PGC Worldwide Lab Call Details

DATE: Friday, February 14th, 2014
PRESENTER: Kerry Ressler, Emory School of Medicine
TITLE: "Post-Traumatic Stress Disorder: Understanding the Intersection of Gene, Environment, and Brain"
START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CET - Central Europe
0000 AEDT – Australia (Saturday, June 22nd, 2013)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
- Operators will be on standby to assist with technical issues. "*0" will get you assistance.
- This conference line can handle up to 300 participants.

PASSCODE: 275 694 38 then #

Lines are Muted **NOW**

Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.

Operators announce callers one at a time during question and answer sessions.

Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.

Dial *0 if you need operator assistance at any time during the duration of the call.

UPCOMING PGC Worldwide Lab

DATE: Friday, March 14th, 2014
PRESENTER: Peter Kraft, PhD, Harvard School of Public Health
TITLE: To Be Announced
START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
0000 AEST – Australia (Saturday, August 10th, 2013)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
- Operators will be on standby to assist with technical issues. “*0” will get you assistance.
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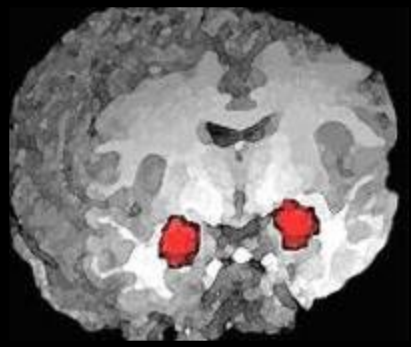
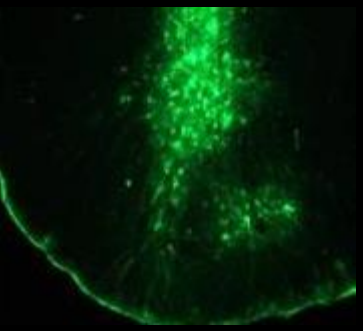
PASSCODE: 275 694 38 then #



Post-Traumatic Stress Disorder: Understanding the Intersection of Gene, Environment, and Brain

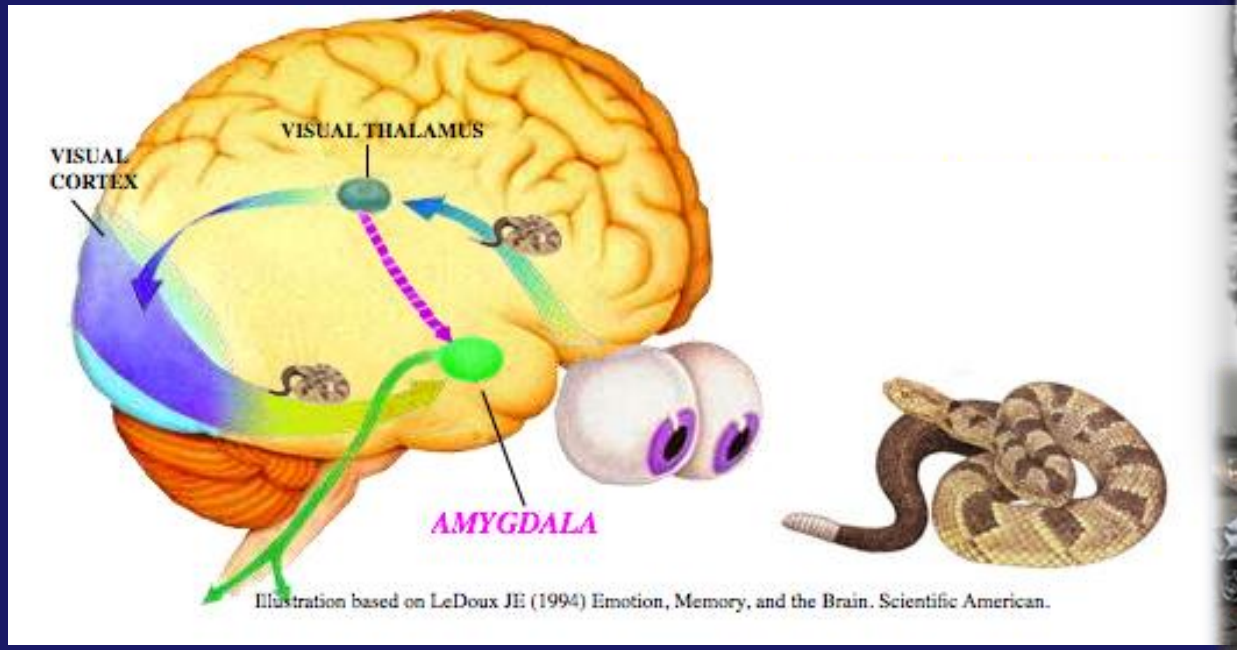


PGC
February 14, 2014

Kerry J. Ressler, MD, PhD
Professor, Psychiatry and Behavioral Sci.
Howard Hughes Medical Institute
Emory University

Fear is evolutionarily useful

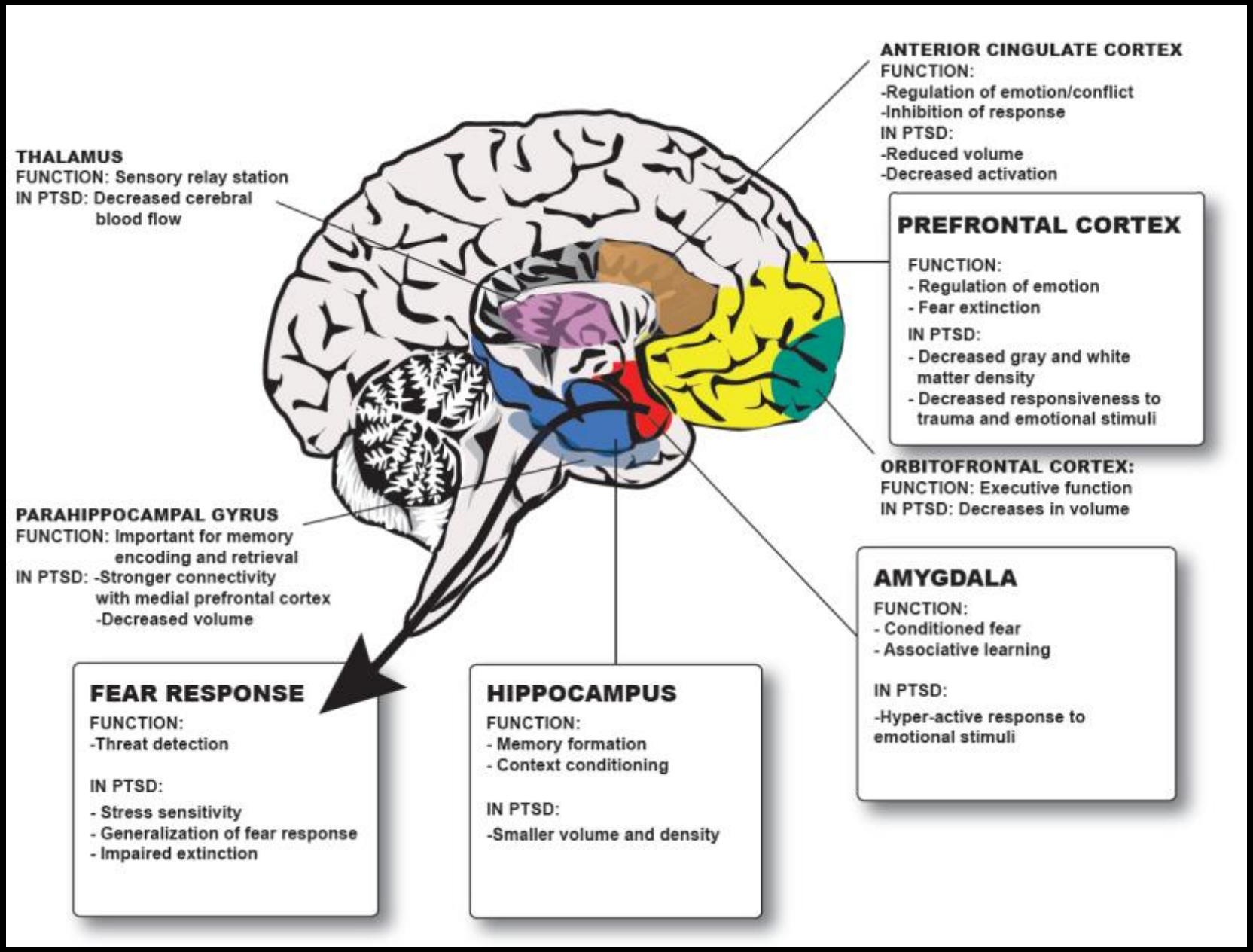
LeDoux, 1996



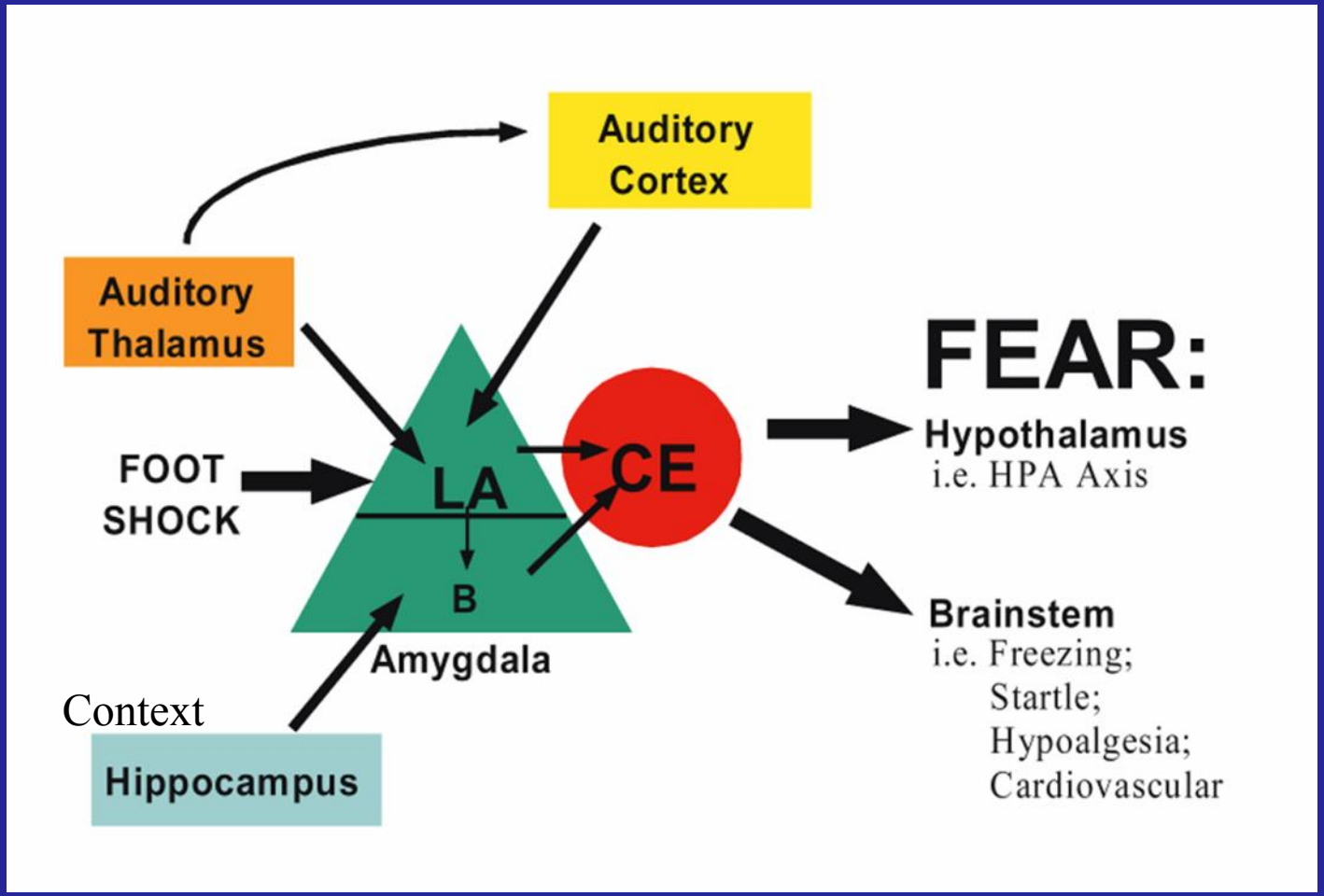
but… Dysregulated Fear leads to Phobia, Panic, and PTSD

- Single or repeated exposure to **extremely traumatic** situations

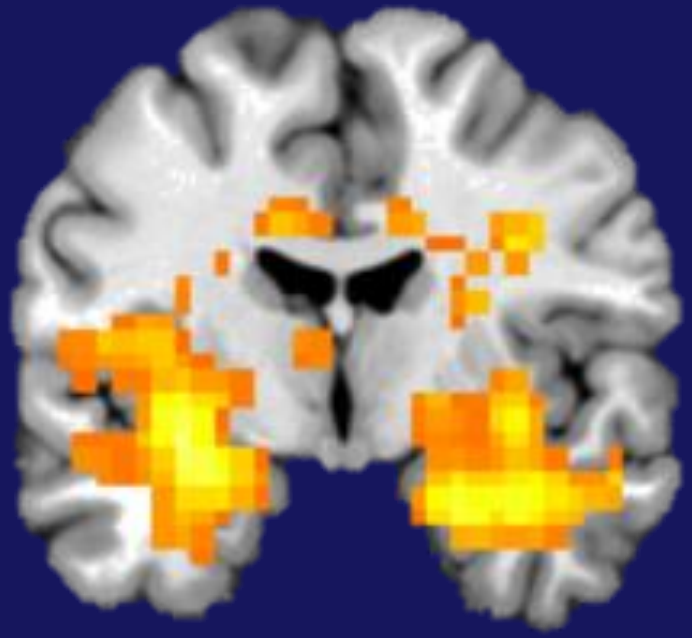
- Characteristic symptoms of PTSD
  - Increased **anxiety** (and hypervigilance)
  - Declarative **memory** alterations
  - Problems in sleep and concentration
  - **Flashbacks**
  - Inability to inhibit **fear**

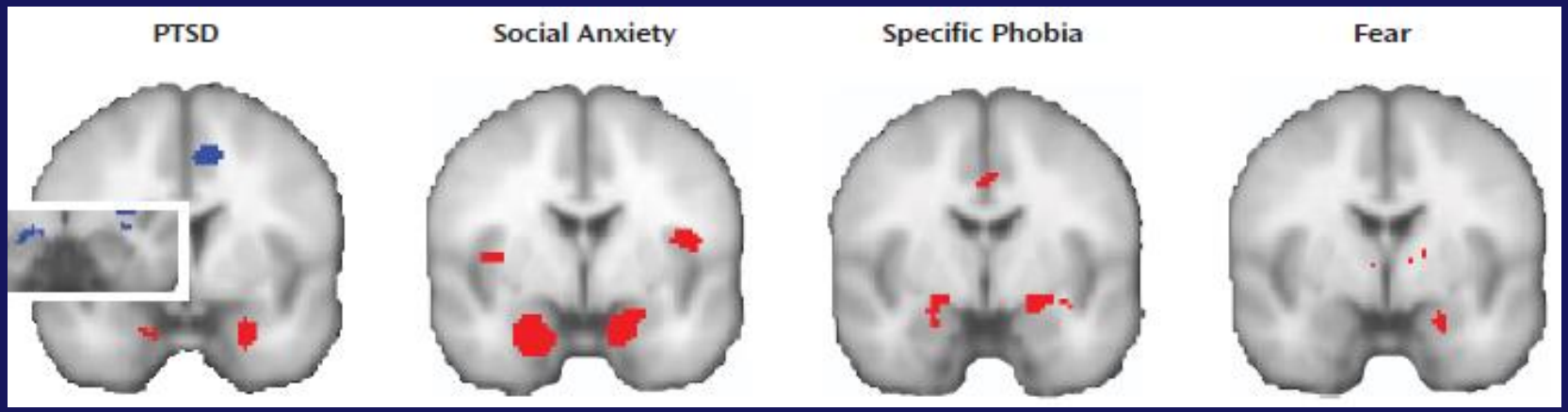

ANTERIOR CINGULATE CORTEX
FUNCTION:
-Regulation of emotion/conflict
-Inhibition of response
IN PTSD:
-Reduced volume
-Decreased activation
THALAMUS
FUNCTION: Sensory relay station
IN PTSD: Decreased cerebral blood flow
PREFRONTAL CORTEX
FUNCTION:
- Regulation of emotion
- Fear extinction
IN PTSD:
- Decreased gray and white matter density
- Decreased responsiveness to trauma and emotional stimuli
ORBITOFRONTAL CORTEX:
FUNCTION: Executive function
IN PTSD: Decreases in volume
PARAHIPPOCAMPAL GYRUS
FUNCTION: Important for memory encoding and retrieval
IN PTSD: -Stronger connectivity with medial prefrontal cortex
-Decreased volume
AMYGDALA
FUNCTION:
- Conditioned fear
- Associative learning
IN PTSD:
-Hyper-active response to emotional stimuli
FEAR RESPONSE
FUNCTION:
-Threat detection
IN PTSD:
- Stress sensitivity
- Generalization of fear response
- Impaired extinction
HIPPOCAMPUS
FUNCTION:
- Memory formation
- Context conditioning
IN PTSD:
-Smaller volume and density

What are the neuroanatomical substrates of fear memory?



The Human Amygdala and Fear





Etkin & Wager, 2007

PANIC ATTACK:

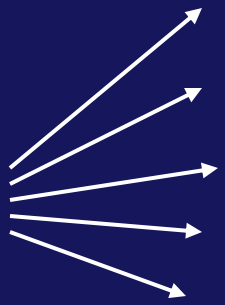
"All of a sudden I felt dizzy, my legs gave out on me, and I couldn't catch a breath. It felt like someone was choking me. I could feel my heart was beating too fast and I was terrified I was dying. I knew I had to get away before I lost it."

Increased heart rate
Chills, hotflushes
Nausea / abdominal distress
Shortness of breath
Expressions of fear

Chest discomfort
Sweating
Lightheadedness / faint
Choking sensation
Fear of dying / losing control

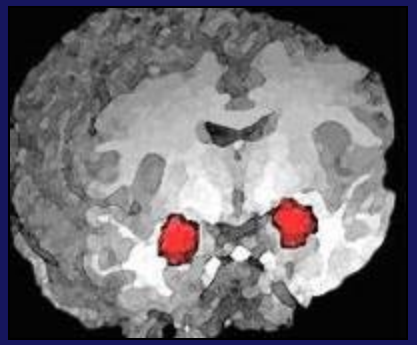
PANIC ATTACK = 'Fear Attack' in Fear-related Disorders

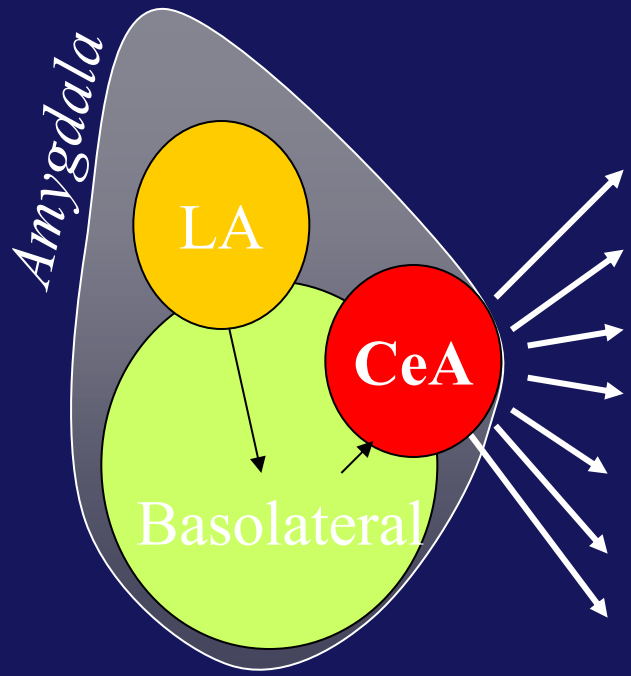
PANIC ATTACK



Panic Disorder
Simple Phobia
Social Phobia (Agoraphobia)
Posttraumatic Stress Disorder
Acute Stress Disorder

The Fear Response is a Hardwired Process involving the Amygdala

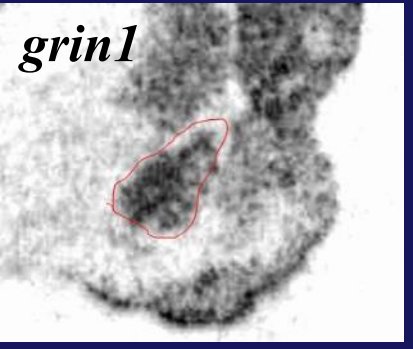


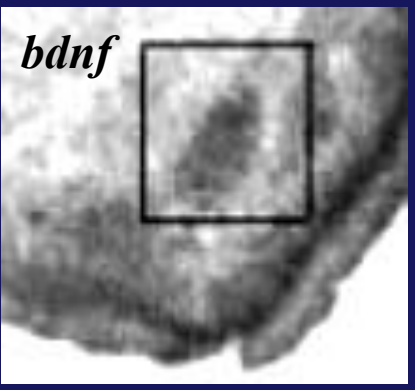


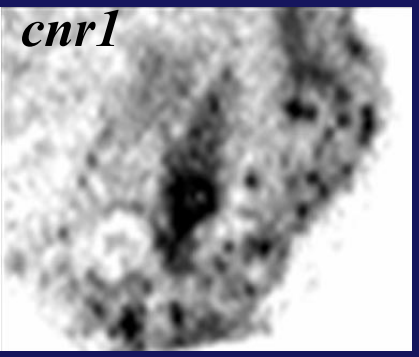
Fear / Panic Symptoms:

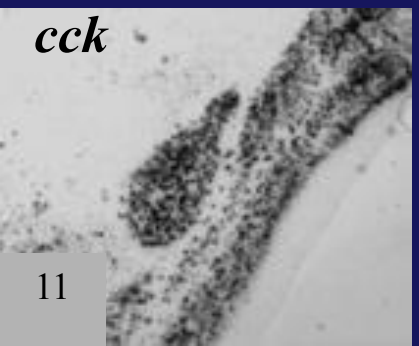
Lateral hypothalamus	→	heart rate, blood pressure
Dorsal vagal N.	→	bradycardia, ulcers
Parabrachial N.	→	panting, respiratory distress
Basal forebrain	→	arousal, vigilance, attention
Retic. Pontis Caudalis	→	increased ***startle response***
Central Gray Area	→	***freezing***, social interaction
Paraventricular N.	→	corticosteroid release

learning *expression*

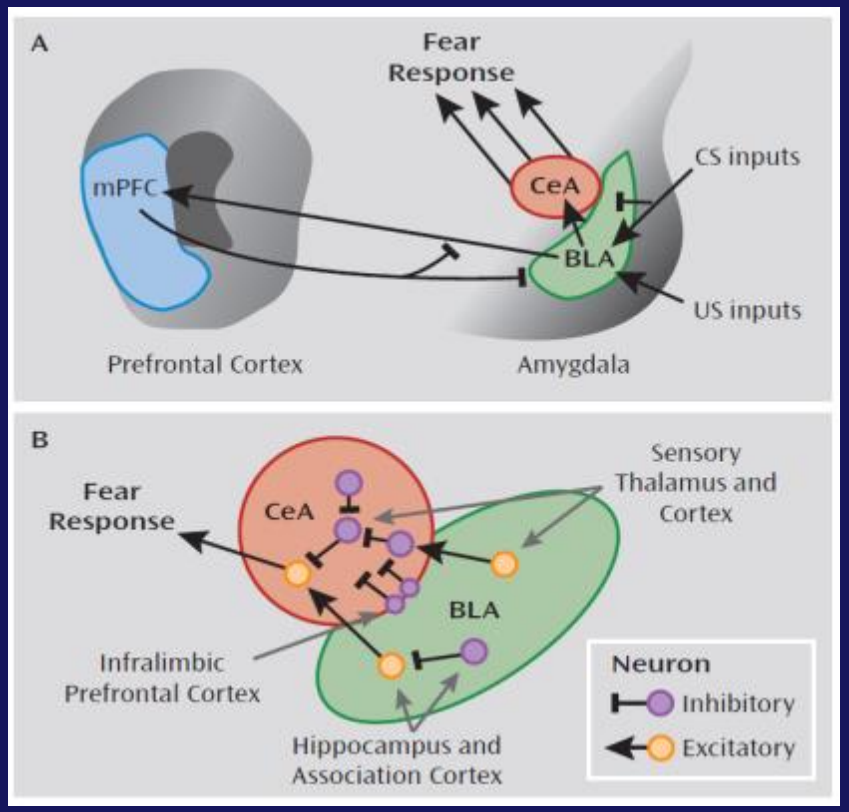




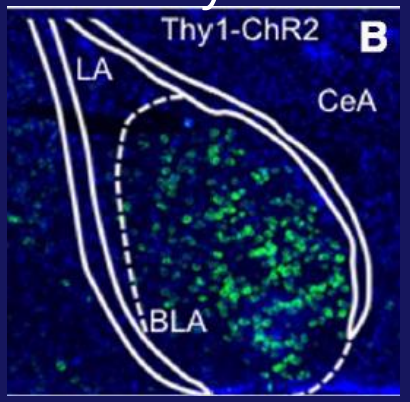




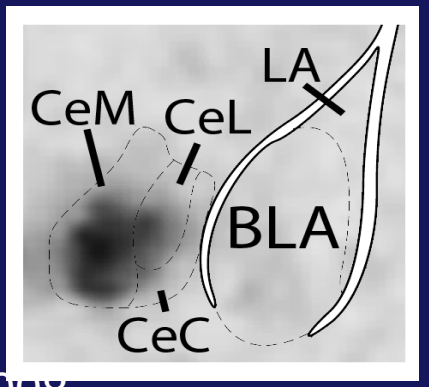
Modulating Fear through Circuitry Modulation has potential to functionally dissect fear-based disorders and clarify genetic pathways



Thy-1



Tac2/Nk3



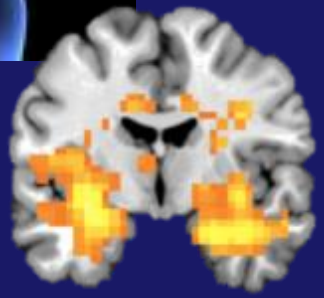
Chhatwal et al., *Nature Neurosci,* 2008
Choi et al., *PNAS*, 2010
Gafford et al., *PNAS*, 2012
Andero et al., *Science Transl Med*, *2013*
Jasnow et al., *J Neurosci, 2013*
Parsons et al., *Nature Neurosci,* 2013

Genes + Environment Increase Risk of Fear Disorders and Posttraumatic Stress

GENES

Development

PTSD



ENVIRONMENT
TRAUMA

Modeling Fear Disorders

Pre-existing Sensitivity
(gene + environment)

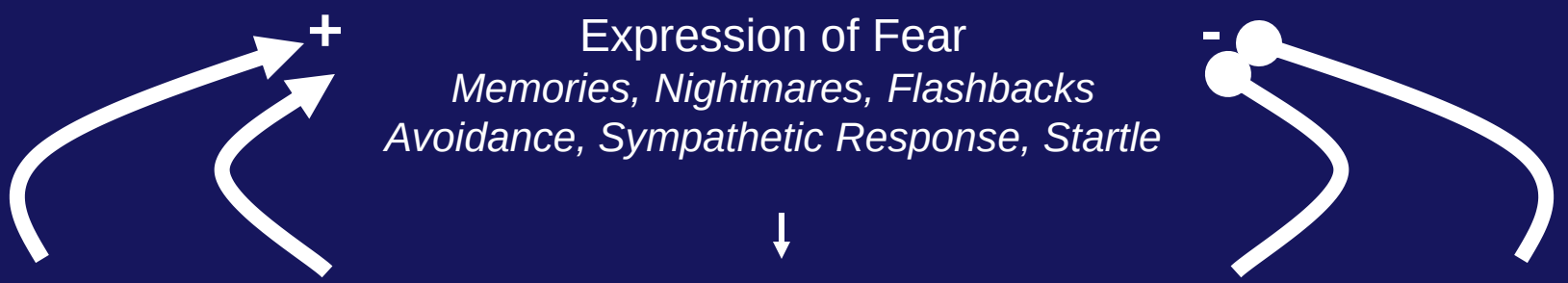
↓

Learning of Fear
(Traumatic event)

↓

PTSD Consolidation of Fear ***recovery***
Hours – days following event

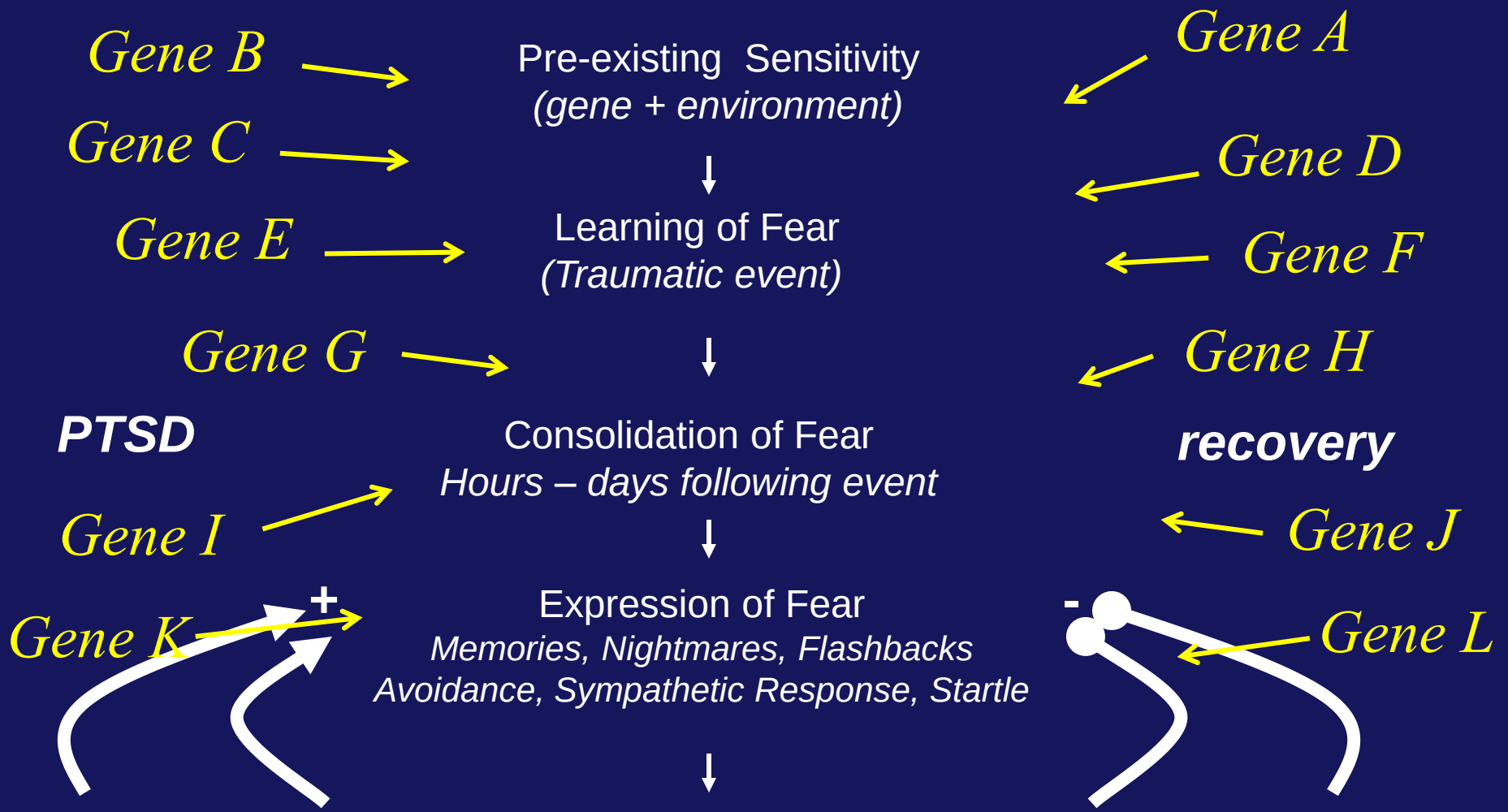
↓



↓

Generalization *Recruitment of Non-associated cues*	**Sensitization** *Increased Fear With repeated exposure*	**Discrimination** *Fear is limited to specific trauma cue*	**Extinction** *Diminished response to cues Over time*

Modeling Fear Disorders



Generalization
Recruitment of Non-associated cues

Sensitization
Increased Fear With repeated exposure

Discrimination
Fear is limited to specific trauma cue

Extinction
Diminished response to cues Over time

Modeling Fear Disorders

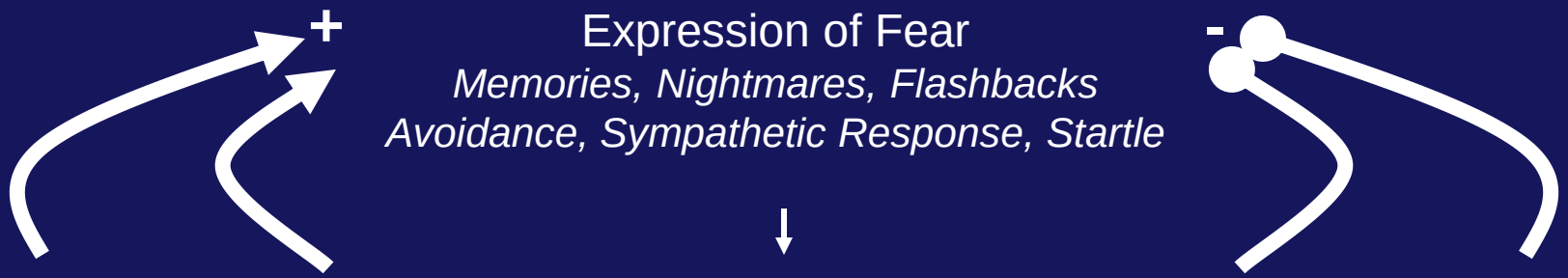
Pre-existing Sensitivity
(gene + environment)

1. **GWAS to date**
2. **HPA-pathway genes / FKBP5 (gxe)**
3. **Convergent Genomics – ADCYAP1R1 (gxe)**
4. **GxE GWAS approaches**

PTSD ***recovery***

Consolidation of Fear
Hours – days following event

+ Expression of Fear -
Memories, Nightmares, Flashbacks
Avoidance, Sympathetic Response, Startle



Generalization
Recruitment of Non-associated cues

Sensitization
Increased Fear With repeated exposure

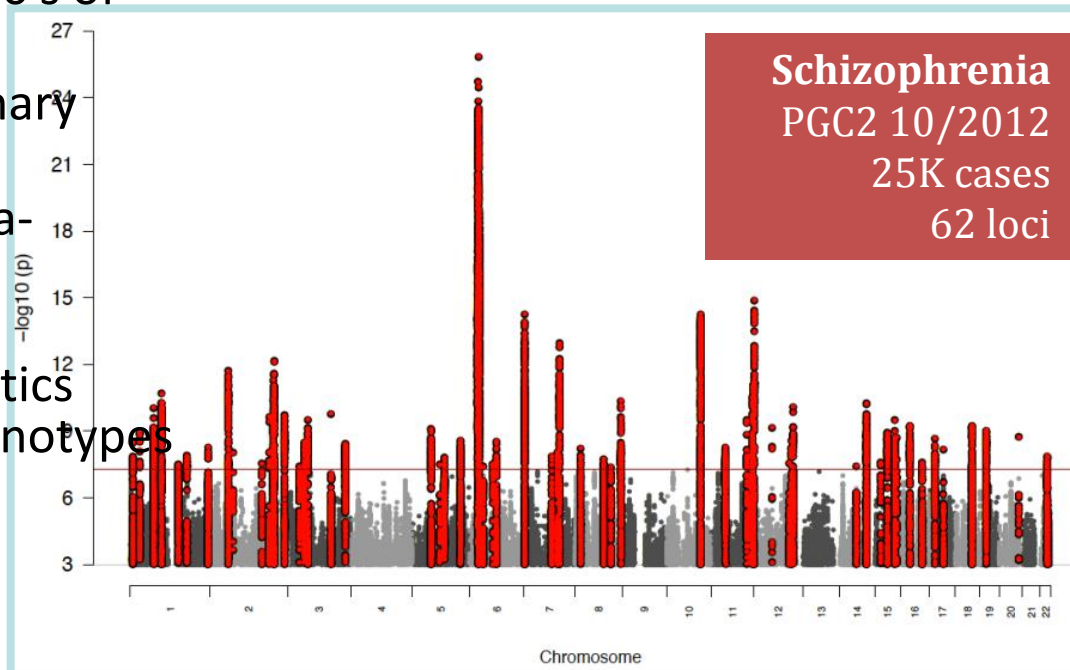
Discrimination
Fear is limited to specific trauma cue

Extinction
Diminished response to cues Over time

PGC PTSD group: Motivation

Koenen, Liberzon, Ressler, Duncan, Nievergelt, Miller, Almli, Logue, Hauser, Beckham, Stein, Aiello, Baker, Jett, Williamson, Morenda, Jovanovic, Bierut, Bradley, Gelernter, Vermetten, Bryant, Smoller

- PTSD is coming late in the game
- Learn from experience with GWAS of other psychiatric disorders
  - Identification of robust genetic association requires
    - VERY large sample sizes (>10's of thousands)
    - International multi-disciplinary collaboration
    - Established well-tested data-management and sharing infrastructure
    - A decade of statistical genetics expertise in psychiatric phenotypes



PTSD Samples

- All groups with data invited
- 4 groups sharing data by December 1
  - 3,849 PTSD cases
  - 9,972 trauma-exposed controls
  - 2 VA groups
    - 2680 PTSD cases 2680
    - 3000 trauma-exposed controls
- 17 other groups invited who have verbally agreed to share data
- Projected total: ~15,000 cases 35,000 controls

PCG PTSD Working Group: Current Participants

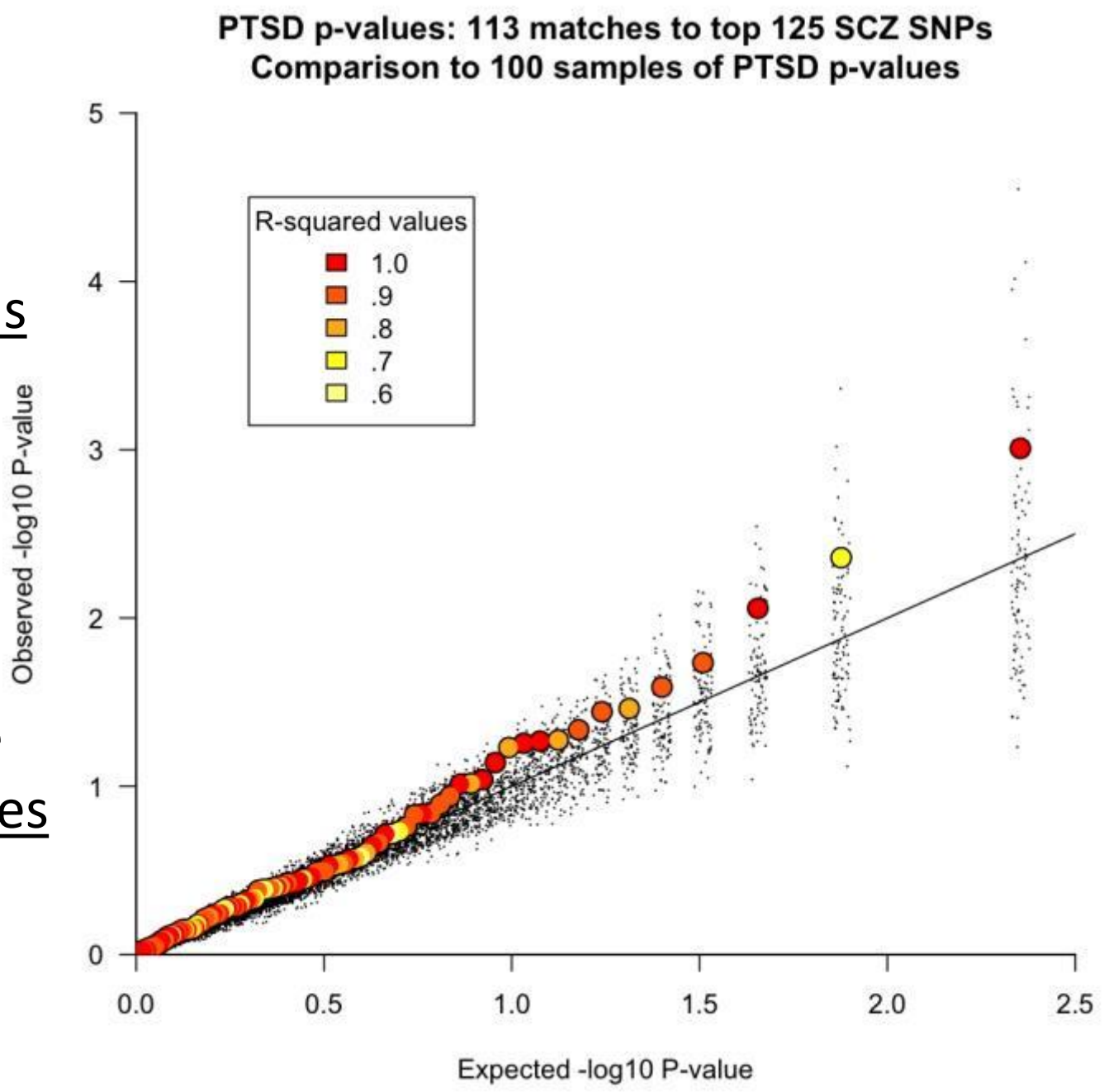
Study	PI	Sample Size Goal Total	N PTSD Cases	N Trauma Exposed Controls	N Other Controls	Population
Nurses Health Study II	Koenen	3013	850	2163	0	Civilian (Women/Cohort/National)
Grady Trauma Project	Ressler	7000	2000	5000	0	Civilian (Urban/Patients/Atlanta)
Predictive Biomarkers	Ressler	500	150	450	0	Civilian (ED/Atlanta/Miami)
Detriot Neighborhood Health Study	Aiello	778	140	584	54	Civilian (Urban/Epi/Atlanta)
Detroit Gracy Project	Liberzon				0	Civilian
Duke Registry	Beckham	5000	2250	2750	0	Veterans and community
Ohio National Guard	Liberzon	2500	500	2000	0	Military -Soldiers (Natl Guard)
Marine Resilience Study	Baker / Nievergelt	2885	965	1445	472	Military - Marine
Strong STAR	Williamson	13821	3849	9972	1401	
PTSD Systems Biology / Walter Reed	Jett	5680	2680	3000	0	
National Center for PTSD/Boston	Miller/Logue	729	430	250	49	Veterans + spouses
Genetics of Substance Dependence	Gelernter/Kranzler	5088	744	2943	1401	Civilian (New Haven)
COGEND	Bierut	1322	74	1044	204	Civilian (National)
Vermetten	Vermetten	1032	36	1032	0	
Stein	Stein	500	-	-	-	
AMC Oxytocin prevention study (BONDS)	Olff	220	50	170	0	
AMC Oxytocin PTSD study (BOOSTER)	Olff	80	40	40	0	
CURRENT TOTAL		**50148**	**14758**	**32843**	**3581**	

PGC-PTSD workgroup Accomplishments

- Regular working group calls and structure established
- Conducted ‘rough’ meta-analysis with results files from 4 groups to identify SNPs for the Psych Chip
- 176 SNPS selected for inclusion
- PTSD samples (likely) selected to be included in PGC2 Psych-Chip genotyping

Distribution of schizophrenia-associated SNPs in the PTSD meta-analysis

Elevation of selected SNPs suggests existence of shared risk alleles



Three Genome-Wide Reports with PTSD to date

ARCHIVAL REPORT

Genome-wide Association Study Identifies New Susceptibility Loci for Posttraumatic Stress Disorder

Pingxing Xie, Henry R. Kranzler, Can Yang, Hongyu Zhao, Lindsay A. Farrer, and Joel Gelernter

Background: Genetic factors influence the risk for posttraumatic stress disorder (PTSD), a potentially chronic and disabling psychiatric disorder that can arise after exposu

Methods: We conducted
African Americans, includi
which yielded approximat

Results: In EAs, we obser
that maps to the first intro
locus reached genome-wi
the association findings f
respectively. In the combi
part of the sample. Genom

ORIGINAL ARTICLE

A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (*RORA*) gene as a significant risk locus

MW Logue[1,2,11], C Baldwin[1,3,11], G Guffanti[4], E Melista[3], EJ Wolf[5,6], AF Reardon[5], M Uddin[7,8], D Wildman[7,9], S Galea[10], KC Koenen[10] and MW Miller[5,6]

tudy (GWAS) of post-traumatic stress disorder (PTSD) performed
cohort of veterans and their intimate partners (295 cases and
yielded evidence of association. One SNP (rs8042149), located in
ed genome-wide significance. Nominally significant associations
eplication samples—one from the veteran cohort (43 cases and
21 controls). However, only the associated SNP from the veteran
le-testing correction. *RORA* has been implicated in prior GWAS
rtant role in neuroprotection and other behaviorally relevant
ntifying the genetic underpinnings of PTSD.

Psychoneuroendocrinology (2013) 38, 3029–3038

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

ELSEVIER

Genome-wide association study implicates a novel RNA gene, the lincRNA *AC068718.1*, as a risk factor for post-traumatic stress disorder in women

Guia Guffanti[a], Sandro Galea[b], Lulu Yan[b], Andrea L. Roberts[c],
Solovieff[d,e,f], Allison E. Aiello[g], Jordan W. Smoller[d,e,f],
ulata De Vivo[c], Hardeep Ranu[h], Monica Uddin[i,j],
E. Wildman[j], Shaun Purcell[d,e,f,k], Karestan C. Koenen[b,*]

ARCHIVAL REPORT

Genome-wide Association Study Identifies New Susceptibility Loci for Posttraumatic Stress Disorder

Pingxing Xie, Henry R. Kranzler, Can Yang, Hongyu Zhao, Lindsay A. Farrer, and Joel Gelernter

CHR	SNP	Nearest Gene	Distance (bp)	p Value in EA GWAS	p Value in Replication EA Samples	p value in Combined EA Samples
7	rs406001	COBL	621900	3.97E-08	0.95	2.77E-04
7	rs382903	COBL	648684	2.70E-07	NT	NT
4	rs6812849	TLL1	intron	2.99E-07	6.28E-06	3.13E-09
7	rs450378	COBL	624219	1.19E-06	0.25	2.03E-04
20	rs4491792	OTOR	8016	1.57E-06	NT	NT
4	rs1503292	TLL1	intron	1.71E-06	NT	NT
4	rs7691872	TLL1	intron	2.22E-06	2.30E-04	1.22E-07
8	rs2272651	NDRG1	intron	3.10E-06	0.76	5.36E-05
9	rs2779551	GABBR2	intron	5.36E-06	0.28	0.019
10	rs16907840	MTRNR2L5	188808	7.59E-06	NT	NT

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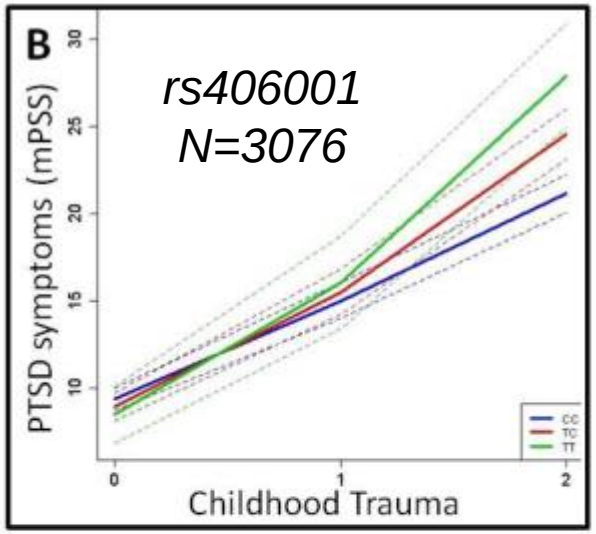
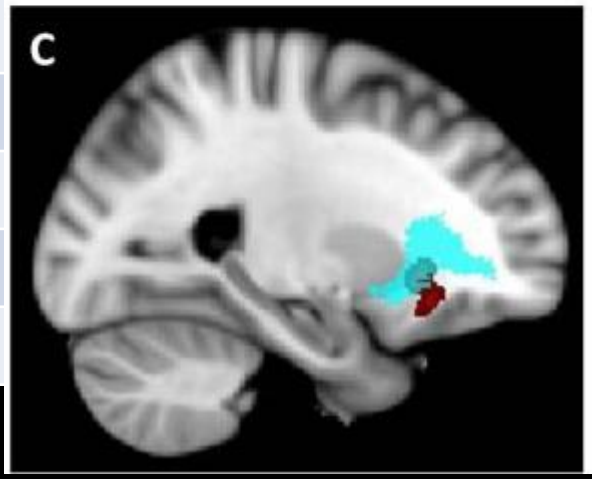
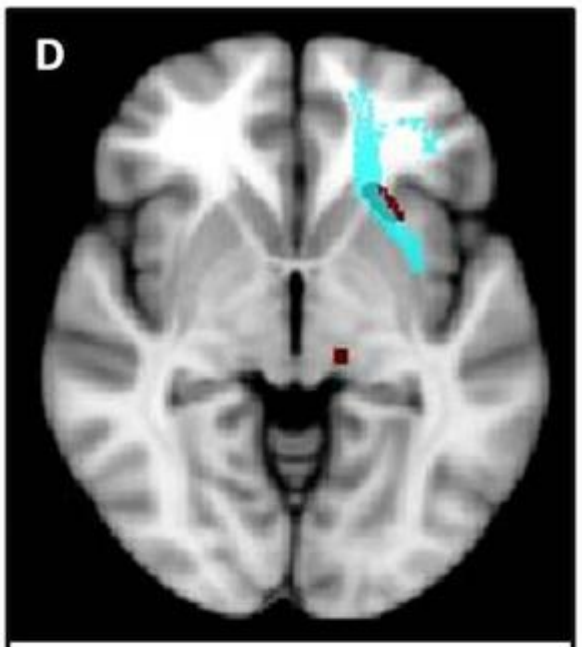
20	rs4491792	OTOR	8016
4	rs1503292	TLL1	intron
4	rs7691872	TLL1	intron
8	rs2272651	NDRG1	intron
9	rs2779551	GABBR2	intron
10	rs16907840	MTRNR2L5	188808







Anatomical Locations	Cluster size (mm^3)	Z max	Z max x	Z max y	Z max z
Inferior fronto-occipital fasciculus	649	0.91	-34	-47	6
Uncinate fasciculus	78	0.90	-23	21	-6
White matter in orbitofrontal cortex	58	0.90	-28	22	-16
Inferior longitudinal fasciculus	34	0.90	-40	-10	-24

Almli et al., in press, *Biological Psychiatry*

Grady Trauma Project: Civilian inner-city trauma

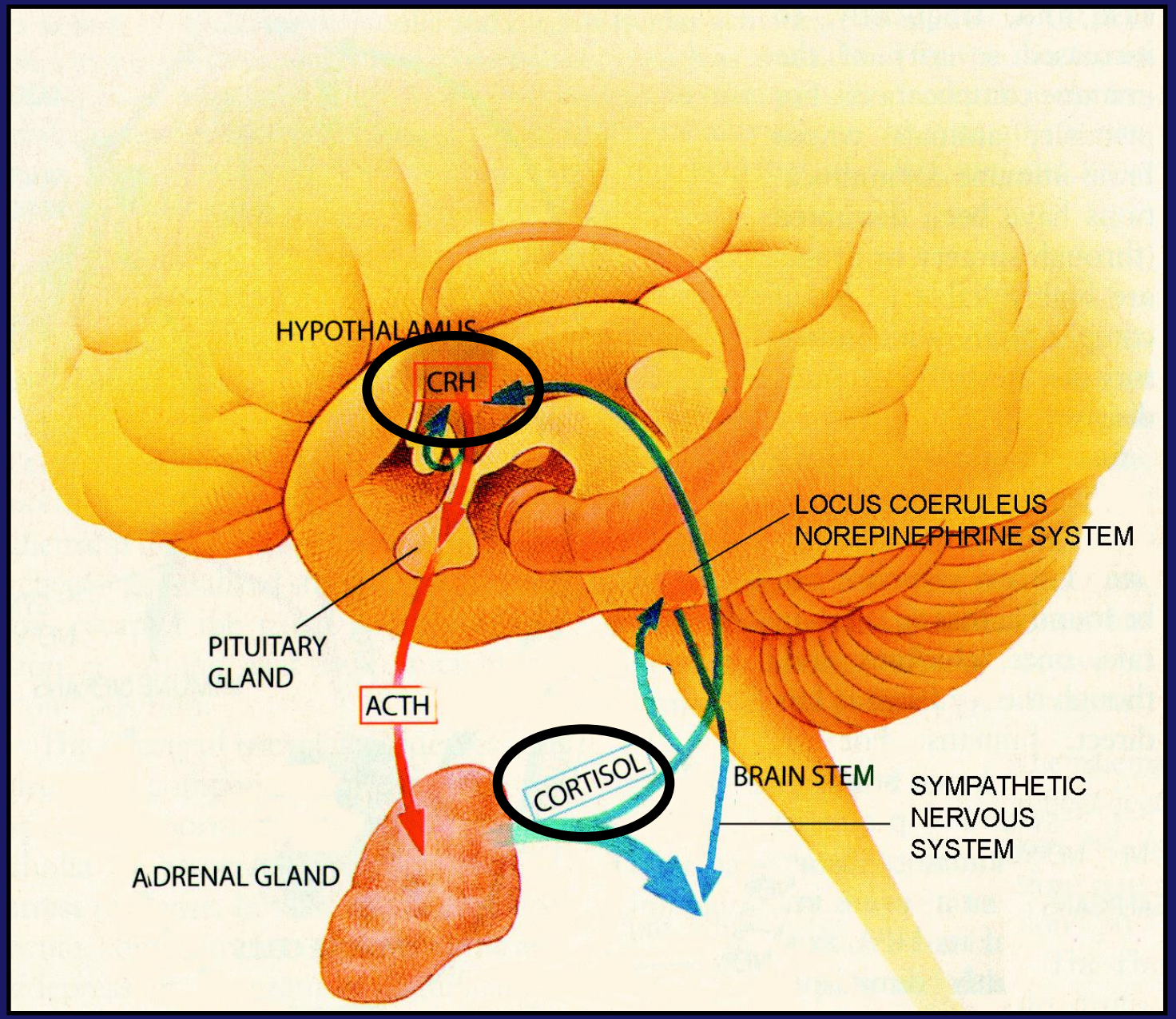
Understanding the Genomic Structure of PTSD

Our Ongoing GWAS:
1M SNPS (Illumina Omni-1M)
+ CNVs

N=8000 all-traumatized
~30% PTSD, ~60% no PTSD
~40% male, ~60% female

Psychiatric Genomic Consortium-PTSD subgroup (*in progress*):
>10,000 cases
>50,000 trauma controls

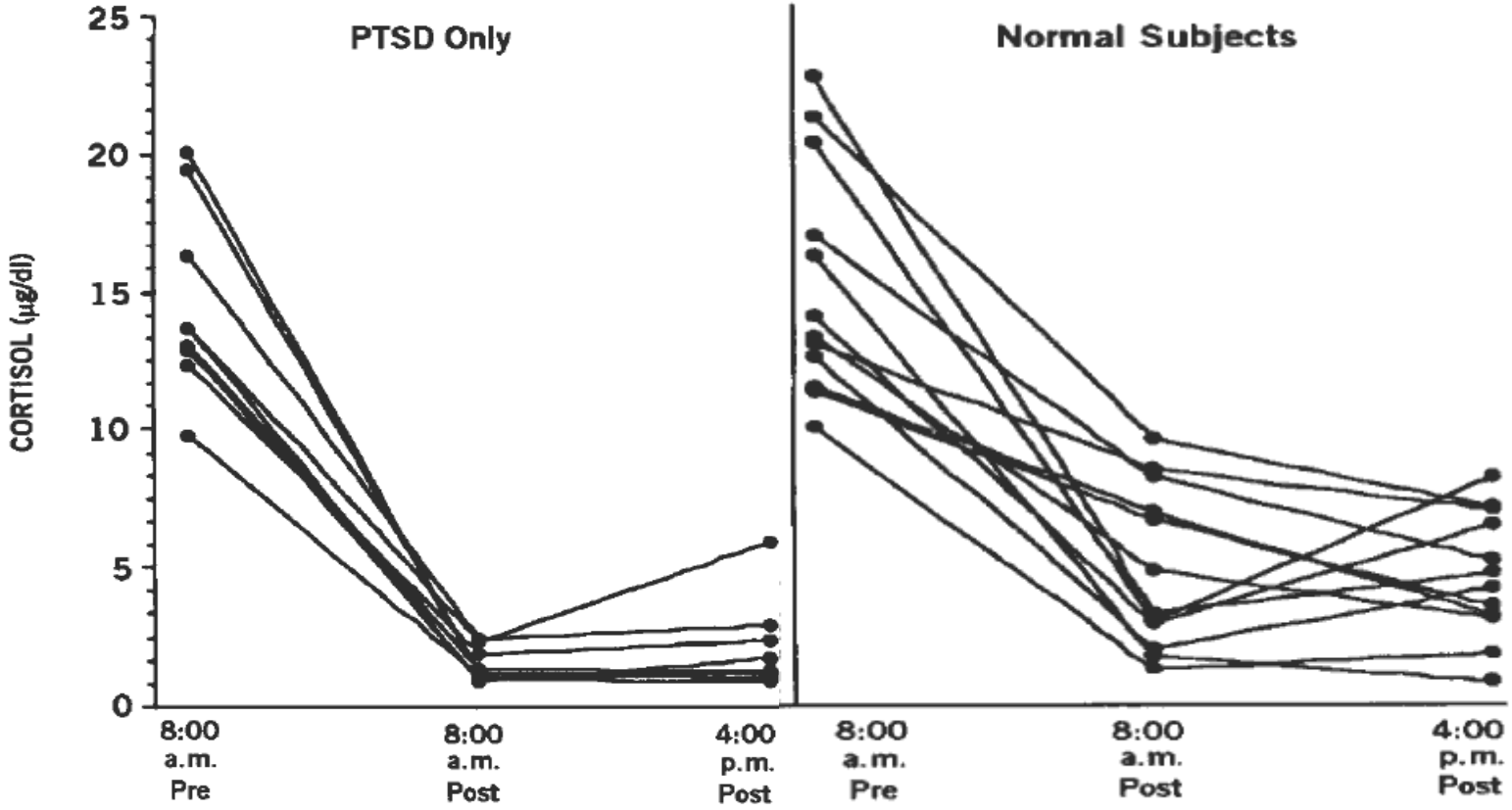
To Date:
>5500 Salivary DNA samples
>750 whole blood, serum, plasma, buffy coats
>500 Startle / human physiology
~500 whole genome methylation
~500 Gene expression array


HYPOTHALAMUS
CRH
LOCUS COERULEUS
NOREPINEPHRINE SYSTEM
PITUITARY
GLAND
ACTH
CORTISOL
BRAIN STEM
SYMPATHETIC
NERVOUS
SYSTEM
ADRENAL GLAND

Enhanced Suppression of Cortisol Following Dexamethasone Administration in Posttraumatic Stress Disorder

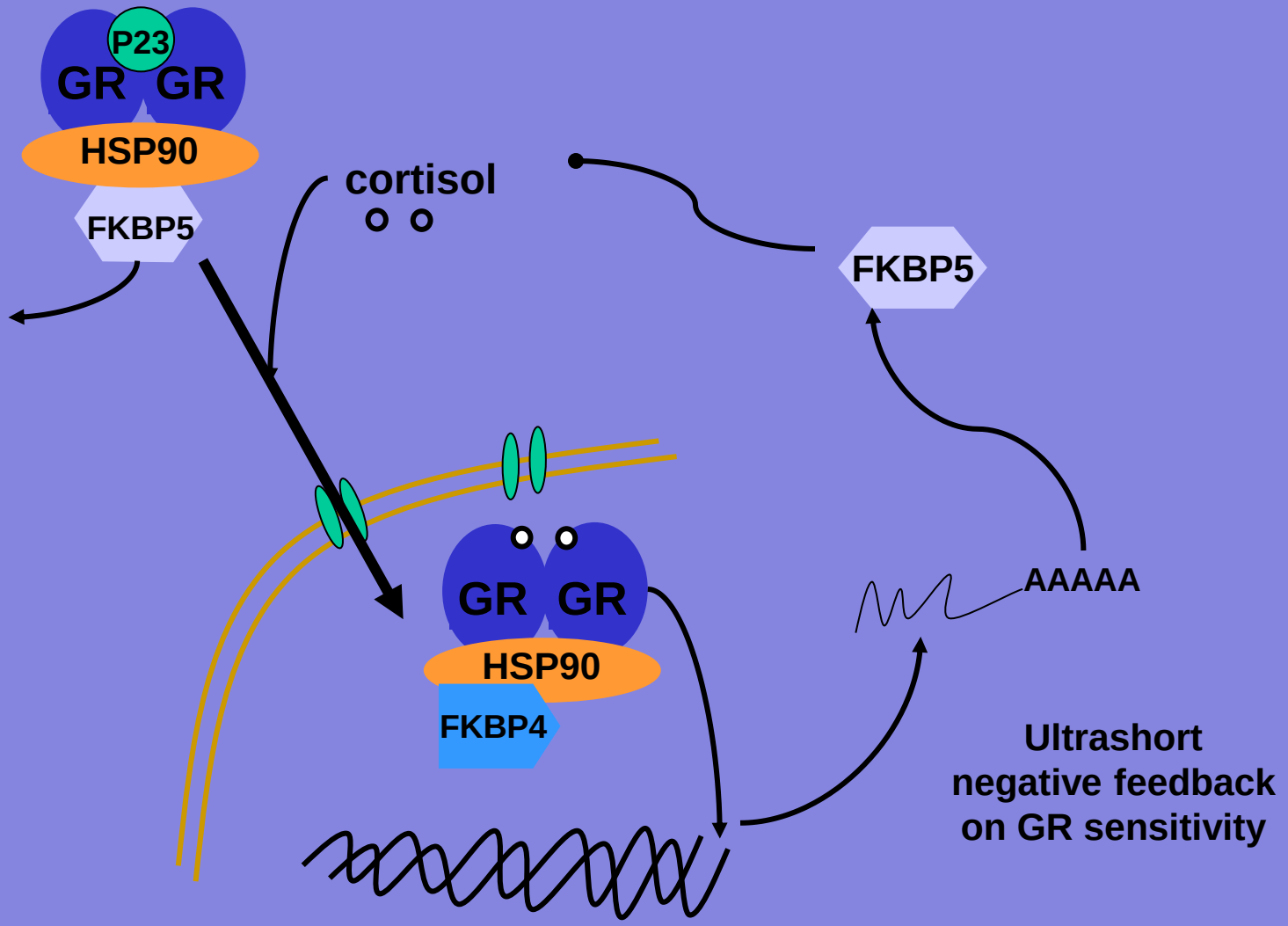
Rachel Yehuda, Ph.D., Steven M. Southwick, M.D., John H. Krystal, M.D.,
Douglas Bremner, M.D., Dennis S. Charney, M.D., and John W. Mason, M.D.

Am J Psychiatry 1983

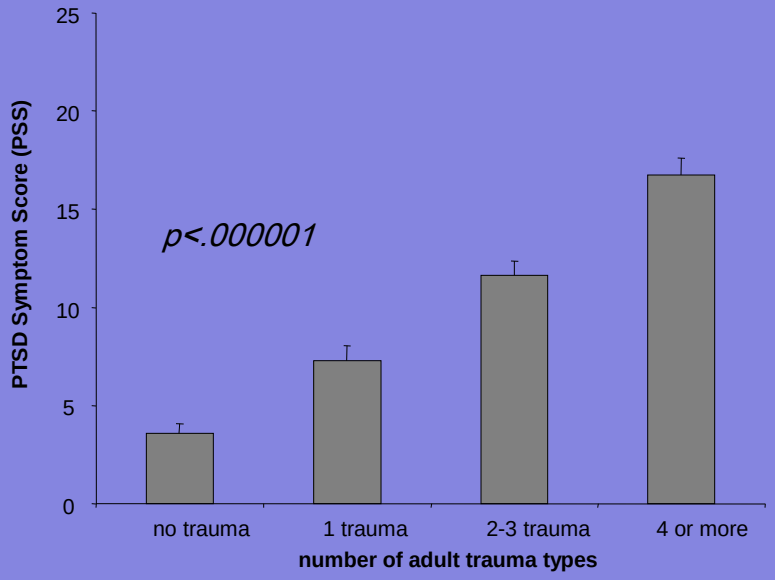


FK506 binding protein = FKBP5

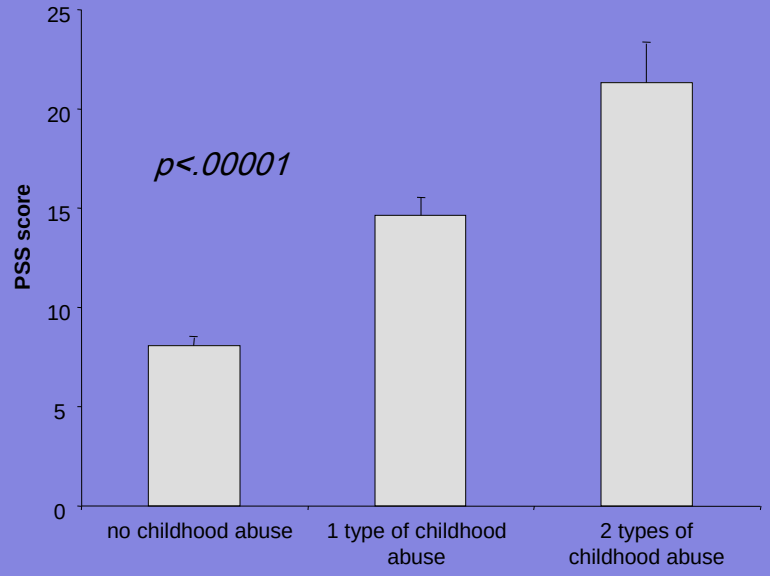
(immunophillin-petidyl-proline isomerase activity-TPR domain)



Both Adult Trauma and Child Abuse strongly predict Adult PTSD symptoms



Level of Non-Child Abuse Trauma[#]	N	PTSD Symptom Scale (PSS) Mean ± sem	95% confidence intervals
None	159	3.58 ± 0.50[*,+]	2.60 – 4.56
1 Type	183	7.30 ± 0.74[$,+]	5.83 - 8.76
2-3 Types	265	11.57 ± 0.72[+]	10.16 – 12.98
≥ 4 Types	215	16.74 ± 0.88[+]	15.00 – 18.47

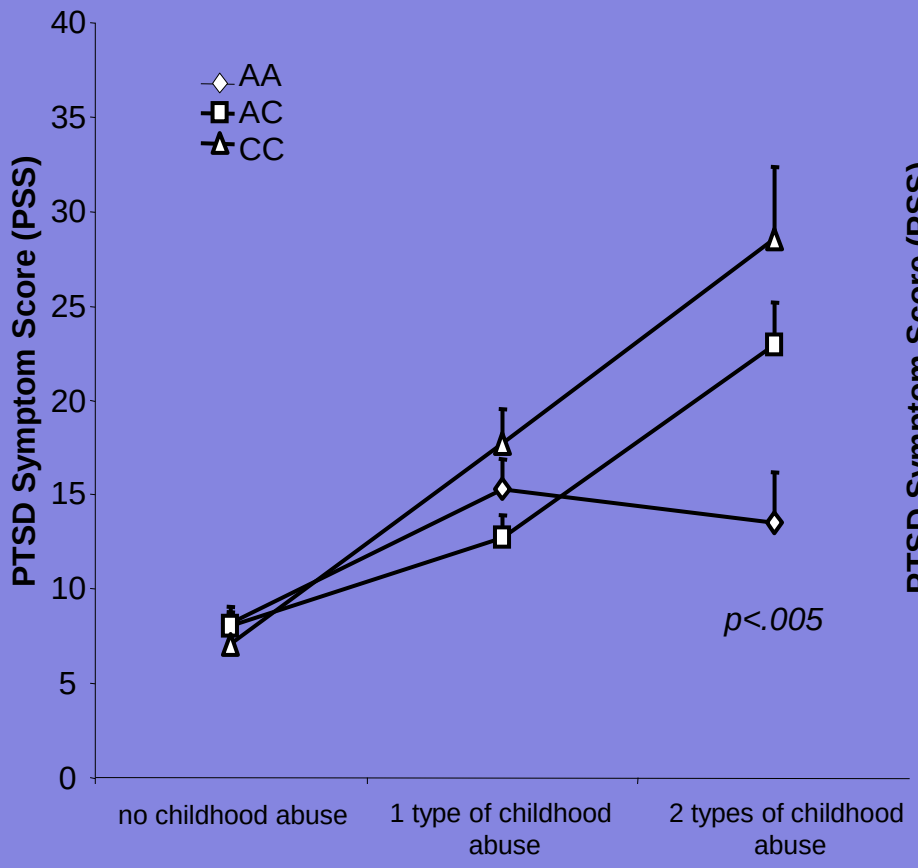


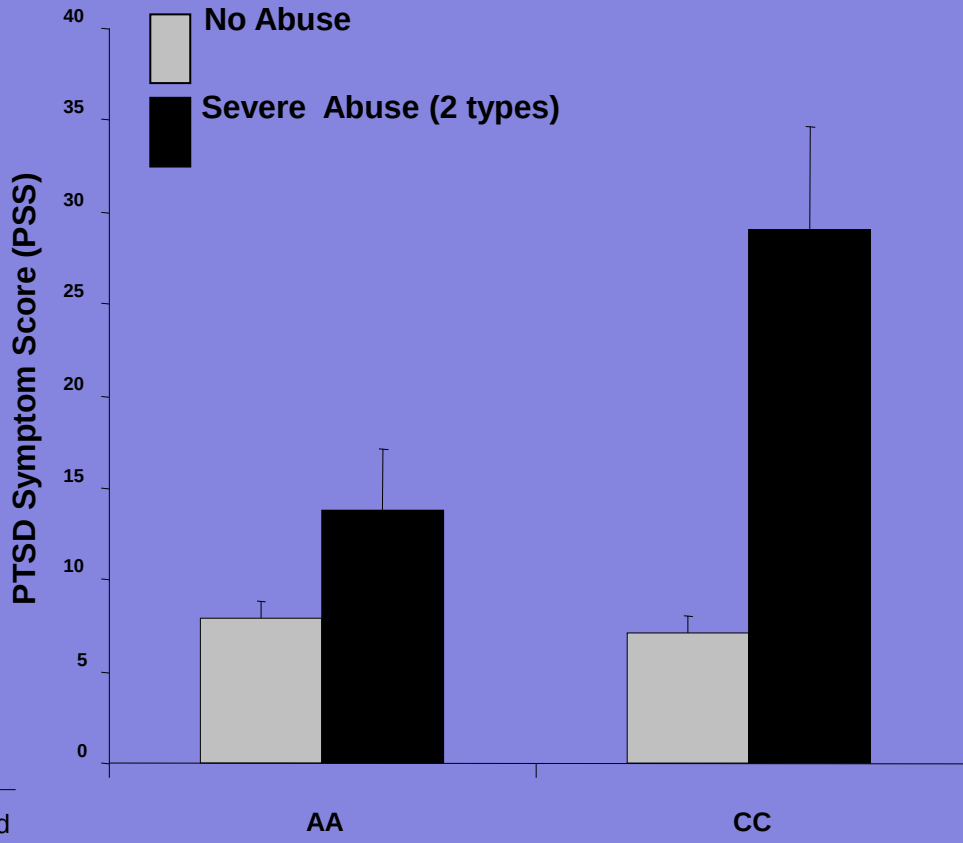
Level of Child Abuse Trauma	N	PTSD Symptom Scale (PSS) Mean ± sem	95% confidence intervals
No Child Abuse	566	8.03 ± 0.44 [*]	7.17 – 8.90
1 Type of Child Abuse	189	14.65 ± 0.87 [$]	12.94 – 16.36
2 Types of Child Abuse	54	20.93 ± 1.95 [+]	17.02 – 24.84

30% have experienced some form of child abuse

Binder et al., JAMA, March, 2008

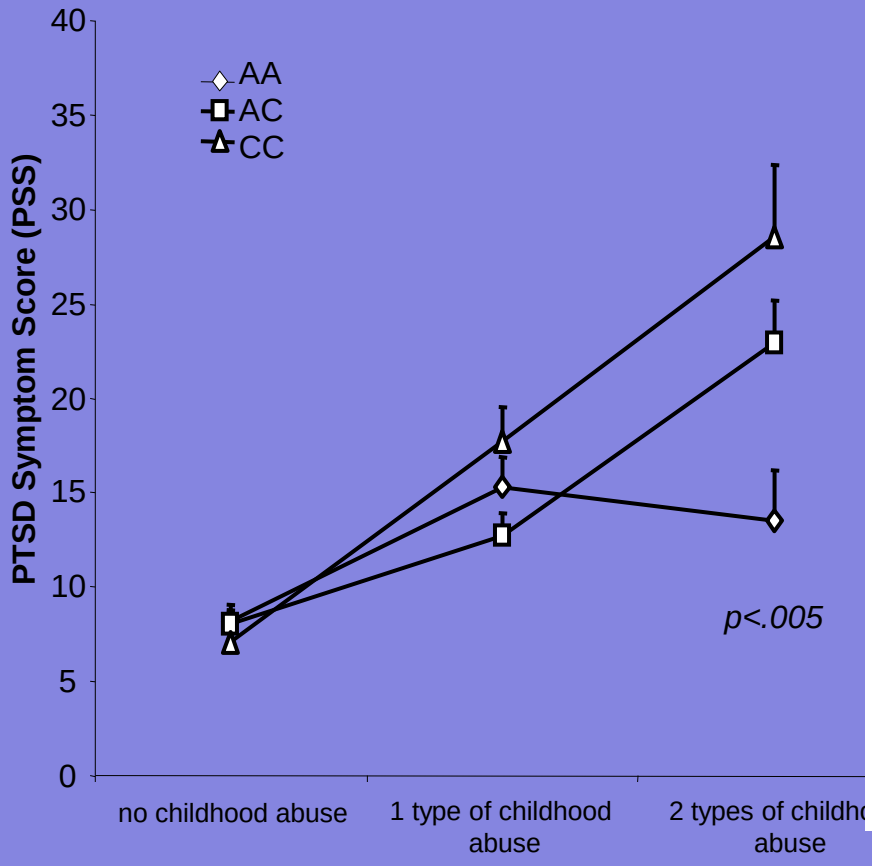
FKBP5 genotype interacts with level of Child abuse to predict level of Adult PTSD Symptoms

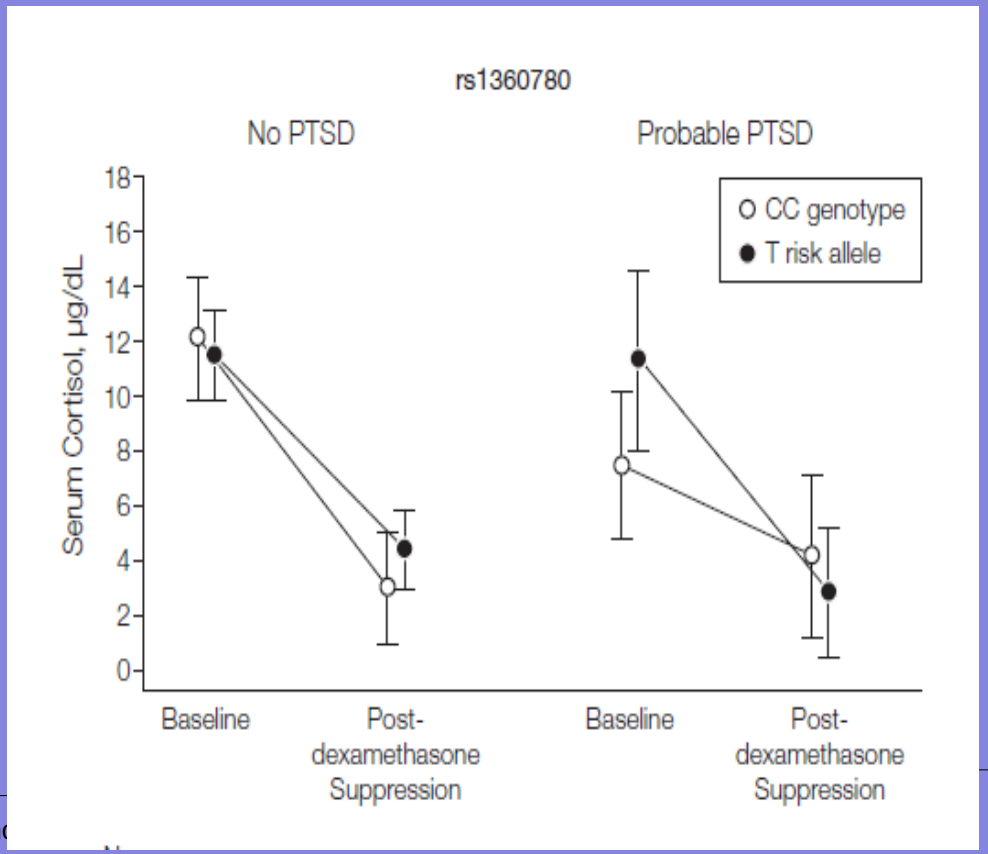




Binder et al., JAMA, March, 2008

FKBP5 genotype interacts with level of Child abuse to predict level of Adult PTSD Symptoms

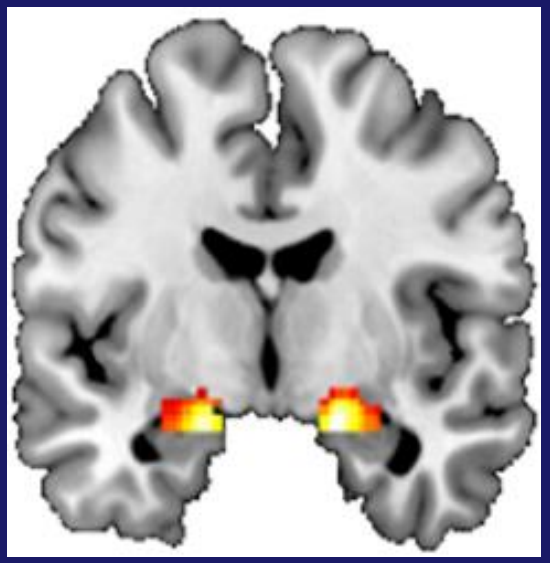




Binder et al., JAMA, March, 2008

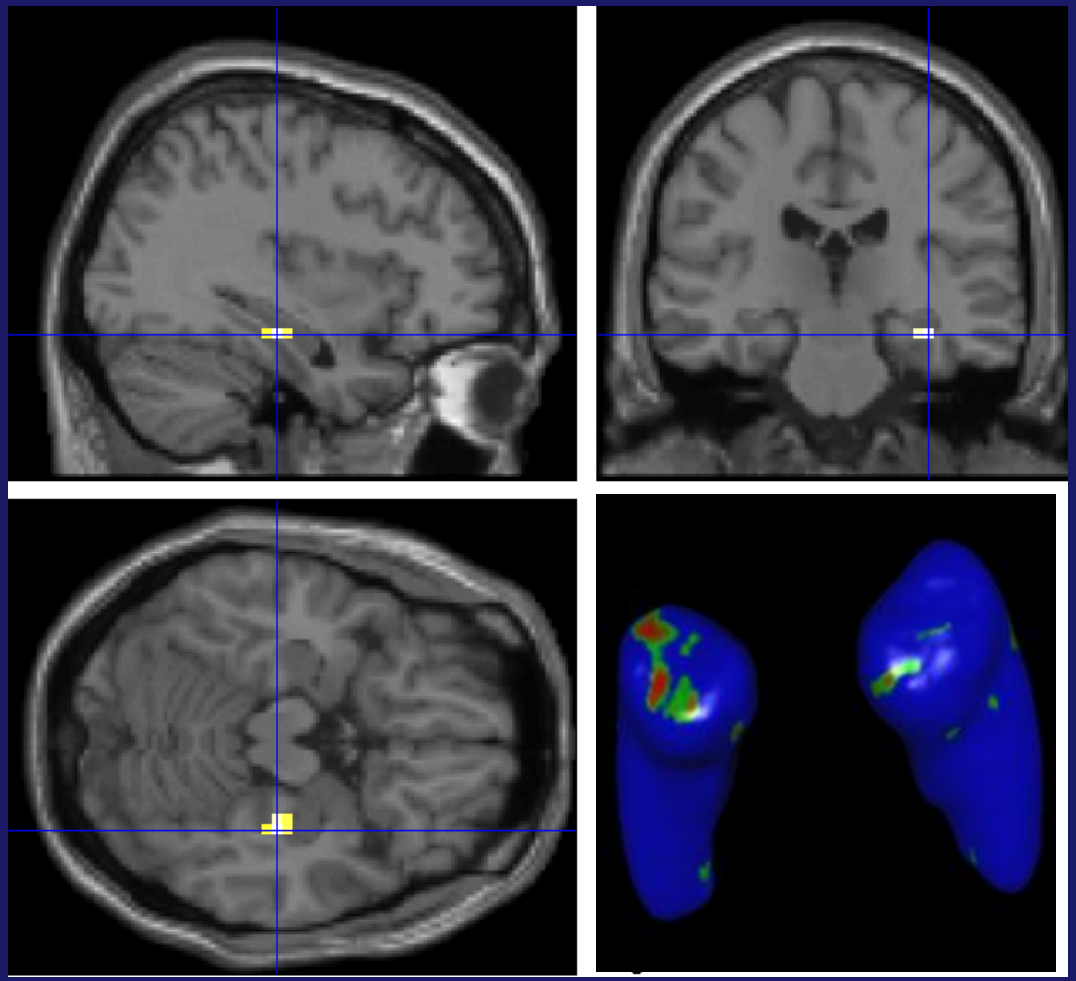
Variants of a stress response gene (FKBP5) + Child Trauma: Effects on PTSD and Amygdala Activation

Binder et al., 2008
JAMA



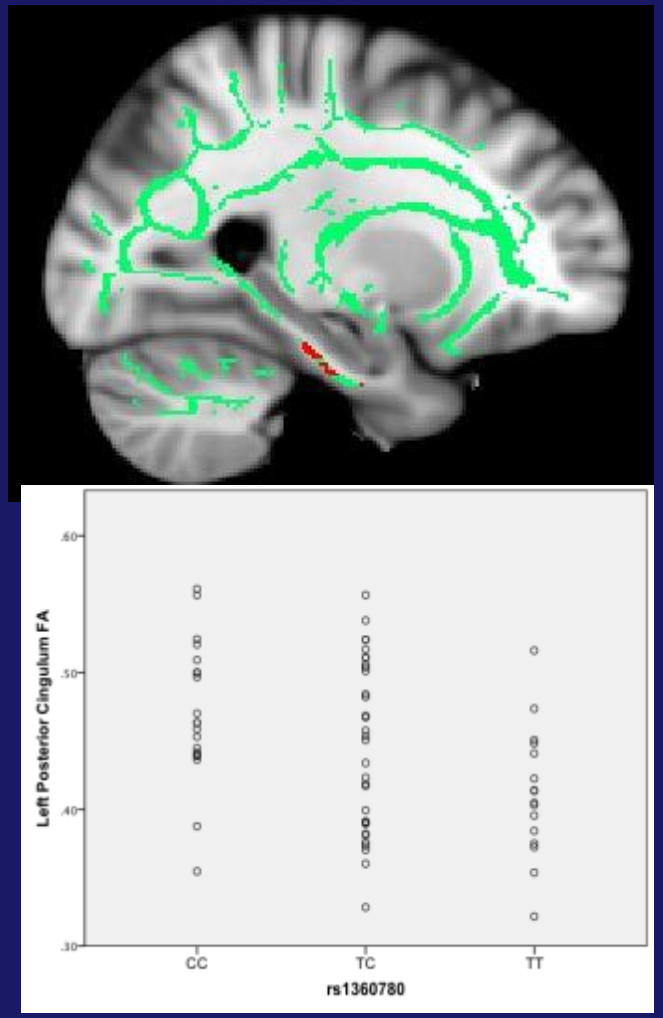
White…Hariri, 2012
Genes, Brain and Behavior

Hippocampal activation and structural differences in FKBP5 risk allele carriers



Statistical parametric map of brain activation during the processing of threat incongruent versus threat congruent faces in TC/TT > CC

Fani et al., 2013, *JAMA Psychiatry*



FKBP5 Genotype and Structural Integrity of the Posterior Cingulum

Fani et al., *in press, Neuropsychopharmacology*

Replications and Extensions

- Levy-Gigi, et. al., 2013, Association among clinical response, hippocampal volume, and FKBP5 gene expression in individuals with posttraumatic stress disorder receiving cognitive behavioral therapy. *Biol Psychiatry*. 74(11):793-800.
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- Mehta D, et al., 2011, Using polymorphisms in FKBP5 to define biologically distinct subtypes of posttraumatic stress disorder: evidence from endocrine and gene expression studies. *Arch Gen Psychiatry*. 2011 Sep;68(9):901-10.
- Boscarino JA, et al., 2011, Association of FKBP5, COMT and CHRNA5 polymorphisms with PTSD among outpatients at risk for PTSD. *Psychiatry Res.* 188(1):173-4.
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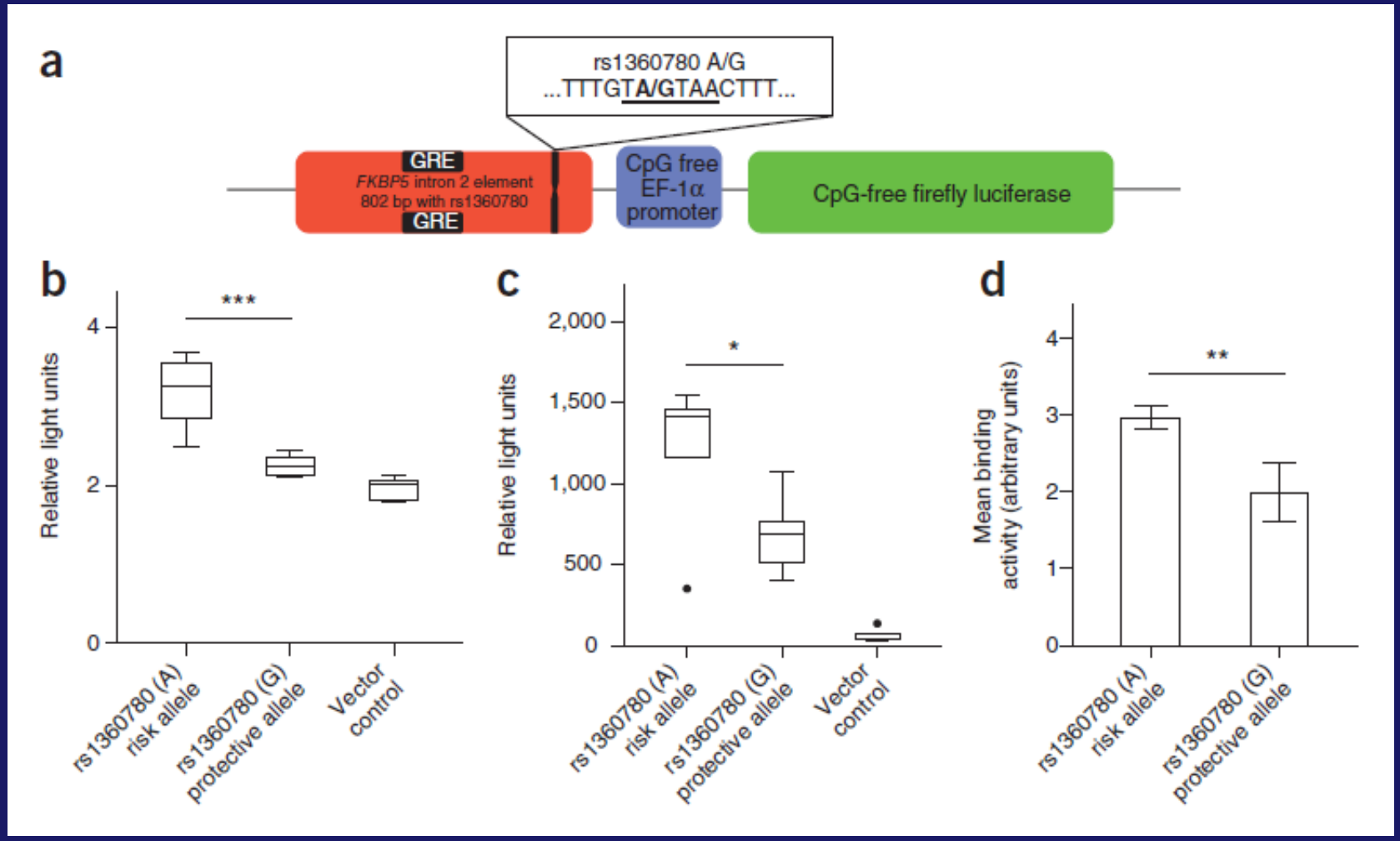
- Xie P, et al., 2010, Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology*. 35(8):1684-92.

Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions

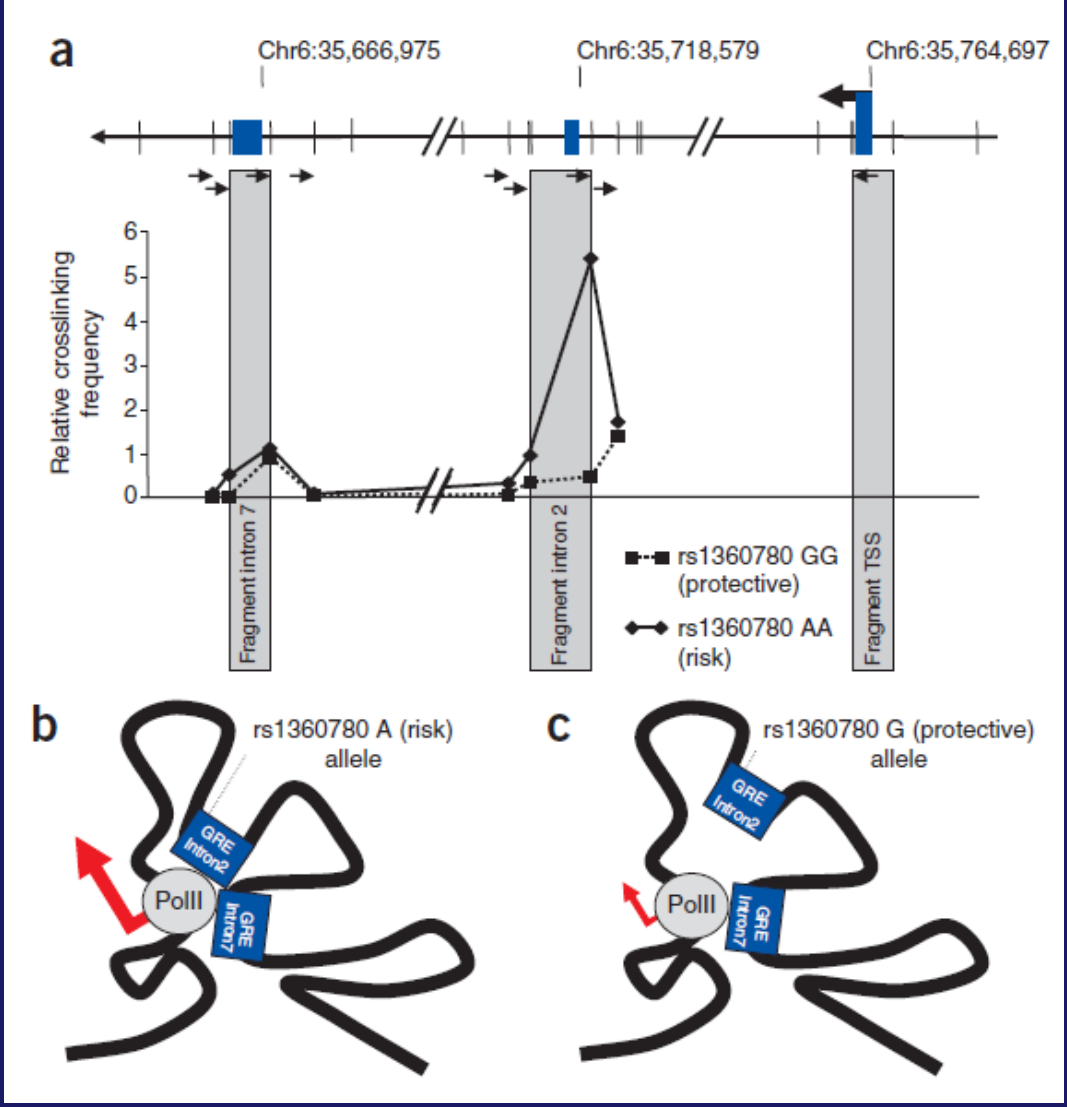
Genotype and GR-dependent enhancer activities of *FKBP5* Intron 2



Klengel … and Binder., 2013, *Nature Neurosci*

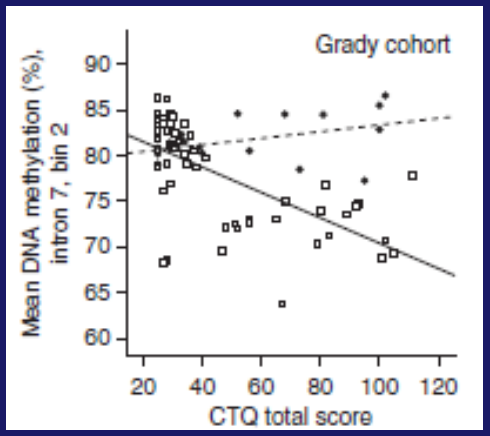
Long-distance interaction GREs in FKBP5

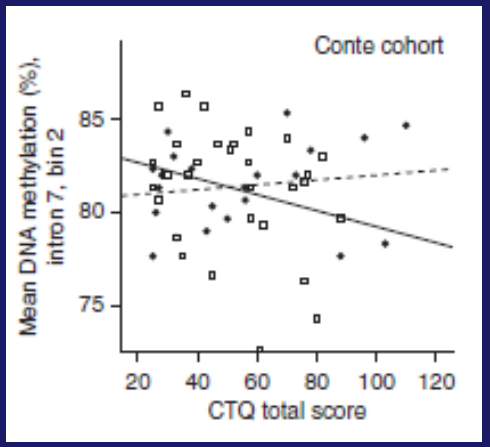
Chromatin capture confirmed a genotype-dependent interaction of the FKBP5 Transcription Start Site with intron 2 and 7 in cell lines

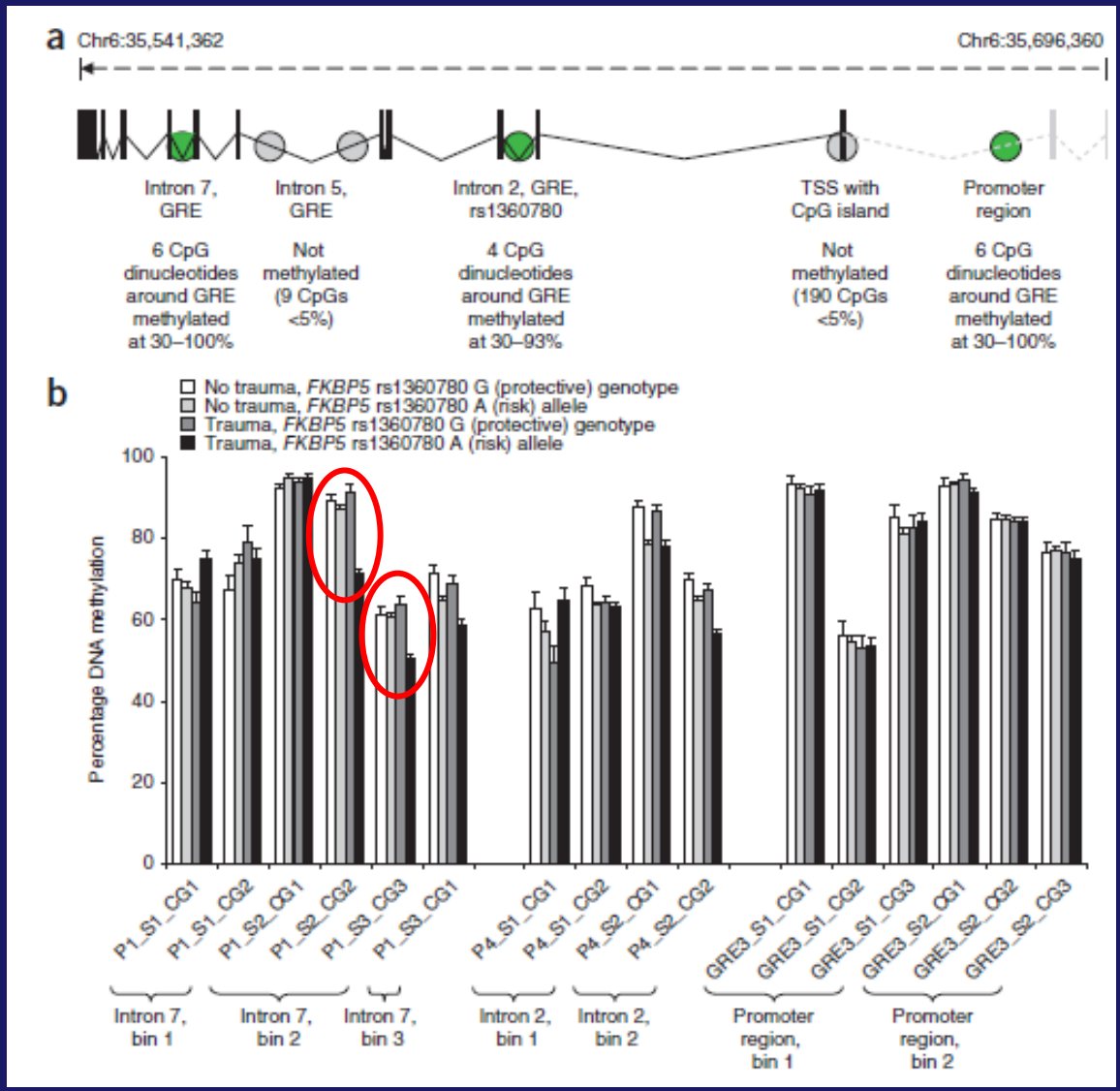


Klengel et al., 2013, *Nature Neurosci*

DNA methylation of the FKBP5 locus: Genotype x Child Trauma Interaction

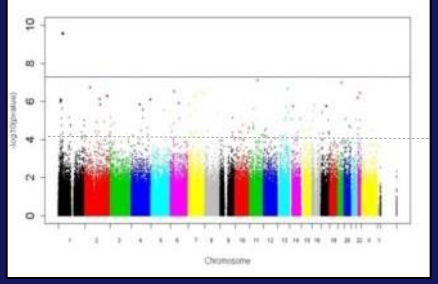


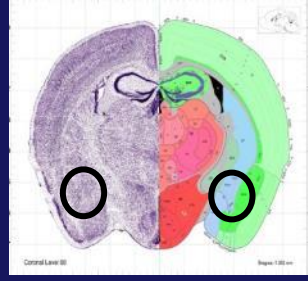




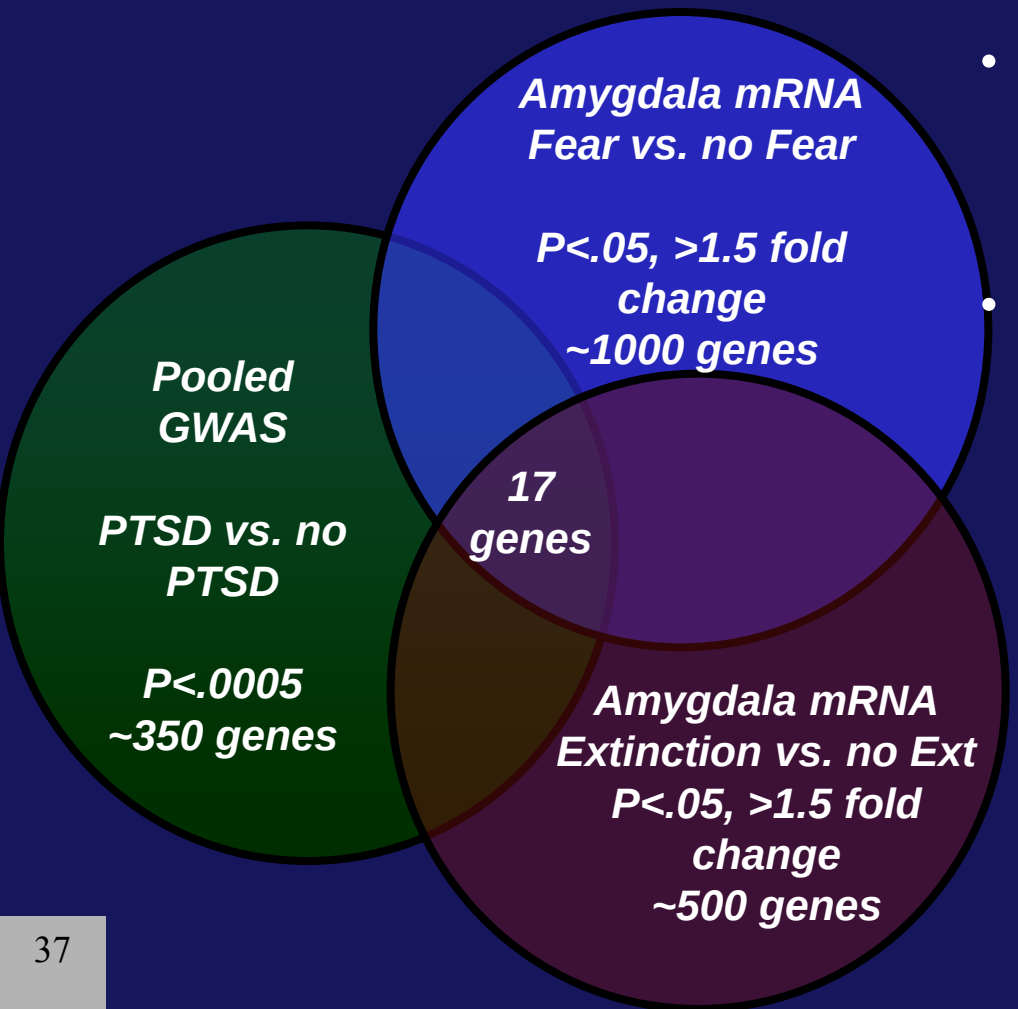
Klengel et al., 2013, *Nature Neurosci*

Finding Genes Involved in PTSD and Fear Neurocircuitry: Convergent Genomics Approaches





- Identify genes in hypothesis neutral fashion that are associated with PTSD *(pooled GWAS N~400)*
- Identify genes in hypothesis neutral fashion associated with Fear Conditioning or Extinction Learning *(mouse amygdala mRNA array)*
- Prioritize genes that are shared in the above



Top Convergent Candidate

ADCYAP1R1

- **adenylate cyclase activating polypeptide 1- pituitary expression, neural development**

- **Pooled GWAS p=.00002**
- **6 mRNA transcripts present in Mouse amygdala regulated by fear and extinction**

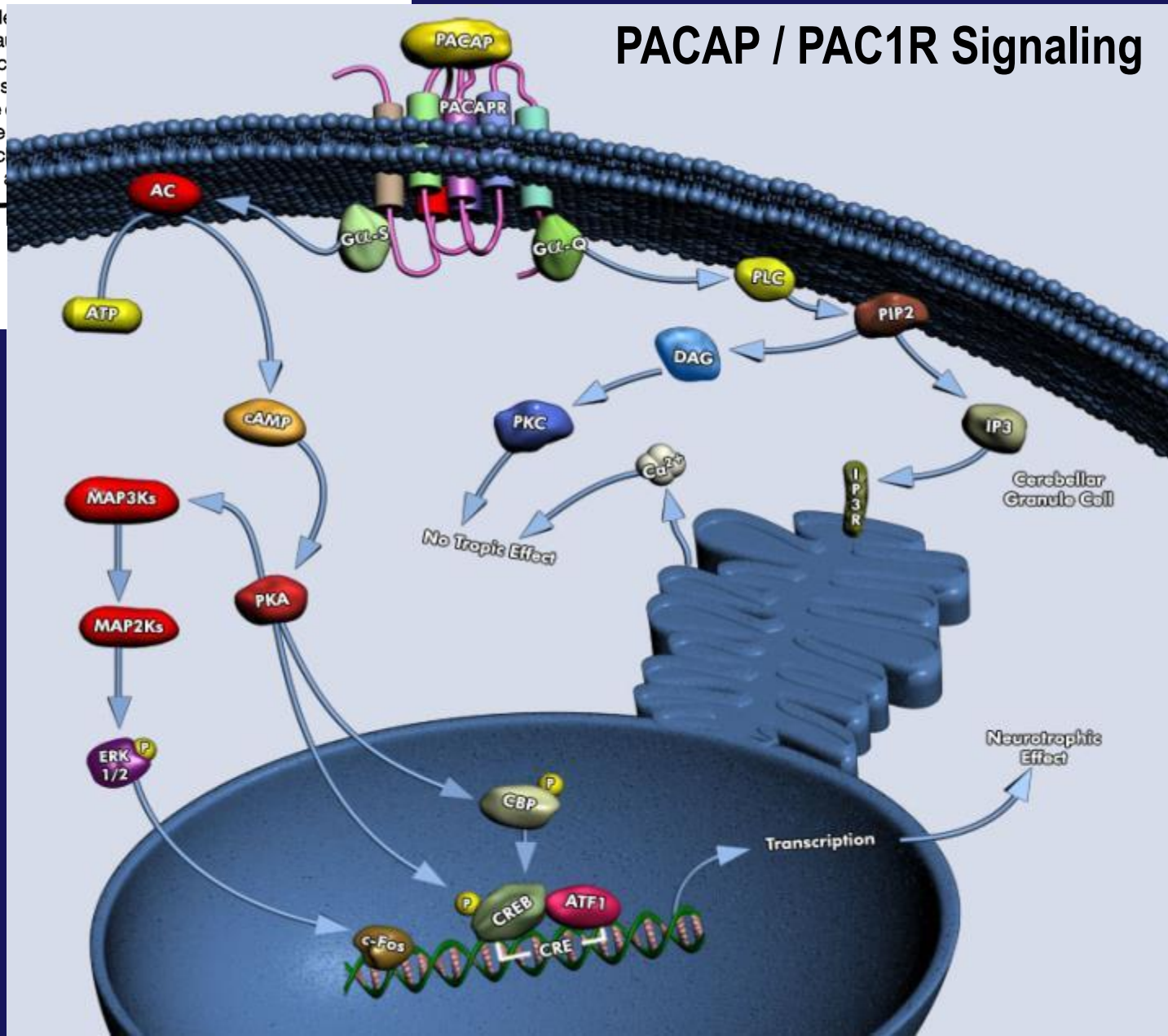
A Neuropeptide Gene Defined by the *Drosophila* Memory Mutant *amnesiac*

Mel B. Feany*† and William G. Quinn

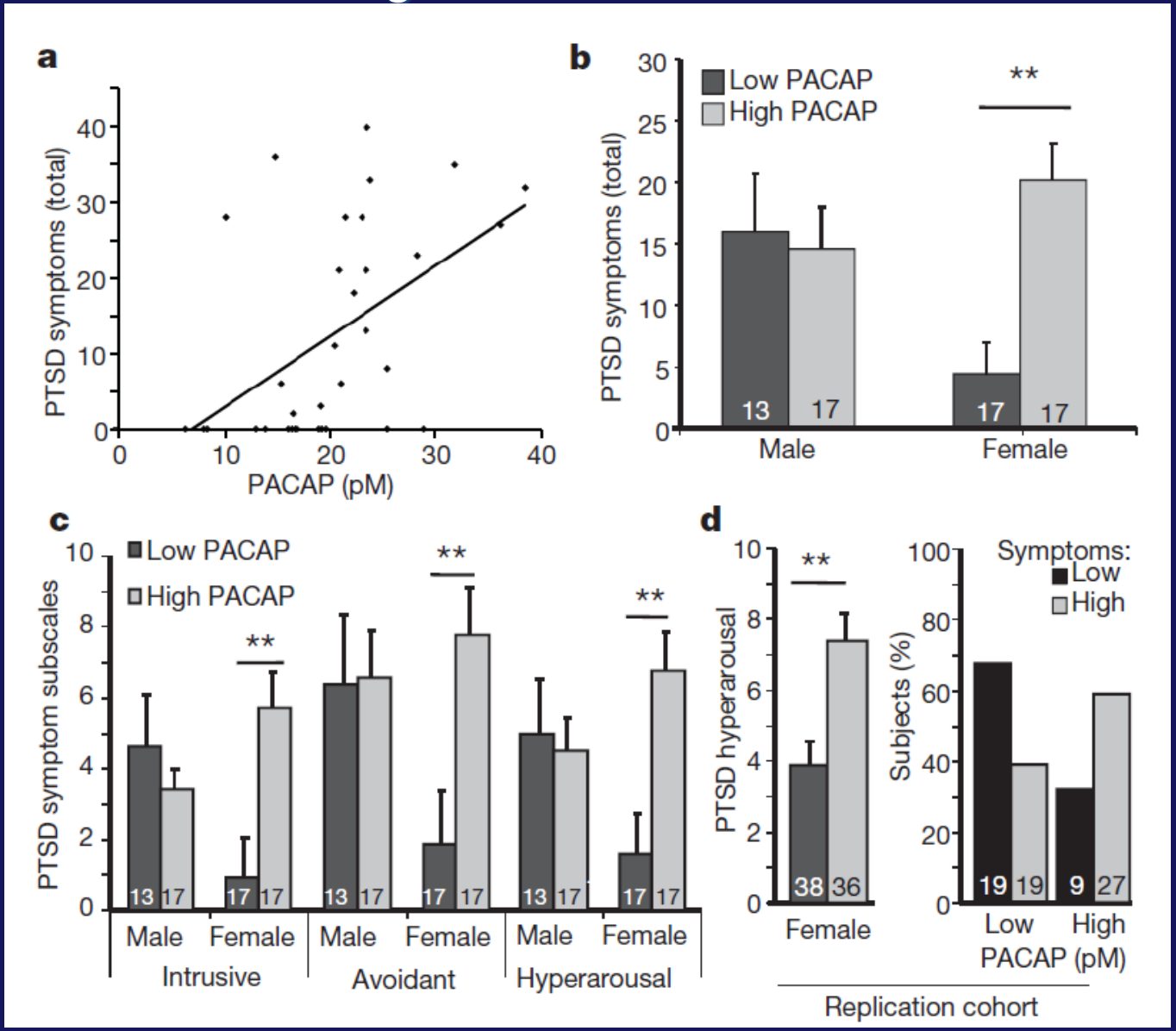
Mutations in genes required for associative le
isolation of the genes has been difficult becau
induced allele. Here, a simplified genetic sc
involved in learning and memory. Second s
sterility phenotype were isolated with the use
mutation that was recovered mapped in the
revealed that *amn* encodes a previously unc
the cloning of *amn*, specific neuropeptides

SCIENCE • VOL. 268 • 12 MAY 1995

PACAP / PAC1R Signaling

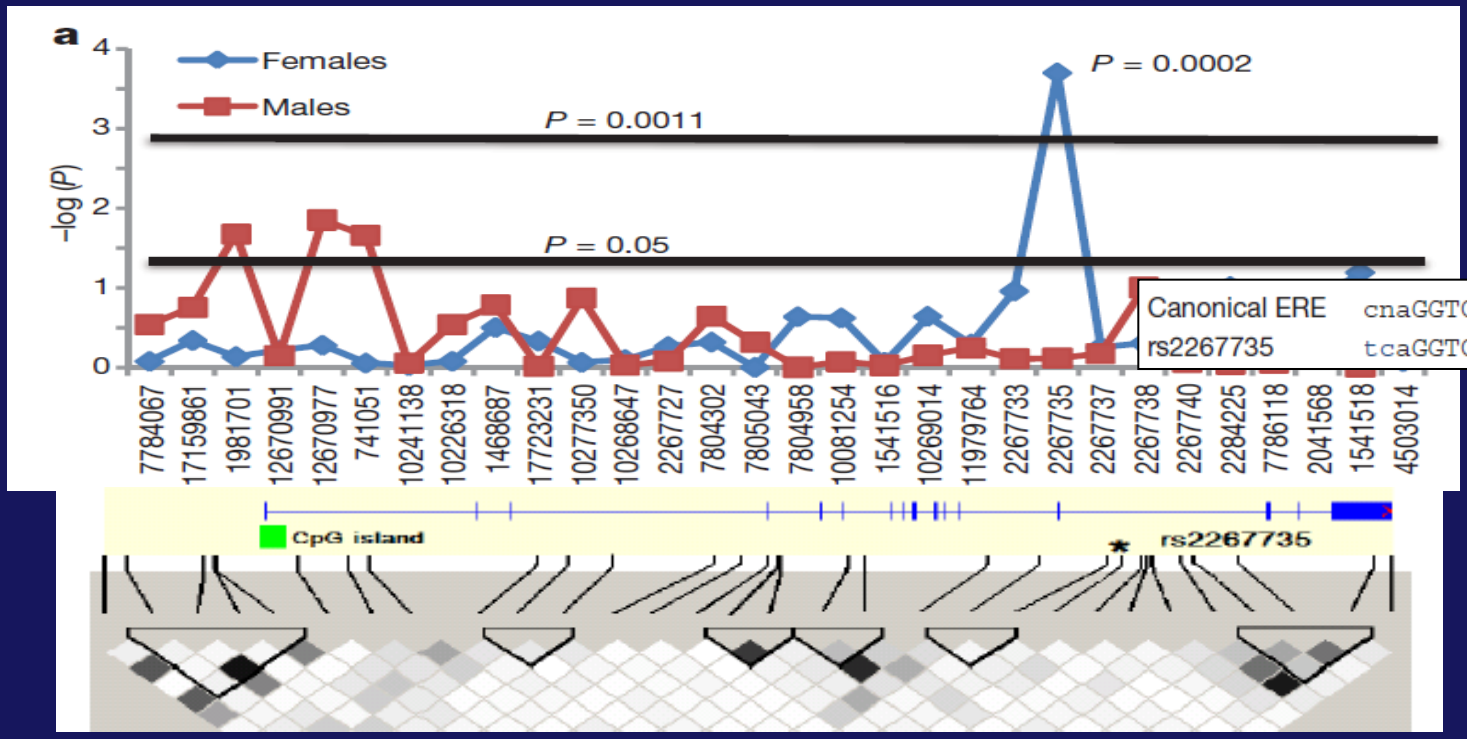


PACAP peptide levels were associated with higher PTSD sx in females

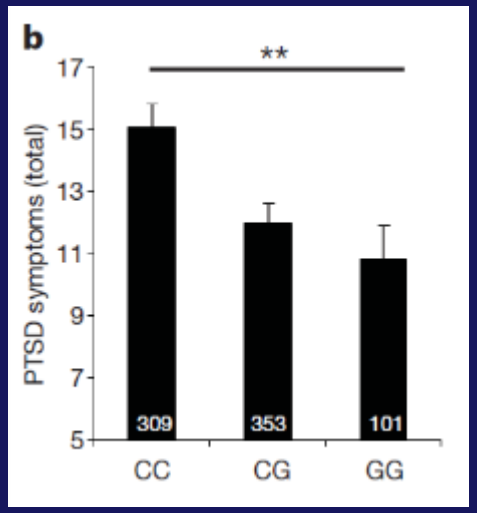


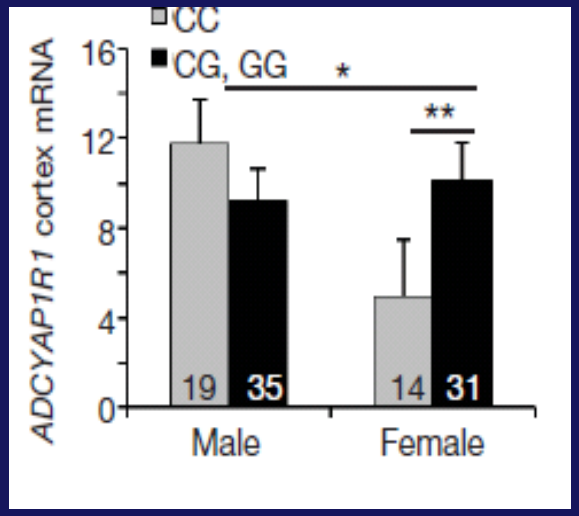
Ressler et al., Nature, 2011

ADCYAP1R1, PAC1R is associated with PTSD in highly traumatized females



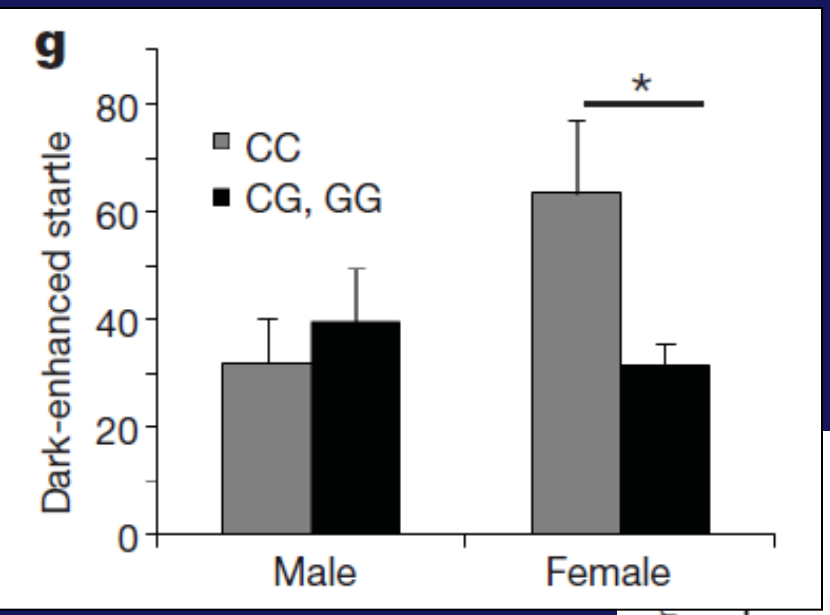
rs2267735–PTSD	*N* (1,237)	*Wald* χ^2	OR (CI)	*P*-value
Male original	295	0.036	1.03 (0.71–1.49)	0.85
Male replication	179	0.57	0.83 (0.52–1.33)	0.45
Male combined	474	0.123	0.95 (0.71–1.27)	0.73
Female original	503	13.7	1.72 (1.29–2.28)	**0.00021**
Female replication	260	4.8	1.54 (1.04–2.29)	**0.029**
Female combined	763	18.4	1.66 (1.32–2.09)	**0.000018**





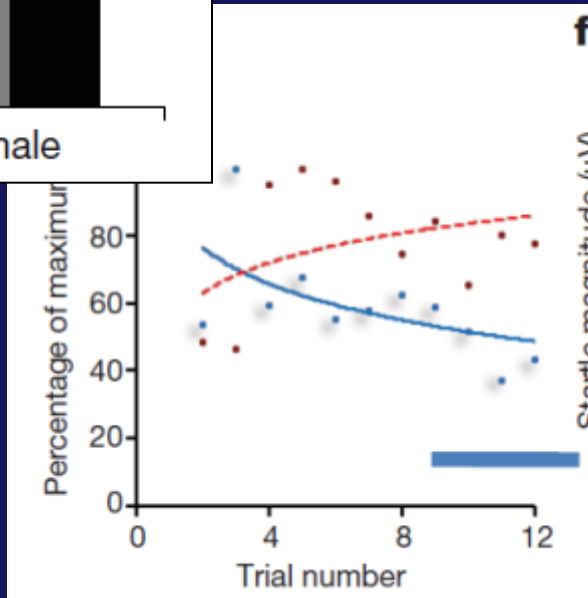
Ressler et al., Nature, 2011

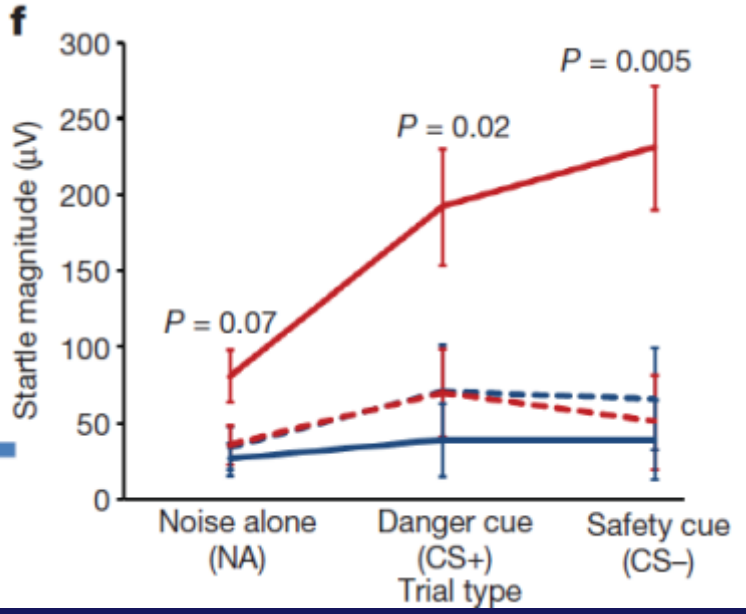
rs2267735 *PAC1* genotype associated with physiological measures of PTSD: Dark-enhanced and fear potentiated startle in women



Dark Enhanced Startle

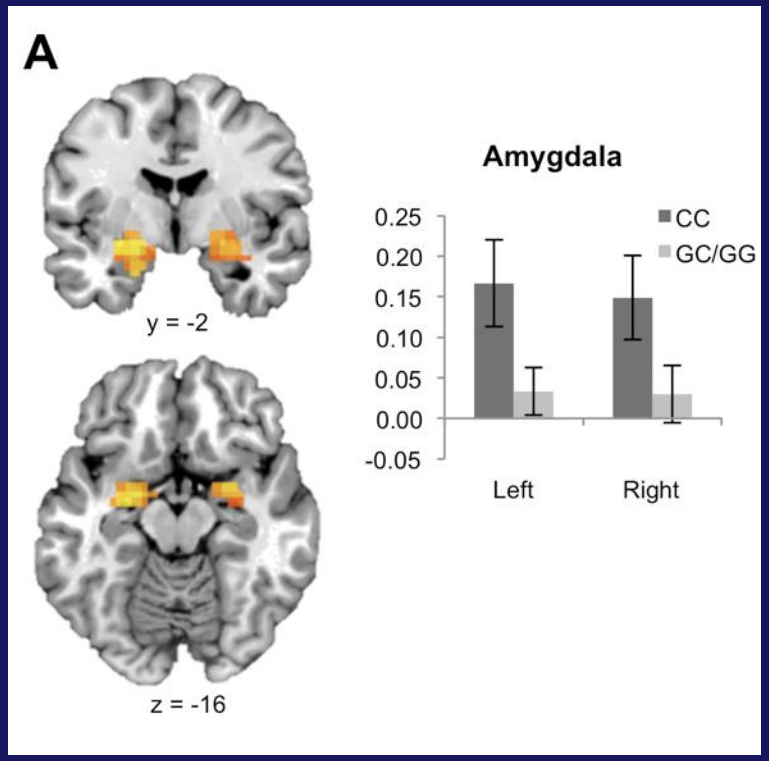
Fear Potentiated Startle

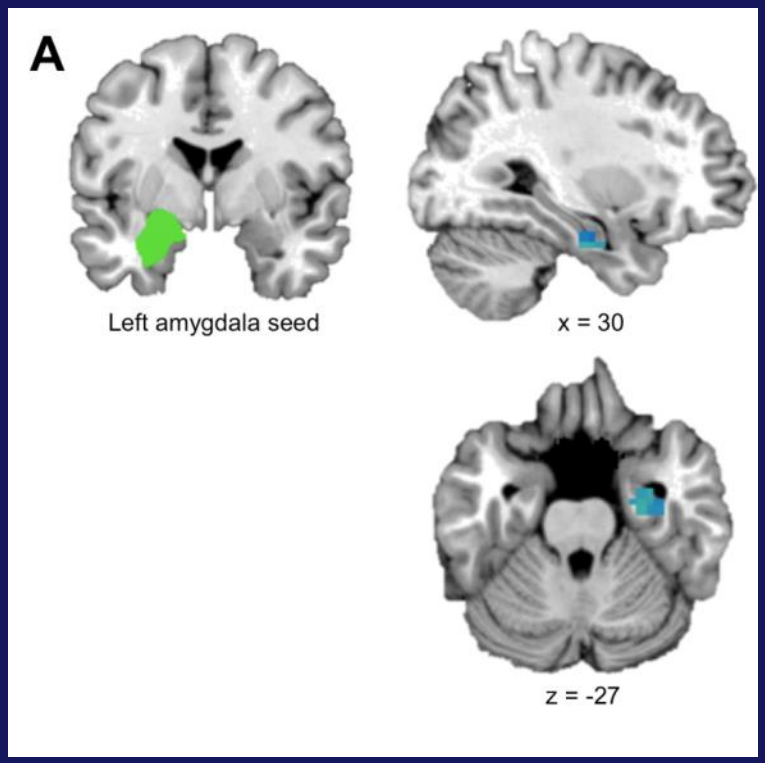




Ressler et al., Nature, 2011

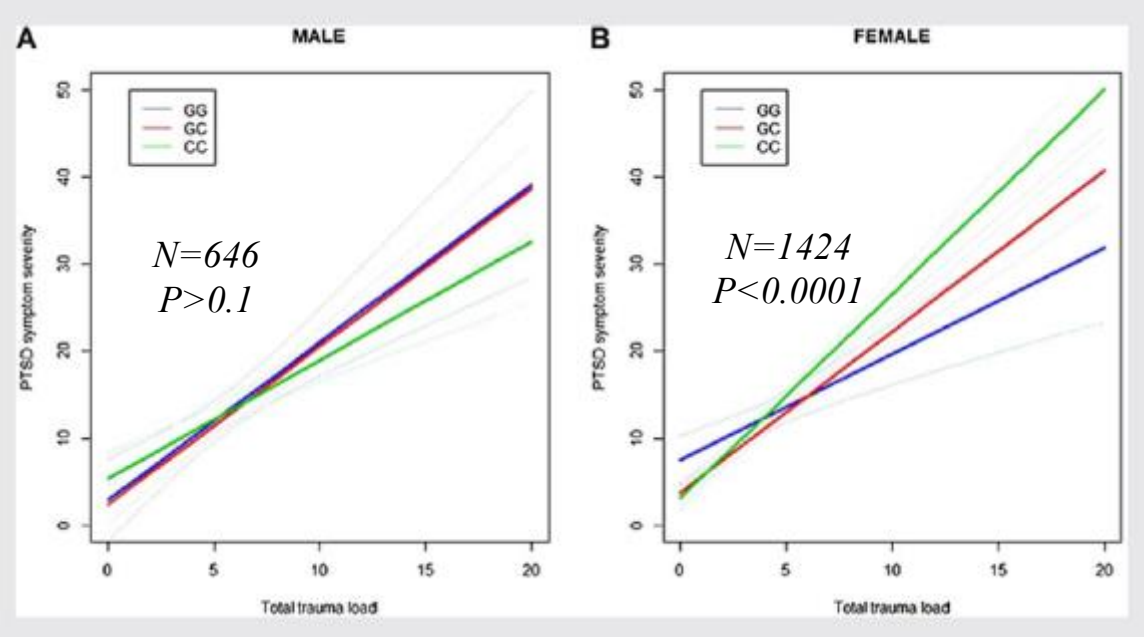
ADCYAP1R1 risk allele is associated with increased amygdala activation (and decreased amygdala-hippocampal connectivity) when viewing fearful faces *(N=49)*

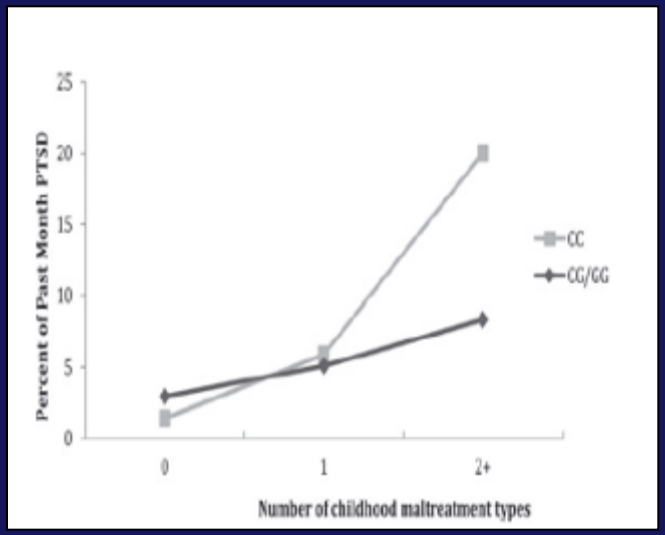




Stevens et al., PNAS, 2014

Recent Replication and Extensions





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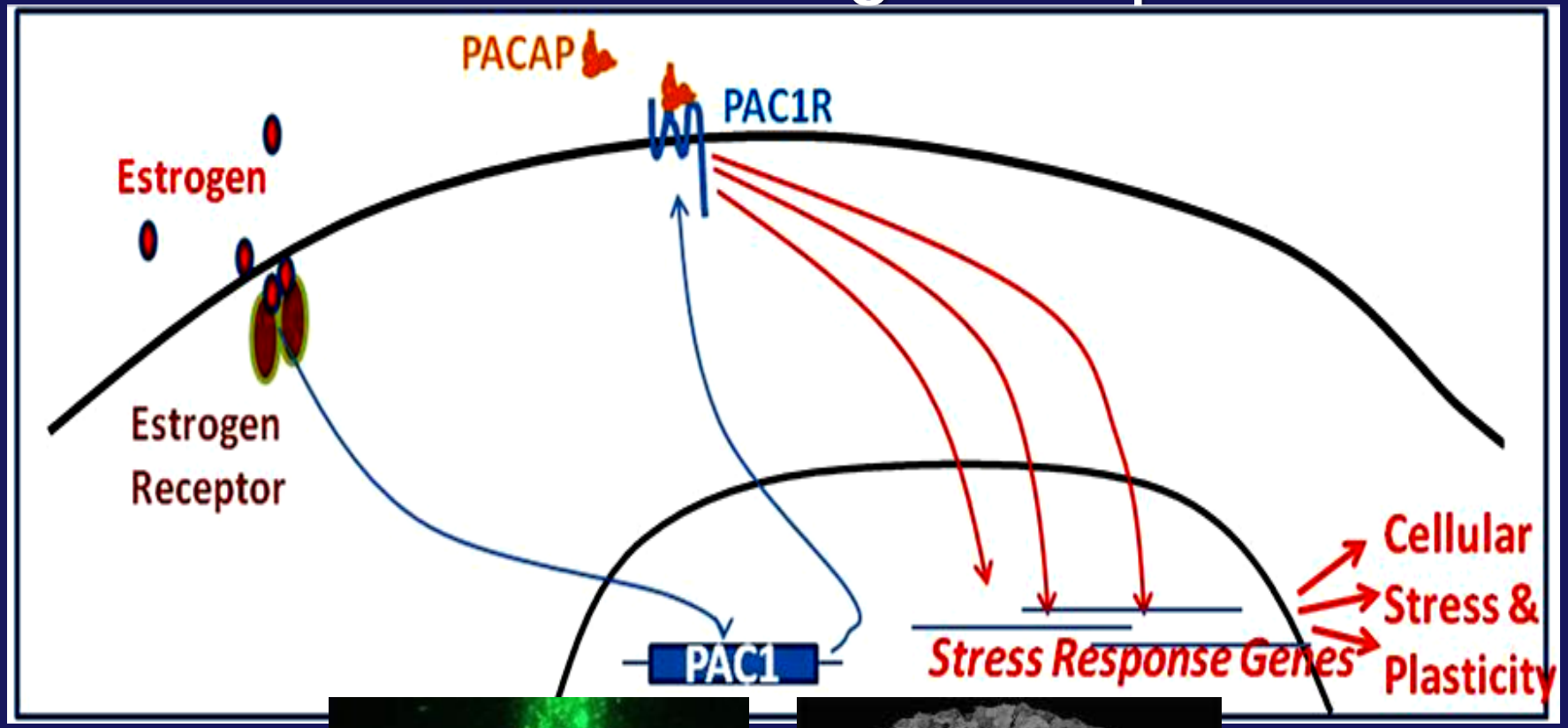
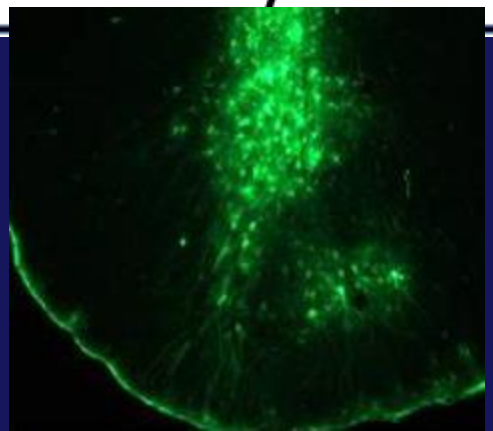
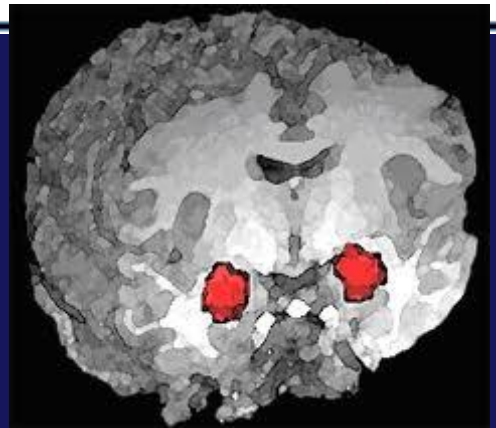
- Wang L, Cao C, Wang R, Qing Y, Zhang J, Zhang XY. PAC1 receptor (ADCYAP1R1) genotype is associated with PTSD's emotional numbing symptoms in Chinese earthquake survivors. *J Affect Disord.* 2013 Feb 7.

Potential Role for PAC1 / PACAP in stress + estrogen response



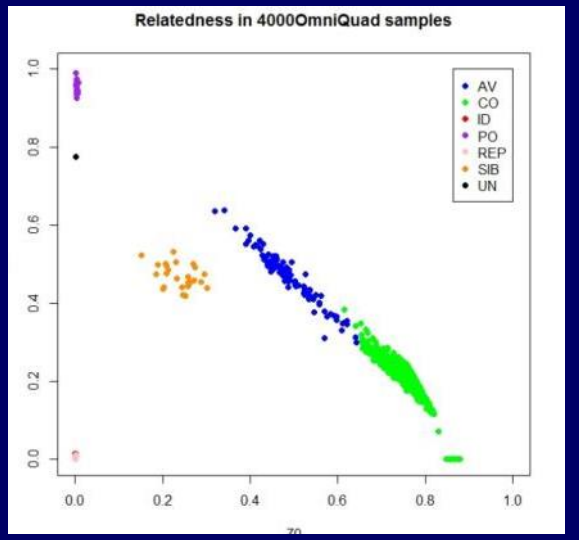


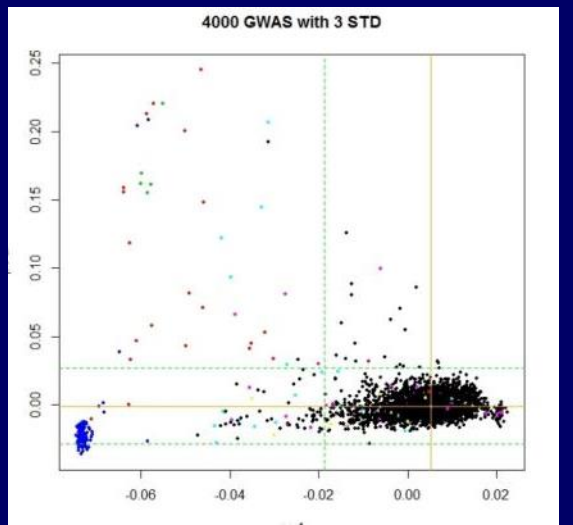


GxE approaches to GWAS analyses

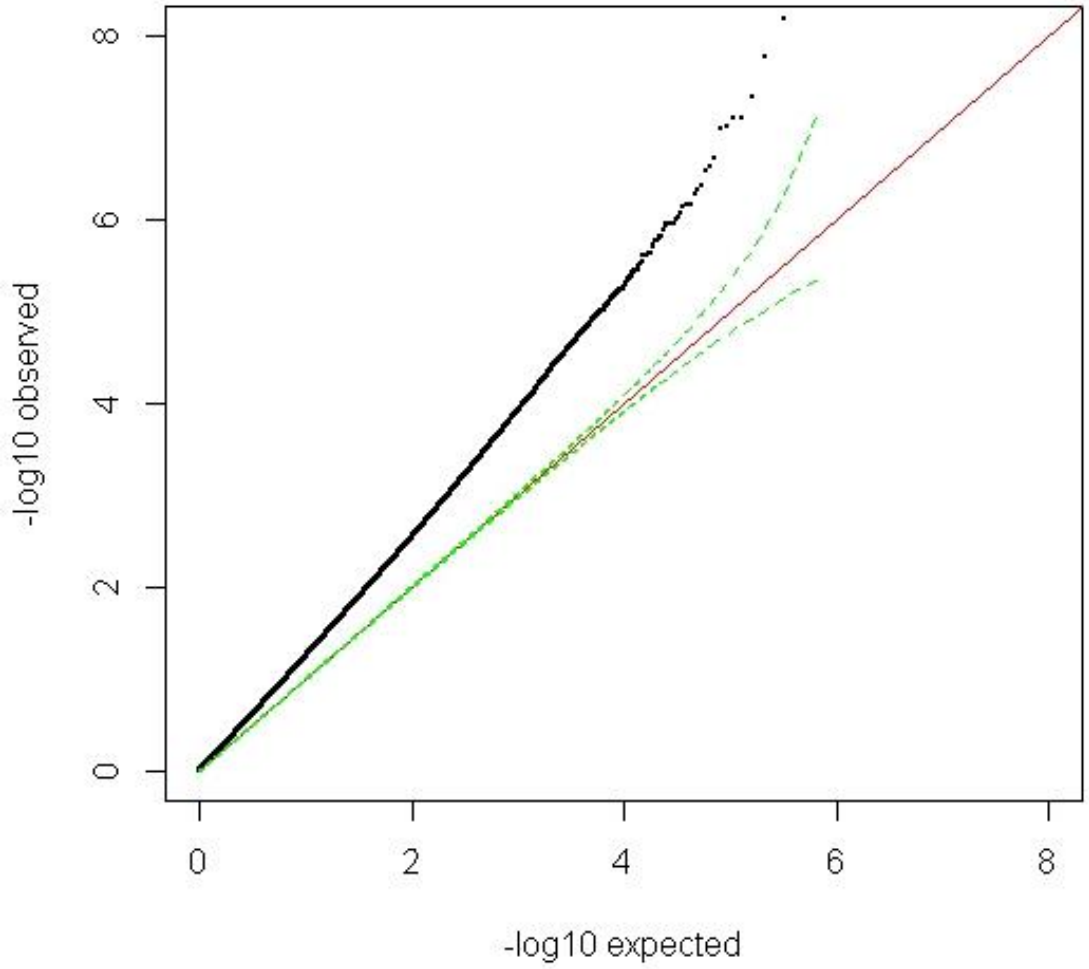
Lynn Almli, PhD, Michael Epstein, PhD, et al.

- Call rate of SNP and Sample >0.98
- MAF cut-off 0.01
- HWE failures flagged and assess when “hits” are found
- Relatives removed through cousins
- Ancestry assessed via PCA, clustering AAs kept for final analysis





Representative gxe GWAS QQplot with genome-wide inflation (not seen in main effects model)

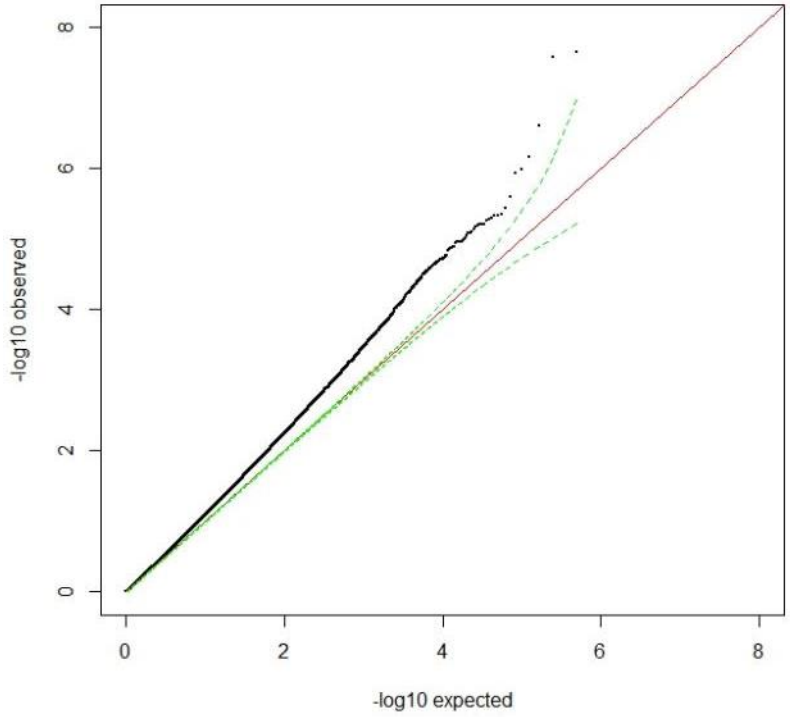


Methods to reduce inflation in gxe's

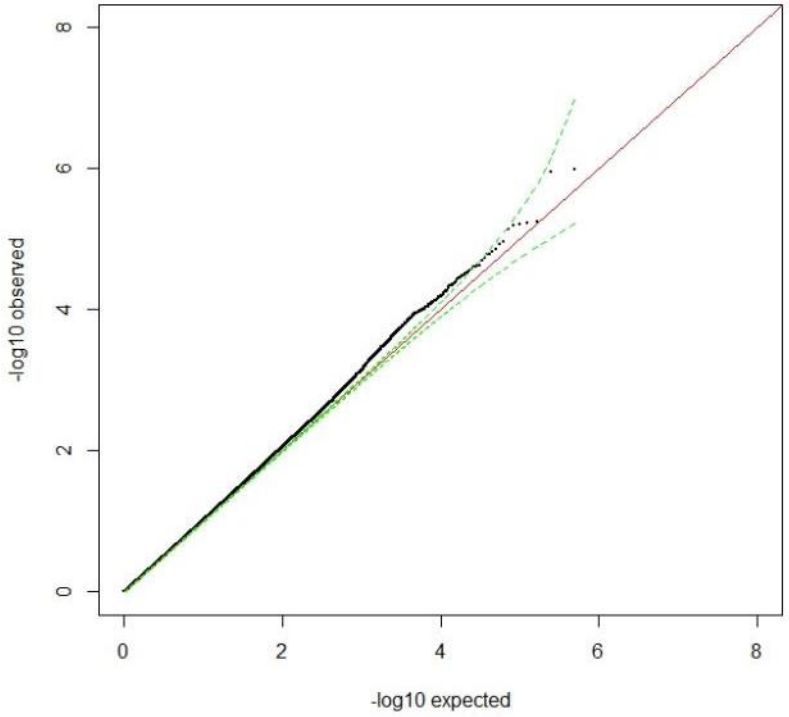
- Restriction to severely traumatized: successful, but kills sample size
- Robust (heteroscedasticity-consistent) standard errors (White, 1980; 'Huber-White' standard errors or 'sandwich' standard errors): uniformly successful (see example)
- Log and sqrt transformation: successful in some models (see example)
- PC adjustment: not successful

Comparison between model based regression approach and model-robust

Model-based



Model-robust



Issues at hand

- Environmental variable overwhelmingly predicts PTSD (~10^{-100} in some cases), as opposed to genotype
- Different levels of environmental variables have different effects on phenotype
- Even robust models do not entirely fix inflation issues

Summary

- Application of methods to utilize gxe GWAS will likely identify new pathways that are not found with main-effect only analyses

Modeling Fear Disorders

Gene B → Pre-existing Sensitivity *(gene + environment)* ← *Gene A*

1. **GWAS to date**
2. **HPA-pathway genes / FKBP5 (gxe)**
3. **Convergent Genomics – ADCYAP1R1 (gxe)**
4. **GxE GWAS approaches**

PTSD

Consolidation of Fear
Hours – days following event

recovery

Gene I → ↓ ← *Gene J*

Gene K (+) → Expression of Fear ← (-) *Gene L*

Memories, Nightmares, Flashbacks
Avoidance, Sympathetic Response, Startle

↓

Generalization *Recruitment of Non-associated cues*	**Sensitization** *Increased Fear With repeated exposure*	**Discrimination** *Fear is limited to specific trauma cue*	**Extinction** *Diminished response to cues Over time*

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