Genes and environment:

The complex etiology of psychiatric disorders

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Outline

1. Introduction to psychiatric disorders

2. Methods used in psychiatric genetics

3. Psychiatry in nutshell, genetic characteristics

4. Environment steps in: gen-environment interactions

5. Therapeutic considerations

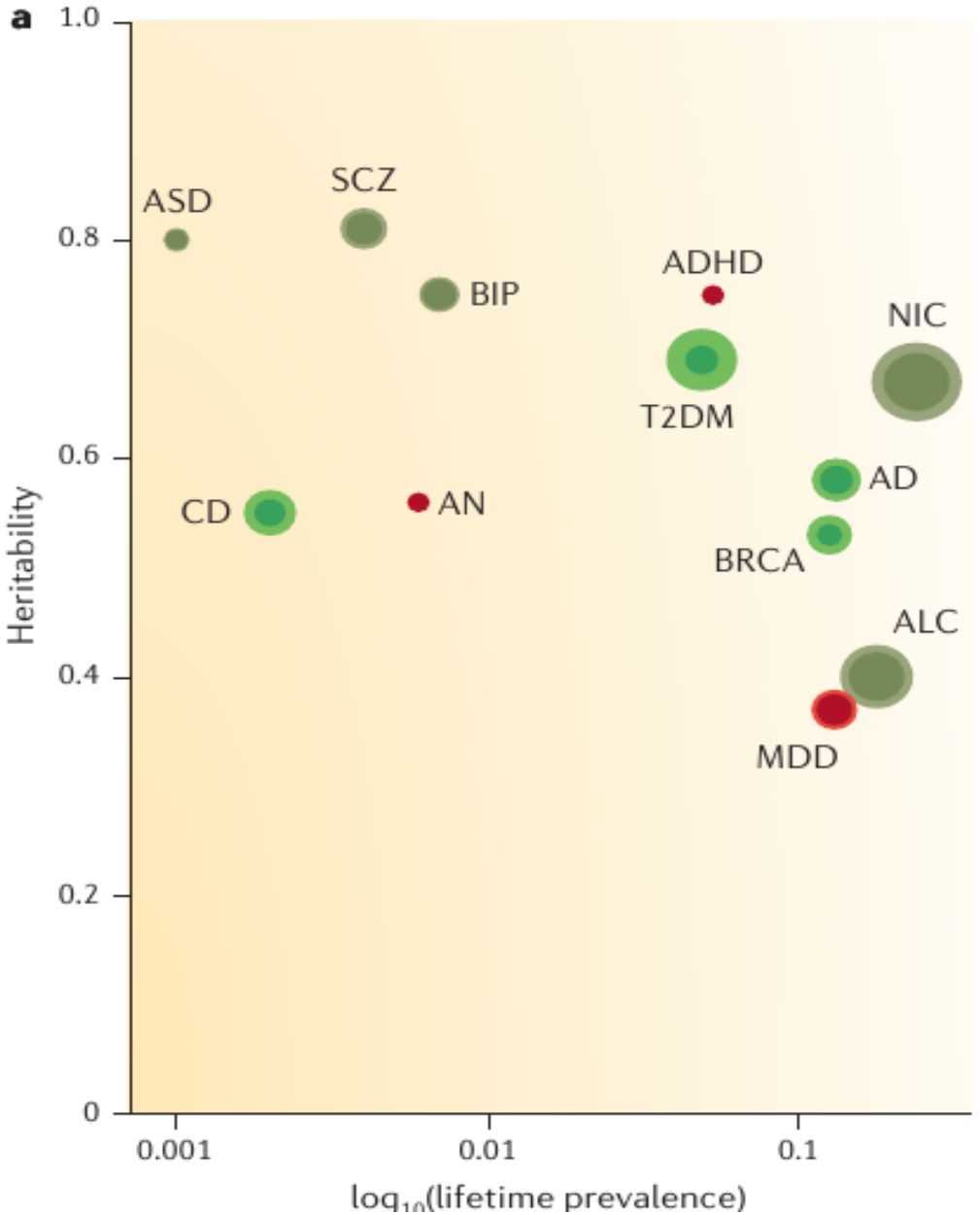
Psychiatric disorders

- 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)

- So 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 its implications. *Nature*

Genetic studies

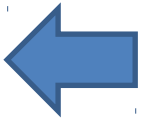
- Population genetics:
  - Family studies
  - Twin studies
  - Adoption studies
- Epidemiologic studies:
  - Genetic cohorts
- Molecular methods
  - Linkage studies
  - Association studies
  - Expression studies
  - (epigenetic analyses)
- Animal models

A typical genetic analysis workflow

Population studies

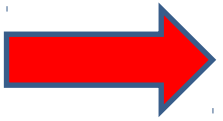
Molecular methods

Candidate genes
(polymorphisms)



biological hypotheses

Epidemiologic analyses

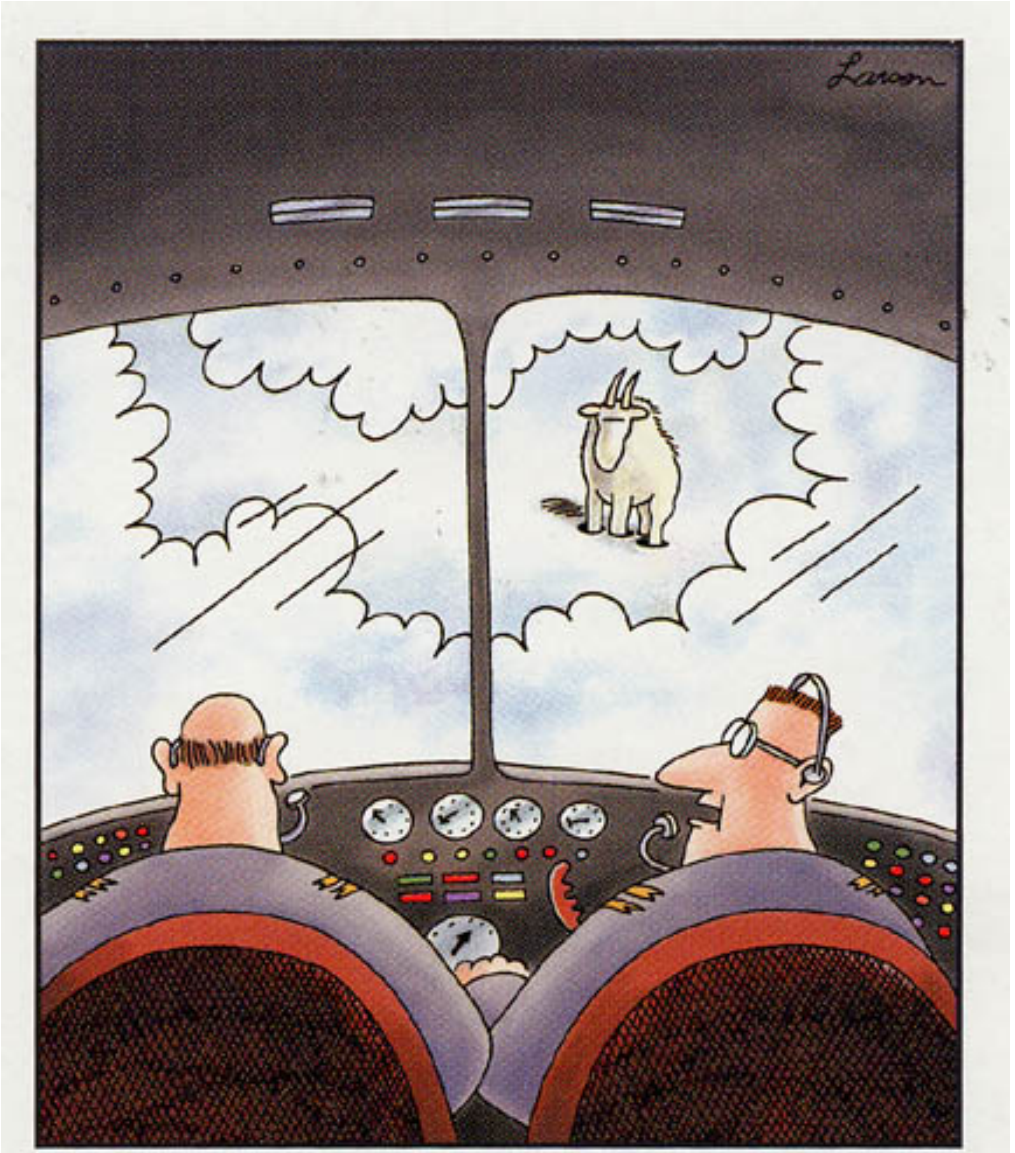


Genetic Risk

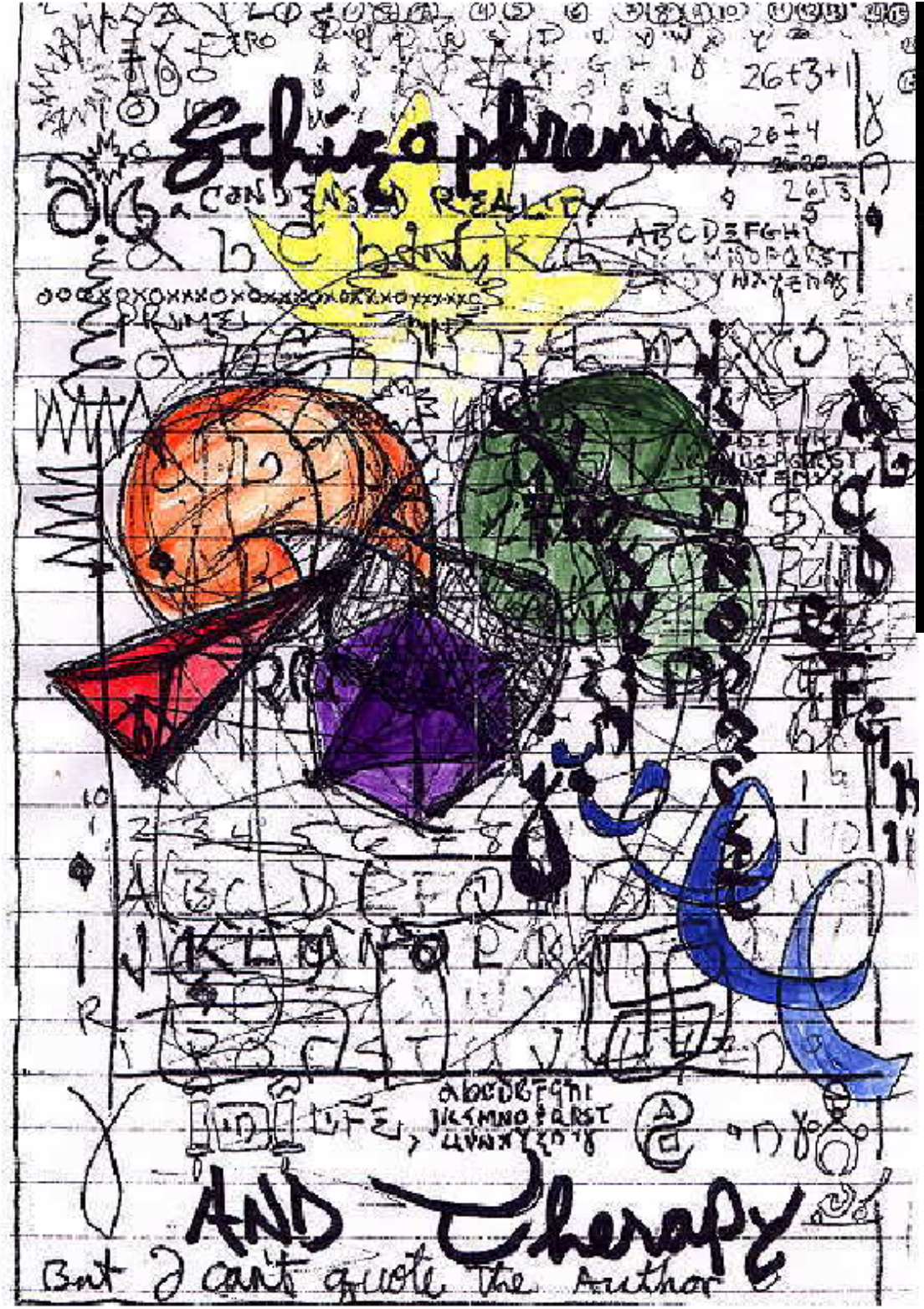
Results of GWAS Studies…

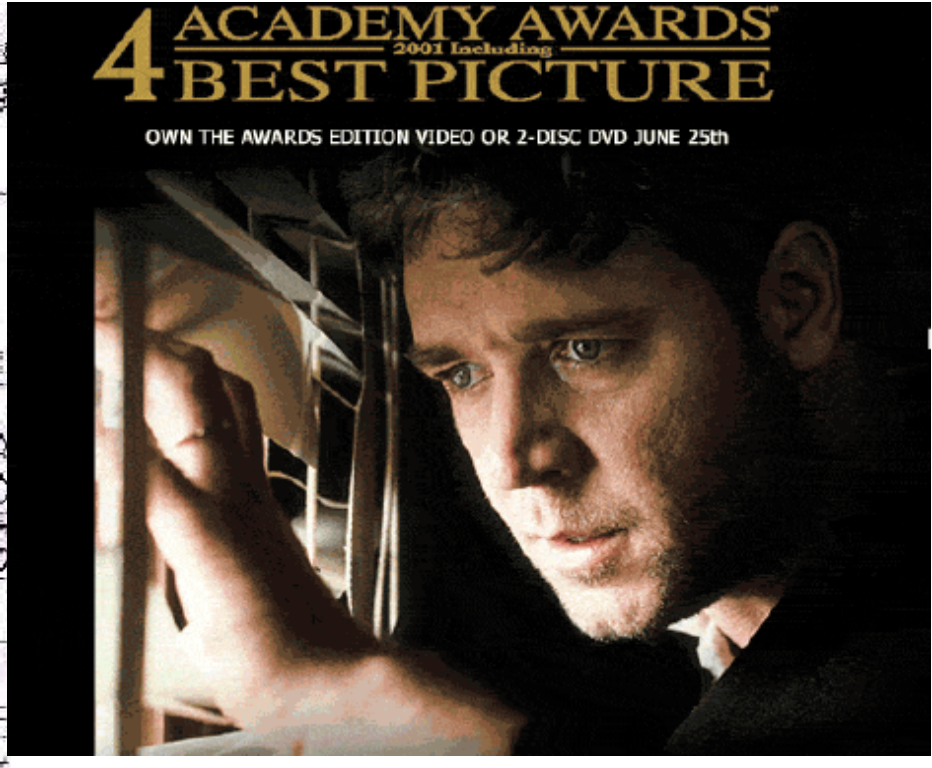
Phenotype	SNP	Location	Discovery GWAS (cases/controls)	Largest meta-analysis (cases/controls)	*P* value	Odds ratio	Nearest gene
Alzheimer's disease	rs3818361	chr1:207784968	2,018/5,324 (REF. 34)	<19,870/39,846 (REF. 35)	3.7×10^{-14}	1.18	*CR1*
	rs744373	chr2:127894615	3,006/14,642 (REF. 193)	<19,870/39,846 (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*

…and their interpretation



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


Schizophrenia
AND Therapy
But I can't quote the Author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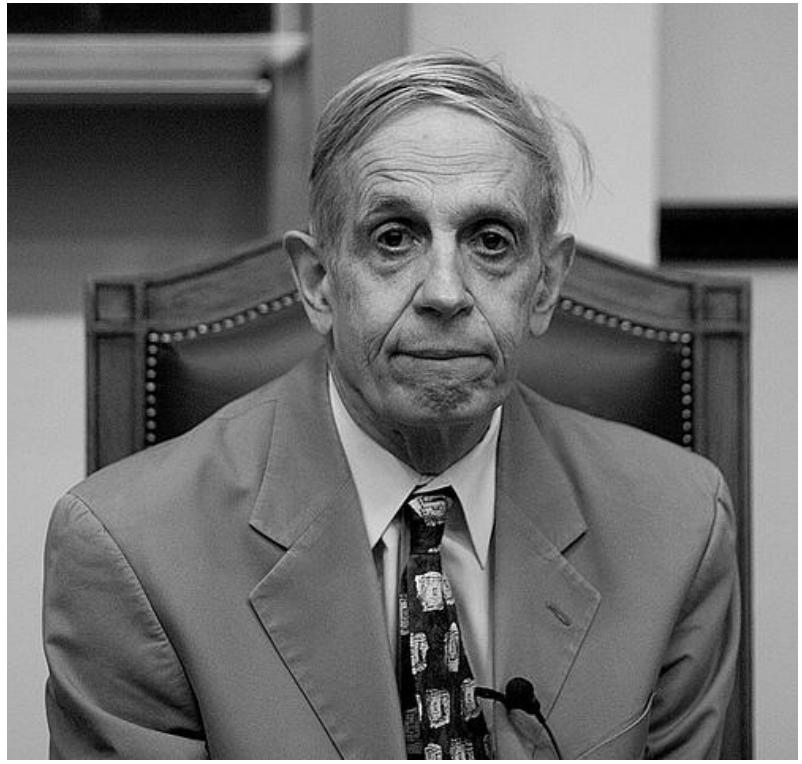


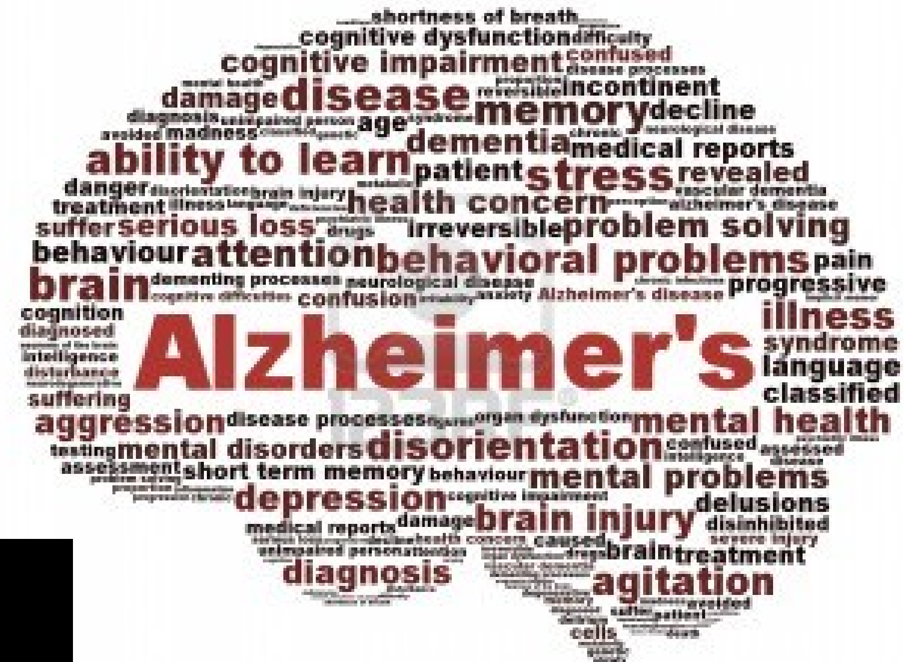
Schizophrenia

- Main symptoms: delusions, hallucinations, disorganized thoughts and behavior, affective disturbances, clustered to positive and negative symptoms
- 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


Science Photo Lib


shortness of breath
cognitive dysfunction
cognitive impairment
confused
damage
disease
memory
incontinent
decline
age
dementia
medical reports
ability to learn
patient
stress
revealed
danger
treatment
health concern
suffer
serious loss
irreversible
problem solving
behaviour
attention
behavioral problems
pain
brain
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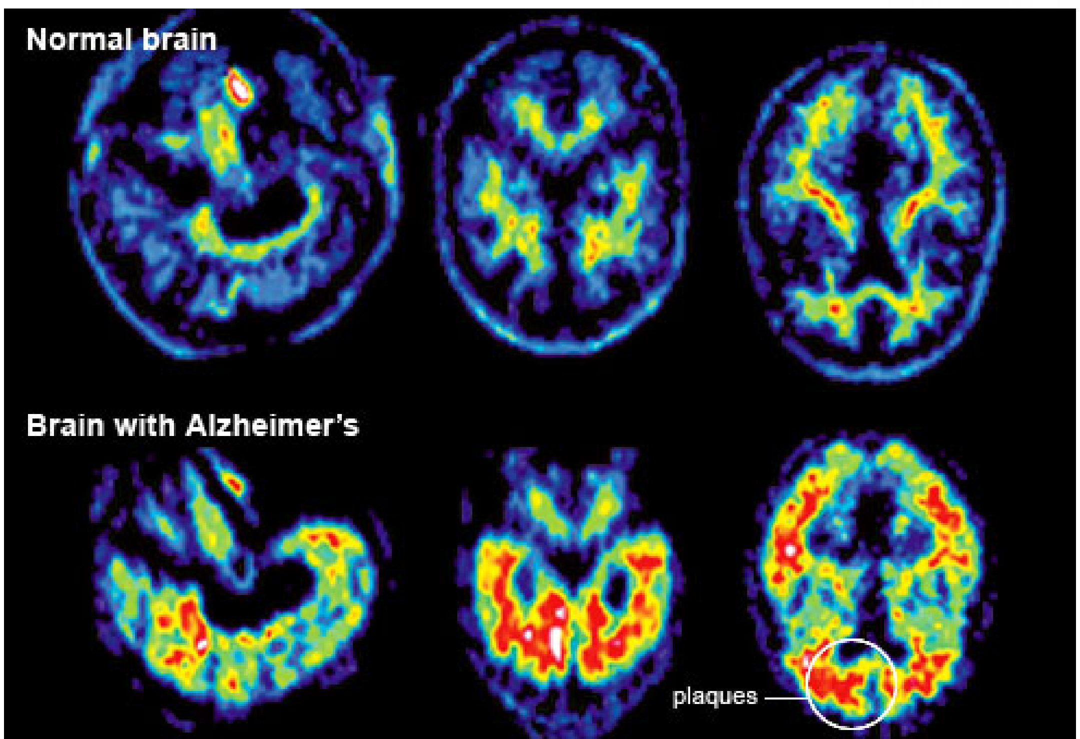
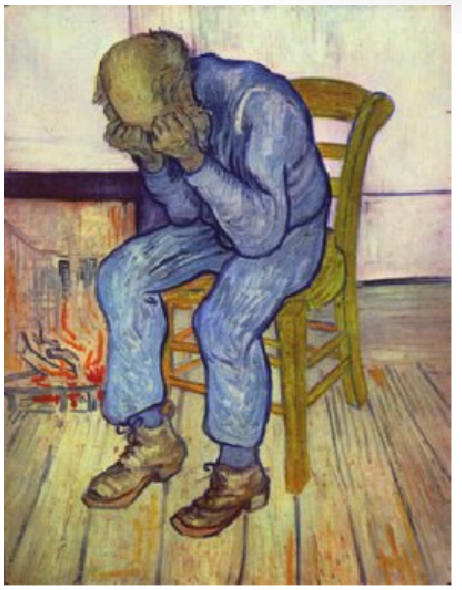

Normal brain
Brain with Alzheimer's
plaques

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, irritability
- Bipolar disorder: cycles of depression and mania, social disability, family problems, high suicide risk and comorbid substance use disorders



Genetics of mood disorders

- Highly prevalent disorders (MDD~15%, BD~6%)
- Familial transmission straightforward in BD (h^2: 0.8, MZ: 65%, DZ: 14%), moderate in MDD (h^2: 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

Posttraumatic stress disorder

- A highly disabling development of symptoms following extreme traumatic events, classified as anxiety disorder in the DSM-IV
- Prevalence of such events is 49-90%, but only 7-12% of the population develops PTSD
- Heritability: 0.3-0.35, shares a large amount a genetic factors with other anxiety disorders and substance use disorders
- No GWAS conducted yet, candidate genes are of HPA axis and monoaminergic pathways. None of the candidate genes associated with PTSD, only FKBP5 (a chaperon protein gene of the CRH receptor) showed significant interactive effect with alcohol dependence and childhood adversities on PTSD.

What’s going on?

- Polygenic inheritance suspected, but independent evaluation of the markers in GWAS studies implies monogenic model, need for statistical models of multimarker effect, e.g. pathway analyses

- We also need to consider epistasis and other gen-gen regulatory interplay

- Are we still missing something?

Health Tip

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

Gene-Environment Interactions

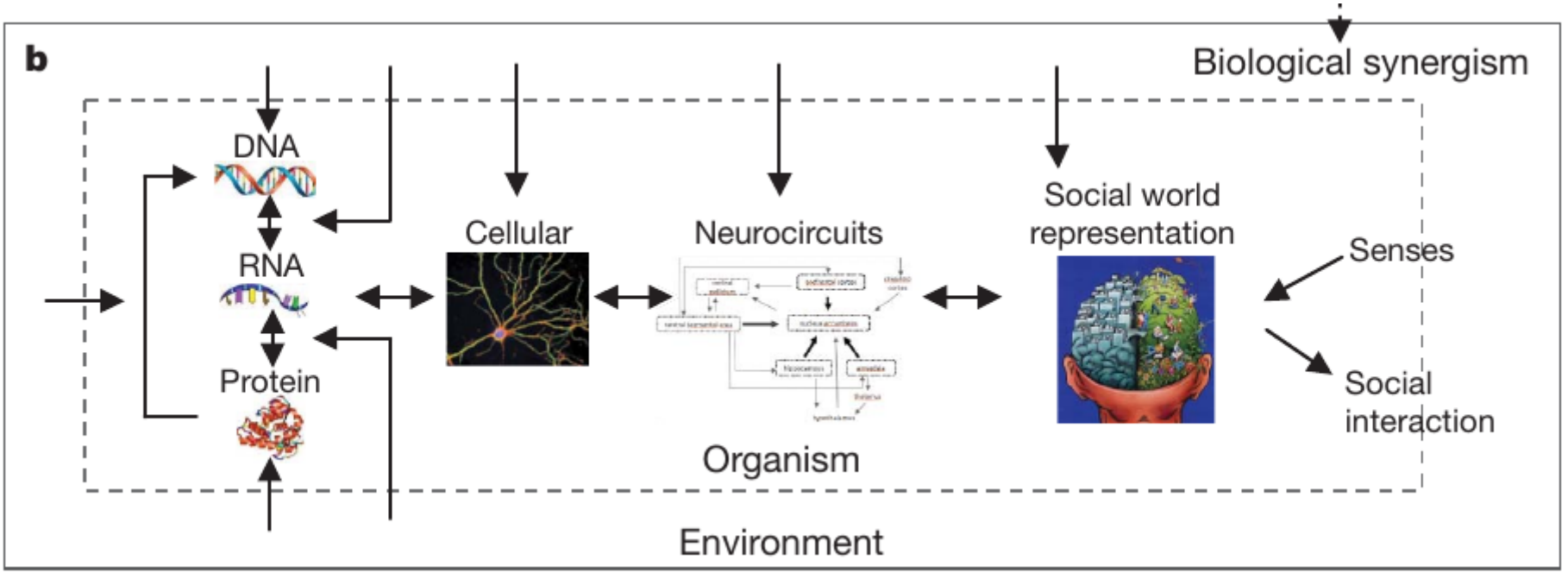
- Refers to the phenomenon where genetic and environmental factors both play a role in the etiology of a disease and possibly strengthen each others effect.
- Especially important in chronic non-communicable diseases and psychiatry.
- Elucidating GxE interactions can lead to better prevention and therapeutic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

Gene-Environment Interactions

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

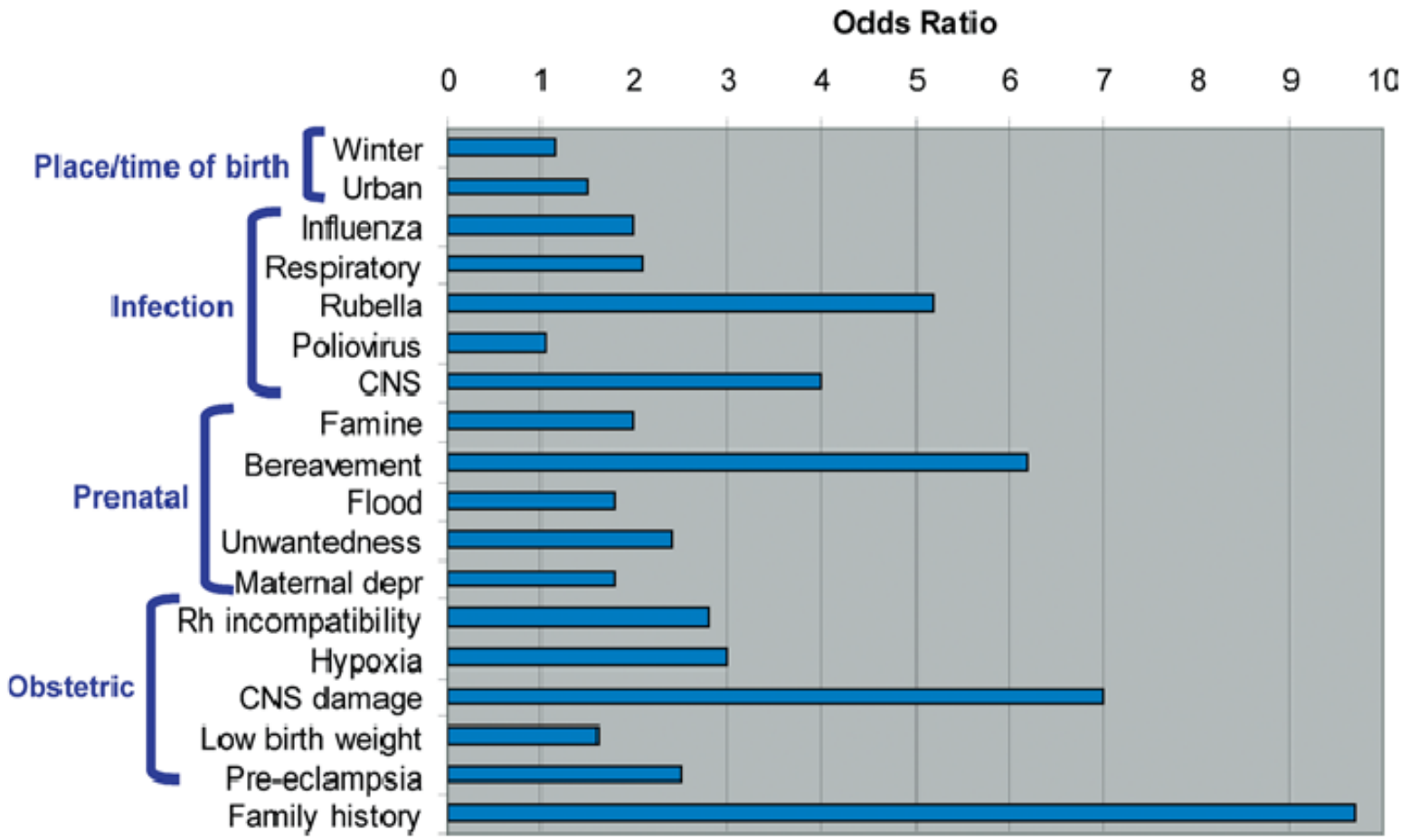
- Vulnerability model: G predispose a sensitivity towards E stressors
- Plasticity model: G may confer susceptibility, but beneficial in optimal E

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

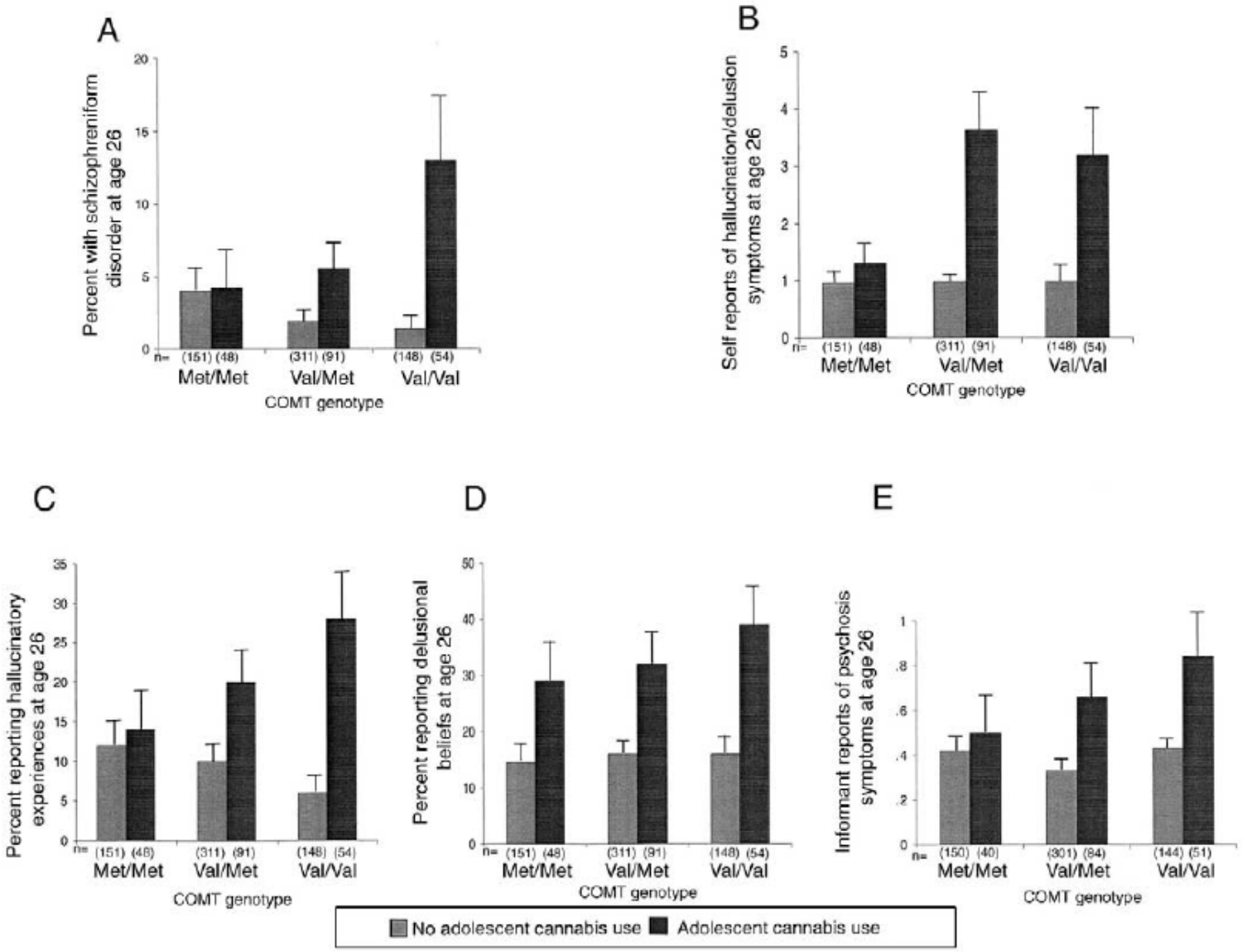
From: van Os et al., 2010. The environment and schizophrenia. *Nature*

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 ($Val^{158}Met$),

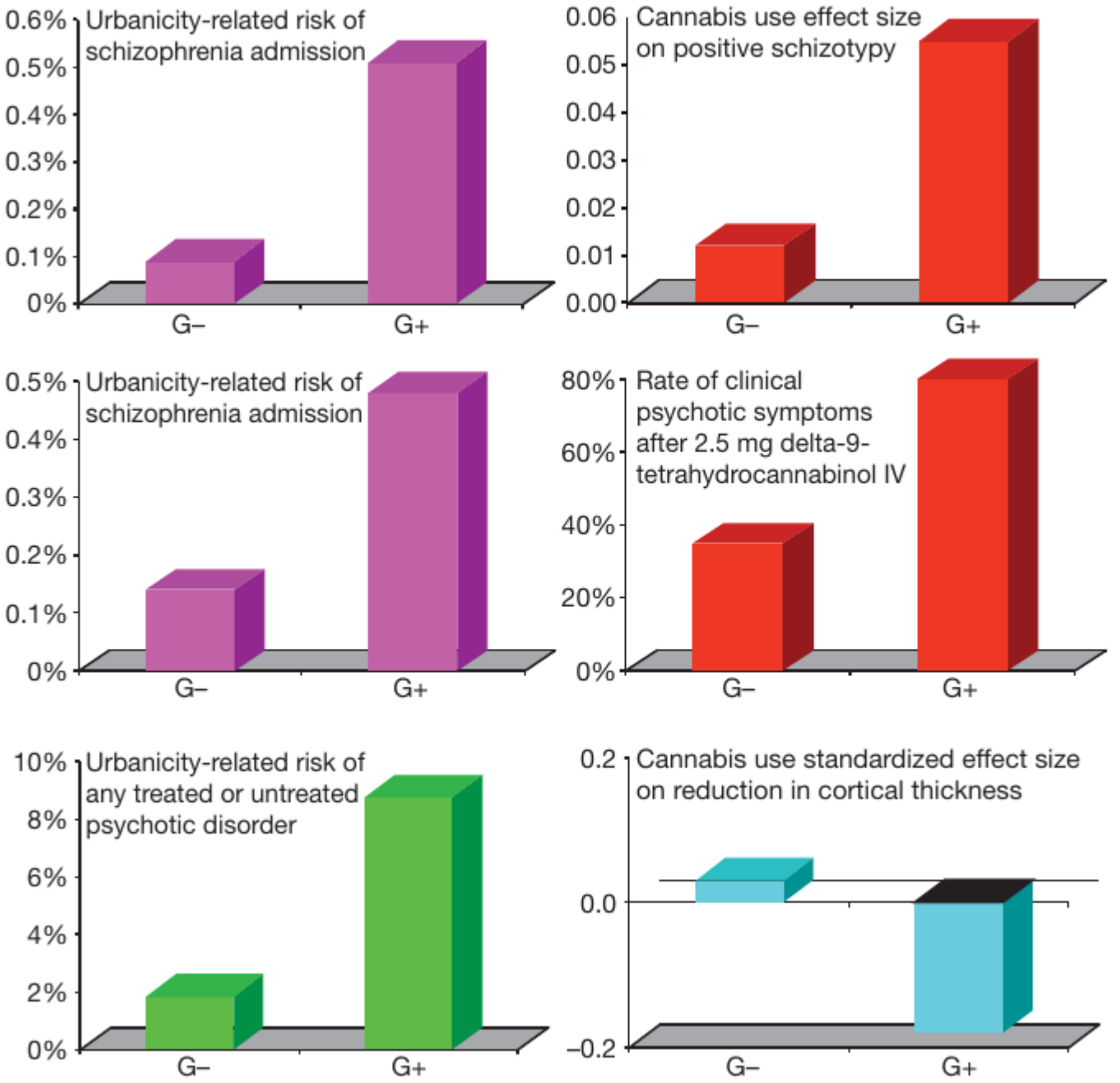
Caspi et al, 2005

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



Caspi et al, 2005.

GxE effect on psychotic outcomes



G+: at familial risk
G-: low-risk group

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”

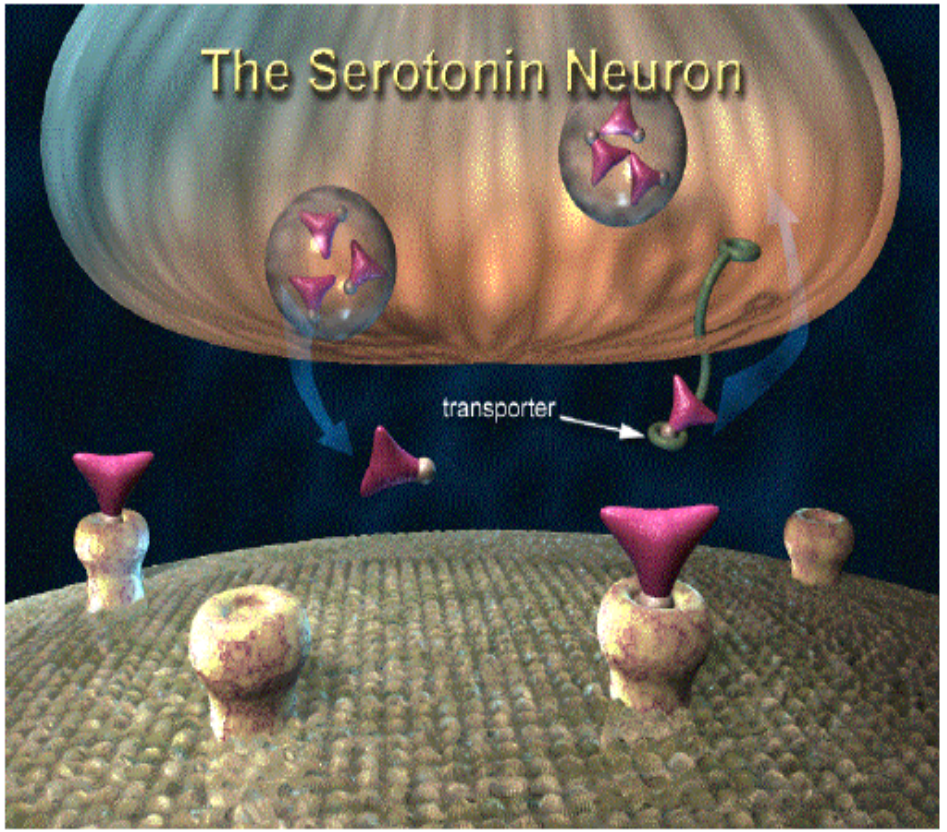
Manifestation of the disease

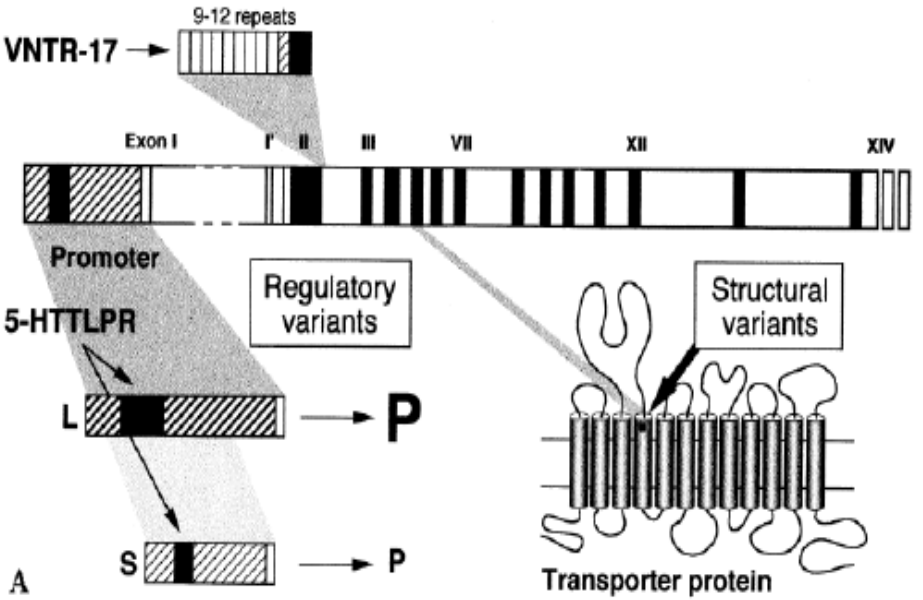
„Third hit”

Deficit-schizophrenia

Non Deficit-schizophrenia

Serotonin transporter (SLC6A4, 5-HTT)



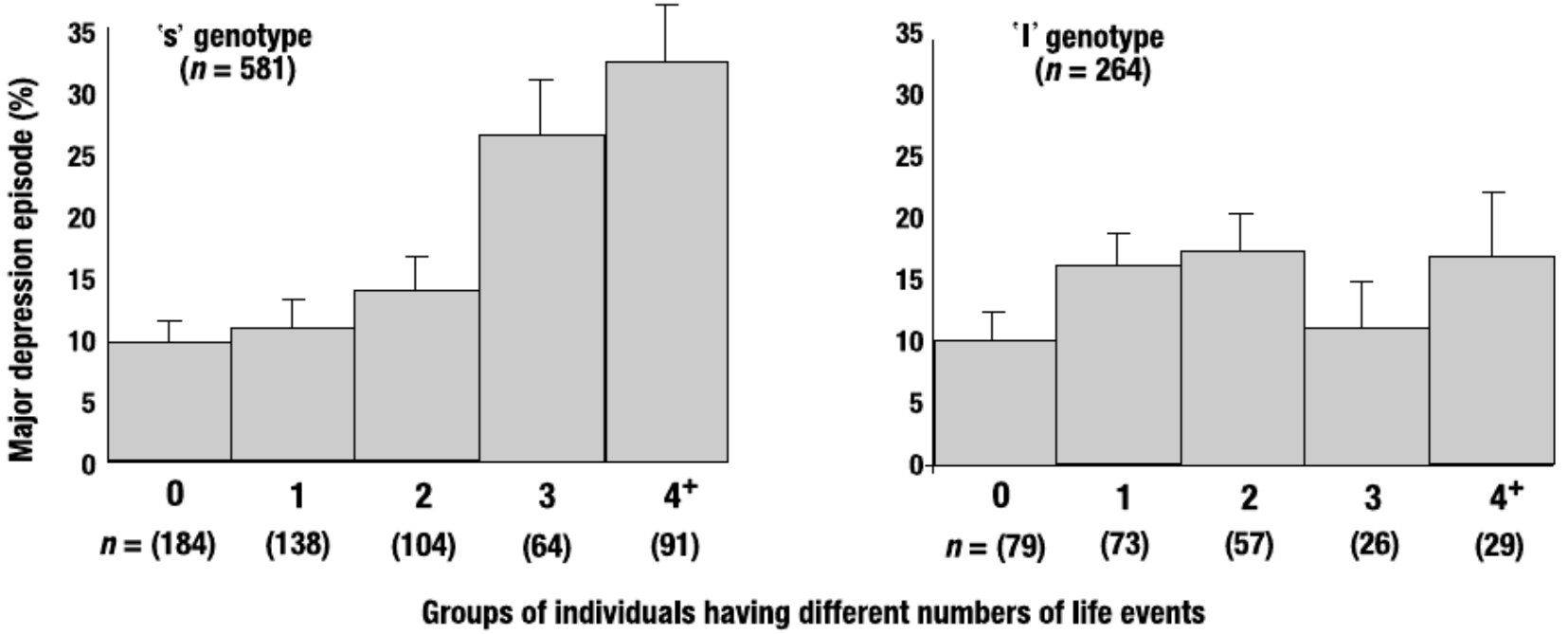


Lesch et al, 1998

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

"Vulnerability model"



From: Caspi et al, 2003. Science

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

“Plasticity model”

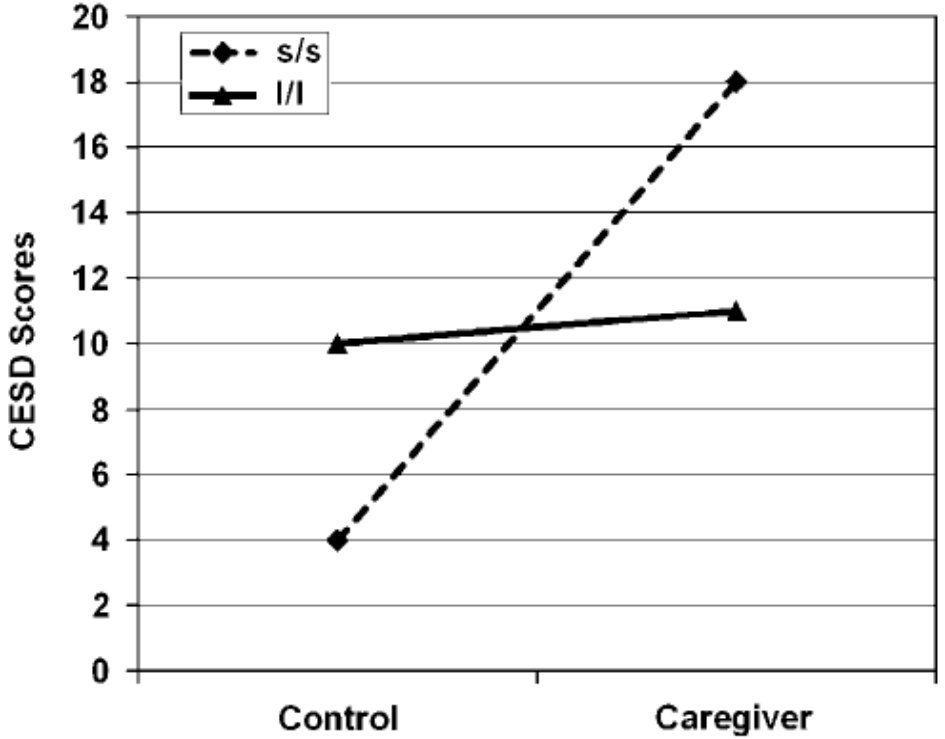


Figure 1 Center for Epidemiological Studies-Depression (CESD) scores for female caregivers and non-caregiver controls by 5-HTTLPR genotype (Brummett *et al.*[27]).

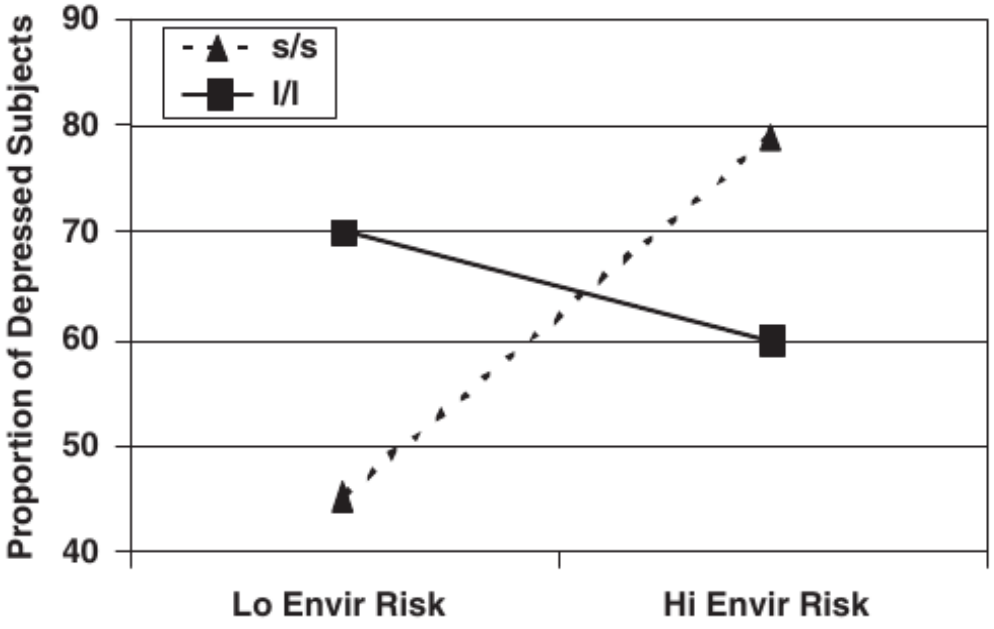
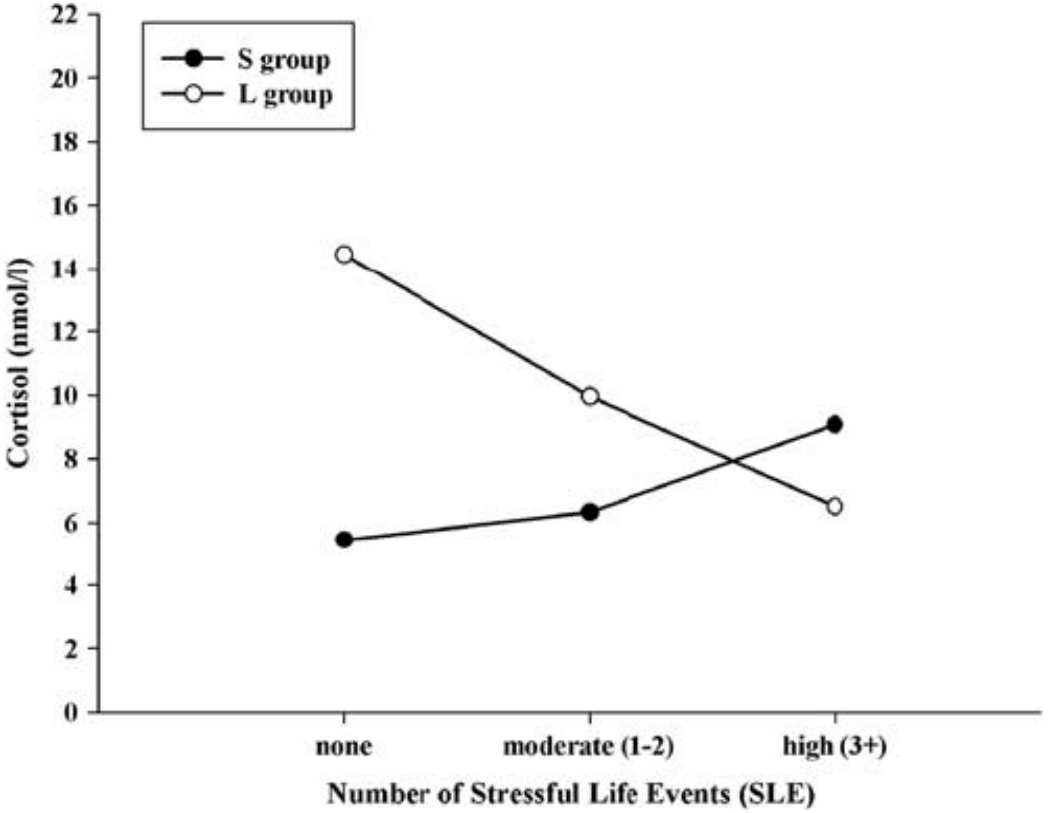


Figure 2 Proportion of female participants with a high level of depression by environmental risk group and 5-HTTLPR genotype (Eley *et al.*[28]).

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

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

"Plasticity model"



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

Sounds great, but...

A recent 30-year long cohort study (Fergusson et al, 2012) and meta-analyses (Munafò et al. 2009, Risch et al., 2009) could not replicate the GxE effect of HTTLPR

An Interface for GxE: Epigenome

- Epigenome: inherited changes without change in DNA sequence (DNA methylation pattern, histone acethylation or methylation), changes in expression pattern
- Especially prone to early-life stressors (malnutrition, lack of maternal caregiving, maltreatment)
- Tissue-specific patterns
- Changes may be conserved till the 3rd generation (animal models, Crews et al, 2011)

Epigenetic evidence

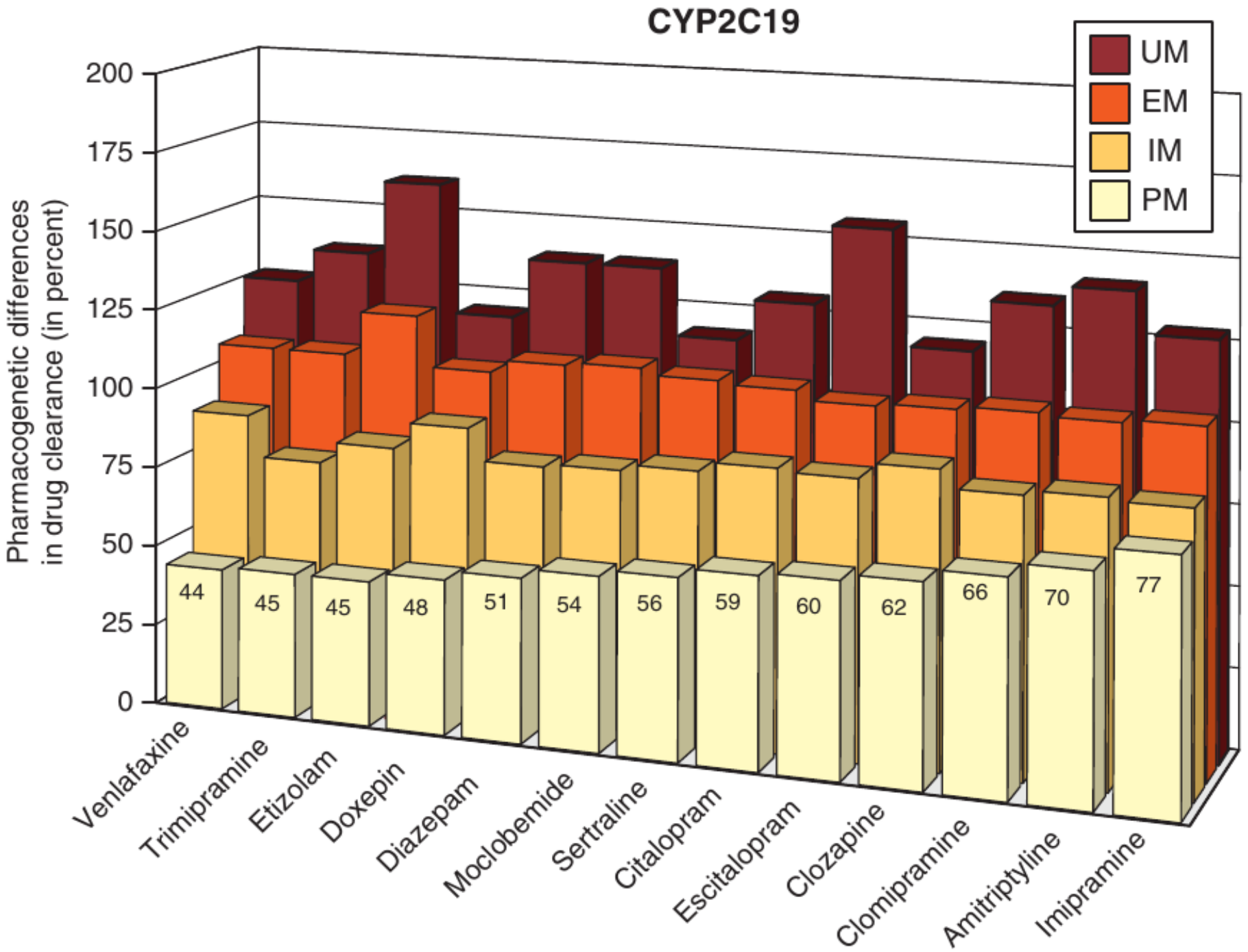
- BDNF promoter methylation pattern can be associated with MDD (Fuchikami et al, 2011) replication needed

- Regular voluntary exercise caused BDNF demethylation in rat brain (Pinilla-Gomez, 2012)

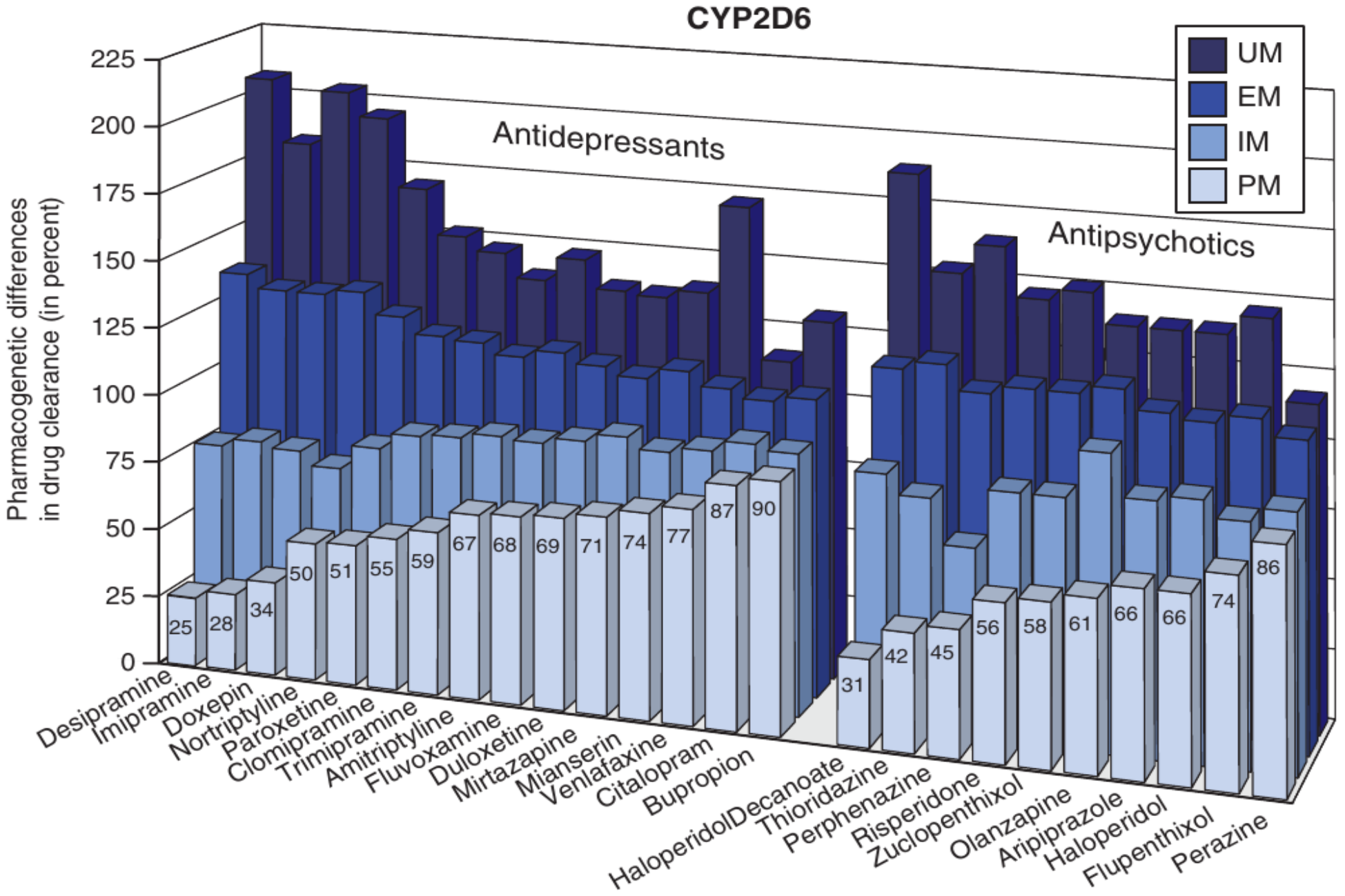
- Heavy exercise and consequent IL-1ß change predicted remission better than SSRI in nonresponder MDD patients (Rethorst et al, 2012)

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
- Risk for side effects: DRD2, DRD3, HTR2A,CYP2D6 for tardive dyskinesia, HTR2C for AP induced weight gain, GRIA1 sexual arousal dysfunction in SSRI

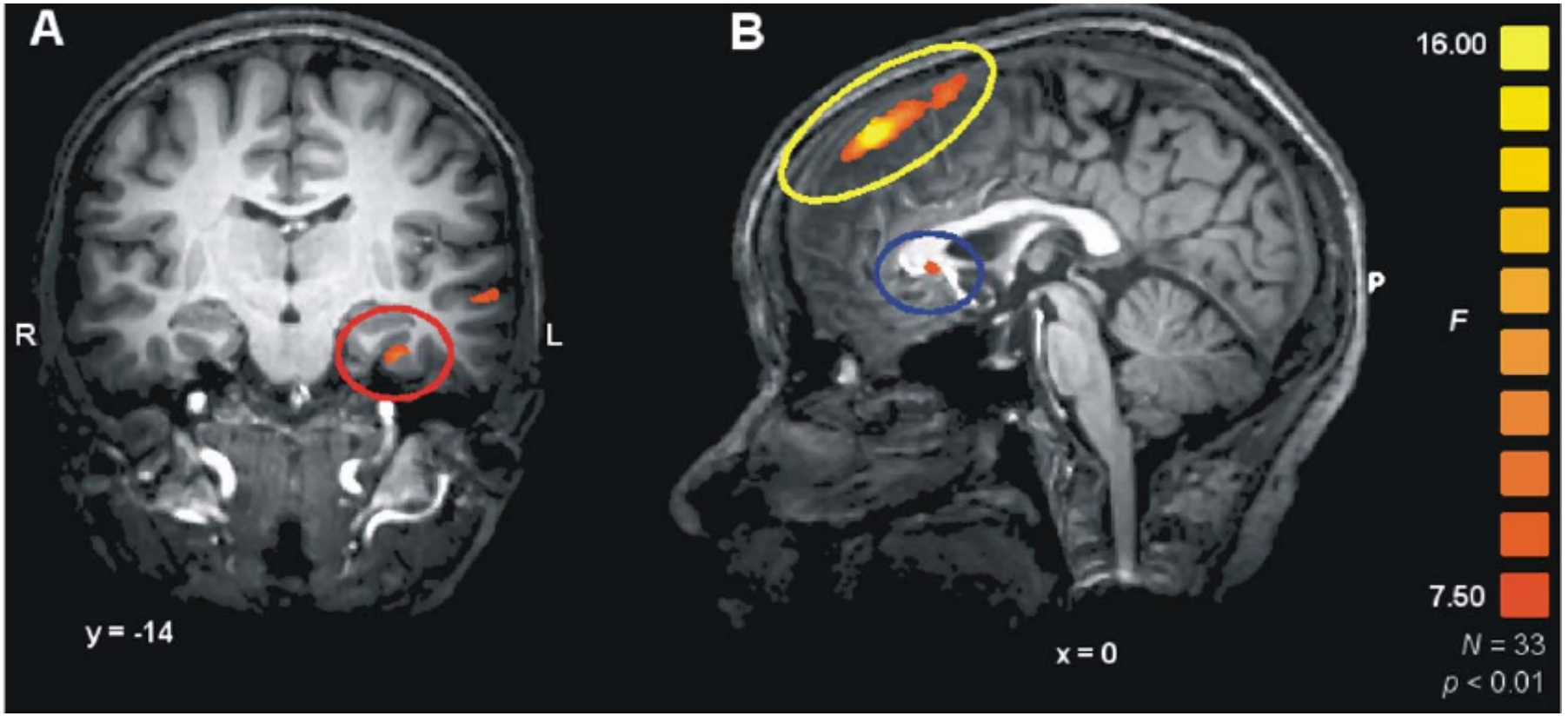


From: JC Stingl et al., Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psych (2012), 1-15



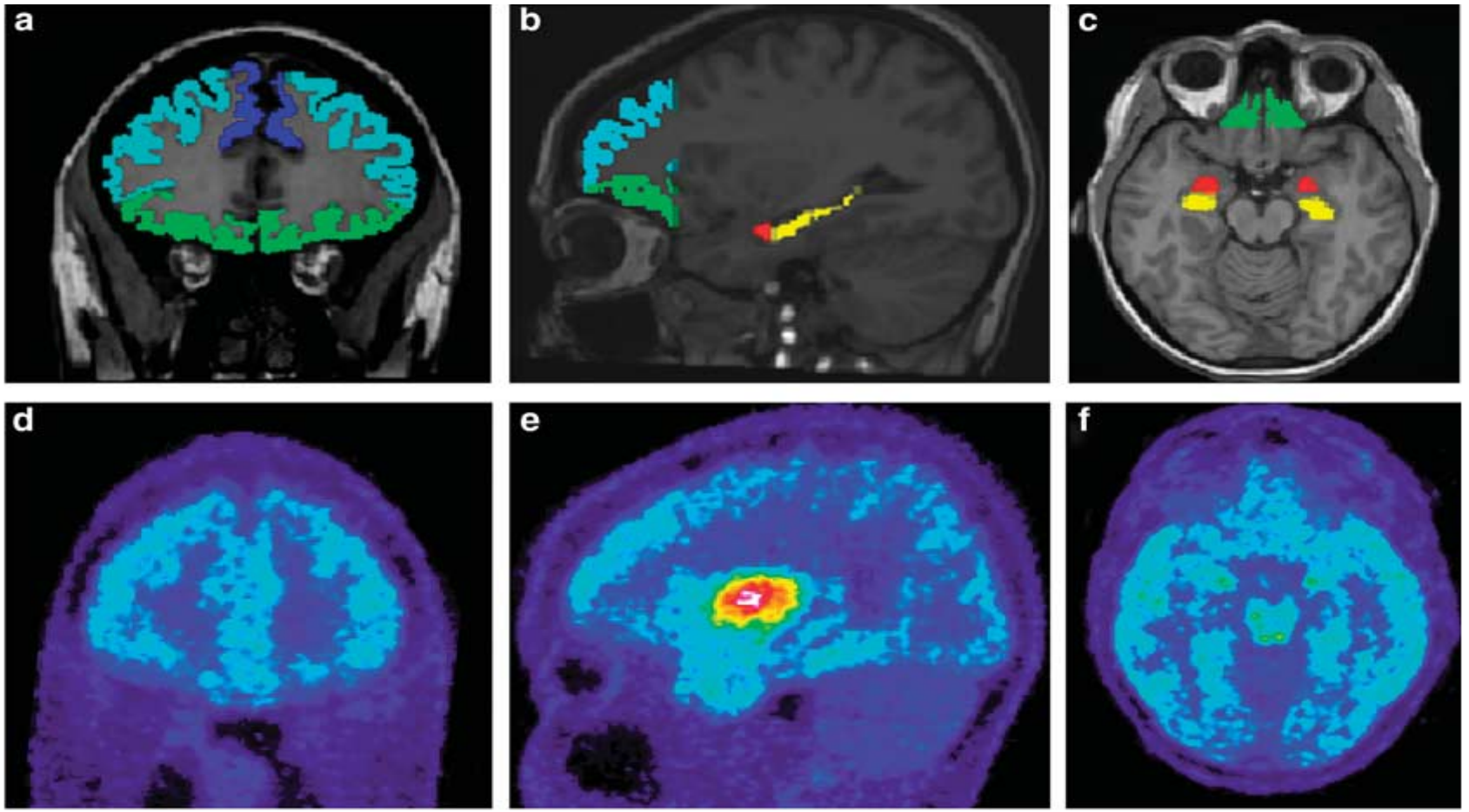
m: JC Stingl et al., Genetic variability of drug-metabolizing enzymes: the dual imp
psychiatric therapy and regulation of brain function. Mol Psych (2012), 1-15

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, genes related to neuro- and synaptogenesis, (“disorder of connectivity”), demonstrated gene-environment interactions for urban upbringing and cannabis use.
- Bipolar disorder: high heritability, genes of synaptic formations and regulations, shares a large portion of genetic susceptibility with schizophrenia
- Major depression: moderate level of heritability, unclear genetic background, possible, but questionable complex GxE interactions between HTTLPR and SLEs and other epigenetic effects
- Understanding gene-environment interactions and epigenetic effects is very important for the treatment as well

Thank you for your attention!