

The Complex Interaction Between Environment and Genes in Depression & Suicide

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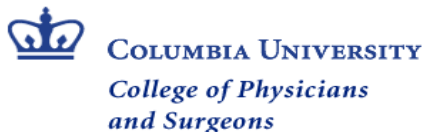
&

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Chair, Israeli council for suicide prevention



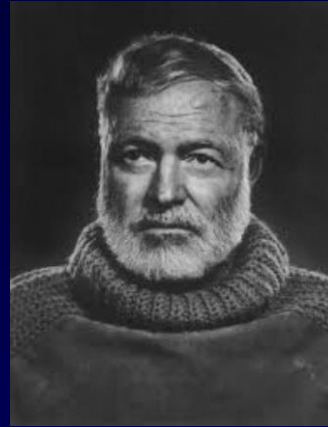
**Gili Adar Institute for Learning and Intervention in Adolescence Mental
Health Crisis and Suicide**



Genetic Vulnerabilities

Suicidal Behavior Runs in Families

(A Roy et al 1990, DA Brent et al., 1996)



Ernest Hemingway

**MZ twins
have 13 times higher risk than in DZ
(Roy 1990)**

Suicide attempt in parent is a strong predictor for child suicide attempt (OR=4.79)



HHS Public Access

Author manuscript

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JAMA Psychiatry. 2015 February ; 72(2): 160–168. doi:10.1001/jamapsychiatry.2014.2141.

Familial Pathways to Early-Onset Suicide Attempt:

A 5.6-Year Prospective Study

David A. Brent, MD, Nadine M. Melhem, PhD, Maria Oquendo, MD, Ainsley Burke, PhD, Boris Birmaher, MD, Barbara Stanley, PhD, Candice Biernesser, LSW, MPH, John Keilp, PhD, David Kolko, PhD, Steve Ellis, PhD, Giovanna Porta, MS, Jamie Zelazny, MPH, RN, Satish Iyengar, PhD, and J. John Mann, MD

Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Brent, Melhem, Birmaher, Biernesser, Kolko, Zelazny, Iyengar); Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Brent, Birmaher, Biernesser, Kolko, Porta, Zelazny); Division of Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia University and New York State Psychiatric Institute, New York (Oquendo, Burke, Stanley, Keilp, Ellis, Mann)

Brent et al., *JAMA Psychiatry* 2015

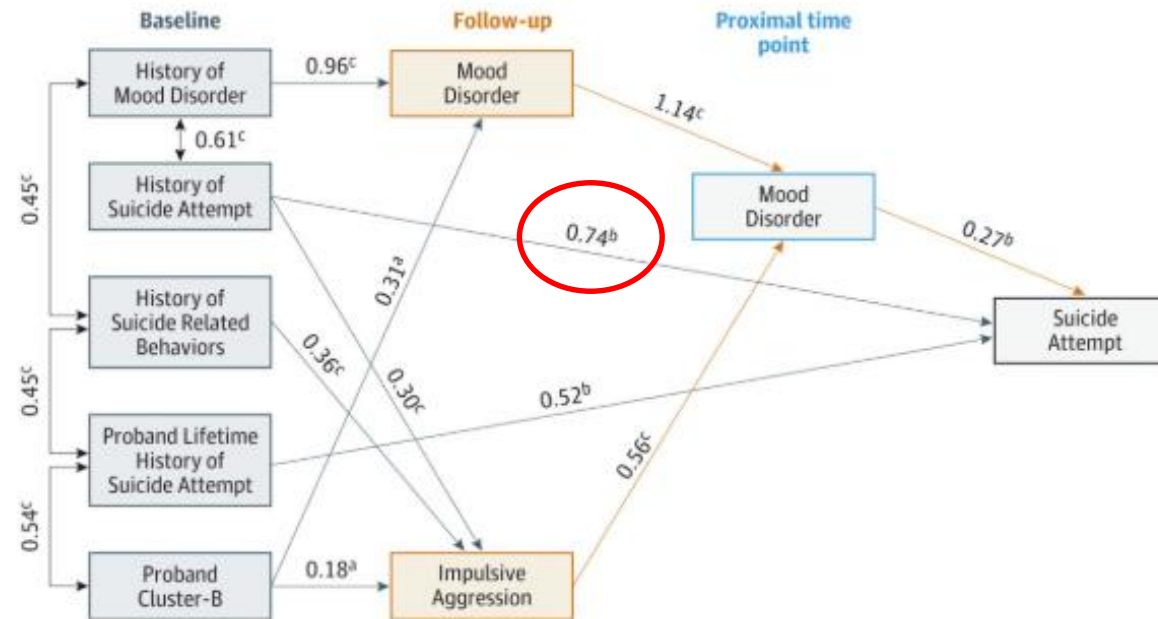
5 years FU on offspring of suicidal parent (n=701)

Path Analysis Including Predictors of Suicide Attempt and Mood Disorder at the Prior Time Point

Black line indicates baseline variables; red line, follow-up variables; and blue line, variables at proximal time points. Numbers are path coefficients. All paths are statistically significant.

Suicide attempt in parent is a strong predictor to suicide in offspring independent of depression

Page 14



Brent et al., JAMA Psychiatry 2015



A pilot genome wide association and gene expression array study of suicide with and without major depression

Hanga Galfalvy, Gil Zalsman, Yung-Yu Huang, Lauren Murphy, Gorazd Rosoklija, Andrew J. Dwork, Fatima Haghighi, Victoria Arango & J. John Mann



Galfalvy, Zalsman, Huang et al., WJBP, 2014

Most markers connected to immune system

Table 3: Literature review for the 19 significant GWAS candidate genes in suicides (based on OMIM database*)

Gene Symbol	Chro. #	Description	Suggested clinical role*	Similar Genes found by others in expression studies
<i>CDH13</i>	16	cadherin 13, H-cadherin (heart)	Lung tumor recurrence?	CDH12, CDH22 (Thalmeier et al., 2008)
<i>NPR3</i>	5	natriuretic peptide receptor C	Maintenance of blood pressure	
<i>CD300LB</i>	17	CD300 antigen-like family member b	Cell surface localization in B and NK cells	
<i>FOXN3</i>	14	forkhead helix transcription	DNA damage correction?	ADAMTS1, IGF1, VIP, WDR39 (Thalmeier et al. 2008)
<i>DISC1</i>	1	disrupted in schizophrenia 1	Susceptibility for schizophrenia (Millar et al. 2000)	
<i>CYP19A1</i>	15	cytochrome P450, family 19, subfamily A, polypeptide 1	Aromatase deficiency	
<i>MYO3A</i>	10	myosin IIIA	Autosomal recessive deafness	MYR8 (Thalmeier et al. 2008)
<i>SFRS11</i>	1	arginine/serine-rich 11 splicing factors	Pre-mRNA splicing?	
<i>LSAMP</i>	3	limbic system-associated membrane protein	Neuronal surface glycoprotein in limbic system (Pimenta et al., 1996)	
<i>DSC2</i>	18	desmocollin 2	Ca dependent glycoprotein important for cell adhesion	
<i>SPTLC1</i>	9	serine palmitoyltransferase, long chain base subunit 1	Hereditary sensory neuropathy	
<i>ACCN1</i>	17	amiloride-sensitive cation channel 1, neuronal (degenerin)	neurodegeneration? KO-mice reduced sensitivity to mechanic sensation	
<i>FLJ23312</i>	5	Hypothetical protein	Not known	FLJ21616 (Sequeira et al. 2007)
<i>MBNL2</i>	13	muscleblind-like 2	May be associated with Myotonic Dystrophy	
<i>CD44</i>	11	CD44 molecule	Migration, cell fusion, tumorigenesis?	(Thalmeier et al.2008, Sequeira et al.2007)
<i>TUBGCP3</i>	13	tubulin, gamma complex associated protein 3	Associated with gama-tubulin in cells and oocytes	

ARTICLE **OPEN**



Genome-wide association study meta-analysis of suicide death and suicidal behavior

Qingqin S. Li ^{1,2}✉, Andrey A. Shabalin ³, Emily DiBlasi³, Srihari Gopal ^{1,7}, Carla M. Canuso¹, FinnGen, International Suicide Genetics Consortium, Aarno Palotie ⁴, Wayne C. Drevets⁵, Anna R. Docherty ^{3,6} and Hilary Coon³

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N=3700, controls= 6500

Li et al., Mol Psychiatry 2023

Significant SNPs

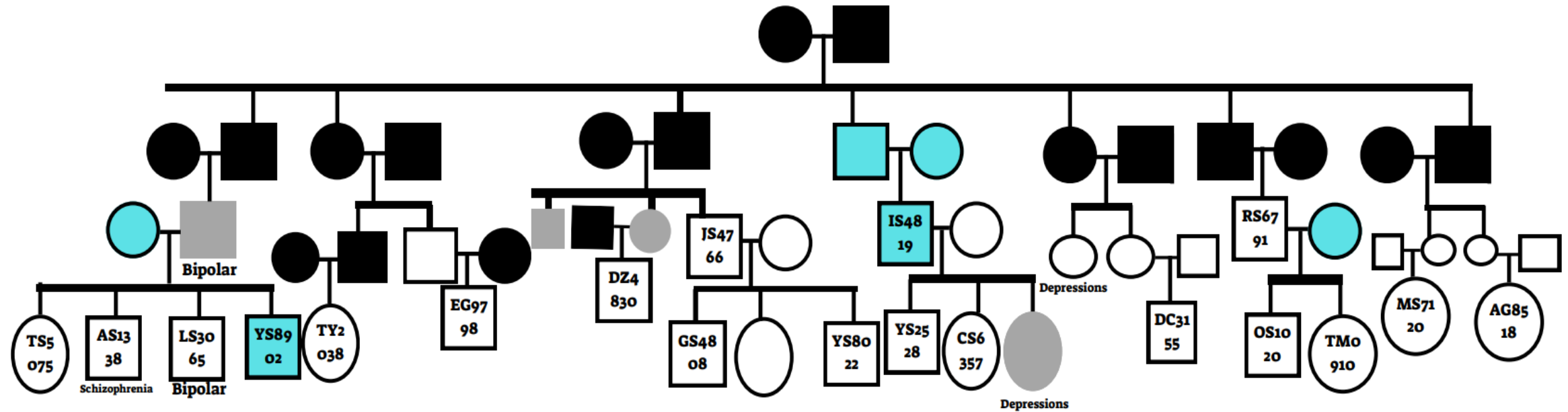
mostly connected to **synaptogenesis**
(probably the SSRIs' real mechanism of action)

Table 3. Replication results for genome-wide significant loci identified in the ISGC and MVP meta-analysis.

CHR	SNP	BP	A1	A2	FRQ_A_4098	FRQ_U_247898	INFO	OR	SE	p	Nearest gene (distance to index SNP in kb)
1	rs3791129	44,480,093	A	G	0.7582	0.7503	0.99	1.06	0.03	0.041	SLC6A9 (0.0)
1	rs2503185	66,461,401	G	A	0.4231	0.4347	1	0.96	0.02	0.078	PDE4B (0.0)
11	rs7131627	113,299,829	A	G	0.4986	0.5107	1	0.96	0.02	0.075	DRD2 (0.0)
12	rs17485141	24,213,634	T	C	0.2325	0.248	1	0.92	0.03	0.003	SOX5 (0.0)
13	rs9525171	96,908,223	G	C	0.4996	0.5072	1	0.97	0.02	0.259	HS6ST3 (0.0)
14	rs850261	57,346,423	G	A	0.4344	0.4274	1	1.04	0.02	0.114	OTX2-AS1 (0.0)
15	rs17514846	91,416,550	A	C	0.3905	0.3936	1	0.99	0.02	0.59	FURIN (0.0)
22	rs2284000	37,053,338	G	C	0.2922	0.2902	0.99	1	0.03	0.853	CACNG2 (0.0)
3	rs7649709	173,129,819	A	C	0.3291	0.3269	0.96	1	0.02	0.965	NLGN1 (0.0)
6	rs62404522	19,307,114	C	T	0.1416	0.1301	1	1.12	0.03	0.001	LOC101928519 (-76.4)
6	rs35869525	26,946,687	T	C	0.04866	0.05079	1	0.98	0.05	0.642	MHC
7	rs62474683	115,020,725	G	A	0.4203	0.4283	1	0.97	0.02	0.172	LINC01392 (-149.3)

Li et al., Mol Psychiatry 2023

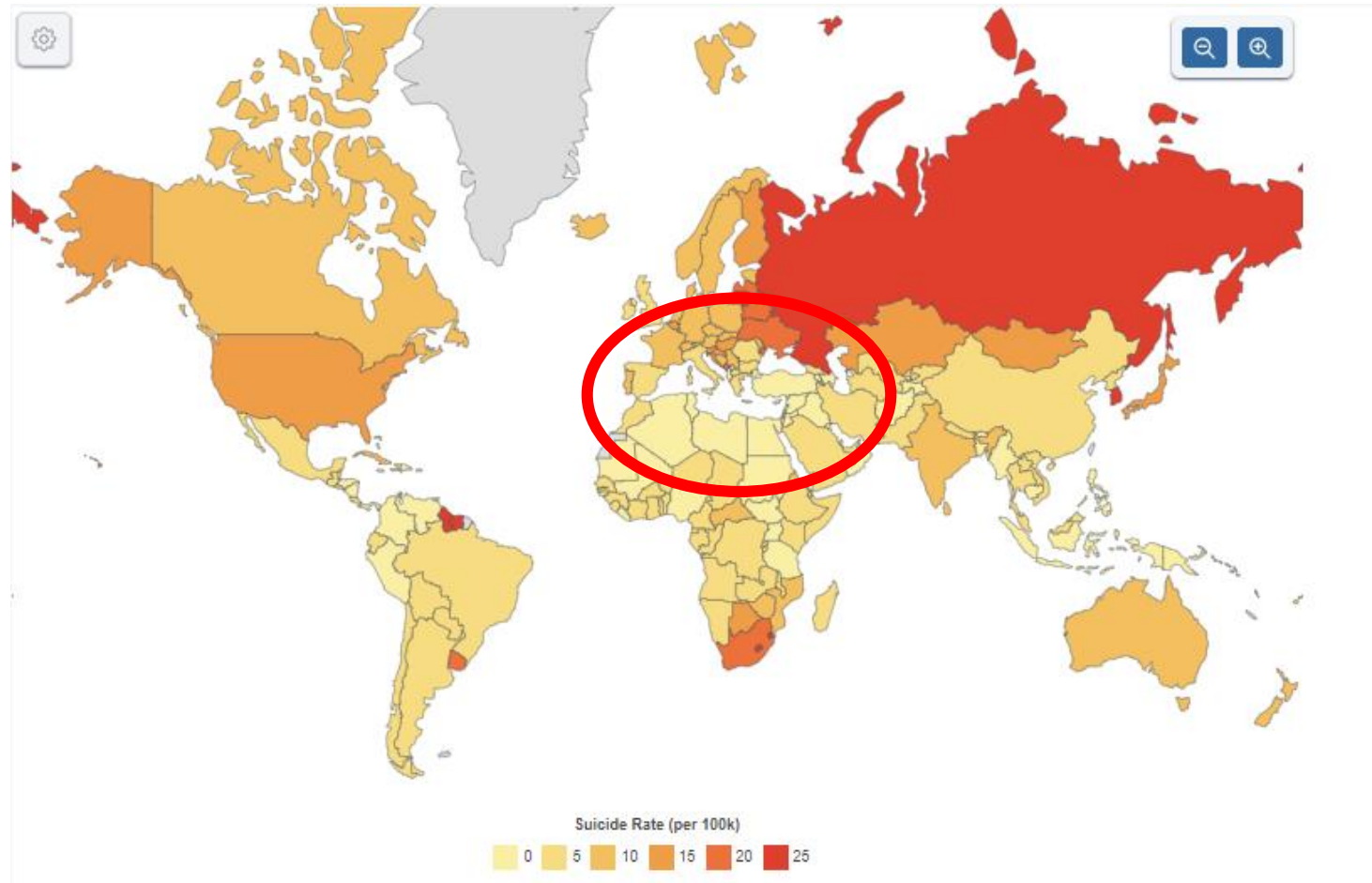
High Genetic Load of Suicide in one Family Tree



From the Gili Adar Institute for Learning and Intervention in Adolescence Mental Health Crisis and Suicide
(Zalsman, Blum.....Mann, In preparation)

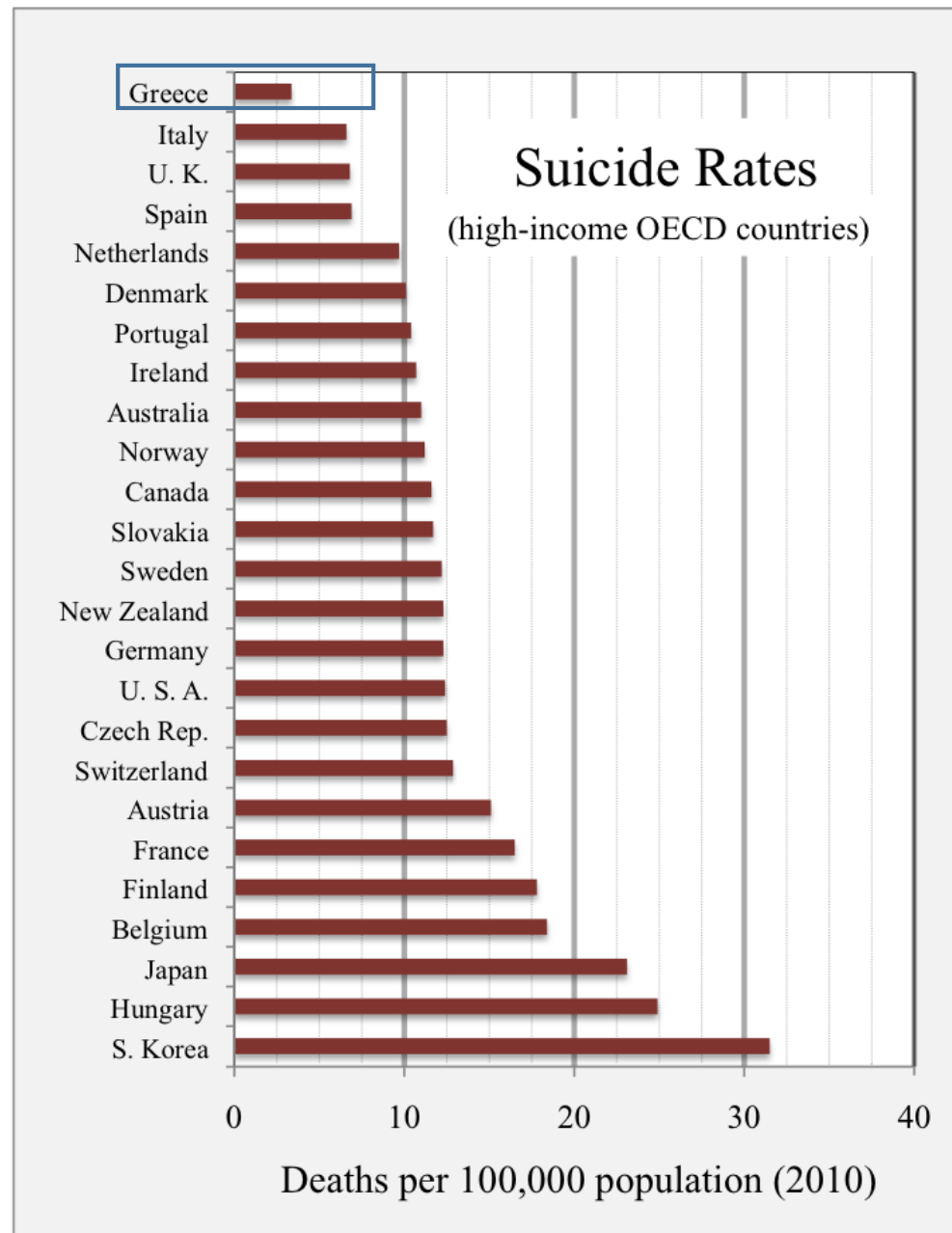
Environmental Vulnerabilities: community level

Estimated Suicide Rates by Country 2024



<https://worldpopulationreview.com/country-rankings/suicide-rate-by-country>

Gil Zalsman MD, Tel Aviv University



Only In Greek language

Siga Siga=slowly slowly

Volta = walking without purpose



- The mean suicide rate overall **rose by 35%** between 2010 and 2012, from 3.37 to 4.56/100 000 population.

Open Access

Research

BMJ Open What has happened to suicides during the Greek economic crisis? Findings from an ecological study of suicides and their determinants (2003–2012)

George Rachiotis,¹ David Stuckler,^{2,3} Martin McKee,^{3,4} Christos Hadjichristodoulou¹

WAR Effect?



JAMA Psychiatry | [Brief Report](#)

Suicidality Calls to a National Helpline After a Terror Attack and War

Joy Benatov, PhD; Liat Itzhaky, PhD; Shiri Daniels, PhD; Gil Zalsman, MD

IMPORTANCE Changes in suicide rates after a nationwide trauma may be different from changes in psychiatric symptoms or general distress after such events. However, very few studies have examined short-term suicide-related reactions after such an event.

OBJECTIVE To evaluate the short-term outcome of the events in Israel on October 7, 2023, a large-scale terror attack and unfolding war, on changes in suicidality as reflected in percentages of suicide-related calls in relation to all calls to a national mental health first aid helpline, the Israeli Association for Emotional First Aid (ERAN).

DESIGN, SETTING AND PARTICIPANTS The data included all interactions via the various ERAN helpline services between January 1, 2022, and December 31, 2023.

EXPOSURES The October 7, 2023, terror attack on Israel.

MEAN OUTCOMES AND MEASURES Changes in the numbers of overall calls and suicide-related calls to the ERAN helpline using an interrupted time-series analysis.

[+ Supplemental content](#)



Decrease in suicide related calls after an extreme national trauma

CONCLUSIONS AND RELEVANCE The findings of this cohort study suggest that although short-term emotional distress increased after national trauma, the percentage of suicide-related calls decreased. These results support previous studies suggesting that suicidality is not one of the immediate reactions to such traumas.

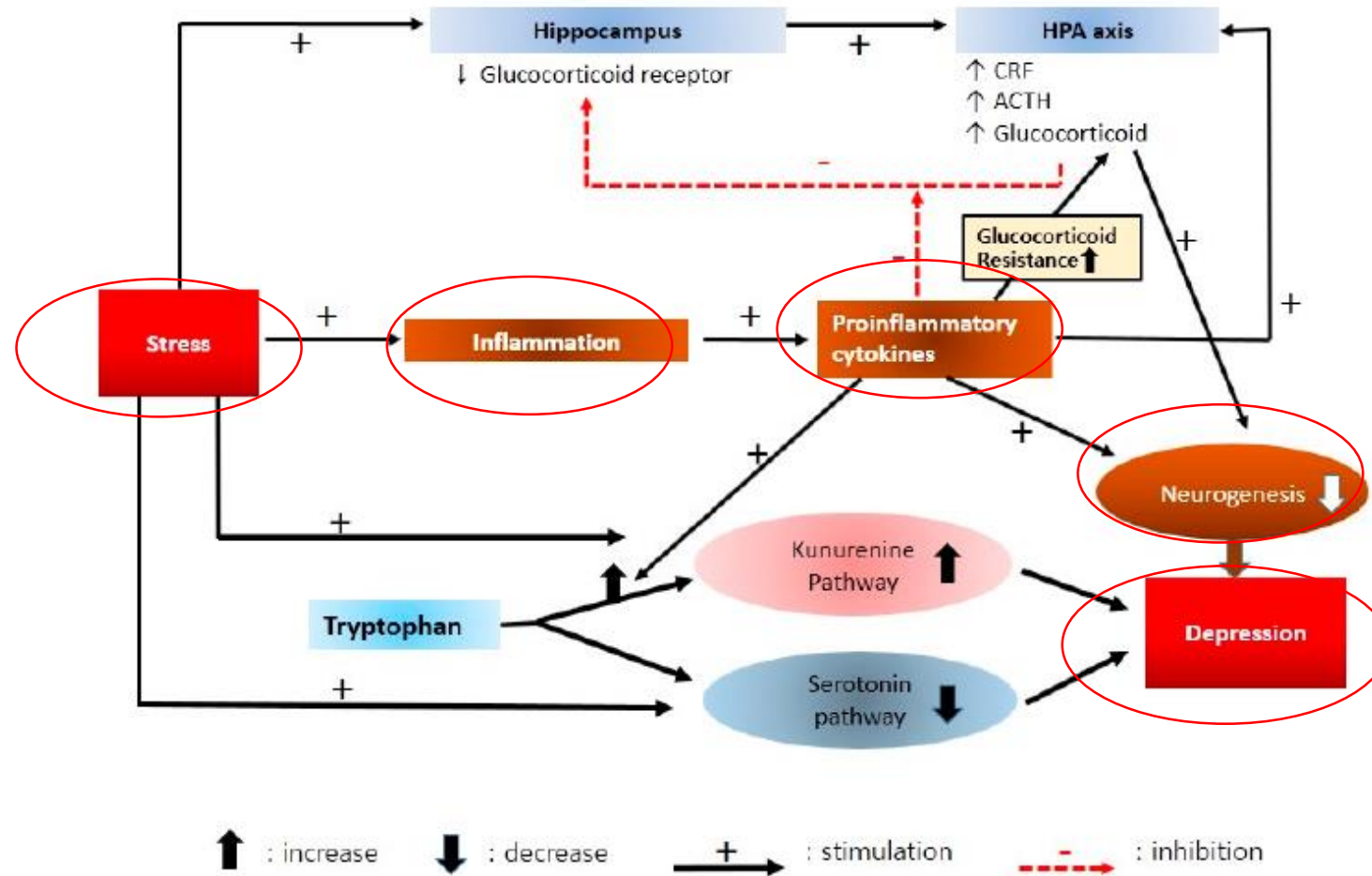
JAMA Psychiatry. ;():1-4. doi:10.1001/jamapsychiatry.2024.2034



National shared distress is not immediate risk factor

Environmental Vulnerabilities: ***Individual level***

Neuro-Inflammatory pathways in the etio-pathogenesis of depression



Molecular Neurobiology and Promising New Treatment in Depression.
Sang Won Jeon and Yong-Ku Kim. Int. J. Mol. Sci. 2016, 17, 381.

Neuro-Inflammatory pathways in the etio-pathogenesis of depression



Molecular Neurobiology and Promising New Treatment in Depression.
Sang Won Jeon and Yong-Ku Kim. Int. J. Mol. Sci. 2016, 17, 381.



www.elsevier.com/locate/euroneuro



REVIEW

Immune-related biomarkers and suicidal behaviors: A meta-analysis



Sudan Prasad Neupane^{a,1,*}, Federico M. Daray^{b,1},
Elizabeth D. Ballard^c, Hanga Galfalvy^d, Liat Itzhaky^{e,j},
Aviv Segev^f, Assaf Shelef^g, Oren Tene^h, Mina M. Rizk^{i,j},
J. John Mann^{k,l,m}, Gil Zalsman^{n,o}

**CRP and IL6
Markers for suicide**



The World Journal of Biological Psychiatry



Taylor & Francis
Taylor & Francis Group

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A pilot genome wide association and gene expression array study of suicide with and without major depression

Hanga Galfalvy, Gil Zalsman, Yung-Yu Huang, Lauren Murphy, Gorazd Rosoklija, Andrew J. Dwork, Fatima Haghighi, Victoria Arango & J. John Mann



Maybe the Immune Vulnerability is Inherited factor?

Galfalvy, Zalsman, Huang et al., WJBP, 2014

***Complex Vulnerability:
Gene X Environment
Interaction***

Association of a Triallelic Serotonin Transporter Gene Promoter Region (5-HTTLPR) Polymorphism With Stressful Life Events and Severity of Depression

Gil Zalsman, M.D.

Yung-yu Huang, M.S.

Maria A. Oquendo, M.D.

Ainsley K. Burke, Ph.D.

Xian-zhang Hu, M.D, Ph.D.

David A. Brent, M.D.

Steven P. Ellis, Ph.D.

David Goldman, M.D.

J. John Mann, M.D.

Objective: The lower expressing allele of the serotonin transporter gene 5' promoter region (5-HTTLPR) polymorphism is reported to be associated with susceptibility to depression and suicidality in response to stressful life events. The authors examined the relationship of a triallelic 5-HTTLPR polymorphism to stressful life events, severity of major depression, and suicidality.

Method: Mood disorder subjects (N=191) and healthy volunteers (N=125), all Caucasian subjects of European origin, were genotyped for the triallelic 5-HTTLPR polymorphism (higher expressing allele: L_A; lower expressing alleles: L_G, S). All subjects underwent structured clinical interviews to determine DSM-IV diagnoses,

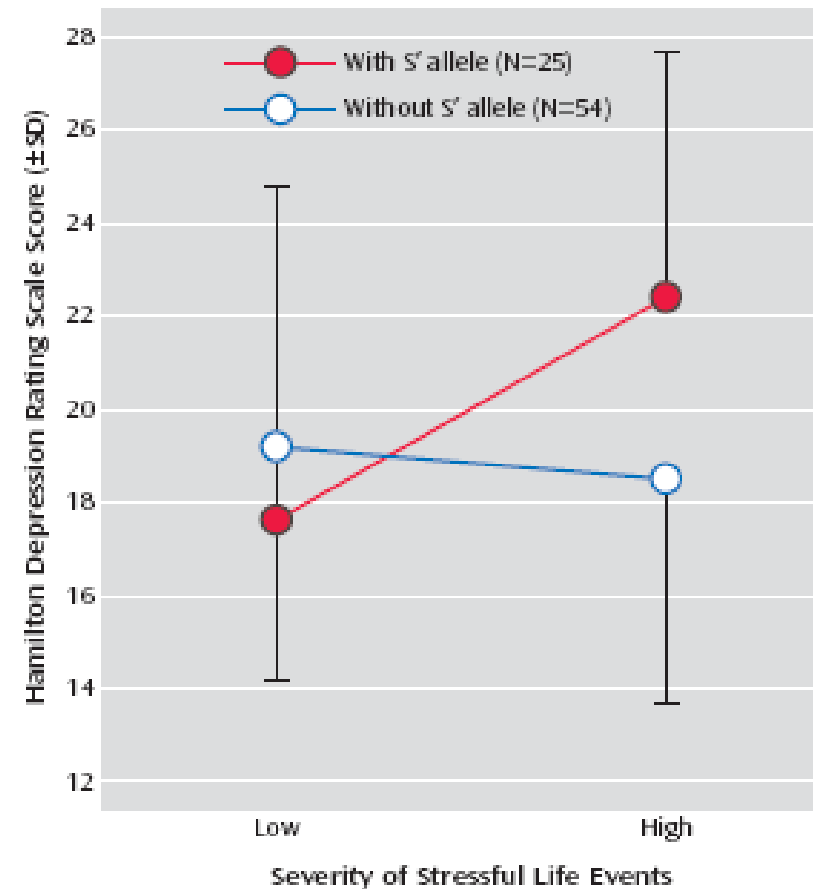
ratings of psychopathology, stressful life events, developmental history, and suicidal behavior. CSF 5-HIAA was assayed in a subgroup of subjects.

Results: Lower expressing alleles independently predicted greater depression severity and predicted greater severity of major depression with moderate to severe life events compared with the higher expressing L_A allele. No associations with suicidal behavior and CSF 5-HIAA were found.

Conclusions: Lower expressing transporter alleles, directly and by increasing the impact of stressful life events on severity, explain 31% of the variance in major depression severity. The biological phenotype responsible for these effects remains to be elucidated.

(Am J Psychiatry 2006; 163:1588–1593)

FIGURE 1. Relationship of Depression Severity and Stressful Life Events by 5-HTTLPR Genotype^a



^a Stressful life events score measured by St. Paul-Ramsey Scale (30, 31). High and low stressful life events were defined using a median split. The overall model was significant ($F=2.22$, $df=13, 78$, $p<0.02$), and independent effects were found for genotype ($F=4.71$, $df=2, 78$, $p<0.02$) and the interaction of genotype and St. Paul-Ramsey Scale score ($F=2.27$, $df=6, 78$, $p<0.05$).

***Complex Vulnerability:
G x E x Timing interaction***

Suggested Model: GxExT interaction

European Psychiatry 25 (2010) 284–286



Available online at
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www.sciencedirect.com

Elsevier Masson France

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Review

Timing is critical: Gene, environment and timing interactions in genetics of suicide in children and adolescents

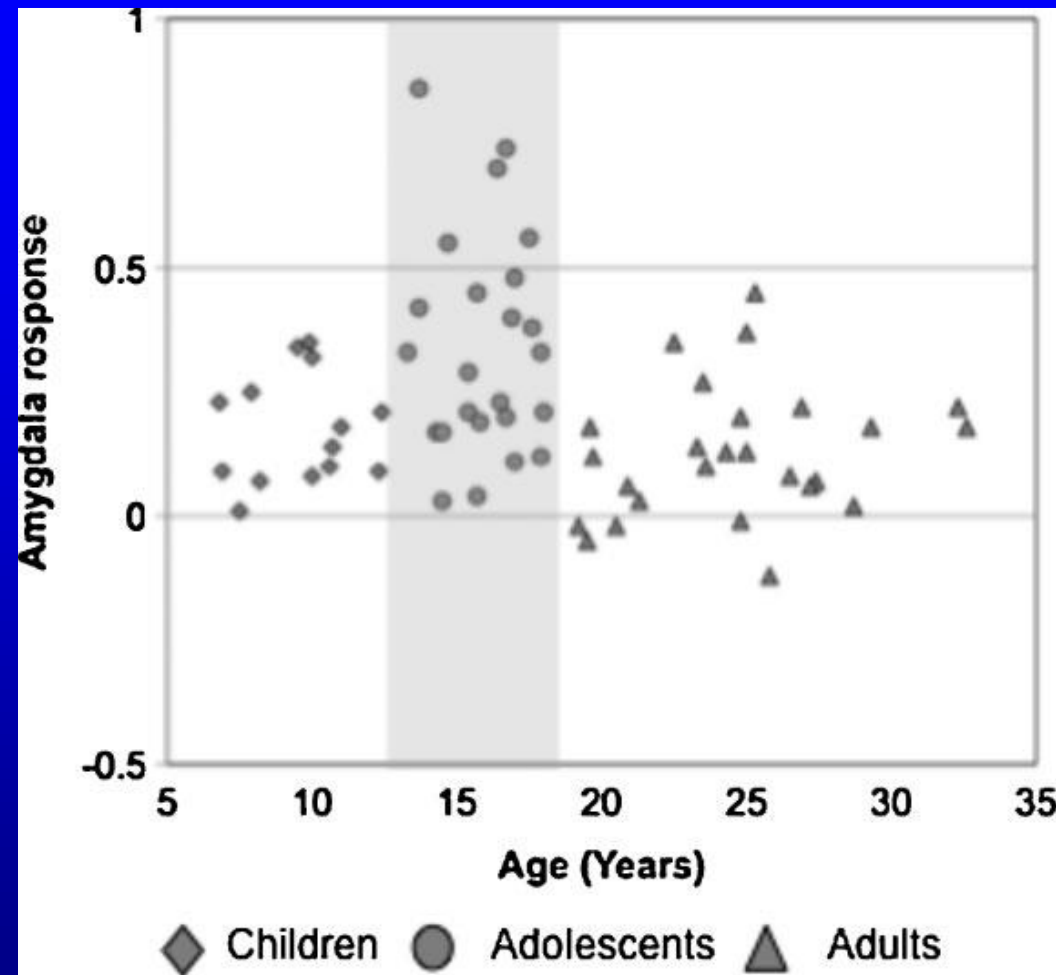
G. Zalsman^{a,*,b,c}

^a Child and Adolescent Psychiatry Division, Geha Mental Health Center, PO Box 102, 49100 Petach Tiqwa, Israel

^b Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^c Molecular Imaging and Neuropathology Division, Psychiatry Department, Columbia University, New York, USA

Amygdala response to fearful faces as a function of age.



Casey et al., Dev Psychobiol 52: 225–235, 2010.

Hare et al., Biological Psychiatry 63:927-934, 2008.



Genetic vulnerability, timing of short-term stress and mood regulation: A rodent diffusion tensor imaging study

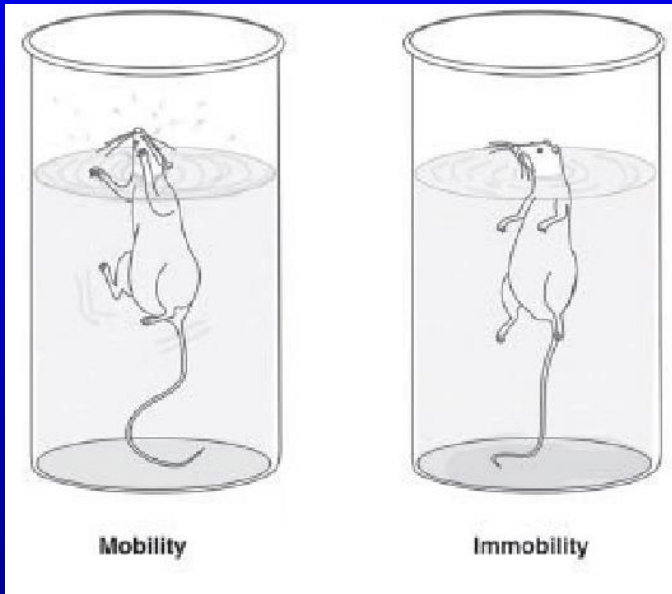


Gil Zalsman^{a,b,*}, Avihay Gutman^{c,d}, Liat Shbiro^d, Ruth Rosenan^d,
J. John Mann^b, Aron Weller^d

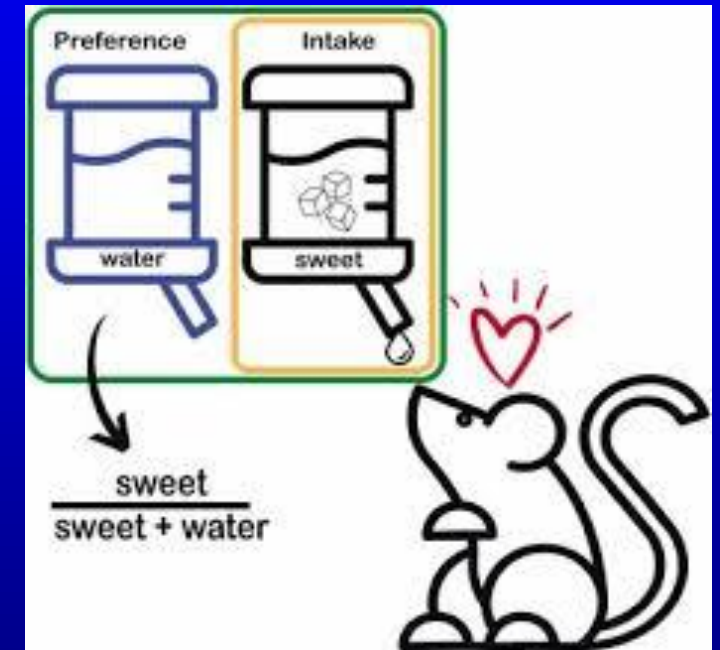
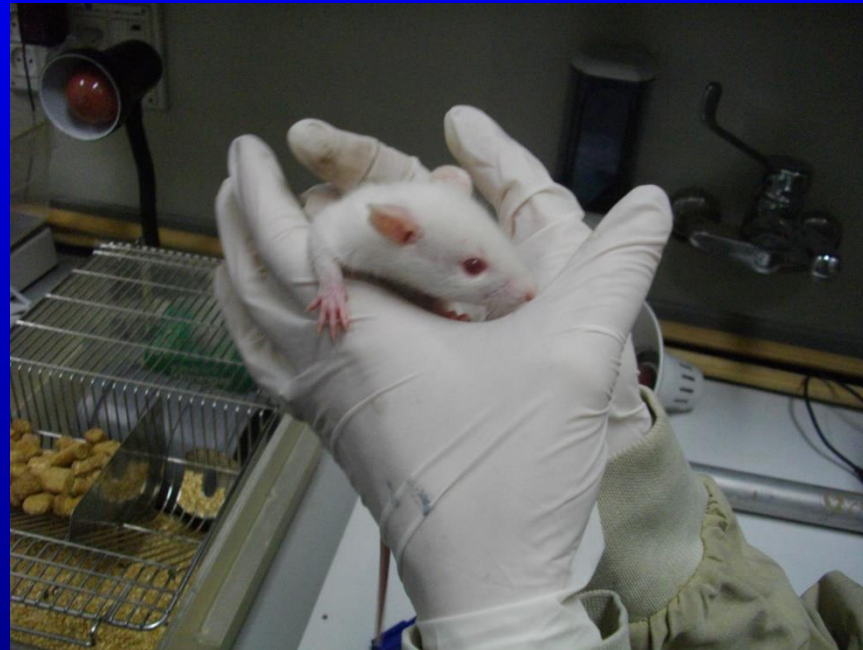
Zalsman et al., Eur Neuropsychopharmacology 2015

Wistar Kyoto Rat model

Despair, Anhedonia, Depression, Anxiety



Forced swim test
Despair



Sucrose preference test
Anhedonia

(Exposure to stress) at different developmental windows

G x **E** x **Gender** x **T**



T1 (27)



T2 (44)



WKY

T3 (58)



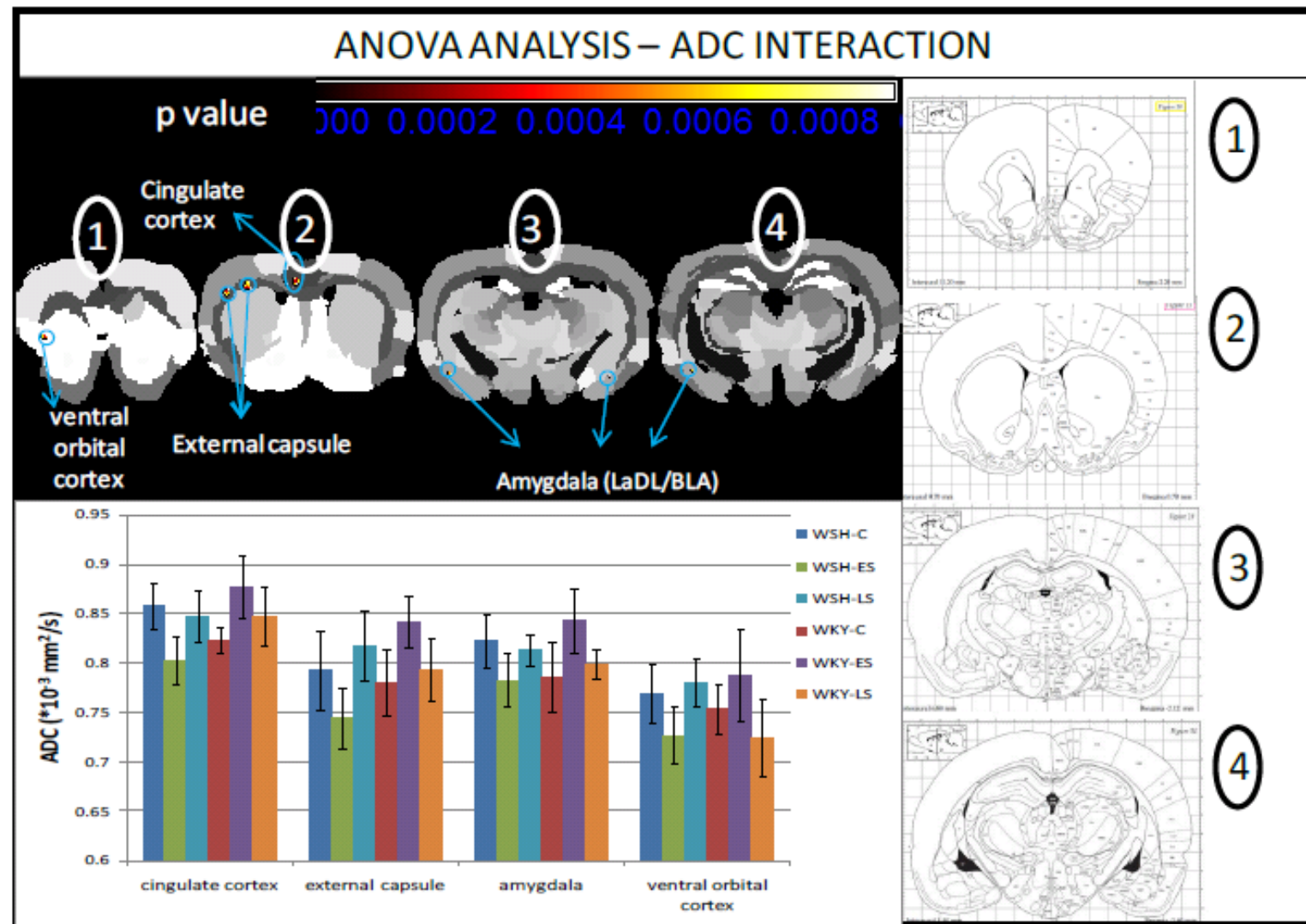
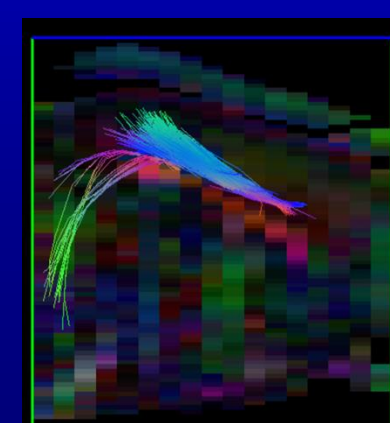
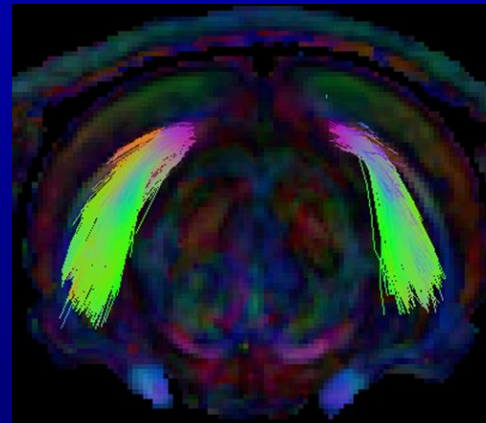
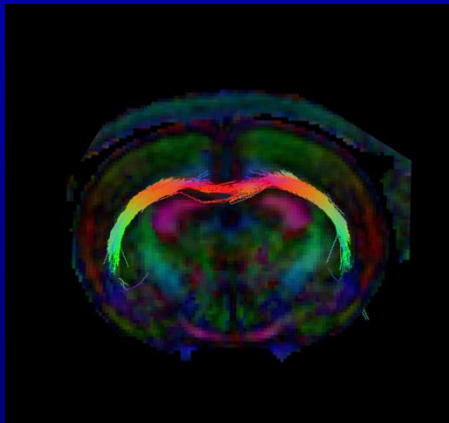


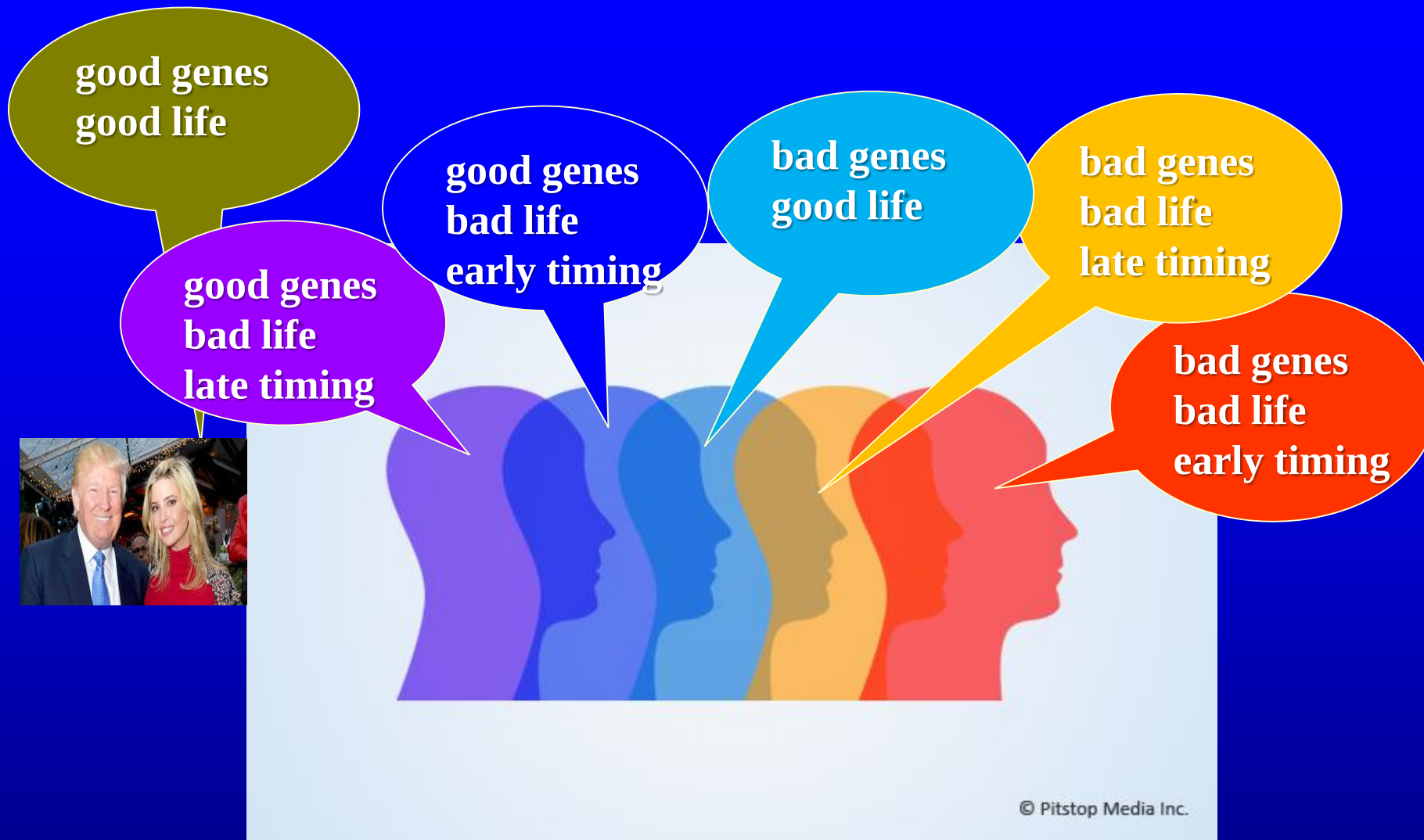
Figure 2: ADC interaction. The graph presents the 6 groups: wistar control- WSH-C (blue); wistar early stress – WSH-ES (green); wistar late stress – WSH-LS (cyan); WKY control – WKY-C (red); WKY early stress – WKY-ES (purple); WKY late stress – WKY-LS (orange). The significant clusters with the interaction marked on the atlas slices regions corresponding to paxinos & watson atlas.



Fibre tract analysis using diffusion tensor imaging reveals aberrant connectivity in a rat model of depression

Gil Zalsman, Aron Weller, Liat Shbiro, Ran Barzilay, Avihay Gutman, Abraham Weizman, J. John Mann, Jerzy Wasserman & Danuta Wasserman





best

OUTCOME

worse

GxExT interaction in depression

Epigenetics

may be the link between genetic vulnerability and environmental risk

Labonte 2013

Article

Genome-Wide Methylation Changes in the Brains of Suicide Completers

Benoit Labonté, M.Sc.

Matt Suderman, Ph.D.

Gilles Maussion, Ph.D.

Juan Pablo Lopez, B.Sc.

Luis Navarro-Sánchez, M.Sc.

Volodymyr Yerko, Ph.D.

Naguib Mechawar, Ph.D.

Moshe Szyf, Ph.D.

Michael J. Meaney, Ph.D.

Gustavo Turecki, M.D., Ph.D.

Objective: Gene expression changes have been reported in the brains of suicide completers. More recently, differences in promoter DNA methylation between suicide completers and comparison subjects in specific genes have been associated with these changes in gene expression patterns, implicating DNA methylation alterations as a plausible component of the pathophysiology of suicide. The authors used a genome-wide approach to investigate the extent of DNA methylation alterations in the brains of suicide completers.

Method: Promoter DNA methylation was profiled using methylated DNA immunoprecipitation (MeDIP) followed by microarray hybridization in hippocampal tissue from 62 men (46 suicide completers and 16 comparison subjects). The correlation between promoter methylation and expression was investigated by comparing the MeDIP data with gene expression profiles generated through mRNA microarray. Methylation differences between groups were validated on neuronal and

nonneuronal DNA fractions isolated by fluorescence-assisted cell sorting.

Results: The authors identified 366 promoters that were differentially methylated in suicide completers relative to comparison subjects (273 hypermethylated and 93 hypomethylated). Overall, promoter methylation differences were inversely correlated with gene expression differences. Functional annotation analyses revealed an enrichment of differential methylation in the promoters of genes involved, among other functions, in cognitive processes. Validation was performed on the top genes from this category, and these differences were found to occur mainly in the neuronal cell fraction.

Conclusions: These results suggest broad reprogramming of promoter DNA methylation patterns in the hippocampus of suicide completers. This may help explain gene expression alterations associated with suicide and possibly behavioral changes increasing suicide risk.

(Am J Psychiatry 2013; 170:511–520)

***Studying a Genetic Isolate to
clarify G and E relationships***

Tracing the GxE interaction

Indigenous Māori population as a suicidal **genetic isolate**

A **genetic isolate** is a population that has little genetic mixing with other populations due to geographic isolation





PARLIAMENTARY SERVICE

Tē Ratonga Whare Pāremata

suicide trends in NZ

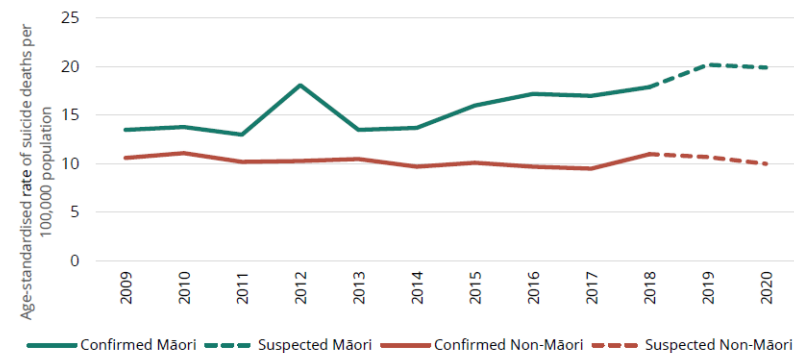
The non-Māori confirmed rate increased from 10.6 in 2009 to 11.1 in 2010 and fell to 11.0 in 2018. The suspected rate decreased from 10.7 in 2019 to 10.0 in 2020. See Table 3 and Graph 3.¹¹

Table 3: Rates of confirmed and suspected suicide deaths for Māori and non-Māori per 100,000 population, year ending 30 June 2009 to 2018 and 2021*

Data status	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Suicide Rates													
Māori	13.5	13.8	13	18.1	13.5	13.7	16.0	17.2	17.0	17.9	20.2	19.9	-
Non-Māori	10.6	11.1	10.2	10.3	10.5	9.7	10.1	9.7	9.5	11.0	10.7	10.0	-
Suicide Deaths													
Māori	90	93	92	130	99	99	117	128	129	138	163	160	129
Non-Māori	414	431	405	402	418	410	426	419	423	505	474	468	478

* 2019 to 2021 figures are for suspected rates and deaths. As Māori population estimates from 2020 onward are unavailable, 2021 rates have not been calculated.

Graph 3: Rates of confirmed and suspected suicide deaths for Māori and non-Māori per 100,000 population, year ending 30 June 2009 to 2021



Interviews with Maori Adolescents in wellness village



- **Children of Single mothers**
- **Multiple children each form a different man**
- **Unemployment**
- **Feeling of ethnic racism and discrimination**
- **Met-amphetamine use in adolescence**

Not a genetic isolate,
not even one ethnic group...
BUT
Discriminated, victimized society



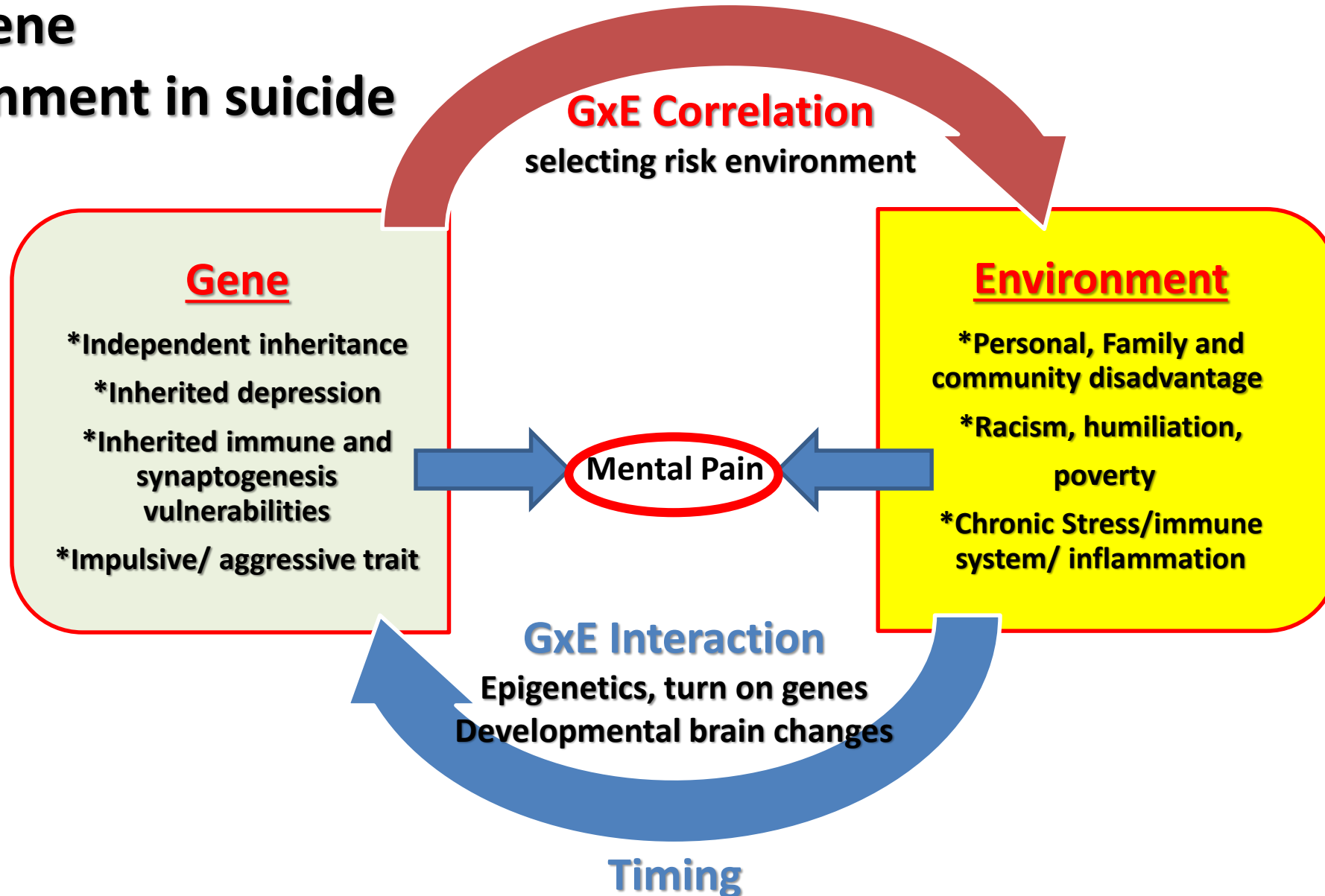
***The case of the Maori suicide:
Gene X Environment
Correlation?***

G x E correlation (r_{GE})

The process by which an individual's genotype influences his or her **exposure to the environment**

(Kendler & Eaves, 1986, Plomin, et al., 1977)

The Complex relationship between gene and environment in suicide



המורה שלי לחיות מעבדה



פרופ' אהרון וולר
המחלקה לפסיכולוגיה
אוניברסיטת בר אילן

Collaboration not Competition

Gili Adar Institute for Learning and Intervention in Adolescence Mental Health Crisis and Suicide

Lab Team:



Gil Zalsman MD
Lab Leader



Reut Hazani
PhD



Michal Har Sinay
MA



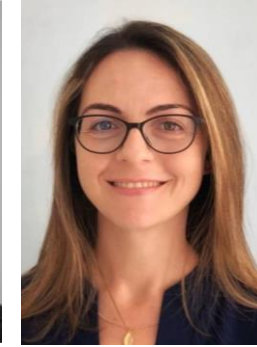
Sabrina Blum
MD



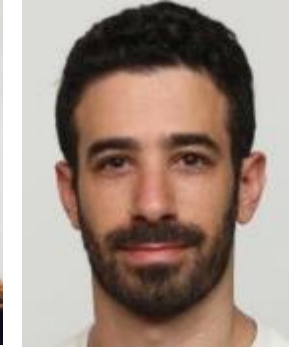
Ella Sarel Mahlev
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Liat Itzhaky
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Joy Benatov
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Uriel Katz
MD

Genetic and Epidemiology Consultants:



Shay Ben Shachar
PhD



Avi Weizman
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John Mann MD

Associate Investigators (alphabetical order):

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- Batya G. Jaffe PhD
- Chmutal Saragusty PhD
- Elena Chubarov PhD
- Maly Solan PhD
- Momi Zisquit MA
- Miri Carmel PhD
- Nir Madjar PhD
- Nizan Teper MD
- Ortal Shinikamin MD
- Sahar Yihia MD
- Tomer Elyahoo MD

גילי אדר

צעירה ערכית, רכזת ההדרכה בצופים, יצאה 3 פעמים להדריך במחנות הקיץ בחו"ל

בתיכון קיבלה את פרס שכטר על התנדבות יוצאת דופן למען הקהילה

בצבא נבחרה לחיילת מצטיינת ביום העצמאות ה 73

שילוב יוצא דופן של שמחת חיים גדולה, כישורי מנהיגות מפותחים, ביחד עם "אישיות טיפולית" הפכו אותה לדמות אהובה ונערצת



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Gili Adar Institute for Learning and Intervention in Adolescence Mental Health Crisis and Suicide

For my slides

www.gilzalsman.org

See you in Tel Aviv 2028, for ESSSB 22 congress on suicide

