GXEXT in Mood Disorders and Suicide

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COLUMBIA UNIVERSITY
College of Physicians and Surgeons

ECNP
european college of neuropsychopharmacology

Geha
Mental Health Center
Affiliated with the Sackler School of Medicine Tel Aviv University

IASR
International Academy of Suicide Research

A birth of an hypothesis

- Depression runs in families
- GxE interaction seems logical but failed replication
- New data on brain development appeared
- A new hypothesis needed a proof
- Animal model proved GxExT interaction

Facts about pediatric depression

- Depression is common
- Depression runs in families
- Depression is different before & after puberty

1. Prevalence
2. Gender ratio
3. Treatment efficacy

Depression in Children & Adolescents

Early Childhood:

- looks sad
- tearful
- slow movements or **irritability**
- monotone voice
- hopeless
- self in negative terms
- school problems
- **somatization!!**

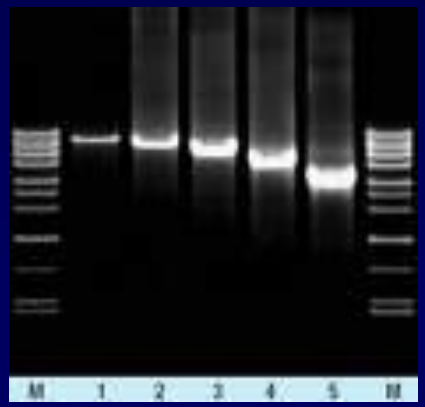
Late childhood and adolescents:

- low self esteem
- apathy
- irritability
- **anxiety**
- low concentration
- **suicide attempts**

Suicidal Behavior Runs in Families

Direct main effect approach

- TPH1
- SERT
- COMT
- MAO
- 5HT's
- DR
- NET
- BDNF
- Wolfram (WFS1)
- Etc……
- TPH2….



→ Equivocal results

→ MZ>DZ but far from 100%

Familial Transmission and Gene-Environment Interaction

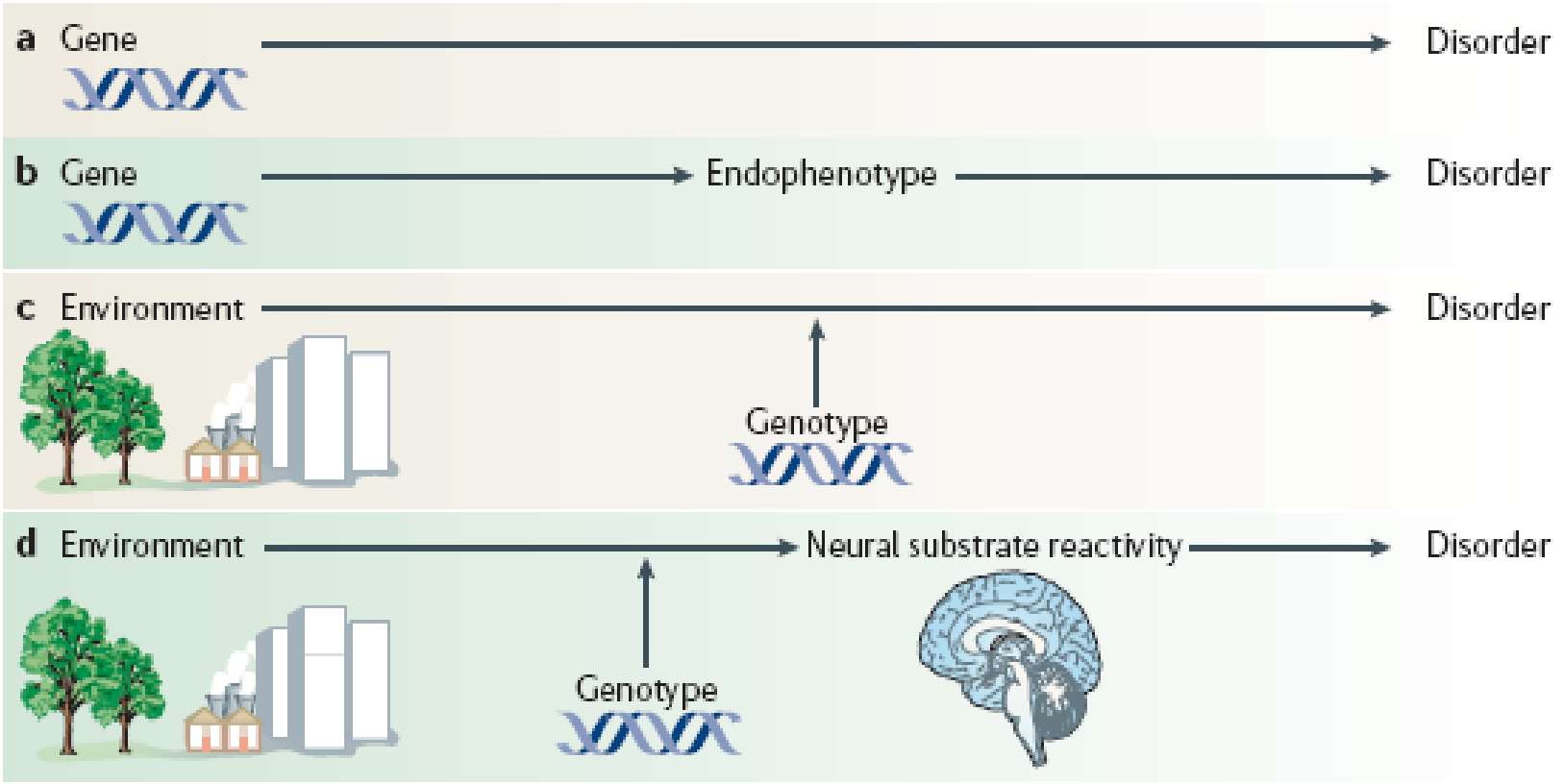


Figure 1 | **Approaches to psychiatric genetics research.** **a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder. **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. **c** | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. **d** | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.

Caspi and Moffitt, Nature Reviews Neuroscience, July 2006, with permission

- G X E Interaction

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

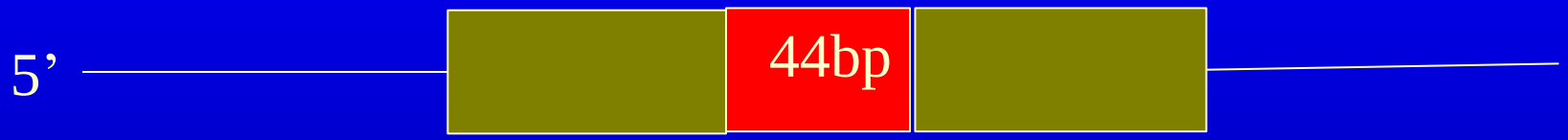
Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2*] Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2] Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3] Antony Braithwaite,[4] Richie Poulton[3]

In a prospective-longitudinal study of a representative birth cohort, we tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

Caspi et al., Science 2003

5-HTT-LPR- serotonin transporter linked polymorphism region

promoter

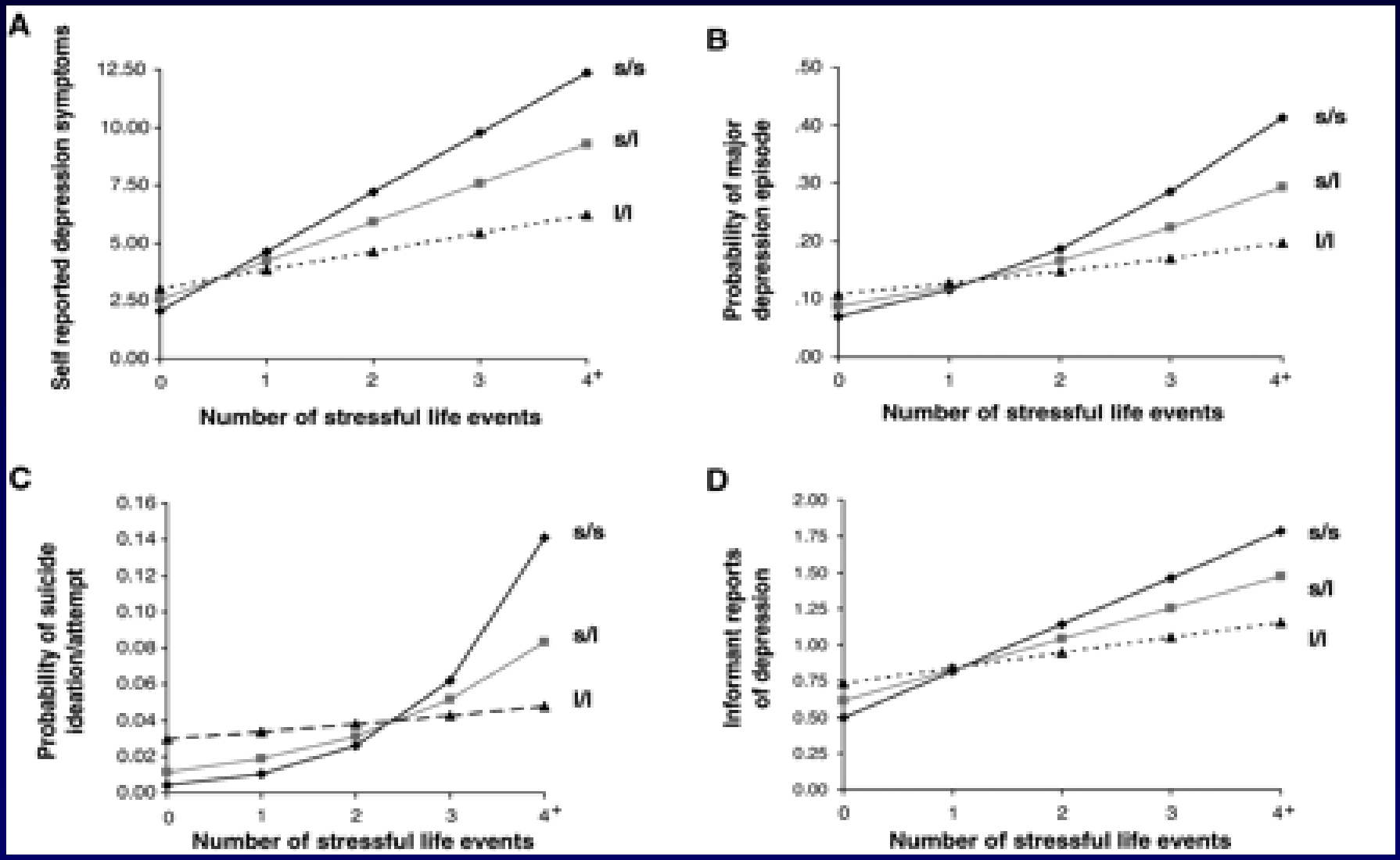


A functional polymorphism consists of two common alleles, a short (S) and long (L) variants, differing by 44 bp

S<<L

Lesch et al. 1994, Heils et al. 1996

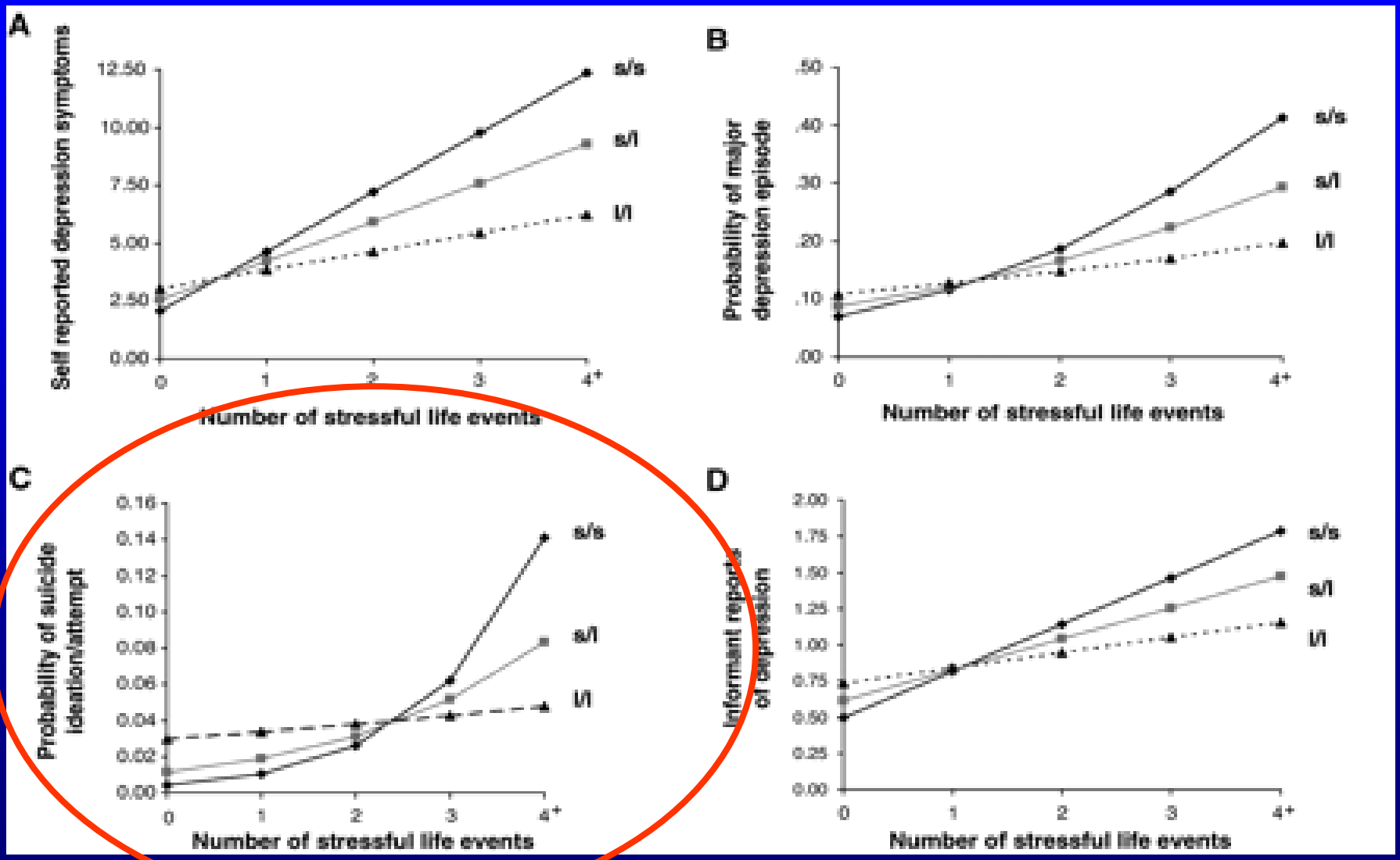
5HTTLPR
Gene X Environment Interaction
Caspi et al. 2003



Caspi et al. Science, 2003

5HTTLPR
Gene X Environment Interaction
Caspi et al. 2003

*counted SLE

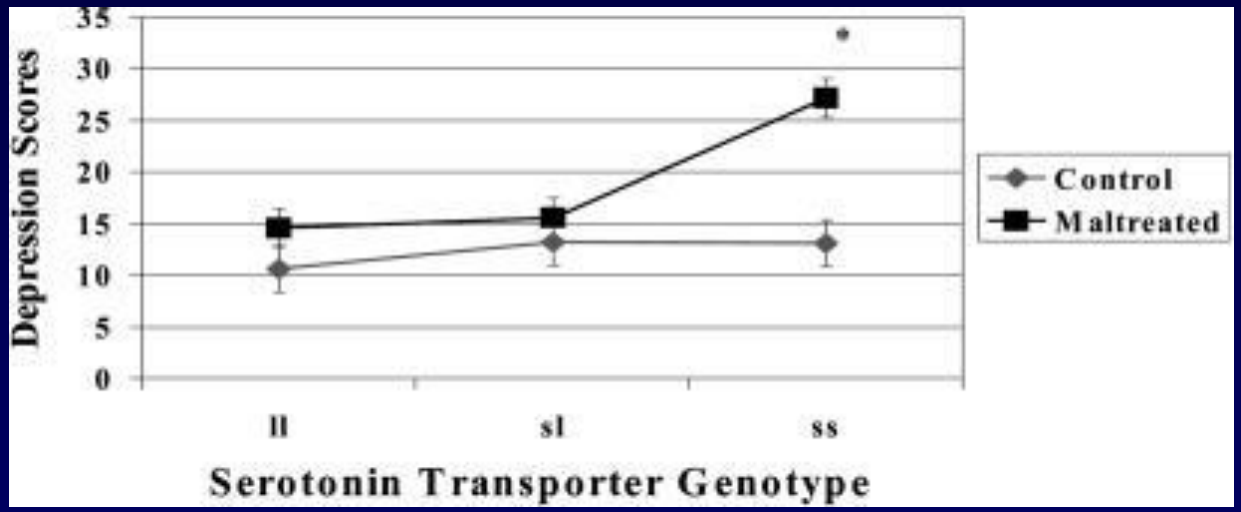


Caspi et al. Science, 2003

Social supports and serotonin transporter gene moderate depression in maltreated children.

Kaufman J et al. **Proc Natl Acad Sci USA 2004; 101:17316-17321**

(N=101)



Maltreated children (57 age 10-15; were removed from their parents' care) with the s/s genotype and no positive supports had the highest depression ratings.

Positive supports reduced risk.

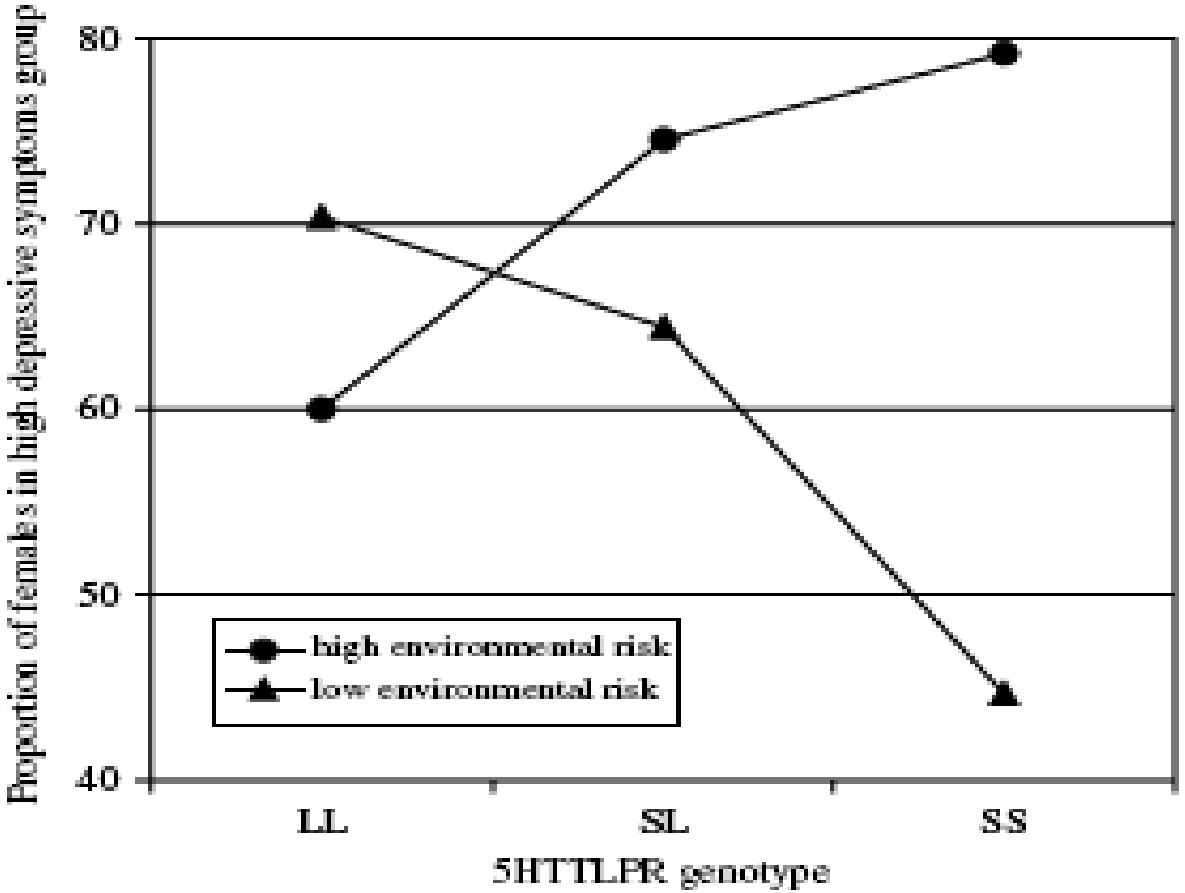


Figure 1 Proportion of female subjects with a high level of depression by environmental risk group and genotype.

♀

N=1990, age 10-20

Eley et al., Mol Psychiatry 2004

Article

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.

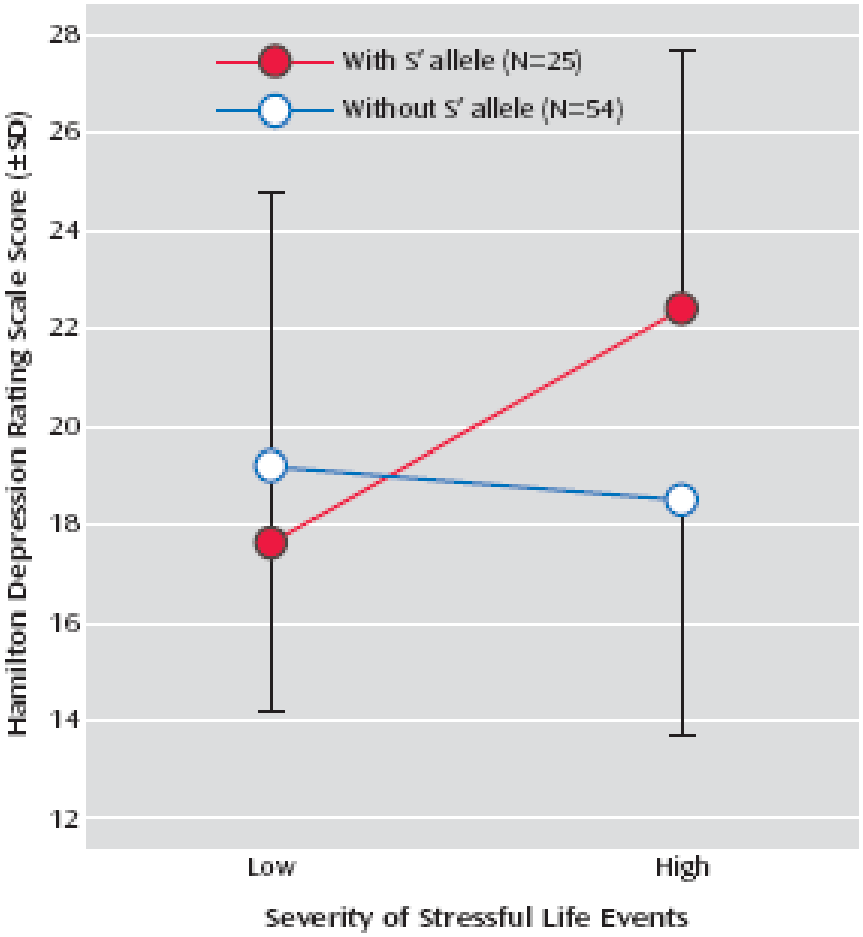
Method: Mood disorder subjects (N=191) and healthy volunteers (N=125), all Caucasian subjects of European origin, were genotyped for the triallelic 5-HTTLPR polymorphism (higher expressing allele: L_A; lower expressing alleles: L_G, S). All subjects underwent structured clinical interviews to determine 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 ($F=2.27$, $df=6, 78$, $p<0.05$).

***Zalsman et al. Am J Psychiatry* 2006, 163:1588-1593**

OOPS!!!!

- Risch N et al. JAMA, 2009;302:492

Meta-analysis of 14 studies found no significant association (OR=1.05)

Karg et al. 2011

META-ANALYSIS

ONLINE FIRST

The Serotonin Transporter Promoter Variant (5-HTTLPR), Stress, and Depression Meta-analysis Revisited

Evidence of Genetic Moderation

Katja Karg, BSc; Margit Burmeister, PhD; Kerby Shedden, PhD; Srijan Sen, MD, PhD

Arch Gen Psychiatry.
Published online January 3, 2011.

Data Synthesis: We included 54 studies and found strong evidence that 5-HTTLPR moderates the relationship between stress and depression, with the 5-HTTLPR *s* allele associated with an increased risk of developing depression under stress ($P = .00002$). When stratifying our analysis by the type of stressor studied, we found strong evidence for an association between the *s* allele and increased stress sensitivity in the childhood maltreatment ($P = .00007$) and the specific medical condition ($P = .0004$) groups of studies but only marginal evidence for an association in the stressful life events group ($P = .03$). When restricting our analysis to the studies included in the previous meta-analyses, we found no evidence of association (Munafò et al studies, $P = .16$; Risch et al studies, $P = .11$). This suggests that the difference in results between meta-analyses was due to the different set of included studies rather than the meta-analytic technique.

One sleepless night hypothesis

- G X E X T Interaction

European Psychiatry 25 (2010) 284–286

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www.sciencedirect.com

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EM|consulte
www.em-consulte.com

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 Devision, Psychitry Department, Columbia University, New York, USA*

Zalsman G., Eur Psychiatry, 2010

Normal Brain Development

243 Scans from 145 healthy children

1. **Giedd JN, et al., Child psychiatry branch of the NIMH longitudinal structural MRI study of human brain development. Neuropsychopharmacology. 2015**

2. **Giedd JN. The amazing teen brain. Sci Am. 2015**

- The brain is developing until age 22-23y.

Giedd JN. The amazing teen brain. Sci Am. 2015 312(6):32-7.

- SLE “meets” a different brain in every time point of development

Are brains of children and adolescents different?

Gray Matter

Brain Development in Healthy Children & Adolescents

Longitudinal and Cross-Sectional Data
(243 Scans from 145 Subjects)

Frontal Gray Matter

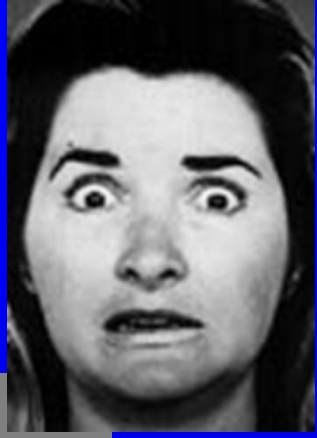
Giedd JN. The amazing teen brain. Sci Am. 2015 312(6):32-7.

From Jay Giedd, NIMH with permission

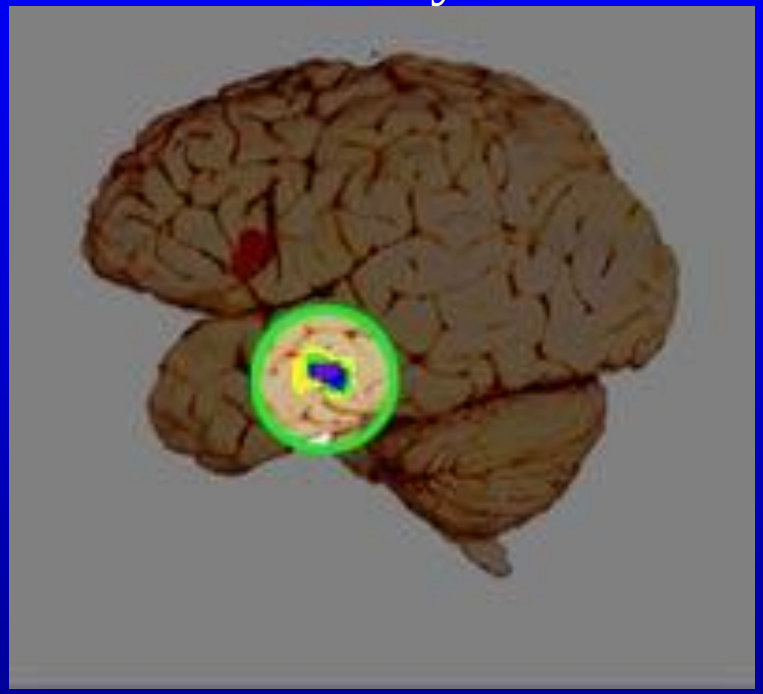
Pruning

The process of removing certain above-ground elements from a plant; in landscaping this process usually involves removal of diseased, non-productive, or otherwise unwanted portions from a plant

Reading Emotions Differently



12y

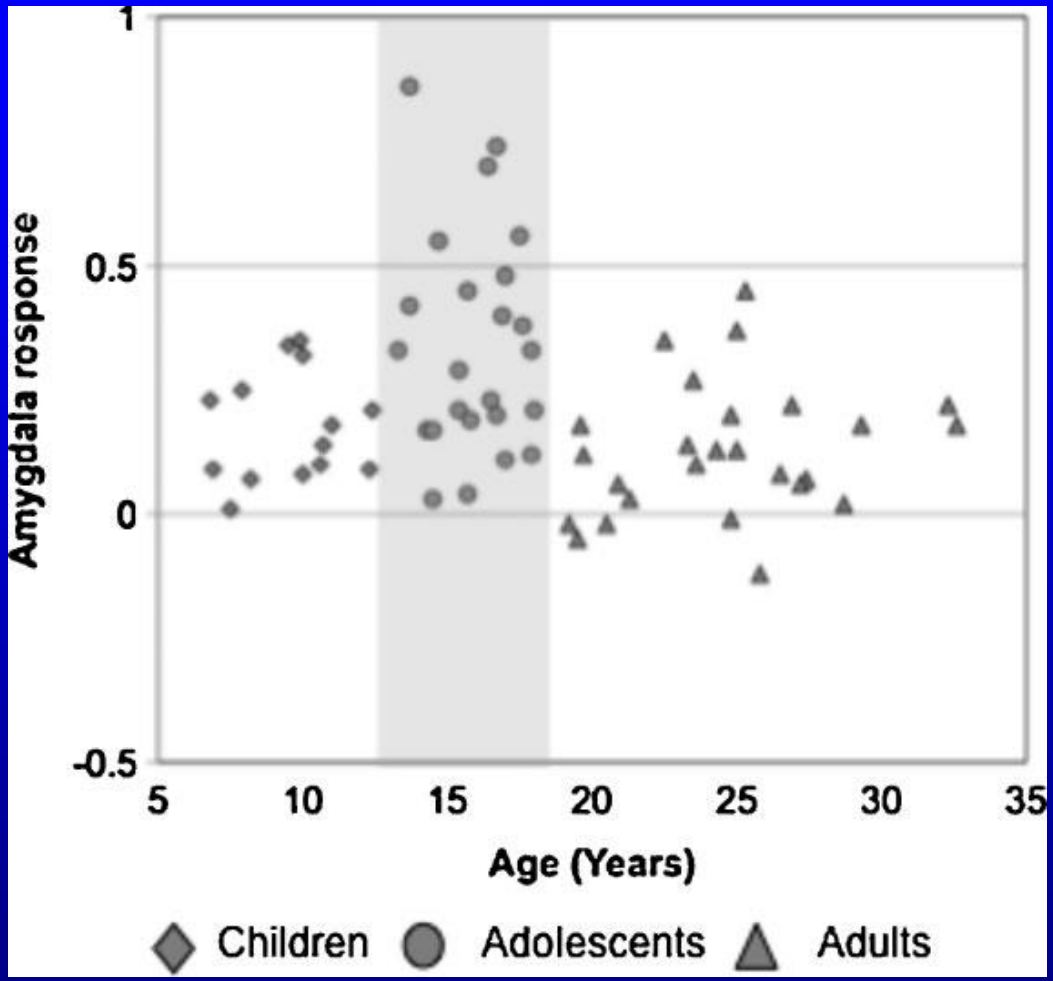


22y

When reading emotion, teens **(left)** rely more on the amygdala, while adults **(right)** rely more on the frontal cortex.

Deborah Yurgelon-Todd, 2000

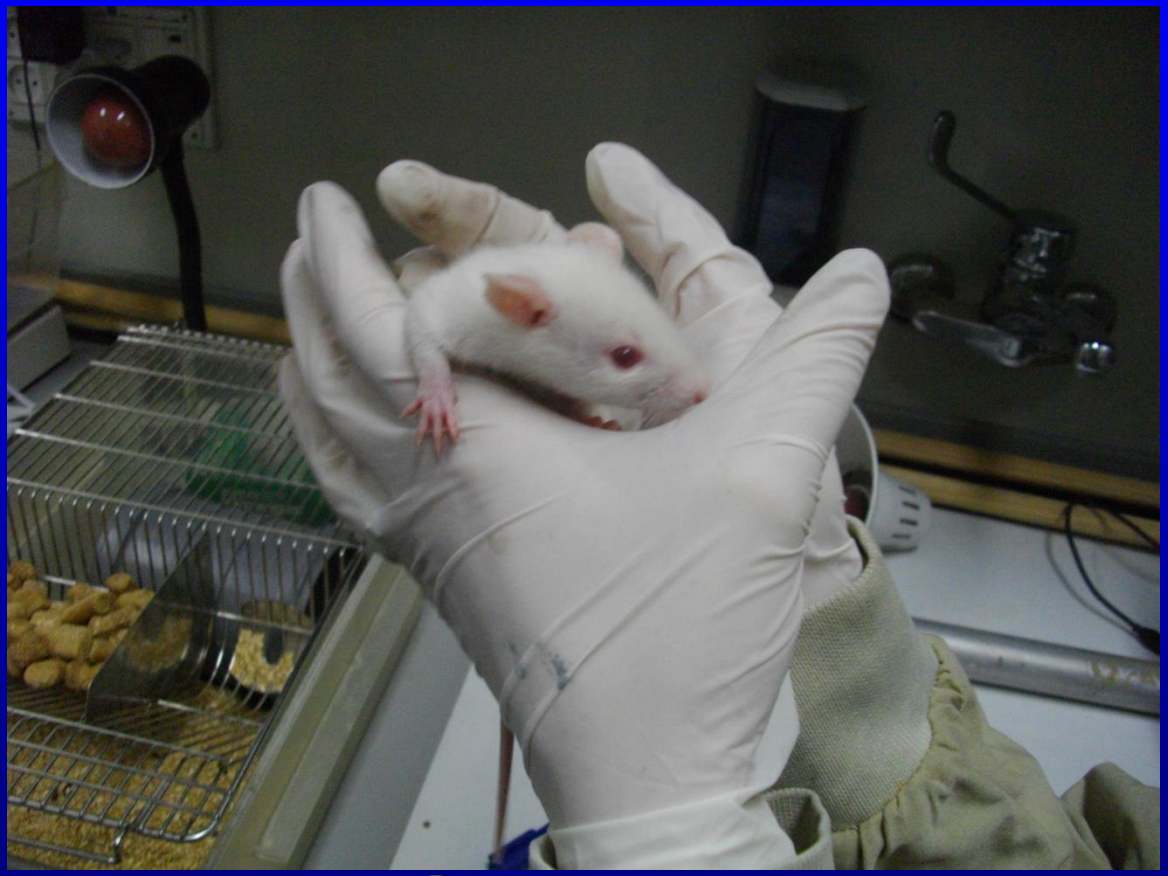
Amygdala response to fearful faces as a function of age.



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

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

WKY Rat
Animal model for depression, despair and anhedonia



GxExT

European Neuropsychopharmacology (2015) 25, 2075-2085

ELSEVIER

www.elsevier.com/locate/euroneuro

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 Neoropsychopharmacology 2015

(Exposure to stress) at different developmental windows

G x E x Gender x T

T1 (27)

T2 (44)

T3 (58)

♂

WKY

Rats MRI

Tel Aviv University MRI

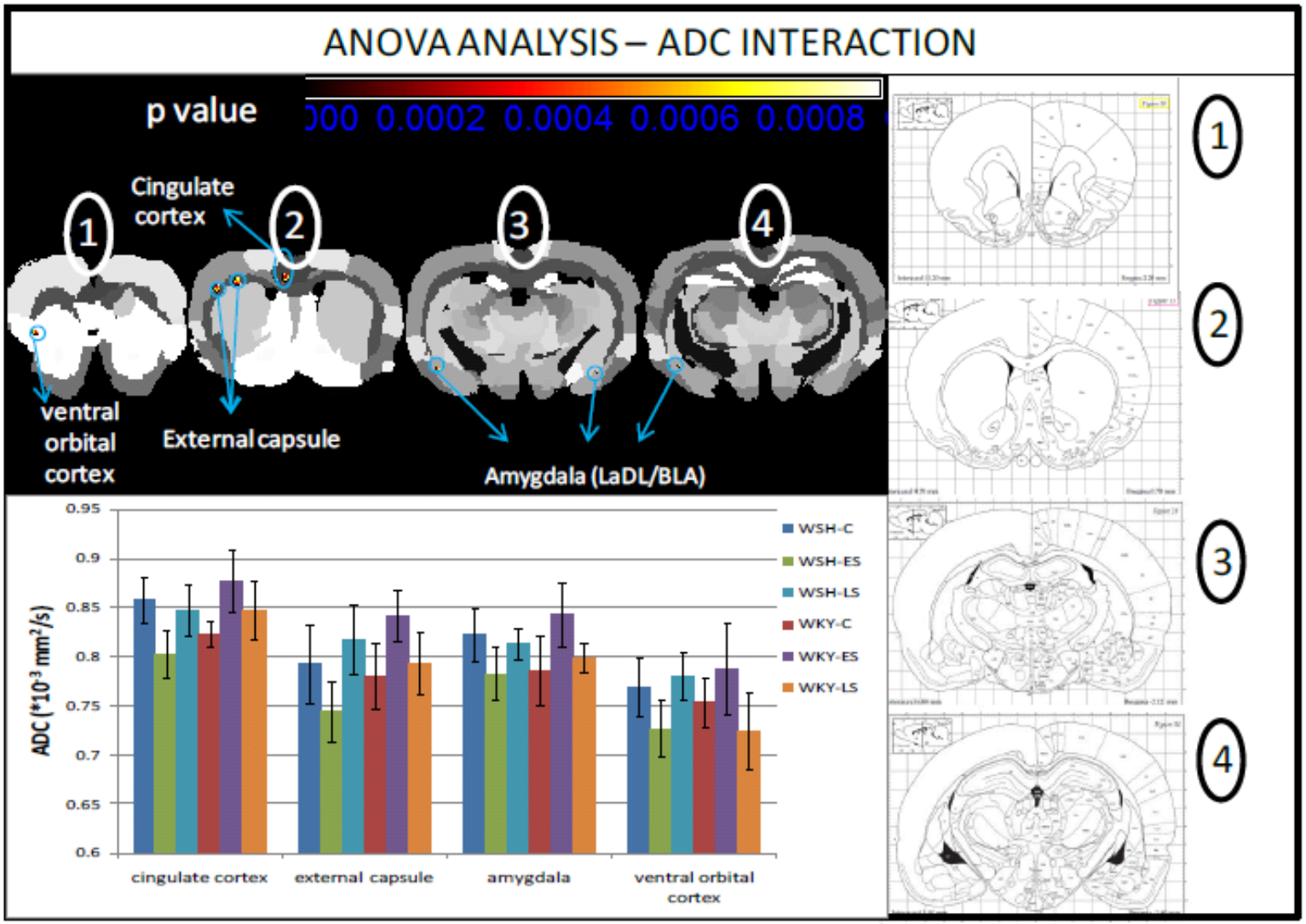


Figure 2: ADC interaction. The graph presents the 6 groups: wistar control- WSH-C (blue); wistar early stress – WSH-ES (green); wistar late stress – WSH-LS (cyan); WKY control – WKY-C (red); WKY early stress – WKY-ES (purple); WKY late stress – WKY-LS (orange). The significant clusters with the interaction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

good genes
good life

good genes
bad life
late timing

good genes
bad life
early timing

bad genes
good life

bad genes
bad life
late timing

bad genes
bad life
early timing

best OUTCOME worse

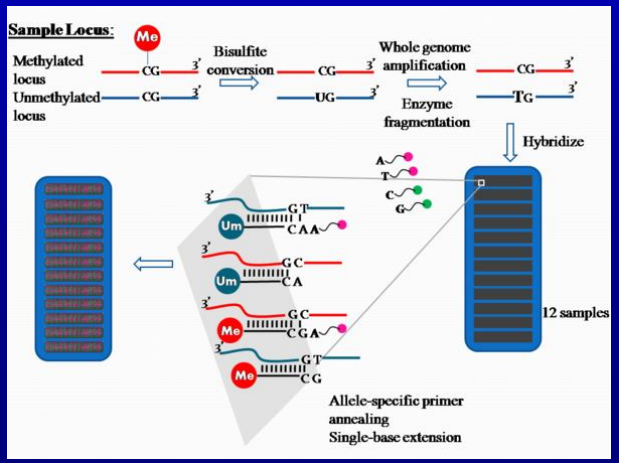
GxExT interaction in depression

Epigenetics may be the link between G and E

Epigenetics

- Changes in DNA that change gene expression. These changes can be permanent (cell type) or temporary (developmental window , environmental ques)
- Types:

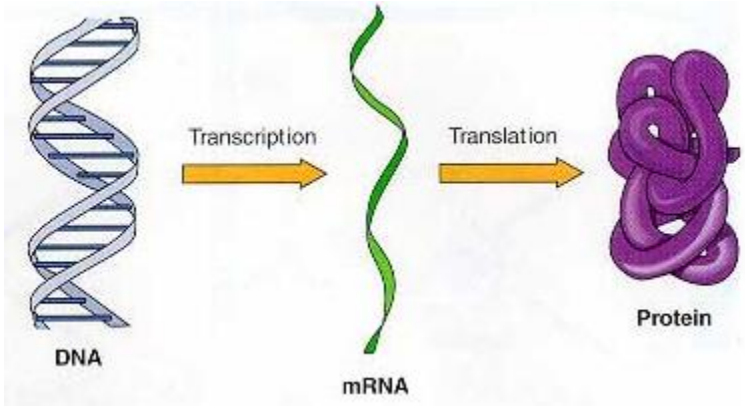
1. Methylation
2. Histones modification
3. Non coding RNAs=MiRNA



From: Yaron Goren with permission

Geha Mental Health Center
Affiliated with the Sackler School of Medicine Tel Aviv University

Future Direction: Micro RNA as a biomarker



Short RNA fragment that prevents the production of a particular protein by binding to and destroying the messenger RNA that would have produced the protein.

MicroRNA 135 Is Essential for Chronic Stress Resiliency, Antidepressant Efficacy, and Intact Serotonergic Activity

Orna Issler,[1,2] Sharon Haramati,[1] Evan D. Paul,[3] Hiroshi Maeno,[4] Inbal Navon,[1] Rayya Zwang,[1] Shosh Gil,[1] Helen S. Mayberg,[5] Boadie W. Dunlop,[5] Andreas Menke,[6] Rajeshwar Awatramani,[7] Elisabeth B. Binder,[5,8] Evan S. Deneris,[4] Christopher A. Lowry,[3] and Alon Chen[1,2,*]

MiR-16 Targets the Serotonin Transporter: A New Facet for Adaptive Responses to Antidepressants

Anne Baudry,[1] Sophie Mouillet-Richard,[1] Benoît Schneider,[1] Jean-Marie Launay,[2,3*] Odile Kellermann[1*]

Research paper

MiR-335 is involved in major depression disorder and antidepressant treatment through targeting GRM4

Jing Li, Huaqing Meng, Wan Cao, Tian Qiu

microRNA as Repressors of Stress-Induced Anxiety: The Case of Amygdalar miR-34

Sharon Haramati,[1] Inbal Navon,[1] Orna Issler,[1] Gili Ezra-Nevo,[1] Shosh Gil,[1] Raaya Zwang,[1] Eran Hornstein,[2] and Alon Chen[1]

Departments of [1]Neurobiology and [2]Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel

Nat Med. 2014 July ; 20(7): 764–768. doi:10.1038/nm.3582.

miR-1202: A Primate Specific and Brain Enriched miRNA Involved in Major Depression and Antidepressant Treatment

Juan Pablo Lopez[1], Raymond Lim[3], Cristiana Cruceanu[1], Liam Crapper[1], Caroline Fasano[2], Benoit Labonte[1], Gilles Maussion[1], Jennie P Yang[1], Volodymyr Yerko[1], Erika Vigneault[2], Salah El Mestikawy[2], Naguib Mechawar[1], Paul Pavlidis[3], and Gustavo Turecki[1]

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)

Gross 2013

Journal of Psychiatric Research 47 (2013) 513–519

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Effects of promoter methylation on increased expression of polyamine biosynthetic genes in suicide

Jeffrey A. Gross, Laura M. Fiori, Benoit Labonté, Juan Pablo Lopez, Gustavo Turecki*

McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, 6875 boul. Lasalle, Verdun, Quebec H4H 1R3, Canada

A birth of an hypothesis

- Depression runs in families
- GxE interaction seems logical but failed replication
- New data on brain development appeared
- A new hypothesis needed a proof
- Animal model proved GxExT interaction

Collaborators - genetic studies

Lab personnel

- Aron Weller
- Liat Shbiro
- Avihai Gutman
- Ruth Rosnan

Columbia University

- J John Mann
- Maria Oquendo
- Young-yu Huang

Tel Aviv University

- Abraham Weizman
- Alan Apter

Karolinska Institute

- Danuta Wasserman

AFSP young investigator grant-2005-2007 (Zalsman)
PHS grants MH62185 and MH48514 (J.J. Mann)
The National Institute for Psychobiology in Israel Grants 29/98, 9b/99 (Zalsman)

End of Part 1

Neurobiology Of Suicide

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WI 260521

IASR International Academy of Suicide Research

Expert Platform on Mental Health
Focus on Depression

ECNP european college of neuropsychopharmacology

Geha Mental Health Center
Affiliated with the Sackler School of Medicine Tel Aviv University

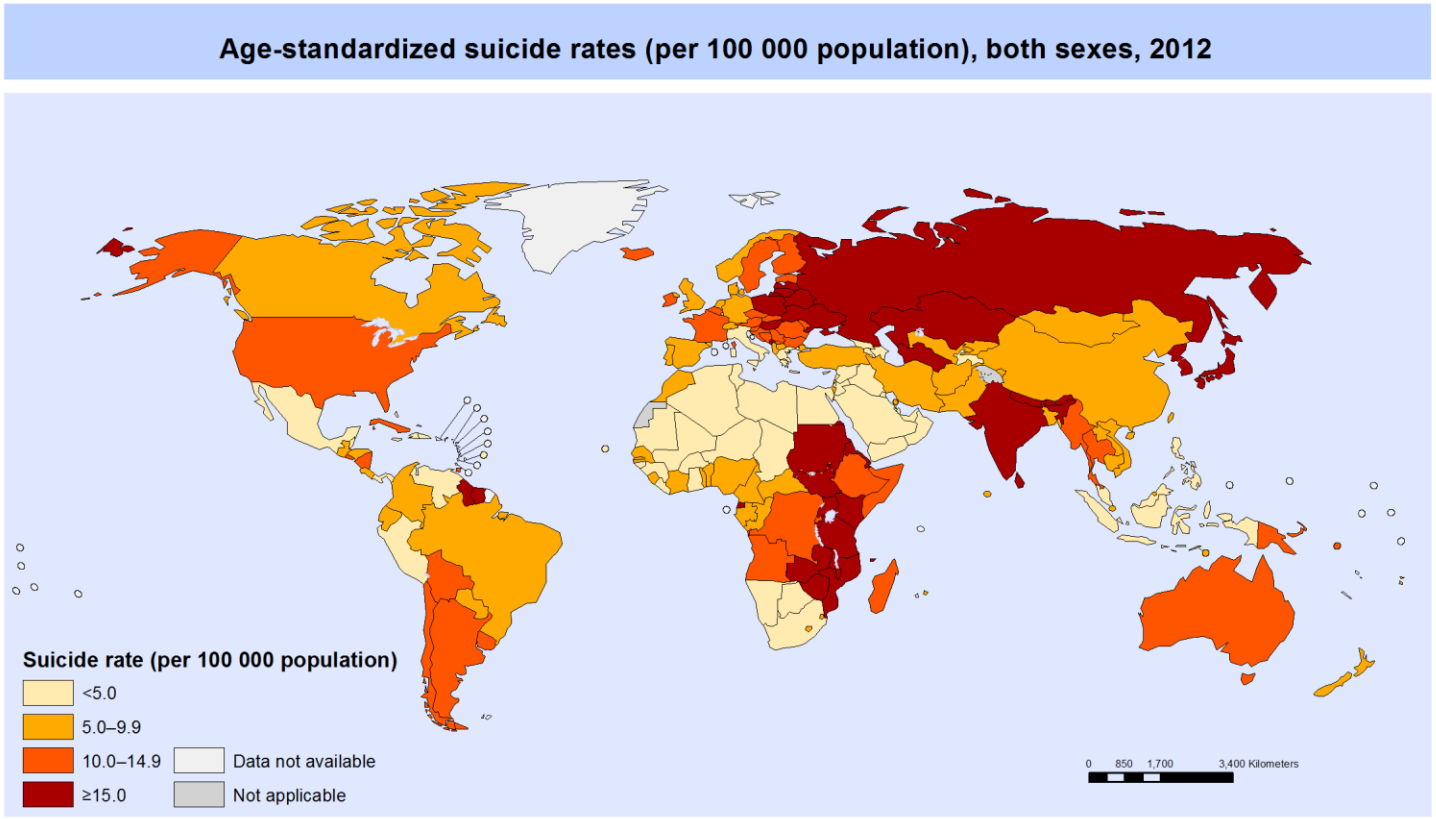
Columbia University College of Physicians and Surgeons

Tel Aviv University Sackler Faculty of Medicine

- The phenomena

World Suicide Rates (WHO)

900,000 a year 10.7:100,000

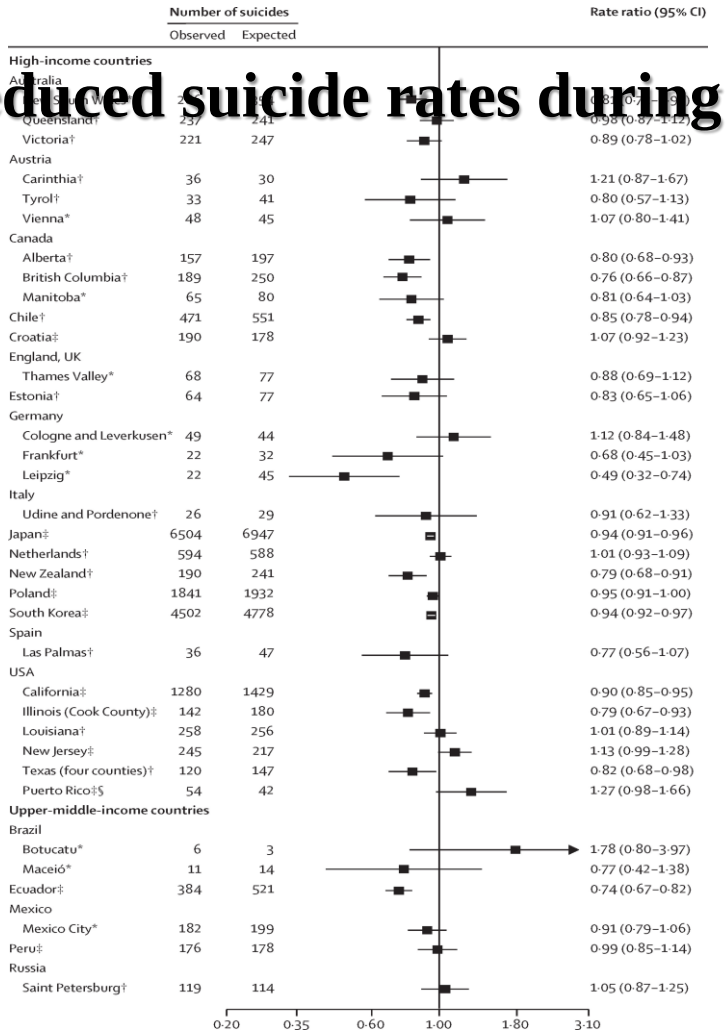


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Worldwide reduced suicide rates during pandemic



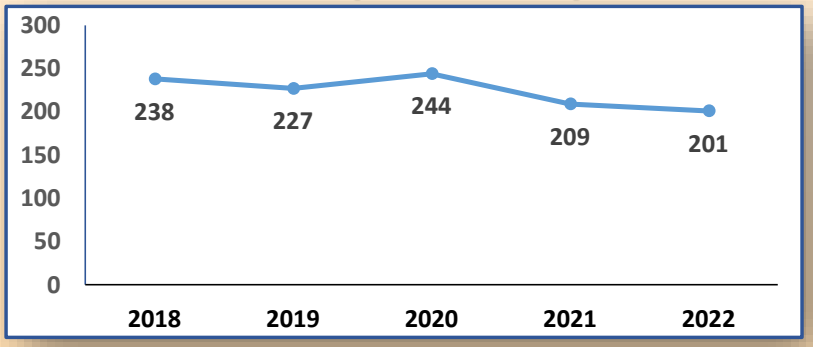
Pirkis et al., 2021

מספר התאבדויות שנרשמו באבו כביר

מספר מקרי חשד להתאבדות שנרשמו במכון לרפואה משפטית, 2018-2022

חודש /שנה	2018	2019	2020	2021	2022
ינואר	22	21	29	19	23
פברואר	22	18	27	16	13
מרץ	32	25	16	26	19
אפריל	16	29	19	21	18
מאי	28	22	33	25	26
יוני	22	19	32	20	11
יולי	24	27	19	19	20
אוגוסט	24	24	25	22	29
ספטמבר	20	24	21	19	25
אוקטובר	28	18	23	22	17
נובמבר	25	28	15	16	
דצמבר	21	24	18	15	
ינואר-אוקטובר	238	227	244	209	201

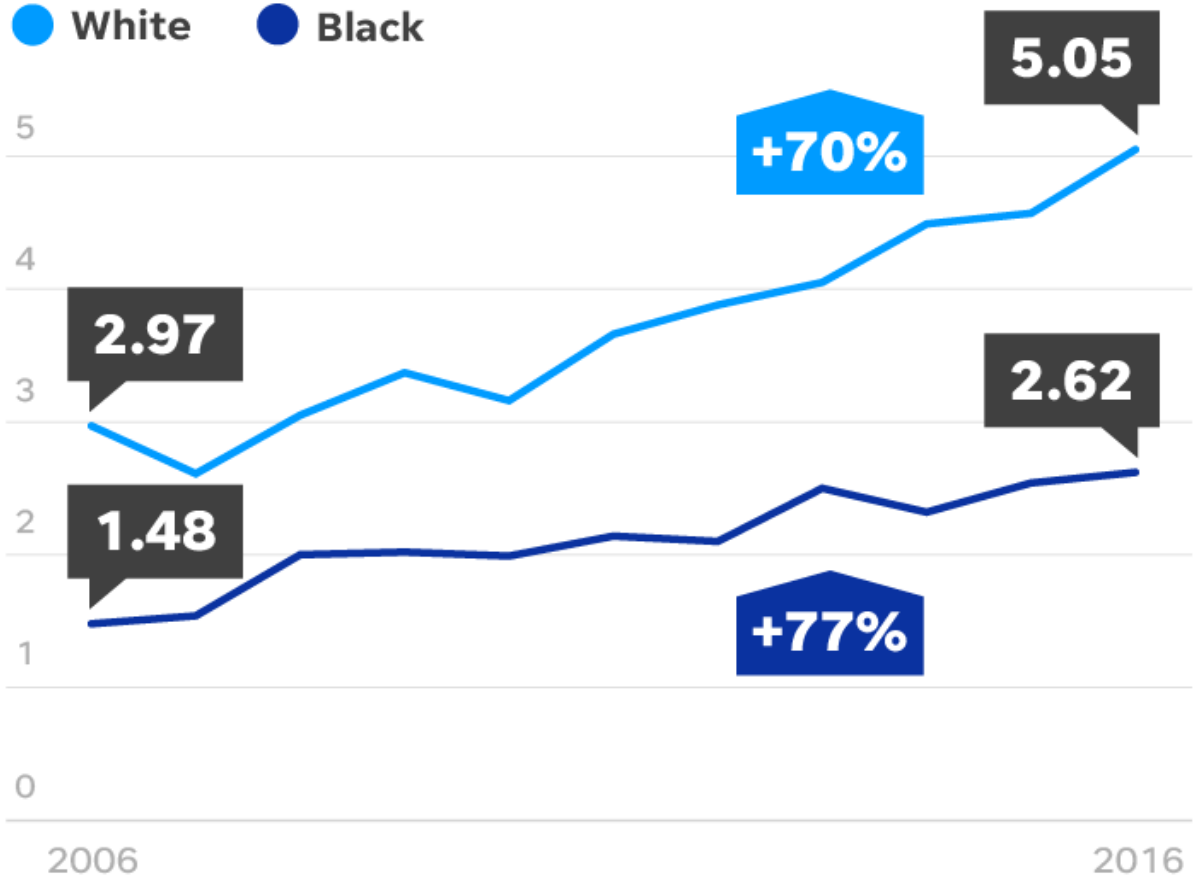
מספר מקרים ינואר-אוקטובר לפי שנה



מספר נמוך יחסית לשנים קודמות.
חדשי תחלואת קורונה גבוהה.

Teen suicide is soaring. The biggest rate increase was among black youth

Suicides per 100,000 10-to-17 year-olds from 2006 to 2016:



SOURCE Centers for Disease Control and Prevention

Karl Gelles/USA TODAY

Social media and suicidal behavior

Empirical Article

aps ASSOCIATION FOR PSYCHOLOGICAL SCIENCE

Clinical Psychological Science
1–15

DOI: 10.1177/2167702617723376
www.psychologicalscience.org/CPS
SAGE

Increases in Depressive Symptoms, Suicide-Related Outcomes, and Suicide Rates Among U.S. Adolescents After 2010 and Links to Increased New Media Screen Time

Jean M. Twenge[1], Thomas E. Joiner[2], Megan L. Rogers[2], and Gabrielle N. Martin[1]
[1]San Diego State University and [2]Florida State University

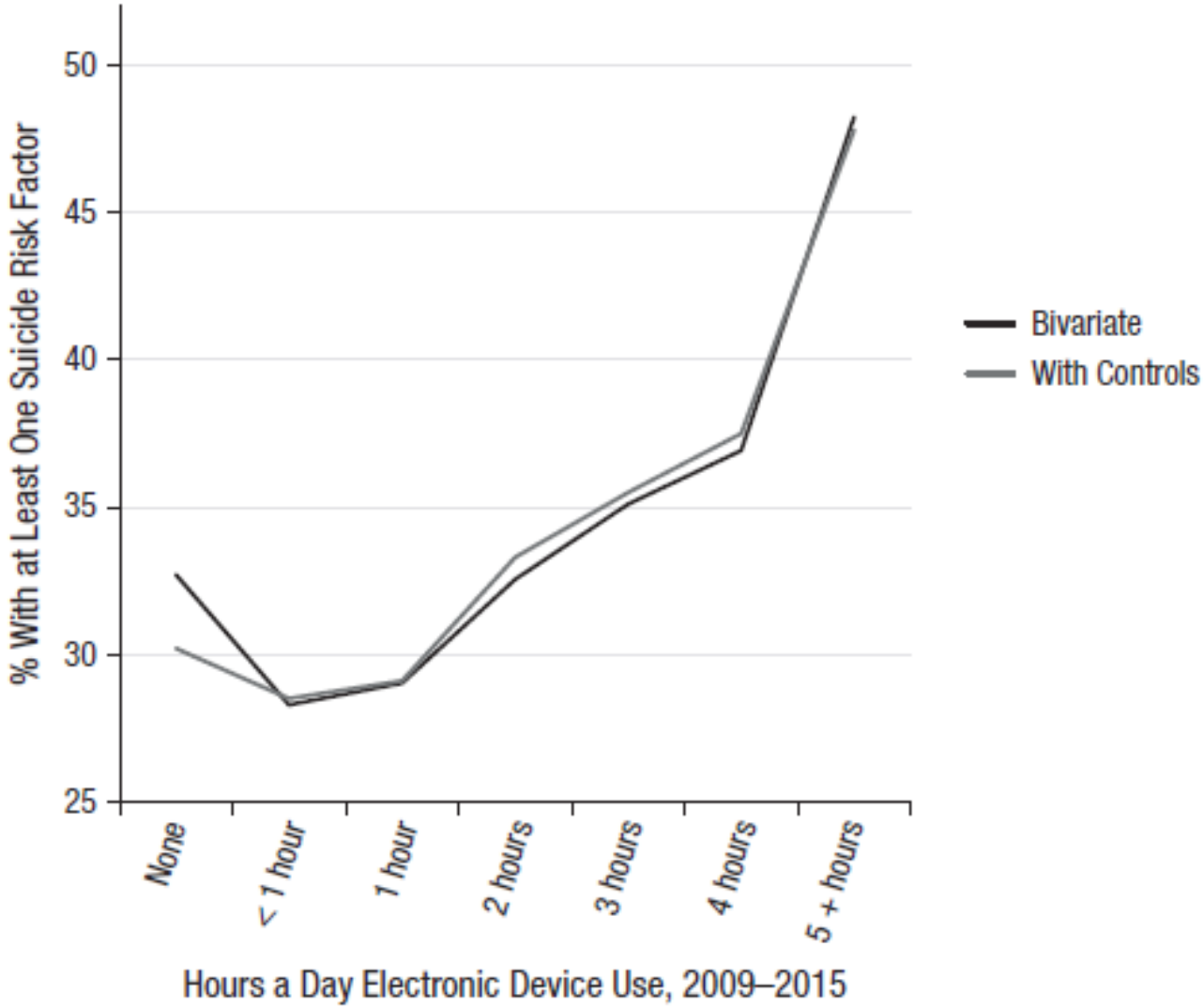


Fig. 2. Exposure-response relationship between electronic device use and having at least one suicide-related outcome, bivariate and with demographic controls for race, sex, and grade, 9–12th graders, Youth Risk Behavior Surveillance Survey (YRBSS), 2009–2015.

If you don't ask you don't know

- 90% of suicide victims suffered from a mental disorder
- 60% of suicide victims met their primary care physician in the month prior to suicide

Mann et al., JAMA, 2005

- Asking is not dangerous

Gould et al., JAMA 2006

- Risk Assessment

Risk Assessment

- **Male!!!**
- **Psychopathology (MDD)**
- **Previous attempt**
- **Impulsive aggression**
- **Loss**
- **Leaving alone**
- **Support system**

Risk Assessment

- **Substance abuse**
- **Problem with the law**
- **Genetics**
- **Hopelessness- Despair**
- **Helplessness**
- **Poor decision making**

- Treatment

Tx of the suicidal patients

- Safety plan
- Restriction of means
- No-suicide contract
- Effective treatment of depression
- Aggressive treatment of psychopathology!!
- Postcard approach-continuous care
- Specific psychotherapies
- Human compassion and true care

Evidence- Based Psychotherapies for Depression and Suicidal Behavior

- CBT, CBT-A
- DBT- specifically for BLPD NSSI
- IPT, IPT-A
- MBCT

Suggested Mechanisms:

- Psychological
- Biological
- GxE interaction

Universal Psychological Characteristics

- **Feeling lonely and isolated**

("nobody understands my mental pain")

- **Narrow cognitive state**

"tunnel vision". The more depressed and desperate, the less open to suggestions

Omer H, Elitzur AC. What would you say to the person on the roof? Suicide Life Threat Behav. 2001 ;31:129-39; Orbach I discussion pp. 140-3.
Shneidman, E. (1982) Voices of Death. N. Y.: Harper & Row.

Mental pain as a mediator of suicidal tendency: A path analysis

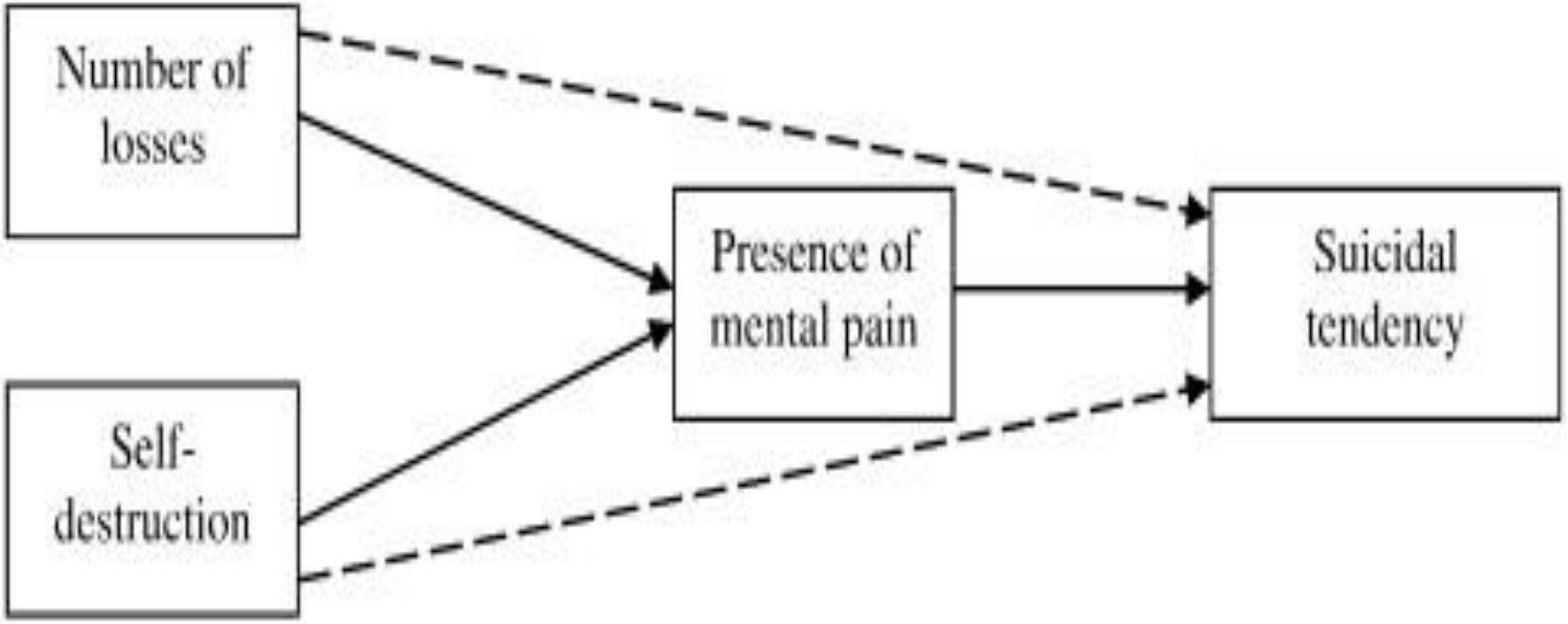


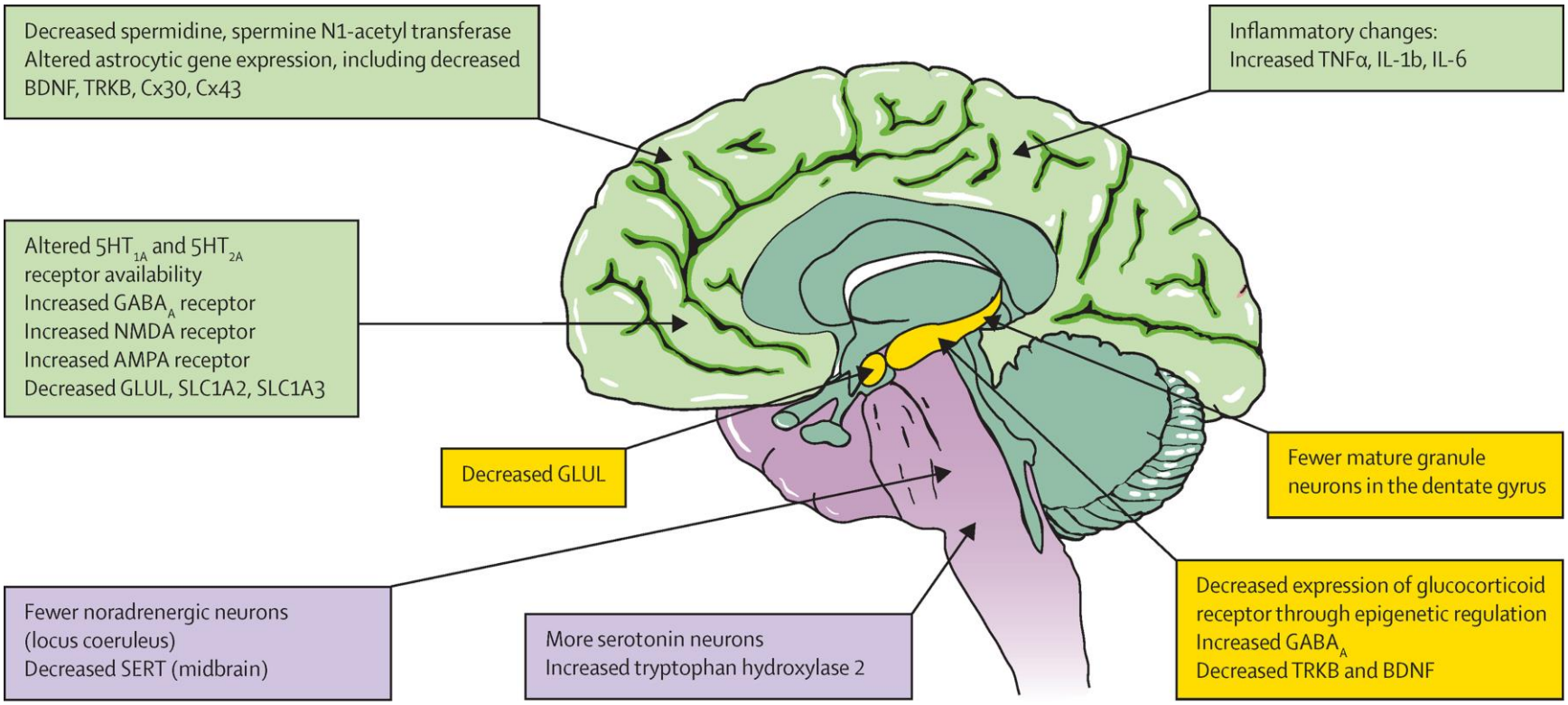
Fig. 1. Proposed model of suicidal tendency.If a mediation effect occurs, the broken lines which represent direct links between the predicting and the predicted variables are annulled (i.e. full mediation) or reduced (i.e. partial mediation).

Nahaliel et al., Comprehensive Psychiatry, Volume 55, Issue 4, 2014, 944–951

Suggested Mechanisms:

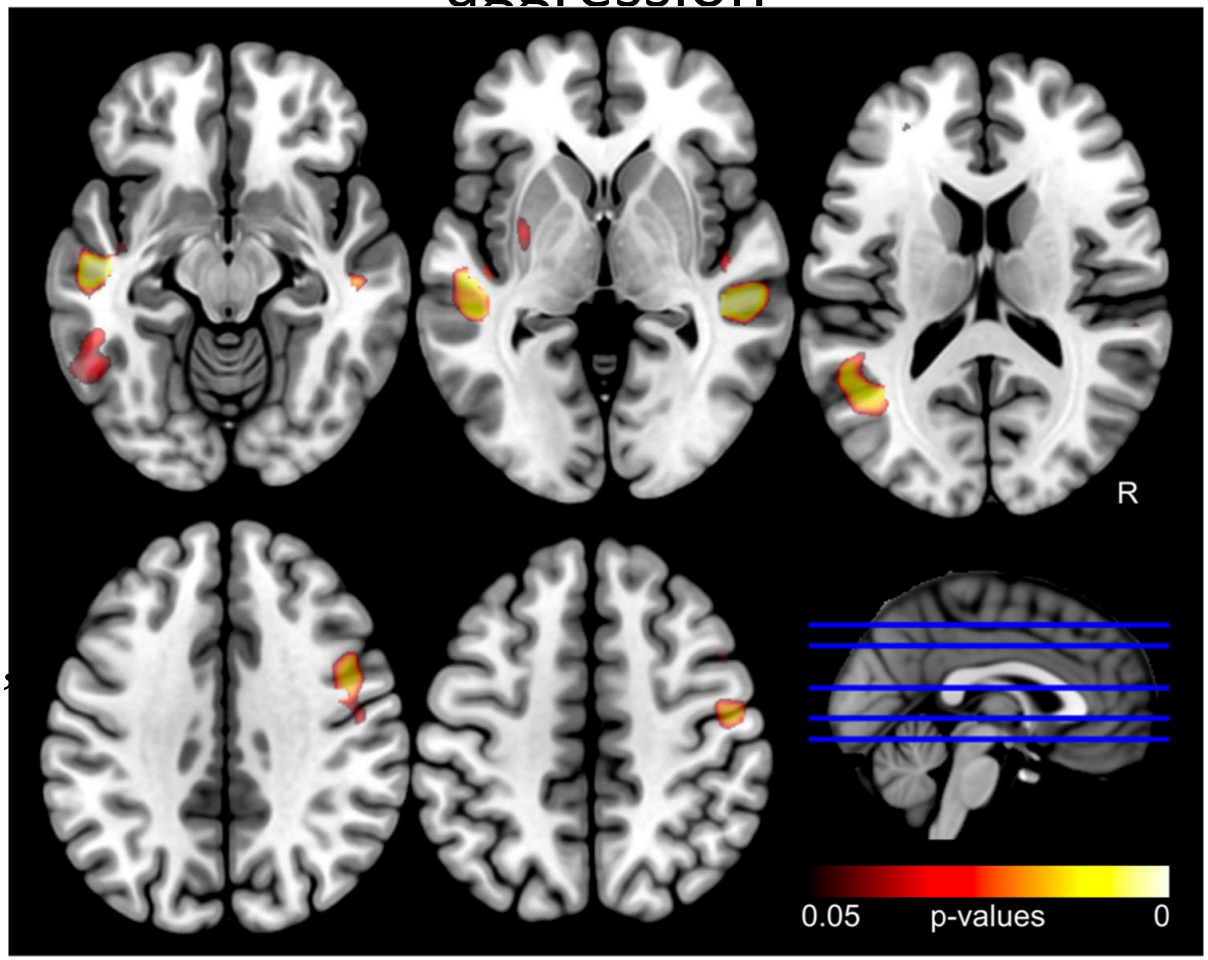
- Psychological
- **Biological**
- GxE interaction

Turecki and Brent Lancet 2015



Reduced volumes of Caudate and Putamen in individuals with vs. without a family history of suicide

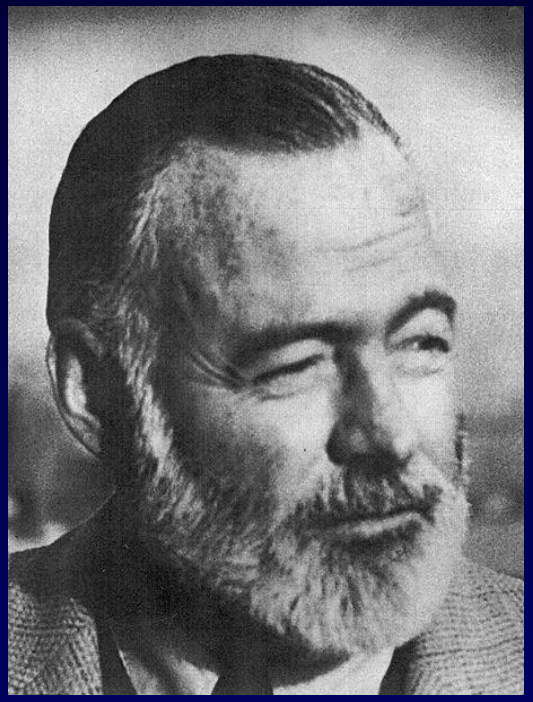
* correlated with mental pain and teen Hx of aggression



Jollant et al., 2018

Suicidal Behavior Runs in Families

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



Ernest Hemingway

- MZ 13 times more risk of suicide than in DZ (Roy 1990)
- $5HT_{2A}$ gene expressed more and SKA2 gene expressed less in brains of teens suicide victims (Pandey G. Int NPP, 2002)

- **DZ 0.7%**
- **MZ 13%**

Ott J et al, 2001

Genetics of Suicide in Adolescents

TABLE 14.1
Published Studies on Genetics of Adolescent Suicide

Reference	Population	Polymorphisms	Main Findings
Zalsman et al. (2001a,b)	Family-based study (HRR): 88 inpatient adolescents of Jewish origin who recently attempted suicide and both biological parents of 40 subjects and from one parent of 9 subjects	A218C in intron 7 of tryptophan hydroxylase (*TPH*) gene	HRR method (chi-square = 0.094; $P = 0.76$), the TDT (chi-square = 0.258; $P = 0.61$), or association analysis to known population frequencies (chi-square = 1.667, $P = 0.19$ for Ashkenazi, and chi-square = 0.810, $P = 0.37$ for non-Ashkenazi). Analysis of variance with the Scheffe test demonstrated a significant difference between CC and AA genotypes in suicide risk and depression among the patients ($n = 88$). The findings suggest that polymorphism A218C has no major relevance to the pathogenesis of adolescent suicidal behavior but may have a subtle effect on some related phenotypes
Zalsman et al. (2001b)	Forty-eight Israeli inpatient adolescents who recently attempted suicide using the haplotype relative risk (HRR)	The serotonin transporter-linked promoter region polymorphism (5-HTTLPR)	No significant allelic association of the 5-HTTLPR polymorphism with suicidal behavior was found. Analysis of variance demonstrated a significant difference in violence measures between patients carrying the LL and LS genotypes
Zalsman et al. (2004)	Sixty-nine Israeli inpatient suicidal adolescents who recently attempted suicide and 167 healthy control subjects	Dopamine receptor subtype 4 (*DRD4*) gene exon III 48 bp repeat polymorphism	No significant association between the DRD4 polymorphism and suicidal behavior was found. Analysis of the suicide-related measures demonstrated a significant difference in depression severity between suicidal inpatients homozygote and heterozygote for the DRD4 alleles

(*continued*)

Zalsman G
In: Dwivedi Y, editor. The Neurobiological Basis of Suicide. 2012. Chapter 14.

TABLE 14.1 (continued)
Published Studies on Genetics of Adolescent Suicide

Reference	Population	Polymorphisms	Main Findings
Zalsman et al. (2005a)	Thirty-two suicidal and 28 non-suicidal Ashkenazi Israeli adolescent psychiatric inpatients	5-HTTLPR polymorphism and platelet transporter binding	The 5-HTTLPR polymorphism was not associated with transporter binding or with suicidality or other clinical phenotypes. However, in the suicidal group, a significant positive correlation between platelet SERT density and anger scores and a negative correlation between platelet count and trait anxiety were observed
Zalsman et al. (2005b)	A family-based method (HRR): 30 families of inpatient adolescents from Jewish Ashkenazi origin, with a recent suicide attempt	5-HT(2A) receptor gene polymorphism T102C	No difference was found in allelic distribution between transmitted and non-transmitted alleles. There was no significant association of genotype with any of the clinical traits
Cicchetti et al. (2010)	Eight hundred and fifty low-income children (478 maltreated; 372 non-maltreated) with self-reported depressive and suicidal symptoms	5-HTTLPR	Higher suicidal ideation was found among maltreated than non-maltreated children; the groups did not differ in 5-HTTLPR genotype frequencies. Children with one to two maltreatment subtypes and s/s or s/l genotypes had higher suicidal ideation than those with the l/l genotype; suicidal ideation did not differ in non-maltreated children or children with three to four maltreatment subtypes based on 5-HTTLPR variation
Zalsman et al. (2010)	Four groups of adolescents were included: suicidal ($N = 35$) and non-suicidal ($N = 30$) psychiatric inpatients, suicide attempters admitted to three psychiatric emergency rooms ($N = 51$), and a community-based control group ($N = 95$)	HTR2A (102T/C) 5-HTTLPR MAOA) and plasma serotonin	Homozygosity for the T allele of the HTR2A 102T/C polymorphism was associated with lower impulsivity and aggression compared to TC carriers. Low activity MAOA genotypes were associated with suicidality. No association was found with p5HT level

Taylor & Francis
Taylor & Francis Group

The World Journal of Biological Psychiatry

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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

100 brains of suicide victims
50 brains of "natural deaths"

Galfalvy et al., WJBP, 2014

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

Suggested Mechanisms:

- Psychological
- Biological
- GxE interaction

PSYCHIATRIC DISORDER IN ADOLESCENT SUICIDE

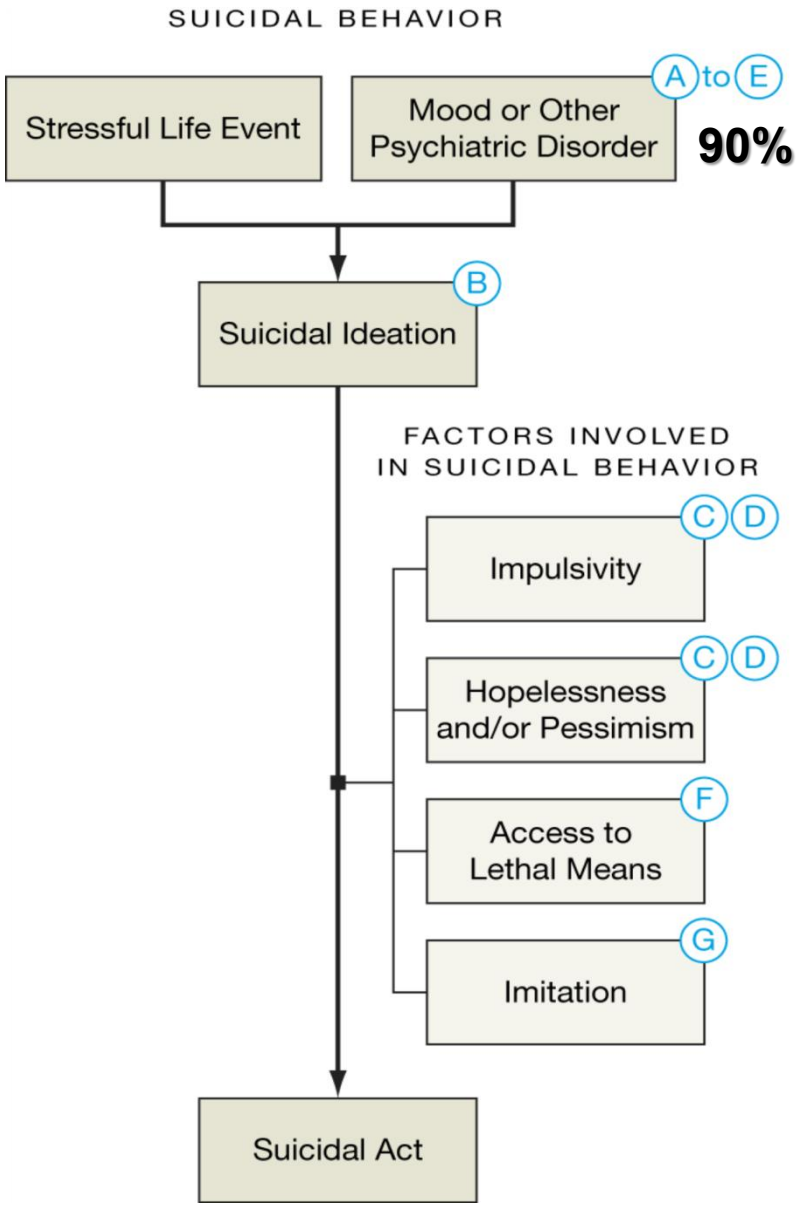
—PSYCHOLOGICAL-AUTOPSY STUDIES—

LOCATION	N	YEARS	%
Israel	43	mid-1980s	90%
*New York	120	1984–1986	90%
Finland	53	1987–1988	94%
*Pittsburgh	140	1984–1994	82%

From David Shaffer with Permission

Apter 1993, Shaffer 1996, Marttunen 1991, Brent 1999; *case-control studies

Suicide Prevention Strategies



PREVENTION INTERVENTIONS

(A) Education and Awareness Programs
- Primary Care Physicians **40%**
- General Public
- Community or Organizational Gatekeepers

(B) Screening for Individuals at High Risk

Treatment

(C) Pharmacotherapy
- Antidepressants, Including Selective Serotonin Reuptake Inhibitors
- Antipsychotics

(D) Psychotherapy
- Alcoholism Programs
- Cognitive Behavioral Therapy

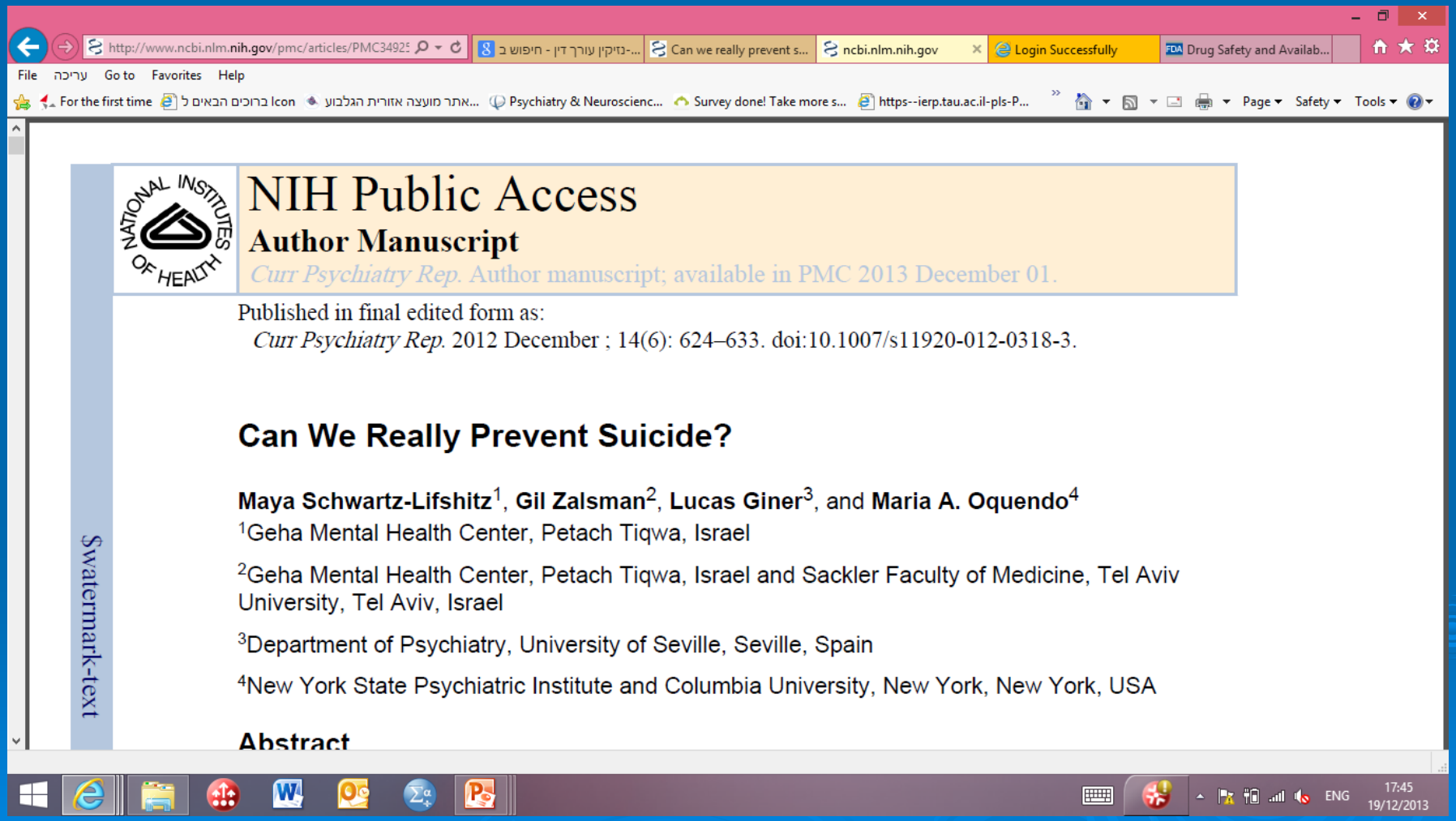
(E) Follow-up Care for Suicide Attempts

(F) Restriction of Access to Lethal Means

(G) Media Reporting Guidelines for Suicide

Mann et al., JAMA. 2005;294(16):2064-2074.

Can we really prevent suicide?



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Published in final edited form as:
Curr Psychiatry Rep. 2012 December ; 14(6): 624–633. doi:10.1007/s11920-012-0318-3.

Can We Really Prevent Suicide?

Maya Schwartz-Lifshitz[1], **Gil Zalsman**[2], **Lucas Giner**[3], and **Maria A. Oquendo**[4]
[1]Geha Mental Health Center, Petach Tiqwa, Israel
[2]Geha Mental Health Center, Petach Tiqwa, Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Department of Psychiatry, University of Seville, Seville, Spain
[4]New York State Psychiatric Institute and Columbia University, New York, New York, USA

Abstract

Lifshitz, Zalsman, Giner, Oquendo, Curr Psy Rep, 2012

Lancet Psychiatry 2016

Articles

Suicide prevention strategies revisited: 10-year systematic review

Gil Zalsman, Keith Hawton, Danuta Wasserman, Kees van Heeringen, Ella Arensman, Marco Sarchiapone, Vladimir Carli, Cyril Höschl, Ran Barzilay, Judit Balazs, György Purebl, Jean Pierre Kahn, Pilar Alejandra Sáiz, Cendrine Bursztein Lipsicas, Julio Bobes, Doina Cozman, Ulrich Hegerl, Joseph Zohar

Summary

Background Many countries are developing suicide prevention strategies for which up-to-date, high-quality evidence is required. We present updated evidence for the effectiveness of suicide prevention interventions since 2005.

Lancet Psychiatry 2016

Published Online

June 8, 2016

THE LANCET Psychiatry

Volume 3 · Issue 7 · July 2016 www.thelancet.com/psychiatry

Methods

- PubMed and the Cochrane Library using multiple terms related to suicide prevention
- between Jan 1, 2005 and Dec 31, 2014.
- 7 interventions: public and physician education, media strategies, screening, restricting access to suicide means, treatments, and internet or hotline support.
- primary outcomes of interest: suicidal behaviour (suicide, attempt, or ideation), and intermediate or secondary outcomes (treatment-seeking, identification of at-risk individuals, antidepressant prescription or use rates, or referrals).
- Because the heterogeneity of populations and methodology we present a narrative analysis.

Classification of evic

Oxford Criteria for Evidence Strength

Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009).

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies

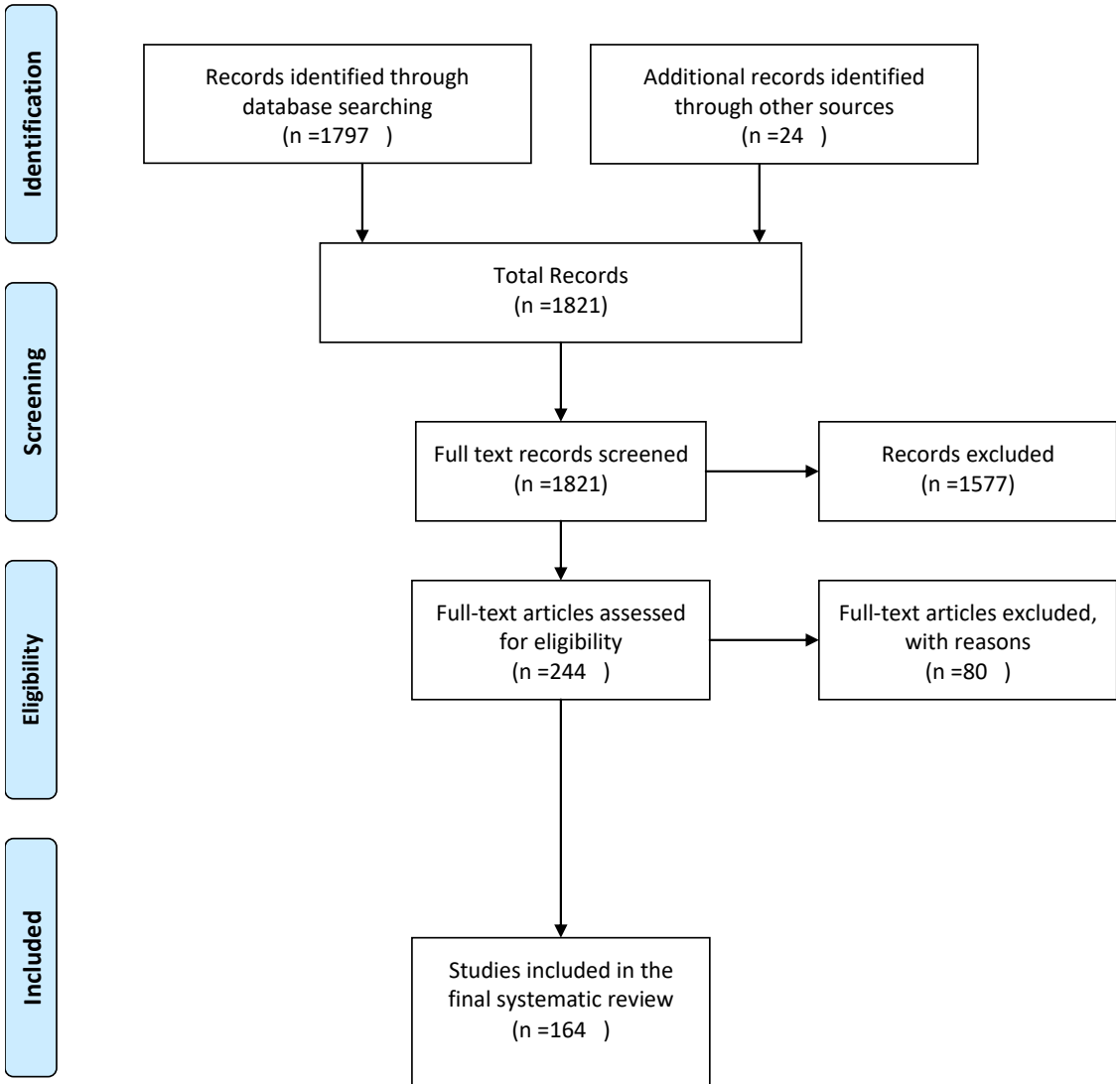

Results

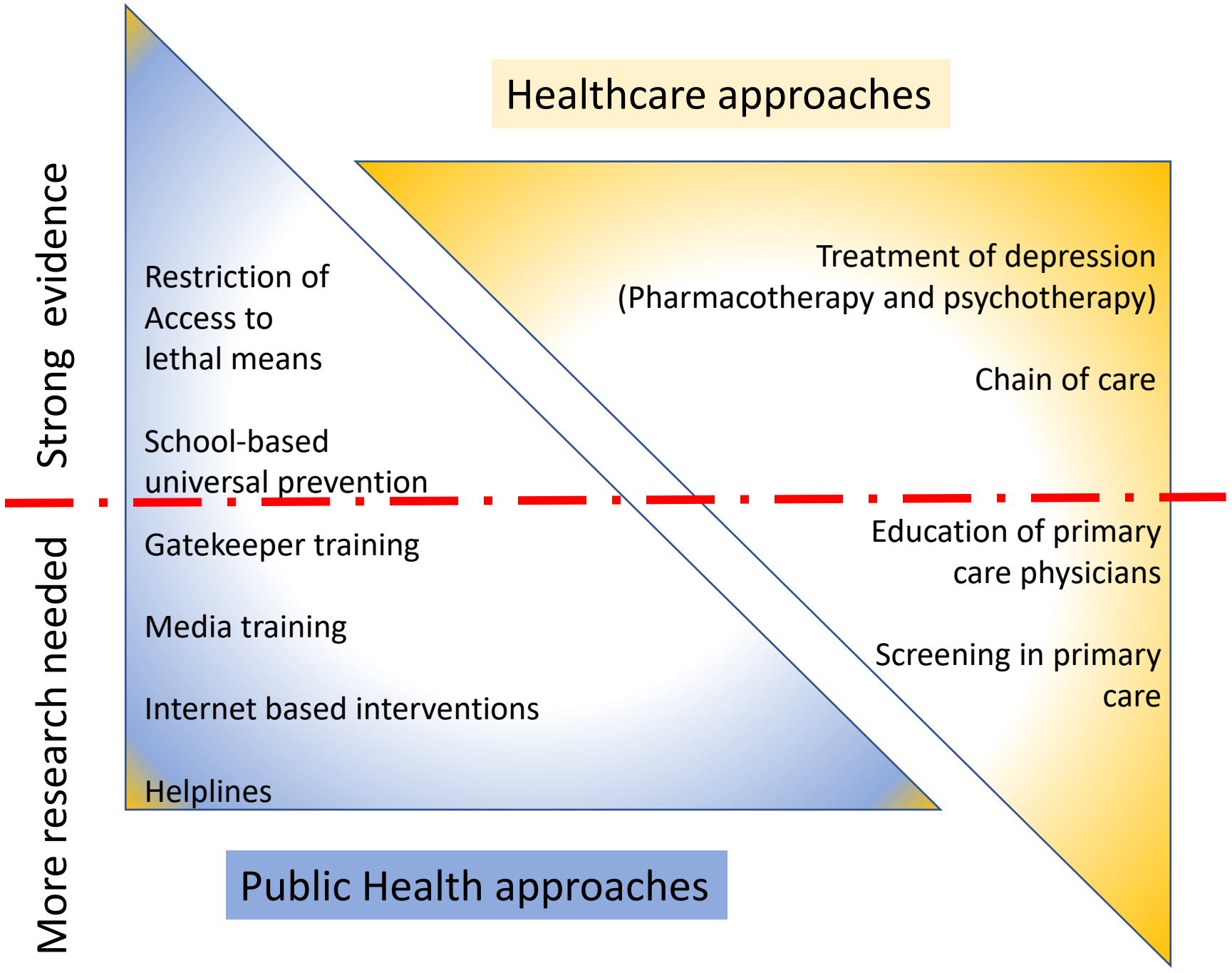
Results

1797 studies were identified including:

23 systematic reviews,
12 meta-analyses,
40 randomized controlled trials (RCTs),
67 cohort trials,
22 ecological or population-based

Figure 1: Records PRISMA Flow Diagram




Healthcare approaches
Strong evidence
More research needed
Restriction of Access to lethal means
School-based universal prevention
Gatekeeper training
Media training
Internet based interventions
Helplines
Treatment of depression (Pharmacotherapy and psychotherapy)
Chain of care
Education of primary care physicians
Screening in primary care
Public Health approaches

School based interventions

European Psychiatry 38 (2016) 8–14

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Psychological autopsy of seventy high school suicides: Combined qualitative/quantitative approach

G. Zalsman [a,b,*,1], Y. Siman Tov [c,d,1], D. Tzuriel [c,e], G. Shoval [a], R. Barzilay [a], N. Tiech Fire [d], M. Sherf [f], J. John Mann [b]

N=70 post mortem cases

Zalsman et al., Eur Psychiatry, 2016

“Typical” suicide victim in Israeli schools 2003-2011(n=70)

- **Male**
- **Low SES**
- **Low graded school**
- **Academic difficulties**
- **School counselor knows him**
- **Suicide risk undetected**
- **Truancy!!**
- **Mean 4 negative life events** (SD 2.5)
- **Low self disclosure** (Horesh Zalsman and Apter 2004)
- **Length of crisis 0.8 year**
- **Peers knew** (46%)
- **Trigger: interpersonal discord M/P humiliation** (60%)
- **Hanging (72%) near home (67%) late night (95%) during January (23%) or September (17%)**


tell someone
encourage
ask for help
listen
Suicide is the third leading cause of death among young people ages 15 to 24.
National Suicide Prevention Lifeline
1-800-273-TALK (8255)
24/7 free and confidential, nationwide network of crisis centers.

Social media and suicidal behavior

Empirical Article

Clinical Psychological Science
1–15

DOI: 10.1177/2167702617723376
www.psychologicalscience.org/CPS

Increases in Depressive Symptoms, Suicide-Related Outcomes, and Suicide Rates Among U.S. Adolescents After 2010 and Links to Increased New Media Screen Time

Jean M. Twenge[1], Thomas E. Joiner[2], Megan L. Rogers[2], and Gabrielle N. Martin[1]
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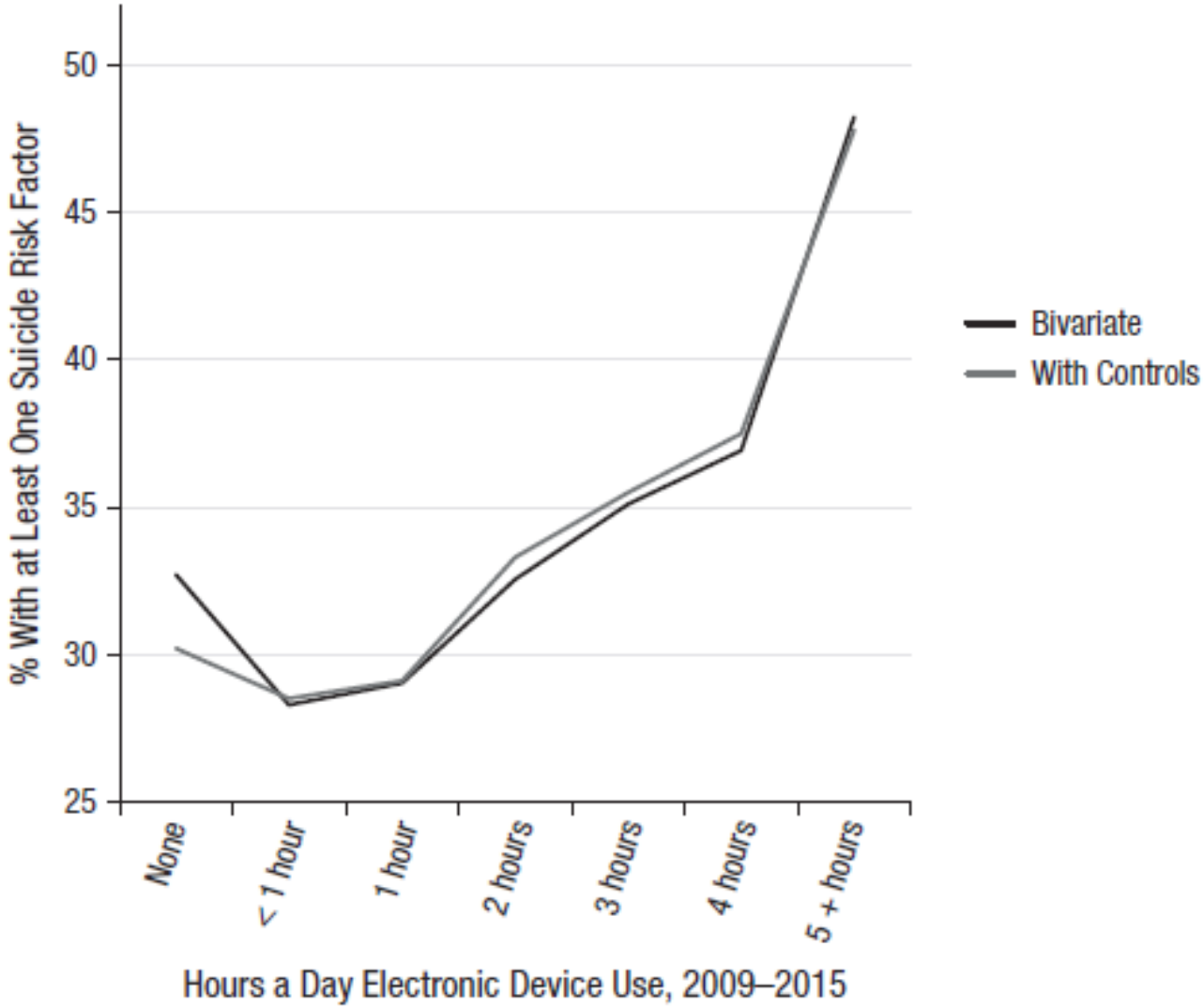

Fig. 2. Exposure-response relationship between electronic device use and having at least one suicide-related outcome, bivariate and with demographic controls for race, sex, and grade, 9–12th graders, Youth Risk Behavior Surveillance Survey (YRBSS), 2009–2015.

Pharmacotherapy of suicidal behavior

Results- Treatments of psychopathology

The anti-suicidal effects of clozapine and lithium have been substantiated, but might be less specific than previously thought. Effective pharmacological and psychological treatments of depression are important in prevention.

Ketamine and Suicide Tx

- Ketamine shows promising results in systematic review as a potentially effective and rapid treatment of suicidal thoughts, independent of improvement in depression, and with minimal side effects (Reinstatler et al., Drugs R D 2015)
- but effects on suicide attempts or death by suicide have not yet been shown and effects on suicidal ideation longer than a few days have not been demonstrated.

- The Daily - Windows Internet Explorer

http://www.thedaily.com/page/2012/08/17/081712-news-anti-suicide-spray-1-4/

Search Results

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SPRAY OF HOPE

Military developing anti-suicide nasal spray as deaths hit record numbers

By Katie Drummond Friday, August 17, 2012

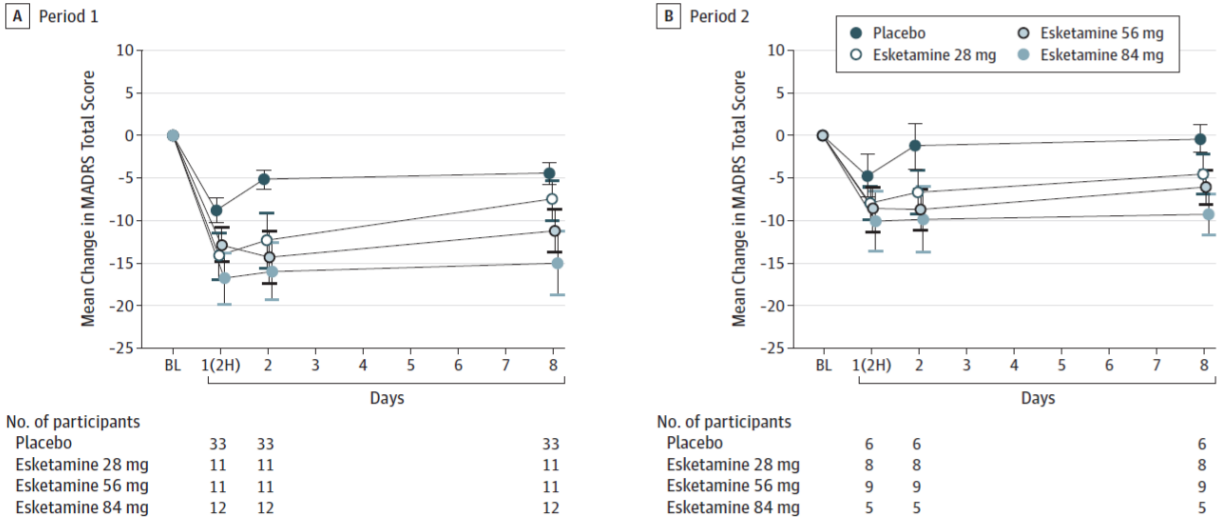
Like 240

Local intranet 100%

start 5 Windo... 3 Micros... 2 Micros... Microsoft ... 2 Micros... - The Daily... Desktop Links HE 100% 00:37

Daly et al., JAMA 2018

Figure 2. Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time in Double-Blind Phase



No. of participants				
Placebo	33	33		33
Esketamine 28 mg	11	11		11
Esketamine 56 mg	11	11		11
Esketamine 84 mg	12	12		12

No. of participants				
Placebo	6	6		6
Esketamine 28 mg	8	8		8
Esketamine 56 mg	9	9		9
Esketamine 84 mg	5	5		5

Changes shown in periods 1 (A) and 2 (B). Period 2 consisted only of participants who had received placebo in period 1 and had moderate to severe symptoms (n = 28). Period 1 (days 1-8) and period 2 (days 8-15) are discussed in the Design section of the Methods and shown in the vertical axis of Figure 1. BL indicates baseline; 2H, 2 hours post dose. Error bars indicate SE.

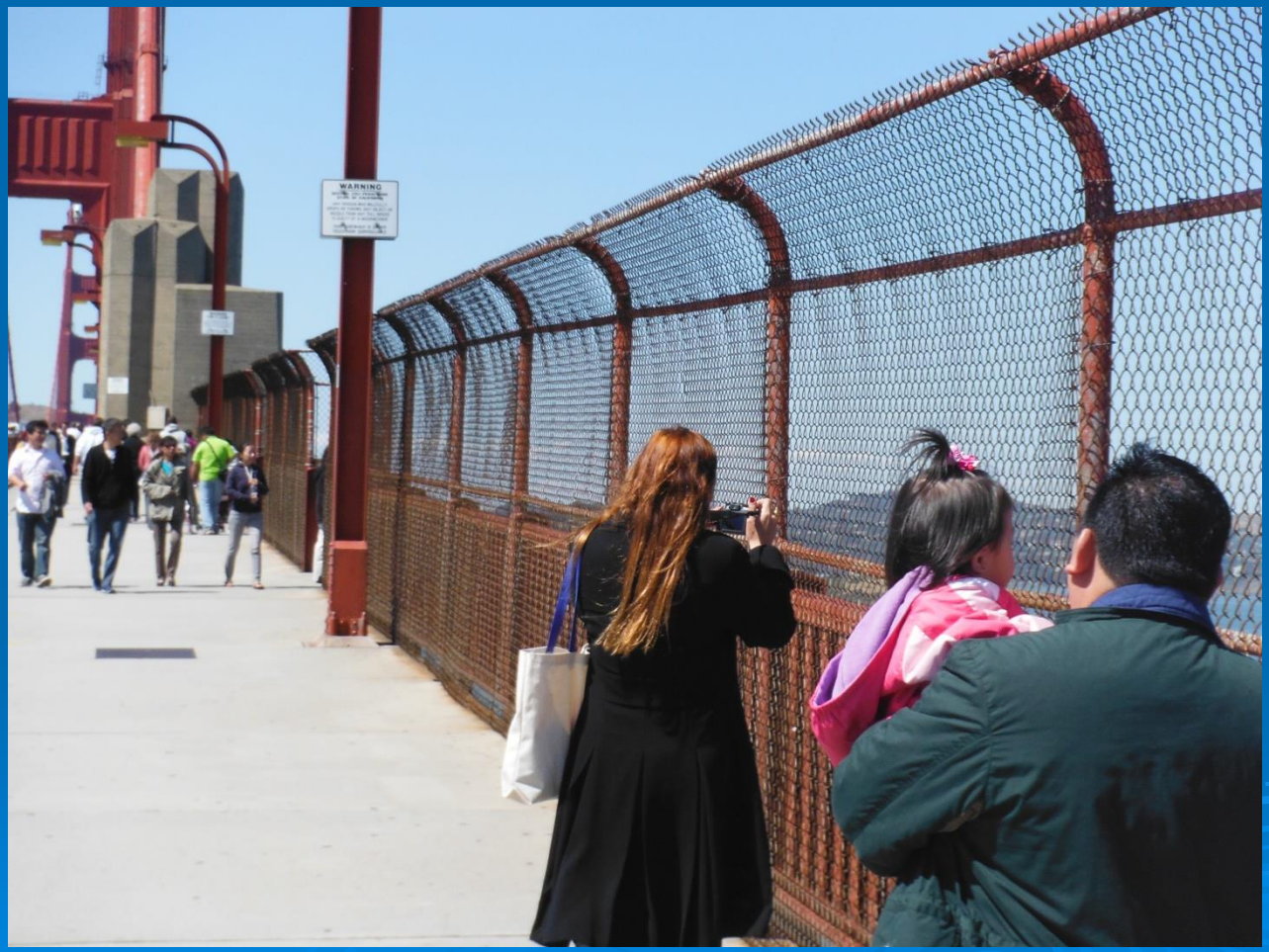
Figure 3. MADRS Total Score: Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score From Baseline to Follow-up End Point for Participants Who Entered the Open-Label Phase

ECT and Suicide Tx

- **ECT was shown to rapidly reduce suicide risk in case series but no controlled trials have been conducted.** (Kellner et al., AJP 2005; Patel M et al., The journal of ECT 2006)

Means Restrictions

Golden Gate - San Francisco Suicide "Hot Spot"


WARNING


CRISIS COUNSELING
THERE IS HOPE
MAKE THE CALL
THE CONSEQUENCES OF JUMPING FROM THIS BRIDGE ARE FATAL AND TRAGIC.


CRISIS COUNSELING
THERE IS HOPE
MAKE THE CALL
THE CONSEQUENCES OF JUMPING FROM THIS BRIDGE ARE FATAL AND TRAGIC.
PUSH FOR HELP
Code Blue

Okland Bridge SF

No suicides

Moher Cliffs, Ireland

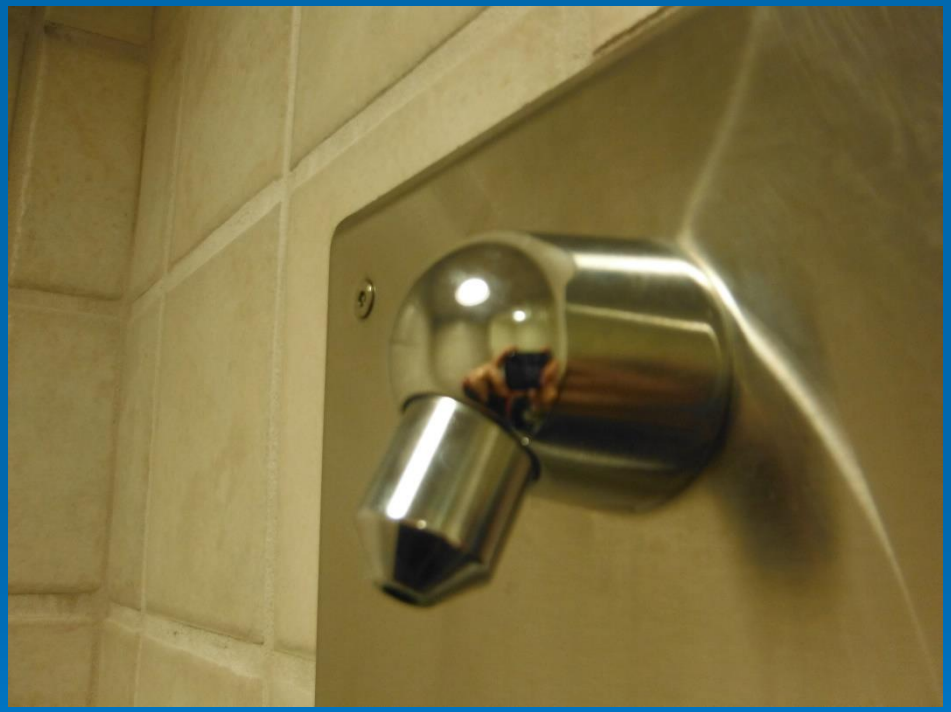
Moher Cliffs, Ireland

Moher Cliffs, Ireland

Psychiatric Hospital Suicides

- Hanging is the prevalent method
- The shower is the most dangerous place

Shepard Pratt Hospital, Baltimore, Maryland



McLean Hospital, Harvard University, Boston


HAMAT
עולם המים של חמת

Limiting pack size of analgesics (Paracetamol & Salicilates) 16/9/98

UK legislation on analgesic packs: before and after study of long term effect on poisonings

Keith Hawton, Sue Simkin, Jonathan Deeks, Jayne Cooper, Amy Johnston, Keith Waters, Morag Arundel, William Bernal, Bridget Gunson, Mark Hudson, Deepak Suri, Kenneth Simpson

- **Deaths lower by 22%**
- **Non fatal OD lowered by 29%**
- **Liver transplant reduced by 30%**
- **Some shift to ibuprofen (not fatal)**

Hawton et al., BMJ, 2004

What this study adds

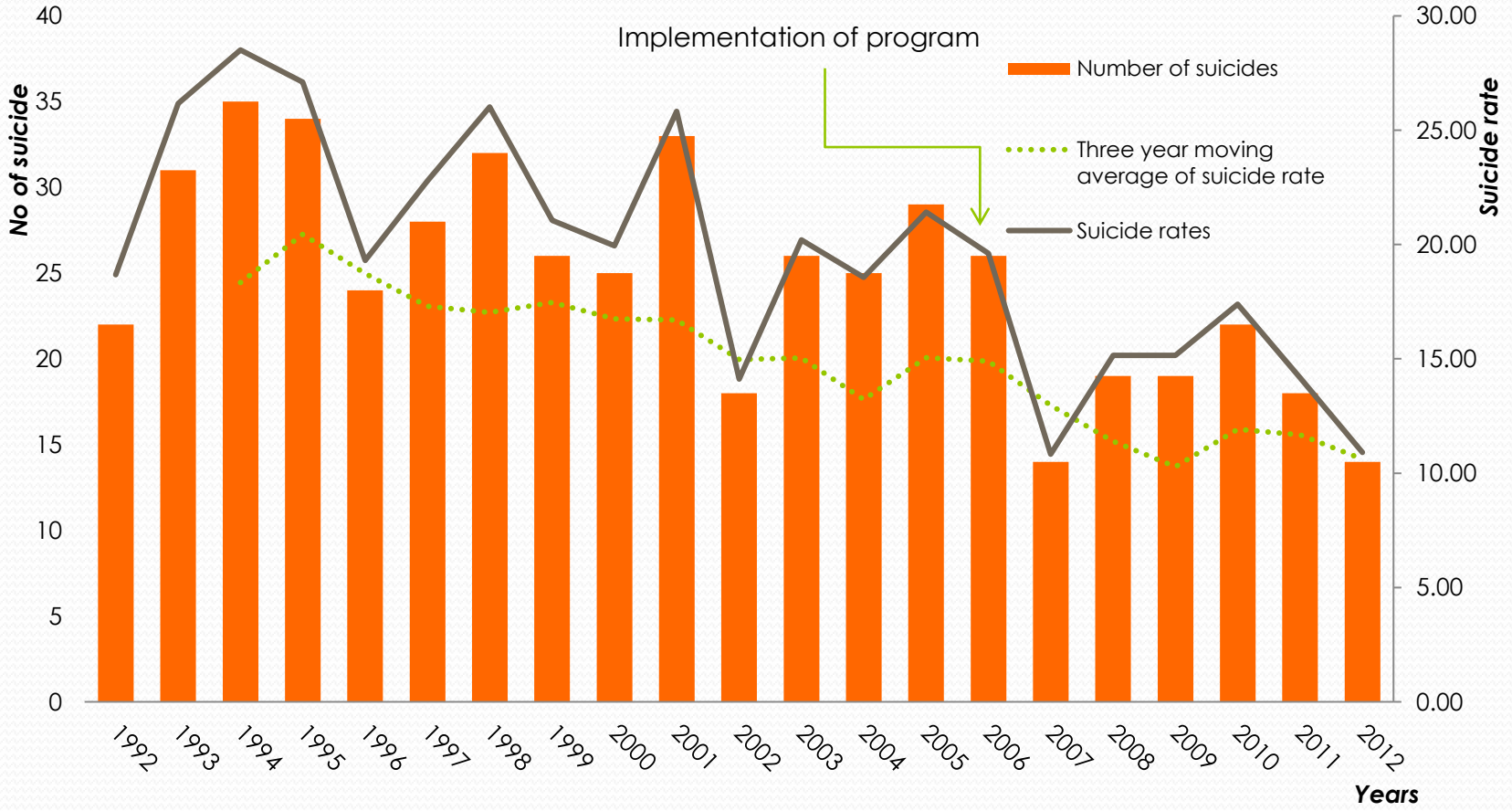
Legislation limiting pack sizes of analgesics has had sustained beneficial effects

Decreases have occurred in mortality and size of non-fatal overdoses and in admissions to liver units and liver transplants due to paracetamol poisoning

Although some substitution with ibuprofen may have occurred, there is no evidence that this has affected mortality

IDF suicide rate in 20 years – effect of guns restrictions

Fig 1 Number of suicides, suicide rates, and three year moving average for rates of suicide, IDF Mandatory service, 1992-2012



Lubin G et al., 2010; Laor L unpublished data; Shelef et al., 2016 in press

My Message

- Suicidal behavior is not rare after puberty
- Complete suicide is rare and hard to predict
- Risk assessment and recording is essential
- Pharmacotherapy include SSRIs, Lithium, Clozapine, ECT and maybe Ketamine
- SSRIs do not cause more completed suicides
- Prevention in the national level is effective
- Connection and Compassion are critical


12:15 PM
PANIC!


remember
COMPASSION

Small Talk Saves Lives – Samaritans
Sara Wilson case

Thank you

SSRIs and Suicide in Pediatric Population

- In children and adolescents with depression, evidence (RCTs) does not support avoidance of use of antidepressant medication because of increased risk of suicidal behaviour, although there is evidence to suggest an increased risk of suicidal ideation in this population.
- Adding cognitive behavioral therapy (CBT) to fluoxetine may lead to less suicidal ideation and behaviour than treatment with fluoxetine alone.

March JS et al., The Treatment for Adolescents With Depression Study (TADS): long-term effectiveness and safety outcomes. Archives of General Psychiatry 2007; 64(10): 1132-43.

Most gunshot suicides in the US are happening in the first year after purchasing a gun

This article addresses the Core Competency of ***Systems-Based Practice***

REVIEWS AND OVERVIEWS

Evidence-Based Psychiatric Treatment

Prevention of Firearm Suicide in the United States: What Works and What Is Possible

J. John Mann, M.D., Christina A. Michel, B.A.

Objective: About 21,000 suicides in the United States in 2014 involved a firearm. The authors reviewed evidence from around the world regarding the relationship between firearm ownership rates and firearm suicide rates and the potential effectiveness of policy-based strategies for preventing firearm suicides in the United States.

Method: Relevant publications were identified by searches of PubMed, PsycINFO, MEDLINE, and Google Scholar from 1980 to September 2015, using the search terms suicide AND firearms OR guns. Excluding duplicates, 1,687 results were found, 60 of which were selected for inclusion; these sources yielded an additional 10 studies, for a total of 70 studies.

Results: Case-control and ecological studies investigating geographic and temporal variations in firearm ownership and firearm suicide rates indicate that greater firearm availability is associated with higher firearm suicide rates. Time-series analyses, mostly from other countries, show that legislation reducing firearm ownership lowers firearm suicide rates. Because the Second Amendment curtails legislation broadly restricting firearm access in the United States, the emphasis is shifted to restricting access for those at risk of harming themselves or others. Most suicides involve guns purchased years earlier. Targeted initiatives like gun violence restraining orders, smart gun technology, and gun safety education campaigns potentially reduce access to already purchased firearms by suicidal individuals. Such measures are too new to have evidence of effectiveness.

Conclusions: Broadly reducing availability and access to firearms has lowered firearm suicide rates in other countries but does not appear feasible in the United States. Approaches restricting access of at-risk individuals to already purchased firearms by engaging the public and major stakeholders require urgent implementation and outcome evaluation for firearm suicide prevention.

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PSYCHIATRIC DISORDER IN ADOLESCENT SUICIDE

—PSYCHOLOGICAL-AUTOPSY STUDIES—

LOCATION	N	YEARS	%
Israel	43	mid-1980s	90%
*New York	120	1984–1986	90%
Finland	53	1987–1988	94%
*Pittsburgh	140	1984–1994	82%

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Apter 1993, Shaffer 1996, Marttunen 1991, Brent 1999; *case-control studies