Epigenetics of trauma and trauma-related disorders: Implications of Immune dysregulation across peripheral and central nervous system

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National Academies of Sciences, Engineering, and Medicine

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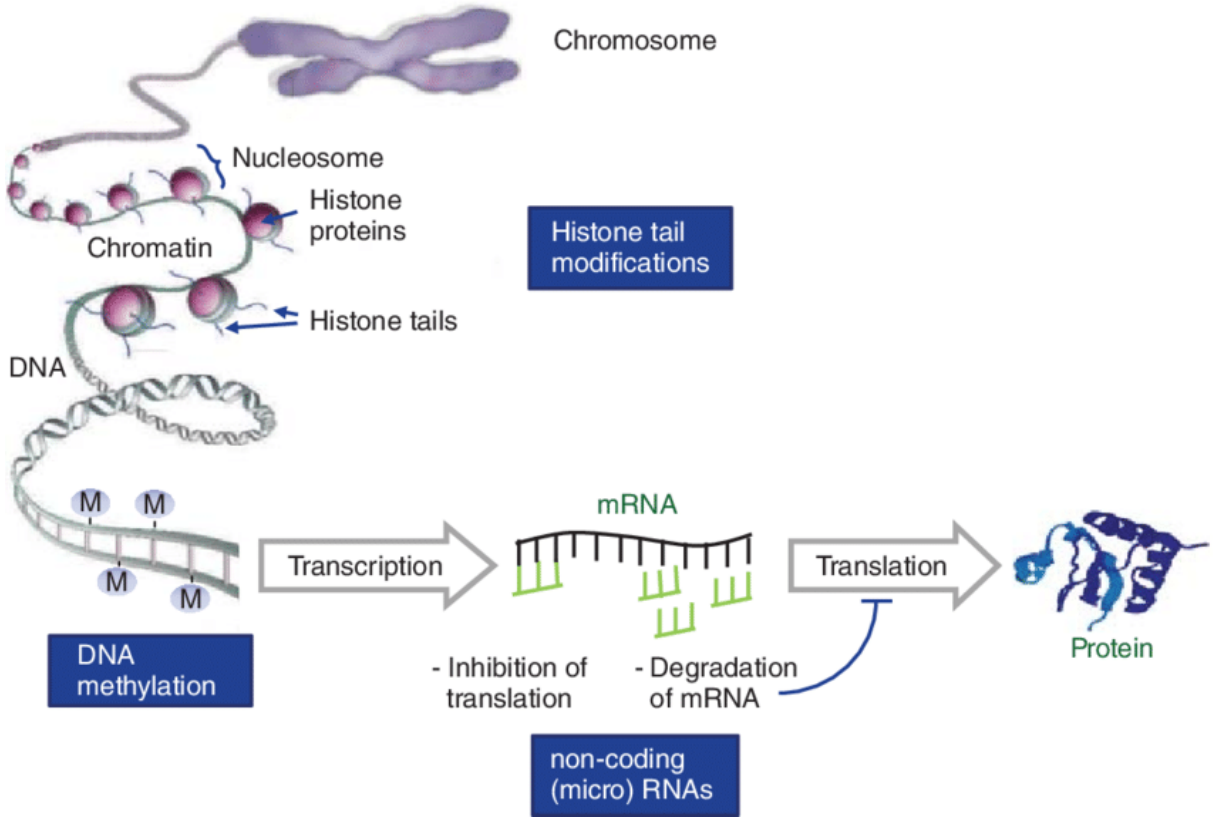
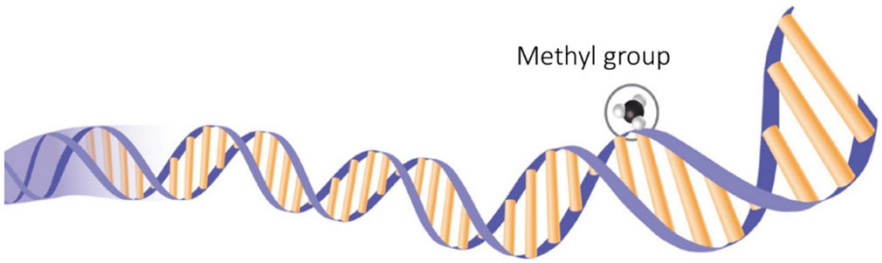
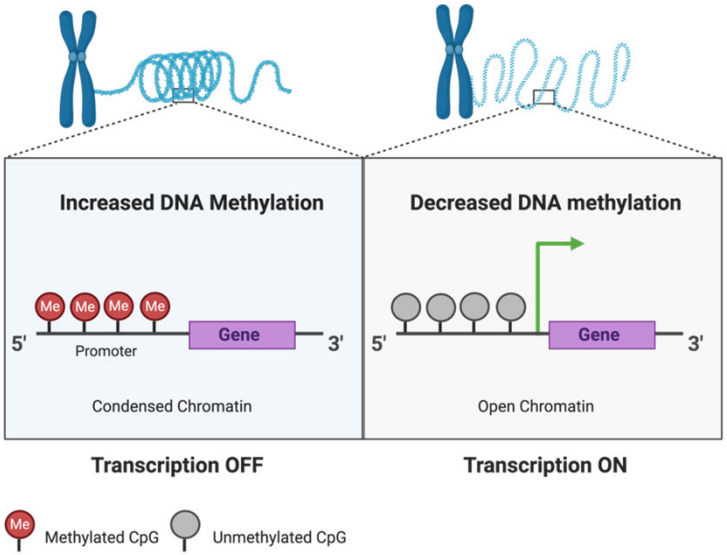
Epigenetics: The Nature of Nurture



Epigenetics: DNA methylation



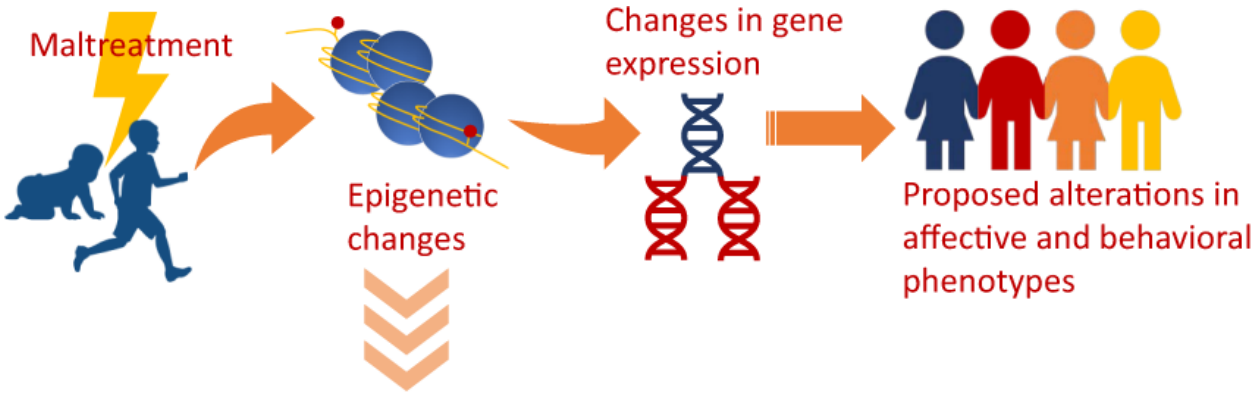
Methylation is the attachment of a methyl group to DNA. Methyl groups can activate or silence genes and operate as biological programs in human cells.



(Montalvo-Ortiz JL, 2022)

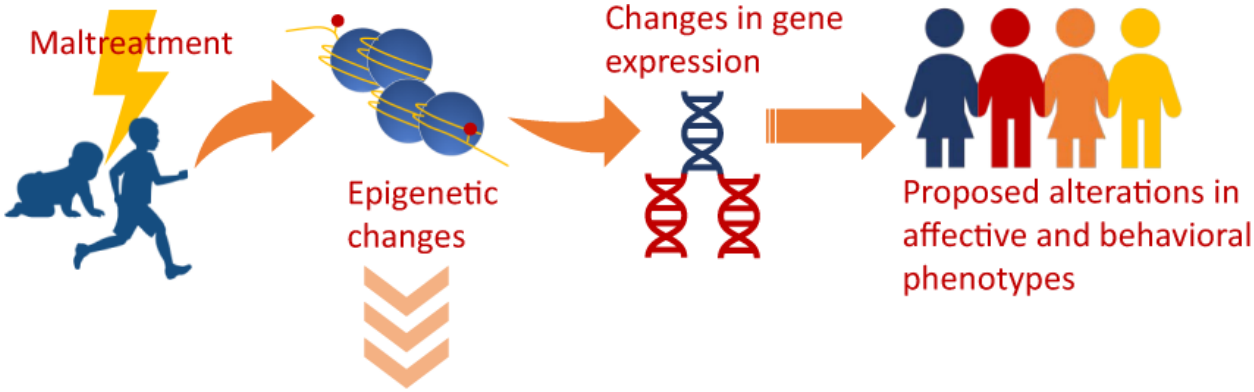
DNA methylation patterns are established during brain development, but may be disrupted by early-life adversity.

Epigenetics of Childhood Trauma



Parade et al., 2021

Epigenetics of Childhood Trauma



Genes with alterations in methylation:

HPA Axis
NR3C1/hGR
FKBP5
CRHR1
POMC

Oxytocin
OXTR

Other endocrine
SSTR4

Serotonin
SLC6A4/5-HTT
HTR2A
5HT3AR

MAO
MAOA
MAOB

Opioid
Kappa

Inflammation
IL-6

Cell growth, migration, division
BDNF
OTX2
SKA2
KITLG

Systems identified in epigenome-wide association studies:

HPA Axis

Endocrine

Neurotransmitters

Inflammation

Cell growth, migration, division

Signal transduction

Apoptosis

Cancer

Metabolic functions

Parade et al., 2021

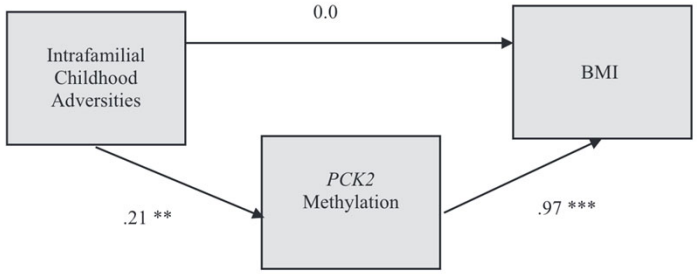
Risk and Resilience study




Adverse Childhood Experiences, Epigenetic Measures, and Obesity in Youth

DNA methylation sites that independently and in interaction with intrafamilial childhood adversity predicts BMI.

Illumina ID	Gene symbol	Chr	Gene location	Methylation *P* value	Trauma *P* value	Interaction *P* value
cg10264529	***PCK2***	14	TSS1500	**7.53E-09**	ns	ns
cg14929207	*DHRS13*	17	TSS1500	**3.70E-08**	ns	ns
cg16110788		7	Intergenic (Enhancer)	**4.79E-08**	ns	ns
cg14855841	***CXCL10***	4	TSS1500	**7.59E-08**	ns	ns
cg26103104			Intergenic	**4.31E-07**	ns	ns
cg01555853	*KCNS3*	2	TSS200	**4.45E-07**	ns	ns
cg15990629	***BCAT1***	12	Body	ns	ns	**4.42E-09**
cg22806444	***HID1***	17	1st Exon (Regulatory)	ns	ns	**1.94E-08**
cg26764244	*GNG12*	1	TSS1500	ns	ns	**2.14E-08**
cg17489690	***PRDM16***	1	Body	ns	ns	**2.52E-08**
cg01507128		19	Intergenic	ns	ns	**5.55E-08**
cg16557308	*OSBPL9*	1	Promoter Associated	ns	ns	**6.27E-08**
cg18839416	*C1orf158*	1	TS1500	ns	ns	**6.34E-08**
cg05559960	***MADD***	11	TSS200	ns	ns	**6.60E-08**
cg24741066	***PXDN***	2	Body (Enhancer)	ns	ns	**2.66E-07**
cg26737766	***GALE***	1	Promoter Associated	ns	ns	**2.75E-07**



Indirect effects of intrafamilial childhood adversities on BMI through methylation of *PCK2.*

Methylation at *PCK2* has been previously linked to BMI.
This gene has been implicated in immune regulation and proliferation.

Kaufman, et al., 2018

OTX2 methylation, depression and brain connectivity in maltreated children

RESEARCH

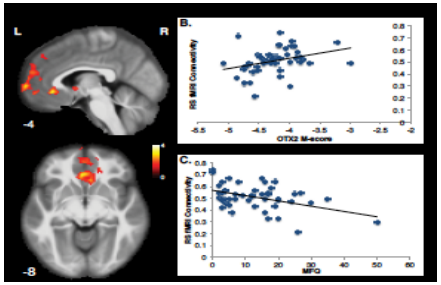
NEURODEVELOPMENT

Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2

Catherine J. Peña,[1] Hope G. Kronman,[1] Deena M. Walker,[1] Hannah M. Cates,[1] Rosemary C. Bagot,[1]* Immanuel Purushothaman,[1] Orna Issler,[1] Yong-Hwee Eddie Loh,[1] Tin Leong,[1] Drew D. Kiraly,[1,2] Emma Goodman,[1] Rachael L. Neve,[3] Li Shen,[1] Eric J. Nestler[1]†

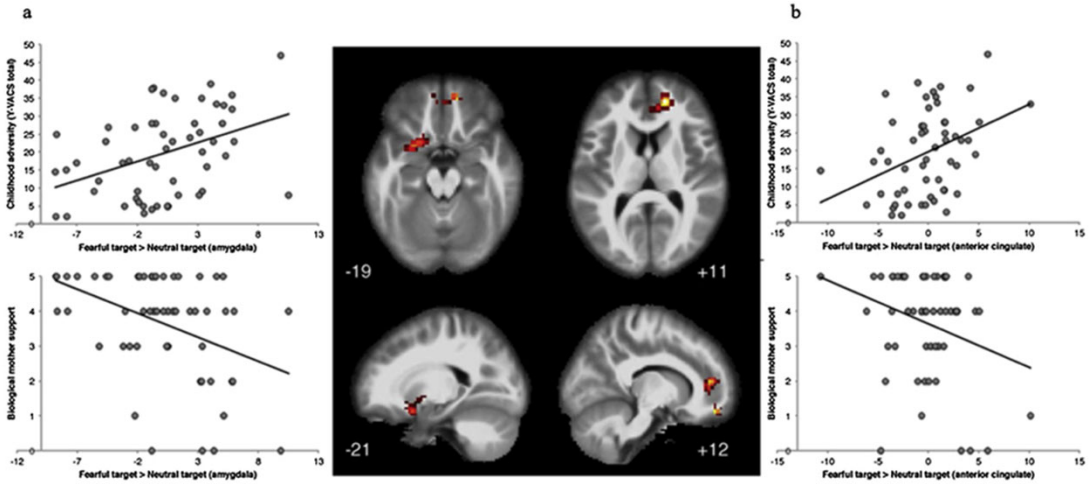
Early life stress increases risk for depression. Here we establish a "two-hit" stress model in mice wherein stress at a specific postnatal period increases susceptibility to adult social defeat stress and causes long-lasting transcriptional alterations that prime the ventral tegmental area (VTA)—a brain reward region—to be in a depression-like state. We identify a role for the developmental transcription factor orthodenticle homeobox 2 (*Otx2*) as an upstream mediator of these enduring effects. Transient juvenile—but not adult—knockdown of *Otx2* in VTA mimics early life stress by increasing stress susceptibility, whereas its overexpression reverses the effects of early life stress. This work establishes a mechanism by which early life stress encodes lifelong susceptibility to stress via long-lasting transcriptional programming in VTA mediated by *Otx2*.

Source	Wald X^2	df	p-value
Age	0.49	1	ns
Sex	1.16	1	ns
Race	3.19	2	ns
CD34	1.77	1	ns
CD14	2.76	1	ns
Buccal	0.21	1	ns
PC1	6.05	1	.014
PC2	5.72	1	.017
PC3	2.65	1	.103
Intrafamilial Adversity	5.23	1	.022
OTX2	7.37	1	.007



Methylation in *OTX2* significantly predicted depression scores in children exposed to adversity. Increased *OTX2* methylation was associated with increased functional connectivity between vmPFC and ACC.

Kaufman, et al., 2018



Increased activation in response to threat stimuli during the Go/No Go task was observed in the amygdala, ACC, insula, nucleus accumbens and frontal lobe.

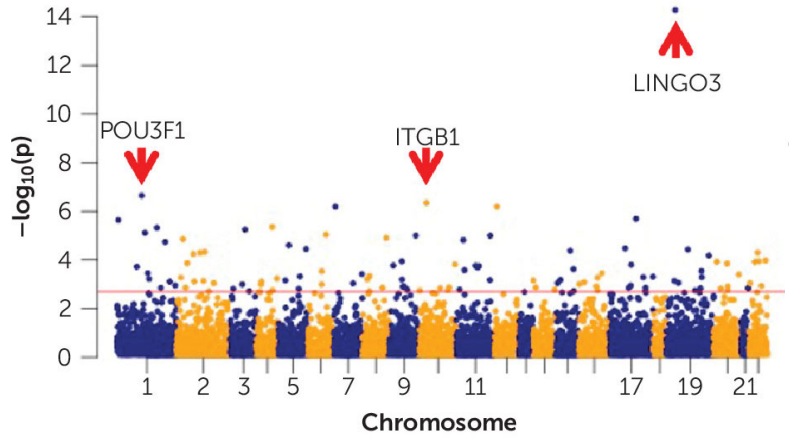
Birth parent support moderates the impact of trauma on brain activation during threat processing and emotional regulation.

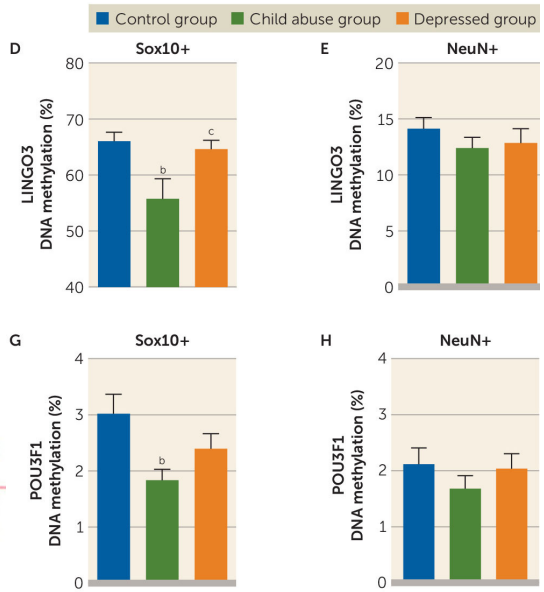
Wymbs, et al., 2020

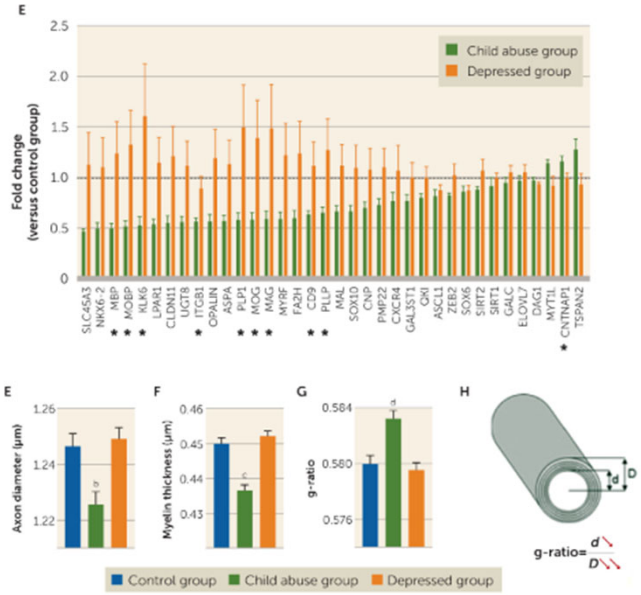
Child abuse and DNA methylation in human postmortem brain

Association of a History of Child Abuse With Impaired Myelination in the Anterior Cingulate Cortex: Convergent Epigenetic, Transcriptional, and Morphological Evidence

Pierre-Eric Lutz, M.D., Ph.D., Arnaud Tanti, Ph.D., Alicja Gasecka, Ph.D., Sarah Barnett-Burns, B.Sc., John J. Kim, B.Sc., Yi Zhou, B.Sc., Gang G. Chen, Ph.D., Marina Wakid, B.Sc., Meghan Shaw, B.Sc., Daniel Almeida, B.Sc., Marc-Aurele Chay, B.Sc., Jennie Yang, M.Sc., Vanessa Larivière, D.C.S., Marie-Noël M'Boutchou, M.Sc., Léon C. van Kempen, Ph.D., Volodymyr Yerko, Ph.D., Josée Prud'homme, B.Sc., Maria Antonietta Davoli, M.Sc., Kathryn Vaillancourt, B.Sc., Jean-François Théroux, M.Sc., Alexandre Bramoullé, M.Sc., Tie-Yuan Zhang, Ph.D., Michael J. Meaney, Ph.D., Carl Ernst, Ph.D., Daniel Côté, Ph.D., Naguib Mechawar, Ph.D., Gustavo Turecki, M.D., Ph.D.







Differential methylation at *POU3F1* and *LINGO3* was specific to oligodendrocytes in the ACC. Decreased expression of myelin-related genes was also observed, accompanied by disrupted myelination and axonal integrity in the ACC of donors with history of child abuse.

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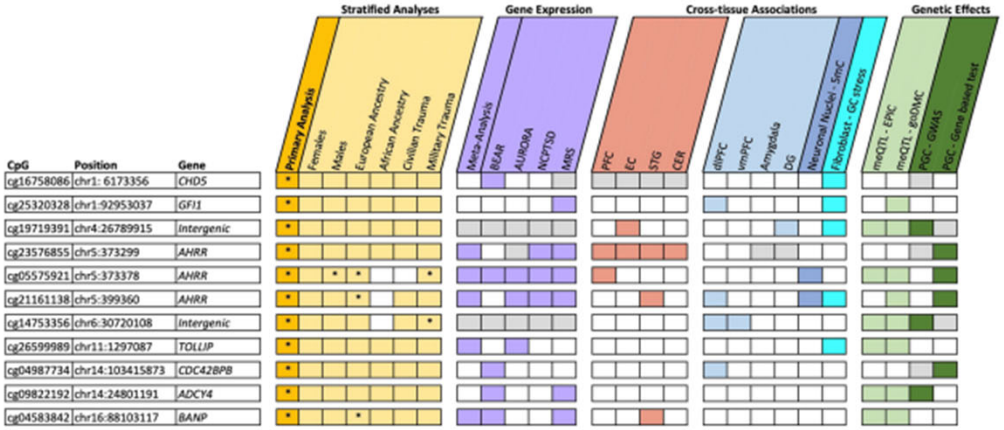
Epigenetics and immune dysregulation in PTSD: Peripheral findings

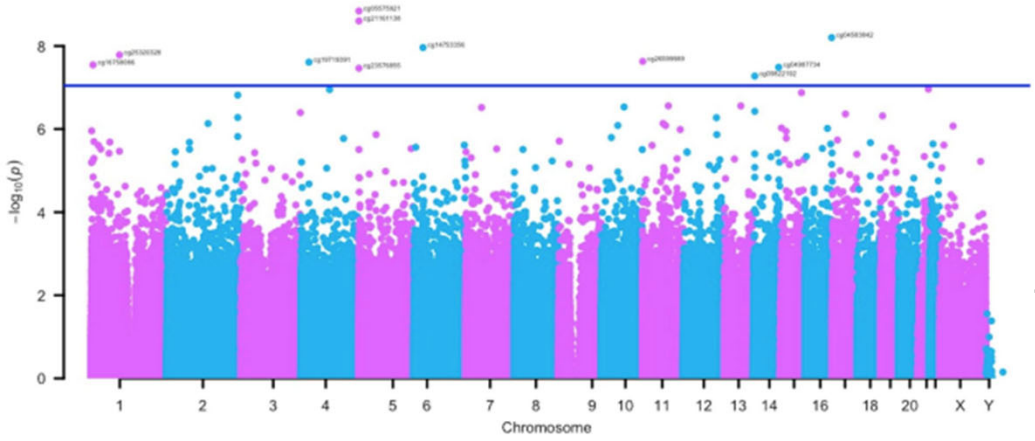
Katrinli *et al. Genome Medicine* (2024) 16:147
https://doi.org/10.1186/s13073-024-01417-1

Genome Medicine

RESEARCH Open Access

Epigenome-wide association studies identify novel DNA methylation sites associated with PTSD: a meta-analysis of 23 military and civilian cohorts



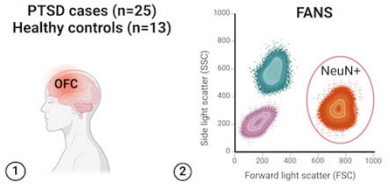


Epigenetically dysregulated genes include *AHRR*, *CDC42BPB, GFI1*, *CHD5*, *TOLLIP*, *ADCY4*, and *BANP*.

Many of these exhibited blood-brain correlation in methylation levels and cross-tissue associations in PTSD.

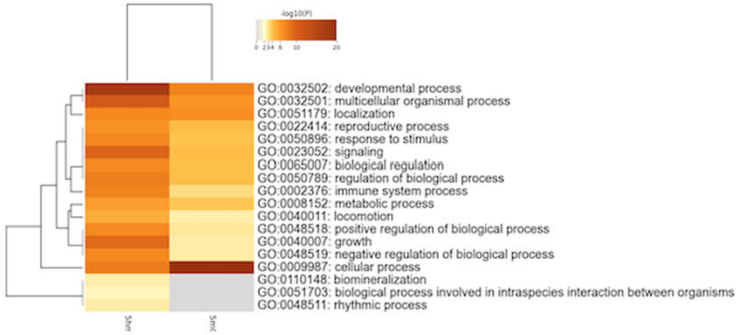
These genes are implicated in synaptic and neural plasticity processes and neuroimmune interactions.

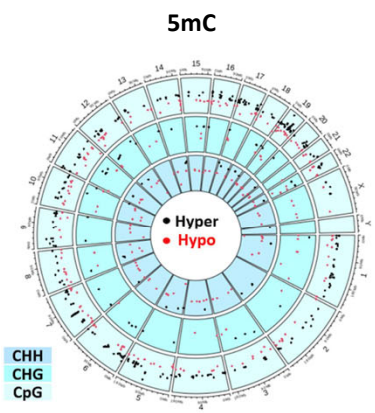
Epigenetics and immune dysregulation in PTSD: Postmortem brain findings

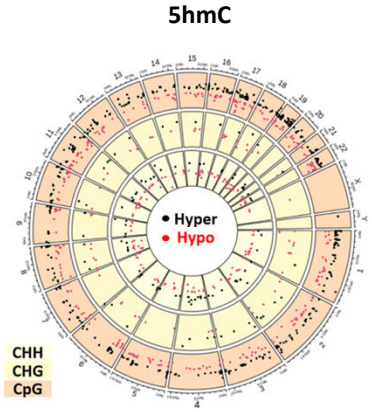


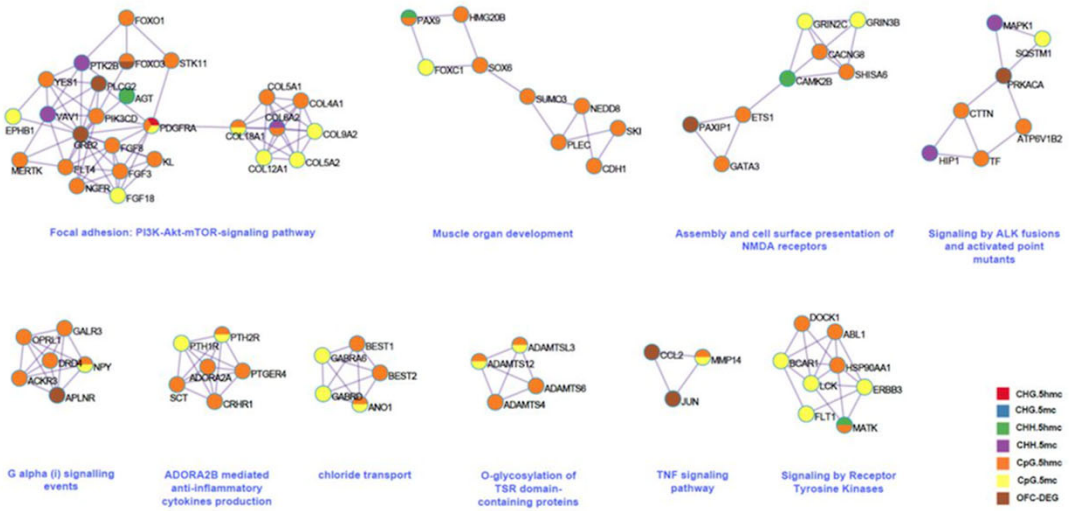
Coverage ④

Site	5mC	5hmC
CpG	1.849.092	1.659.917
CHG	1.668.889	1.458.007
CHH	3.284.099	2.840.577









By evaluating DNA methylation, hydroxymethylation, and gene expression in neurons from the orbitofrontal cortex, we observed dysregulation of genes involved in immune system process in PTSD.

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Núñez-Rios, et al. In preparation

Neuroimmune suppression and activation of peripheral immune markers in PTSD

nature COMMUNICATIONS

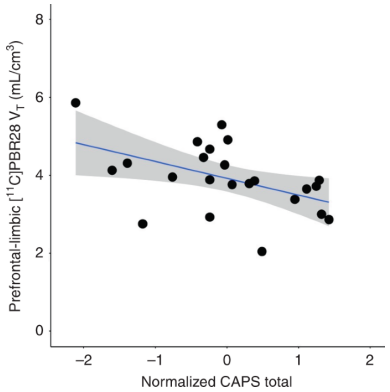
ARTICLE

https://doi.org/10.1038/s41467-020-15930-5 OPEN

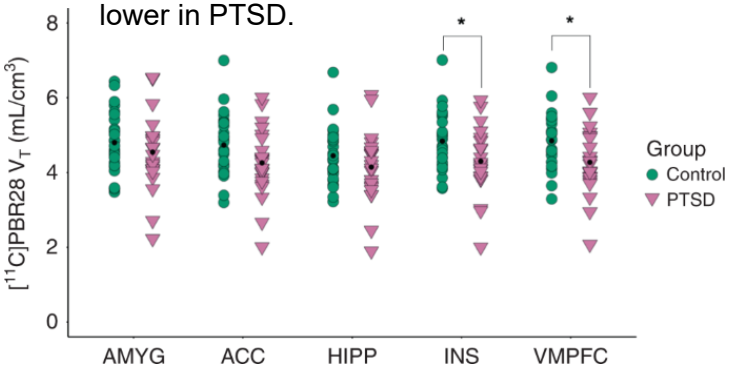
PTSD is associated with neuroimmune suppression: evidence from PET imaging and postmortem transcriptomic studies

Shivani Bhatt[1], Ansel T. Hillmer[2,3,4], Matthew J. Girgenti[3,5], Aleksandra Rusowicz[3], Michael Kapinos[4], Nabeel Nabulsi[2,4], Yiyun Huang[2,4], David Matuskey[2,3,4], Gustavo A. Angarita[3,4], Irina Esterlis[1,3,4,5], Margaret T. Davis[3], Steven M. Southwick[3,5], Matthew J. Friedman[6], Traumatic Stress Brain Study Group*, Ronald S. Duman[3], Richard E. Carson[2,4], John H. Krystal[3,5], Robert H. Pietrzak[3,5] & Kelly P. Cosgrove[1,2,3,4,5]✉

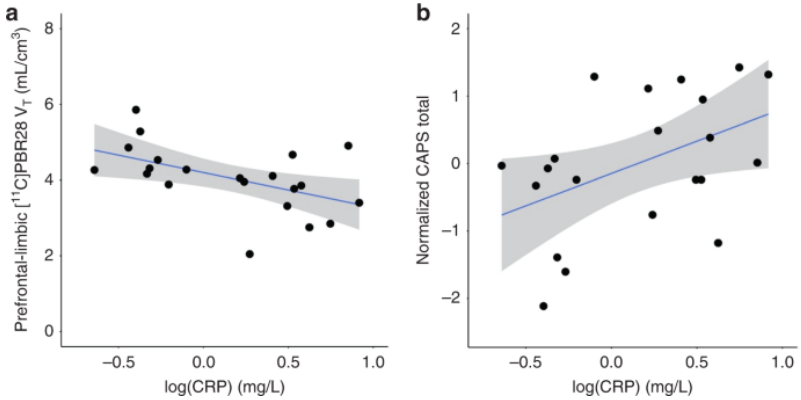
Prefrontal-limbic TSPO availability was associated with PTSD severity.



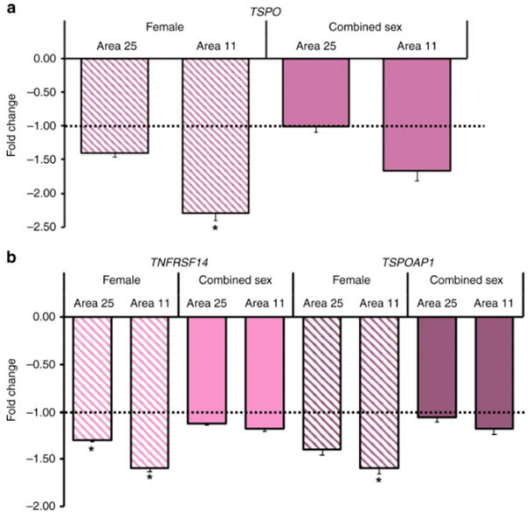
Prefrontal-limbic circuit TSPO availability is lower in PTSD.



CRP is negatively associated with prefrontal-limbic TSPO availability and positively associated with PTSD severity.



Expression of TSPO and related genes is decreased in the postmortem PFC.



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Complex peripheral-to-neural immune system relationship in PTSD

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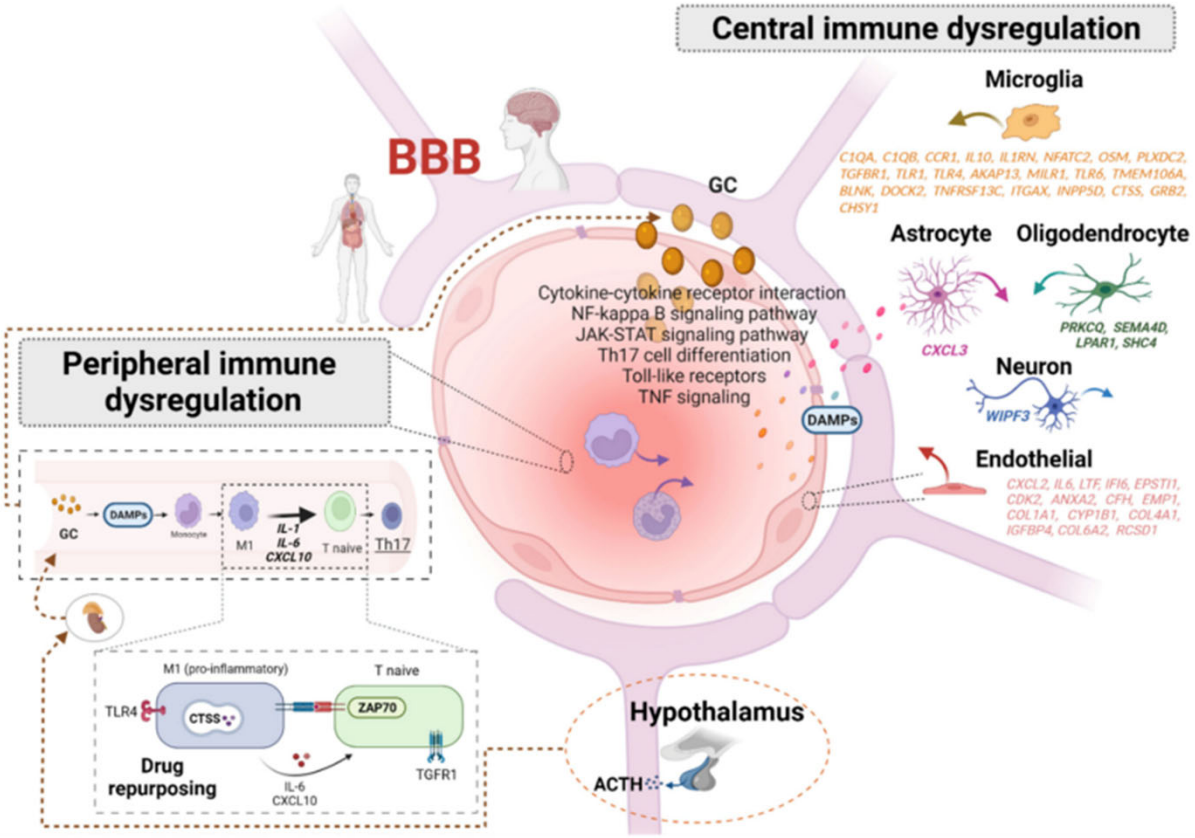
Systemic immune dysregulation in PTSD

Impaired homeostasis of the central and peripheral immunological response



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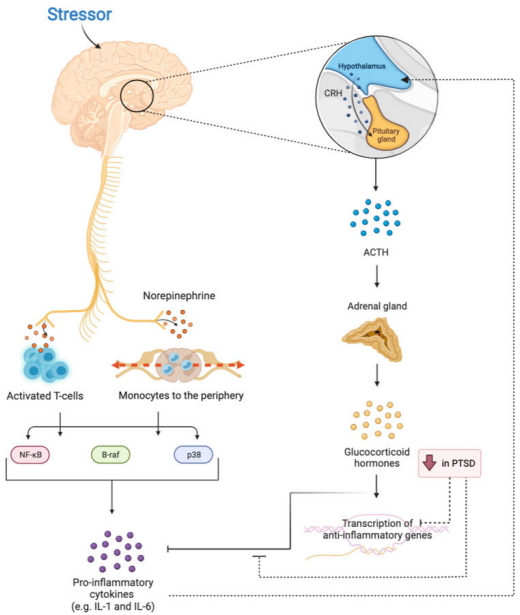
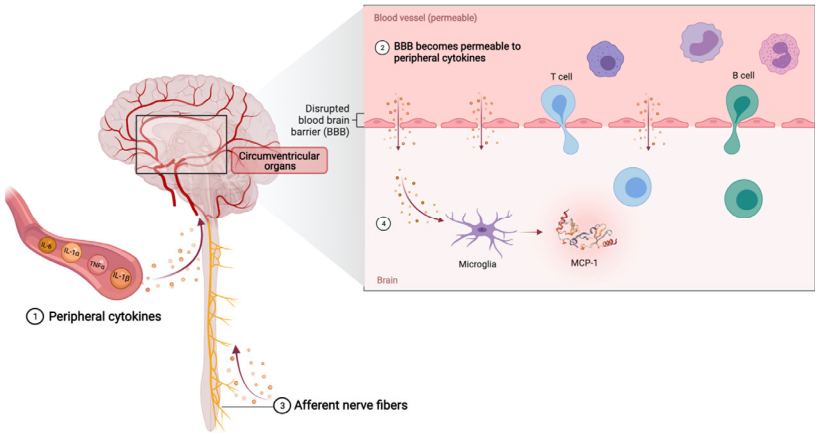
Núñez-Rios, et al. 2022

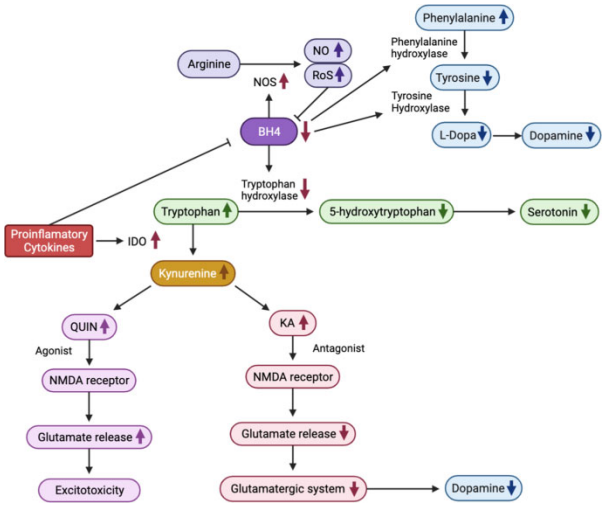
Central and peripheral immune crosstalk in PTSD



(1) HPA axis dysregulation

(2) Trafficking of peripheral inflammatory signals to brain.





(3) Pro-inflammatory cytokines changes in neurotransmitter systems.

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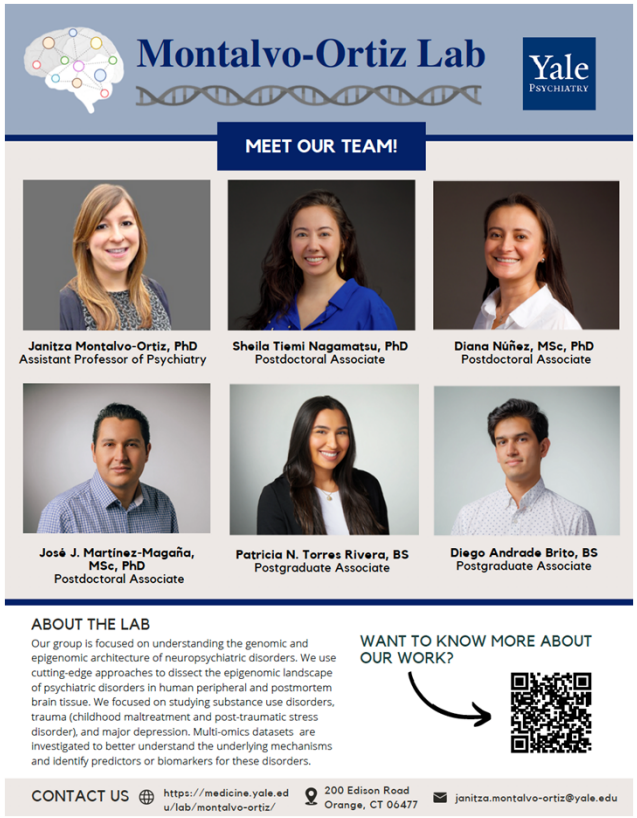
Katrinli, et al. 2022

Potential therapeutic approaches targeting PTSD immune dysregulation

- TF inhibitor (Adalimumab, Etanercept, or Infliximab)
- Non-steroidal anti-inflammatory drugs and COX-2 inhibitors
- NLRP2 inflammasome inhibitors (BHB)
- Glucocorticoid treatment (Hydrocortisone)
- Noradrenergic beta-receptor blockers (Propanolol*)
- Angiotensin-converting enzyme inhibitors (Candersartan) and angiotensin receptor blockers (Losartan*)
- Cannabinoids (Nabilone)
- Psychotherapy (Eye movement desensitization, reminder-focused positive psychiatry) and behavioral interventions (yoga, and mindfulness).

Acknowledgements



NIH National Institute on Drug Abuse
Advancing Addiction Science

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

National Center for PTSD
POSTTRAUMATIC STRESS DISORDER

Department of Veterans Affairs Biorepository Brain Bank
VABBB
Committed to research on brain disorders that affect Veterans

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