Genomics of PTSD: Reexperience It!

Murray B. Stein MD, MPH on behalf of the CSP575B and MVP PTSD Team

Disclosure Statement

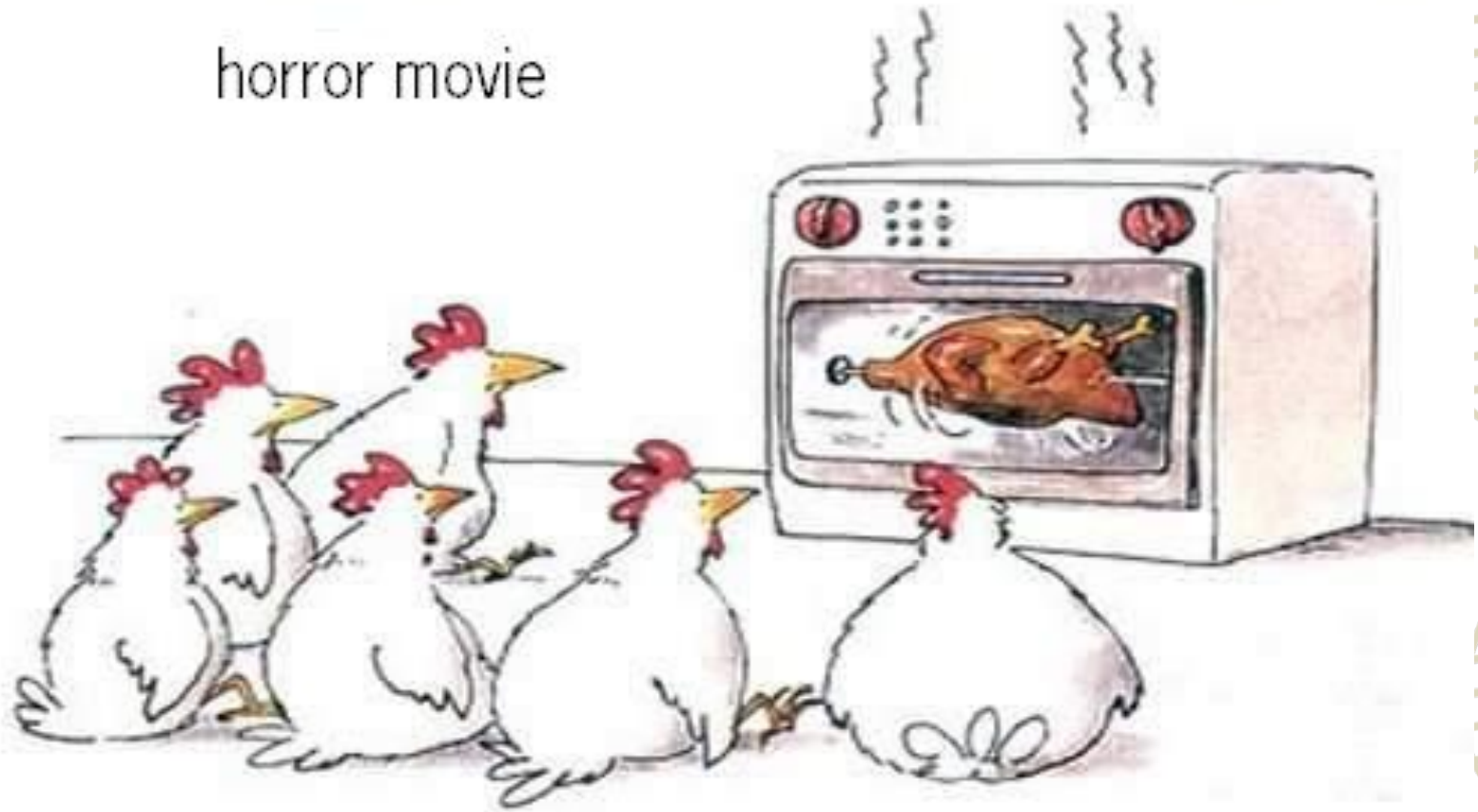
- Murray B. Stein, MD, MPH has in the past 3 years received research support from
  - National Institute of Mental Health
  - National Institute of Alcoholism and Alcohol Abuse
  - US Department of Defense
  - US Department of Veterans Affairs
  - He has in the past 3 years been a paid consultant for:
    - Aptinyx
    - Bionomics
    - Janssen
    - Oxeia Biopharmaceuticals
    - Turing Pharmaceuticals
- He has also been paid for editorial work on:
  - the peer-reviewed journals
    - *Depression and Anxiety* (Editor-in-Chief)
    - *Biological Psychiatry* (Deputy Editor)
  - the evidence-based peer-reviewed physician resource
    - *UpToDate* (Co-Editor-in-Chief for Psychiatry)

PTSD Criteria (DSM-5)

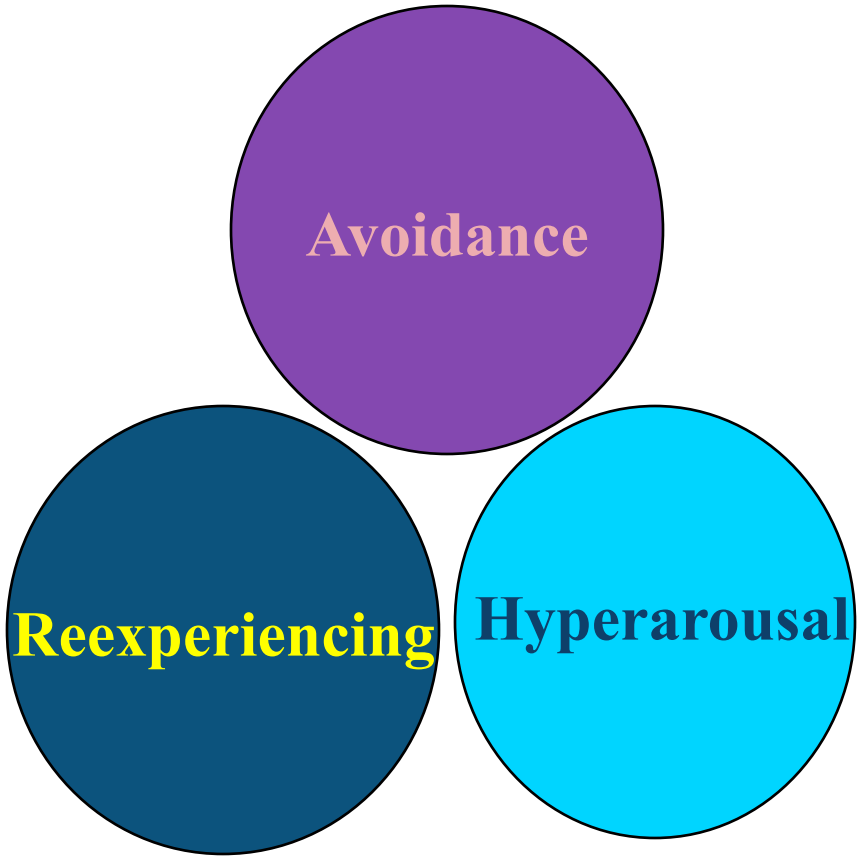
- A. Exposure to actual or threatened a) death, b) serious injury, or c) sexual violation, in one or more of the following ways:
- 1. directly experiencing the traumatic event(s)
- 2. witnessing, in person, the traumatic event(s) as they occurred to others
- 3. learning that the traumatic event(s) occurred to a close family member or close friend; cases of actual or threatened death must have been violent or accidental
- 4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse); this does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work-related.

American Psychiatric Association, DSM-5, 2013

Criterion A Event?



PTSD Symptoms (DSM-IV and ICD-11)

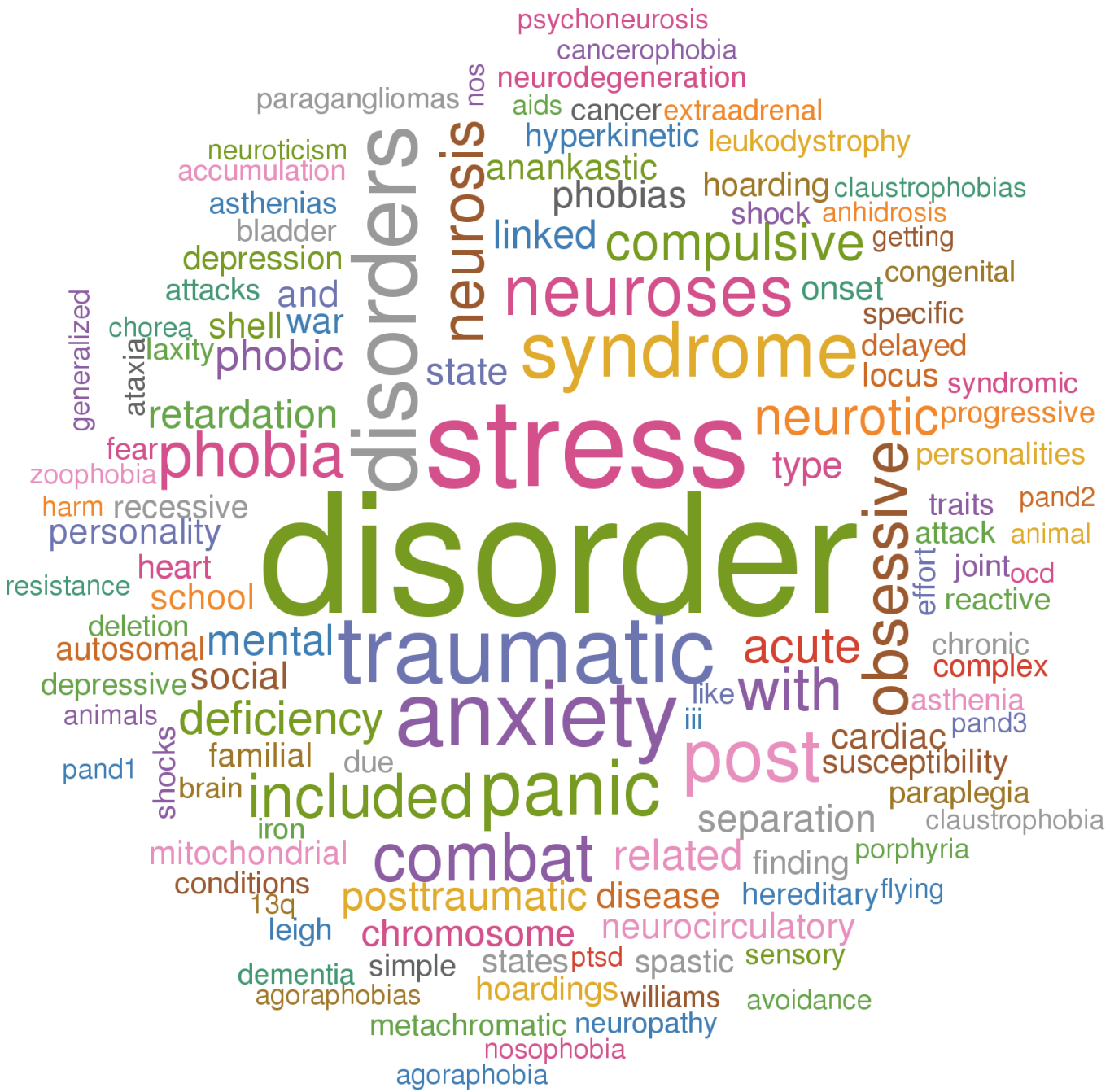


PTSD Prevalence

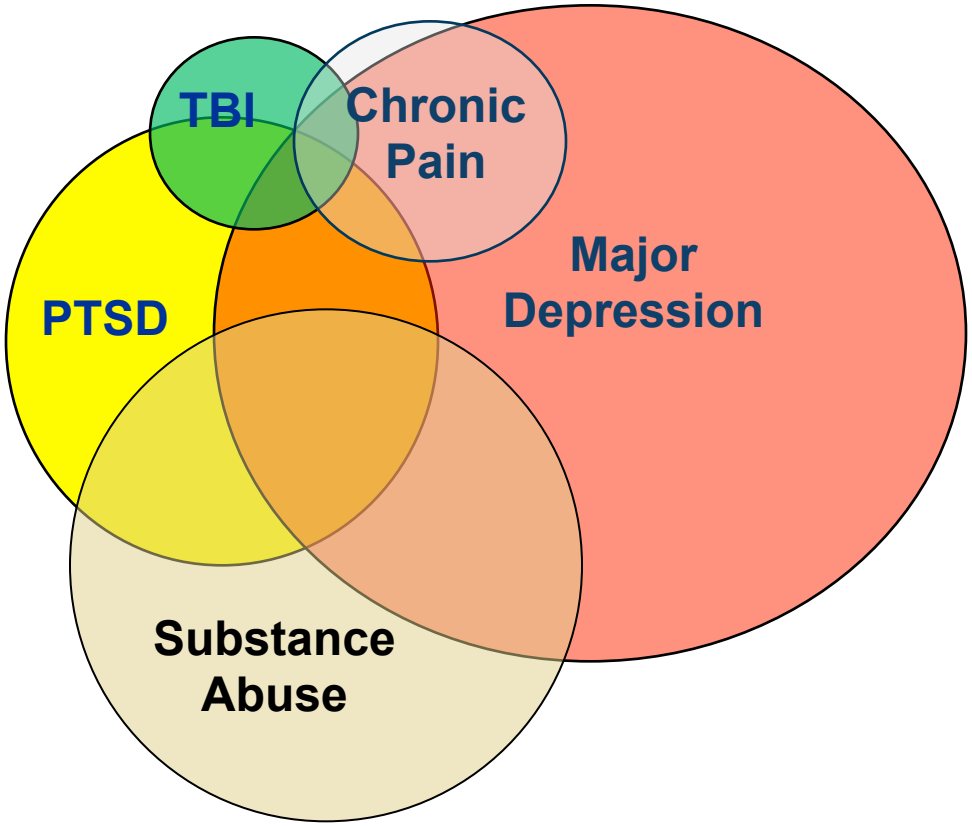
- US general population
  - 3.5% (se 0.3) in NCS-R[1]
    - Lifetime 6.8% (se 0.4) in NCS-R
      - Female:Male ~ 2:1
- Prevalence higher in some US subpopulations
  - 2 to 3X in American Indians on reservations[2]
    - Most prevalent disorder in women is PTSD (~20%)
  - Cambodian refugees in US, 20 years later[3]
    - 12-month prevalence 62%

NCS-R, National Comorbidity Survey Replication

[1]Kessler RC et al. *Arch Gen Psychiatry.* 2005;62:617-627; [2]Beals J et al. *Arch Gen Psychiatry.* 2005;62:99-108; [3]Marshall G et al. *JAMA.* 2005:294:571-579.

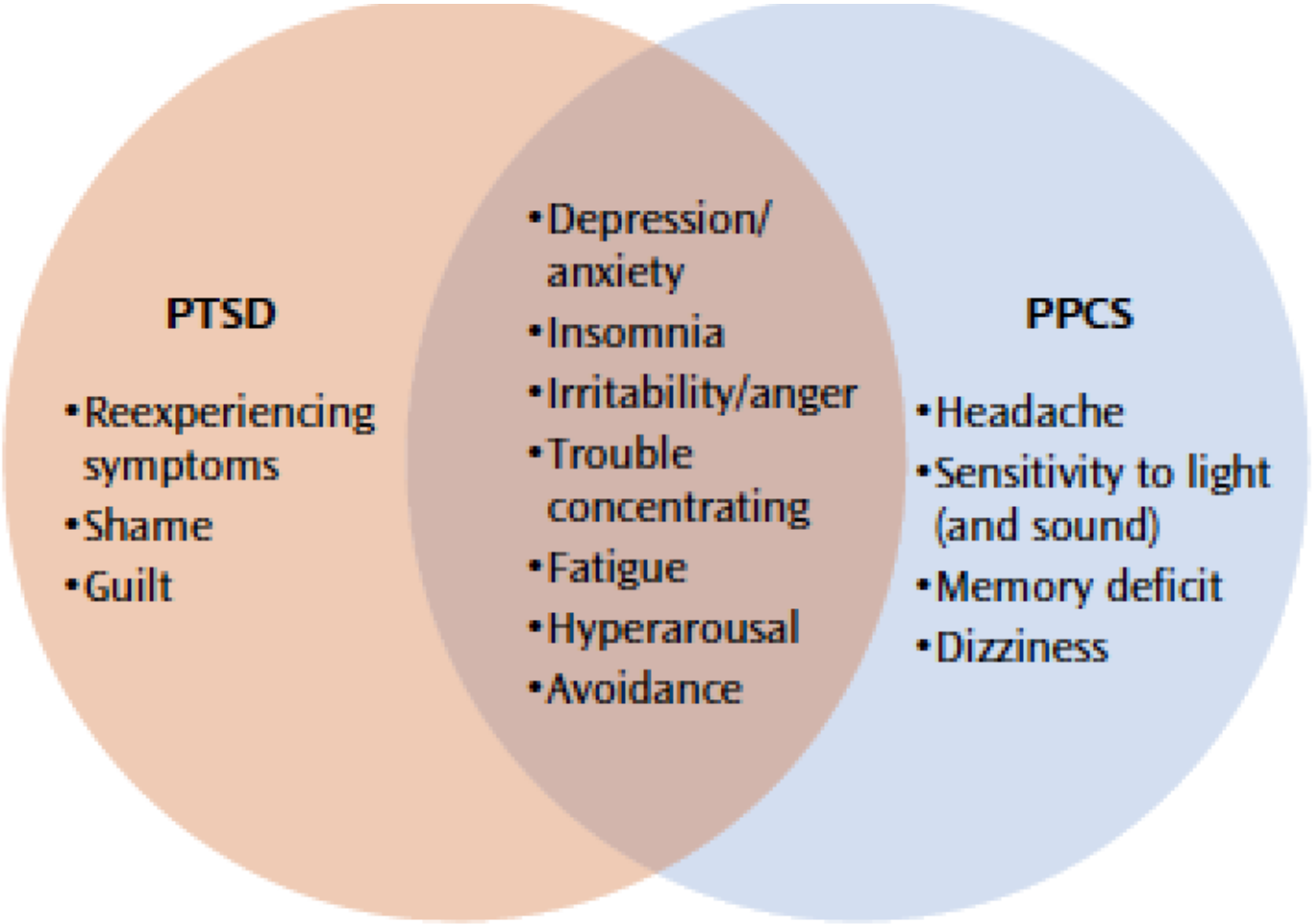

psychoneurosis
cancerophobia
neurodegeneration
paragangliomas
nos
aids
cancer
extraadrenal
hyperkinetic
leukodystrophy
neuroticism
accumulation
anankastic
phobias
hoarding
claustrophobias
asthenias
shock
anhidrosis
bladder
linked
compulsive
getting
depression
congenital
attacks
and
neuroses
onset
specific
chorea
shell
war
syndrome
delayed
generalized
ataxia
laxity
phobic
state
locus
syndromic
retardation
neurotic
progressive
fear
phobia
stress
type
personalities
zoophobia
disorders
neurosis
obsessive
harm
recessive
disorder
traits
pand2
personality
attack
animal
heart
effort
joint
ocd
resistance
school
reactive
deletion
autosomal
mental
traumatic
acute
chronic
depressive
social
complex
like
with
asthenia
animals
deficiency
anxiety
iii
pand3
cardiac
shocks
familial
post
susceptibility
pand1
due
panic
brain
included
paraplegia
separation
claustrophobia
iron
mitochondrial
combat
related
finding
porphyria
conditions
posttraumatic
disease
hereditary
flying
13q
leigh
chromosome
neurocirculatory
dementia
simple
states
ptsd
spastic
sensory
agoraphobias
hoardings
williams
avoidance
metachromatic
neuropathy
nosophobia
agoraphobia

PTSD Comorbidity



TBI, traumatic brain injury
Stein MB, McAllister TW. *Am J Psychiatry.* 2009;166:768-776.

The Interface of PTSD and Persistent Post-concussive Symptoms (PPCS) Following Mild TBI



Stein MB & McAllister TW. *Am J Psychiatry* 2009; 166:768-776

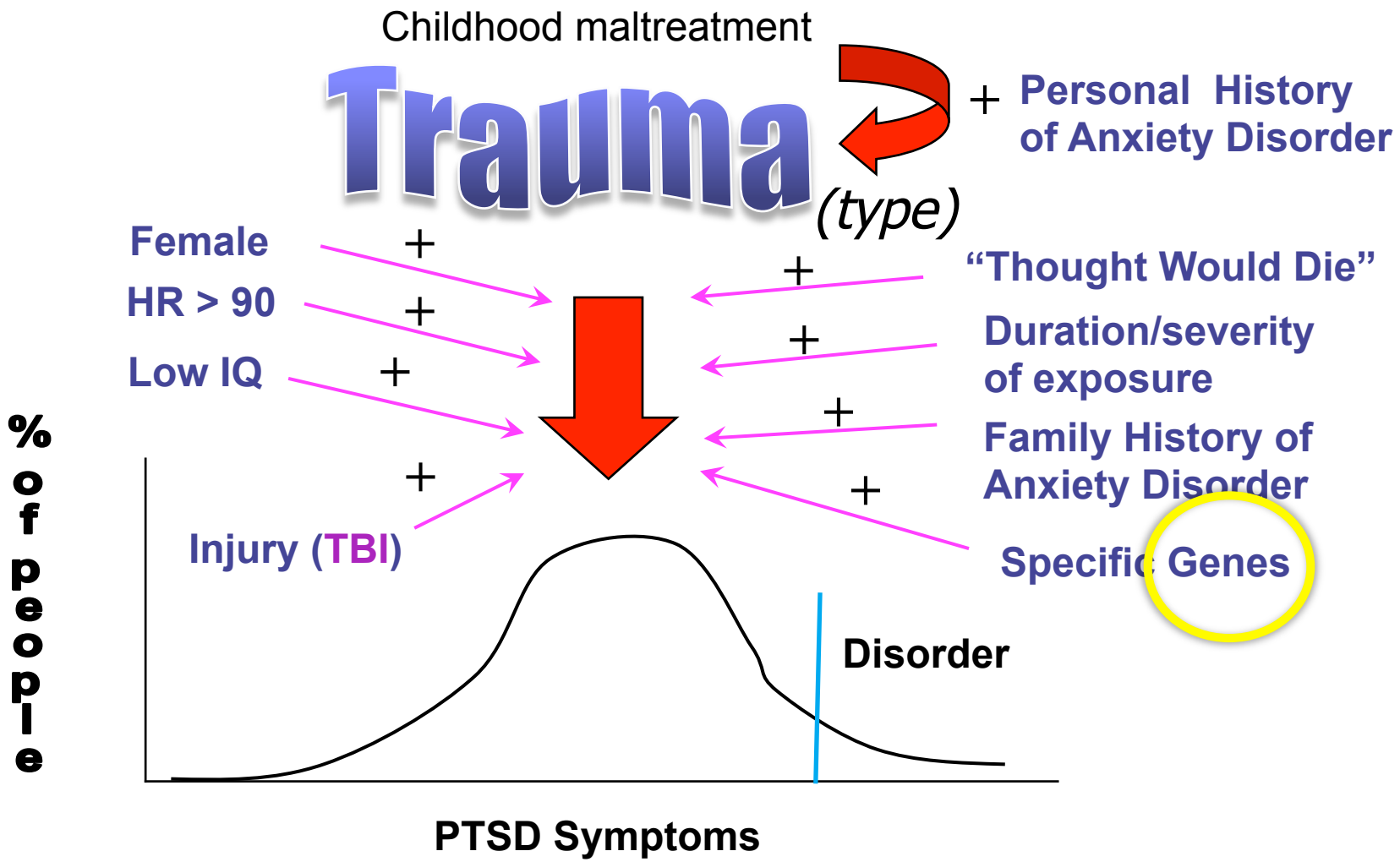
TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

mTBI and PTSD after Traumatic Injury

- Cohort of N = 1155 mTBI patients seen in ED
  - Comparison N = 230 non-head orthopedic trauma injury
- PCL-5 ≥ 33 used to indicate probable PTSD
  - 19.2% (se 1.4) of mTBI patients at 6 months
  - 9.8% (se 2.8) of orthopedic injury patients at 6 months (p = 0.016)
- Risk factors for PTSD among mTBI patients
  - Lower education (OR 0.89, 95% CI 0.82-0.97; per year)
  - Race: African (OR 5.11, 95% CI 2.89-9.05)
  - Pre-injury mental health problems (OR 3.57, 95% CI 2.09-6.09)
  - Injury: Violent/Assault (OR 3.43, 95% CI 1.56-7.54)
  - ~~Loss of consciousness or posttraumatic amnesia~~
  - ~~CT positive (e.g., subarachnoid hemorrhage or parenchymal injury)~~
  - ~~Hospital (+/- ICU) admission~~

Stein MB et al. TRACK-TBI Investigators. *JAMA Psychiatry* 2019

PTSD Risk

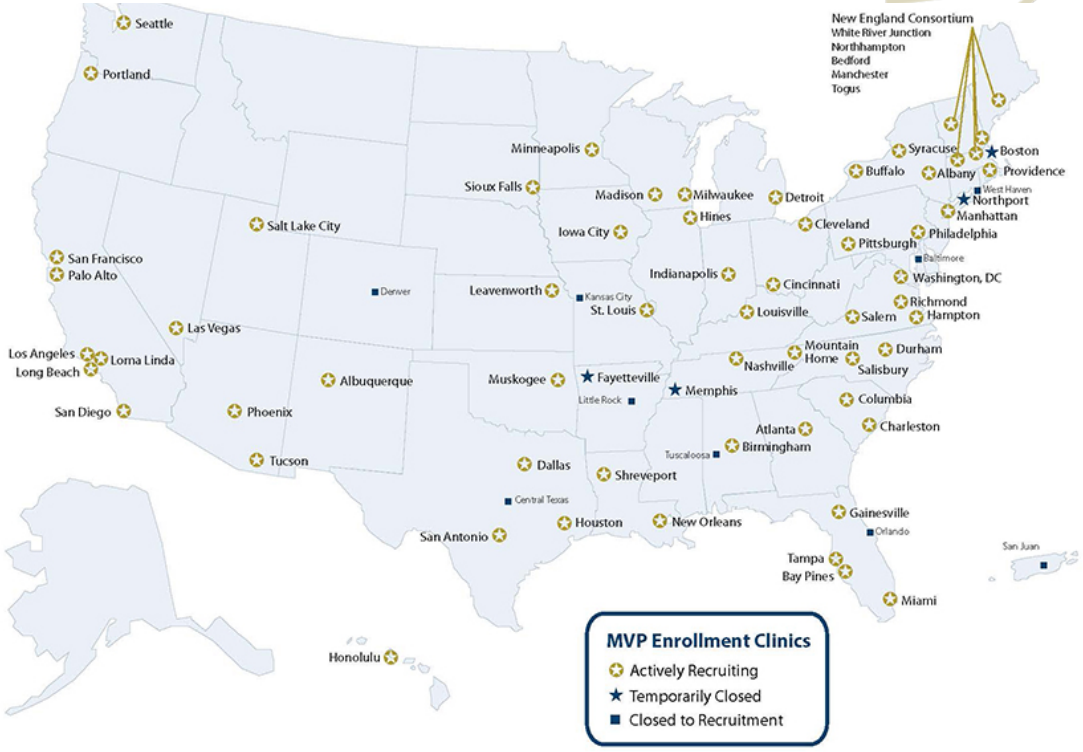


HR, heart rate; IQ, intelligence quotient.
Stein MB. Unpublished

Million Veteran Program

MVP is a national research program to learn how genes, lifestyle, and military exposures affect health and illness. Since launching in 2011, over 775,000 Veteran partners have joined one of the world's largest programs on genetics and health

MILLION VETERAN PROGRAM



PTSD Diagnosis Algorithm

Journal of Traumatic Stress
April 2019, *32*, 226–237

ISTSS International Society for Traumatic Stress Studies

Validation of an Electronic Medical Record–Based Algorithm for Identifying Posttraumatic Stress Disorder in U.S. Veterans

Kelly M. Harrington,[1,2] Rachel Quaden,[1] Murray B. Stein,[3,4] Jacqueline P. Honerlaw,[1] Shadha Cissell,[3] Robert H. Pietrzak,[5,6] Hongyu Zhao,[7,8] Krishnan Radhakrishnan,[7,9] Mihaela Aslan,[7,10] John Michael Gaziano,[1,11] John Concato,[7,10] David R. Gagnon,[1,12] Joel Gelernter,[5,6,13] and Kelly Cho,[1,11] on behalf of the VA Million Veteran Program and Cooperative Studies Program

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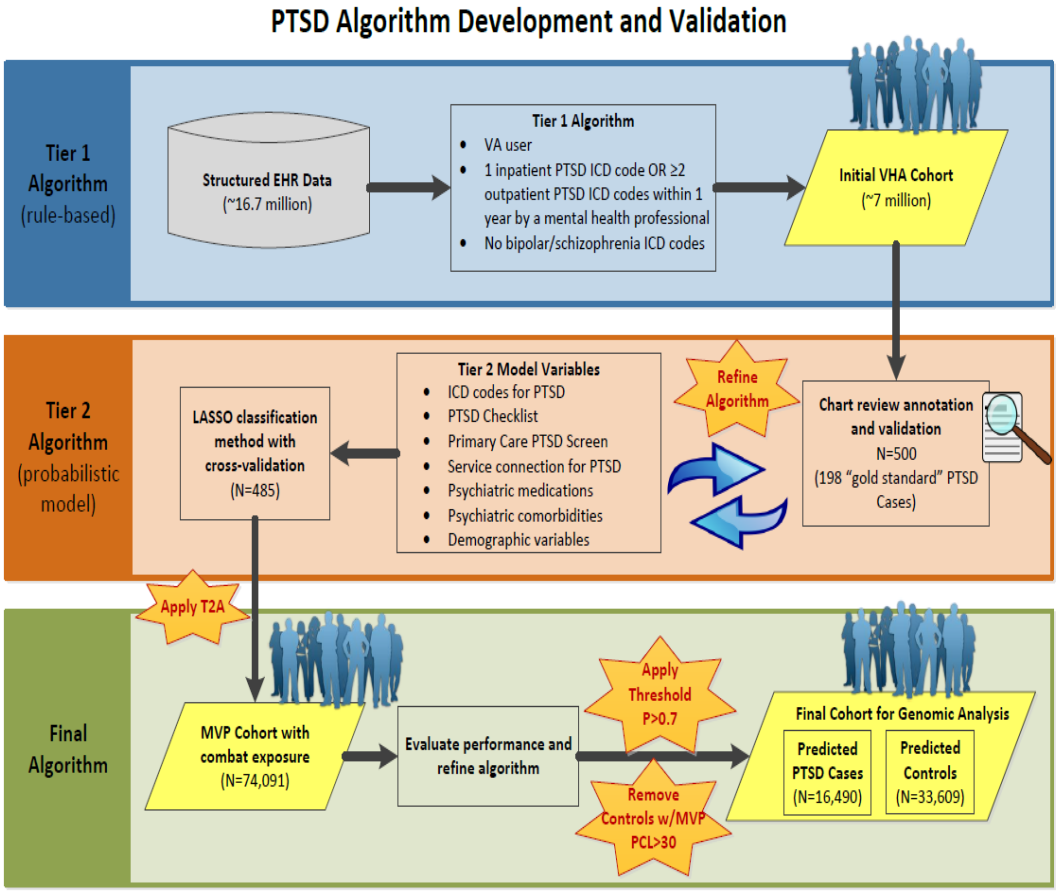
[8]Department of Biostatistics, Yale University School of Public Health, New Haven, Connecticut, USA
[9]Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Kentucky, USA
[10]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA
[11]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[12]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA
[13]Departments of Genetics and Neuroscience, Yale University School of Medicine, New Haven, Connecticut, USA

DOI: 10.1002/jts.22399

We developed an algorithm for identifying U.S. veterans with a history of posttraumatic stress disorder (PTSD), using the Department of Veterans Affairs (VA) electronic medical record (EMR) system. This work was motivated by the need to create a valid EMR-based phenotype to identify thousands of cases and controls for a genome-wide association study of PTSD in veterans. We used manual chart



Based on framework developed by MVP Phenomics Core

Algorithm Performance

		Sensitivity* (95% CI)	Specificity * (95% CI)	PPV* (95% CI)	NPV* (95% CI)
Tier 1 Algorithm (VHA)	Drop Possible PTSD	0.96 (0.889-1)	0.995 (0.986-1)	0.962 (0.898-1)	0.995 (0.985-1)
	Group Possible + Case	0.753 (0.657-0.939)	0.976 (0.958-0.990)	0.884 (0.80-0.952)	0.94 (0.915-0.963)
	Group Possible + Control	0.859 (0.754-0.945)	0.974 (0.959-0.988)	0.818 (0.727-0.906)	0.981 (0.967-0.993)
Tier 2 Algorithm (VHA)	Drop Possible PTSD	0.962 (0.9-1.0)	0.997 (0.988-1.0)	0.978 (0.919-1.0)	0.994 (0.984-1.0)
	Group Possible + Case	0.649 (0.559-0.735)	0.995 (0.986-1.0)	0.973 (0.924-1.0)	0.907 (0.875-0.935)
	Group Possible + Control	0.951 (0.885-1.0)	0.954 (0.930-0.972)	0.719 (0.609-0.829)	0.993 (0.985-1.0)

* Statistics are proportionally weighted based on chart review selection

Algorithm Performance (cont'd)

Prob (Cntrl) Cut-Off	# Controls	% Controls retained	Estimated misclass
>0.6	48,047	95.6%	1.3%
>0.7	*46,884	93.2%	1.0%
>0.8	38,274	76.1%	0.3%

Prob (Case) Cut-Off	# Cases	% Cases retained	Estimated misclass	Sensitivity*	Specificity*
LASSO	22,651	100.0%	18.2%	0.83	0.92
>0.5	21,980	97.0%	18.0%	0.82	0.93
>0.6	19,058	84.1%	12.9%	0.80	0.96
>0.7	16,490	72.8%	9.2%	0.78	0.98
>0.8	15,416	68.1%	9.6%	0.77	0.98
>0.9	13,359	59.0%	3.6%	0.76	0.99

* N = 46,884 controls used for calculating sensitivity and specificity

New Results

Comment on this paper

Genomic Characterization of Posttraumatic Stress Disorder in a Large US Military Veteran Sample

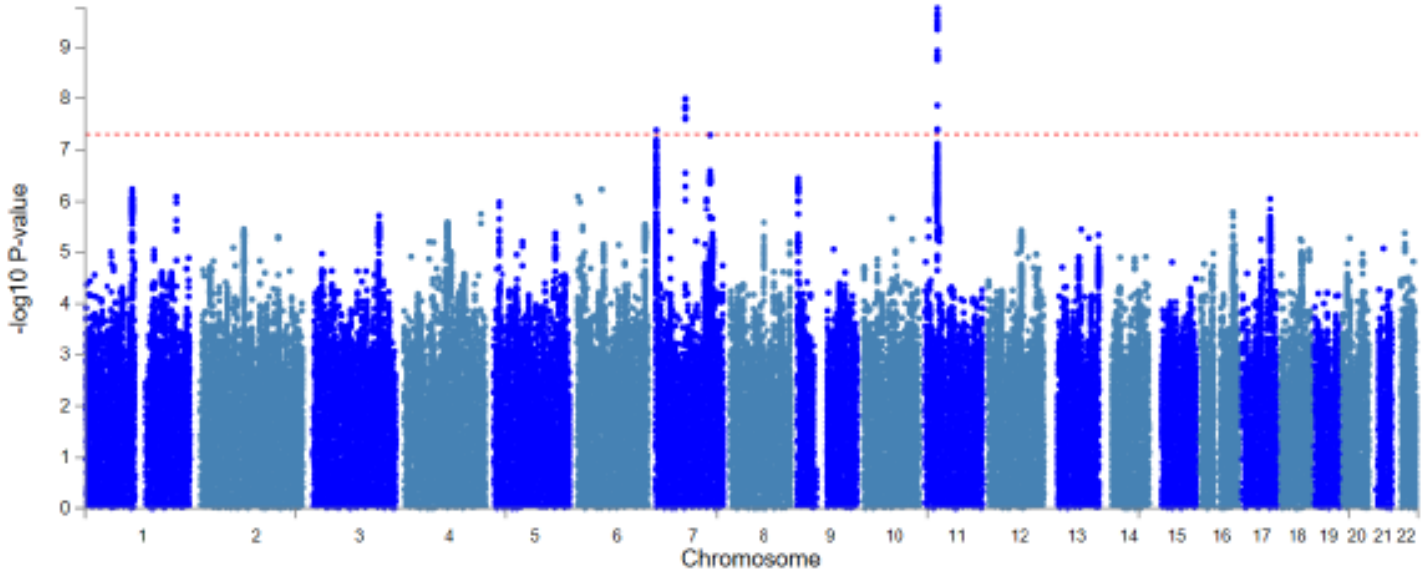
Murray B Stein, Daniel F Levey, Zhongshan Cheng, Frank R Wendt, Kelly Harrington, Kelly Cho, Rachel Quaden, Krishnan Radhakrishnan, Matthew J Girgenti, Yuk-Lam Anne Ho, Daniel Posner, PTSD Working Group of the Psychiatric Genomics Consortium, Traumatic Stress Brain Research Study Group, VA Million Veteran Program, VA Cooperative Studies Program, Mihaela Aslan, Ronald S Duman, Hongyu Zhao, Renato Polimanti, John Concato, Joel Gelernter

doi: https://doi.org/10.1101/764001

Abstract

Individuals vary in their liability to develop Posttraumatic Stress Disorder (PTSD), the symptoms of which are highly heterogeneous, following exposure to life-threatening trauma. Understanding genetic factors that contribute to the biology of PTSD is critical

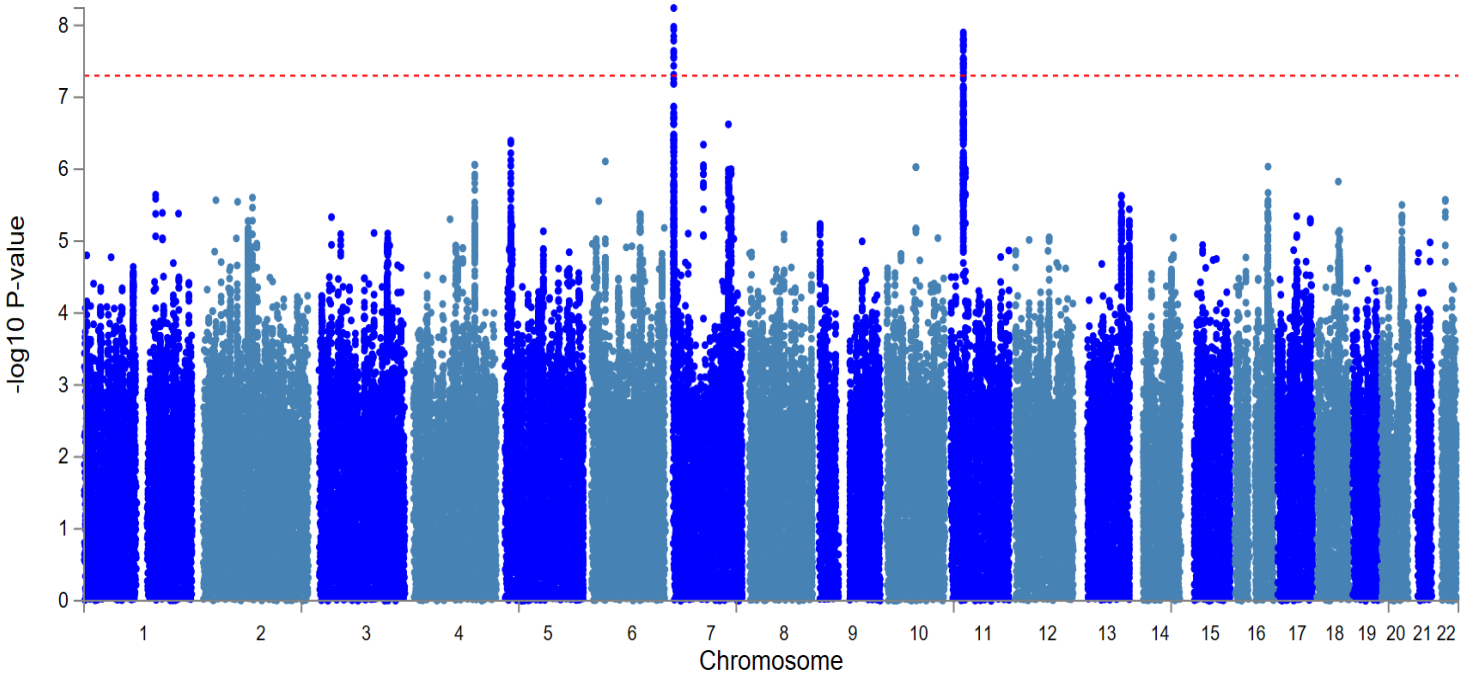
Binary Case-Control GWAS



uniqID	rsID	chr	pos	P-value	start	end	nSNPs	CaseCon
11:28707675:C:T	rs10767744	11	28707675	1.75E-10	28591168	28710118	190	METTL15
7:70219946:C:CCA	rs137999048	7	70219946	1.03E-08	70217631	70234438	11	AUTS2
7:1855531:A:G	rs7680	7	1855531	4.17E-08	1847623	1892529	40	MAD1L1

There are 3 significant signals for the algorithmically derived case (N = 36,301) *vs.* control (N = 178,107) European meta-analysis

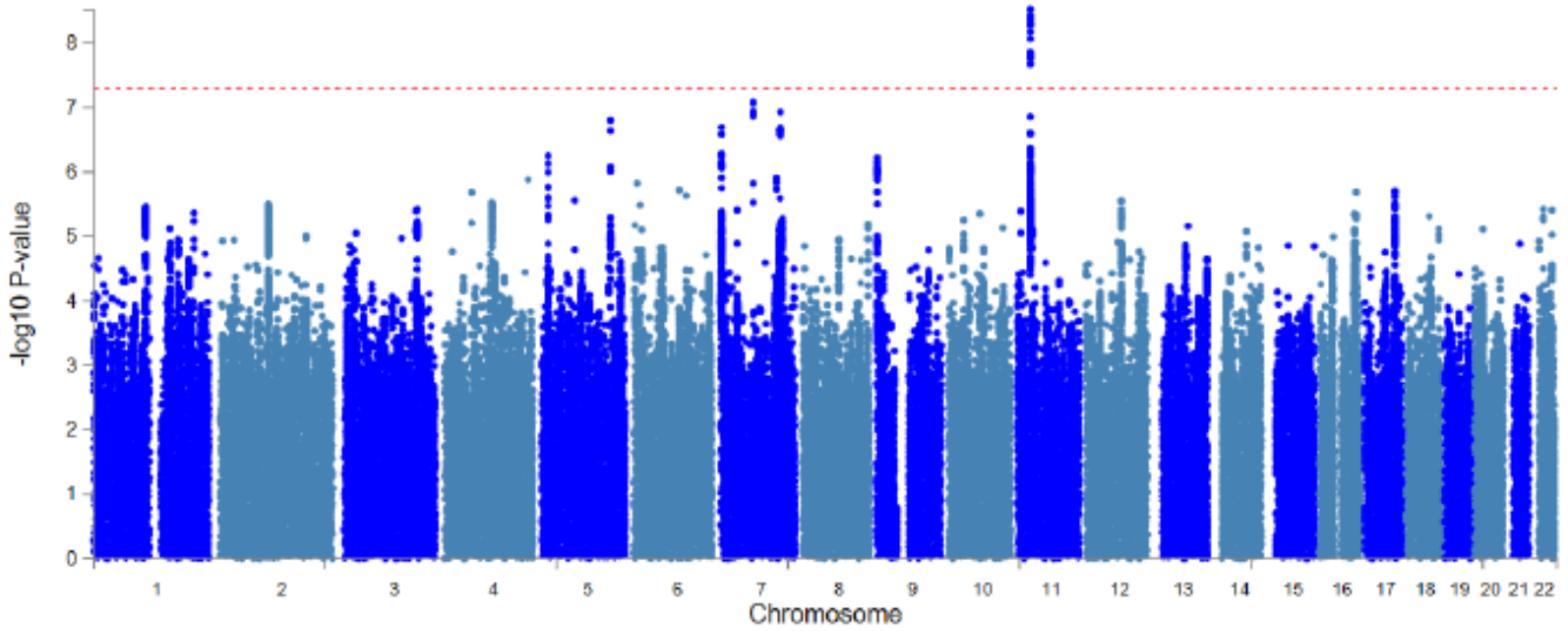
Binary Case-Control GWAS



uniqID	rsID	chr	pos	P-value	start	end	nSNPs	TransAncCaseCon
7:1959634:T:TCCAGTGACACGGAGGTCC	rs137944087	7	1959634	5.74E-09	1829530	1964357	104	MAD1L1
11:28678870:A:G	rs10767739	11	28678870	1.25E-08	28583767	28710118	196	METTL15

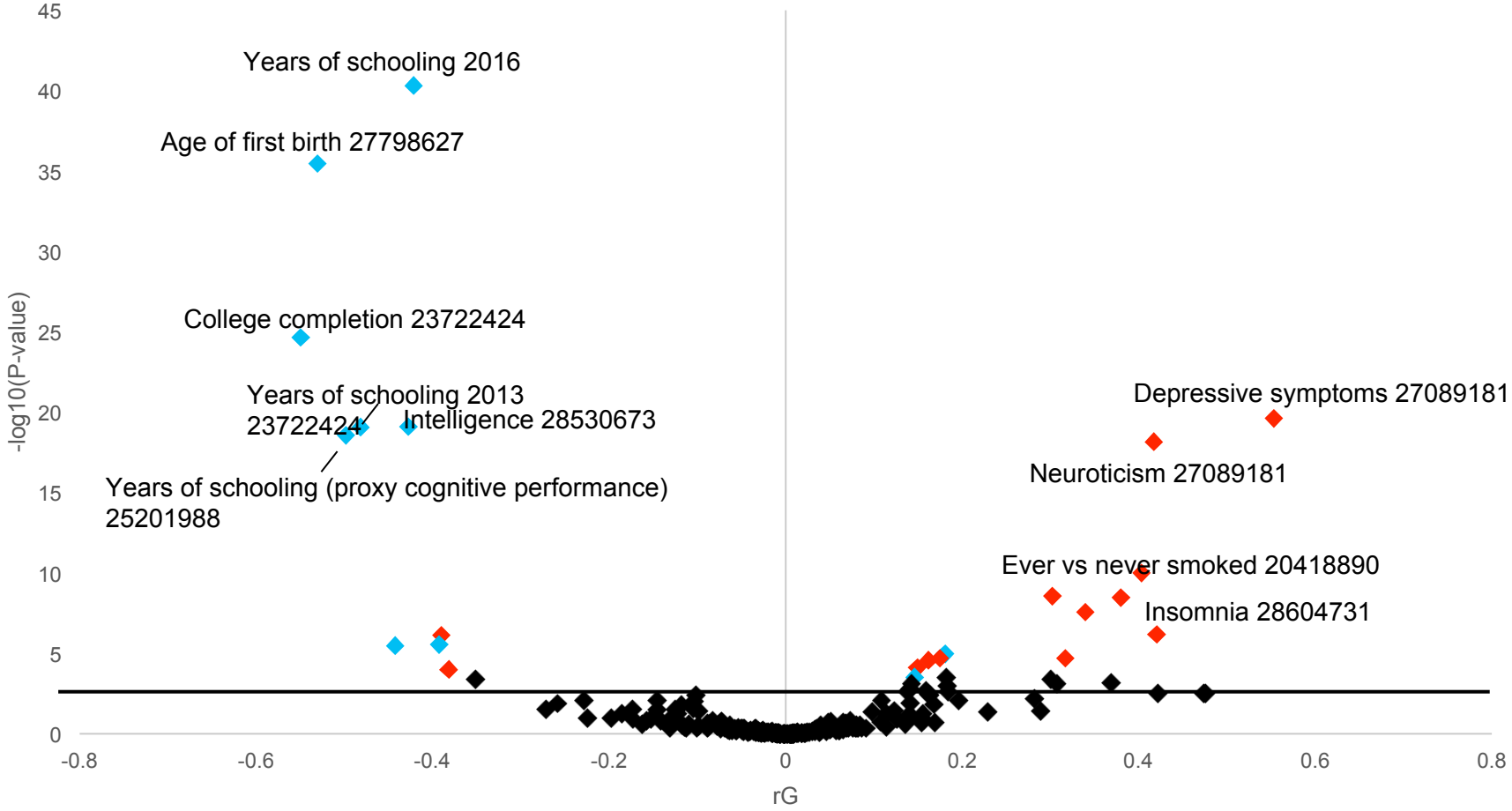
There are 2 significant signals for the algorithmically derived case (N = 48,221) *vs.* control (N = 217,223) trans-ancestral meta-analysis

mtCOJO
Binary Case-Control GWAS

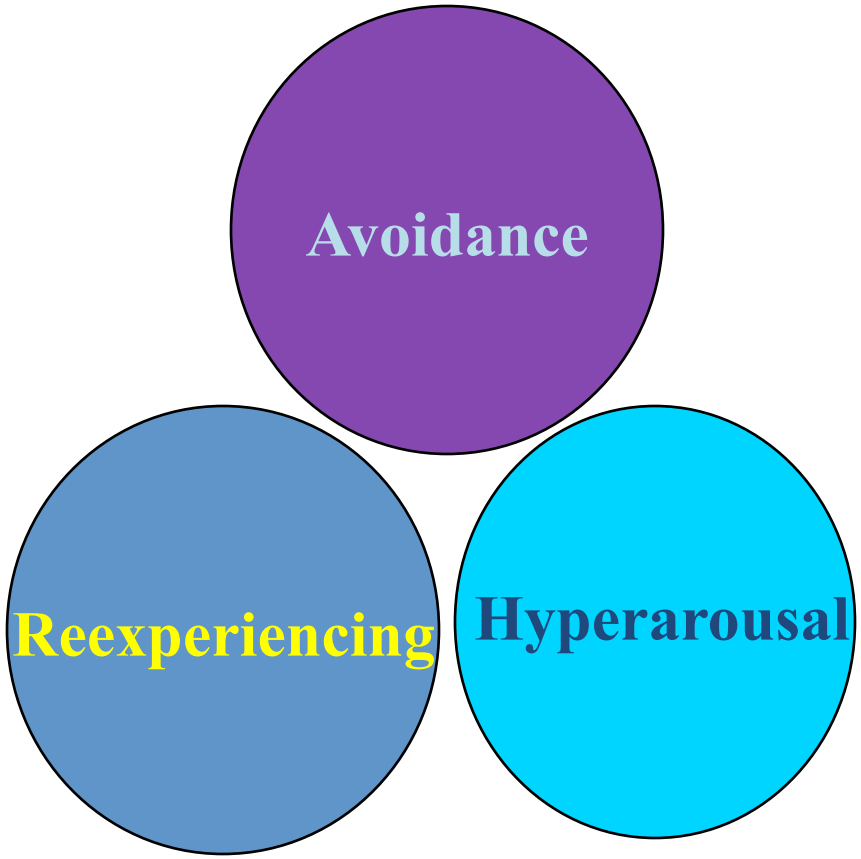


mtCOJO conditional GWAS Adjusted for PGC-MDD ex23andMe

Binary Case-Control r_g (LDHub)



PTSD Symptoms (DSM-IV and ICD-11)



PTSD Checklist (PCL-C)

- Widely used 17-item self-report measure of PTSD symptoms (DSM-IV) *"in the past month…"*
  - Re-experiencing – 5 items
  - Avoidance – 7 items
  - Hyperarousal – 5 items

- Sample re-experiencing item:
  - **Item**: In the past month, how much were you been bothered by: "Repeated, disturbing, and unwanted memories of the stressful experience?"
  - **Response**: 5-point Likert (1 = "Not at all" to 5 = "Extremely")

- Whereas hyperarousal and avoidance are characteristic of many anxiety-related disorders, reexperiencing symptoms are largely unique to PTSD. *They are core to the diagnosis…*

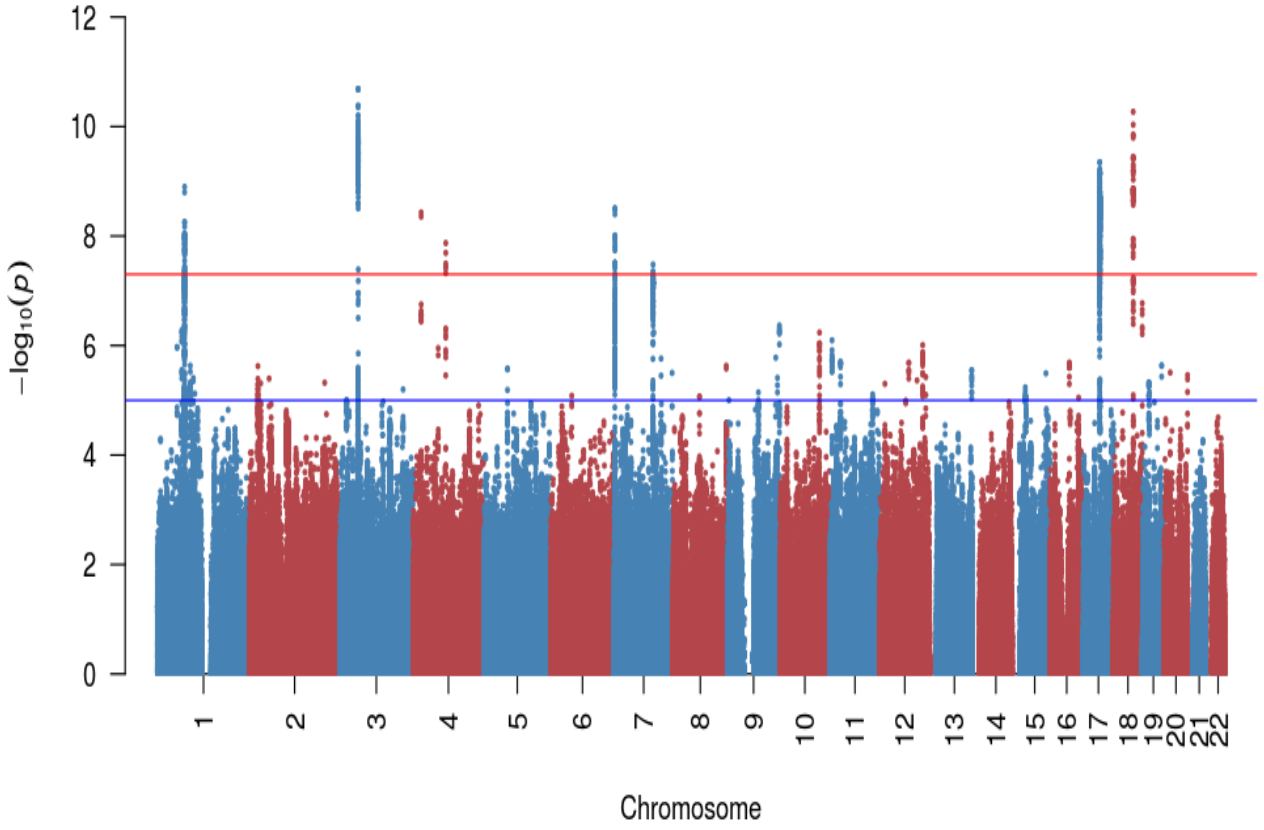
Veterans Health Administration
R&D
www.research.va.gov

Million Veteran Program
Lifestyle Survey

33. Below is a list of problems and complaints that Veterans sometimes have in response to stressful life experiences. Please read each one carefully and check the box on each line that indicates how much you have been bothered by that problem in the PAST MONTH.

	Not at all	A little bit	Moderately	Quite a bit	Extremely
Repeated, disturbing *memories, thoughts or images* of a stressful experience from the past?	☐	☐	☐	☐	☐
Repeated, disturbing *dreams* of a stressful experience from the past?	☐	☐	☐	☐	☐
Suddenly *acting or feeling* as if a stressful experience were happening again (as if you were reliving it)?	☐	☐	☐	☐	☐
Feeling *very upset* when something reminded you of a stressful experience from the past?	☐	☐	☐	☐	☐
Having *physical reactions* (e.g., heart pounding, trouble breathing, sweating) when *something reminded you* of a stressful experience from the past?	☐	☐	☐	☐	☐

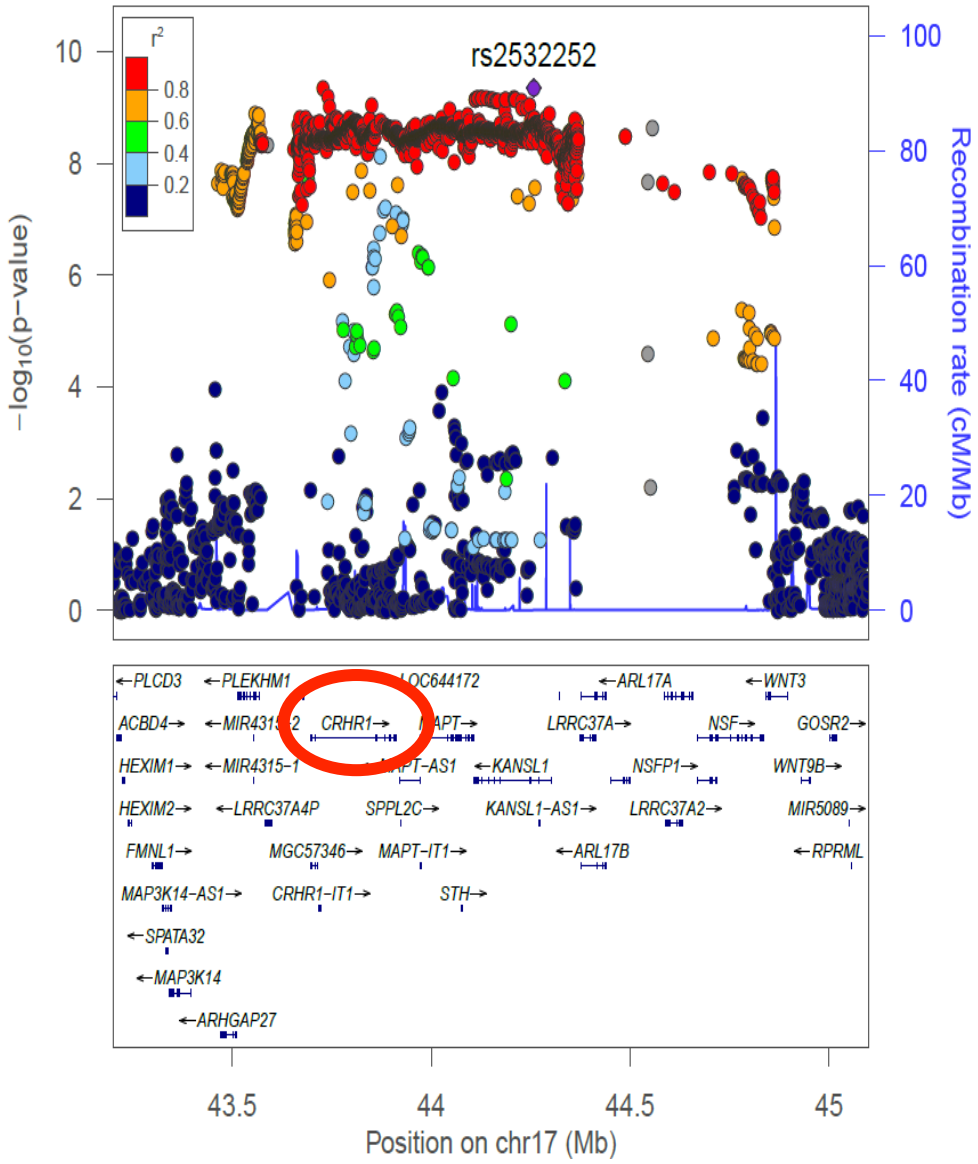
Re-experiencing GWAS – European-Americans



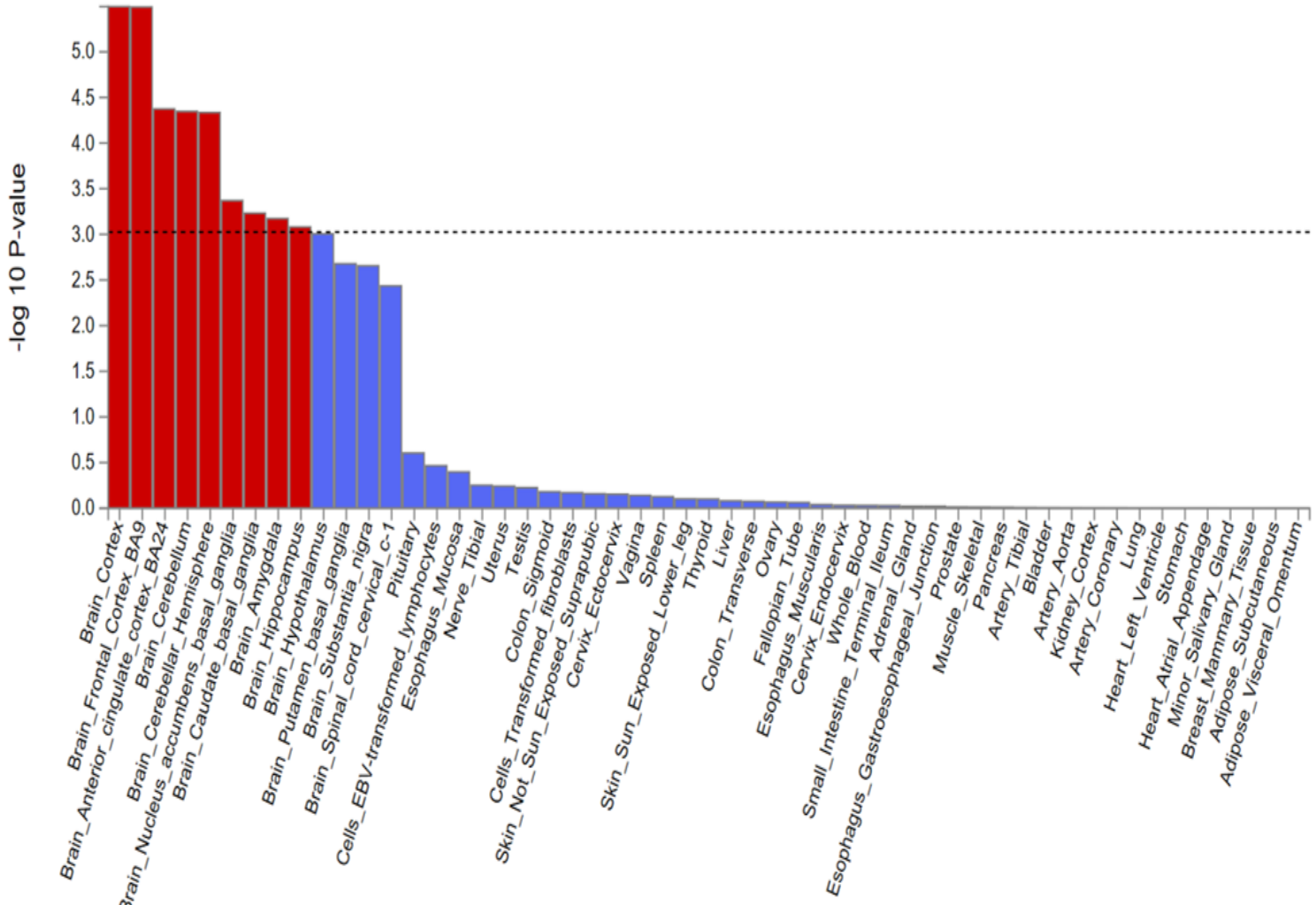
N=146,660 European-American

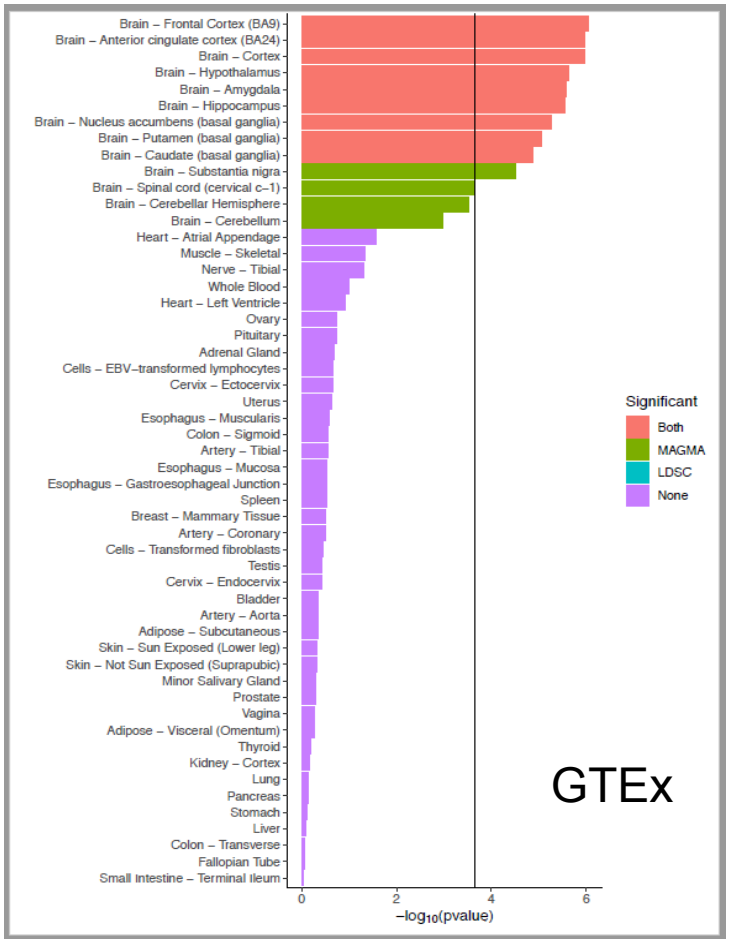
Gelernter et al., *Nat Neurosci* 2019

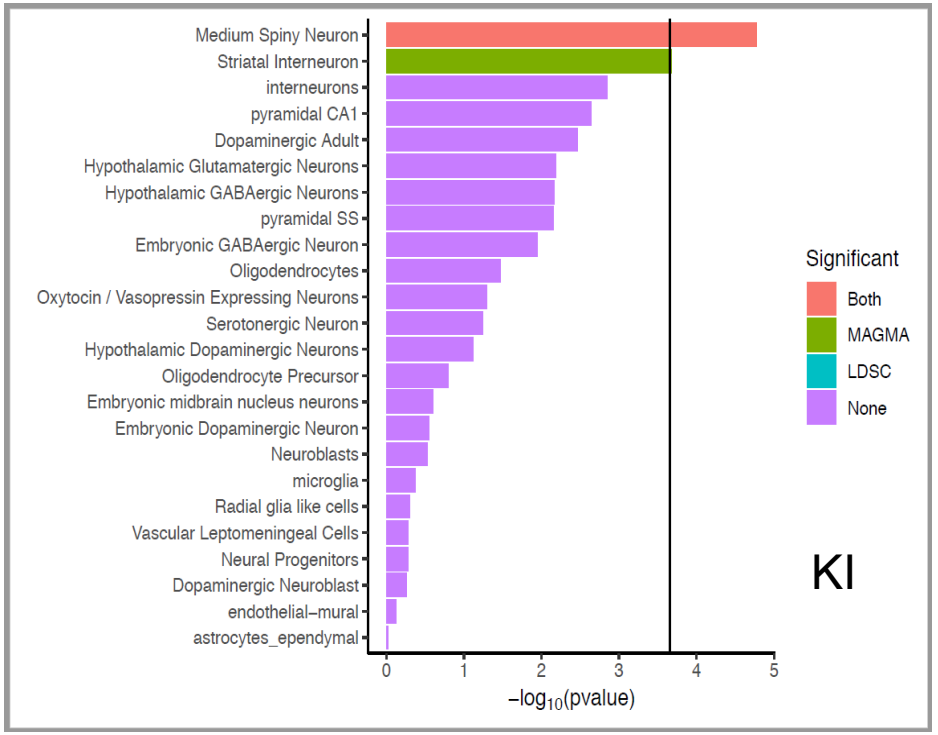
Extended region containing *CRHR1* – lead SNP rs2532252 (4.5E-10), closest to *KANSL1*



GTEX v7 – 53 tissue types



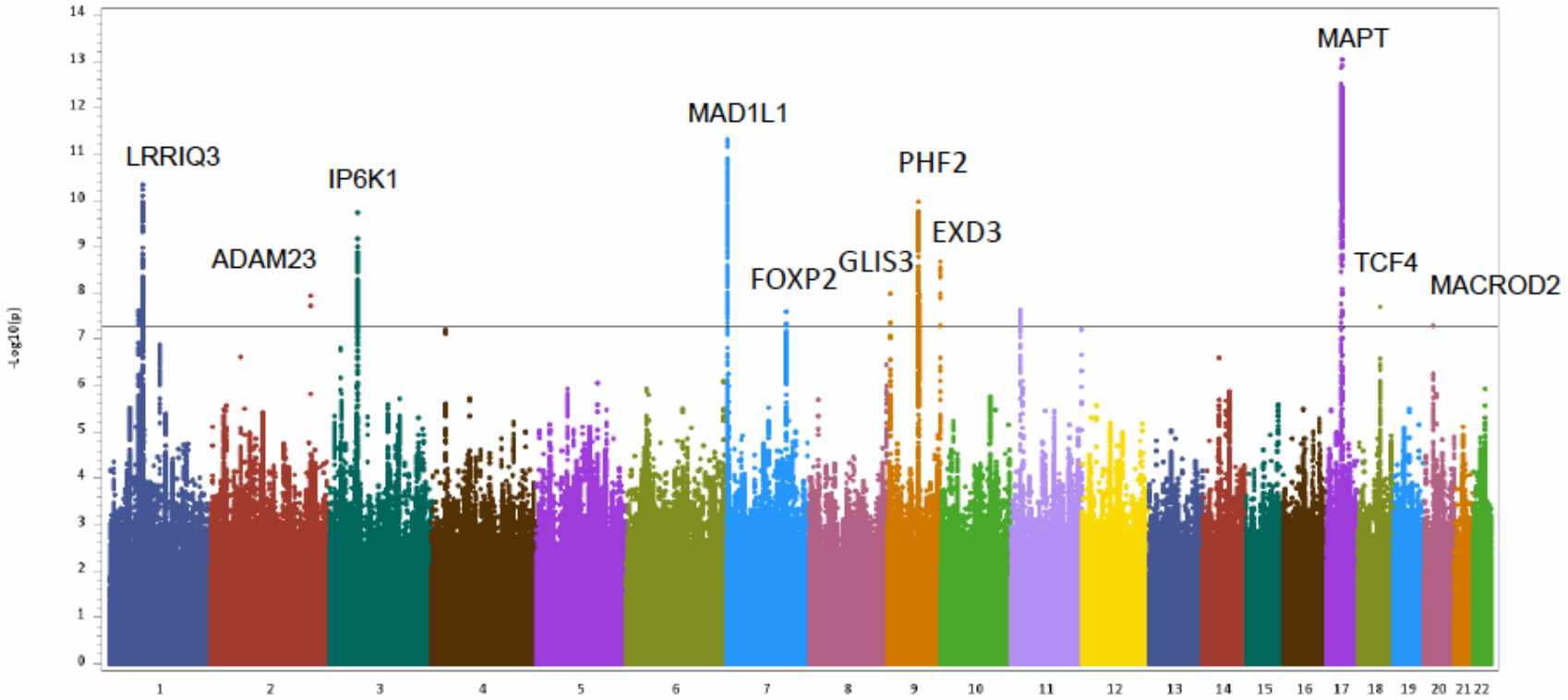




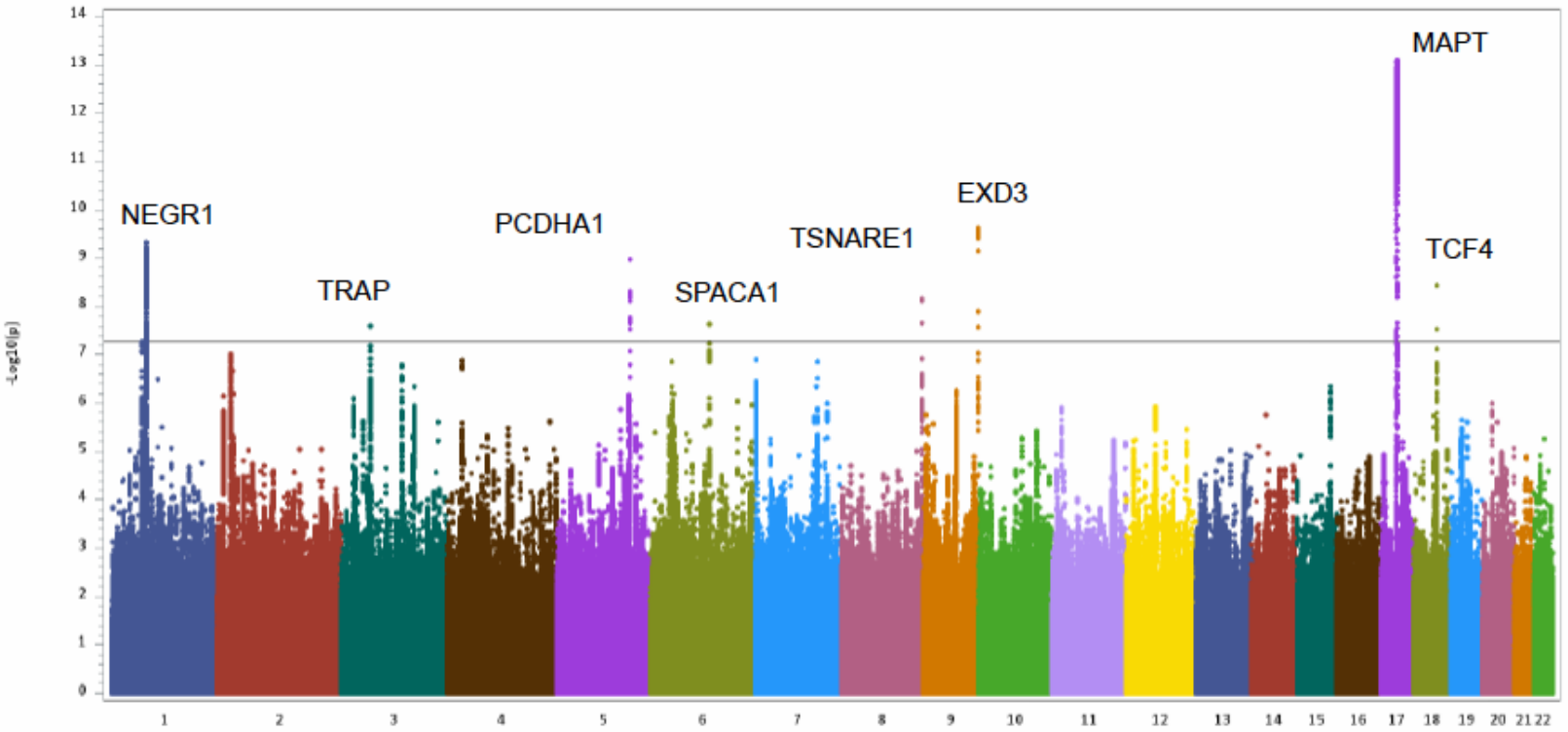
N=146,660 European-American

Gelernter J et al., *Nat Neurosci*, 201

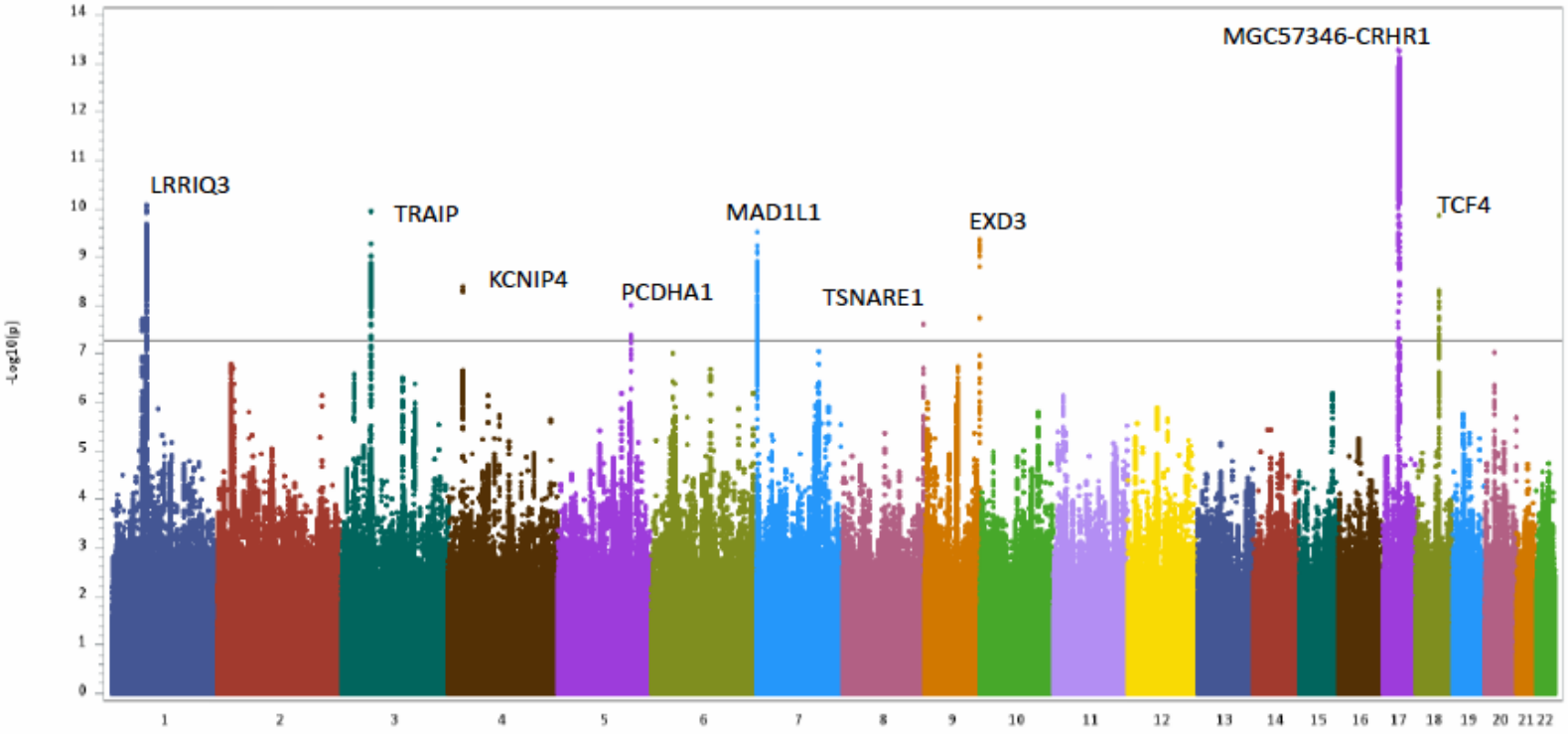
Hyperarousal EA Manhattan Plot



Avoidance EA Manhattan Plot

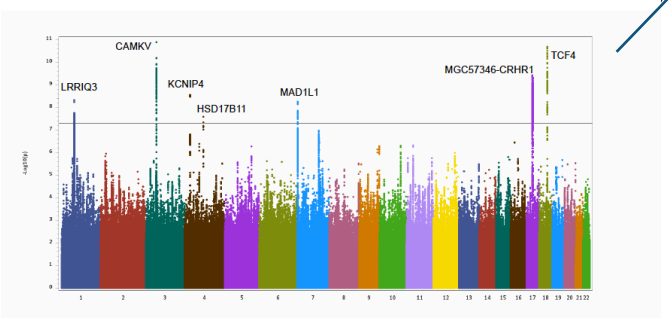


EA Manhattan Plot for PTSD GWAS Based on Summarized Score of 3 Subphenotypes

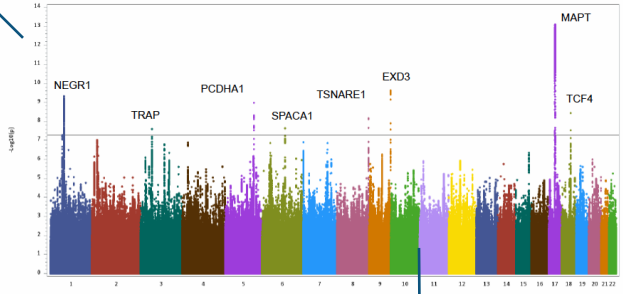


rg = 0.93 (se
)

Reexperience EA Manhattan Plot

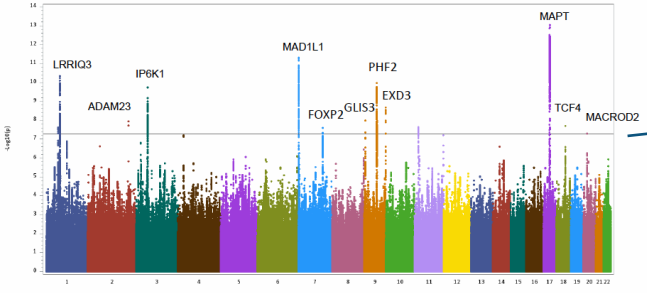


Avoidance EA Manhattan Plot



rg = 0.94 (se
0.01)

Hyperarousal EA Manhattan Plot

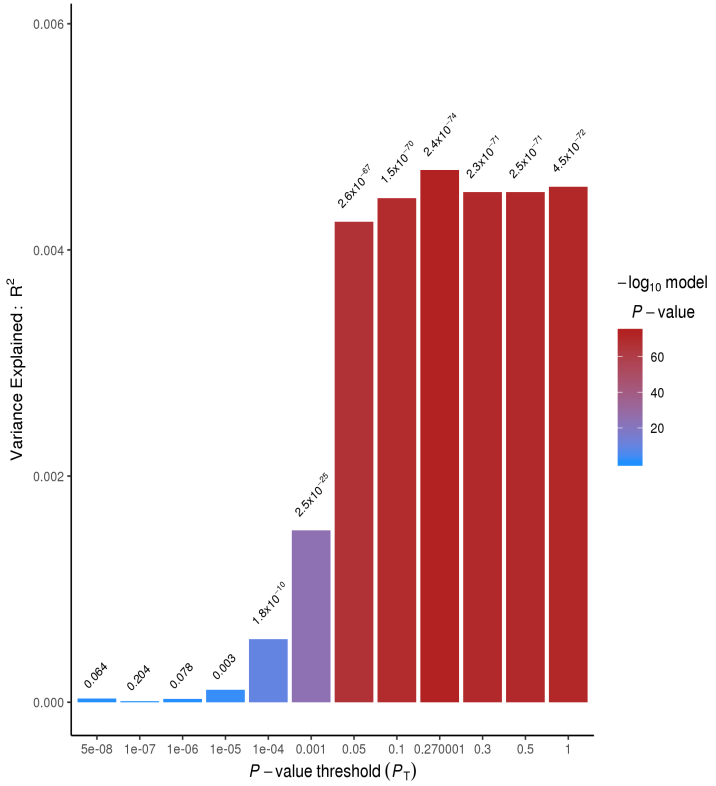


rg = 0.93 (se
0.01)

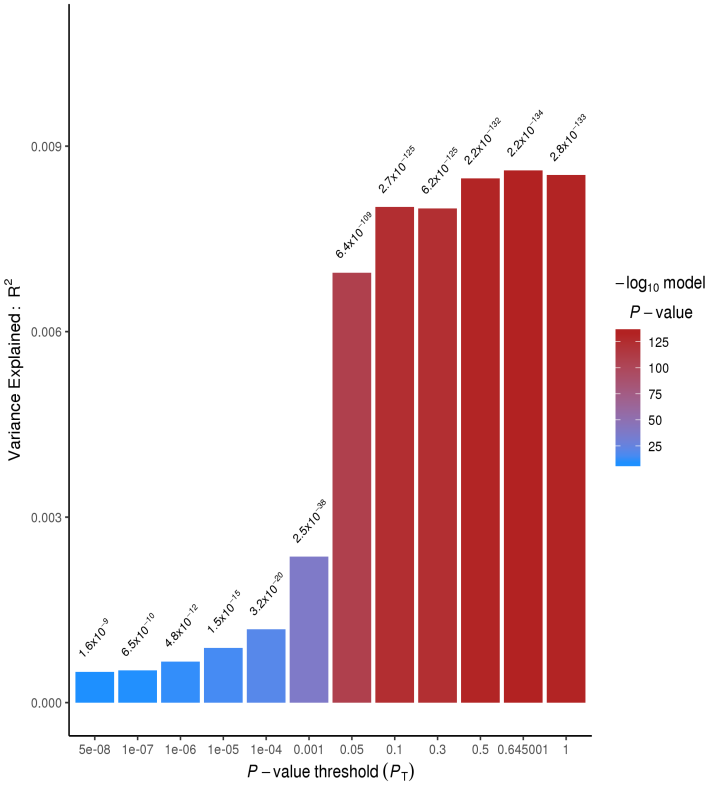
Phenotypic (above diagonal) and genetic (below the diagonal) correlations between algorithmic case-control diagnosis, PCL-total, and PCL-subscores

	Algorithm*	Total PCL	Reexp	Avoid	Hyper
Algorithm* h^2: 6.4%		0.86 0.857-0.860 n=111362	0.83 0.831-0.835 n=91879	0.82 0.824-0.826 n=110739	0.8 0.796-0.800 n=112133
Total PCL h^2: 9.2%	0.959 0.903-1.014		0.92 0.923-0.925 n=141076	0.96 0.964-0.965 n=160504	0.93 0.932-0.934 n=162348
Reexp h^2: 9.3%	0.977 0.903-1.014	0.973 0.966-0.979		0.85 0.849-0.852 n=130341	0.80 0.801-0.805 n=145990
Avoid h^2: 9.3%	0.915 0.856-0.974	0.984 0.98-0.988	0.931 0.916-0.946		0.85 0.849-0.852 n=159002
Hyper h^2: 10.1%	0.953 0.896-1.009	0.979 0.972-0.987	0.935 0.919-0.951	0.943 0.929-0.958	

Polygenic risk score (PRS) from MVP to PGC-PTSD 2.0 case-control phenotype with varying P-value thresholds



MVP EUR case-control



MVP EUR PCL-total

PTSD MVP GWAS Summary

- Case-control phenotype in PTSD has several solid GWS hits
  - Given experience with other mental health disorders, larger N likely to yield many more
    - Collaboration with PGC, UKB should get us there
  - Disorder heterogeneity may be an issue
- GWAS of symptom subphenotypes in MVP
  - Sample size advantages of quantitative trait over case-control
  - GWS SNPs in *multiple* loci
    - Some novel and some well worn “candidates”
  - Overlapping (and some distinct) risk variants by subphenotype
    - r_g very high!
      - Suggests subphenotyping may be less relevant than adequately characterizing symptom burden
- Some evidence of cell-type specificity
  - Medium spiny neurons (GABA, DA)….

Overall Summary: Questions..

- Posttraumatic stress is a consequence of exposure to emotionally traumatic events
- Postconcussive symptoms are a consequence of exposure to concussive forces to the brain
- PTS and PCS frequently co-occur following traumatic injury
  - And incidence of either increases risk of the other
- Similar risk factors for PTS and PCS
- Could this response to trauma represent a distinct “disease”?
  - With shared genetic risk factors?
  - GWAS in TRACK-TBI in process

SUMMARY

- Case-control phenotype in PTSD has several solid GWS hits
  - Given experience with other mental health disorders, larger N likely to yield many more
  - Disorder heterogeneity may be an issue
- GWAS of symptom subphenotypes in PTSD
  - Sample size advantages of quantitative trait over case-control
  - GWS SNPs in *multiple* loci
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      - Suggests subphenotyping may be less relevant than adequately characterizing symptom burden
- Some evidence of cell-type specificity
  - Medium spiny neurons (GABA, DA)….
    - May point to therapeutic targets

- Next steps
  - Investigation of relationship with other highly comorbid medical phenotypes
    - **CVD** (collaboration of MVP MH Working Group with CVD, Lipids, and Metabolic WGs)
    - **TBI** (collaboration of TRACK-TBI with other groups)

Thanks!

- MVP and TRACK-TBI Participants!
- MVP PTSD Genomics Co-PI Joel Gelernter MD (Yale) and colleagues
- TRACK TBI Team
  - Geoff Manley MD, PhD (UCSF) and colleagues

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