Functional alleles & intermediate phenotypes in alcoholism and dyscontrol disorders

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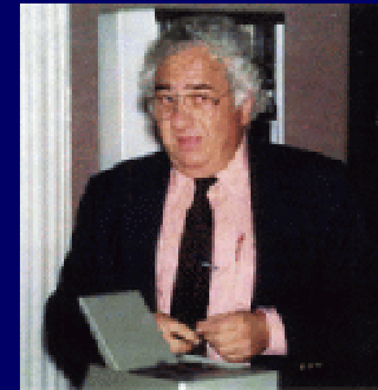
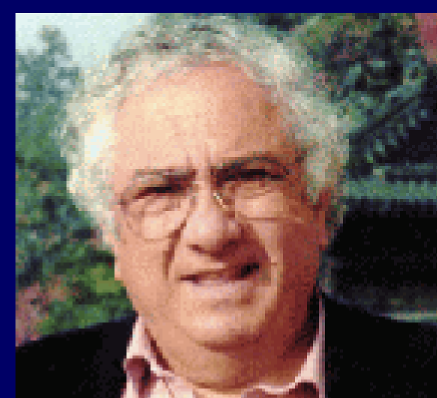
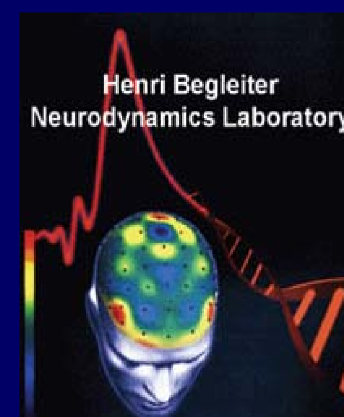






1935-2006

Begleiter, H., and Platz, A. (1969).
Evoked potentials: Modifications by conditioning.
Science 166:769-771.

Begleiter, H., Porjesz, B., Yerre, C., and Kissin, B. (1973).
Evoked potential correlates of expected stimulus intensity.
Science 179(4075):814-816.

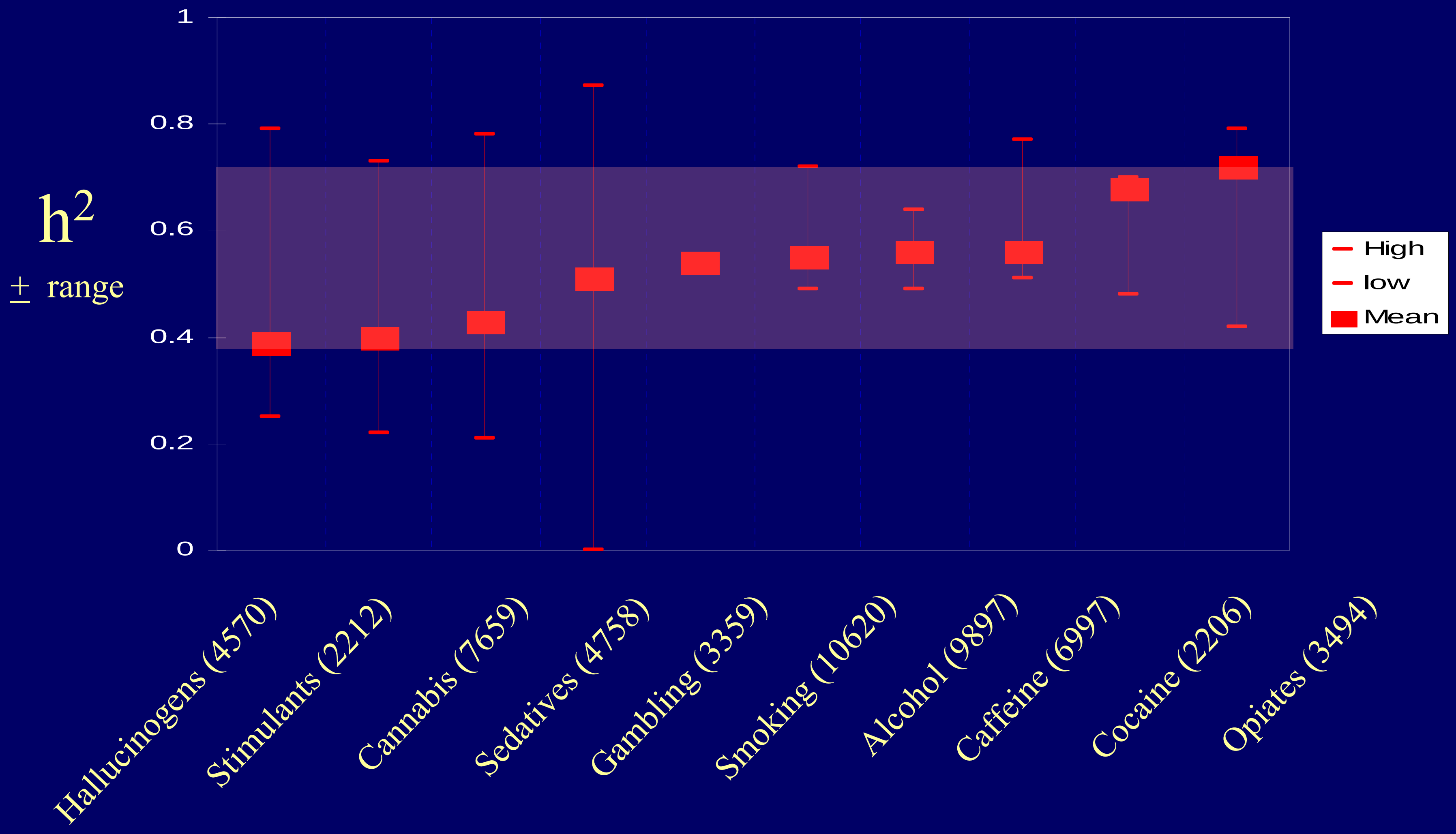
Begleiter, H., and Porjesz, B. (1975).
Evoked brain potentials as indicators of decision-making.
Science 187:754-755.

Begleiter, H., and Porjesz, B. (1975).
On evoked potentials, cognition, and memory.
Science 190:1004-1006.

Begleiter, H., Porjesz, B., and Chou, C.L. (1981).
Auditory brainstem potentials in chronic alcoholics.
Science 211:1064-1066.

Begleiter, H., Porjesz, B., Bihari, B., and Kissin, B. (1984).
Event-related potentials in boys at risk for alcoholism.
Science 225:1493-1496.

The heritability of addictive disorders



Nature Genetics Reviews, 2005

Alcoholism and other addictions: The intermediate phenotypes

Frontal cortical function/behavioral inhibition
Drug metabolism and response/tolerance
Reward
Anxiety-dysphoria/stress response
Obsession/Craving

....

Electrophysiology
Imaging: brain structure and function
Neuropsychology
Metabolomics
Gene expression

Gene, stress, & substances in dyscontrol

MAOA rare & common alleles: GxE, fMRI

COMT Val158Met: Roles in cognition & resiliency

HTTLPR: GxE for depression and suicidality

Genes with alleles proven to modulate human behavior

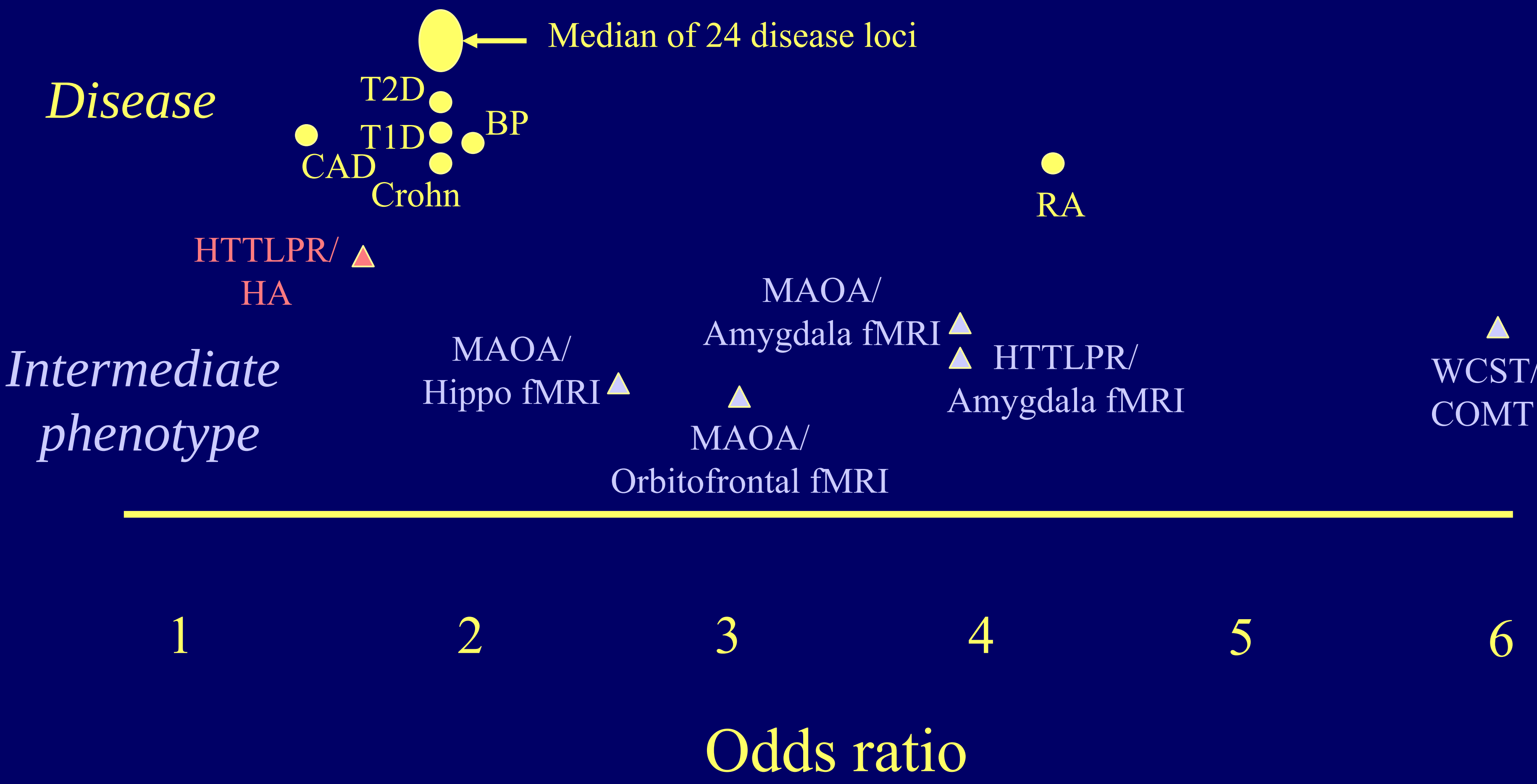
Rare → Common

Deterministic ← Probablistic

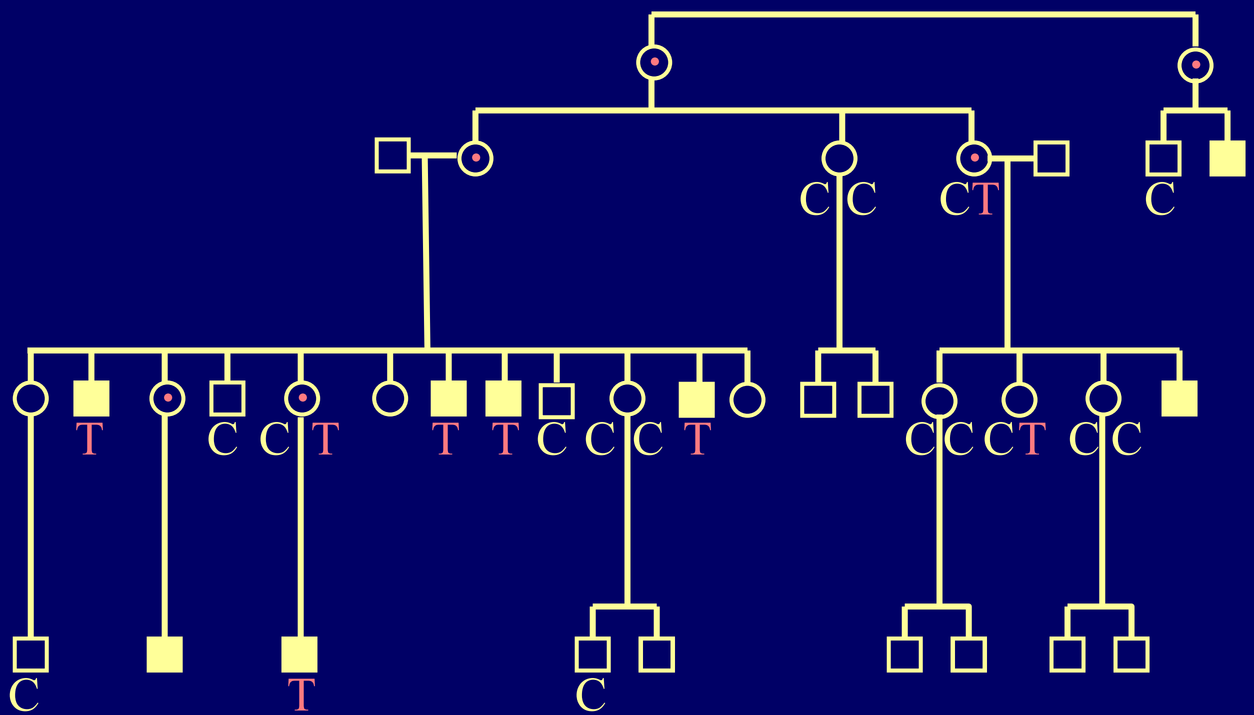
MAOA	Brunner Syndrome
HTT	OCD
HPRT	Lesch-Nyhan Syndrome
ERBA	ADHD
*MAOA**	Dyscontrol
*HTT**	Anxiety, OCD
COMT	Cognition, anxiety
BDNF	Episodic memory
ALDH2	Alcoholism
ADH1B	Alcoholism

**Regulatory*

For risk genes, odds ratios are larger for Intermediate Phenotypes than for Diseases (Wellcome Trust medians)



Brunner syndrome: X-linked dyscontrol due to the MAOA C936T stop-codon



Unaffected

Borderline mental retardation

Dyscontrol behaviors:

- Aggressive outbursts
- Arson
- Attempted rape
- Exhibitionism

No fibroblast MAOA activity

Abnormal monoamine metabolism:
↓ urinary HIAA, HVA, VMA
↑ urinary normetanephrine & tyramine

Brunner et al., *Science*, 1993

Expanding the stress connection to behavioral dyscontrol: Predisposition, early exposure, and substance abuse

Child sexual abuse and psychiatric disorders in females

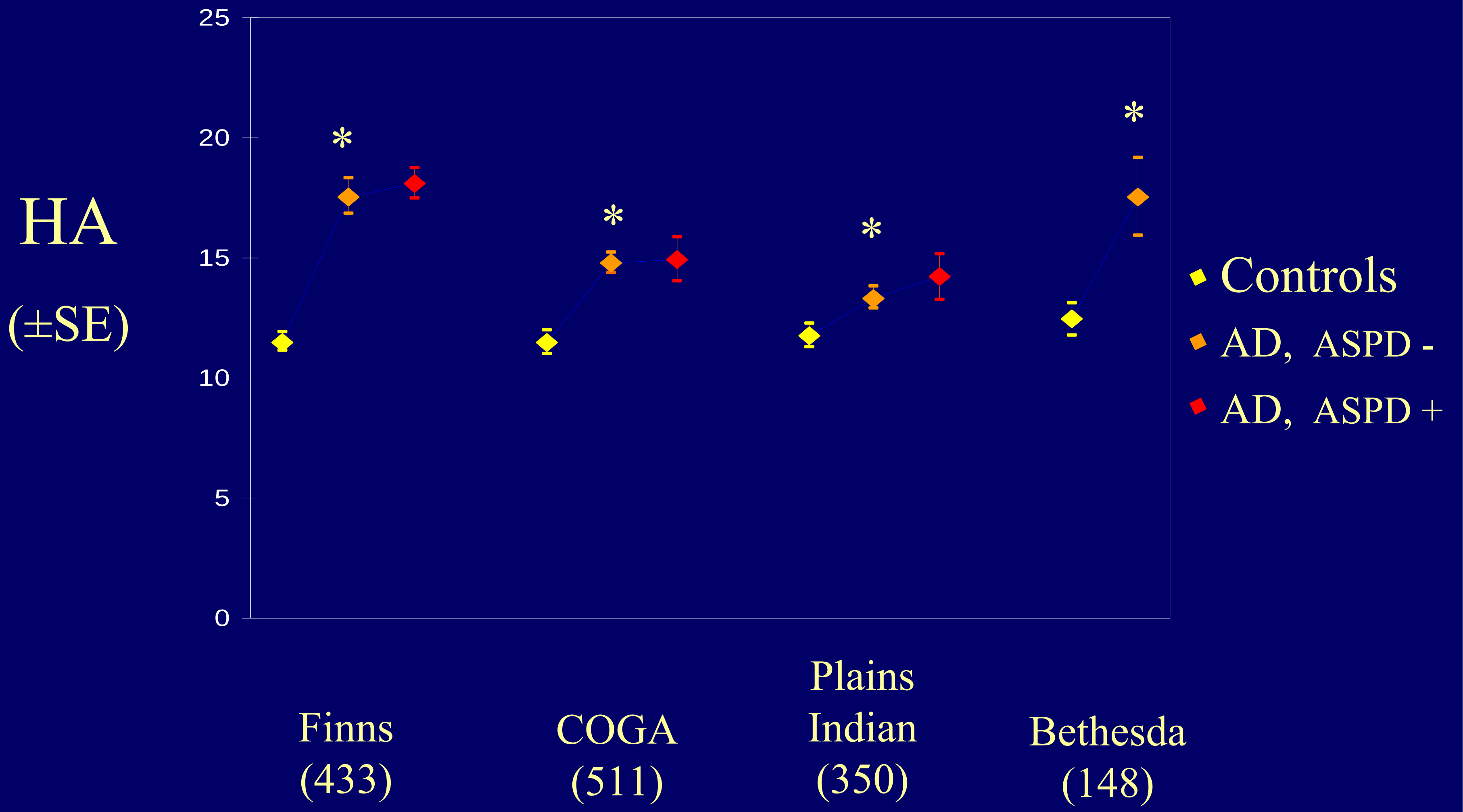
• ASPD	2.9 [1.4-6.0]
• Alcoholism [Abuse +Dep]	2.1 [1.2-3.6]
• Substance abuse	4.2 [2.2-7.8]
• Affective disorder	2.3 [1.3-4.0]
• Anxiety disorder	1.8 [1.0-3.1]
• PTSD	5.3 [2.2-12.7]

Robin et al, Amer J. Psychiatry, 1997

Addictions: A cause and effect of stress/trauma and dyscontrol

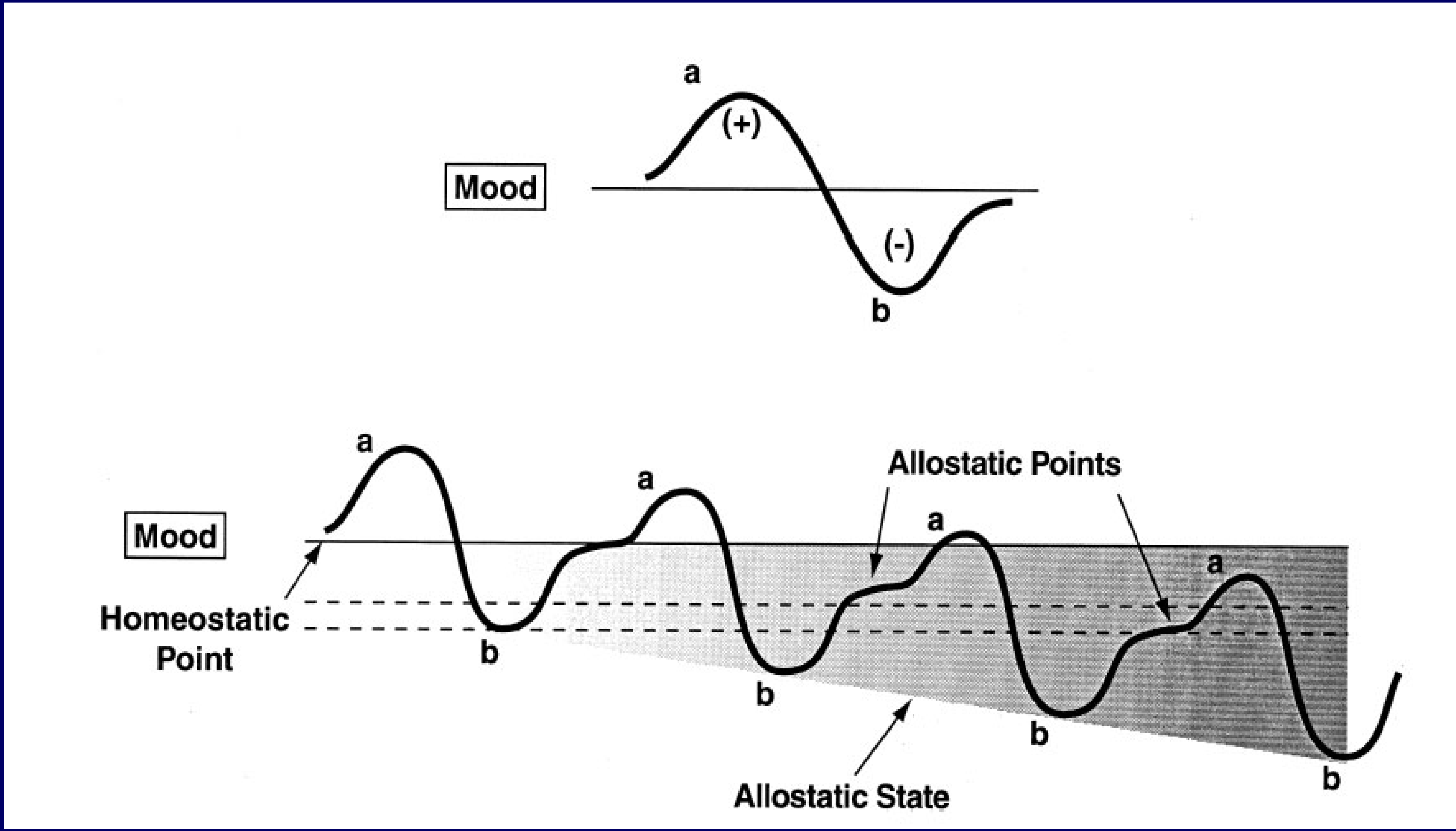
- Key factor in accidents, violence and sexual trauma
- A consequence of trauma
- Consequences of underage drinking
- A cause of allostatic changes
- Genes mediate liability

Alcoholics Tend to Be Anxious



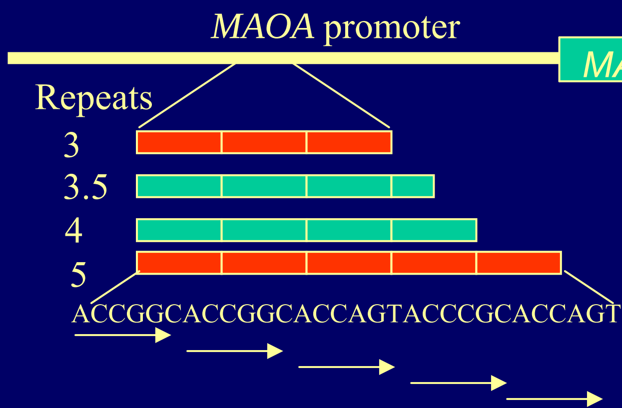
Ducci et al, 2007

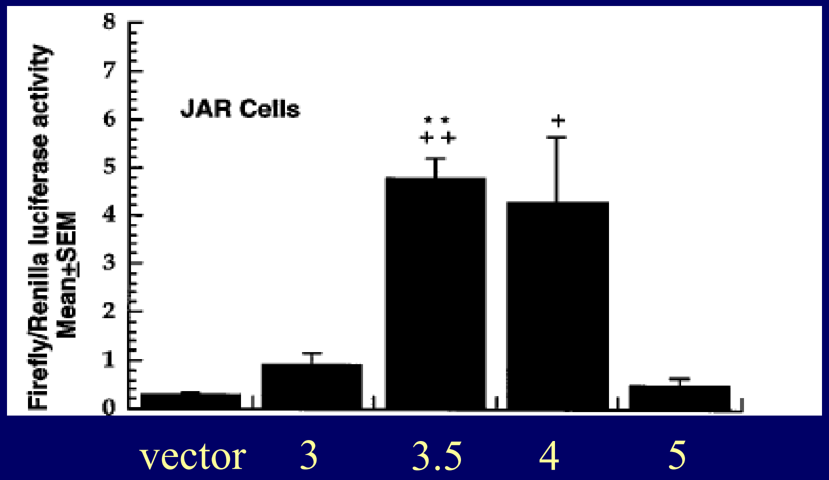
Allostasis and Addiction

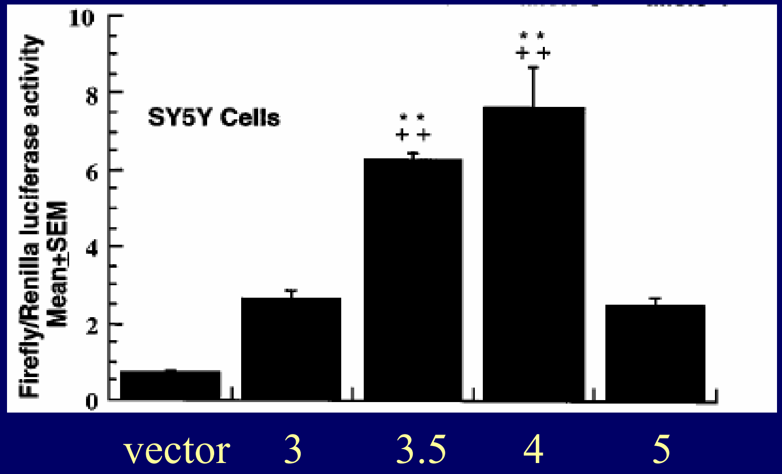


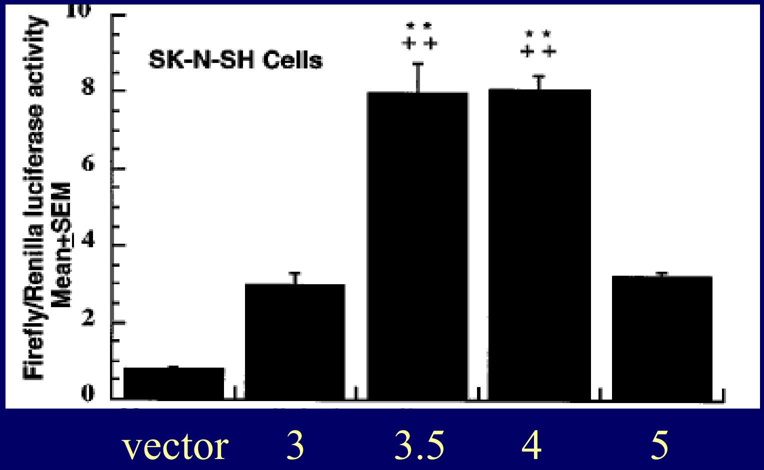
G. Koob, B. McEwen

A functional promoter polymorphism (*MAOA-LPR*) predicts MAOA expression



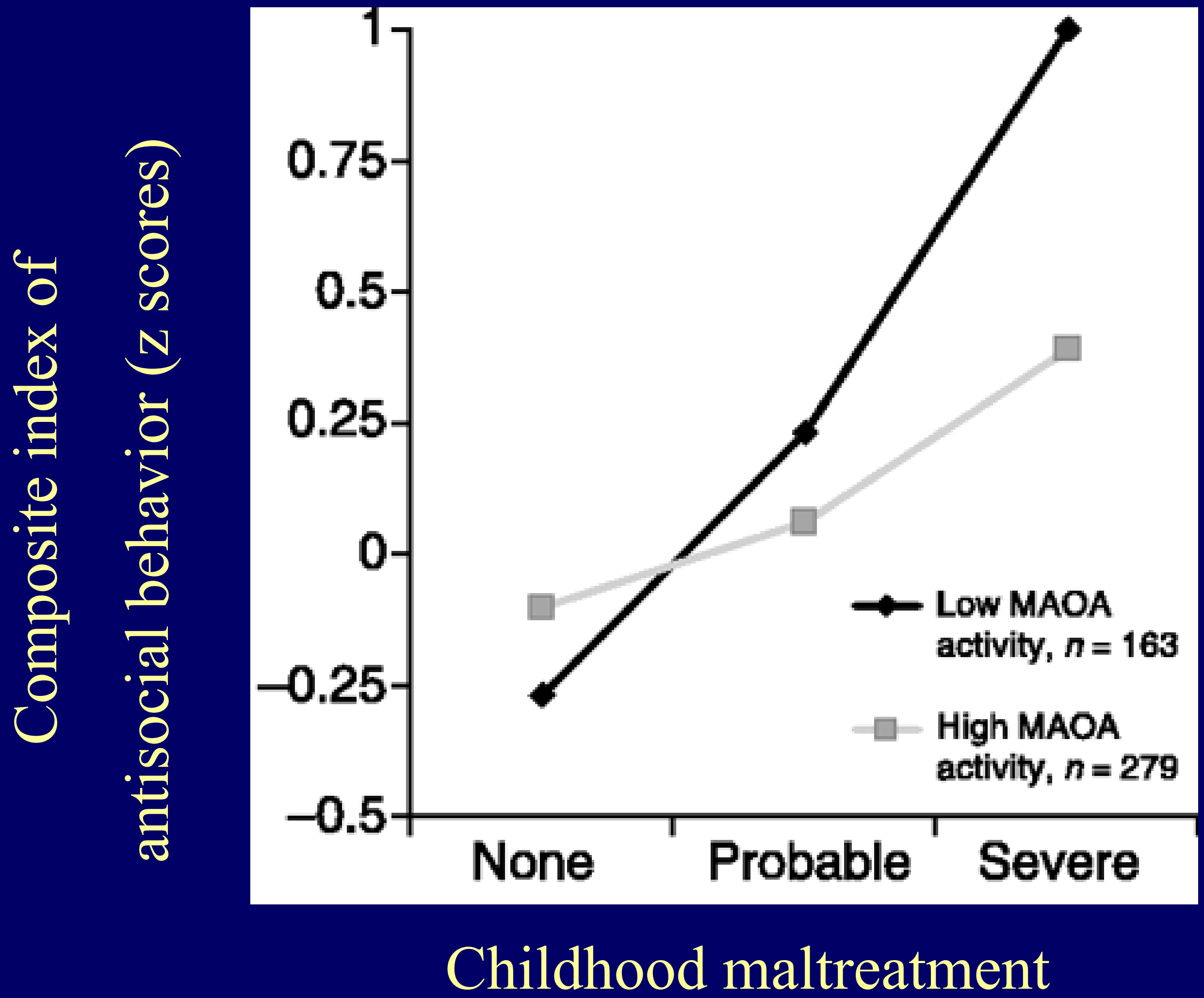






Sabol et al, Hum Genet, 1998

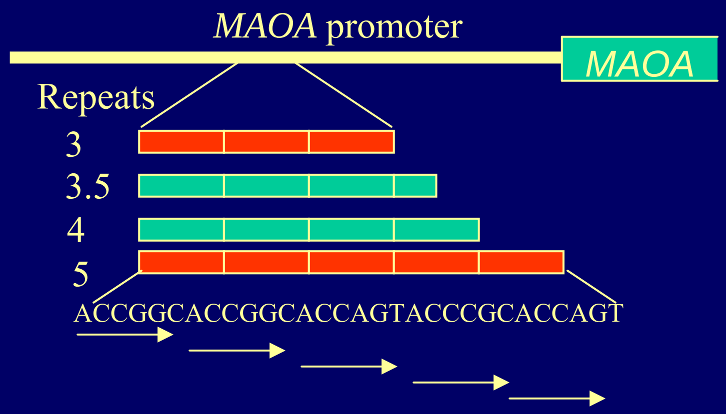
GxE interaction of *MAOA-LPR* and childhood maltreatment on antisocial behavior, in males

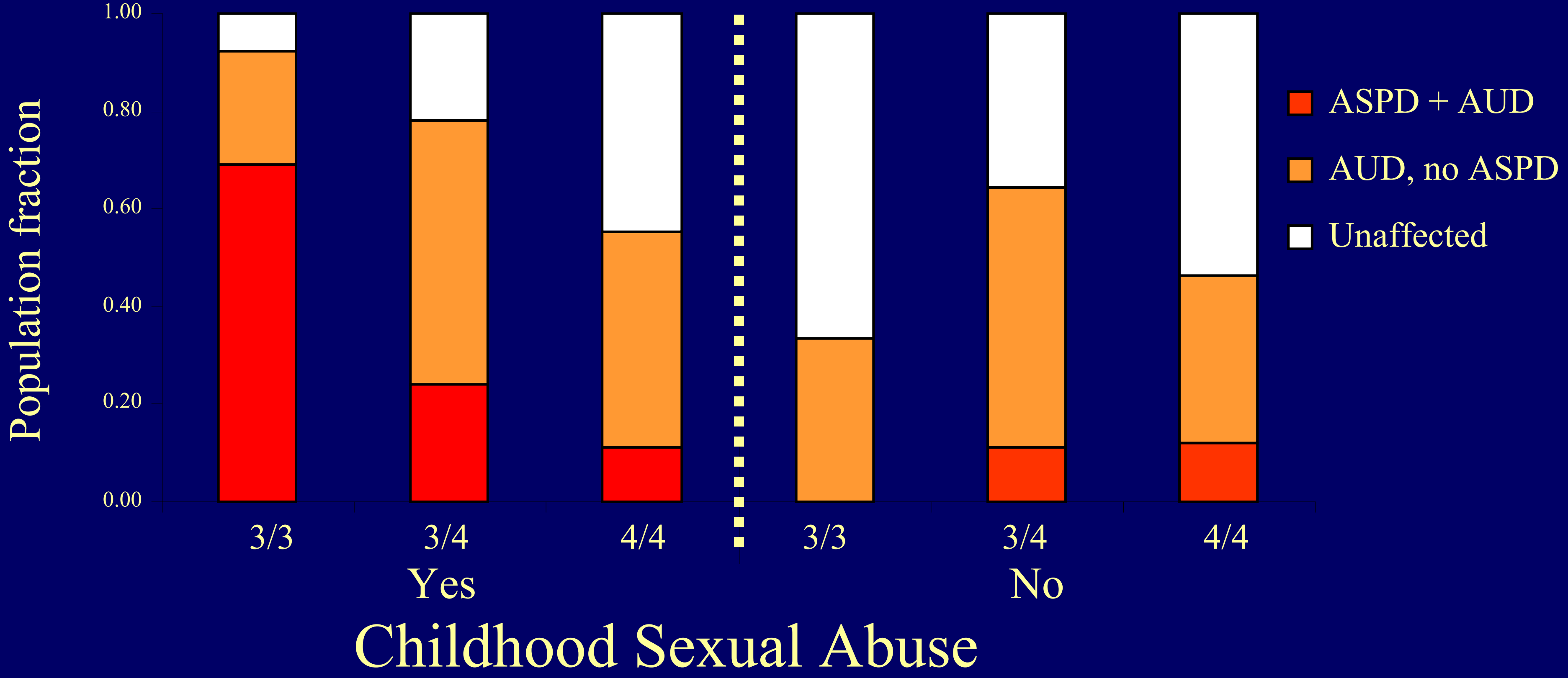


Caspi et al. Science., 2002

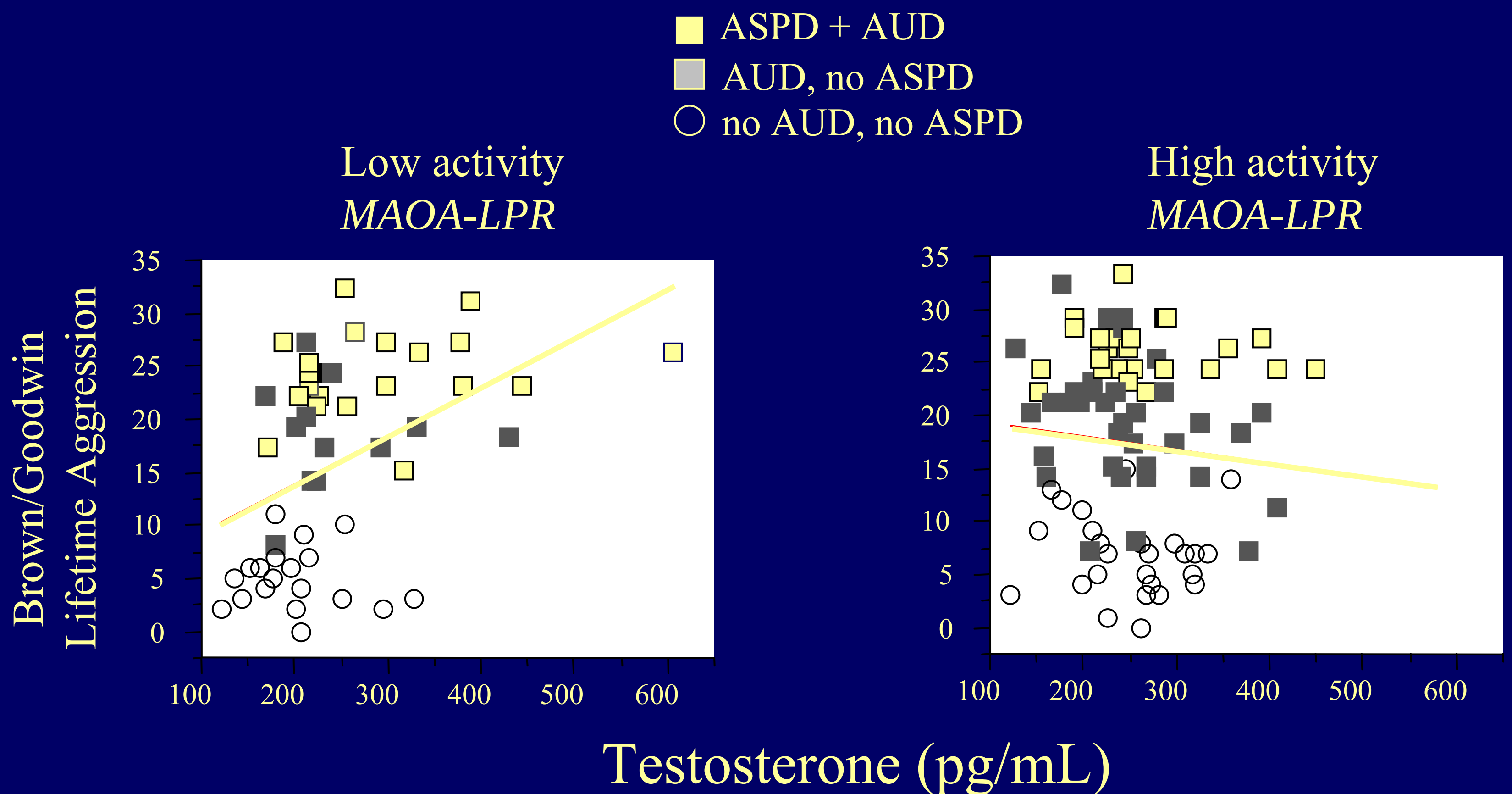
GxE interaction of *MAOA-LPR* & childhood sexual abuse for ASPD & alcoholism

Ducci et al, Molecular Psychiatry, 2007





Non-additive interaction of *MAOA-LPR* and testosterone predicts antisocial behavior

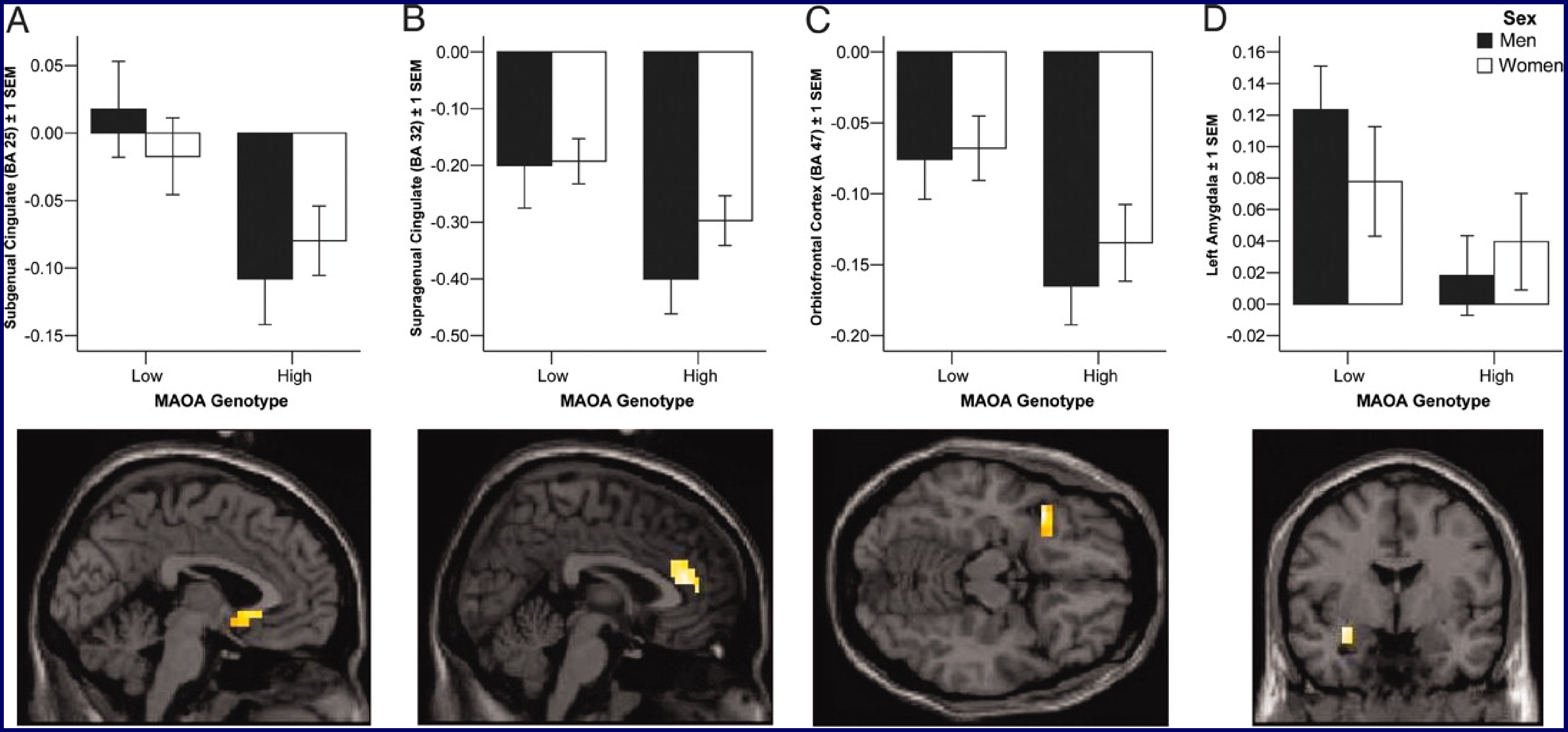


β_a (SE) = 3.49 (1.01); p=0.001

β_a (SE) = –0.94 (1.04); p=0.37

Sjoberg et al., *Neuropsychopharmacology* 2007

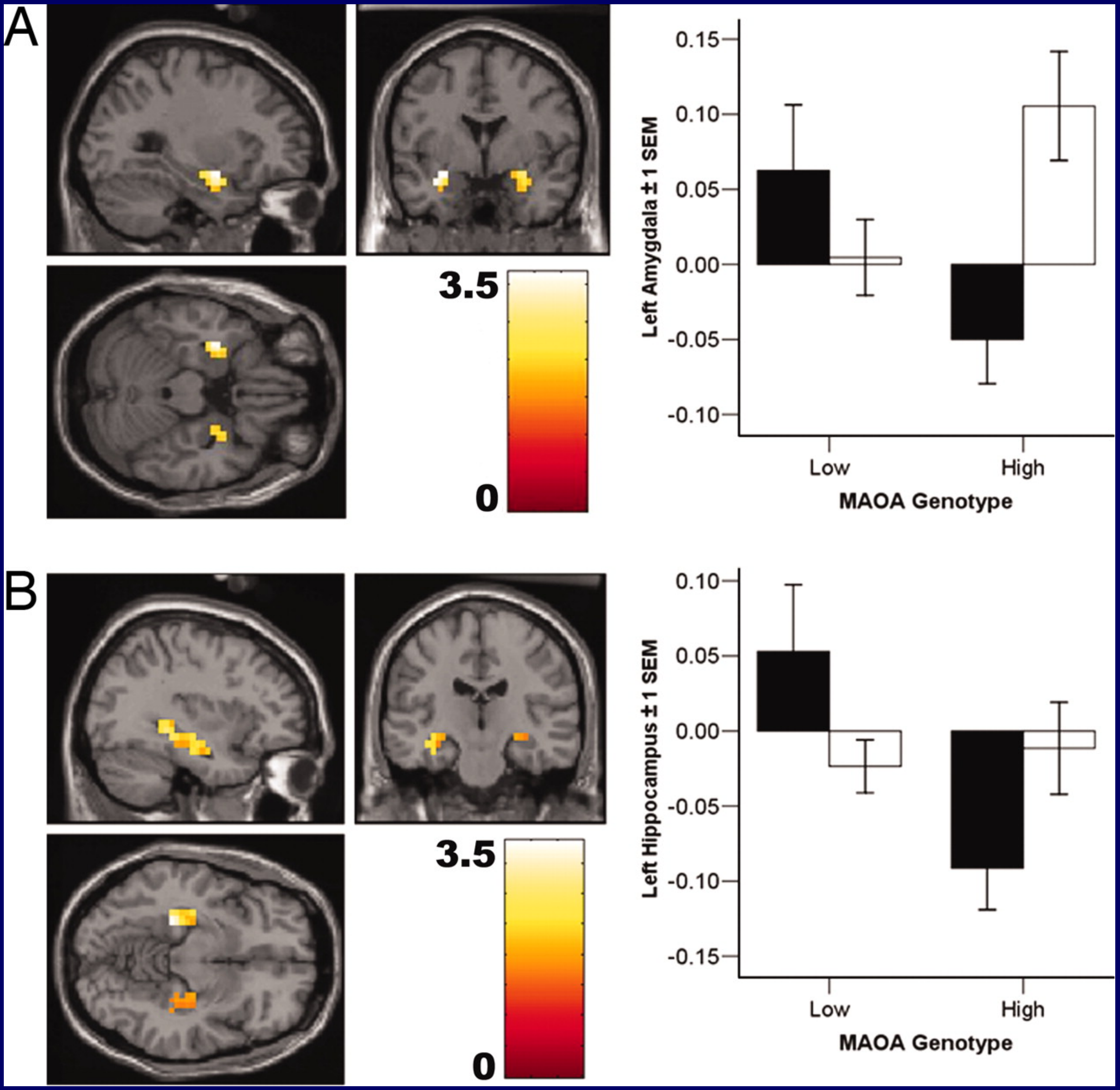
MAOA-LPR predicts differential fMRI activations to angry and fearful faces in limbic and paralimbic regions (n = 142)



Subgenual Cingulate | Supragenual Cingulate | Orbitofrontal Cortex | L Amygdala

Andreas Meyer-Lindenberg (2006) PNAS 103, 6269-6274

MAOA-LPR predicts fMRI limbic activations during retrieval of aversive memories (n = 90)



L Amygdala

L Hippocampus

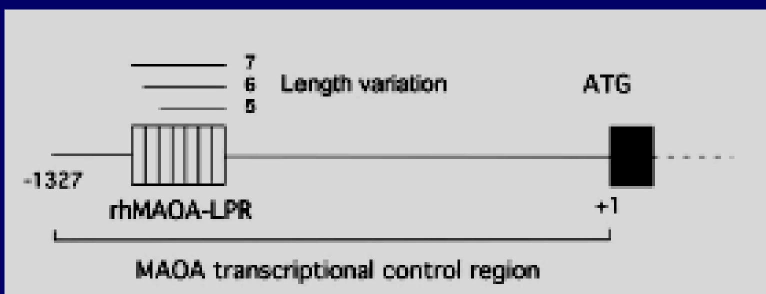
Andreas Meyer-Lindenberg (2006) PNAS 103, 6269-6274

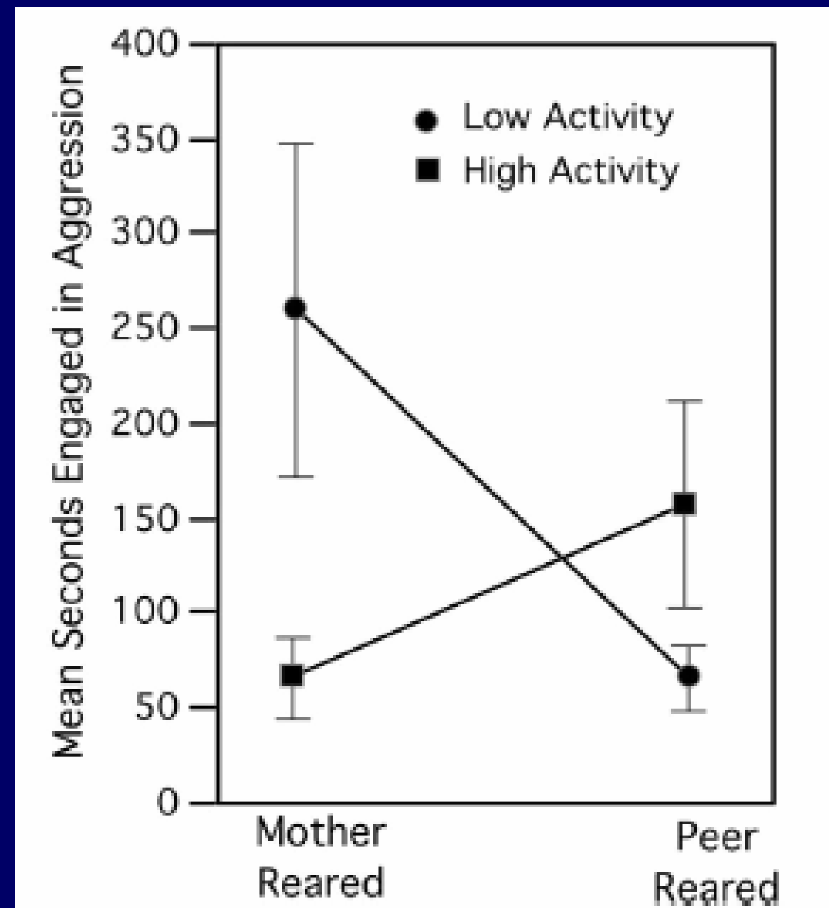
Monoamine Oxidase A Gene Promoter Variation and Rearing Experience Influences Aggressive Behavior in Rhesus Monkeys

Timothy K. Newman, Yana V. Syagailo, Christina S. Barr, Jens R. Wendland, Maribeth Champoux, Markus Graessle, Stephen J. Suomi, J. Dee Higley, and Klaus-Peter Lesch

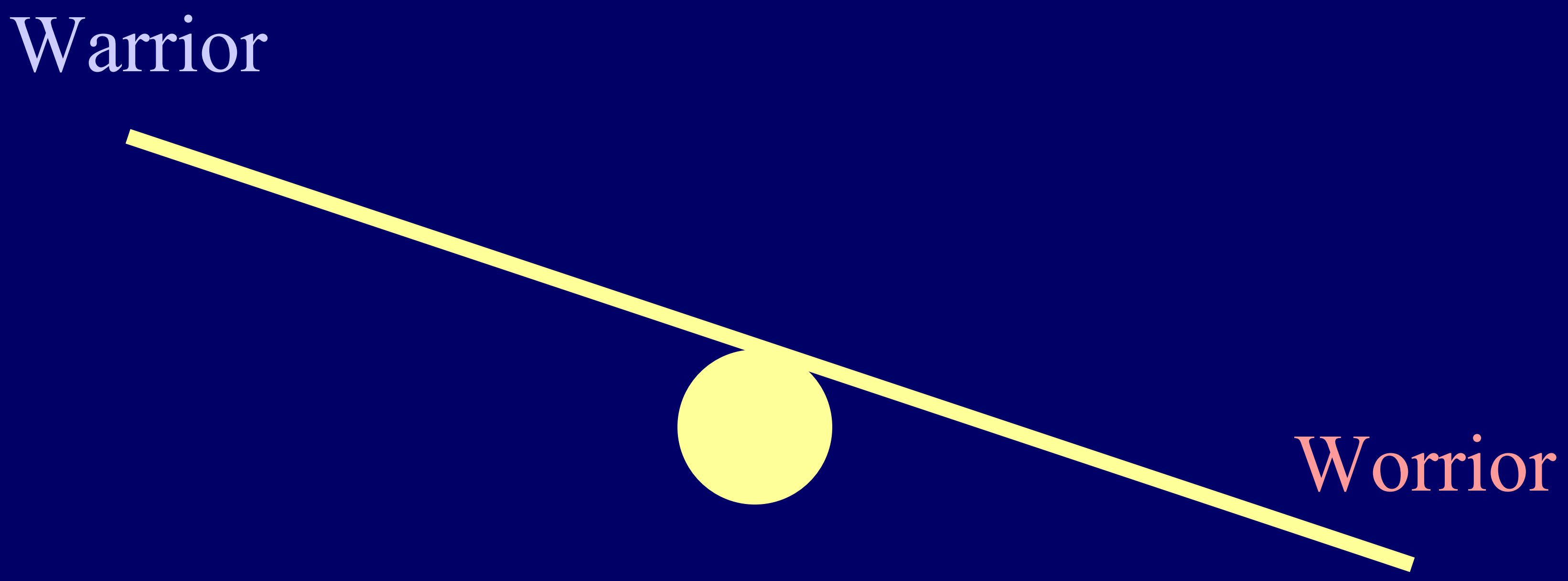
BIOL PSYCHIATRY 2005;57:167–172

rhMAOA-LPR →

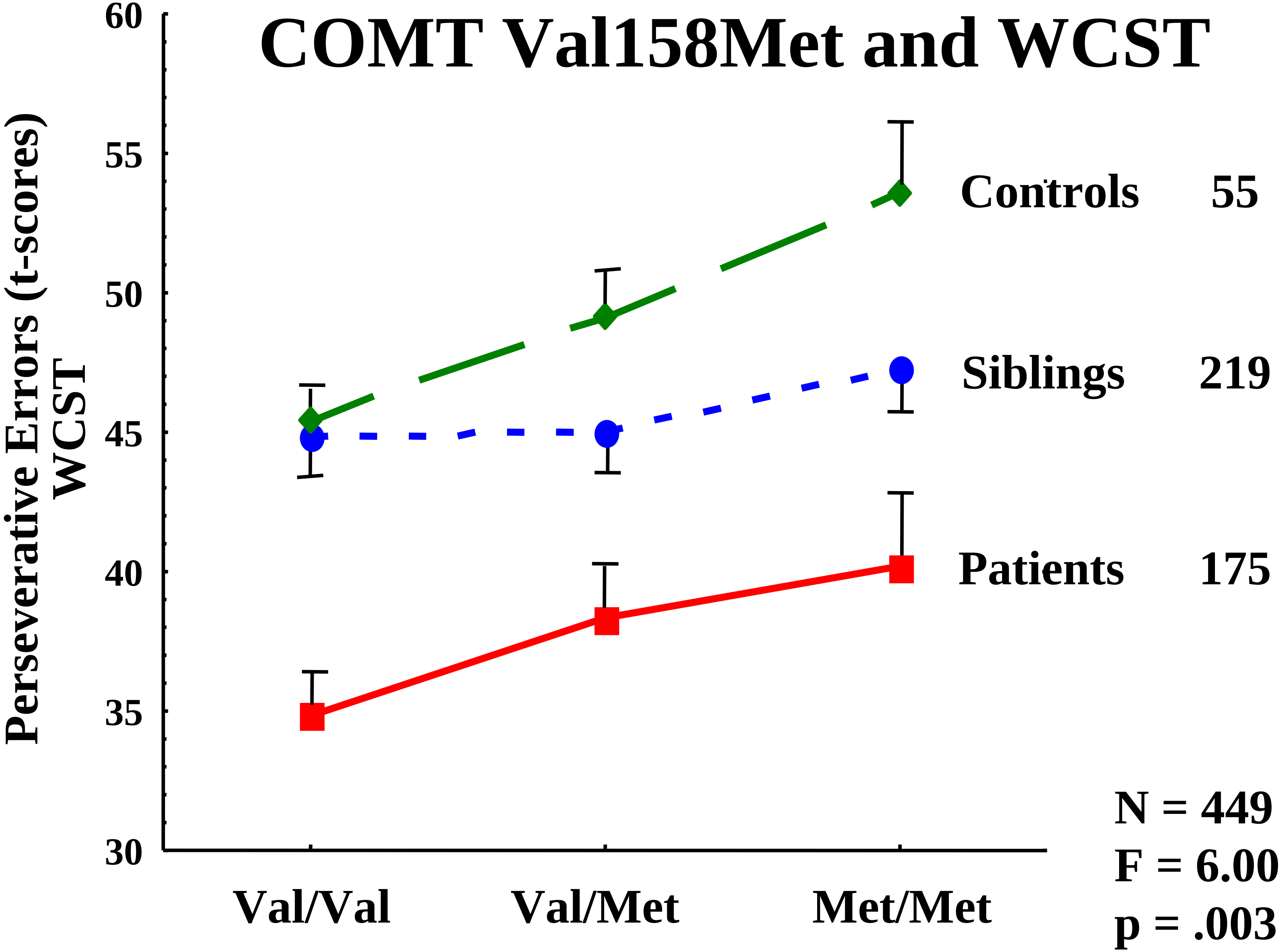




COMT Val158Met:
Apparent counterbalancing effects in cognition and stress/anxiety

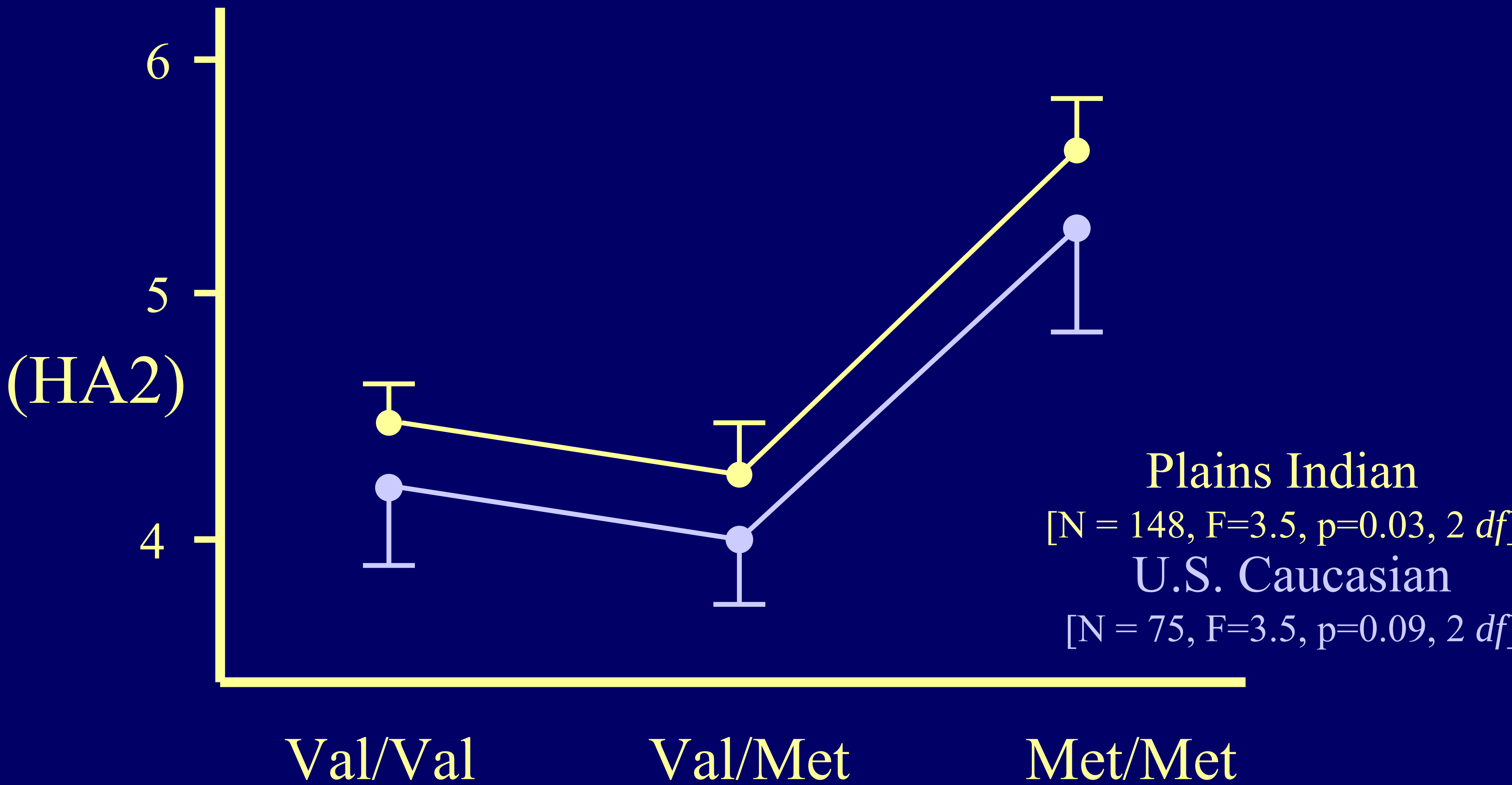


COMT Val158Met and WCST



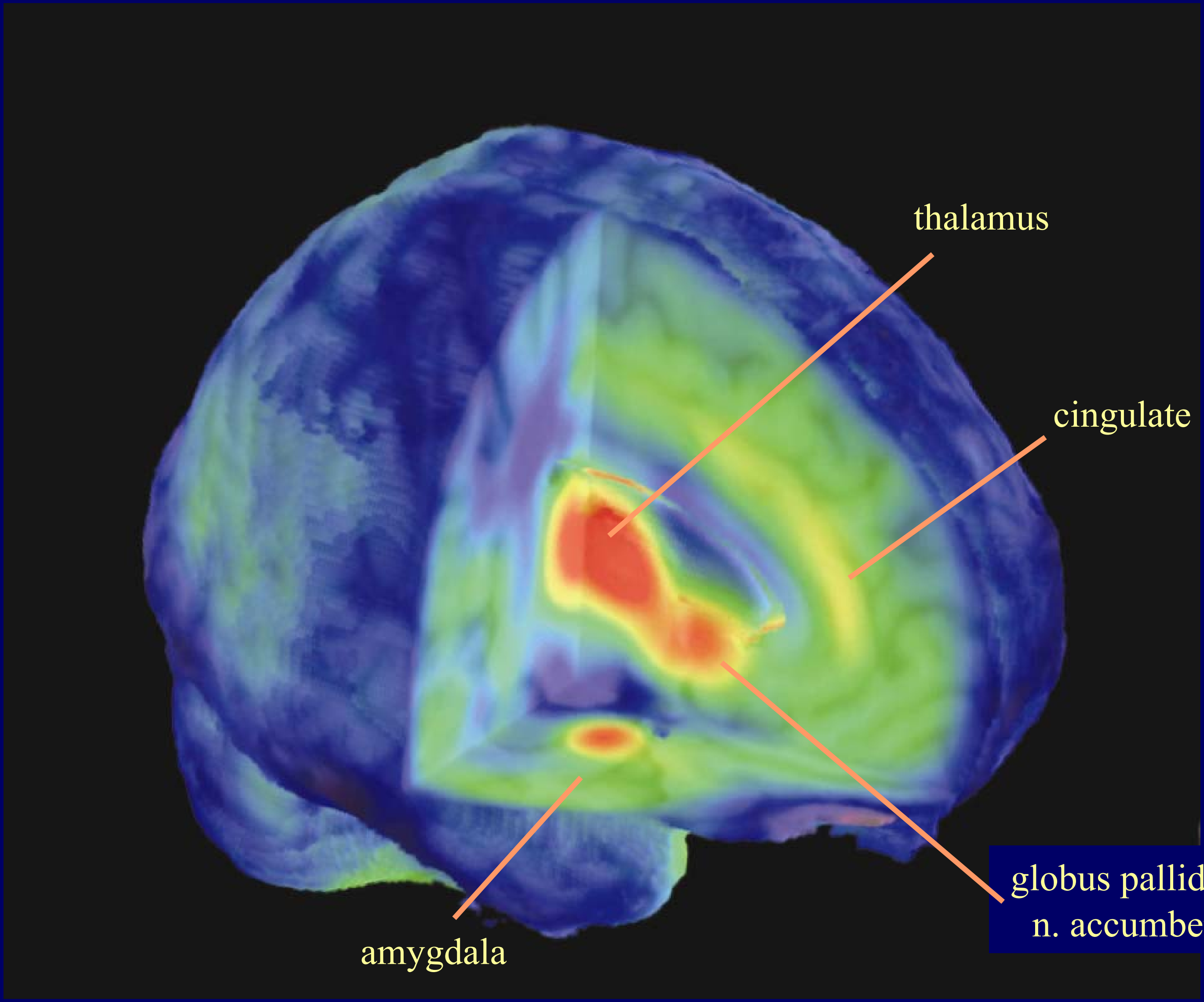
Egan et al, PNAS, 2001

Fear of Uncertainty (HA2) and *COMT* Val158Met in females from two populations



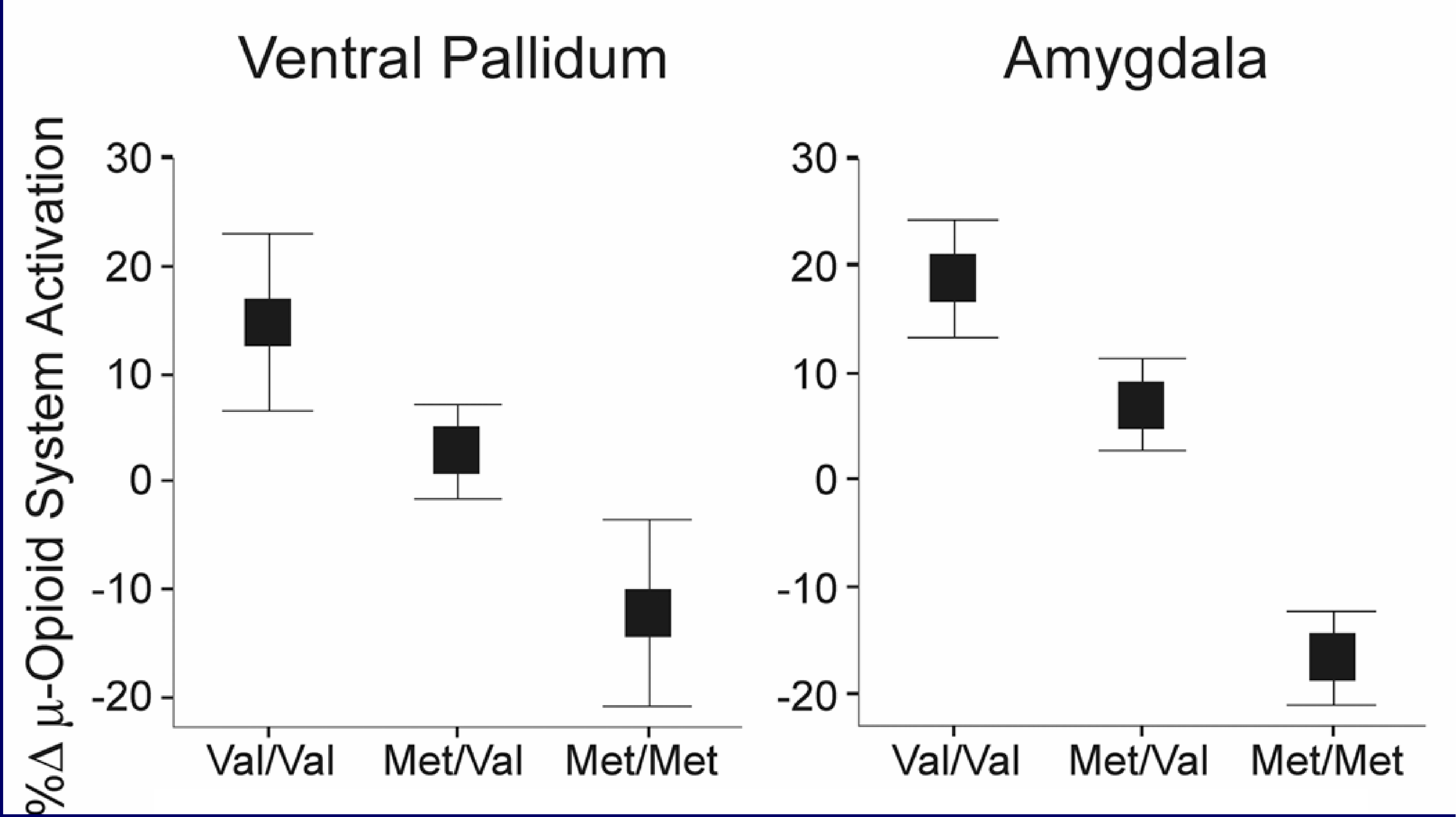
Enoch et al, Psychiatric Genetics, 2003

[^{11}C]-Carfentanil binding in brain



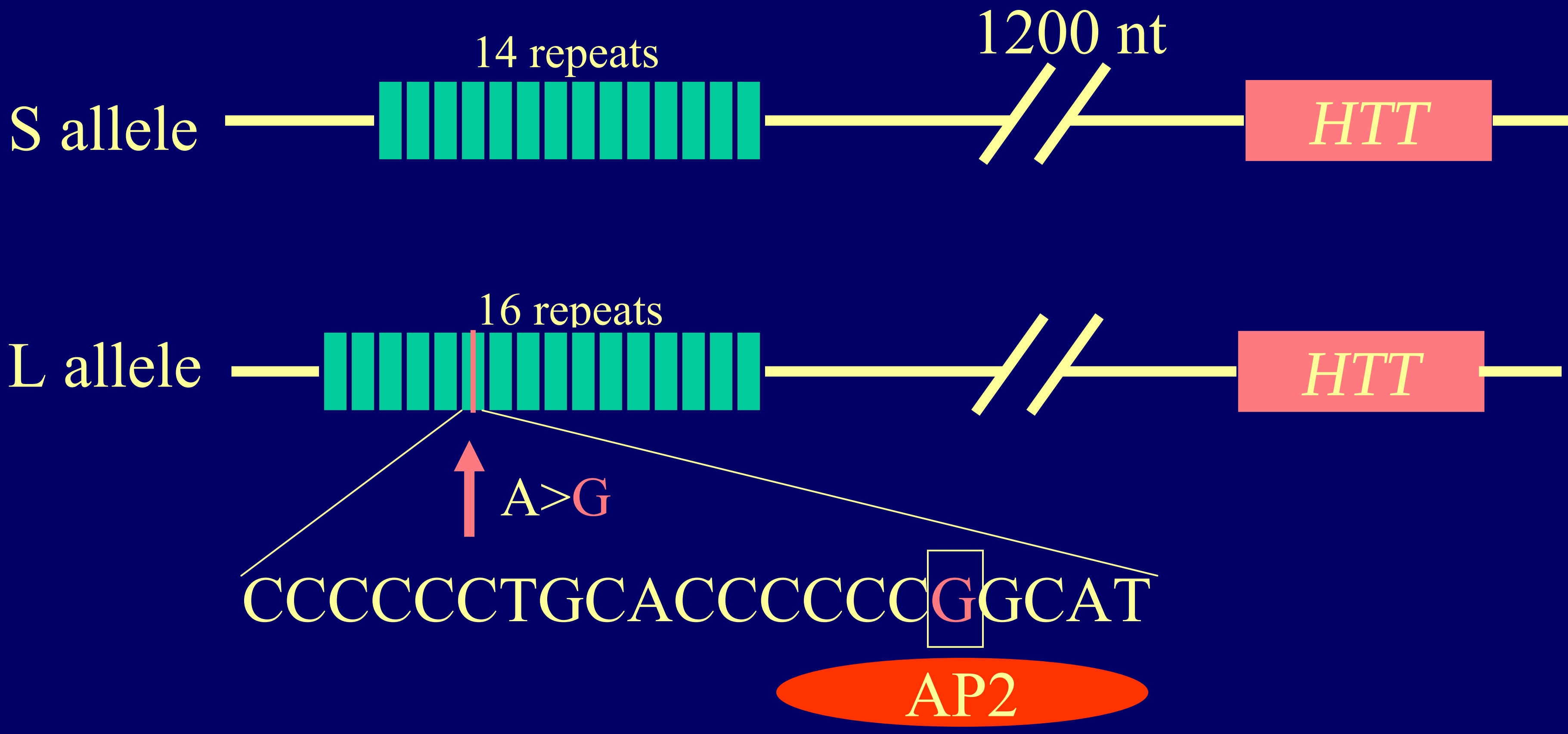
Source:Jon-Kar Zubieta

COMT Met158Val and μ-opioid system activation in response to sustained pain



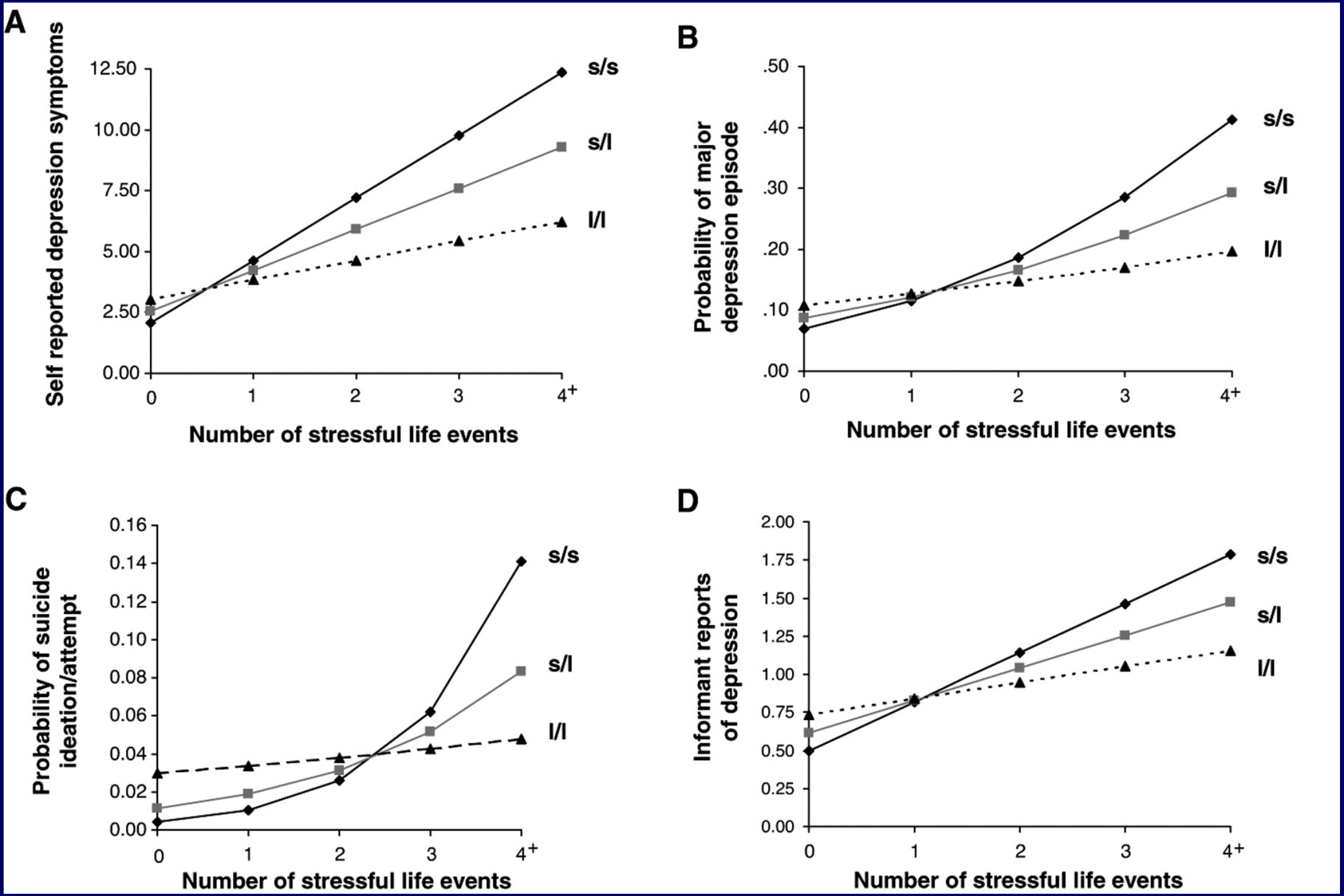
Zubieta et al, Science, 2003

HTTLPR: Still psychiatric genetics' most popular locus



Hu et al, AJHG, 2006

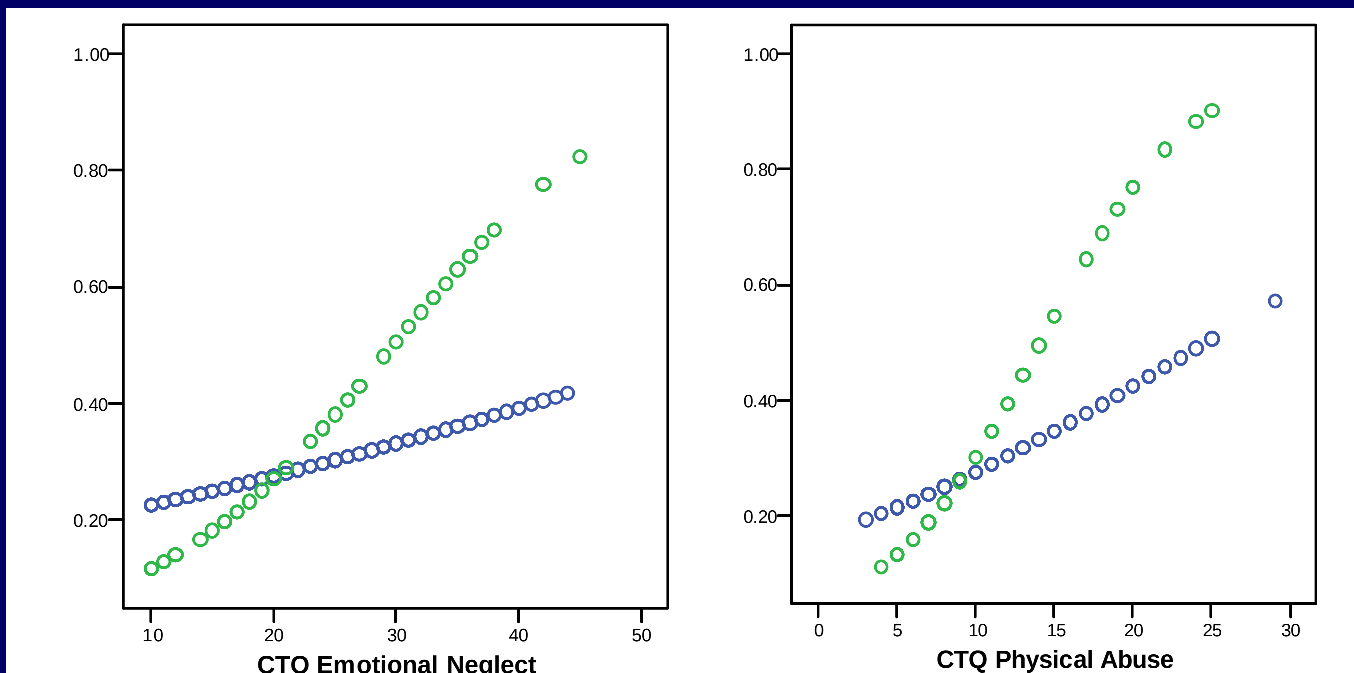
GxE: Interaction of HTTLPR and stress in depression



Caspi et al, Science 2003

Gene x Environment (HTT x Childhood stress) predicts suicide attempts in abstinent, African American, Substance Dependent patients (N=306)

Probability of Suicide Attempt

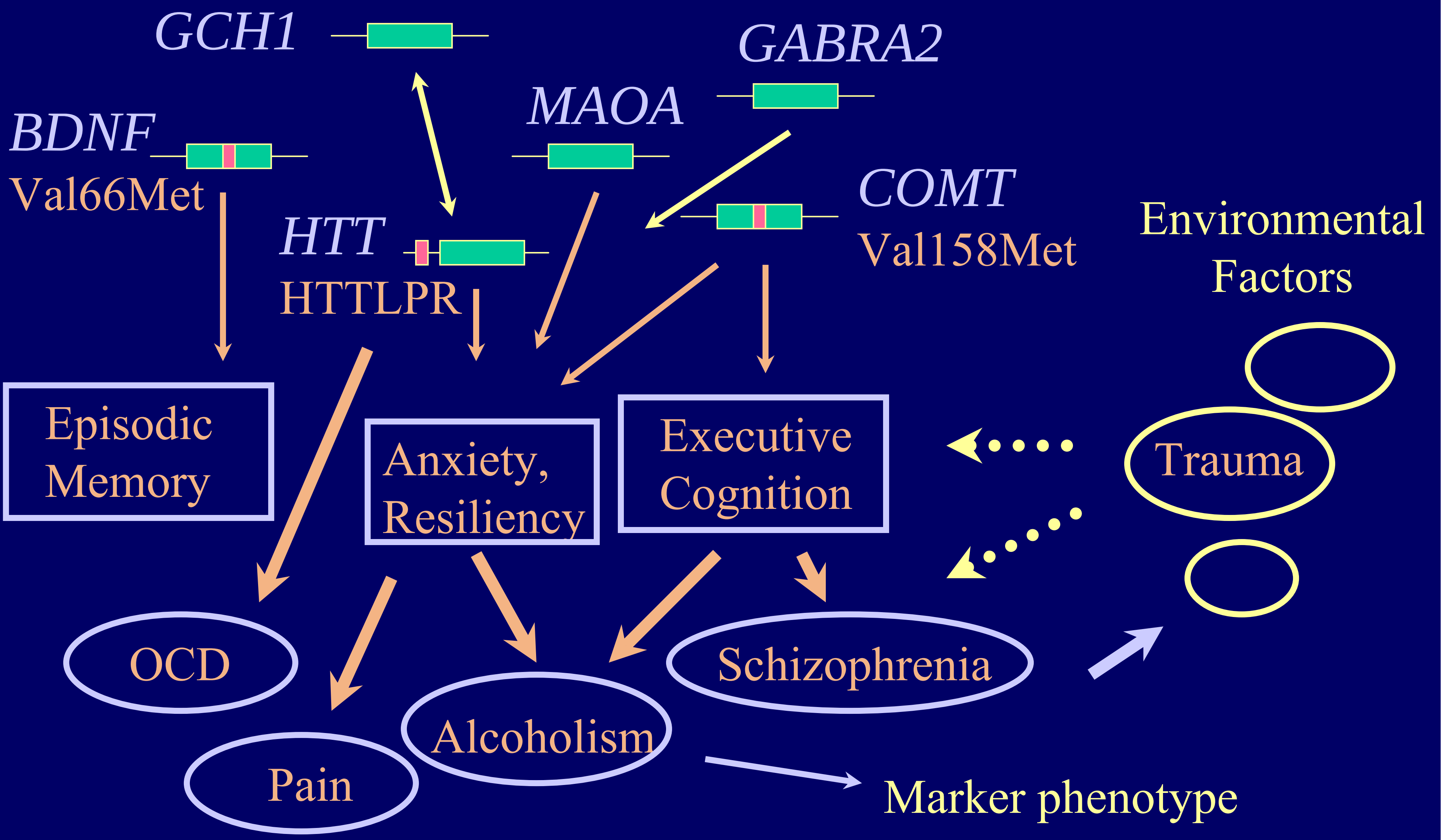


HTT genotypes
Low expressing
High expressing

CTQ Emotional Neglect CTQ Physical Abuse

Roy et al, In press

Functional Allele to Complex Behavior



Thanks!

Mary-Anne Enoch
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Robert Lipsky
Peihong Shen
Qiaoping Yuan
Colin Hodgkinson

Rob Robin
Bernard Albaugh
Alec Roy

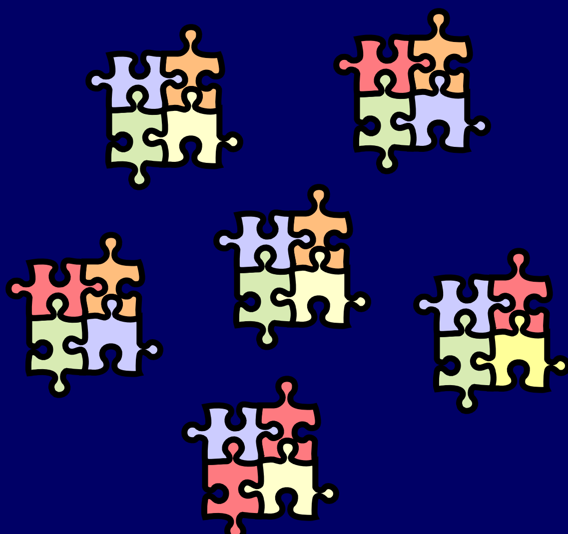
Ahmad Hariri
Deborah Mash
Rajita Sinha
Jon-Kar Zubieta
Mary Heitzig
David Scott

Genetic Complexity

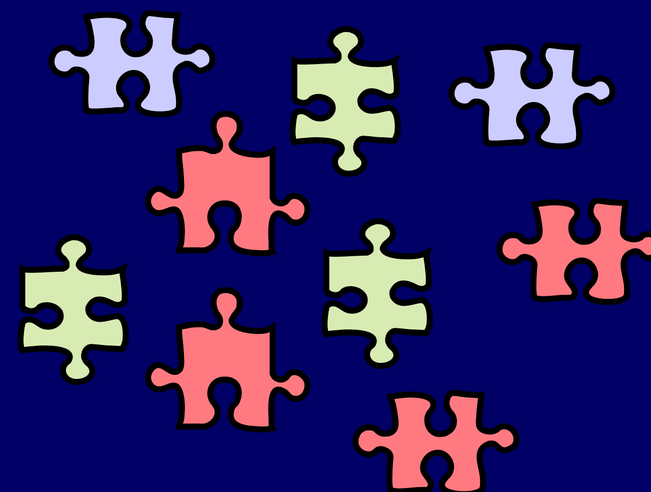
Polygenicity: Multiple genetic variants confer risk in combination.

Heterogeneity: Multiple genetic variants confer risk in different individuals.

Genetic complexity in affected populations

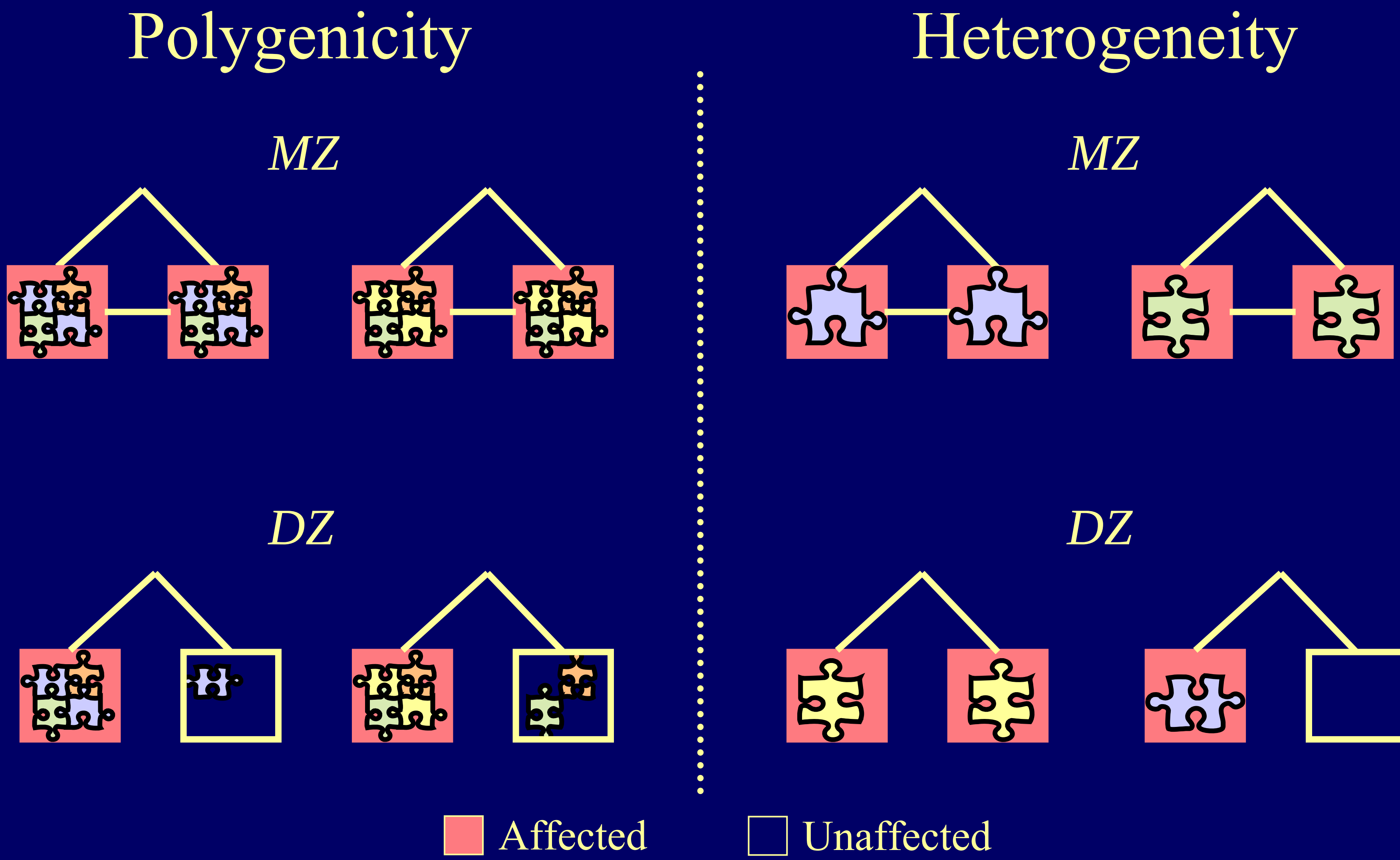


Polygenicity

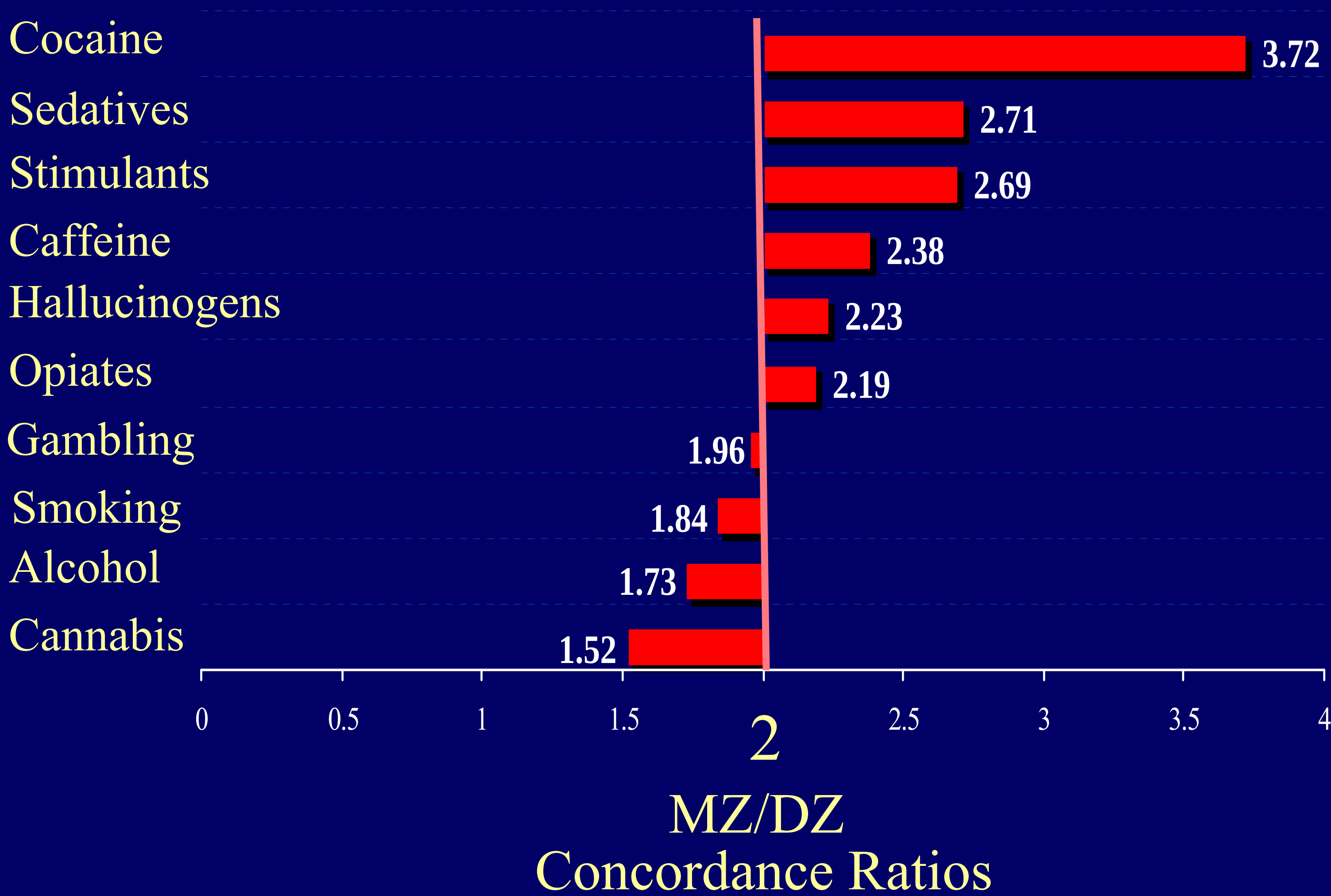


Heterogeneity

Genetic complexity and twin concordance

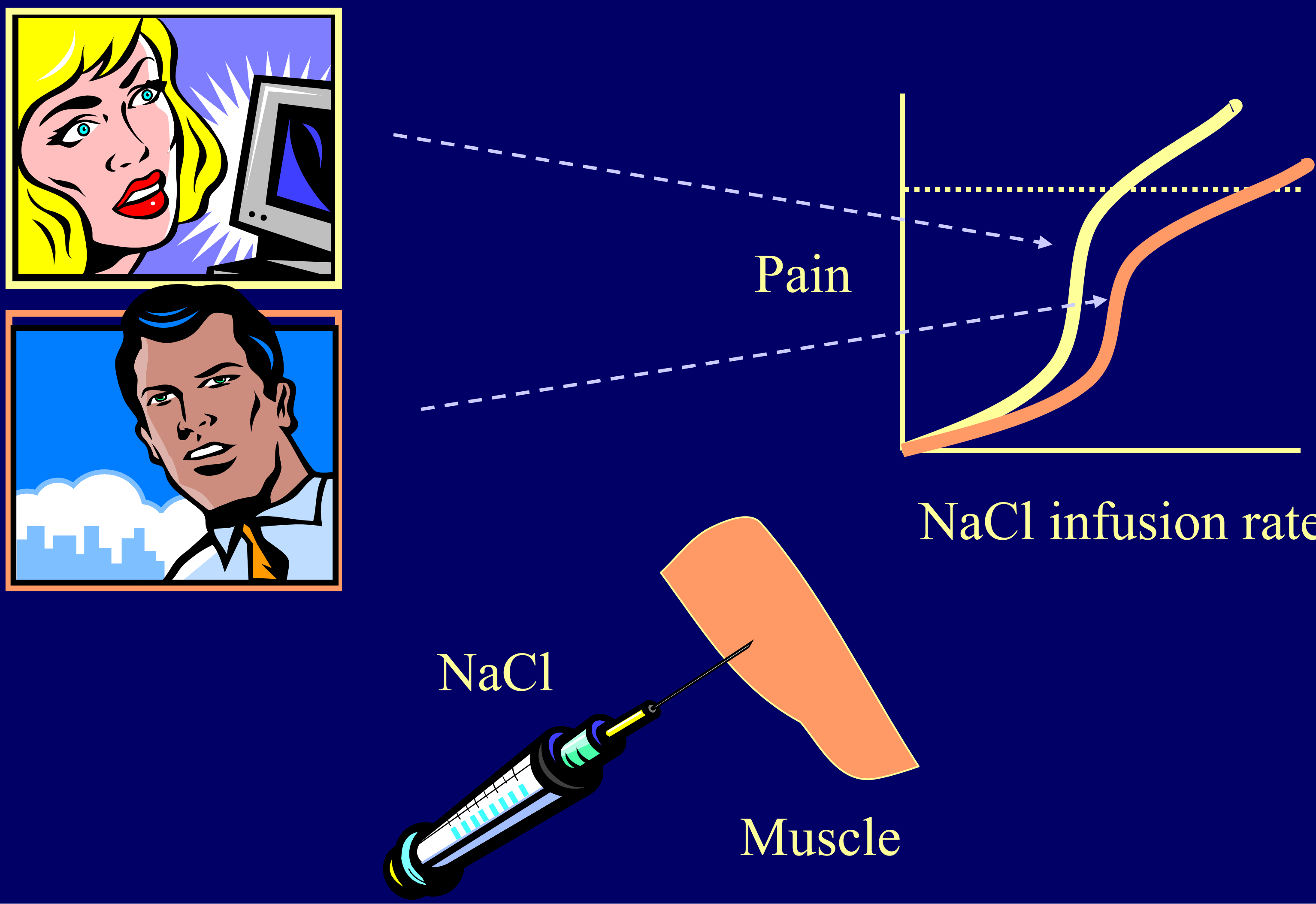


Lack of evidence for polygenic inheritance of addictions

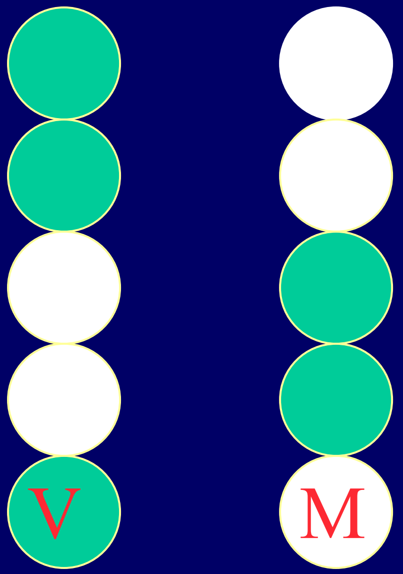


Nature Genetics Reviews, 2005

Pain/Stress Challenge:
Hypertonic saline infusion to masseter muscle



COMT yin/yang haplotypes in five populations & *Linkage to Opioid addiction* & *Alcoholism*



Case/Control		V	M	*p value*
477/361	Chinese	0.25	0.24	*.003*
167/294	African American	0.09	0.08	*.03*
490/192	German Caucasian	0.24	0.28	*.02*
178/283	Finnish Caucasian	0.15	0.27	*<.001*
175/175	Plains Indian	0.09	0.22	

COMT Val158Met and Addiction

- Polysubstance abuse: Val158
  - Vandenburgh, Uhl and colleagues
- Late onset alcoholism: Met158
  - [Hallikainen et al, 2000] 62 early onset, 132 late onset, 267 controls. Odds ratio of 3 for late onset, p=0.017
  - [Tiihonen et al, 1999] 67 & 56 late onset, 3140 blood donors, 267 matched controls. Met/Met vs Val/Val Odds ratio 2.5, p =0.006, Attributable risk for Met/Met vs Val/Val 13.3%

COMT Val158Met

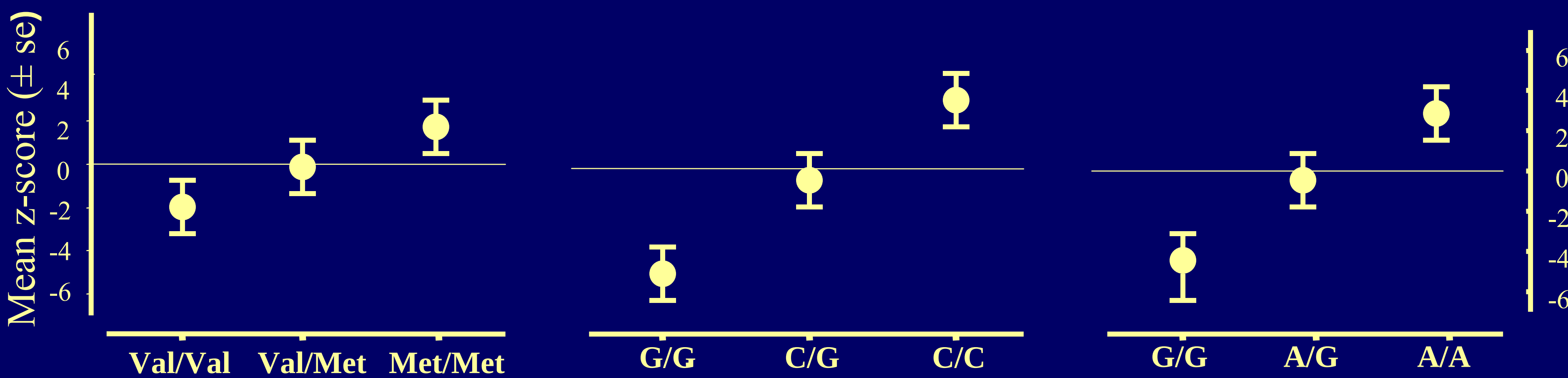
Val158 → *Behavioral Dyscontrol*

Met158 → *High anxiety, Stress reactive*

Alcoholism and other substance abuses

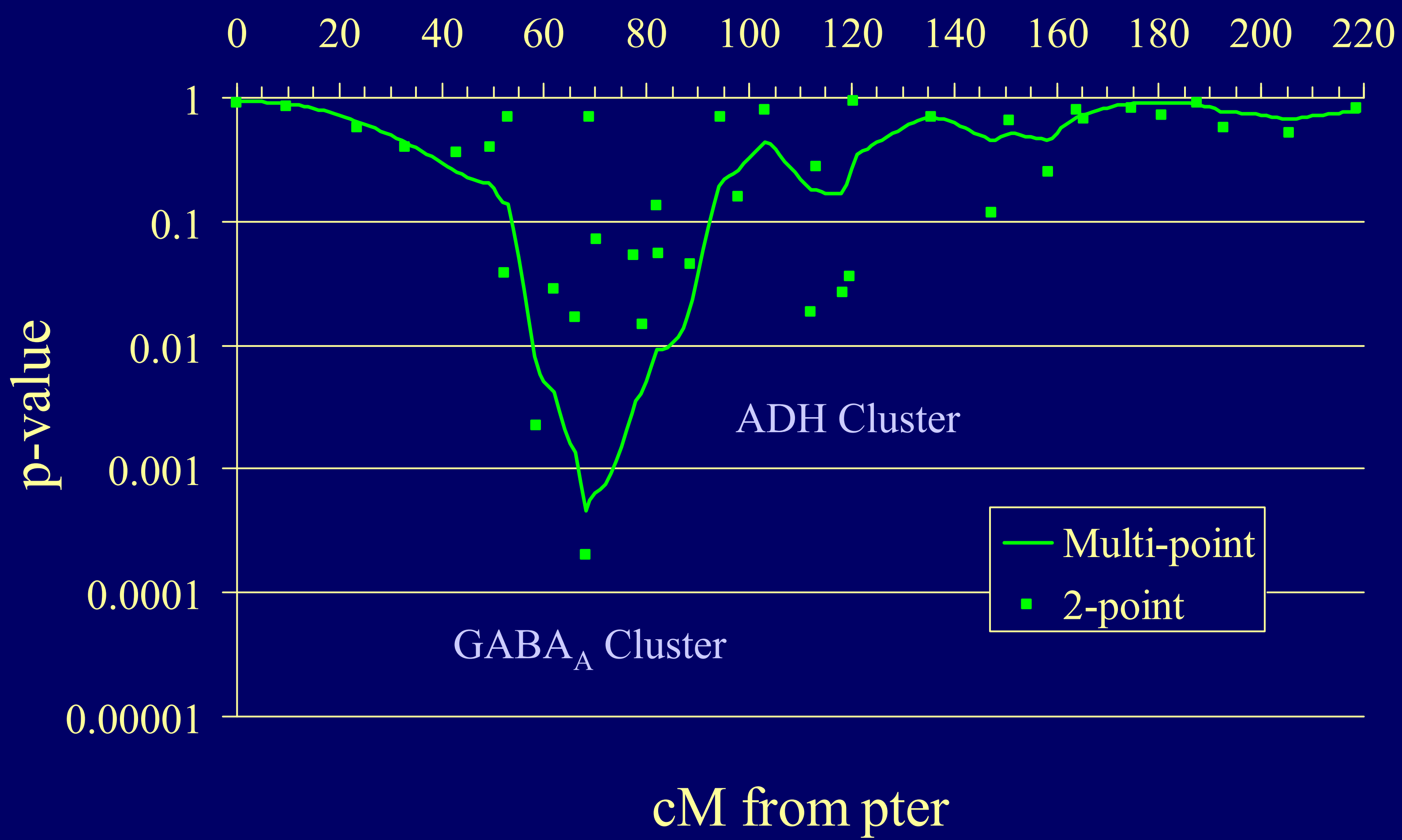
Replication of COMT in experimental pain in 202 females prospectively followed for TMJ

(Diatchenko et al, Hum Mol Genetics, 2005)



Val158/Met158	rs4818	rs6269
ANOVA: p=0.18	*p<0.01*	*p<0.01*

Chromosome 4



Long et al, 1998

GABRA2 LD and Alcoholism Linkages

Edenberg et al * * *

Kranzler et al * * *

Enoch et al * * *

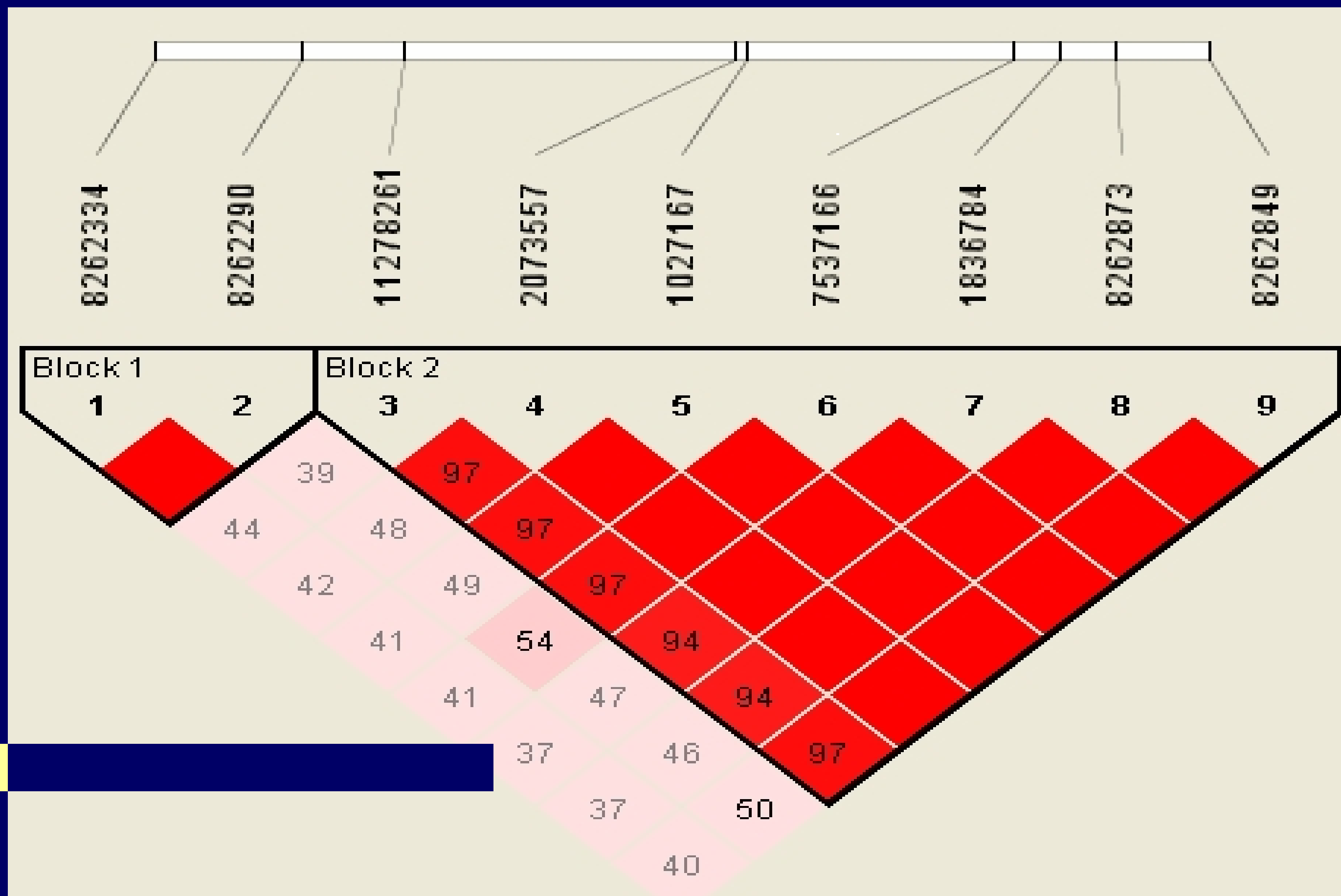
Same alleles, Same haplotype

Haplotype Tagging

1121121

2212212

2212211



Addictions Array for 130 Candidate Genes

- 1536 SNPs
- Tagging of haplotypes > 0.6% in frequency
- Avg of >11 SNPs/gene, Range 4 - 35
- 186 "perfect" genomic control SNPs (AIMs)
  - Balanced set with cross-population Δ>0.7, and >10x
- $ <0.05/genotype
- 25,000 individuals genotyped (Yale, Rockefeller, Wash U, Columbia [2], Univ. Colorado, Emory, VCU, NICHD)

Addictions Array 130 Genes Tagged with 1350 SNPs

HPA & Stress

CRH
CRHBP
CRHR1
CRHR2
GAL
NPY
NPY1R
NPY2R
NPY5R

Adrenergic

ADRA1A
ADRA2A
ADRA2B
ADRA2C
ADRB2
ARRB2
SLC6A2
DBH

Other

BDNF
CCK
CCKAR
CCKBR
CLOCK
HCRT
OXT
NR3C1
SLC29A1
TAC1
CART

Metabolic

ALDH1A
ALDH2
CAT
CYP2E1
ADH1A
ADH1B
ADH1C
ADH4
ADH5
ADH6
ADH7

Dopamine

DDC
DRD1
DRD2
DRD3
DRD4
DRD5
SLC18A2
TH
COMT

Serotonin

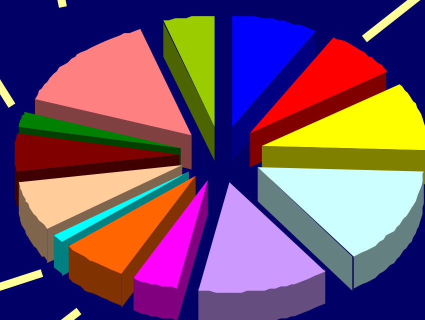
HTR1A
HTR1B
HTR2A
HTR2C
HTR3A
HTR3B
MAOA
MAOB
SLC6A3
SLC6A4
TPH2

Signal Transduction

ADCY7
AVPR1A
AVPR1B
CDK5R1
CREB1
CSNK1E
FEV
FOS
FOSL1
FOSL2
GSK3B
JUN
MAPK1
MAPK3
MPDZ
NGFB
NTRK2
NTSR1
NTSR2
PPP1R1
BPRKCE

Cholinergic

CHRM1
CHRM2
CHRM3
CHRM4
CHRM5
CHRNA4
CHRNB2



GABA

GABRA2
GABRA4
GABRA6
GABRB1
GABRB2
GABRB3
GABRD
GABRG2
GABRG3
SLC6A11
SLCSA13
GAD1
GAD2
VIAAT
DBI

Cannabinoid

CNR1
FAAH

NMDA

GRIK1
GRIN1
GRIN2A
GRIN2B
GRM1

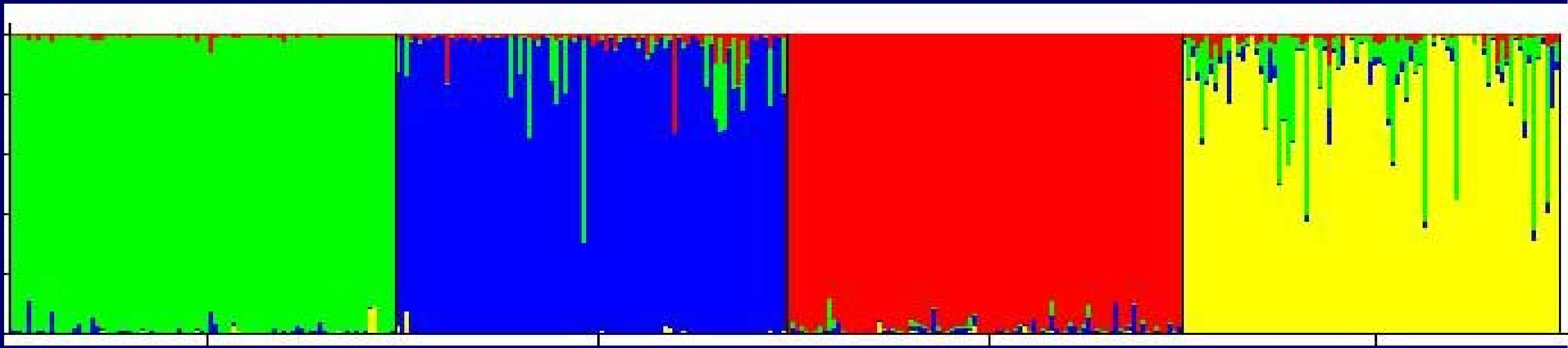
Glycine

GLRA1
GLRA2
GLRB
GPHN

Opioid

OPRM1
OPRD1
OPRK1
OPRL1
PDYN
PENK
PNOC
POMC

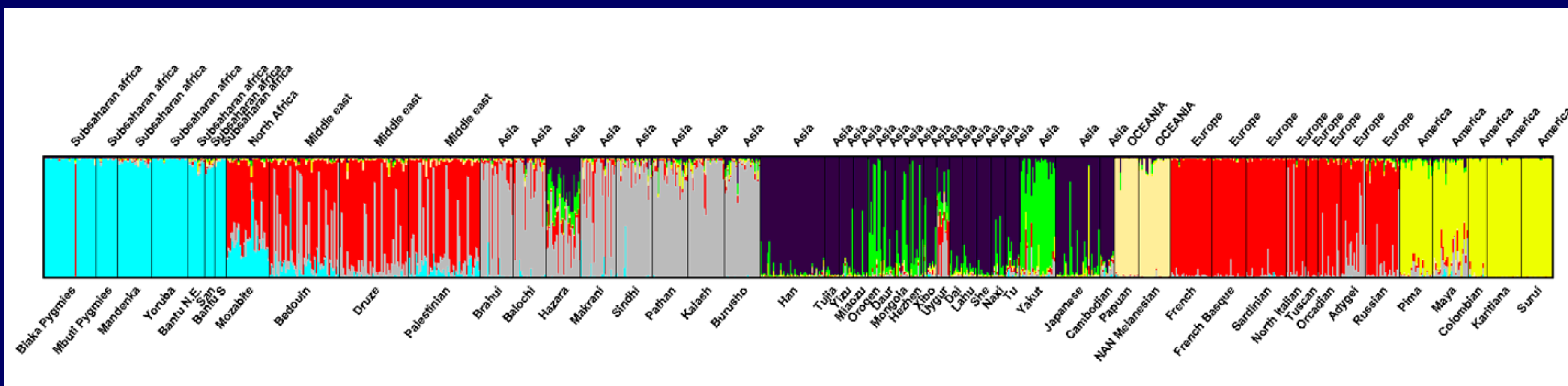
Assignment of ancestry with 186 Ancestry-informative SNPs (Structure2, Four-factor solution)



Finns	Plains Indians	Han Chinese	African American
0.98	0.05	0.01	0.11
0.01	0.92	0.01	0.02
0.01	0.02	0.98	0.02
0.00	0.00	0.00	0.85

Ethnic factor scores of 1051 individuals in 52 CEPH populatio with 186 AIMs

7-factor solution, Structure 2

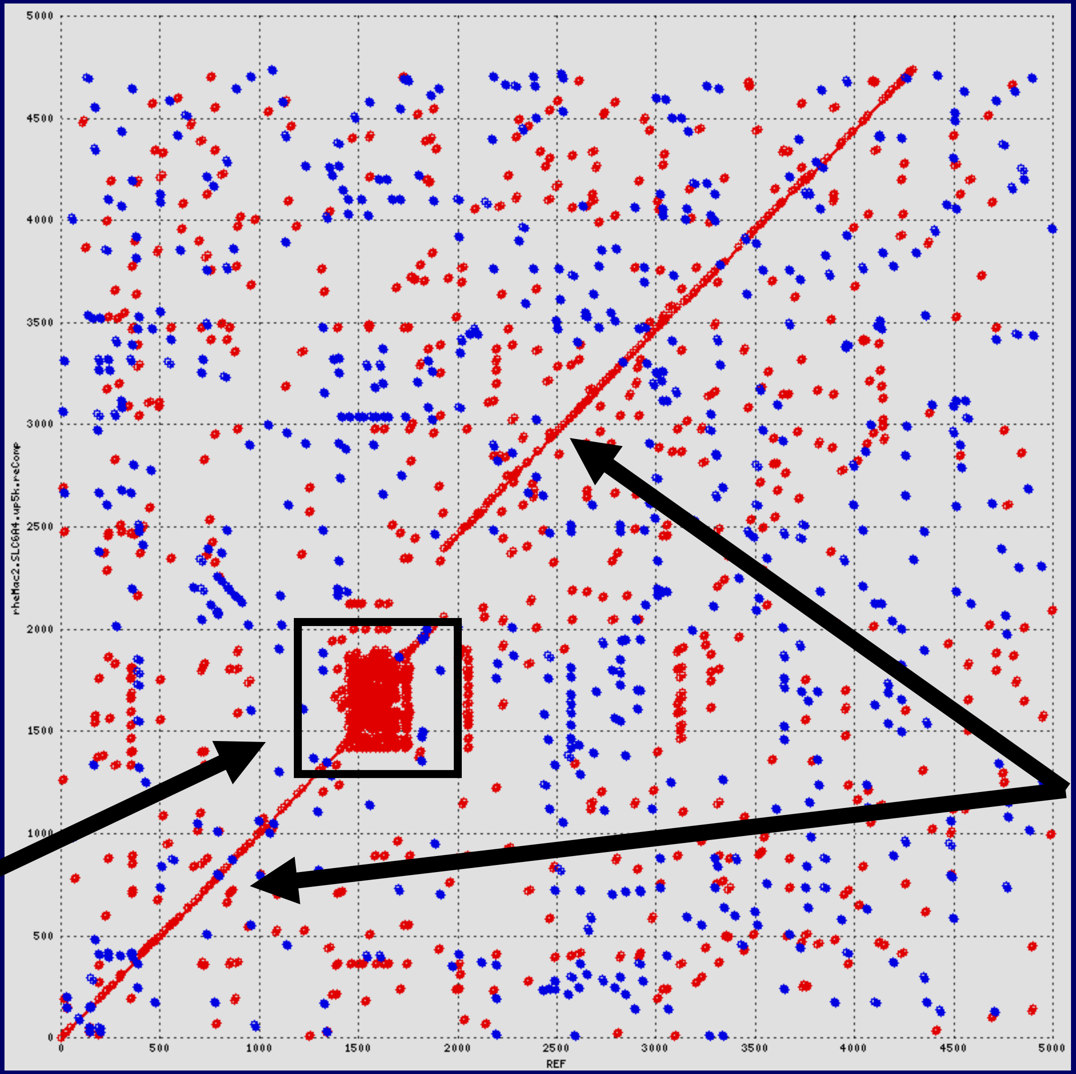


Africa | Middle East | Asia | Oceania | Europe | America

Hodgkinson et al, unpublished

Repeats in the 5 Kb region upstream of 5-HTT in Macaca mulatta and Homo sapiens

Macaque



Human

20-22 bp Imperfect repeats

Sequence Identity

rh-HTTLPR has GxE effects on alcohol preference & stress response

Interaction Between Serotonin Transporter Gene Variation and Rearing Condition in Alcohol Preference and Consumption in Female Primates

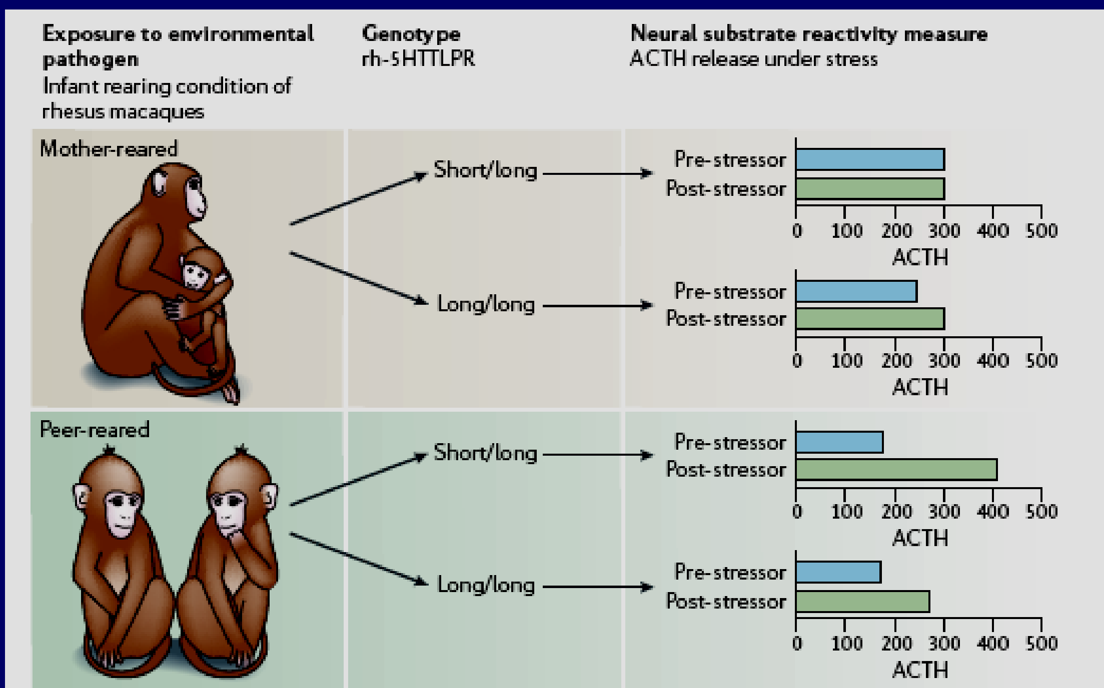
Christina S. Barr, VMD, PhD; Timothy K. Newman, PhD; Stephen Lindell, BA; Courtney Shannon, BA; Maribeth Champoux, PhD; Klaus Peter Lesch, MD; Stephen J. Suomi, PhD; David Goldman, MD; J. Dee Higley, PhD

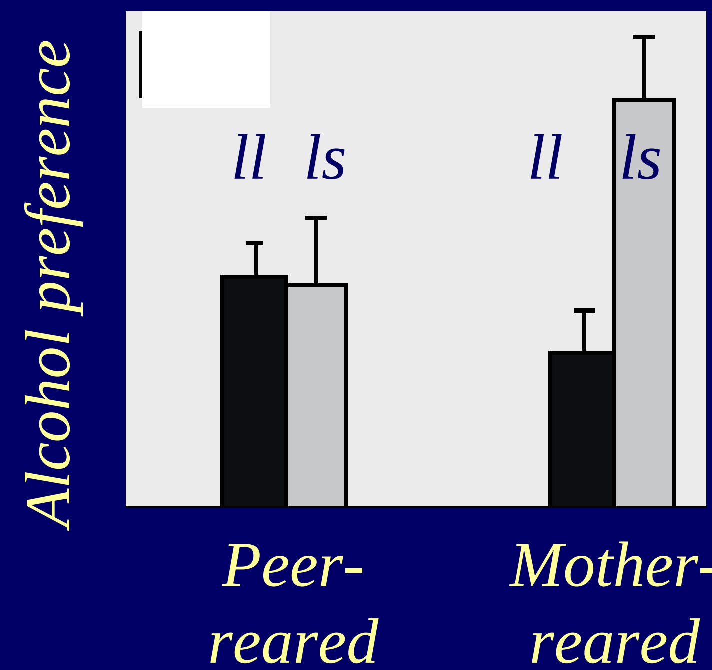
Arch Gen Psych 61: 1146, 2004

Rearing Condition and rh5-HTTLPR Interact to Influence Limbic-Hypothalamic-Pituitary-Adrenal Axis Response to Stress in Infant Macaques

Christina S. Barr, Timothy K. Newman, Courtney Shannon, Clarissa Parker, Rachel L. Dvoskin, Michelle L. Becker, Melanie Schwandt, Maribeth Champoux, Klaus Peter Lesch, David Goldman, Stephen J. Suomi, and J. Dee Higley

Biol Psych 55: 733, 2004





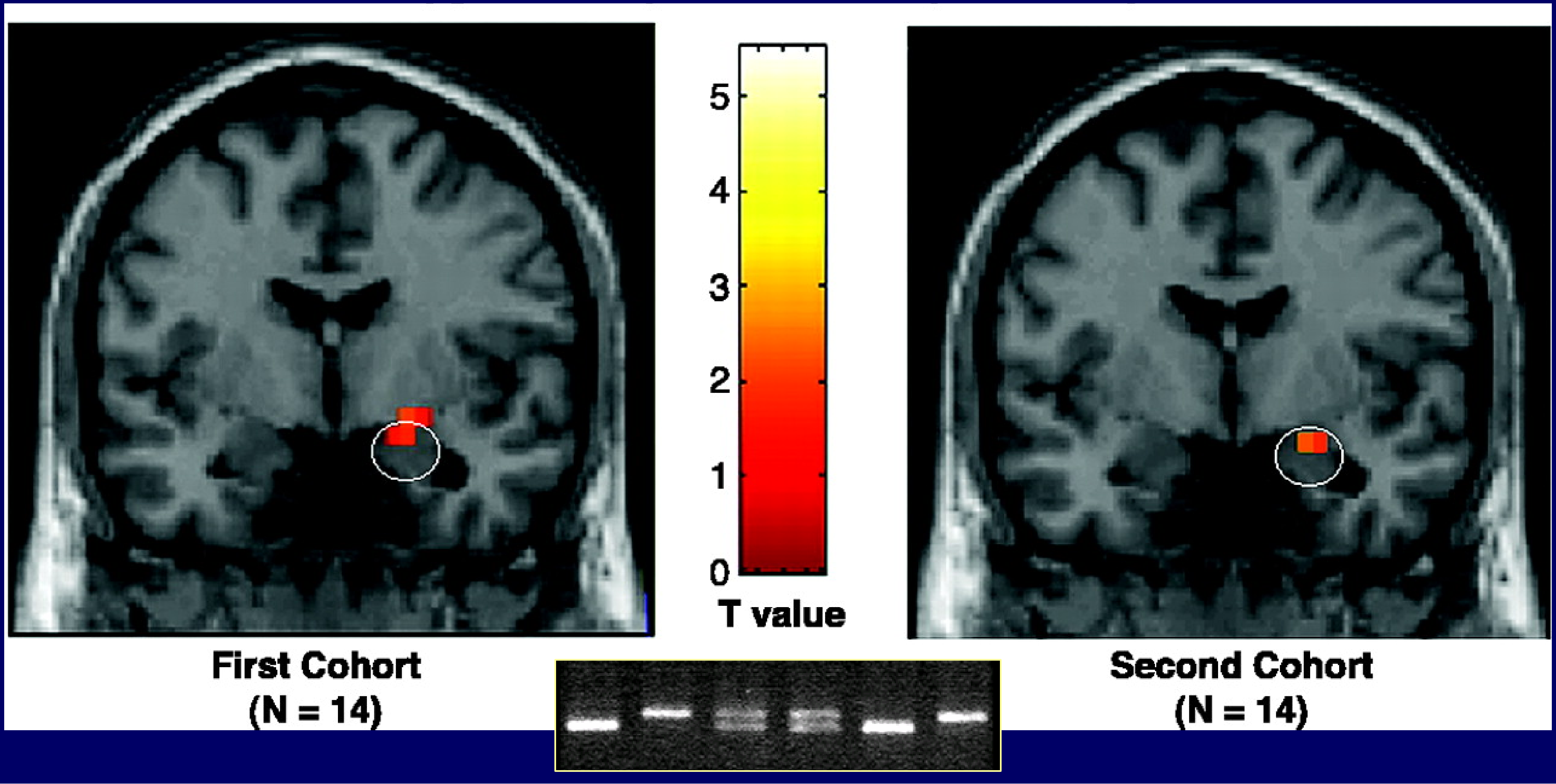
Serotonin Transporter Genetic Variation and the Response of the Human Amygdala

Science 2002 July 19; 297(5580):400-3

Ahmad R. Hariri,[1] Venkata S. Mattay,[1] Alessandro Tessitore,[1] Bhaskar Kolachana,[1] Francesco Fera,[1] David Goldman,[2] Michael F. Egan,[1] Daniel R. Weinberger[1*]

[1] Clinical Brain Disorders Branch, NIMH, NIH.

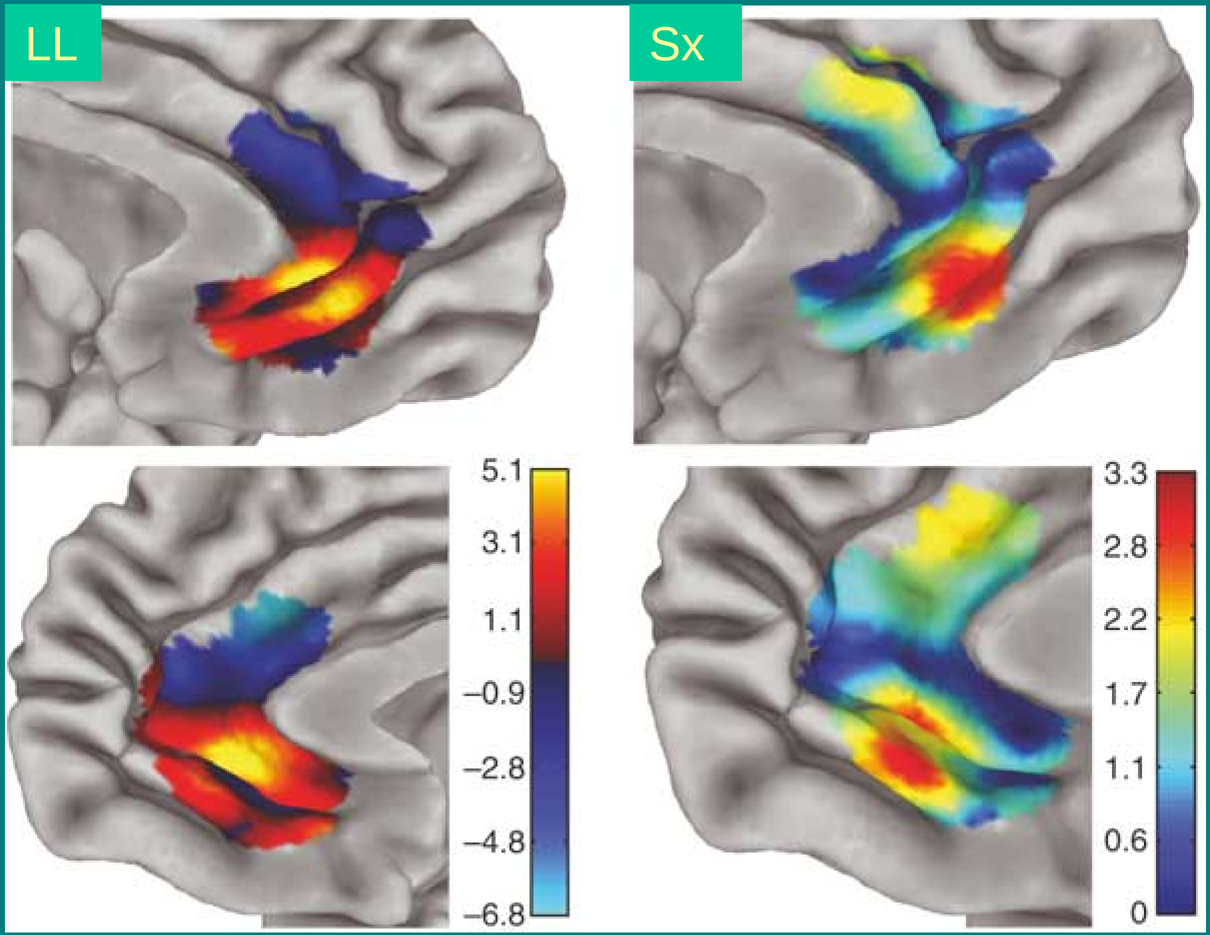
[2] Laboratory of Neurogenetics, NIAAA, NIH.



Nature Neuroscience **8**, 828 - 834 (2005)

5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression

Lukas Pezawas, Andreas Meyer-Lindenberg, Emily M Drabant, Beth A Verchinski, Karen E Munoz, Bhaskar S Kolachana, Michael F Egan, Venkata S Mattay, Ahmad R Hariri & Daniel R Weinberger

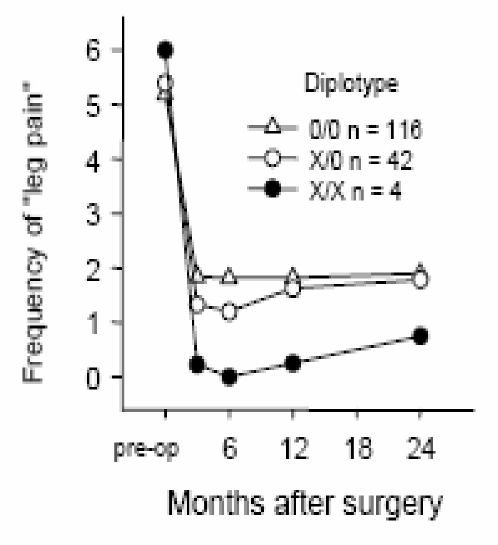


Statistical functional connectivity maps between bilateral amygdala and perigenual anterior cingulate cortex

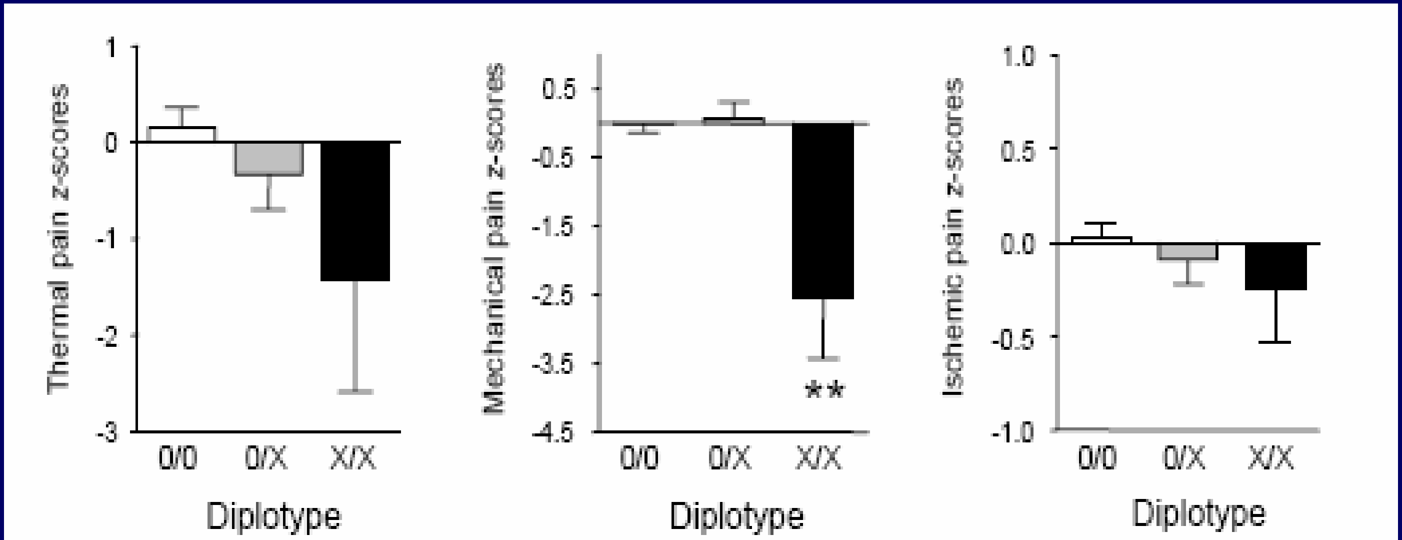
A common, functional NPY haplotype influencing anxiety and stress response
(Zhifeng Zhou et al, submitted)

- The common haplotype predicts reduced brain and lymphoblast mRNA levels and plasma NPY
- The reduction of function haplotype predicts:
  - Trait anxiety
  - Reduced amygdala emotional fMRI activation
  - Reduced amygdala pain/stress induced opioid release
- A functional promoter locus was identified via *in vitro* reporter constructs

A functional human GCH1 haplotype predicts post-diskectomy clinical pain and experimental pain



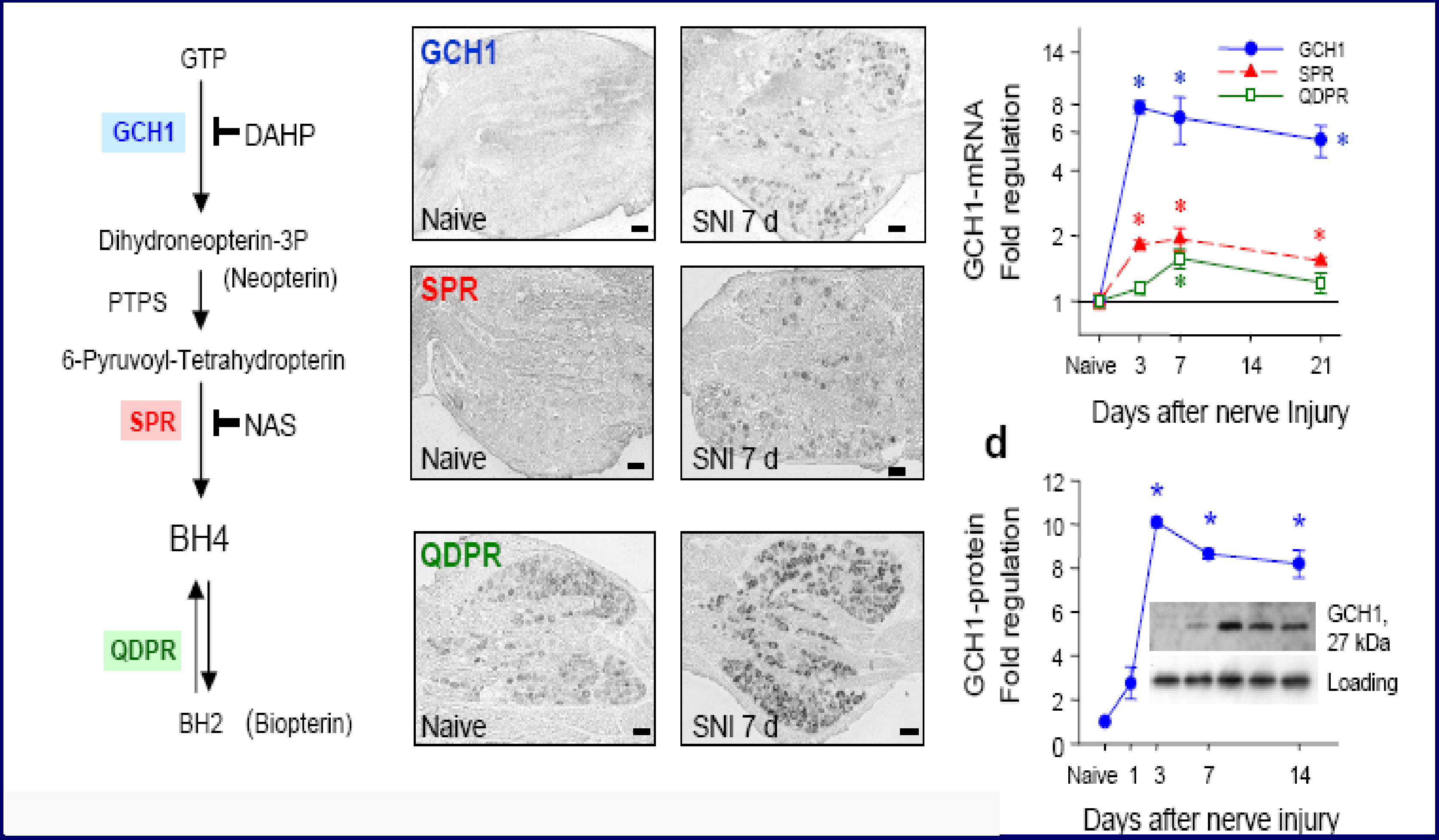
162 post-diskectomy patients



547 normal controls

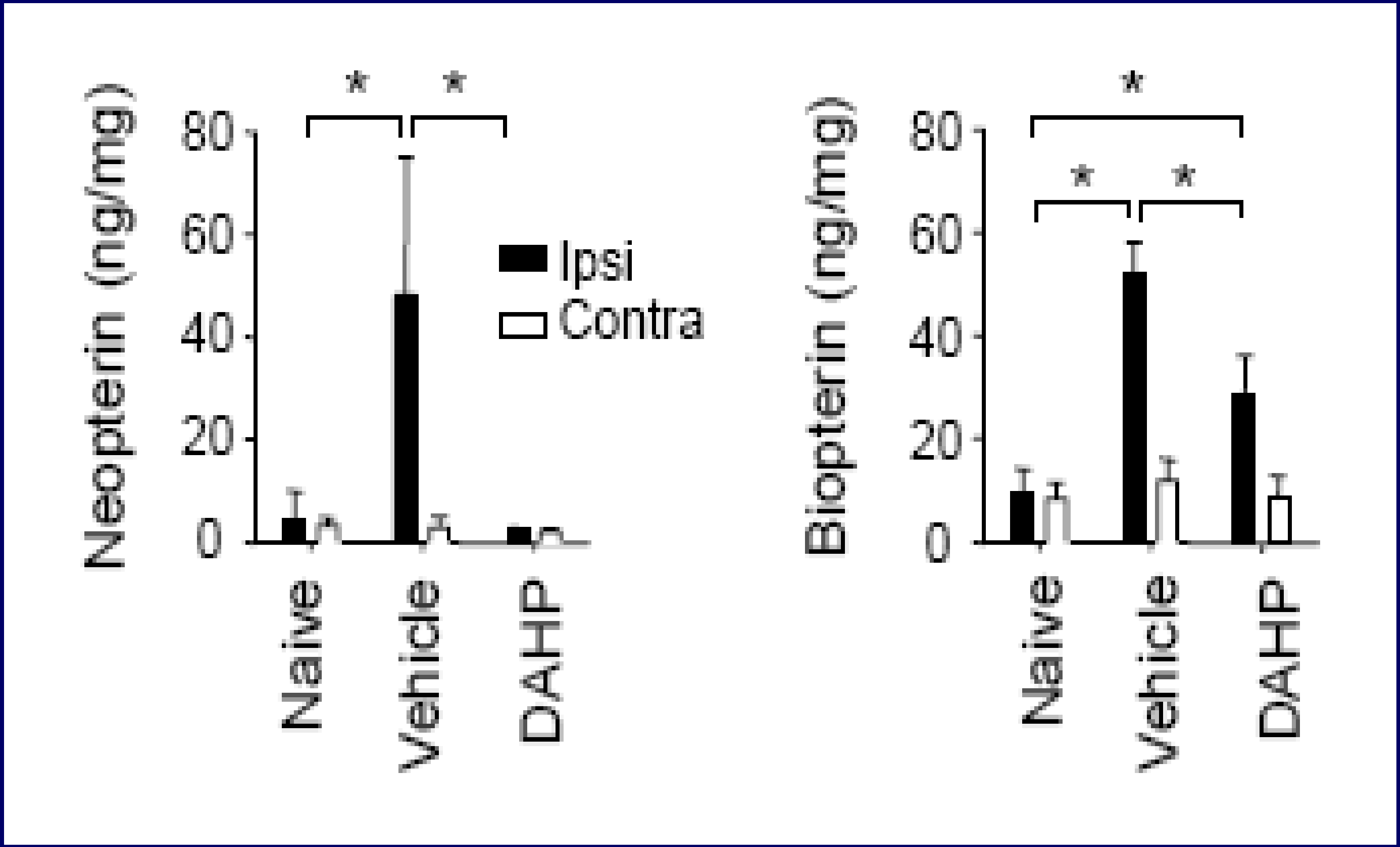
Tegeder et al, Nature Medicine, 2006

GCH1 mRNA and protein in rat DRG are upregulated by nerve injury



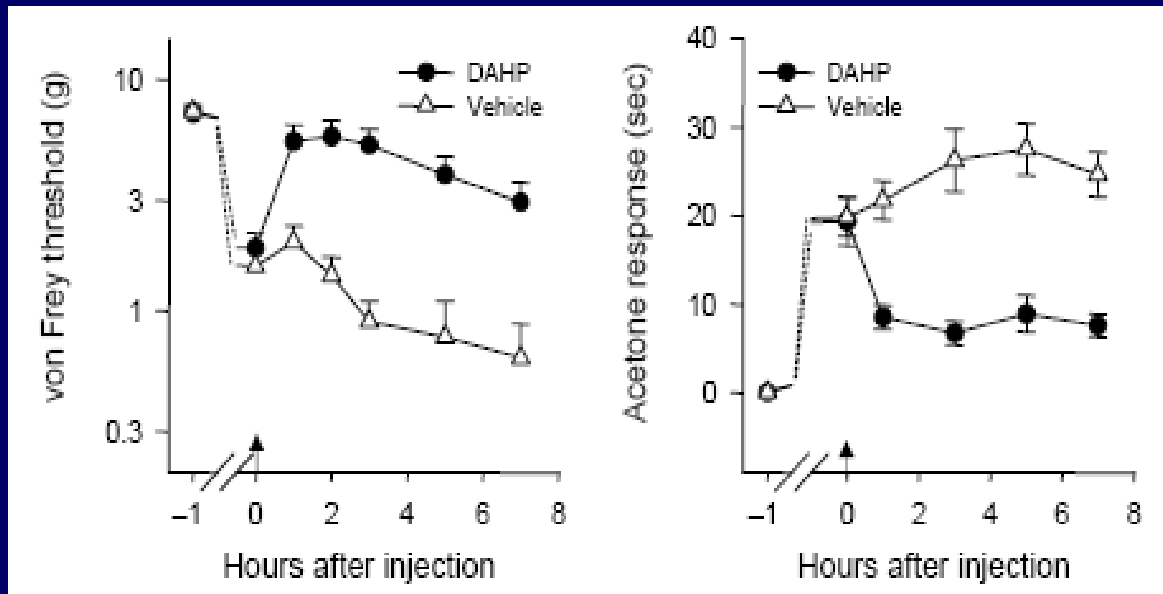
Tegeder et al, Nature Medicine, 2006

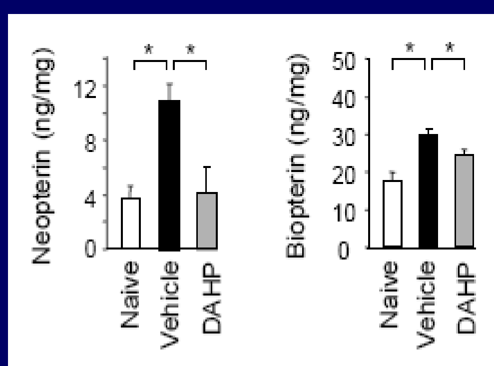
Biopterin synthesis in rat DRG is upregulated by nerve injury and blocked by a GCH1 inhibitor

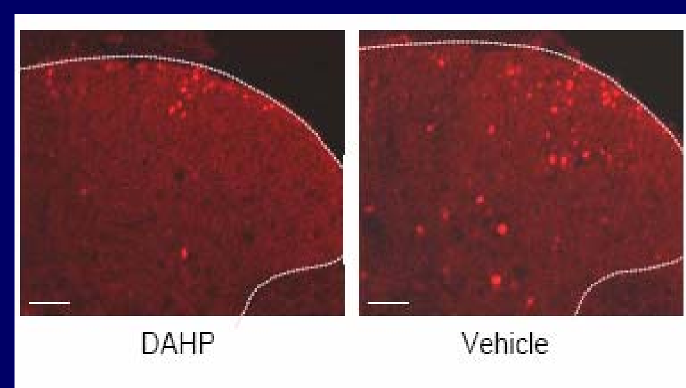


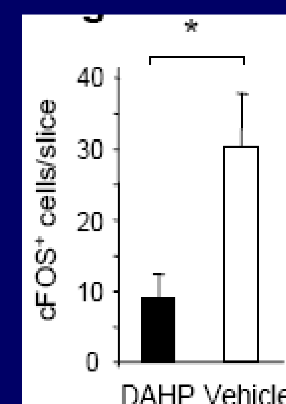
Tegeder et al, Nature Medicine, 2006

Rapid inhibition of pain and DRG neuronal activation by the GTP cyclohydrolase inhibitor, 2,4-diamino-6-hydroxypyrimidine (DAHP)



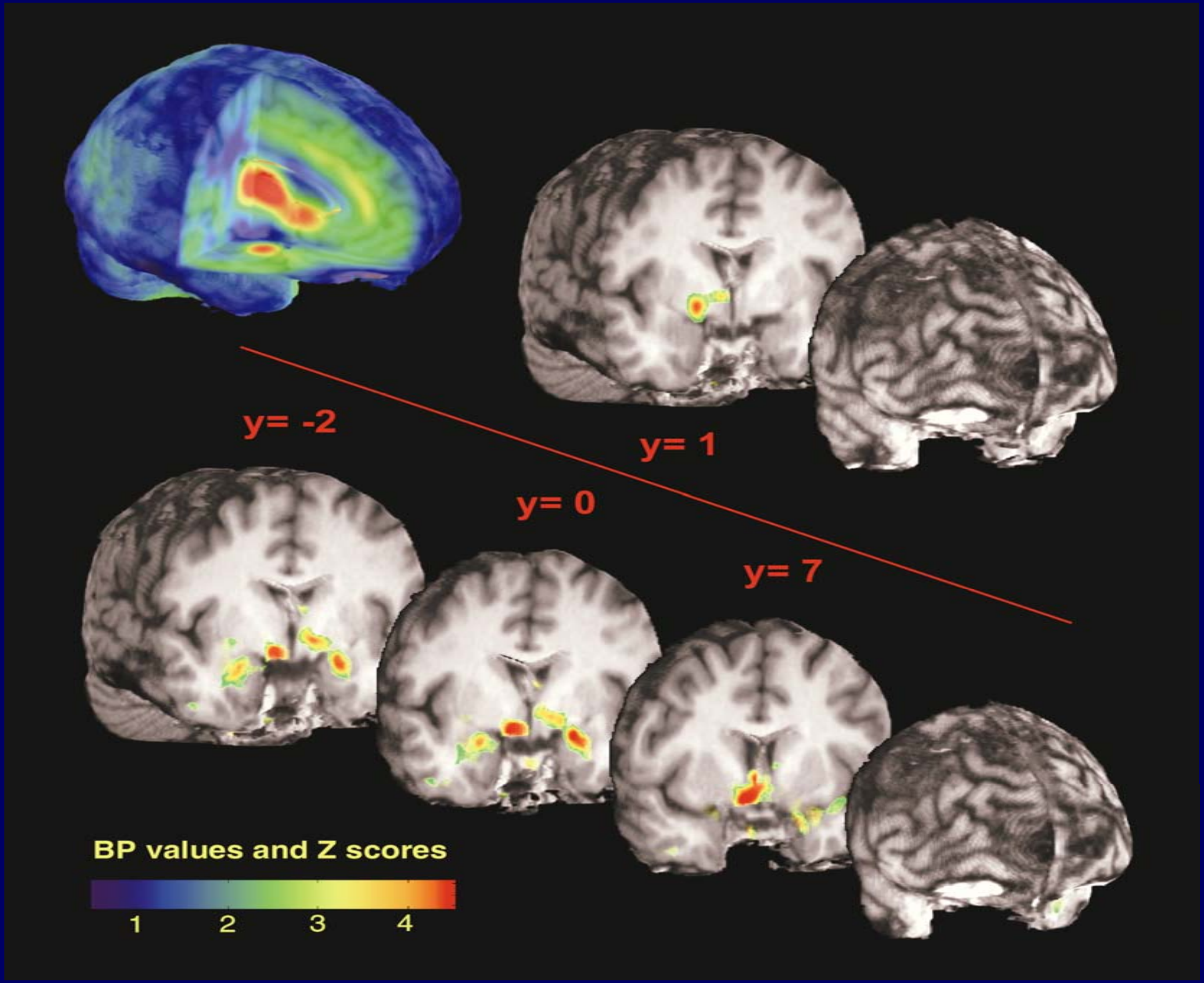






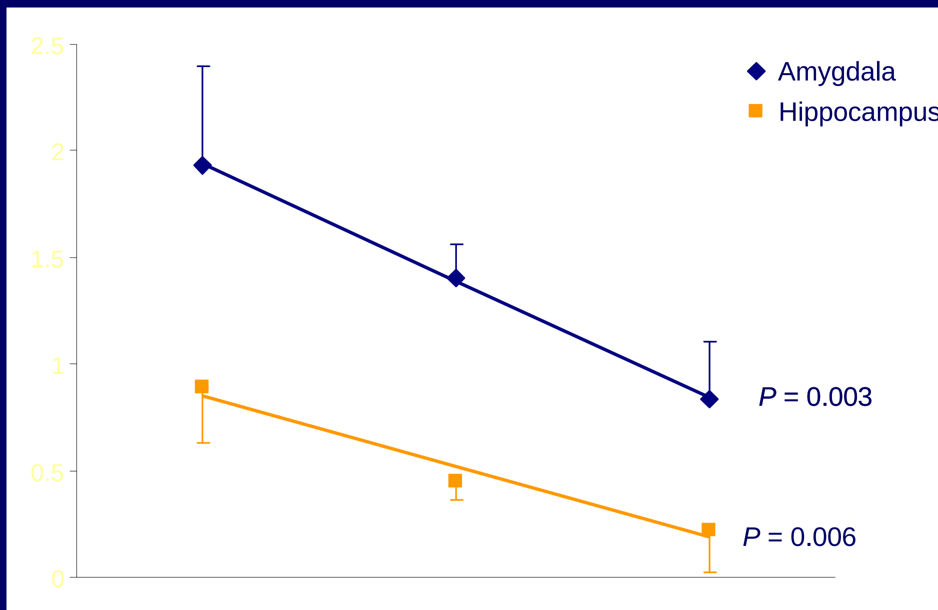
Tegeder et al, Nature Medicine, 2006

Genotype-predicted NPY expression predicts pain/stress induced opioid activation
Zhou et al, submitted



Genotype-predicted NPY expression predicts emotion-induced fMRI activation
Zhou et al, submitted

fMRI Activation (Arbitrary Units)



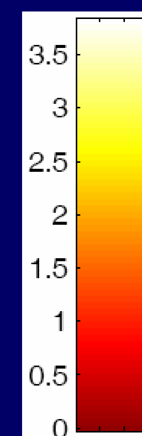
LL (n = 11) **LH** (n = 42) **HH** (n = 18)

***NPY* Diplotype**

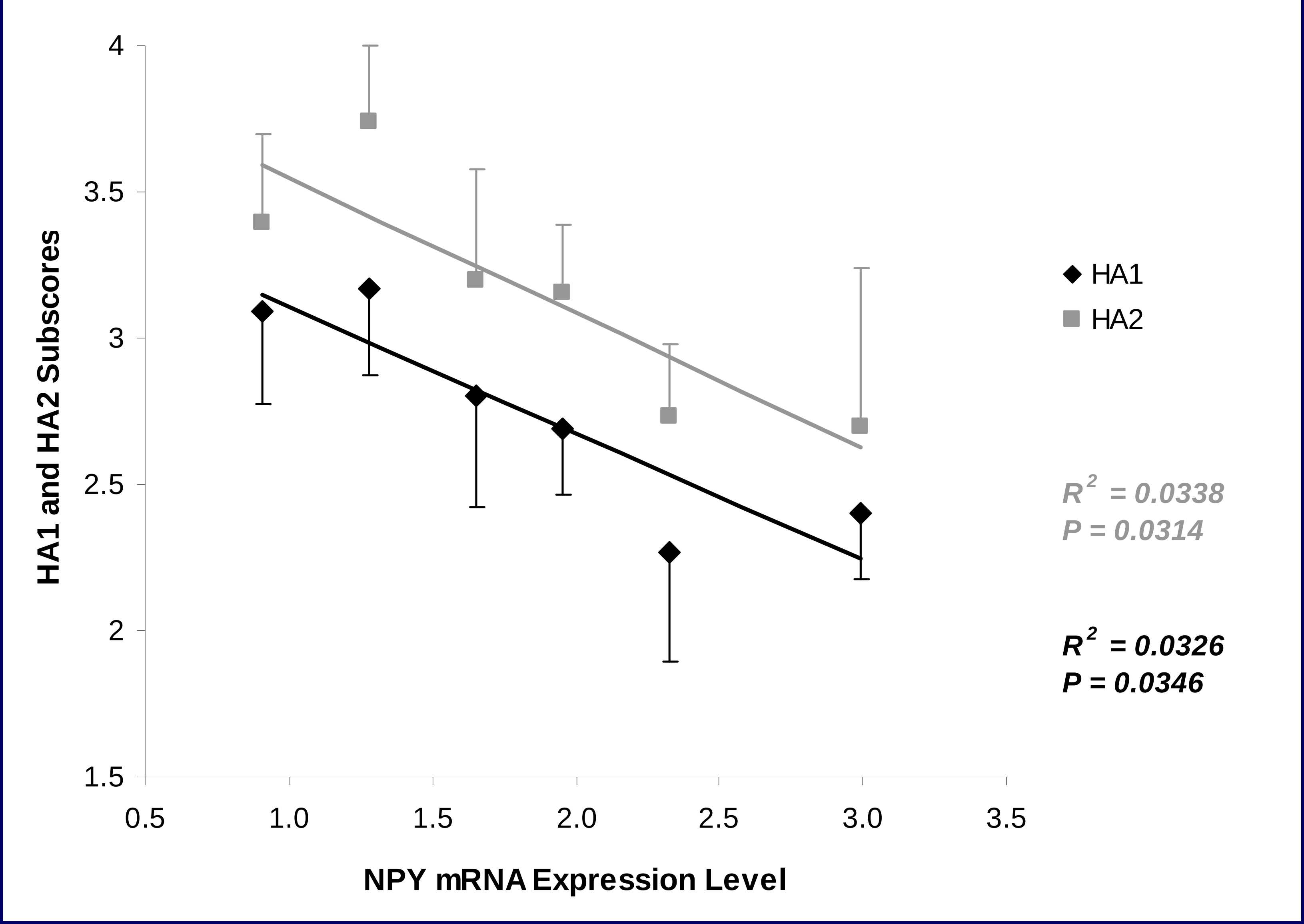
Amygdala

Hippocampus

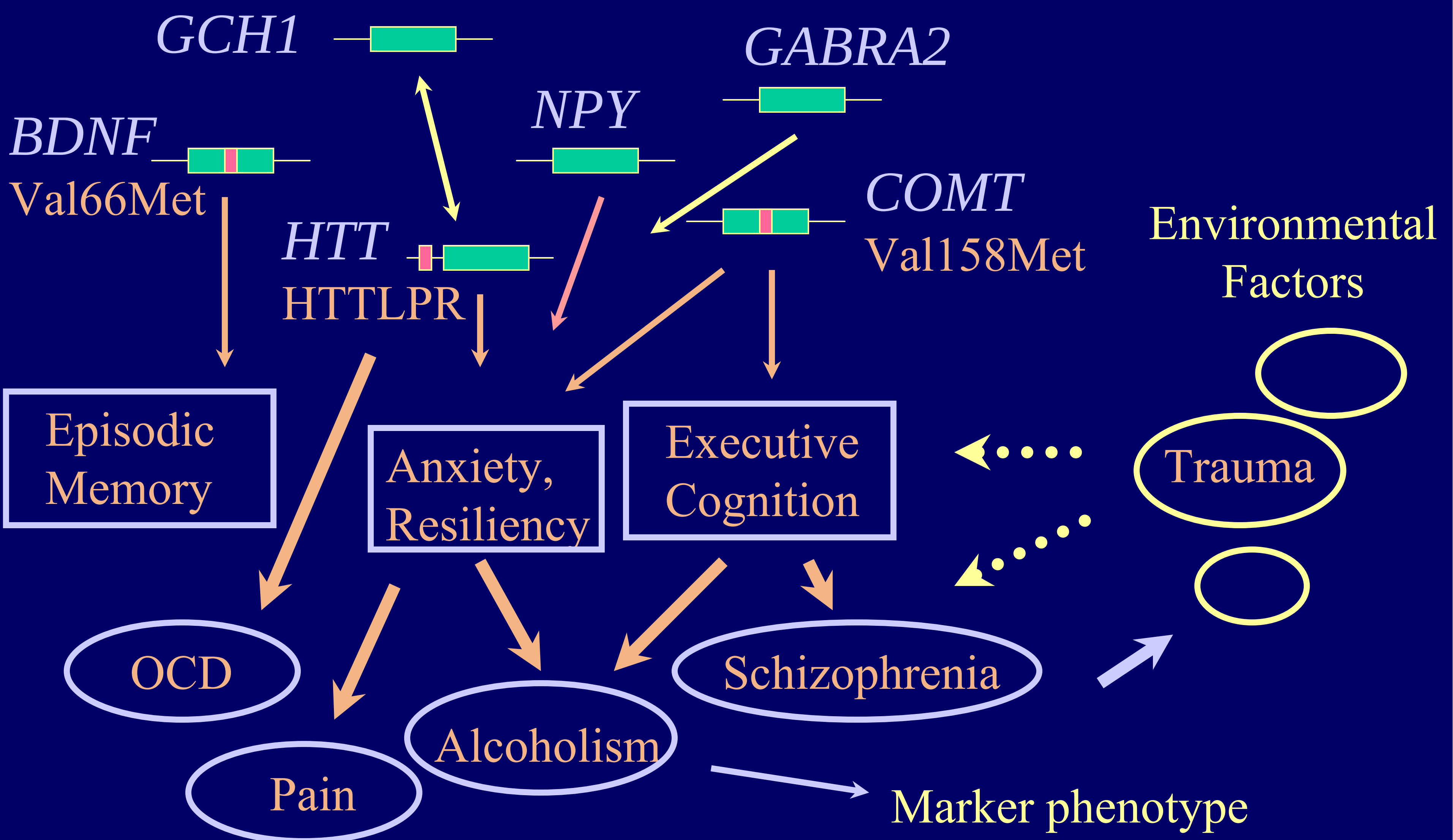
T Value



Genotype-predicted NPY expression predicts anxiety
Zhou et al, submitted



Functional Allele to Complex Behavior



HTTLPR and anxiety

[Sen, Burmeister and Ghosh, 2004]

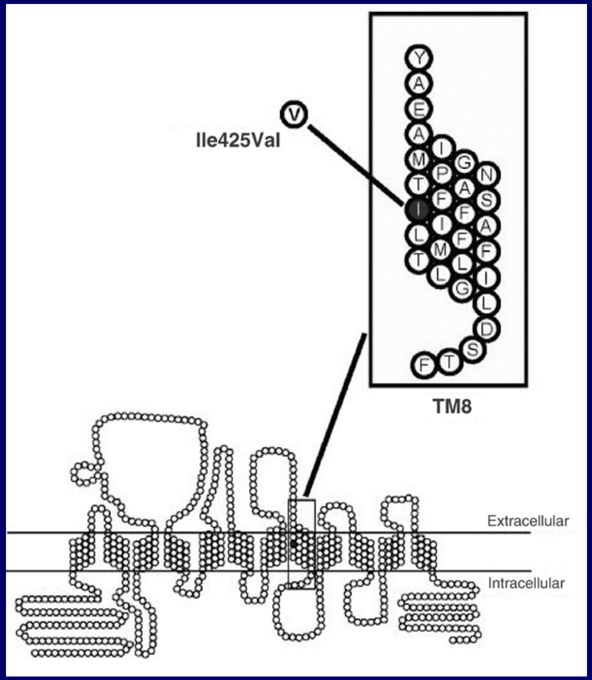
- 26 Studies, 5,629 subjects
- $p = 0.087$
- Substantial effect of inventory and inter-study heterogeneity
- $p < 0.000016$, NEO, corrected for heterogeneity
- 0.1 SD increment in TPQ Harm avoidance or NEO Neuroticism per ”s” allele

Triallelic Functionality at HTTLPR

- S and L_G are equivalent in expression in lymphoblasts and raphe-derived neurons
- AP2 transcription factor binds to L_G and acts as a repressor of transcription
  - Gel-shift and supershift assays
  - Allele-specific, AP2-specific decoy DNA eliminates the L_A:L_G difference

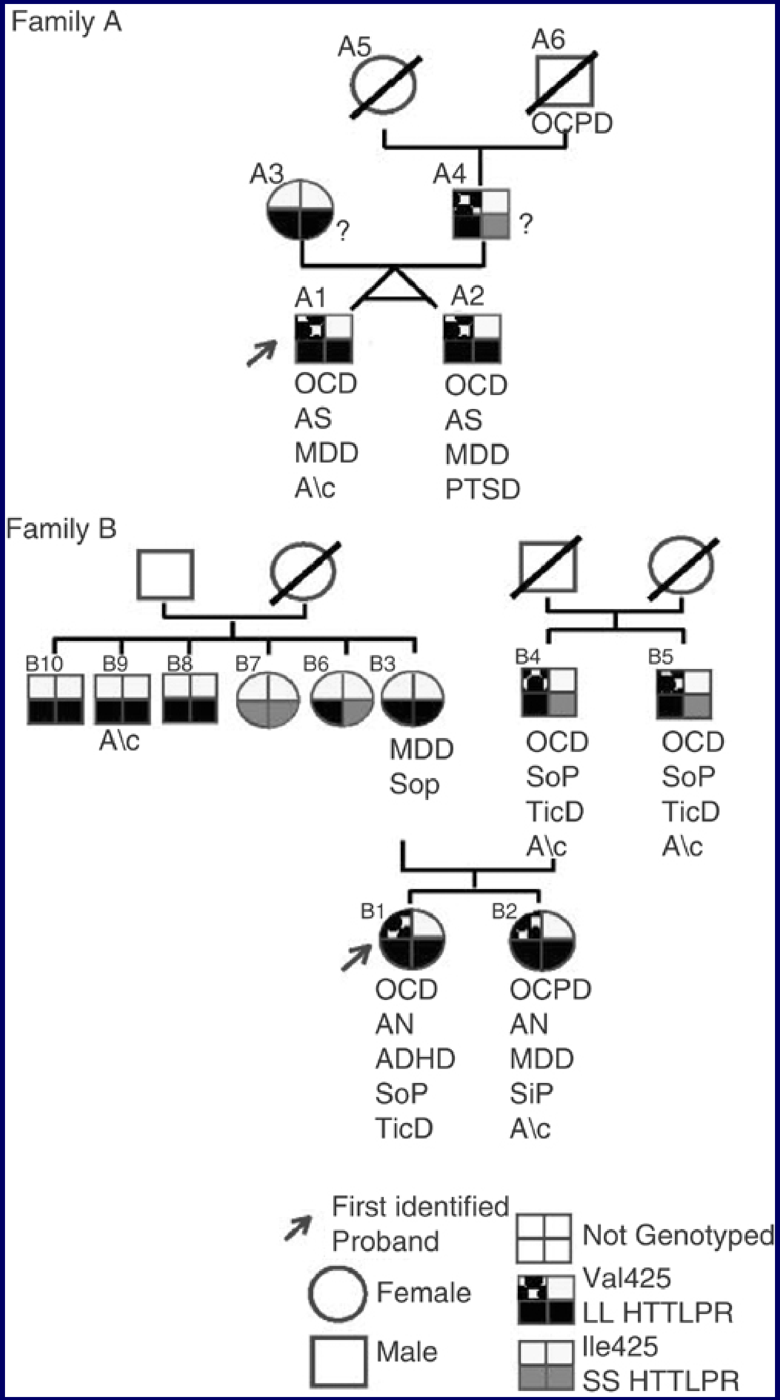
Hu et al, AJHG, 2006

HTT



Ile425Val

Ozaki et al, Mol Psych, 2003



Replication of HTTLPR-OCD linkage in Parent/child trios
Collaboration with James Kennedy, Clarke Centre, Toronto

Triallelic

	S	L_G	L_A
Transmitted	27	11	48
Untransmitted	44	16	26

$p = 0.023$

Low/High

	S, L_G	L_A
Transmitted	20	41
Untransmitted	41	20

$p = 0.010$

Hu et al, AJHG, 2006

HTTLPR genotype and allele frequencies in 169 OCD patients and 253 controls

	Genotypes						Alleles		
	SS	SL_A	SL_G	L_AL_A	L_AL_G	L_GL_G	S	L_A	L_G
OCD	0.21	0.34	0.03	0.34	0.07	0.01	0.38	0.56	0.06
Control	0.16	0.47	0.08	0.19	0.08	0.02	0.44	0.47	0.10

Genotypes: $\chi 2 = 19.4$, $p = 0.001$

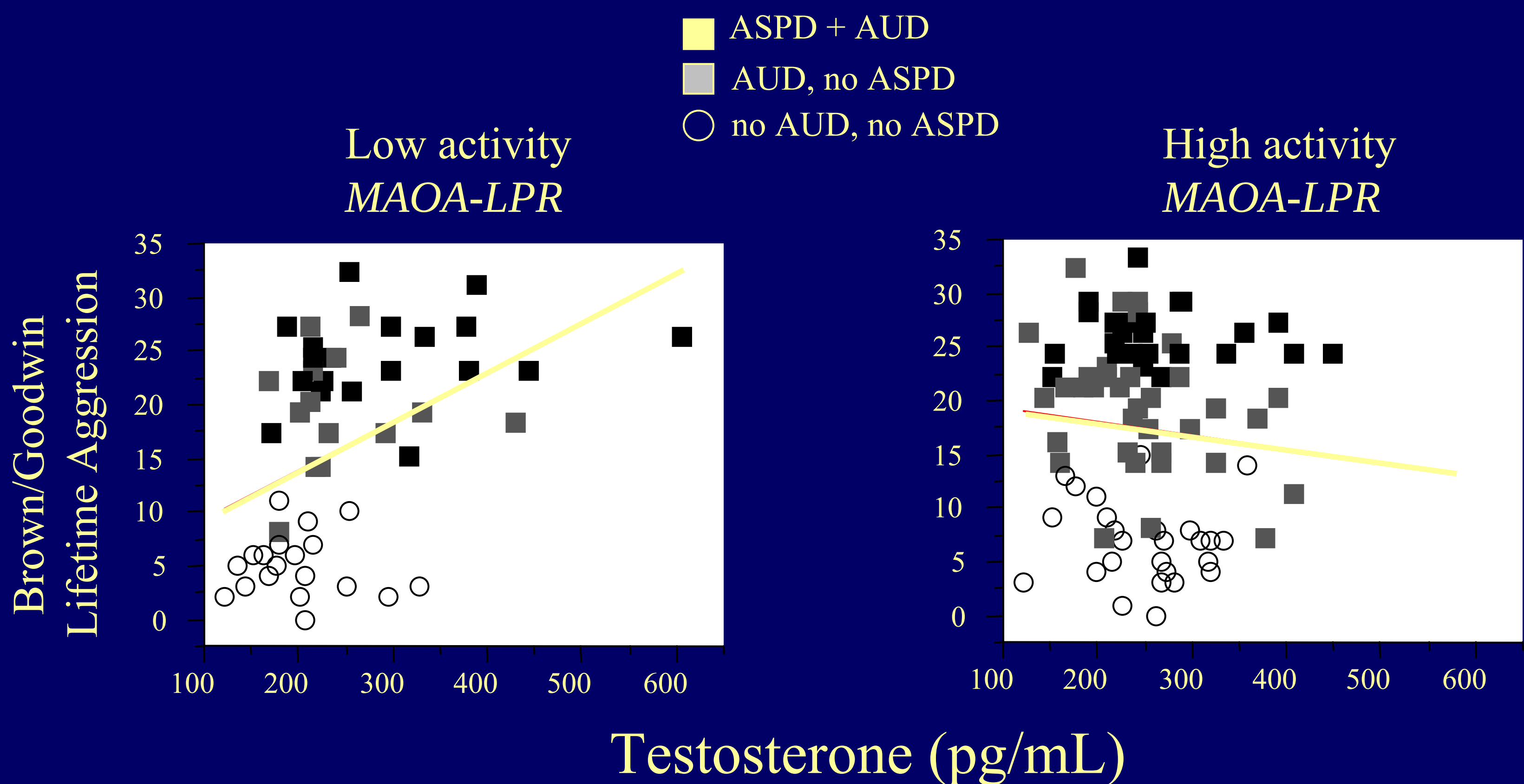
Alleles: $\chi 2 = 6.6$, $p = 0.036$

	SS	SL	LL	S	L
OCD	0.21	0.37	0.42	0.39	0.61
Control	0.16	0.55	0.29	0.44	0.56

Genotypes: $\chi 2 = 15.0$, $p = 0.001$

Alleles: $\chi 2 = 1.5$, $p = 0.216$

Non-additive interaction of *MAOA-LPR* and testosterone predicts antisocial behavior



β_a (SE) = 3.49 (1.01); p=0.001

β_a (SE) = −0.94 (1.04); p=0.37

Sjoberg et al., *Neuropsychopharmacology* 2007