# IV Seminario de Prevenção do Suicídio no Espírito Santo: resiliência em situações de suicídio, fatores de risco e proteção

Vitória 23 e 24 de setembro de 2016

Humberto Corrêa
Professor Titular de Psiquiatria da UFMG
Presidente da ABEPS
Presidente da ASULAC

## Conflitos de Interesse

*Considerando o disposto nas resoluções do Conselho Federal de Medicina (CFM n° 1.595/00 de 18/05/2000) e da Agência Nacional de Vigilância Sanitária (ANVISA n° 102/2000 de 30/11/2000), DECLARAMOS que:*

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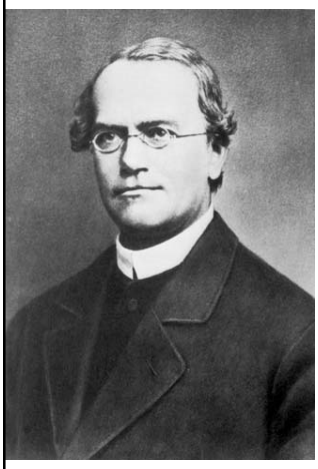
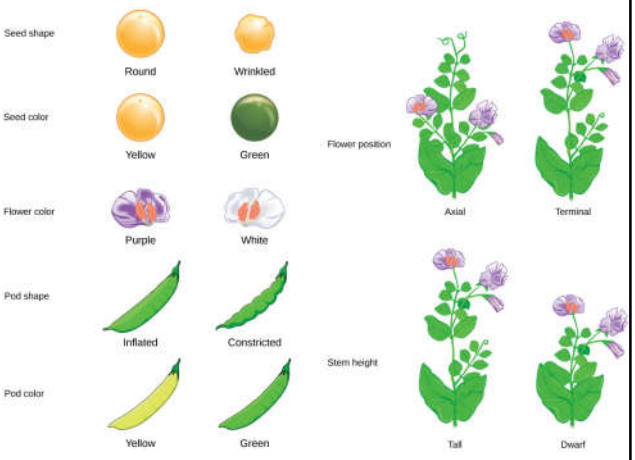
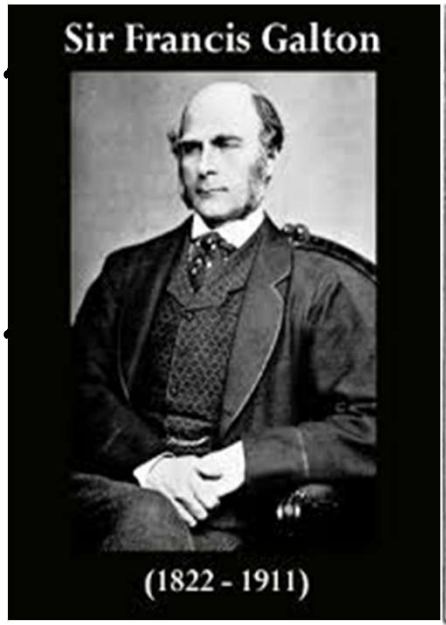
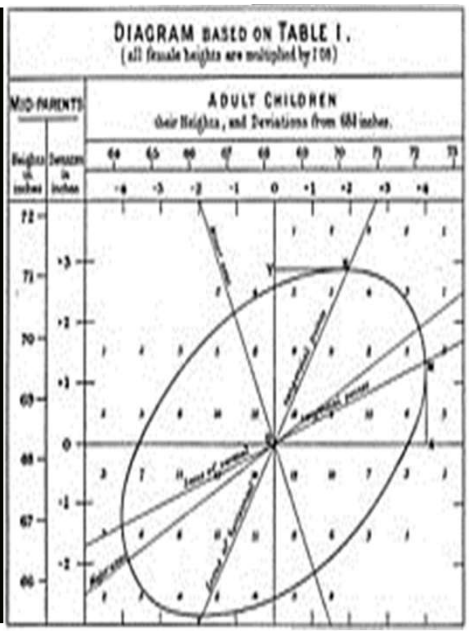


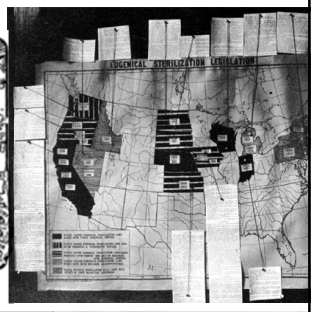


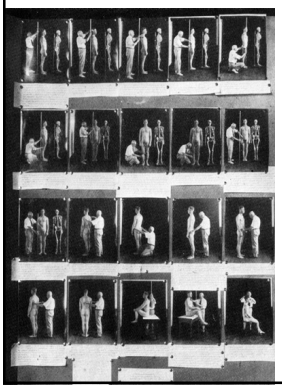
# Sir Francis Galton








Plymouth
Azores
Tenerife
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Galapagos
Callao
Lima
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Rio de
Janeiro
Valparaiso
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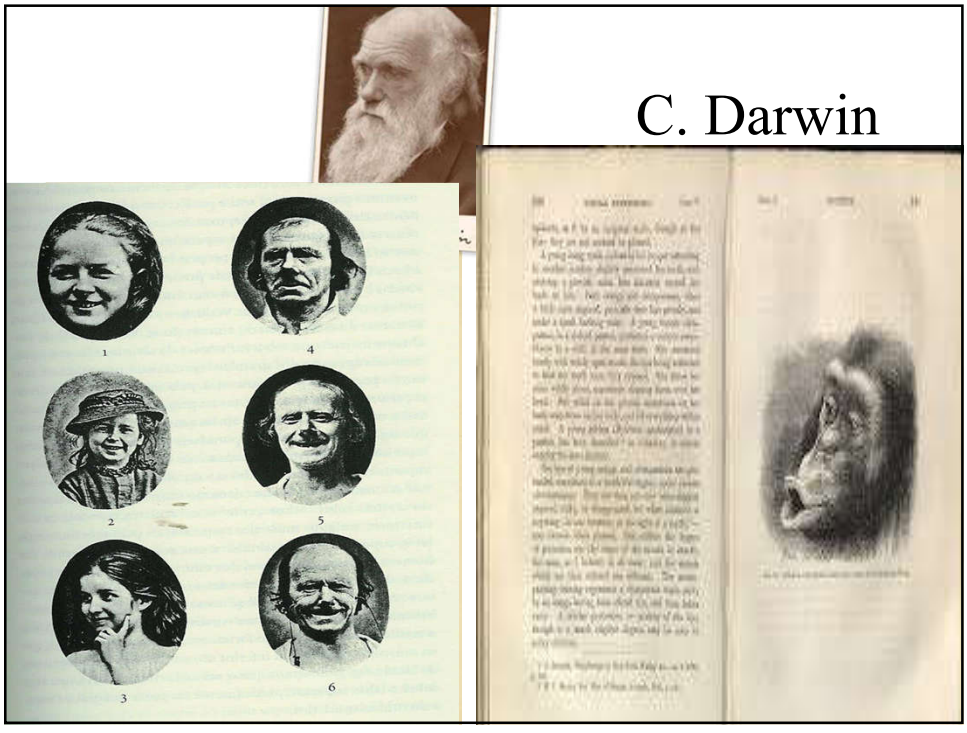
Falkland
Islands
Cape Town
Mauritius
Cocos
(Keeling) Isl.
Sydney
King George's
Sound
Hobart


C. Darwin
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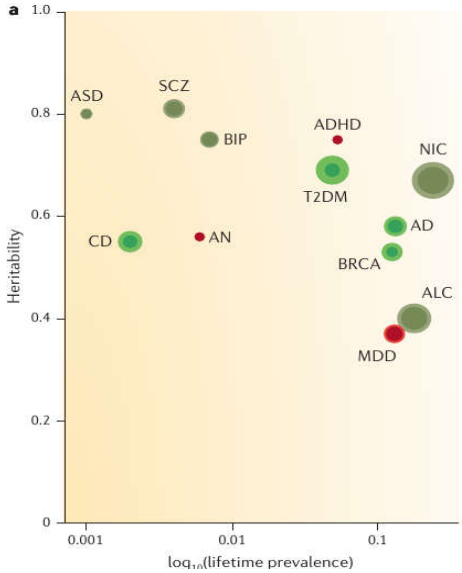
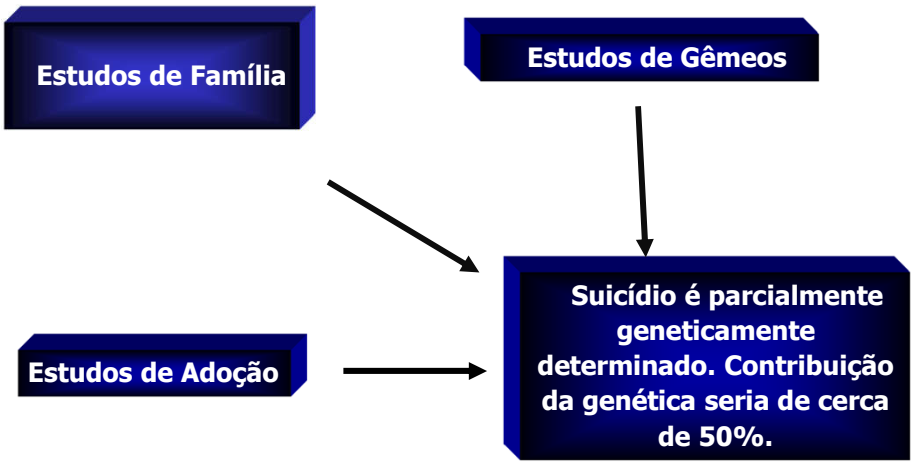
# Herdabilidade das doenças psiquiátricas

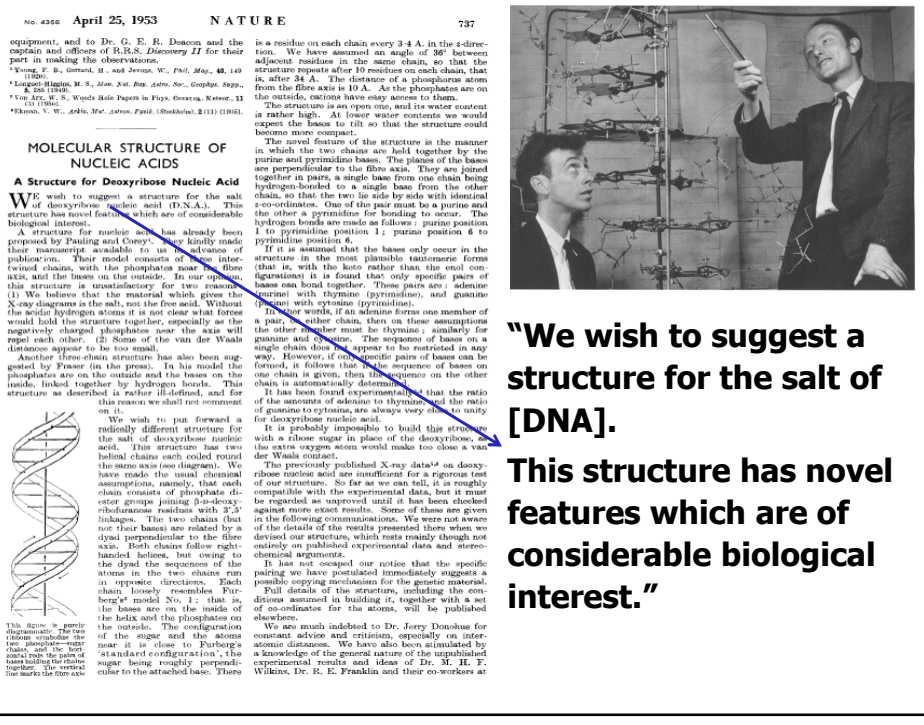



ASD: transtornos do espectro autista
AD: Alzheimer
ADHD: Transtorno do deficit de atanção e hiperatividade
AN: Anorexia nervosa
ALC: Dependência ao alcool
BIP: Transtorno Bipolar
BRCA: Cancer de mama
CD: Doença de Crohn
MDD: Transtorno depressivo maior
NIC: Dependencia de nicotina
SCZ: Esquizofrenia
T2DM: Diabetes tipo II

Sullivan et al, 2012. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature*

# Estudos de Genética Epidemiológica



No. 4356 April 25, 1953 NATURE 737

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1949).
[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).
[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

## MOLECULAR STRUCTURE OF NUCLEIC ACIDS

### A Structure for Deoxyribose Nucleic Acid

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three interwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[3,4] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

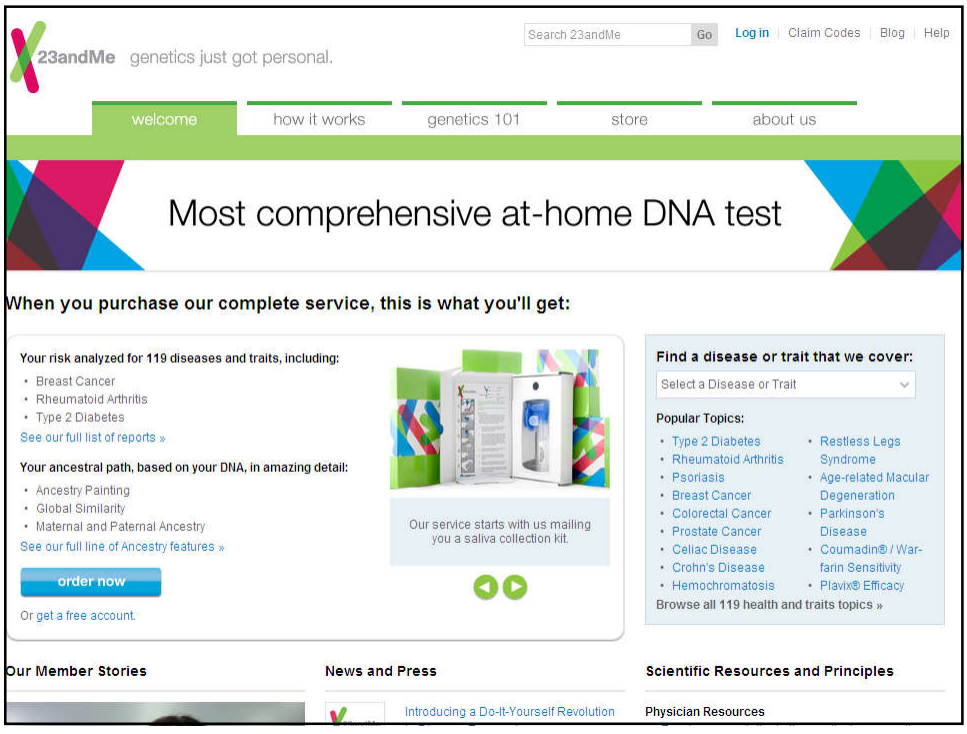
We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

**"We wish to suggest a structure for the salt of [DNA].**

**This structure has novel features which are of considerable biological interest."**


THE DRA
My Lord, they have discovered the human genome!
Damn hackers, I will have to change the password now.
ture
the human genome
GEDDA E.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SCIENCE VOL 319 18 JANUARY 2008

NEWSFOCUS

## Gene Tests for Psychiatric Risk Polarize Researchers

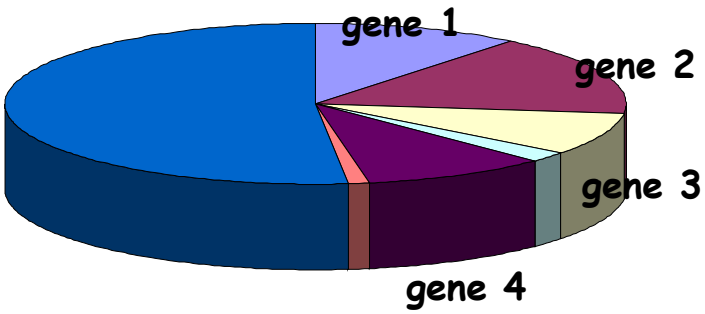
A small California company is the first to venture into psychiatric gene testing. But is the science ready?


Players in the Psychiatric Gene-Testing Business

| Company | Test available | Disease | Type of test | Number of genes |
|---|---|---|---|---|
| NeuroMark | mid–2008 | Major depression | Risk of suicidality from antidepressants | 4 |
| Psynomics | now | Bipolar disorder | Diagnosis and response to antidepressants | 2* |
| SureGene | mid–2009 | Schizophrenia | Risk of psychosis and response to antipsychotics | 6 |

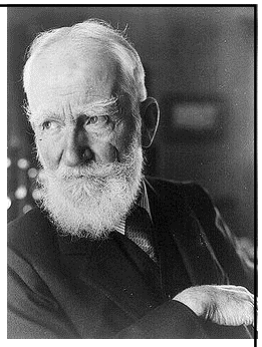
* Psynomics plans to add five more genes early this year.

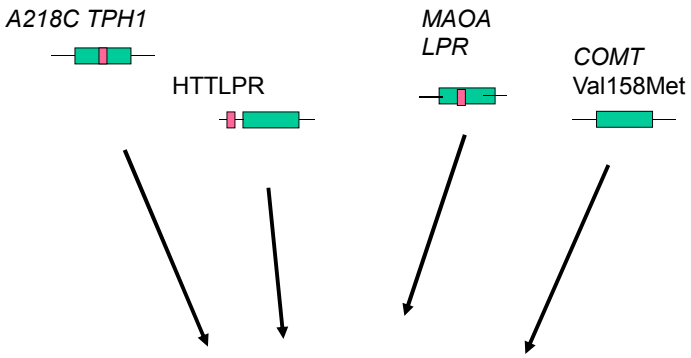
# Quais são os 04 genes da suicidabilidade??



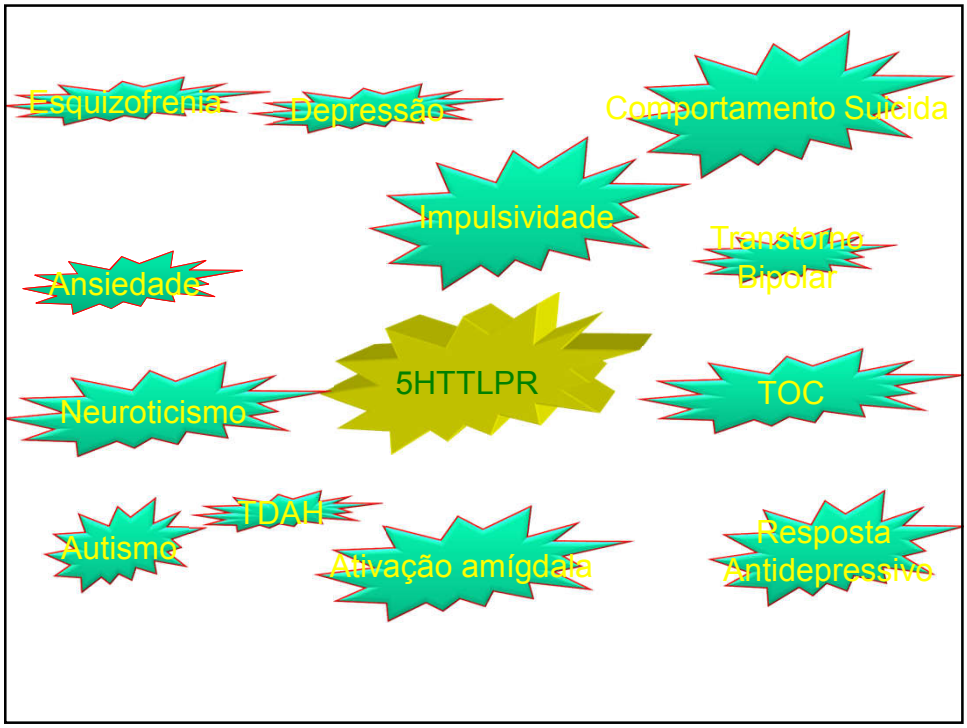
"Para todo problema complexo, existe uma solução clara, simples...

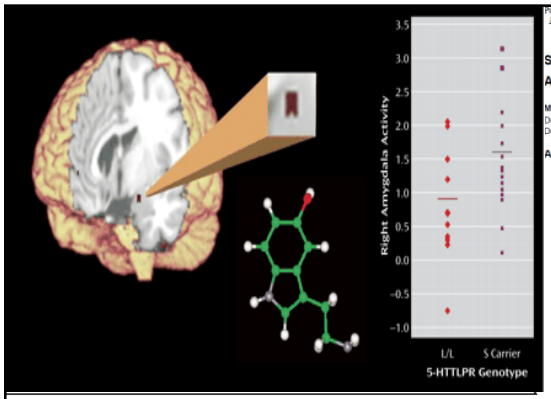
e errada."






**Comportamento Suicida**

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*Biol Psychiatry*. 2008 May 1; 63(9): 852–857. doi:10.1016/j.biopsych.2007.08.016.

## Serotonin Transporter (5-HTTLPR) Genotype and Amygdala Activation: A Meta-Analysis

**Marcus R. Munafò**, **Sarah M. Brown**, and **Ahmad R. Hariri**
Department of Experimental Psychology (MRM), University of Bristol, United Kingdom; Departments of Psychiatry and Psychology (SMB, ARH), University of Pittsburgh, Pennsylvania.

**Abstract**

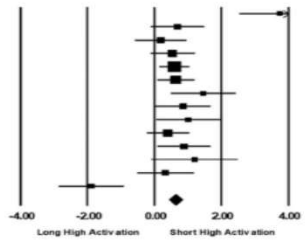
**Background:** We evaluated the magnitude of the reported associations between amygdala activation and the serotonin transporter gene linked polymorphic region (5-HTTLPR) and the likely effect size of this relationship.

**Methods:** We used meta-analytic techniques to combine data from existing published and unpublished studies. We also tested for possible publication bias and explored possible moderating influences on any association, such as sample ancestry.

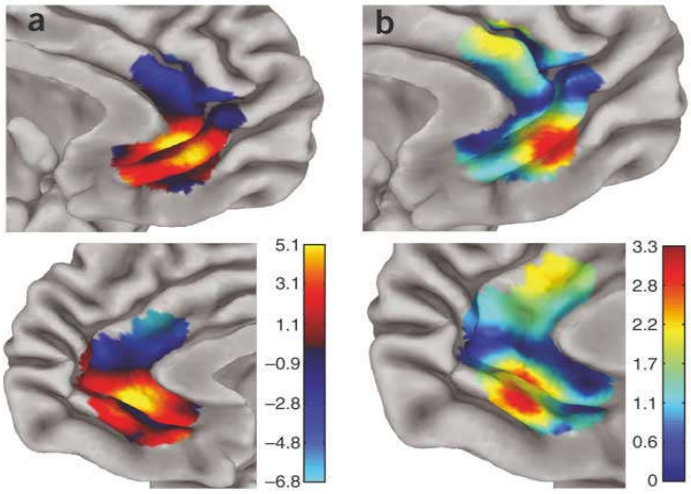
**Results:** Our results provide support for the association of the 5-HTTLPR polymorphism and amygdala activation and suggest that this locus may account for up to 10% of phenotypic variance. Although we did not observe evidence for potential publication bias in our main analysis, this was due in part to efforts to obtain unpublished data pertinent to this meta-analysis, and when three unpublished data sets were excluded we did observe evidence of such bias. We also observed evidence that the first published study may provide an overestimate of the true effect size, which is consistent with findings from genetic association studies of other phenotypes.

**Conclusions:** Although our analysis provides support for the association of the 5-HTTLPR polymorphism and amygdala activation, it also suggests that most studies to date are nevertheless lacking in statistical power. Increasing the sample sizes of future imaging genetics studies will allow a more accurate characterization of any true effect size and afford adequate power to examine the impact of multiple polymorphisms that likely work in concert to affect gene function and, in turn, bias neural processes mediating dispositional traits such as temperament and personality.

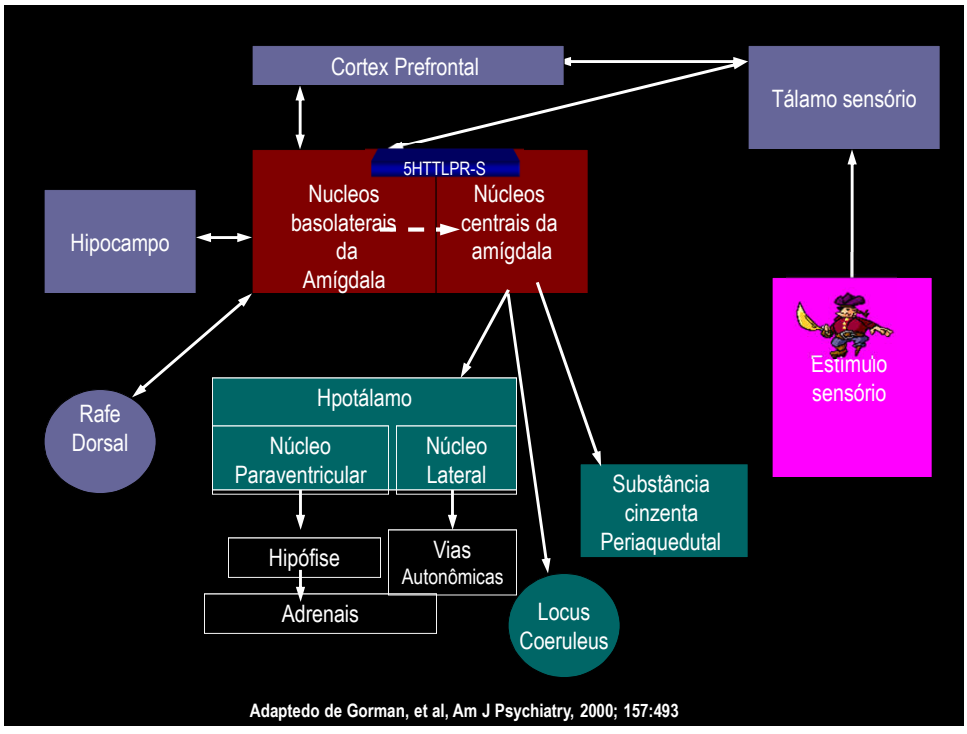
| Studyname | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z Value | p Value |
|---|---|---|---|---|---|---|---|
| Hariri 2002 | 3.748 | .627 | .394 | 2.518 | 4.977 | 5.973 | .000 |
| Heinz 2004 | .688 | .411 | .169 | - .118 | 1.495 | 1.673 | .094 |
| Bertolino 2005 | .193 | .395 | .156 | - .581 | .968 | 0.490 | .624 |
| Canli 2005 | .542 | .341 | .116 | - .128 | 1.210 | 1.590 | .112 |
| Hariri 2005 | .603 | .233 | .054 | .145 | 1.060 | 2.583 | .010 |
| Brown 2006 | .643 | .284 | .081 | .086 | 1.200 | 2.261 | .024 |
| Canli 2006 | 1.459 | .503 | .253 | .474 | 2.444 | 2.903 | .004 |
| Danniowski 2006 | .868 | .425 | .181 | .034 | 1.699 | 2.039 | .041 |
| Domschke 2006 | 1.014 | .495 | .245 | .043 | 1.985 | 2.046 | .041 |
| Danniowski 2007 | .403 | .328 | .108 | - .240 | 1.045 | 1.228 | .219 |
| Rao 2007 | .892 | .411 | .169 | .086 | 1.698 | 2.168 | .030 |
| Steinunpub | 1.204 | .664 | .440 | - .096 | 2.505 | 1.815 | .070 |
| Surguladze unpub | .333 | .436 | .190 | - .522 | 1.188 | 0.764 | .445 |
| Taylor unpub | -1.882 | .499 | .249 | -2.861 | - .903 | -3.769 | .000 |
| | .626 | .103 | .011 | .424 | .828 | 6.087 | .000 |



*Nature Neuroscience* 8, 828 - 834 (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression
Lukas Pezawas et al.




Integridade dessa via córtico-amígdala seria comprometida em portadores do alelo S resultando em perda da integração e regulação inibitória da Amígdala.



# HPA Axis Reactivity: A Mechanism Underlying the Associations Among 5-HTTLPR, Stress, and Depression

Ian H. Gotlib, Jutta Joormann, Kelly L. Minor, and Joachim Hallmayer

**Background:** Recent evidence indicates that individuals who are homozygous for the short (*s*) allele in the promoter region of the serotonin transporter gene have higher rates of depression and other psychiatric disorders as a function of exposure to increasing levels of stressful life events than do individuals who have one or two copies of the long (*l*) allele. Despite the reliability of this association, the mechanism by which this polymorphism confers risk for psychopathology in the presence of stress is not understood. This study was designed to examine the formulation that individuals who are homozygous for the *s* allele are characterized by a greater biological reactivity to stress than are their counterparts who have one or two copies of the *l* allele.

**Methods:** Girls at high (*n* = 25) and low (*n* = 42) risk for depression by virtue of the presence or absence of a family history of this disorder were genotyped and exposed to a standardized laboratory stress task. Cortisol levels were assessed before the stressor, after the stressor, and during an extended recovery period.

**Results:** Girls who were homozygous for the *s* allele produced higher and more prolonged levels of cortisol in response to the stressor than did girls with an *l* allele.

**Conclusions:** These findings indicate that the 5-HTTLPR polymorphism is associated with biological stress reactivity, which may increase susceptibility to depression in the face of stressful life events.

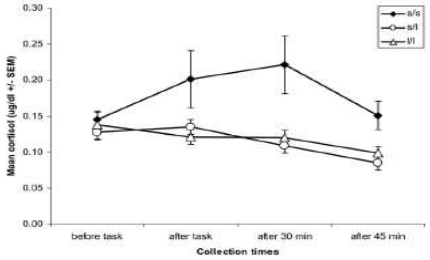



**Figure 1.** Stress reactivity by genotype.

of measurements (31), $F(2,63) = 4.26$, $p < .05$, reflecting the elevated cortisol production in response to stress in daughters who were homozygous for the *s* allele.[2]

# Genetic Variation in Brain-Derived Neurotrophic Factor Is Associated with Serotonin Transporter but Not Serotonin-1A Receptor Availability in Men

Susanne Henningsson, Jacqueline Borg, Johan Lundberg, Jessica Bah, Mats Lindström, Erik Ryding, Hristina Jovanovic, Tomoyuki Saijo, Makoto Inoue, Ingmar Rosén, Lil Träskman-Bendz, Lars Farde, and Elias Eriksson

**Background:** The serotonergic system, including the serotonin transporter (5-HTT), which is the target of many antidepressants, seems to be influenced by brain-derived neurotrophic factor (BDNF).

**Methods:** Positron emission tomography (PET) was used to address, in 25 and 53 healthy volunteers, respectively, the possible association between six polymorphisms in the gene encoding BDNF and the availability of two proteins expressed by serotonergic neurons: the 5-HTT, measured with the radioligand [$^{11}$C]MADAM, and the serotonin-1A (5-HT1A) receptor, measured with [$^{11}$C]WAY-100635.

**Results:** Several single nucleotide polymorphisms were associated with [$^{11}$C]MADAM binding potential (BP) in most brain regions, male carriers of the valine/valine genotype of the Val66Met polymorphism displaying higher availability. Effect sizes ranged from a 50% to a threefold increase. In contrast, there was no association for [$^{11}$C]WAY-100635 BP. The observation that BDNF polymorphisms were associated with 5-HTT availability could be partly replicated in an independent population comprising nine male suicide attempters and nine matched control subjects, in which transporter availability had been measured with single photon emission computed tomography with $^{123}$I-β-CIT as ligand.

**Conclusions:** Our results suggest that genetic variation in BDNF influences 5-HTT but not 5-HT1A receptor density in the human brain.

**Key Words:** BDNF, imaging, PET, serotonin, serotonin transporter, SPECT

and synaptic localization, exerts its effects via another receptor, p75NTR (21,23).

BIOL PSYCHIATRY 2009;66:477–485


# 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.

Depression is among the top five leading causes of disability and disease burden throughout the world (*1*). Across the life span, stressful life events that involve threat, loss, humiliation, or defeat influence the onset and course of depression (*2*–*5*). However, not all people who encounter a stressful life experience succumb to its depressogenic effect. Diathesis-stress theories of depression predict that individuals' sensitivity to stressful events depends on their genetic makeup (*6*, *7*). Behavioral genetics research supports this prediction, documenting that the risk of depression after a stressful event is elevated among people who are at high genetic risk and diminished among those at low genetic risk (*8*). However, whether specific genes exacerbate or buffer the effect of stressful life events on depression is unknown. In this study, a functional polymorphism in the pro-

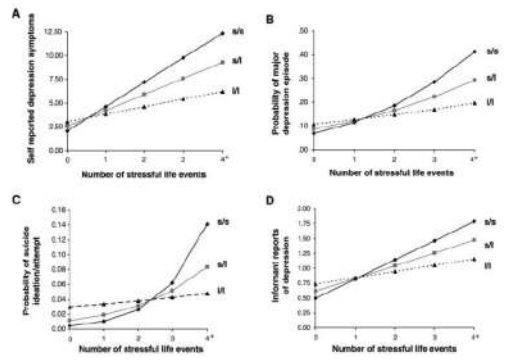
[1]Medical Research Council Social, Genetic, and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, PO80 De Crespigny Park, London, SE5 8AF, UK. [2]Department of Psychology, University of Wisconsin, Madison, WI 53706, USA. [3]Dunedin School of Medicine, [4]Department of Pathology, University of Otago, Dunedin, New Zealand.

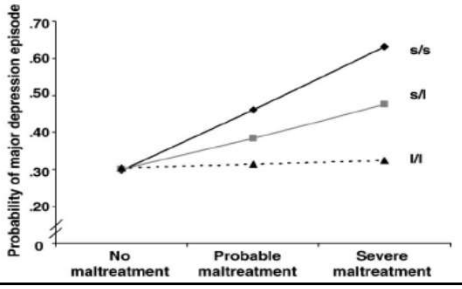
*To whom correspondence should be addressed. E-mail: t.moffitt@iop.kcl.ac.uk

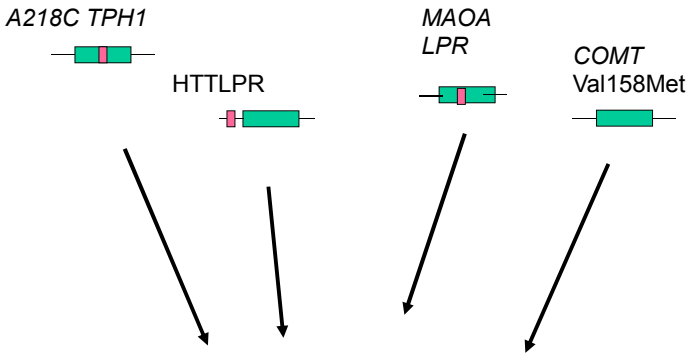











**Comportamento Suicida**

Published online: July 4, 2015

# Epigenetic Dysregulation in the Prefrontal Cortex of Suicide Completers

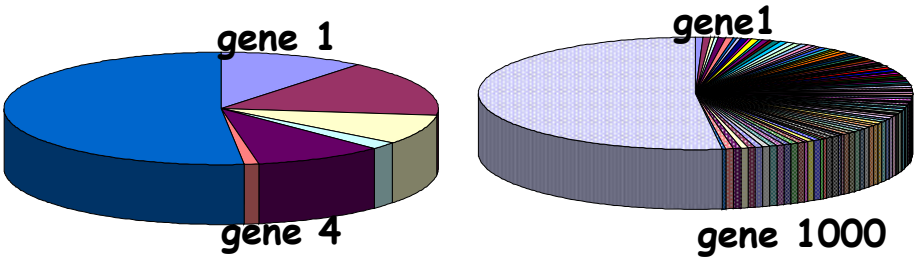
Eberhard Schneider[a] Nady El HajJ[a] Fabian Müller[b] Bianca Navarro[c] Thomas Haaf[a]

[a]Institute of Human Genetics, University of Würzburg, Würzburg, [b]Max Planck Institute for Informatics, Saarbrücken, and [c]Institute of Legal Medicine, University Medical Center, Mainz, Germany

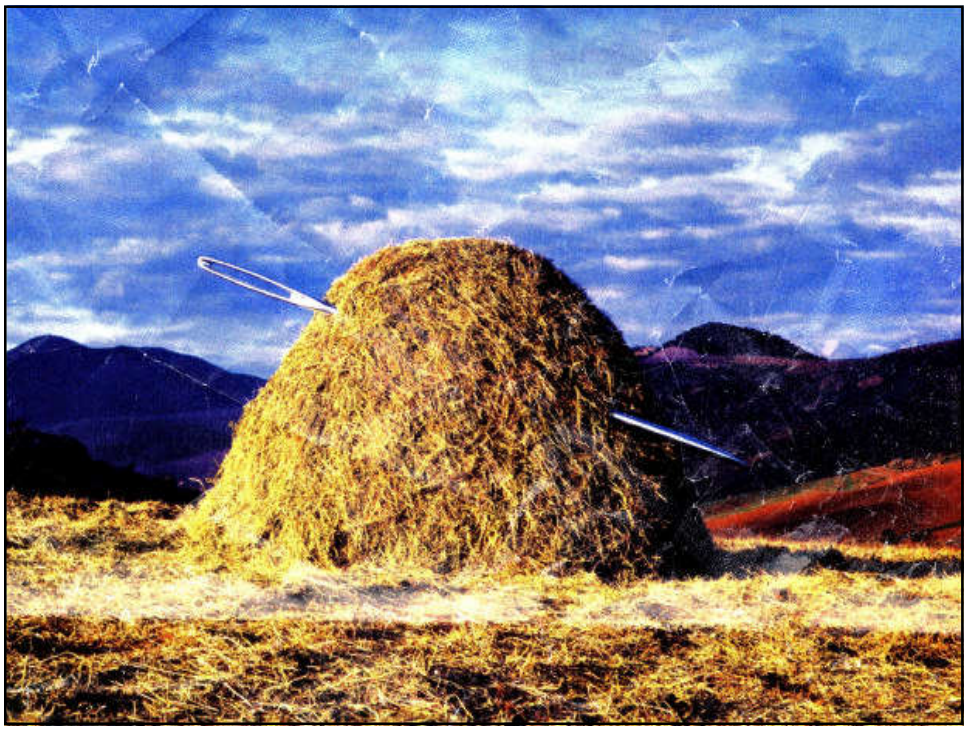
**Table 2.** Suicide candidate genes that have been replicated in genetic association, brain expression and methylation studies, respectively

| Gene* | Genetic asso-ciation | DNA methyl-ation | Expres-sion | Gene* | Genetic asso-ciation | DNA methyl-ation | Expres-sion | Gene* | Genetic asso-ciation | DNA methyl-ation | Expres-sion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *ABAT* | | | X | *HTR2A* | X | | X | *RPL19* | | X | |
| *AC004507.1* | | X | | *HTR2C* | X | | X | *RPS6KA1* | | X | |
| *ACCN3* | | X | | *HTRA1* | | | X | *S100A10* | X | | X |
| *ADCY8* | | X | | *IFNG* | | X | | *S100B* | | | X |
| *AMD1* | | | X | *IL1R2* | | X | | *SCD* | | | X |
| *APLP2* | | | X | *ITPR1* | | | X | *SFRS5* | | X | |
| *AQP4* | | | X | *KCNJ12* | | X | | *SGK2* | | X | |
| *ARG2* | | X | X | *KLHL34* | | X | | *SLC1A2* | | | X |
| *ARVCF* | | X | | *KRT37* | | X | | *SLC1A3* | | | X |
| *ASB3* | | X | | *LASS2* | | X | | *SLC6A4* | X | | X |
| *ATP1B2* | | | X | *LEPR* | | | X | *SLC14A1* | | X | |
| *ATP6V0A1* | | | X | *LIMS1* | | X | | *SMOX* | | | X |
| *BDNF* | X | X | X | *LOC100129652* | | | X | *SMS* | | | X |
| *BTG1* | | | X | *LOC440917* | | | X | *SNAP25* | | | X |
| *C1orf120* | | X | | *MAPKAP1* | | X | | *SNORA68* | | X | |
| *C4orf21* | | X | | *MARCKS* | | | X | *SNORD31* | | X | |
| *C8orf45* | | X | | *MCRS1* | | X | | *SNORD59B* | | X | |
| *C8orf71* | | X | | *MBP* | | | X | *SNORD114-14* | | X | |
| *CD9* | | | X | *ME1* | | X | | *SNORD115-7* | | X | |
| *CENPP* | | X | | *MIR10B* | | X | | *SNORD115-22* | | X | |
| *CLEC12B* | | X | | *MIR555* | | X | | *SNPH* | | | X |
| *COMT* | X | | | *MOG* | | | X | *SOX9* | | | X |
| *CREB* | | | X | *MSI1* | | X | | *SPTBN1* | | | X |
| *CRHR2* | X | | | *MSMP* | | X | | *SSAT* | X | X | X |
| *CTNNB1* | | | X | *NME1-NME2* | | X | | *SST* | | X | |
| *DEDD* | | X | | *NR3C1* | | X | X | *SYN2* | | | X |
| *DLEC1* | | X | | *NTRK2* | | X | X | *SYNE2* | | X | |
| *DTNA* | | | X | *NUAK1* | | X | | *SYNPO2* | | | X |
| *DYRK2* | | X | | *OR13G1* | | X | | *SYNPO2L* | | X | |
| *ECHDC1* | | X | | *PCDHA2* | | X | | *SYPL1* | | | X |
| *EZR* | | X | X | *PCTP* | | X | | *TAF5L* | | X | |
| *F10* | | X | | *PHACTR3* | | X | | *TFPT* | | X | |
| *FAM49B* | | X | | *PHC1B* | | X | | *TGM7* | | X | |
| *FAM96A* | | X | | *PKM2* | | X | | *TGOLN2* | X | | |
| *GABBR2* | | | X | *PLCZ1* | | X | | *TMPRSS6* | | X | |
| *GABRA1* | | | X | *PLSCR4* | | | X | *TNFA* | X | | |
| *GABRB1* | | | X | *PMF1* | | X | | *TOP1* | | | X |
| *GATM* | | | X | *PMP22* | | | X | *TPH1* | X | | |
| *GJA1* | | X | X | *PNMAL2* | | X | | *TPH2* | X | | X |
| *GLUL* | | | X | *POMP* | | X | | *TSPYL1* | | | X |
| *GP5* | | X | | *PRKCI* | | | X | *UBC* | | | X |
| *GPM6B* | | | X | *PRPF40A* | | X | | *UGT1A9* | | X | |
| *GPR133* | | X | | *PTDSS1* | | X | | *USP25* | | X | |
| *GRIA2* | | | X | *PTN* | | | X | *USP27X* | | X | |
| *GSK3B* | X | | X | *PTP4A2* | | | X | *VAMP3* | | | X |
| *H3F3B* | | X | | *RAB31* | | X | | *VAV3* | | X | |
| *HIST2H2AB* | | X | | *RAC1* | | | X | *VTA1* | | X | |
| *HOMEZ* | | X | | *RFT1* | | X | | *YWHAE* | | | X |
| *HSD17B6* | | | X | *RIMS1* | | X | | *ZNF185* | | X | |
| *HTR1A* | X | | | *RNF6* | | X | | *ZNF259* | | X | |
| *HTR1B* | X | | | *RPL13A* | | | X | *ZNF546* | | X | |

* Genes highlighted in bold belong to the top 1,000 DMRs.


gene 1
gene 4


gene1
gene 1000



Molecular Psychiatry (2003) 0, 000–000

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SCIENTIFIC CORRESPONDENCE

# Association of the serotonin transporter promoter polymorphism with suicidal behavior

*Molecular Psychiatry* (2003) **0**, 1–2. doi:10.1038/sj.mp.4001381

is important because a significant degree of past suicidal behavior may not be recorded during routine clinical assessment.[4] Furthermore, we evaluated, for the most lethal lifetime suicide attempt; the lethality, using the Lethality Rating Scale (LRS), scored 0–8,[1,2] with a score of 3 or greater as a cutoff point; the intention with the Suicide Intent Scale (SIS);[5] and the methods, classified as nonviolent (drug overdose) or violent (cutting beyond a superficial scratch, jumping from a height, shooting, hanging).

$P = 0.001$). In S-carriers, LL-carriers as reference, the odds ratio were 2.34 (95% CI (1.32–4.15)), 2.44 (95% CI (0.93–6.53)) and 3.97 (95% CI(1.37–11.91)), respectively, to number of suicide attempts, lethality greater than 2 and violent suicide attempt.

**AC Campi-Azevedo[1,4], W Boson[1], LA De Marco[1,2], MA Romano-Silva[1,2,4] and H Correa[1,3,4]**

[1]*Laboratório de Farmacogenética, ICB, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil;* [2]*Departamento de Farmacologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil;* [3]*Departamento de Morfologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil;* [4]*Grupo de*

Molecular Psychiatry (2003) 0, 000–000

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[1]*Laboratório de Farmacogenética, ICB, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil;* [2]*Departamento de Farmacologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil;* [3]*Departamento de Morfologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil;* [4]*Grupo de Pesquisa em Neuropsiquiatria Clínica e Molecular, Universidade Federal de Minas Gerais, Belo Horizonte-MG, Brazil*

Correspondence should be addressed to Professor H Correa, Departamento de Morfologia–ICB, Universidade Federal de Minas Gerais, Av. Antônio Carlos 6627, 31220-901 Belo Horizonte-MG, Brazil.
E-mail:

AJMB-06-0310.R1(30563)

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 9999:1–3 (20



*Brief Research Communication*

## Is the *5-HTTLPR* Polymorphism Associated With Bipolar Disorder or With Suicidal Behavior of Bipolar Disorder Patients?

**F.S. Neves,[1] G. Silveira,[2] M.A. Romano-Silva,[2] L. Malloy-Diniz,[2] A.A. Ferreira,[1] L. De Marco,[3] and H. Correa[2]***

[1][IPSEMG][2], *Belo Horizonte, Brazil*
[2]*Department of Mental Health, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil*
[3]*Department of Pharmacology, Universi*


EPIGENETICS

# Tales of adversity

*Genetic studies of people conceived during famine reveals that prenatal malnutrition lingers long after the event.*

# “Hongerwinter” 1944

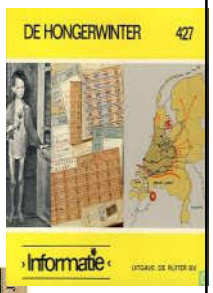


Crianças nascidas nesse período tiveram menores na estatura, e tinham muitas doenças incluindo edema, anemia, diabetes e depressão, esquizofrenia…

Figure 1. Rations in Calories in Three-Month Averages from June 1944 through November 1945.

| | WEST | NORTH | SOUTH |
|---|---|---|---|
| 1944 | | | |
| Mar-May | 1,572 | 1,572 | 1,572 |
| Sept-Nov | 1,414 | 1,450 | 1,491 |
| 1944-45 | | | |
| Dec-Feb | 1,572 | 1,572 | 1,572 |
| Mar-May | 670 | 1,392 | 1,692 |
| June-Aug | 1,755 | 1,755 | 1,864 |
| Sept-Nov | 2,083 | 2,083 | 2,083 |

O **“Dutch Famine Birth Cohort”** mostrou que as mulheres, vinte ou trinta anos depois, tiveram filhos também com mais problemas de saúde como: hipertensão, diabetes, depressão, esquizofrenia e transtornos de personalidade.





Ravelli, G.-P., et al. N Engl J Med 1976; 295:349-353

[Epigenetics 3:2, 97-106; March/April 2008]; ©2008 Landes Bioscience

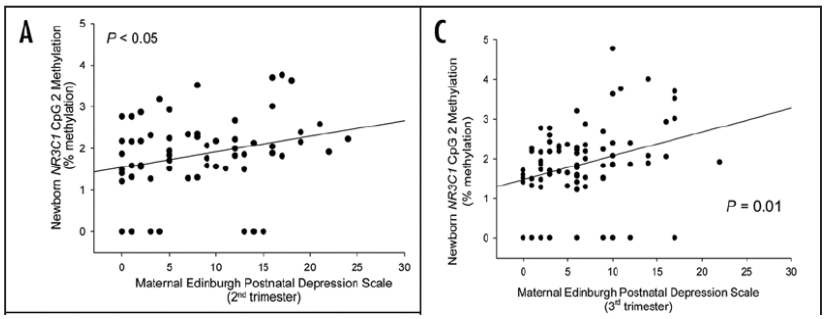
Research Paper

## Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress responses

Tim F. Oberlander,[1,2,*] Joanne Weinberg,[2,3] Michael Papsdorf,[1] Ruth Grunau,[1,2] Shaila Misri[4] and Angela M. Devlin[1,2]

[1]Department of Pediatrics; Early Human Experience Unit; [2]Child and Family Research Institute; [3]Department of Cellular and Physiological Sciences; [4]Department of Psychiatry; University of British Columbia; Vancouver, British Columbia Canada

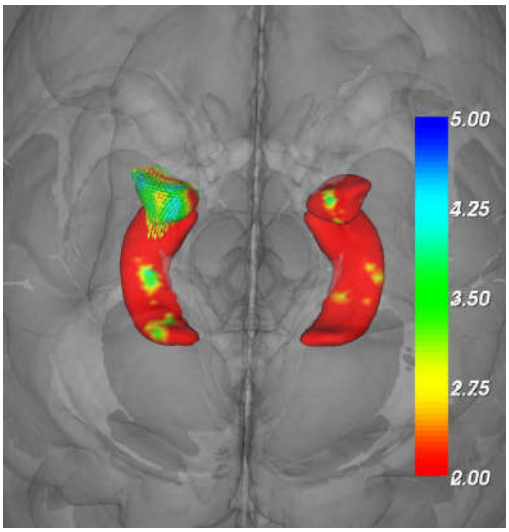
Key words: *NR3C1* methylation, prenatal maternal depression, hypothalamic pituitary adrenal, (HPA), infant stress response



# Fetal exposure to maternal cortisol is associated with child brain development

- **Altas concentrações de cortisol na gestação são associadas com maiores volumes do corpo amigdaloide e mais problemas psiquiátricos futuros.**

- A magnitude do aumento é substancial: 1 SD de aumento no cortisol materno associado com 6.4% de aumento.



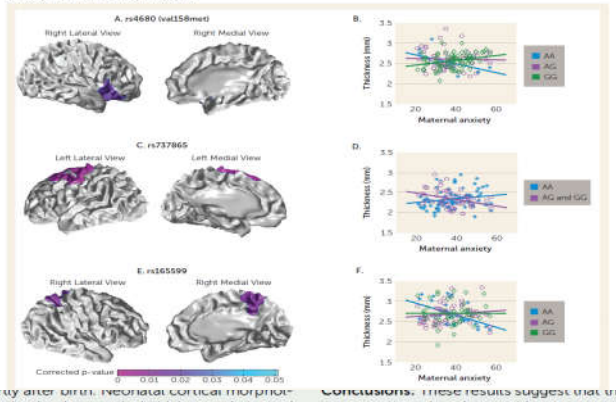

*Buss et al., Proceedings of the National Academy of Science, 2012, 109, E1312-1319*



COMT H … natal
Materna … gy

Anqi Qiu, Ph.D., T … h.D.,
Birit F.P. Broekmar … an, Ph.D.,
Marielle V. Fortier,

FIGURE 2. Statistical Maps of Interactive Effects of Antenatal Maternal Anxiety and Individual Single-Nucleotide Polymorphisms (SNPs) on Cortical Thickness in Neonates[a]

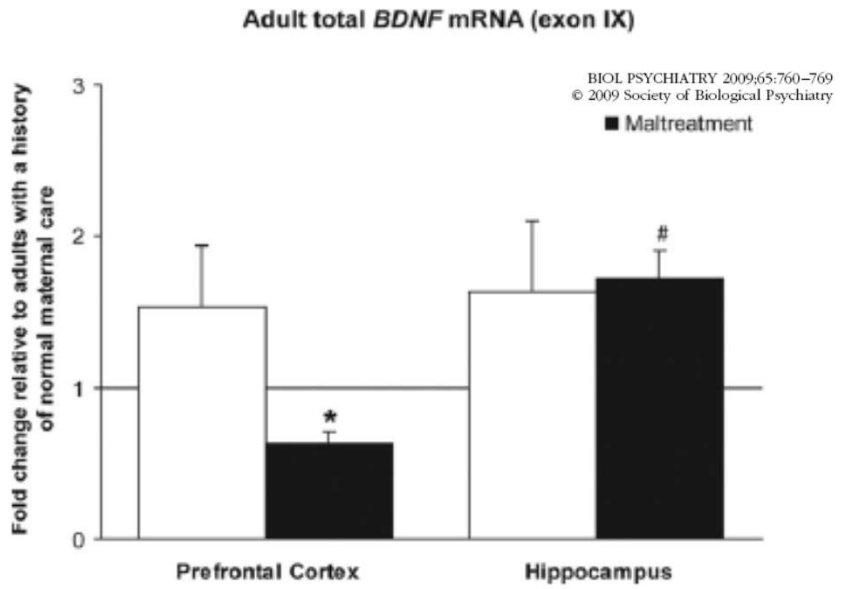



**Objective:** Exp… egression
plex genetic var… val158*met*-
particular, the … e proba-
located on chr… l maternal
signaling in the … teral pre-
pain, and stress … ortex and
dividual single-… ype prob-
gene and their … natal ma-
antenatal mater… precentral

**Method:** A tota… derwent MRI shortly after birth. Neonatal cortical morphology was characterized using cortical thickness. Antenatal maternal anxiety was assessed using the State-Trait Anxiety Inventory at week 26 of pregnancy.

**Results:** Individual COMT SNPs (*val158met*, rs737865, and rs165599) modulated the association between antenatal maternal anxiety and the prefrontal and parietal cortical … **Conclusions:** These results suggest that the association between maternal anxiety and in utero neurodevelopment is modified through complex genetic variation in *COMT*. Such genetic moderation may explain, in part, the variation in phenotypic outcomes in offspring associated with maternal emotional well-being.

*Am J Psychiatry 2015; 172:163–172; doi: 10.1176/appi.ajp.2014.14030313*



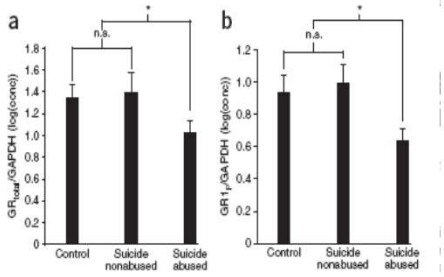
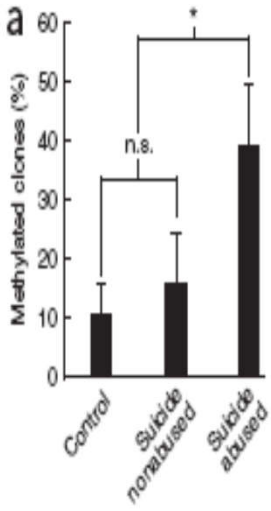




**Figure 1** Hippocampal glucocorticoid receptor expression. (a,b) Mean ± s.e.m. expression levels of total glucocorticoid receptor (GR) mRNA (a) and glucocorticoid receptor $1_F$ ($GR1_F$) in 12 suicide victims with a history of childhood abuse, 12 nonabused suicide victims and 12 control subjects (b). Outliers excluded from analysis included $n = 2$ control subjects, $n = 1$ suicide victims with a history of childhood abuse for glucocorticoid receptor $1_F$ and an additional $n = 1$ suicide victim with a history of childhood abuse, and $n = 3$ nonabused suicide victims for overall levels of glucocorticoid receptor. * indicates $P < 0.05$; n.s. indicates not statistically significant.





ORIGINAL ARTICLE

# Alternative Splicing, Methylation State, and Expression Profile of Tropomyosin-Related Kinase B in the Frontal Cortex of Suicide Completers

*Carl Ernst, MSc; Vesselina Deleva, MSc; Xiaoming Deng, MD; Adolfo Sequeira, PhD; Amanda Pomarenski, BSc; Tim Klempan, PhD; Neil Ernst, MSc; Remi Quirion, PhD; Alain Gratton, PhD; Moshe Szyf, PhD; Gustavo Turecki, MD, PhD*

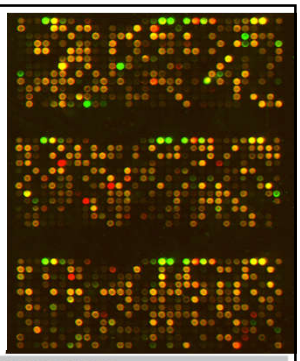
**Context:** Although most of the effort to understand the neurobiology of depressive states and suicide has focused on neuronal processes, recent studies suggest that astroglial dysfunction may play an important role. A truncated variant of the tropomyosin-related kinase B (TrkB.T1) is expressed in astrocytes, and brain-derived neurotrophic factor–TrkB signaling has been linked to mood disorders.

**Objective:** To test the hypothesis that TrkB.T1 expression is downregulated in suicide completers and that this downregulation is mediated by an epigenetic process.

**Design:** Postmortem case-control study.

periments were performed to control for drug and alcohol effects. Genetic and epigenetic studies were performed by means of direct sequencing and bisulfite mapping.

**Results:** We found that 10 of 28 suicide completers (36%) demonstrated significant decreases in different probe sets specific to TrkB.T1 in Brodmann areas 8 and 9. These findings were generalizable to other frontal regions but not to the cerebellum. The decrease in TrkB expression was specific to the T1 splice variant. Our results were not accounted for by substance comorbidity or by reduction in astrocyte number. We found no effect of genetic variation in a 2500–base pair promoter region or at relevant splice junctions; however, we detected an effect of



OPEN ACCESS Freely available online

PLoS one

# Global Brain Gene Expression Analysis Links Glutamatergic and GABAergic Alterations to Suicide and Major Depression

**Adolfo Sequeira[1]*, Firoza Mamdani[1], Carl Ernst[1], Marquis P. Vawter[2], William E. Bunney[2], Veronique Lebel[1], Sonia Rehal[1], Tim Klempan[1], Alain Gratton[3], Chawki Benkelfat[3], Guy A. Rouleau[3], Naguib Mechawar[1], Gustavo Turecki[1]***

[1] McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada, [2] Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada, [3] Jon Jones Hospital, Université de Montréal, Montreal, Quebec, Canada, [4] Department of Psychiatry and Human Behavior, School of Medicine, University of California Irvine, Irvine, California, United States of America

**Abstract**

*Background:* Most studies investigating the neurobiology of depression and suicide have focused on the serotonergic system. While it seems clear that serotonergic alterations play a role in the pathogenesis of these major public health problems, dysfunction in additional neurotransmitter systems and other molecular alterations may also be implicated. Microarray expression studies are excellent screening tools to generate hypotheses about additional molecular processes that may be at play. In this study we investigated brain regions that are known to be implicated in the neurobiology of suicide and major depression are likely to represent valid global molecular alterations.

*Methodology/Principal Findings:* We performed gene expression analysis using the HG-U133AB chipset in 17 cortical and subcortical brain regions from suicides with and without major depression and controls. Total mRNA for microarray analysis was obtained from 603 brain samples isolated from 39 male subjects, including 26 suicide cases and 13 controls diagnosed by means of psychological autopsies. Independent brain samples from 34 subjects and animal studies were used to control for the potential confounding effects of comorbidity with alcohol. Using a Gene Ontology analysis as our starting point, we identified molecular pathways that may be involved in depression and suicide, and performed follow-up analyses on these possible targets. Methodology included gene expression measures from microarrays, Gene Score Resampling for global ontological profiling, and semi-quantitative RT-PCR. We observed the highest number of suicide specific alterations in prefrontal cortical areas and hippocampus. Our results revealed alterations of synaptic neurotransmission and intracellular signaling. Among these, Glutamatergic (GLU) and GABAergic related genes were globally altered. Semi-quantitative RT-PCR results investigating expression of GLU and GABA receptor subunit genes were consistent with microarray data.

*Conclusions/Significance:* The observed results represent the first overview of global expression changes in brains of suicide victims with and without major depression and suggest a global brain alteration of GLU and GABA receptor subunit genes in these conditions.

ARTICLE IN PRESS

ARCHIVAL REPORT

# Characterization of QKI Gene Expression, Genetics, and Epigenetics in Suicide Victims with Major Depressive Disorder

Timothy A. Klempan, Carl Ernst, Vesselina Deleva, Benoit Labonte, and Gustavo Turecki

**Background:** A number of studies have suggested deficits in myelination and glial gene expression in different psychiatric disorders. We examined the brain expression and genetic/epigenetic regulation of QKI, an oligodendrocyte-specific RNA binding protein important for cell development and myelination.

**Methods:** The microarray-based expression of QKI was evaluated in cortical and subcortical brain regions from suicide victims with a diagnosis of major depression ($n = 16$) and control subjects ($n = 13$). These findings were also assessed with a real-time (quantitative polymerase chain reaction [qPCR]) approach, with QKI protein levels evaluated through immunoblotting. Identification of a QKI promoter sequence was then used to examine genetic and epigenetic variation at the QKI locus.

**Results:** The messenger RNA (mRNA) levels of multiple transcripts of QKI were evaluated on Affymetrix microarrays, revealing significant reductions in 11 cortical regions and the hippocampus and amygdala of suicide victims compared with control subjects. Microarray findings were confirmed by qPCR, and reduced expression of QKI protein was identified in orbitofrontal cortex. Analysis of promoter variation and methylation state in a subset of individuals did not identify differences at the genetic or epigenetic level between depressed suicide victims and control subjects.

**Conclusions:** The observation of consistent reductions in multiple isoforms of QKI mRNA in depressed suicide victims supports the growing body of evidence for a role of myelination-related deficits in the etiology of psychiatric disorders. A specific role of QKI in this process is implied by its reduced expression and known interactions with genes involved in oligodendrocyte determination; however, QKI gene variation responsible for these changes remains to be identified.

Brief report

# *Increased DNA methylation in the suicide brain*

*Fatemeh Haghighi, PhD; Yurong Xin, PhD; Benjamin Chanrion, PhD; Anne H. O'Donnell, MD, PhD; Yongchao Ge, PhD; Andrew J. Dwork, MD; Victoria Arango, PhD; J. John Mann, MD*

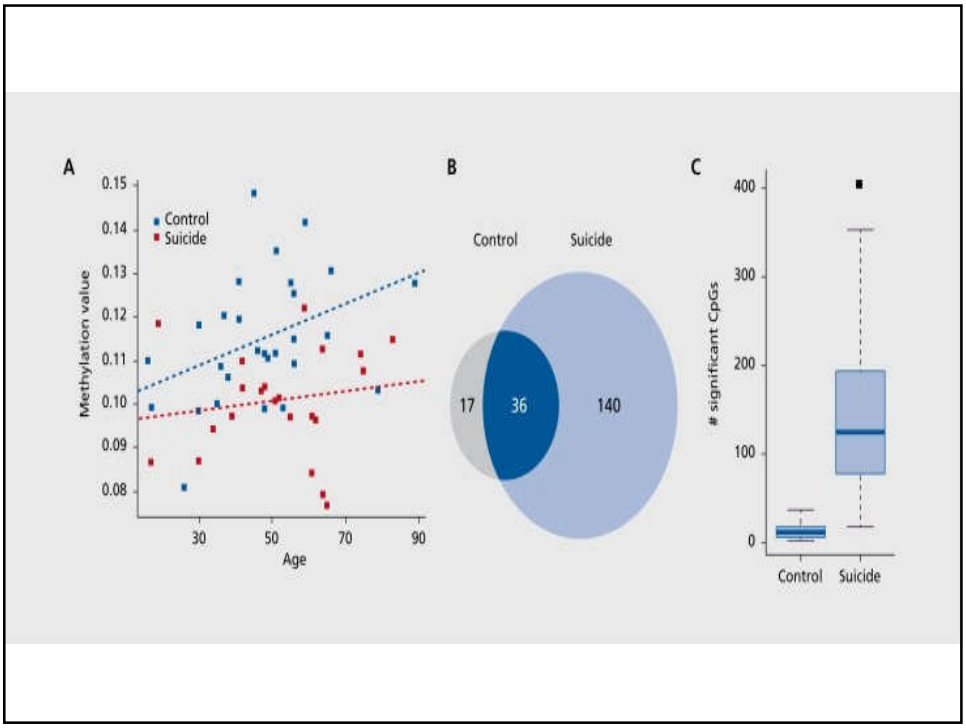
***Clinical studies find that childhood adversity and stressful life events in adulthood increase the risk for major depression and for suicide. The predispositions to either major depression or suicide are thought to depend on genetic risk factors or epigenetic effects. We investigated DNA methylation signatures postmortem in brains of suicides with diagnosis of major depressive disorder. DNA methylation levels were determined at single C-phosphate-G (CpG) resolution sites within ventral prefrontal cortex of 53 suicides and nonpsychiatric controls, aged 16 to 89 years. We found that DNA methylation increases throughout the lifespan. Suicides showed an 8-fold greater number of methylated CpG sites relative to controls ($P<2.2\times10^{-16}$), with greater DNA methylation changes over and above the increased methylation observed in normal aging. This increased DNA methylation may be a significant contributor to the neuropathology and psychopathology***

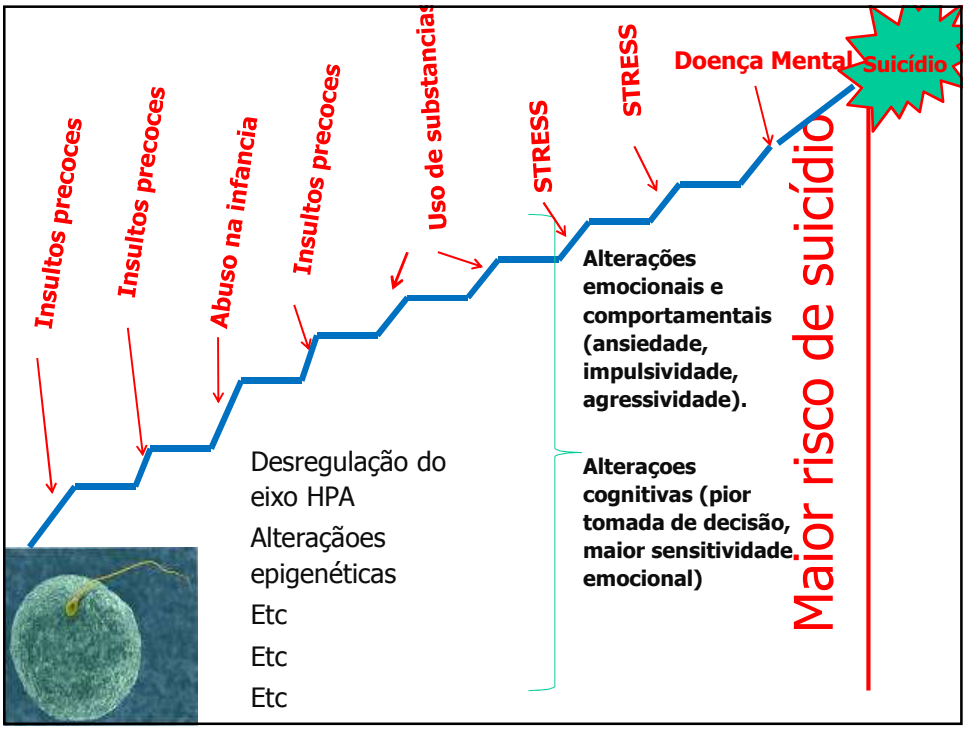
## Introduction

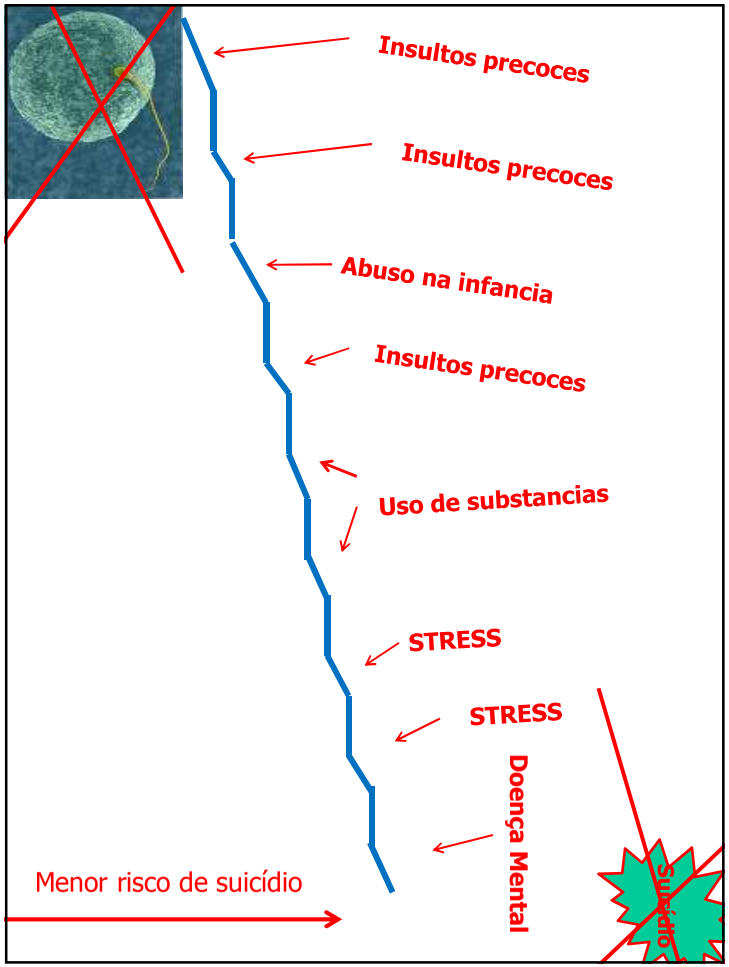
The World Health Organization estimates that nearly 1 million people die from suicide yearly (World Health Organization figures, 2012). Psychological autopsies find that about 90% of suicides in Western nations have a psychiatric illness at the time of suicide.[1] Of those, about 60% are suffering from a mood disorder. Suicide risk is influenced by a wide range of factors. Although some genetic risk factors have been identified, environmental events such as childhood adversity or repeated exposure to life-threatening situations typical in war and active combat have also been reported to contribute to the increased risk of suicidal behavior.[2] Exposure to stress can confer lasting biological and behavioral effects, such as altered responses to stress, throughout the lifespan, and as such these effects may be mediated by epigenetic factors like DNA methyla-

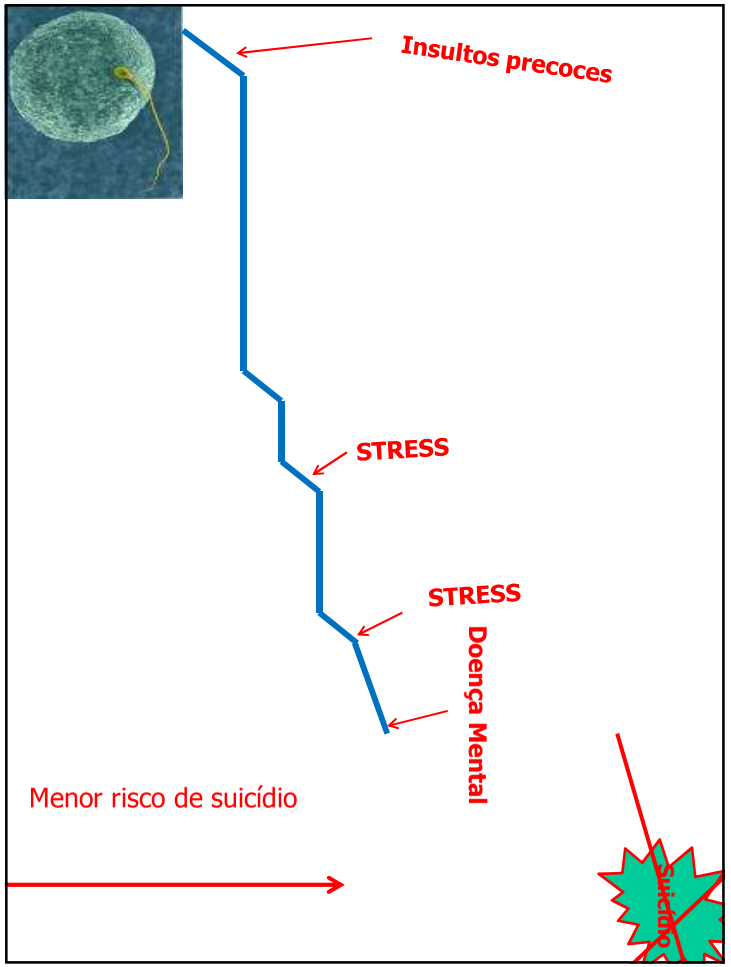
**Keywords:** *aging; depression; DNA methylation; epigenetics; mood disorder; suicide*

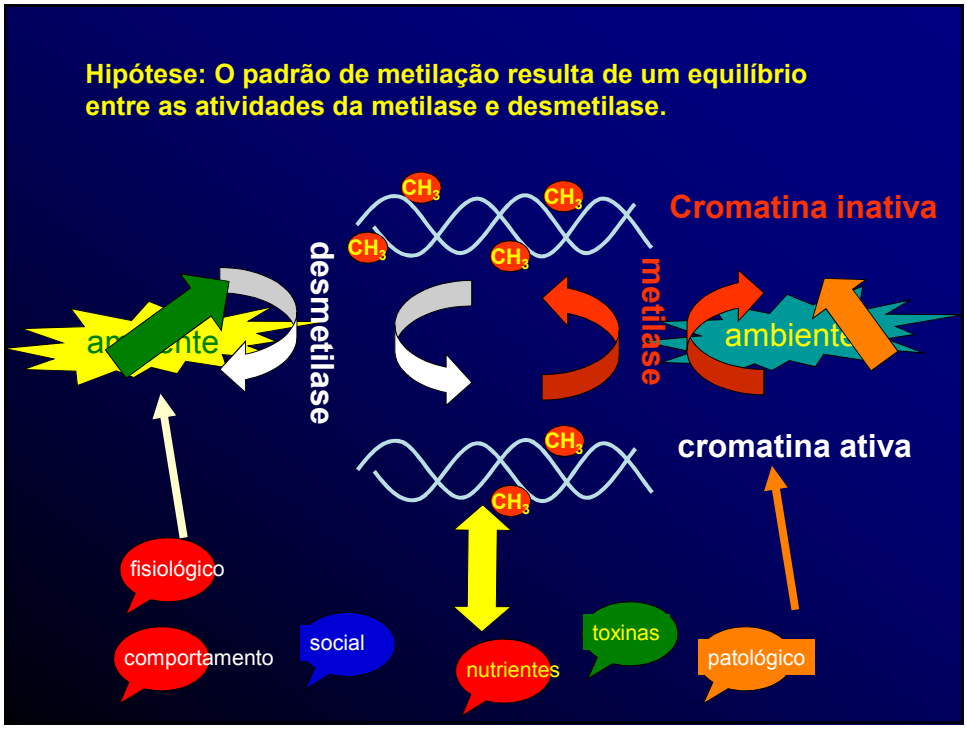
**Author affiliations:** James J. Peters Veterans Affairs Medical Center; Fishberg Department of Neuroscience, Mount Sinai School of Medicine (Fatemeh Haghighi); Department of Psychiatry, Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, Columbia University (Fatemeh Haghighi, Yurong Xin, Benjamin Chanrion, Anne H. O'Donnell, Andrew J. Dwork, Victoria Arango, J. John Mann); Depart-


A
Methylation value
Age
Control
Suicide
B
Control
Suicide
17
36
140
C
# significant CpGs
Control
Suicide


Insultos precoces
Insultos precoces
Abuso na infancia
Insultos precoces
Uso de substancias
STRESS
STRESS
Doença Mental
Suicídio
Maior risco de suicídio
Alterações emocionais e comportamentais (ansiedade, impulsividade, agressividade).
Alteraçoes cognitivas (pior tomada de decisão, maior sensitividade emocional)
Desregulação do eixo HPA
Alteraçãoes epigenéticas
Etc
Etc
Etc


Insultos precoces
Insultos precoces
Abuso na infancia
Insultos precoces
Uso de substancias
STRESS
STRESS
Doença Mental
Menor risco de suicídio
Suicídio


Insultos precoces
STRESS
STRESS
Doença Mental
Menor risco de suicídio
Suicídio

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COMMENTARY

# Psychotherapy as an epigenetic 'drug': psychiatric therapeutics target symptoms linked to malfunctioning brain circuits with psychotherapy as well as with drugs

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Obrigado pela Atenção