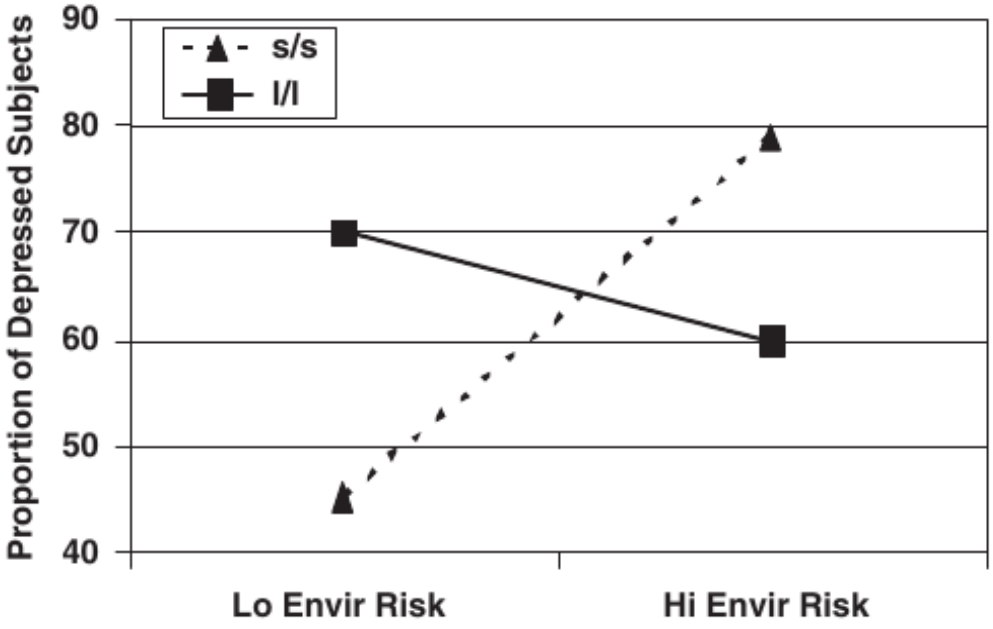
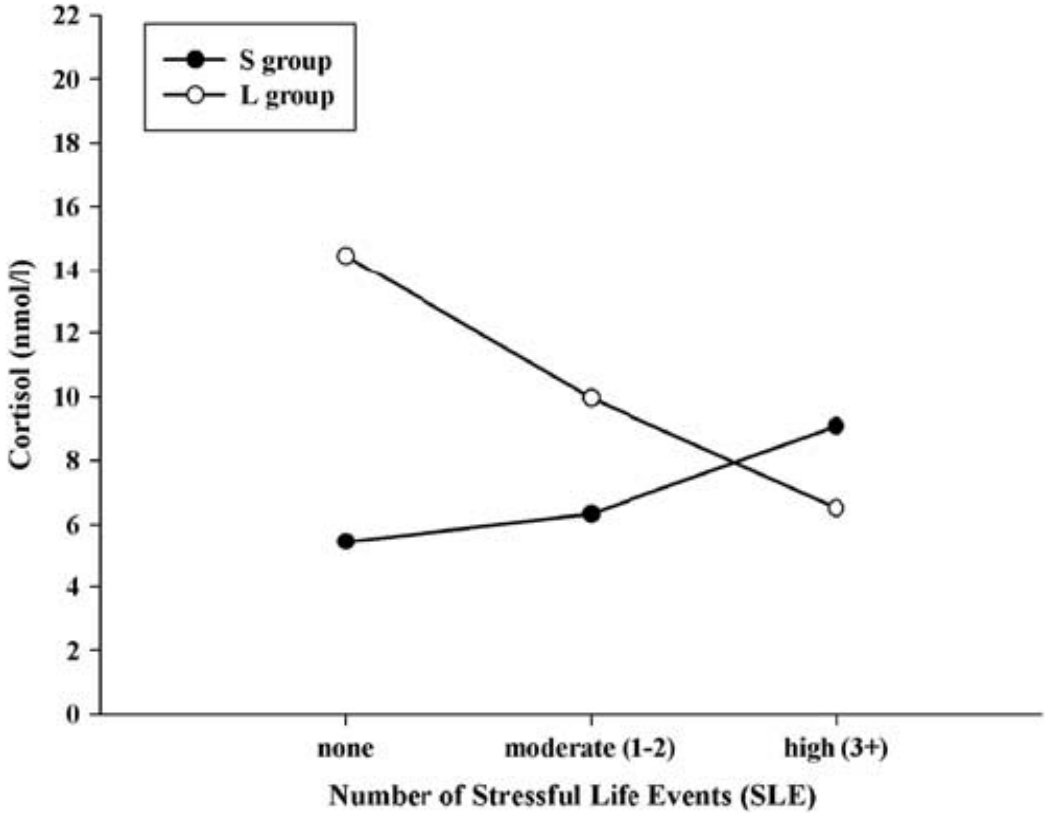


Figure 2 Proportion of female participants with a high level of depression by environmental risk group and 5-HTTLPR genotype (Eley *et al.*[28]).

From: Belsky et al., 2009. Vulnerability genes or plasticity genes? *Molecular Psychiatry*

Influence of 5-HTTLPR on Stress-Reactivity: Moderation by Environmental Risk



From: Muller et al, 2011. Interaction of Serotonin Transporter Gene-Linked Polymorphic Region and Stressful Life Events Predicts Cortisol Stress Response. *Neuropsychopharmacology*

Sounds good so far, but…

Reanalysis of the original data, and new data from the 30 year follow-up study (Dunedin cohort)(Fergusson et al, 2012, Munafò et al., 2009, Risch et al, 2009) don’t support the original interaction between 5-HTTLPR and stressful life events.

The interface of GXE: The epigenome

- Epigenome: Charactreistics of the genome that are not related to the DNA-sequence (DNA methylation pattern, histon acethylation or methylation, chromatin structure)
- Many changes in early phases of development (malnutrition, parebtal neglect, abuse)
- Tissue-specific
- Epigenetic changes can be inherited up to 3 generations

Epigenetics findings

- Methylation status of BDNF promoter is associated with MDD in a Japanese sample (Fuchikami et al, 2011).

- Voluntary exercise in mice induces demethylation in neurons (Pinilla-Gomez, 2012)

- Intense exercise and IL-1ß, TNF-α change in humans predicts remission of patients with depression (Rethorst et al., 2012)

SCIENCE VOL 319 18 JANUARY 2008

Critics of the scientific community: Current results don't support the use of genetical testing for diagnostic purposes.

Ethical problems!

Players in the Psychiatric Gene-Testing Business

Company	Test available	Disease	Type of test	Number of genes
NeuroMark	mid–2008	Major depression	Risk of suicidality from antidepressants	4
Psynomics	now	Bipolar disorder	Diagnosis and response to antidepressants	2*
SureGene	mid–2009	Schizophrenia	Risk of psychosis and response to antipsychotics	6

* Psynomics plans to add five more genes early this year.

Welcome to Psynomics

Psynomics is the first and only company in the world to offer DNA-based diagnostic and therapeutic tests to help millions of people suffering from mental illness.

Our first two products:

Psynome™ – tests for two mutations of a gene that are associated with bipolar disorder.

Psynome2™ –tests for gene mutations in the Promoter L allele gene that predicts patient response to serotonin-based drugs, the most commonly prescribed drug therapies in psychiatry today. These tests are useful to your doctor in making a timely and accurate diagnosis of your condition and prescribing the right medication. The tests can be ordered individually or combined.

LEARN
more about our company

Most comprehensive at-home DNA test

When you purchase our complete service, this is what you'll get:

Your risk analyzed for 119 diseases and traits, including:

- Breast Cancer
- Rheumatoid Arthritis
- Type 2 Diabetes

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- Hemochromatosis
- Restless Legs Syndrome
- Age-related Macular Degeneration
- Parkinson's Disease
- Coumadin® / Warfarin Sensitivity
- Plavix® Efficacy

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News and Press

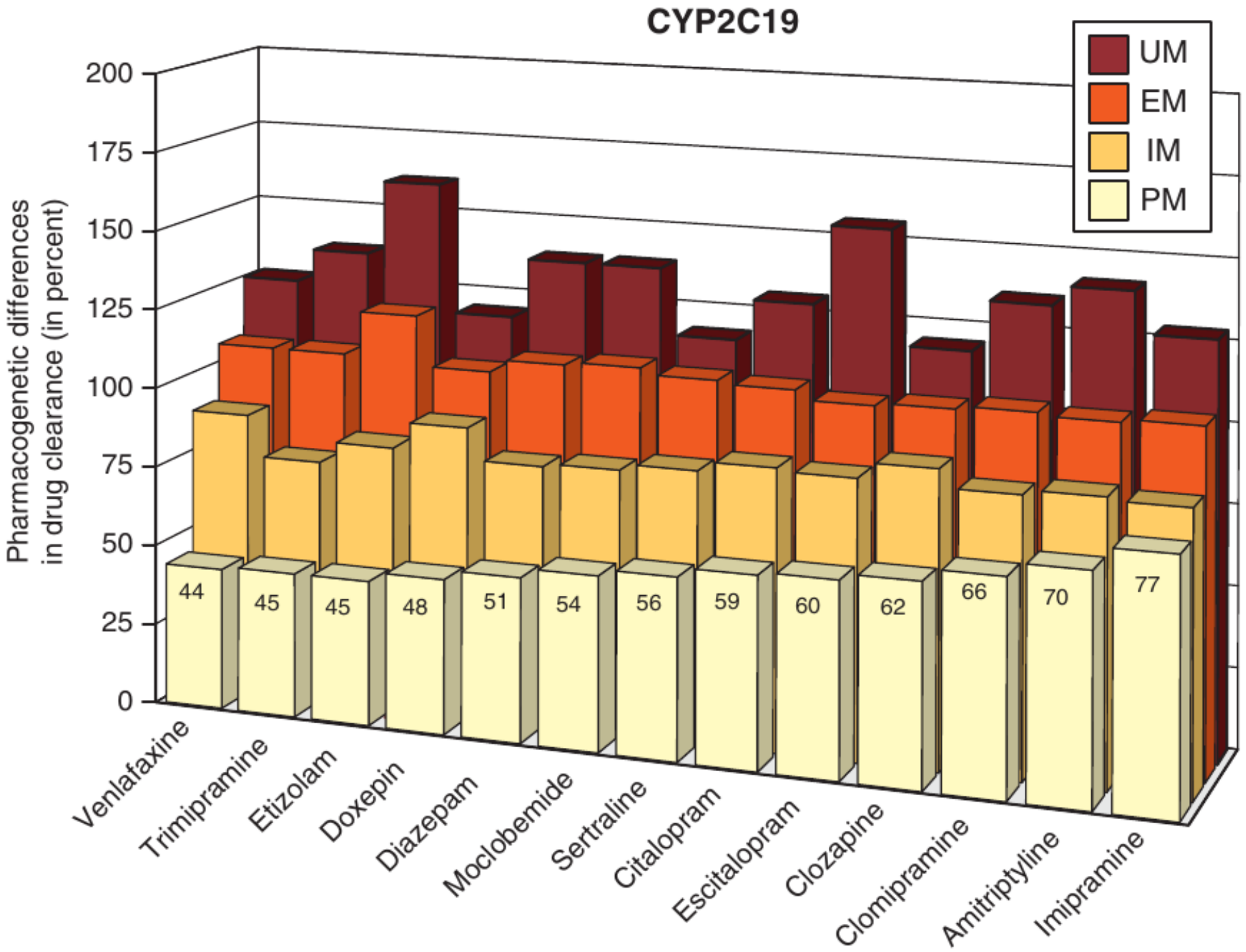
Introducing a Do-It-Yourself Revolution

Scientific Resources and Principles

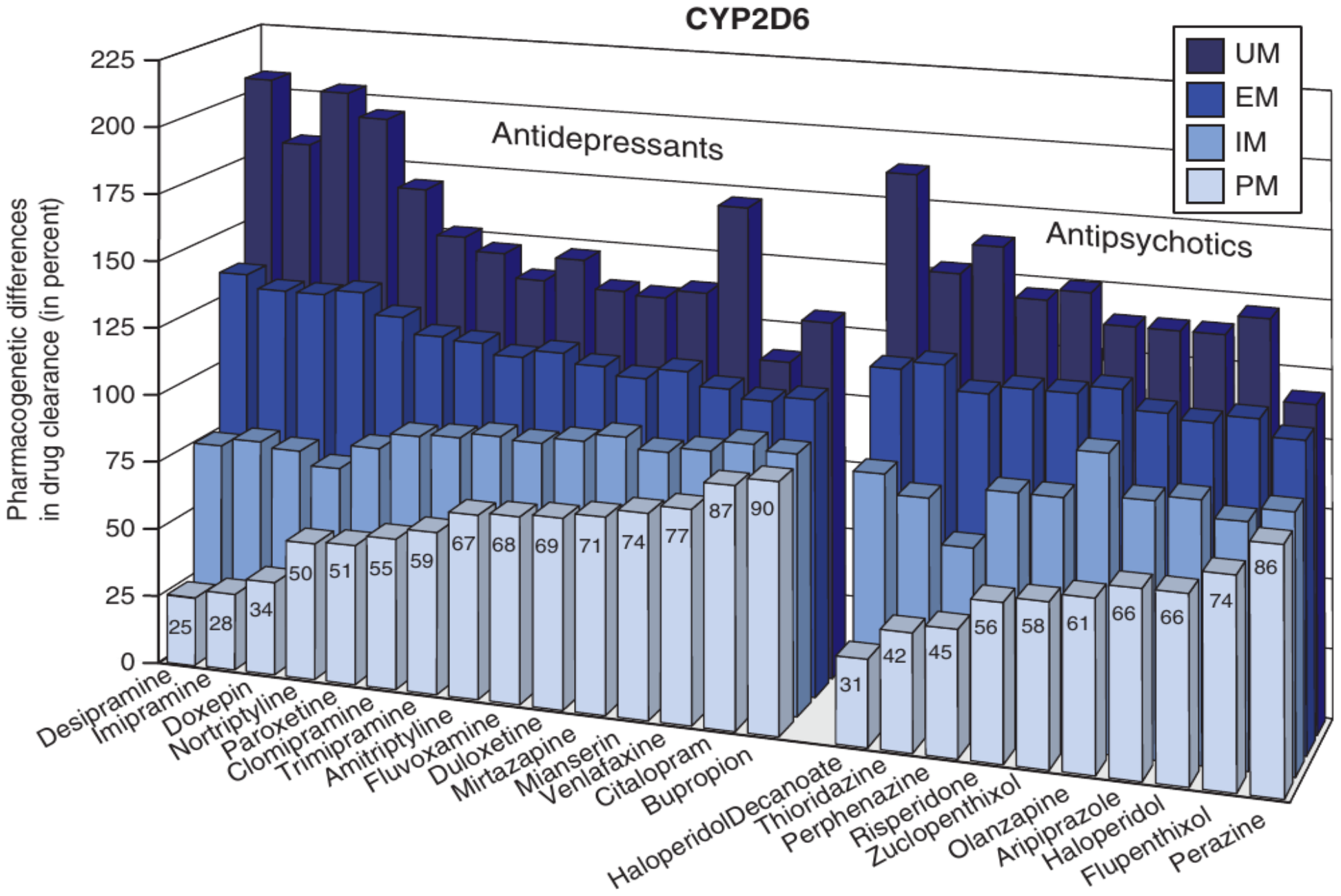
Physician Resources

GxE and Therapy

- Therapy itself is an environmental factor, introducing epigenetic modifications
- Pharmacogenetic variations are important in predicting treatment response (eg. COMT Val158Met, CYP2D6, CYP3A4, HTR2A polymorphisms on response to clozapin)
- CYP2D6, CYP2C19 poor or ultrarapid metabolizers need personalized dosage of psychotrop meds

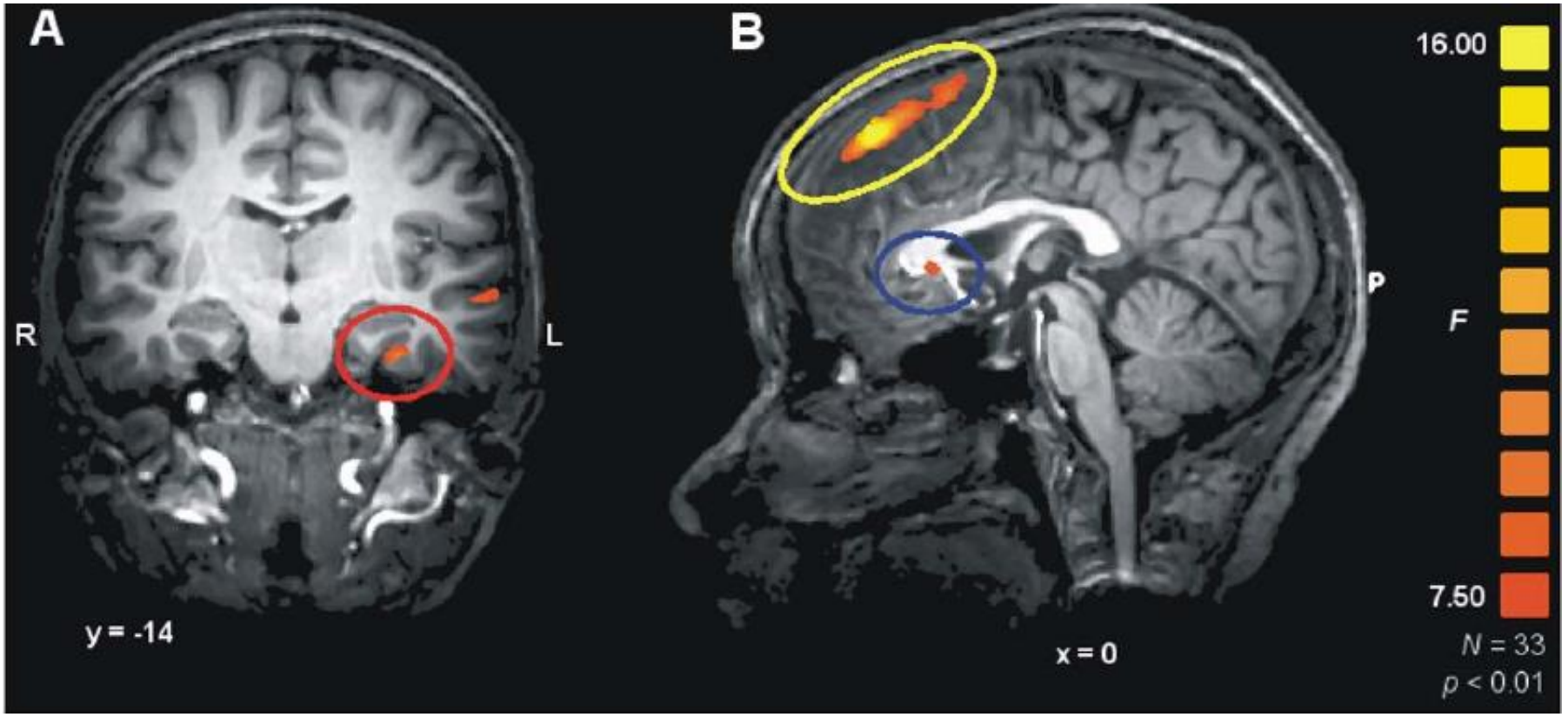


From: JC Stingl et al., Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psych (2012), 1-15



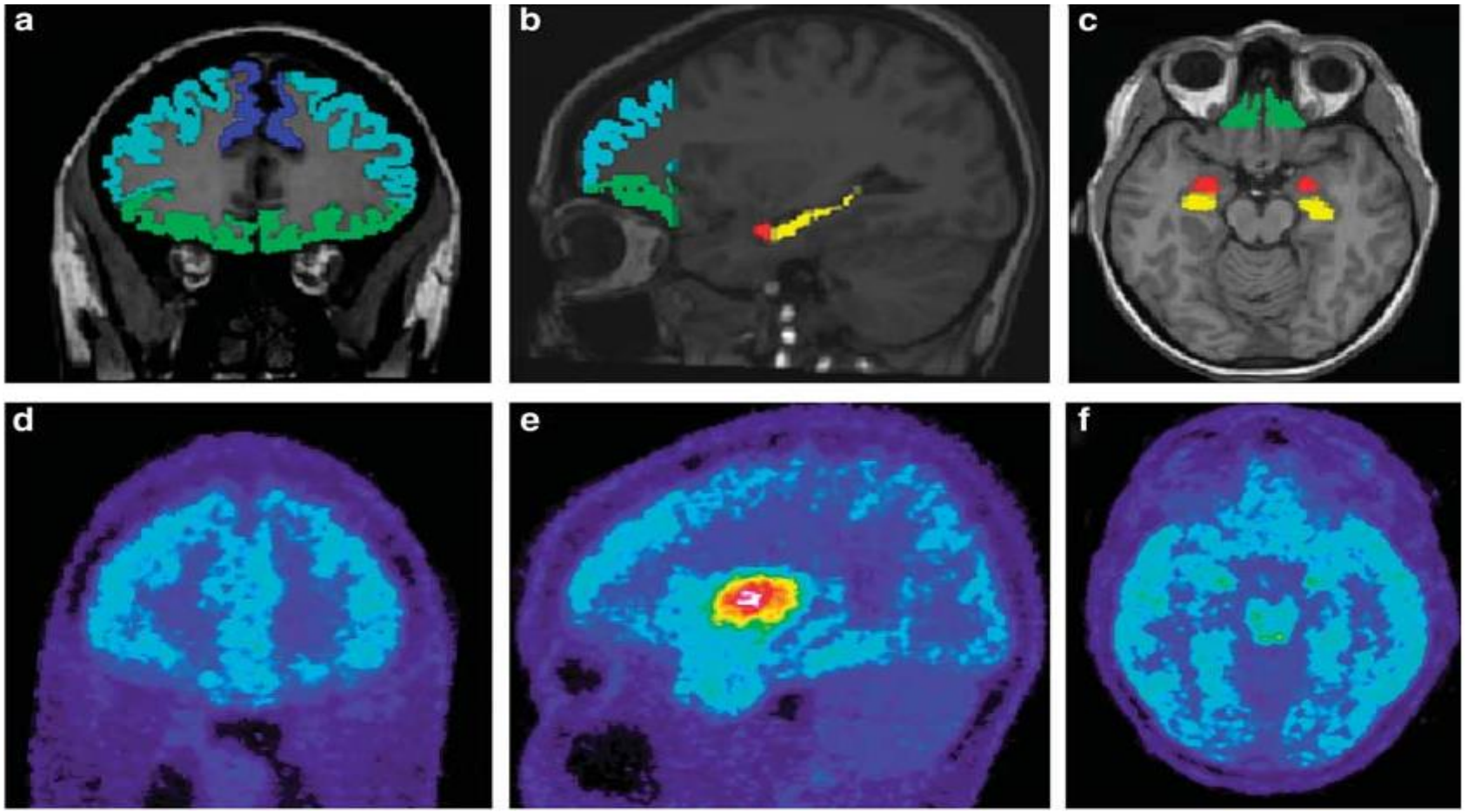
From: JC Stingl et al., Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psych (2012), 1-15

Changes in activity of amygdala, prefrontal cortex and hippocampus in depressed patients after successful psychodynamic psychotherapy



Buchheim et al., 2012

Differences in D2 receptor binding after successful cognitive-behavior therapy in patients with social anxiety



From: Cervenka S. et al, 2012

Take-home messages

- Genetic and environmental factors are both extremely important in the etiology of psychiatric disorders
- Schizophrenia: high heritability, demonstrated gene-environment interactions for urban upbringing and cannabis use.
- Major depression: moderate level of heritability, demonstrated interactions between HTTLPR and stressful life events
- Understanding gene-environment interactions is very important for the treatment as well

Thank you for your attention!

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