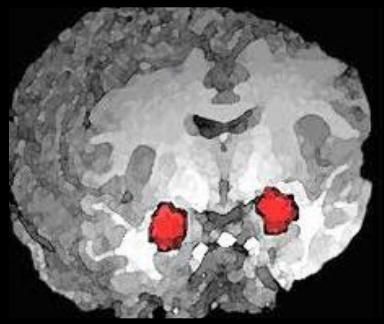
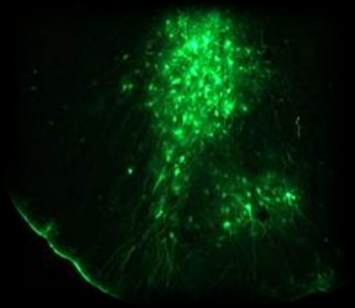
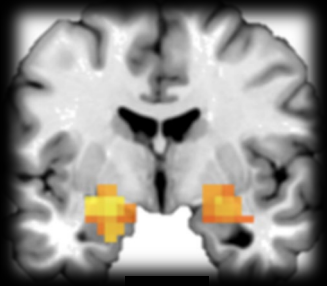


Resilience from Trauma and Stress:
Observations from studying Fear and PTSD



Applying Neurobiological Insights on Stress to Foster Resilience



National Academies
Monday, March 24, 2025

Kerry J. Ressler, MD, PhD
McLean Hospital
Harvard Medical School

Disclosures

Industry Relationships: Past 12 months.
Dr. Ressler has served on Scientific Advisory Boards for:

Sage Therapeutics
Boehringer Ingelheim
Senseye Inc

Dr. Ressler has performed scientific consultation or received sponsored research from:

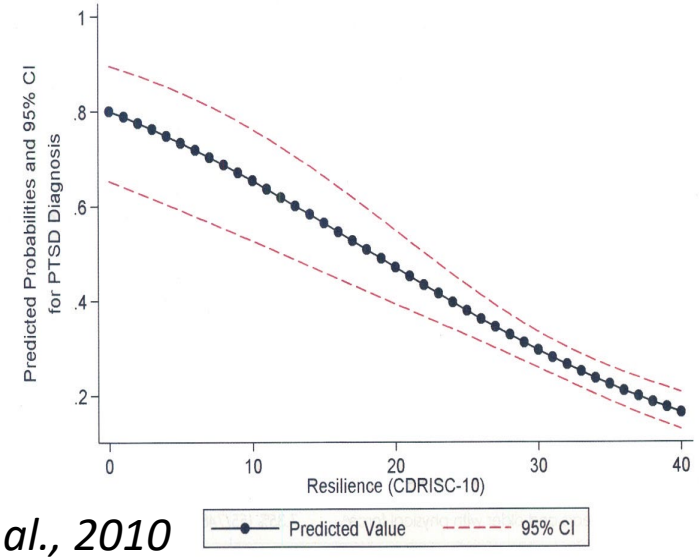
Bioxcel
Bionomics
Acer therapeutics
Jazz Pharma
Alto Neuroscience

Additional Non-Industry, non-profit relationships: Dr. Ressler is on Scientific Advisory Boards for the National Center for PTSD, the Brain Research Foundation, the Laureate Institute for Brain Research, The Army STARRS Project, UCSD VA Center of Excellence for Stress and Mental Health – CESAMH, and the Anxiety and Depression Association of America. He receives research funding from NIH and the Wellcome Leap Foundation.

Grady Trauma Project (GTP): Risk and Resiliency

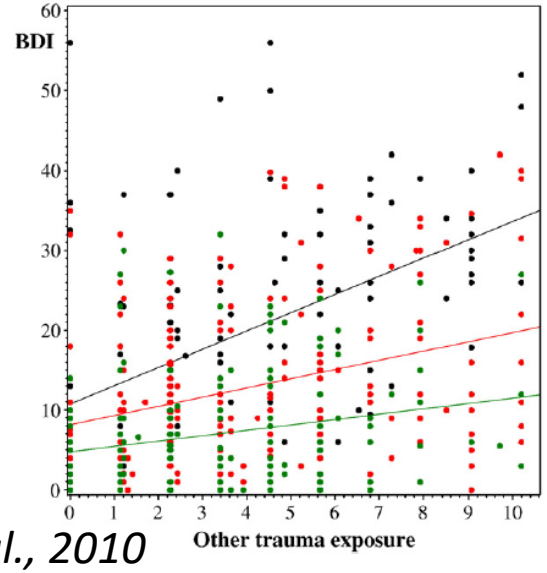
Resilience factors mitigate effect of trauma exposure on PTSD and depression in a highly at risk, impoverished, minoritized population

PTSD



Wrenn et al., 2010

Depression



Wingo et al., 2010

Connor-Davidson Resilience Scale *(2001, 2003, 2007 by KM Connor, JRT Davidson)*

- ***Adapt easily****
- ***Bounce back after illness, hardship****
- *See humorous side of problems*
- *Under pressure can think clearly*
- *Not easily discouraged*
- *Coping with stress makes stronger*
- *Able to handle unpleasant feelings*

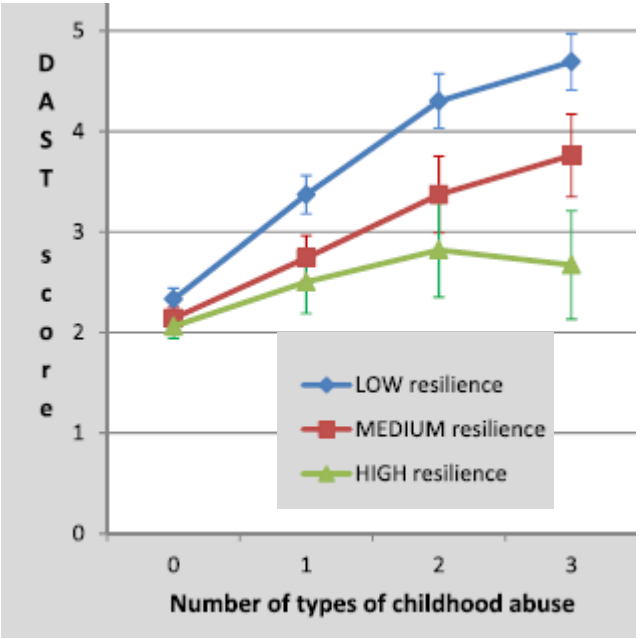
(CD-RISC-10, Sills & Stein, 2007)

Grady Trauma Project: Substance & Alcohol Misuse is highly correlated with childhood trauma exposure.
But – this relationship is almost *entirely mitigated by Resilience*

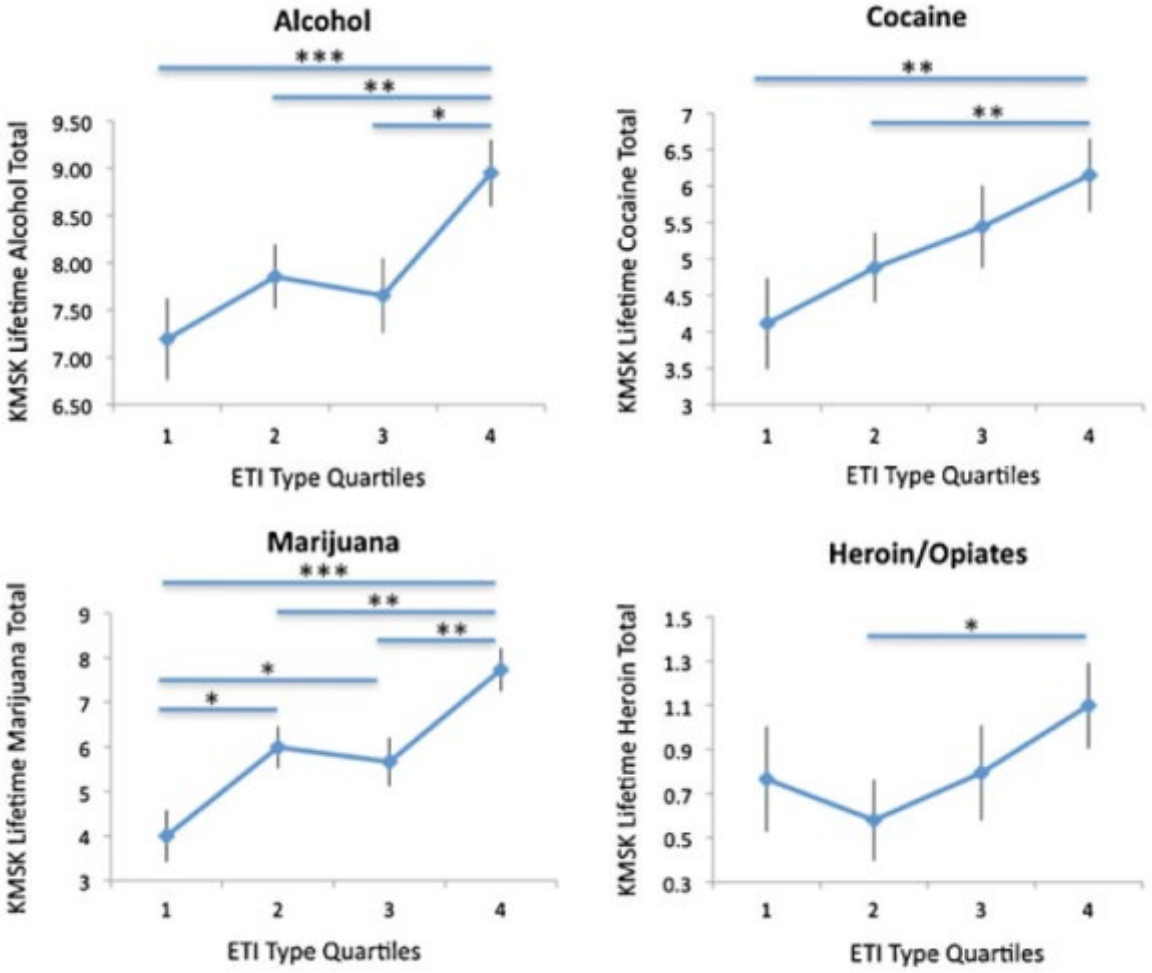
High rates of lifetime dependence:

- 39% alcohol
- 34.1% cocaine
- 6.2% heroin/opiates
- 44.8% marijuana

N=587, 61% Female, 91% Black



Wrenn et al., 2014



Khoury et al., 2010

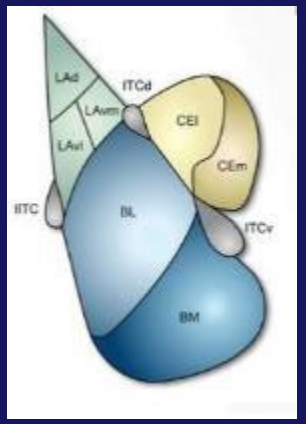
Mechanisms of *Fear* vs *Resilience* after Trauma

1) Genetics & Genomics of Resilience and Positive affect

- Large scale genomics
- Potential molecular pathways

ensitivity
nment)

ear
ent)



PTSD (Risk)

Consolidation of Fear
Hours – days following event

Recovery

2) Extinction / Inhibiting Fear

- *Role of Amygdala*
- *Olfactory Fear across generations*

+

Expres
Memories, Nigl
Avoidance, Sympa

Generalization
Recruitment of Non-associated cues

Sensitization (*Reconsolidation*)
Increased Fear With repeated exposure

Discrimination
Fear is limited to specific trauma cue

Extinction (*Fear Inhibition*)
Diminished response to cues Over time

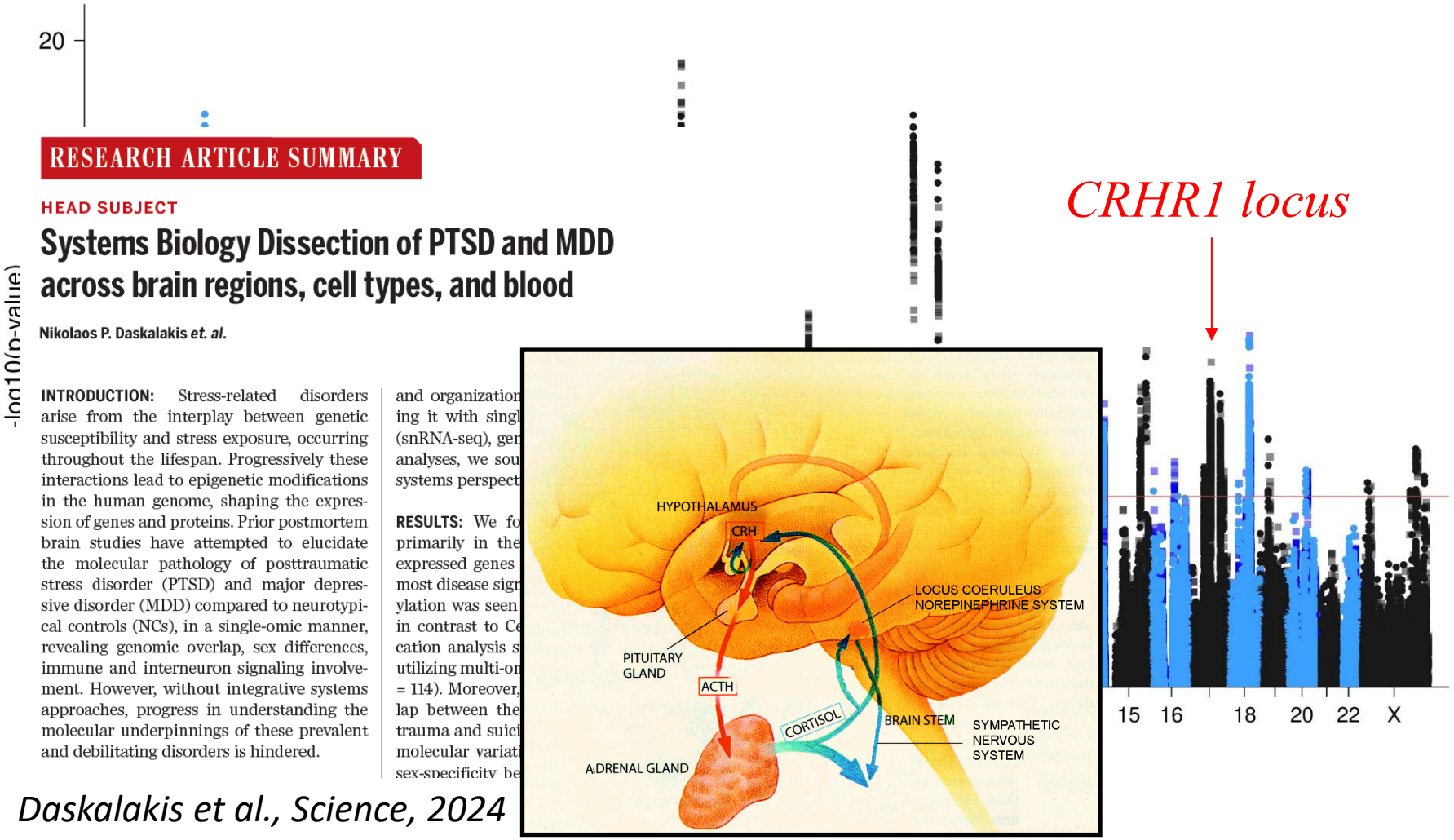
Human Trauma & PTSD: Genetics of risk (but also of resilience?)

PGC-PTSD Freeze 3 GWAS, Meihofer, Nievergelt and many others

>1M participants, >95 Loci Genome wide significant for PTSD

Nievergelt…PGC-PTSD Wkg Gp…Ressler, Koenen, Nature Genetics, 2024

Nievergelt et al, *Nature Genetics, 2024*



RESEARCH ARTICLE SUMMARY

HEAD SUBJECT

Systems Biology Dissection of PTSD and MDD across brain regions, cell types, and blood

Nikolaos P. Daskalakis *et. al.*

INTRODUCTION: Stress-related disorders arise from the interplay between genetic susceptibility and stress exposure, occurring throughout the lifespan. Progressively these interactions lead to epigenetic modifications in the human genome, shaping the expression of genes and proteins. Prior postmortem brain studies have attempted to elucidate the molecular pathology of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) compared to neurotypical controls (NCs), in a single-omic manner, revealing genomic overlap, sex differences, immune and interneuron signaling involvement. However, without integrative systems approaches, progress in understanding the molecular underpinnings of these prevalent and debilitating disorders is hindered.

and organizatio
ing it with singl
(snRNA-seq), ge
analyses, we sou
systems perspect

RESULTS: We fo
primarily in the
expressed genes
most disease sig
ylation was seen
in contrast to C
cation analysis s
utilizing multi-o
= 114). Moreover,
lap between the
trauma and suici
molecular variati
sex-specificity be

Daskalakis et al., Science, 2024

B-catenin, Dicer, & miRNA pathways repeatedly implicated in Resilience and Plasticity in emotional brain areas, species, and negative and positive valence

Nature. 2014 Dec 4;516(7529):51-5. doi: 10.1038/nature13976. Epub 2014 Nov 12.

β-catenin mediates stress resilience through Dicer1/microRNA regulation.

Dias C[1], Feng J[1], Sun H[1], Shao NY[1], Mazei-Robison MS[1], Damez-Werno D[1], Scobie K[1], Bagot R[1], LaBonté B[1], Ribeiro E[1], Liu X[1], Kennedy P[1], Vialou V[1], Ferguson D[1], Peña C[1], Calipari ES[1], Koo JW[1], Mouzon E[1], Ghose S[2], Tamminga C[2], Neve R[3], Shen L[1], Nestler EJ[1].

The dynamic role of beta-catenin in synaptic plasticity

Kimberly A. Maguschak[a], Kerry J. Ressler[b,c,*]

β-catenin is required for memory consolidation

Kimberly A Maguschak & Kerry J Ressler

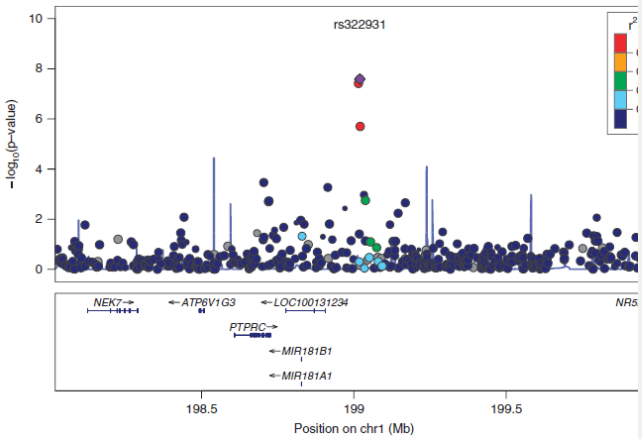
ORIGINAL ARTICLE

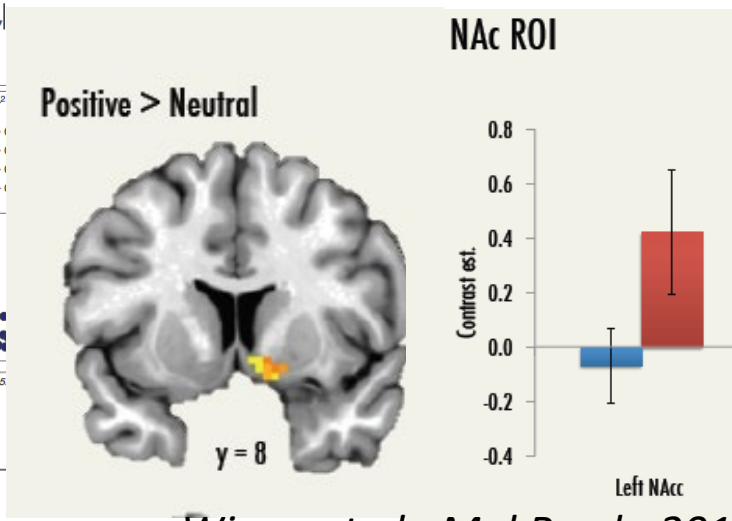
Genome-wide association study of positive emotion identifies a genetic variant and a role for microRNAs

AP Wingo[1,2,9], LM Almli[2,9], JS Stevens[2,9], T Jovanovic[2], TS Wingo[1,3,4], G Tharp[5], Y Li[4], A Lori[2], M Briscione[1,2], P Jin[4], EB Binder[6], B Bradley[1,2], G Gibson[7] and KJ Ressler[2,8]

miR-181a is strongly enriched in the **synaptodendritic compartment of the NAc** and influences **synaptic plasticity** through regulating **glutamate receptor 2 subunit of AMPA-type** glutamate receptors.

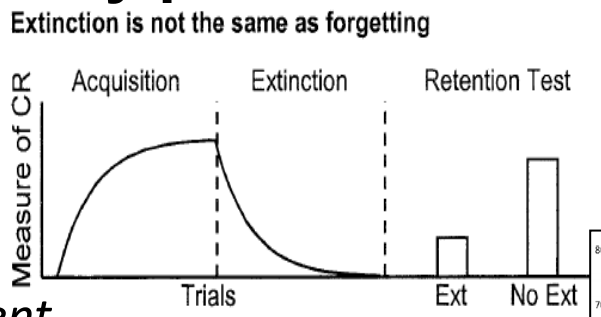
Hence, rs322931 may mediate synaptic plasticity, positive emotion, and resilience





Wingo et al., Mol Psych, 201

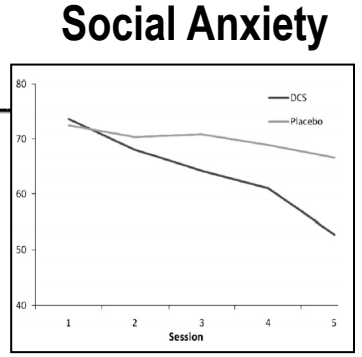
Synaptic plasticity – eg via BDNF or NMDA activation – enhances extinction and may promote resilience



Fear Extinction:

- Gradual reduction in fear reaction
- Basis of exposure-based therapy
- BDNF, NMDA, synaptic plasticity dependent

Form of 'Adaptability' and 'Bouncing back', aka Resilience?



Modulating Plasticity and Extinction:

- NMDA activation – D-cycloserine
  - *Walker et al., J Neurosci, 2002*
  - *Ressler et al., Am J Psych 2004*
- NMDA/AMPA plasticity – ketamine
  - *Feder et al., JAMA Psych, 2014*
  - *Feder et al., Am J Psych, 2021*
- TrkB activation – BDNF
  - *Chhatwal, et al., 2006, Nature Neuros*
  - *Heldt et al, Molecular Psychiatry , 200*
  - *Solimon et al., Science, 2010*

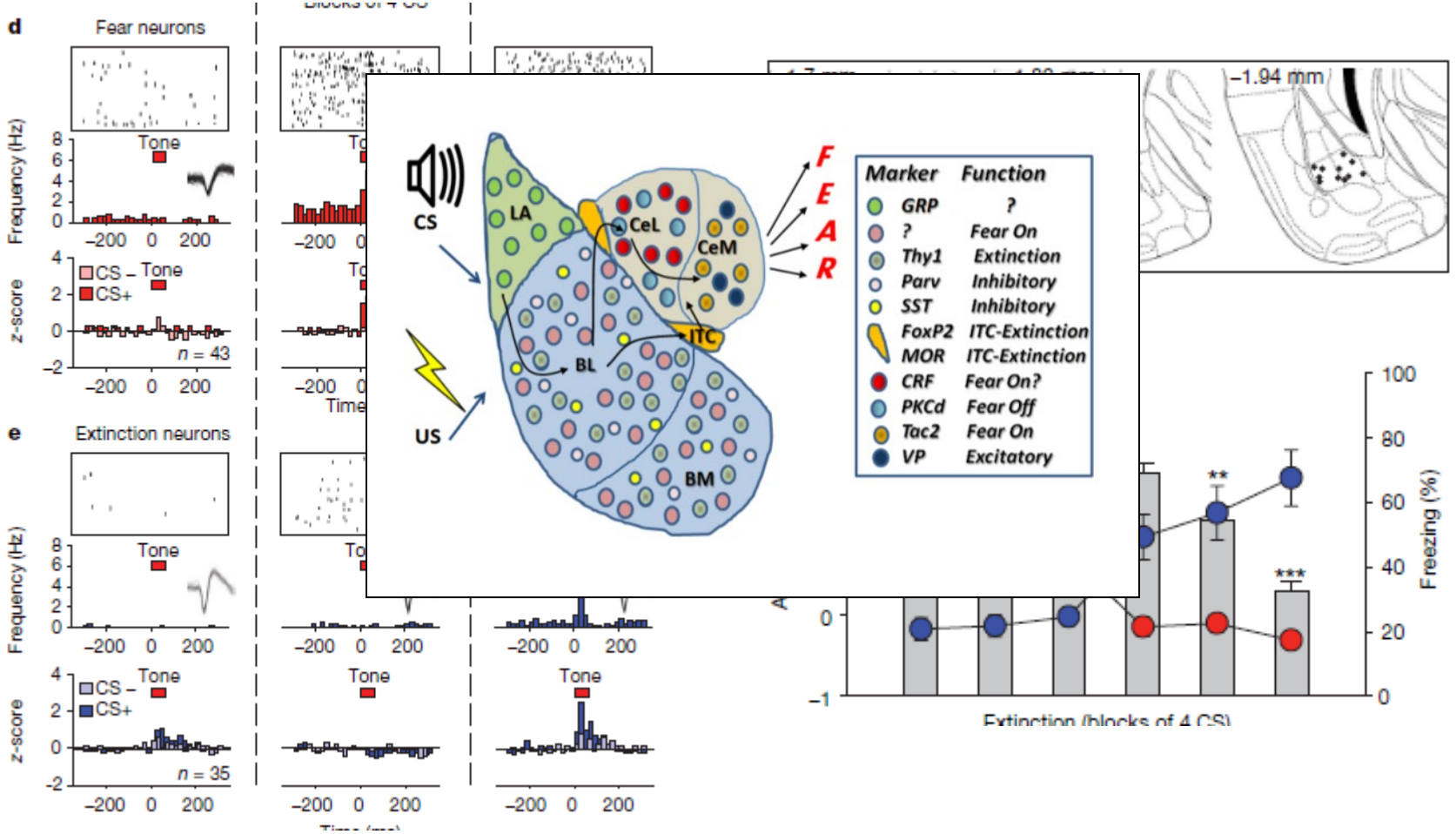
However – not all studies positive, and preclinical studies (Everett and colleagues) suggest DCS *increases reconsolidation* depending on timing.

Thus, enhancement of plasticity may enhance Reconsolidation (*Risk*) in addition to effects on Extinction (*Resilience*).

Might we be able to enhance synaptic plasticity specifically in *Fear Inhibition* or '*Resilience*' promoting pathways?

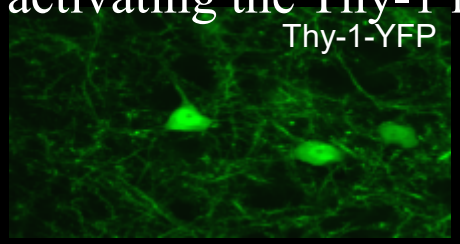
Switching on and off fear by distinct neuronal circuits

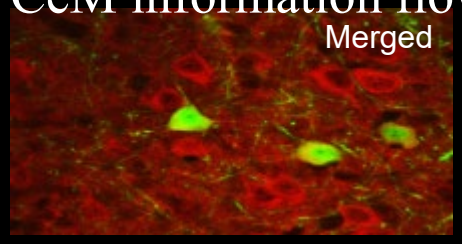
Cyril Herry[1]*, Stephane Ciocchi[1]*, Verena Senn[1], Lynda Demmou[1], Christian Müller[1] & Andreas Lüthi[1]



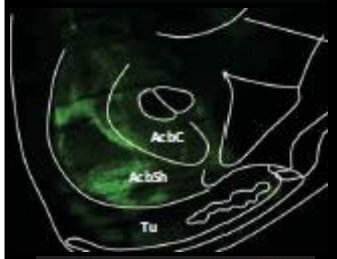
‘Extinction’ Neurons – are they also *Fear Off* & *Resilience* Cells?

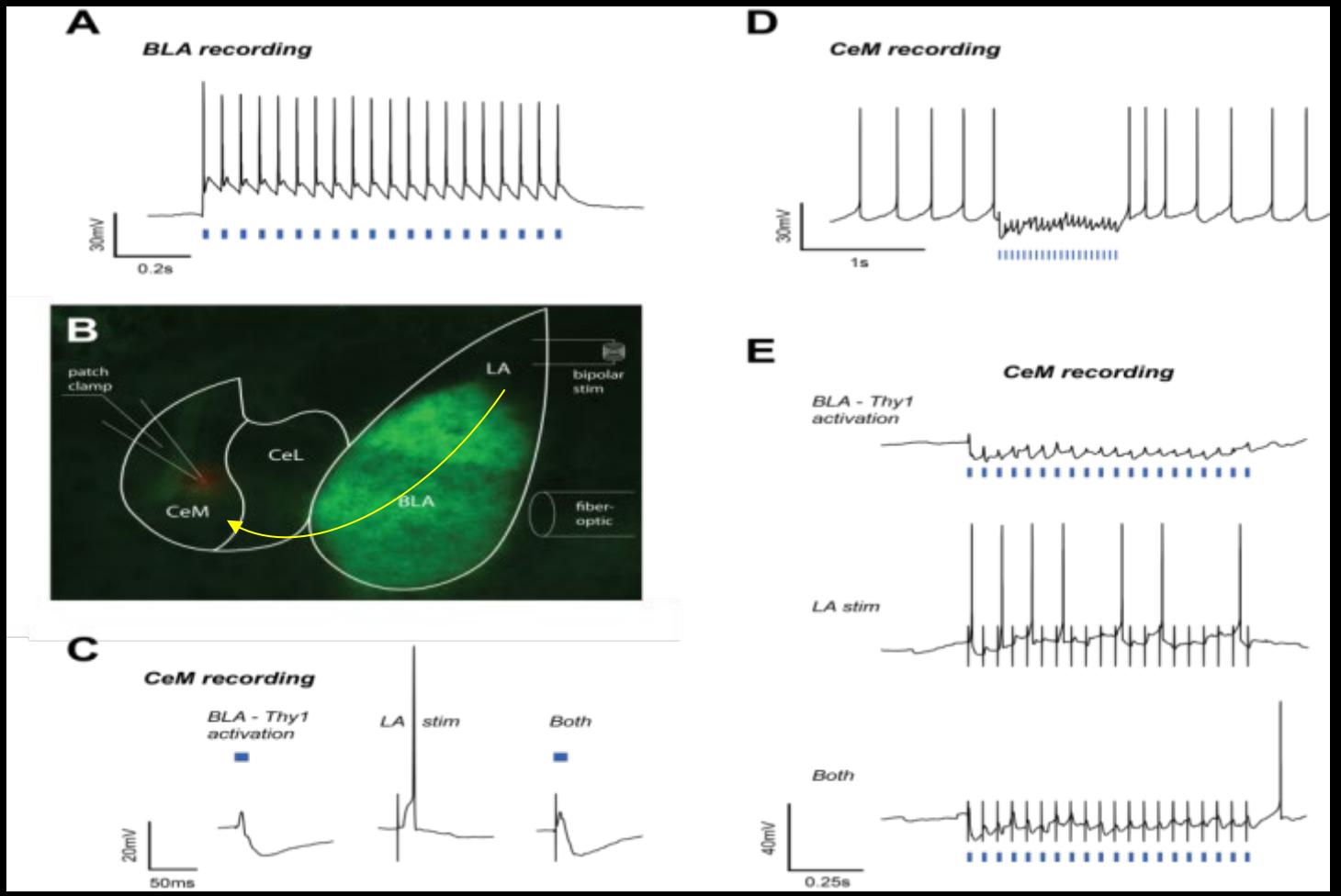
Optogenetically activating the Thy-1 neurons inhibits LA - CeM information flow





Thy1 cells project to Nac and mPFC, but NOT CeA

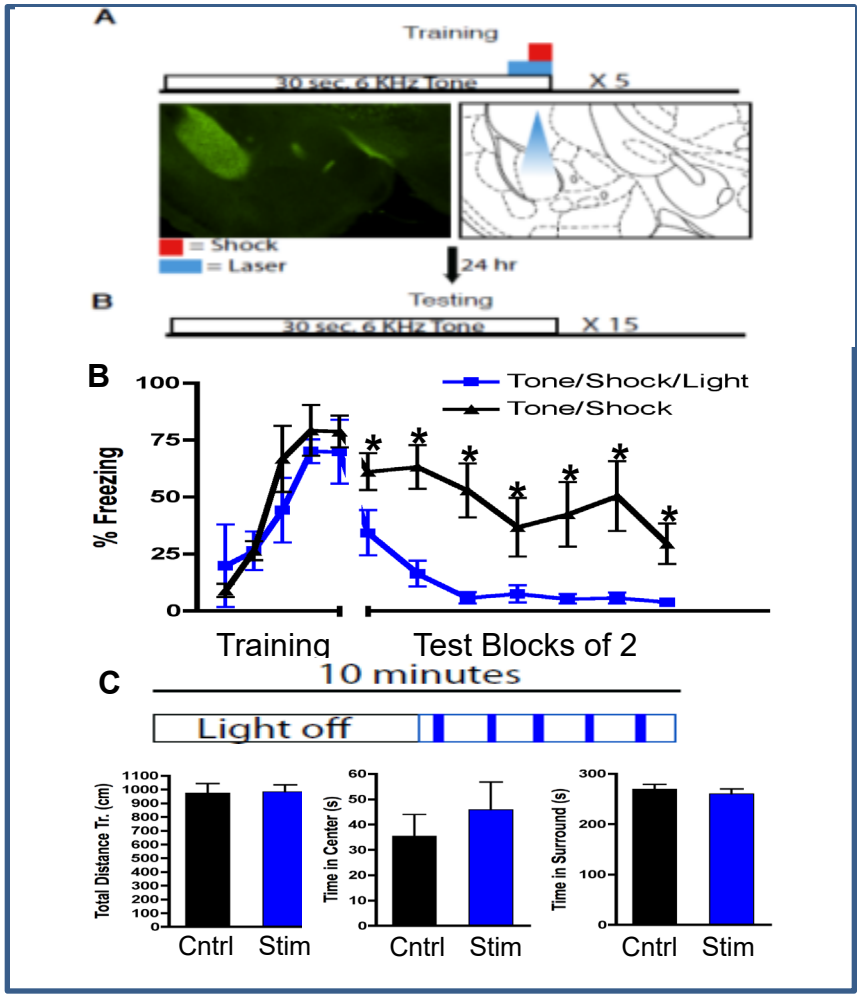




Jasnow et al., 2013, *J Neurosci*

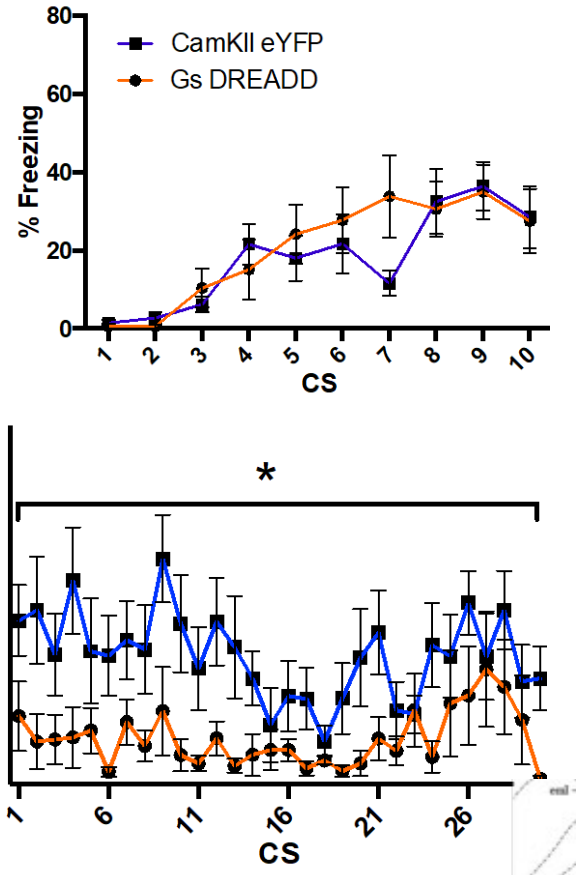
Optogenetically and Chemogenetically activating the Thy-1 neurons *in vivo*

Inhibits fear consolidation / Enhances Fear Extinction

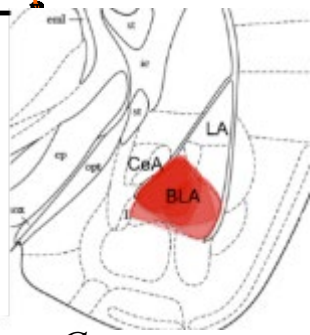


Thy1 ^{h} – ChR2 transgenic

Jasnow et al., 2013, *J Neurosci*

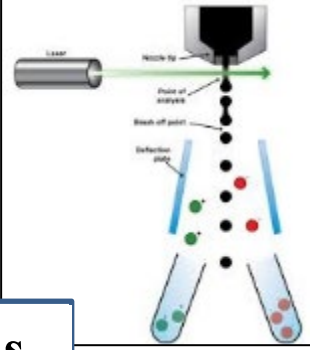


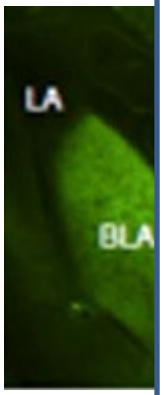
AAV-DIO-Gs-IRES-mCherry



McCullough et al., 2016, *Nature Comm*

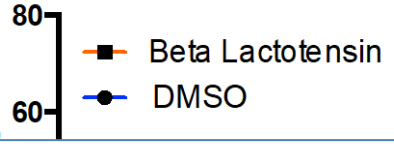
Genes identified in Thy1 (Fear Off) Neurons through FACS / RNAseq

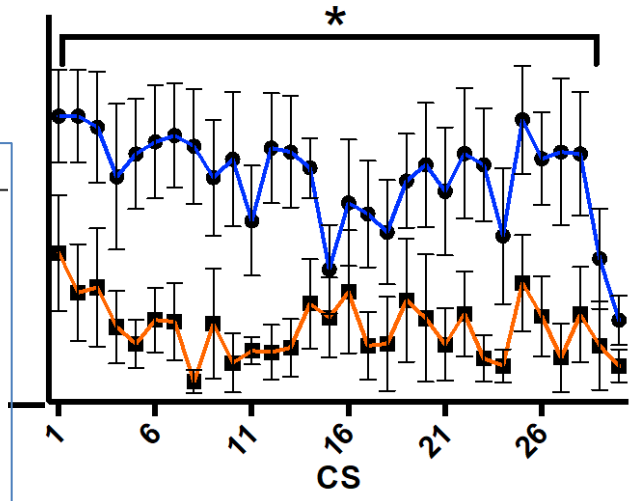




Activation of Neurotensin receptor (*NTSR2*)in Thy1 Neurons, a putative 'fear off' BLA population, blocks fear expression

Auditory Fear Conditioning (10 CS/US) → 24 hours → Fear Expression (30 CS)





McCullough et al., Nature Communications, 2016

Article

Neurotensin orchestrates valence assignment in the amygdala

Li et al., Nature, 2023

https://doi.org/10.1038/s41586-022-04964-y
Received: 22 February 2018
Accepted: 10 June 2022
Published online: 20 July 2022
Check for updates

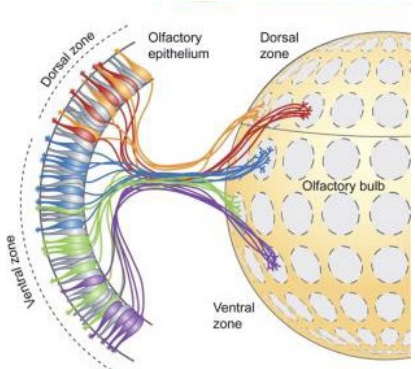
Hao Li[1,25], Praneeth Namburi[2,25], Jacob M. Olson[2,3,25], Matilde Borio[1,2], Mackenzie E. Lemieux[1,2], Anna Beyeler[2,4], Gwendolyn G. Calhoon[2,5], Natsuko Hitora-Imamura[2,6,7], Austin A. Coley[1], Avraham Libster[1,2], Aneesh Bal[1,8], Xin Jin[9,10], Huan Wang[11], Caroline Jia[1,12], Sourav R. Choudhury[10], Xi Shi[10,13], Ada C. Felix-Ortiz[2], Verónica de la Fuente[2,14,15], Vanessa P. Barth[2,16], Hunter O. King[2,17], Ehsan M. Izadmehr[2], Jasmin S. Revanna[1,18], Kanha Batra[1,19], Kyle B. Fischer[1], Laurel R. Keyes[1], Nancy Padilla-Coreano[1], Cody A. Siciliano[2,20], Kenneth M. McCullough[21,22], Romy Wichmann[1,2], Kerry J. Ressler[21,22], Ila R. Fiete[11], Feng Zhang[10,12,23], Yulong Li[11] & Kay M. Tye[1,2,24]

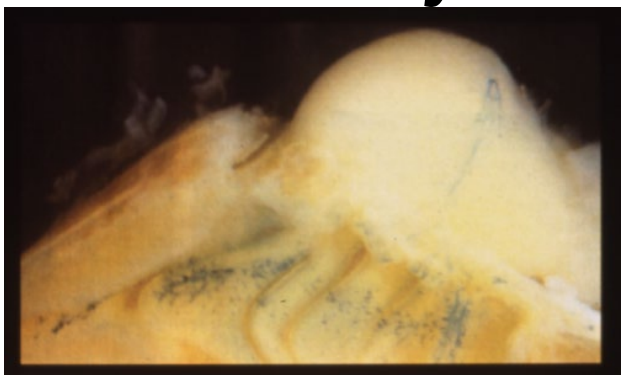
Intergenerational Cycles of Trauma Risk (& Resilience!)

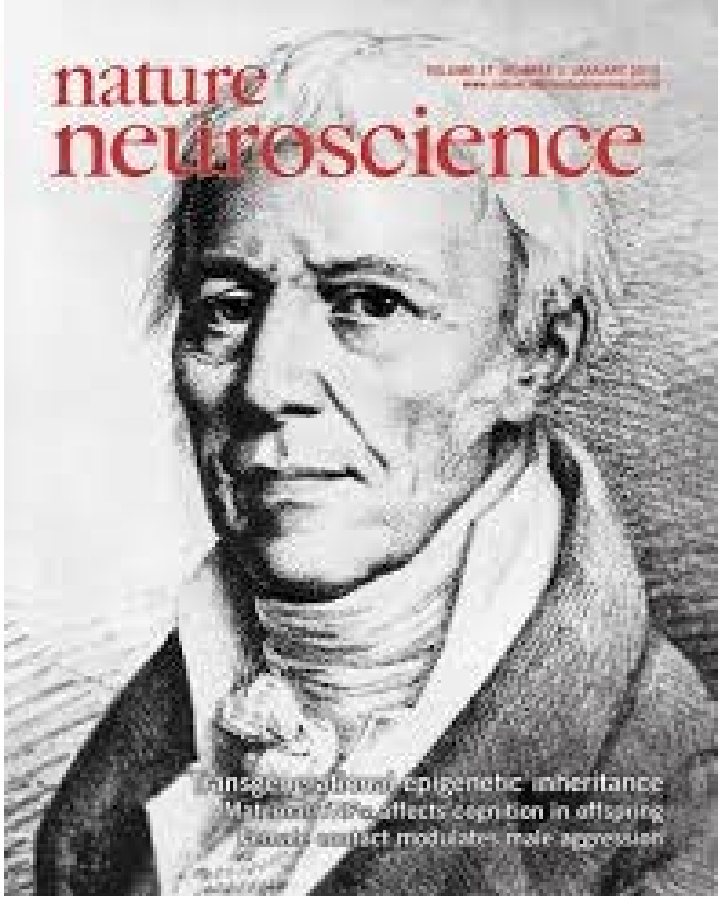
- Parenting / Observation
- Shared Risk Environment
- Shared Genetics
- Epigenetic Inheritance

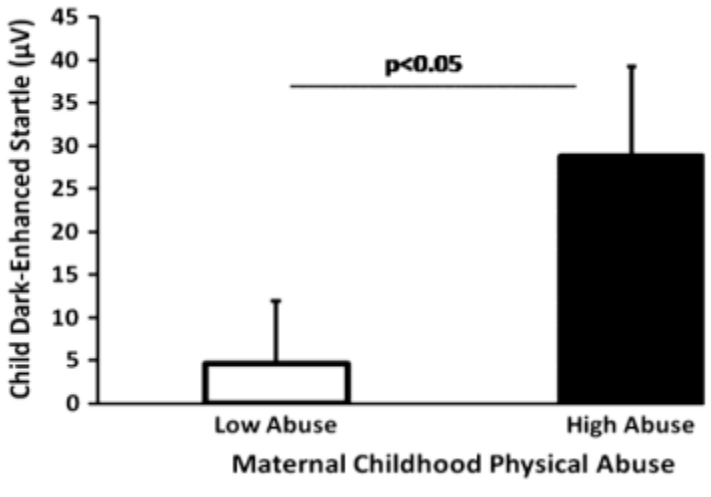
Need Tractable System for Molecular Level Identification

Transgenerational Transmission of Olfactory Fear



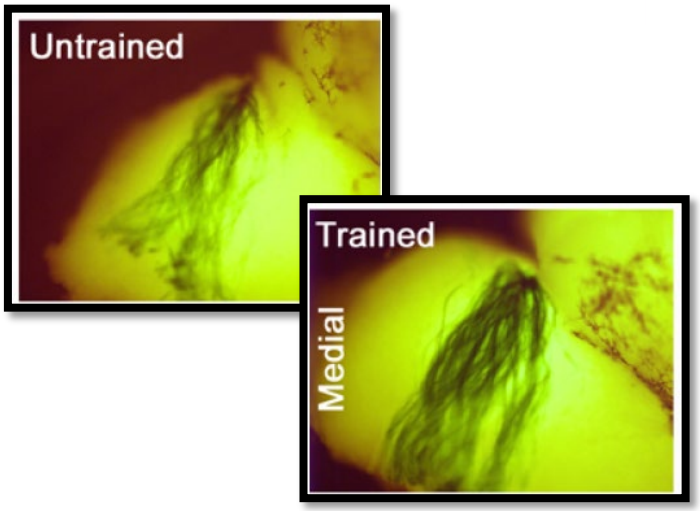


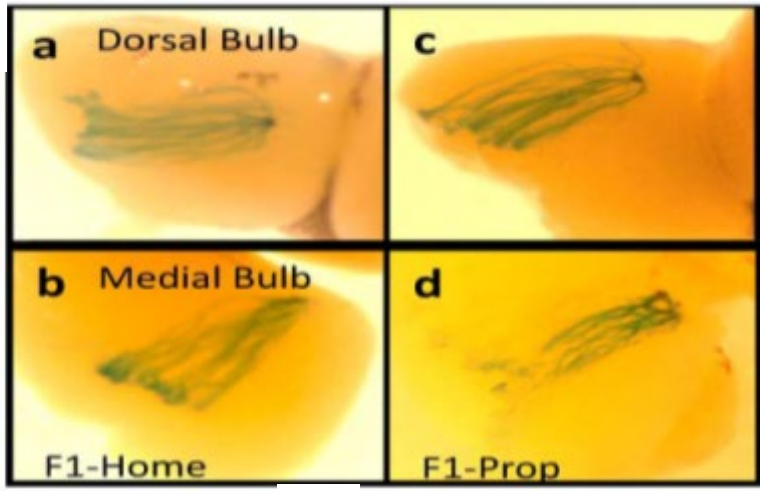




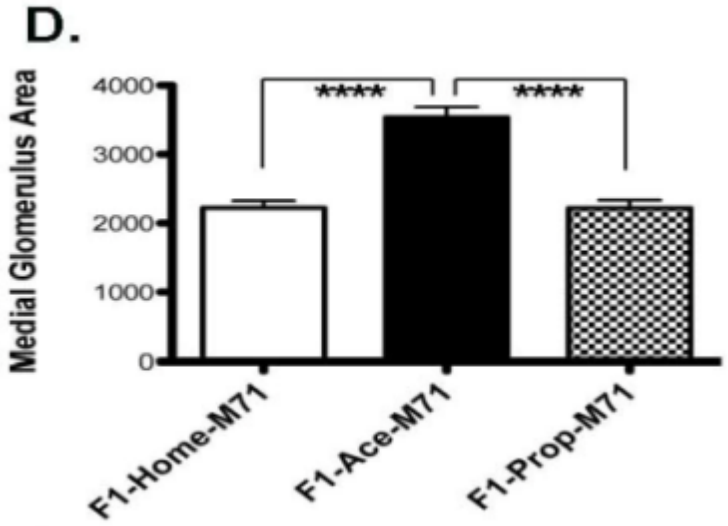
Intergenerational Transmission of Olfactory Sensitivity: Naïve Offspring Have More Axons and Larger Olfactory Glomeruli in the Brain, Specific to Father's Fear-Trained Odor

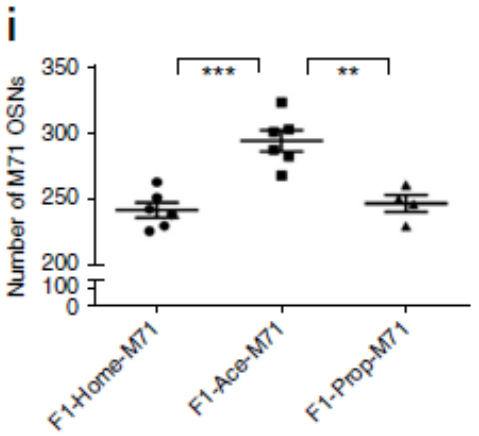
Father Acetophenone-Fear trained (not Prop)





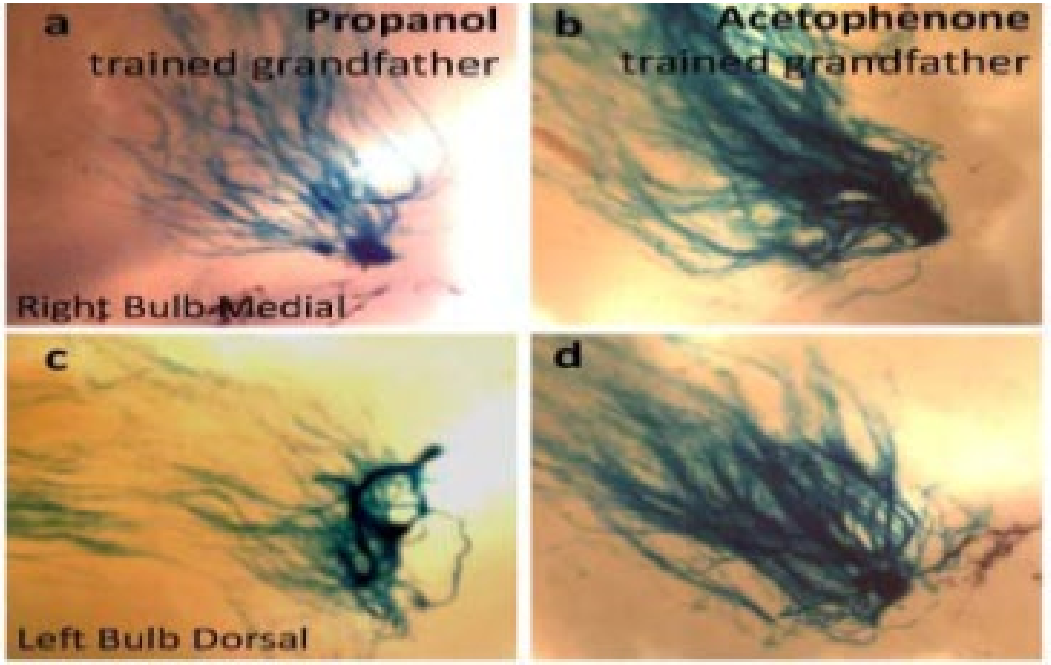
Jones et al, J Neurosci, 2007

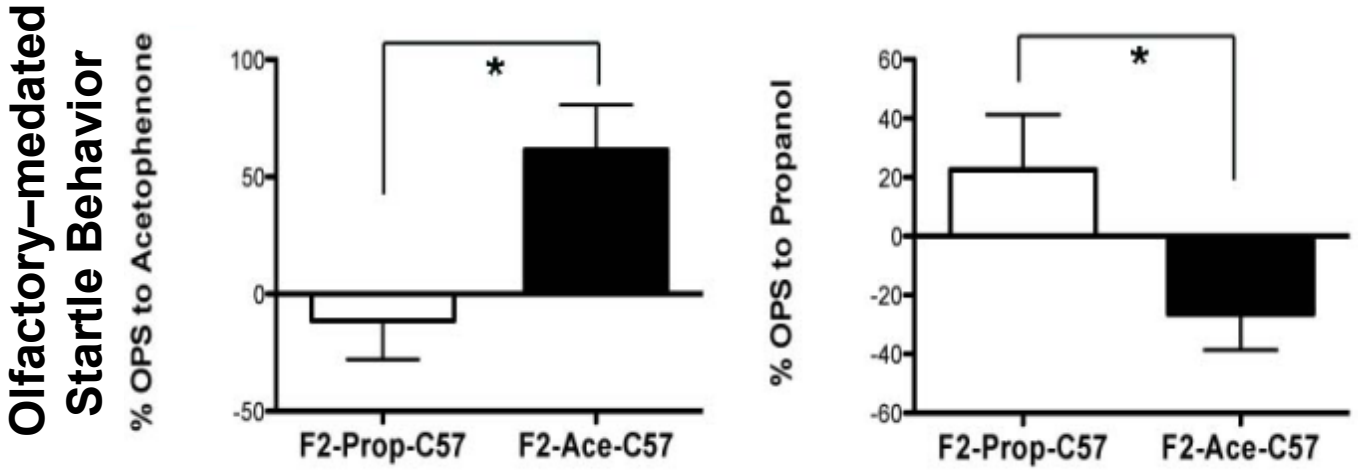




Brian Dias, PhD, Nature Neuroscience, 2014

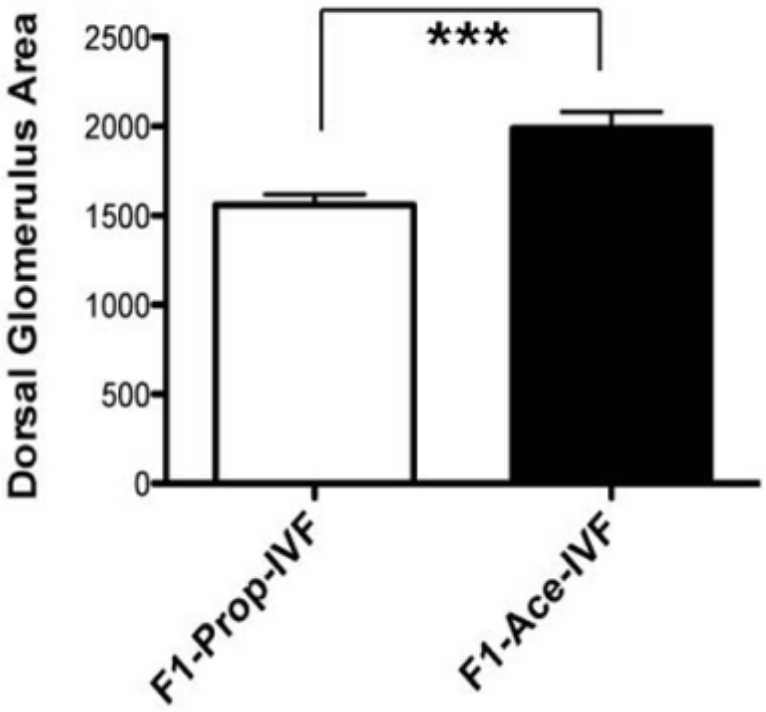
Naïve grandchildren inherit same fear-induced effects as Parents

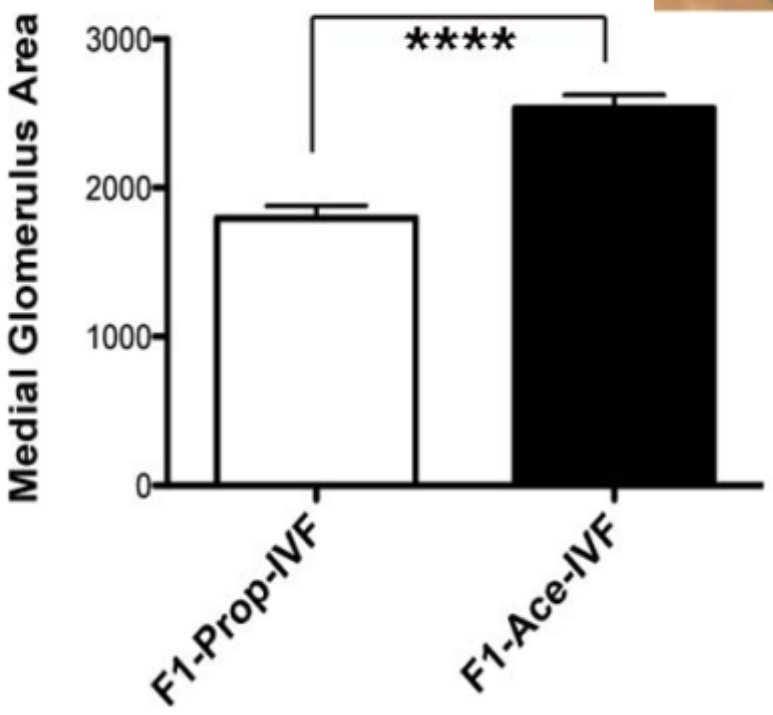




Brian Dias, PhD, Nature Neuroscience, 2014

Paternal Olfactory Fear Conditioning Causes *in vitro* fertilized Offspring to have similar effects in the Brain



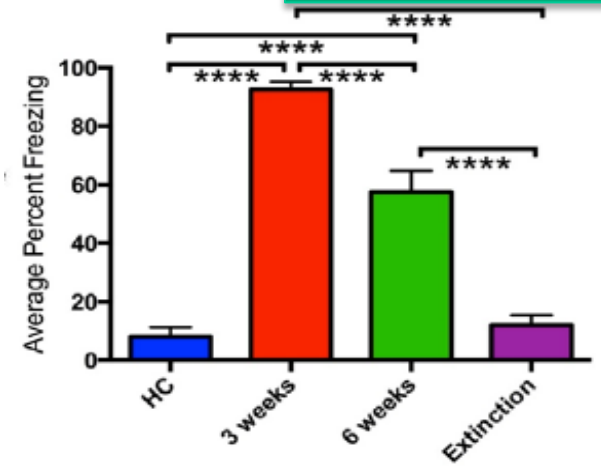


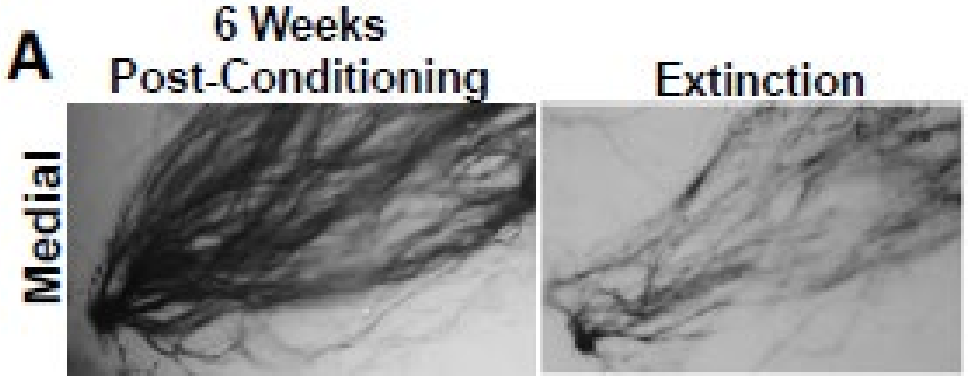
Offspring derived from *in vitro* fertilization

Brian Dias, PhD, Nature Neuroscience, 2014

In adults, we see *Reversal* of Fear Behavior and Olfactory Structural Marks with Extinction (a measure of Resilience?)

Can olfactory fear extinction be transmitted across generations?

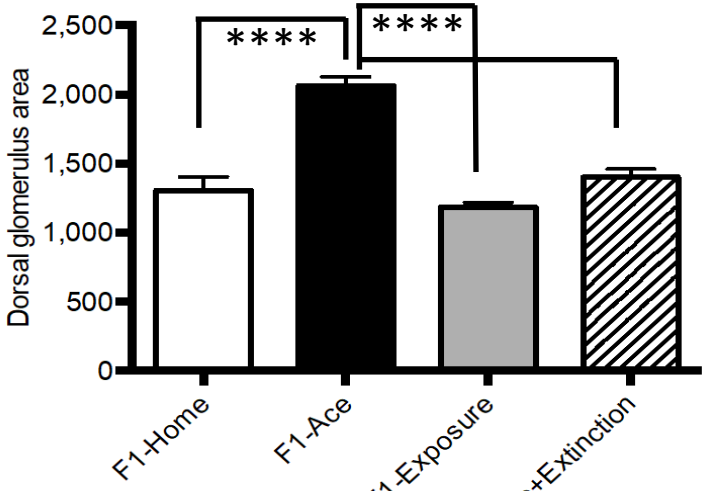




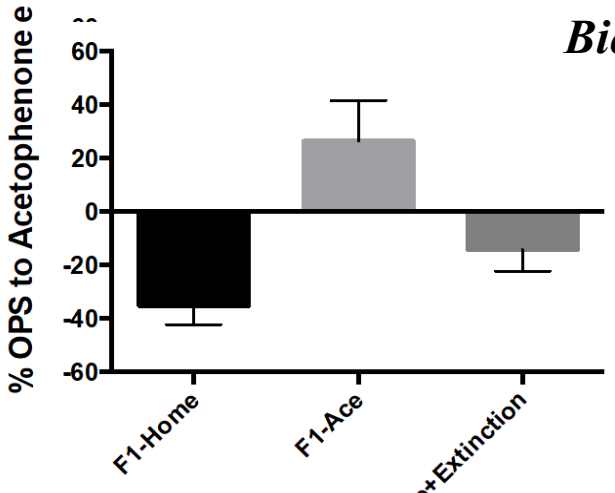
Morrison et al., PNAS, 2015

Extinction of olfactory fear in parental generation reverses inherited behavior and structure: *Inherited Resilience?*

Glomerular Structure

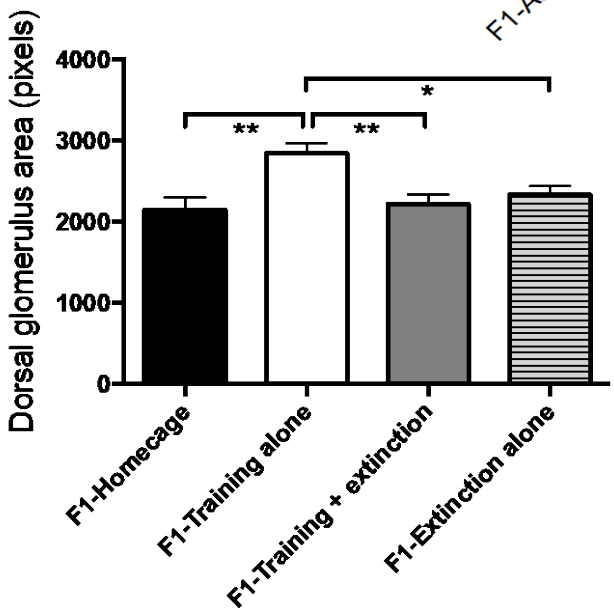


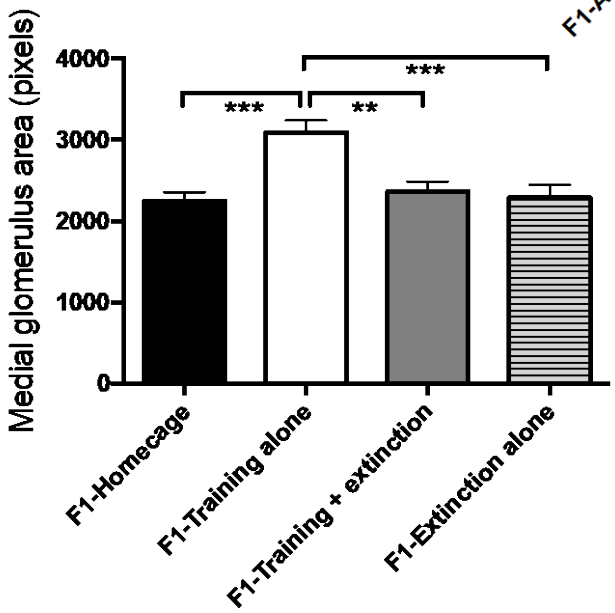
Behavior

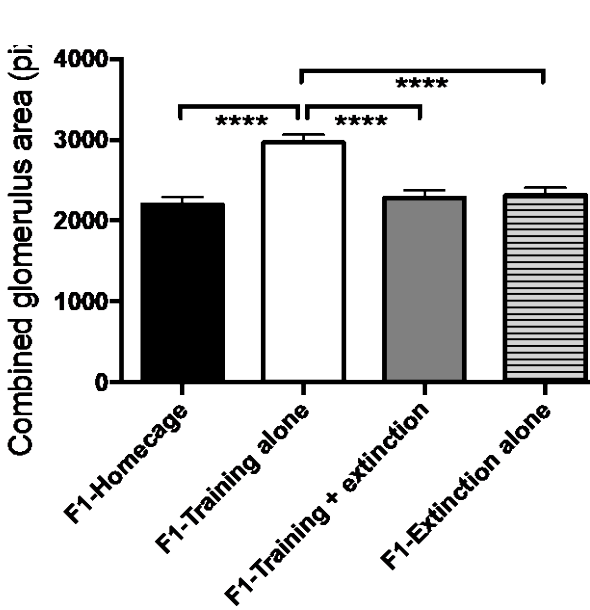


Aoued....Dias, Biol Psychiatry, 2019

REPLICATION







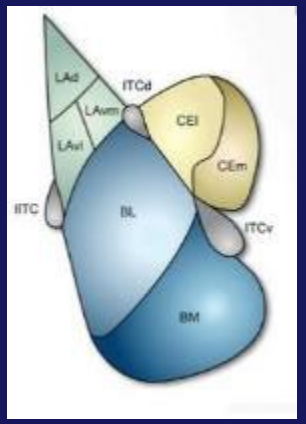
Mechanisms of Fear & Possibly *Resilience* after Trauma

1) Genetics & Genomics of resilience and positive affect

- Large scale genomics
- Potential molecular pathways

ensitivity
nment)

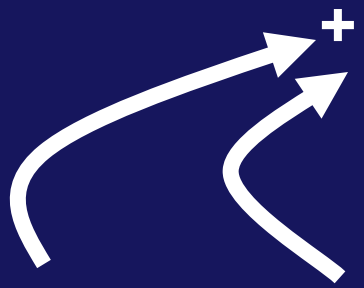
ear
ent)



PTSD (Risk)

Consolidation of Fear
Hours – days following event

Recovery (Resilience)



Expressi
Memories, Nighti
Avoidance, Sympath

2) Extinction / Inhibiting Fear

- *Role of Amygdala*
- *Olfactory Fear across generations*

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

Thank You!!

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