

PERSPECTIVAS DEL TDAH EN EL SIGLO XXI

Hospital Universitario
Ramón y Cajal



**Abordaje Multidisciplinar
de los
Trastornos del Neurodesarrollo
en la Infancia (XIII)**

Organizado por:



Servicio de Pediatría. B. García Cuartero. Jefa de Servicio

2 y 3 de Noviembre de 2017

Salón de Actos. Planta 0 D.
Hospital Universitario Ramón y Cajal

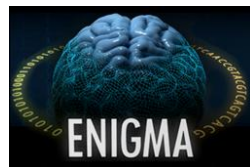
UAB

Universitat Autònoma de Barcelona

**Vall
d'Hebron**
Barcelona Campus Hospitalari

cibersam

Centro de Investigación Biomédica En
Red
de Salud Mental



PGC
Psychiatric Genomics Consortium

Declaración de Intereses

Company	Speaker	Consultant	Grants
Lilly	X	X	X
Shire	X	X	X
Nesplora			X
Ferrer		X	X
Psious			X
B-Gaze		X	X
Medice	X	X	
Roche			X
Janssen			X
Lundbeck			X
Instituto Carlos III- EU FP7-H2020		X	X



INDICE

- **Introducción general**
- **Estudios de neuroimagen**
- **Estudios genéticos**
- **Tratamiento**
- **Conclusiones**

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VIAJE POR LA HISTORIA

Weikard

Augusto Vidal Perera

Metilfenidato

1775

1907

1957

1902

1937

1967

2017...

George Still

Charles Bradley
Benzedrina

Menkes
Estudios en
adultos

Genética
Neuroimagen
Evolución
Repercusiones
Tratamientos



PREVALENCIA

Infancia: 5,27%

Polanczyk et al. Am J Psych 2007

Adultez: 3,4%

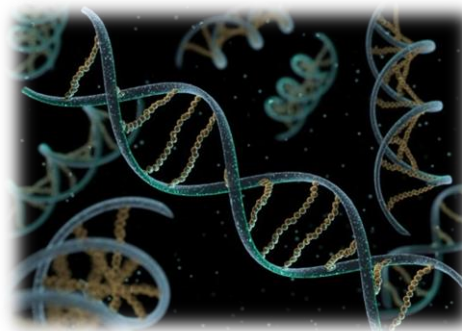
Fayyad et al. BJP 2007

Vejez: 2,8%

Michielsen et al., BJP 2012

76%

Cross-Disorder Group of the Psychiatric
Genomics Consortium. Nature
Genetics;45(9):984-94(2013)



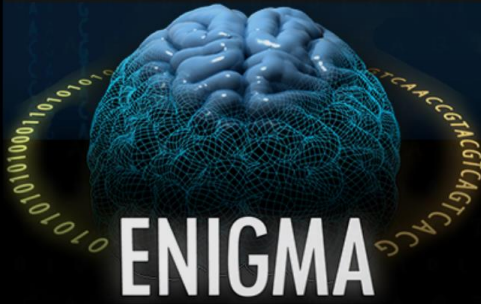
24%



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CONSORCIO ENIGMA



ABOUT ENIGMA WORKING GROUPS PUBLICATIONS RESEARCH PRESS ENIGMAVis

PROTOCOLS EVENTS TRAINING JOIN ENIGMA JOIN OUR MAILING LIST!

ENHANCING NEURO IMAGING GENETICS THROUGH META ANALYSIS

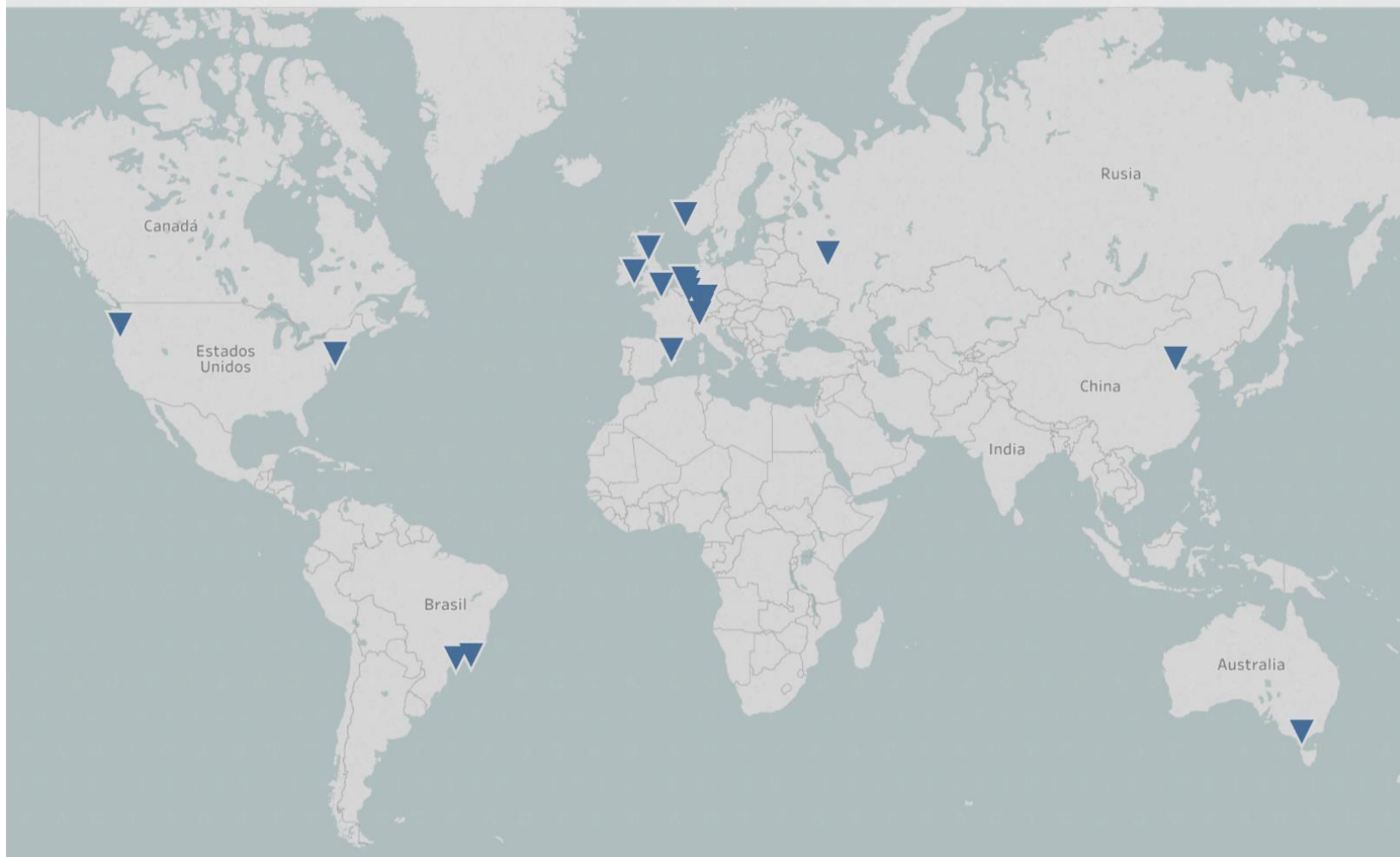
Disease Healthy Variation Genomics Algorithm Development Collaborations

What is **ENIGMA**?

The **ENIGMA Network** brings together researchers in imaging genomics to understand brain structure, function, and disease, based on brain imaging and genetic data. We welcome brain researchers, imagers, geneticists, methods developers, and others interested in cracking the neuro-genetic code!

CONSORCIO ENIGMA

ENIGMA-ADHD Cohort Locations



ESTRUCTURAS SUBCORTICALES

Articles

Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis



Martine Hoogman, Janita Bralten, Derrek P Hibar, Maarten Mennes, Marcel P Zwiers, Lizanne S J Schweren, Kimm J E van Hulzen, Sarah E Medland, Elena Shumskaya, Neda Jahanshad, Patrick de Zeeuw, Eszter Szekely, Gustavo Sudre, Thomas Wolfers, Alberdingk M H Onnink, Janneke T Dammers, Jeanette C Mostert, Yolanda Vives-Gilabert, Gregor Kohls, Eileen Oberwelland, Jochen Seitz, Martin Schulte-Rüther, Sara Ambrosino, Alysia E Doyle, Marie F Høvik, Margaretha Dramsdahl, Leanne Tamm, Theo G M van Erp, Anders Dale, Andrew Schork, Annette Conzelmann, Kathrin Zierhut, Ramona Baur, Hazel McCarthy, Yuliya N Yoncheva, Ana Cubillo, Kaylita Chantiluke, Mitul A Mehta, Yannis Paloyelis, Sarah Hohmann, Sarah Baumeister, Ivanei Bramati, Paulo Mattos, Fernanda Tovar-Moll, Pamela Douglas, Tobias Banaschewski, Daniel Brandeis, Jonna Kuntsi, Philip Asherson, Katya Rubia, Clare Kelly, Adriana Di Martino, Michael P Milham, Francisco X Castellanos, Thomas Frodl, Mariam Zentis, Klaus-Peter Lesch, Andreas Reif, Paul Pauli, Terry L Jernigan, Jan Haavik, Kerstin J Plessen, Astri J Lundervold, Kenneth Hugdahl, Larry J Seidman, Joseph Biederman, Nanda Rommelse, Dirk J Heslenfeld, Catharina A Hartman, Pieter J Hoekstra, Jaap Oosterlaan, Georg von Polier, Kerstin Konrad, Oscar Vilarroya, Josep Antoni Ramos-Quiroga, Joan Carles Soliva, Sarah Durston, Jan K Buitelaar, Stephen V Faraone, Philip Shaw, Paul M Thompson, Barbara Franke

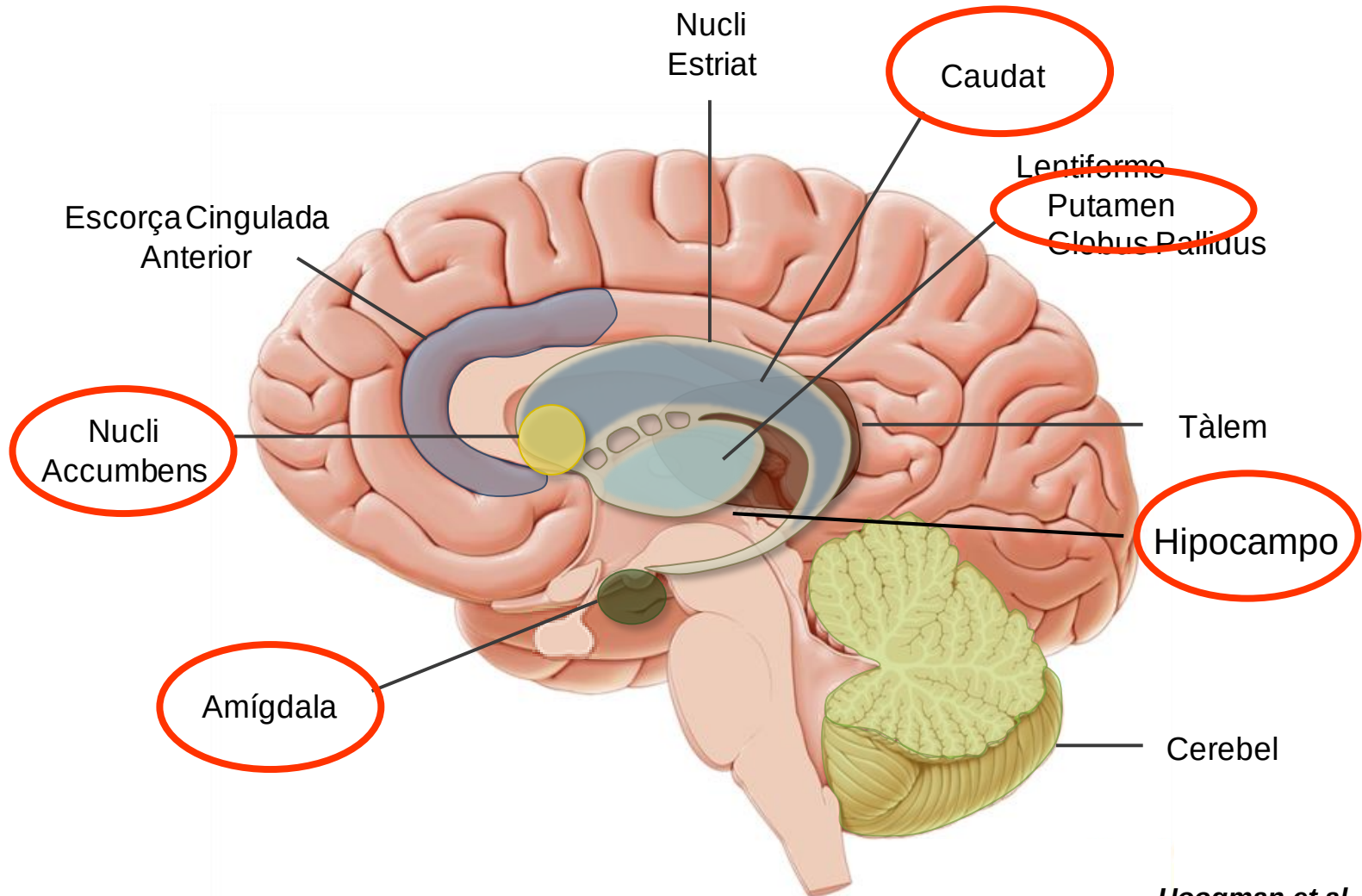
Hoogman et al., 2017

CARACTERÍSTICAS

- **Muestra:** 1713 participantes con TDAH y 1529 controles.
- **Edad media** 14 años (rango 4–63 años).
- **23 centros de investigación.**
- **Análisis** transversal, megaaanálisis.
- **False discovery rate** de $p=0.0156$.

Hoogman et al., 2017

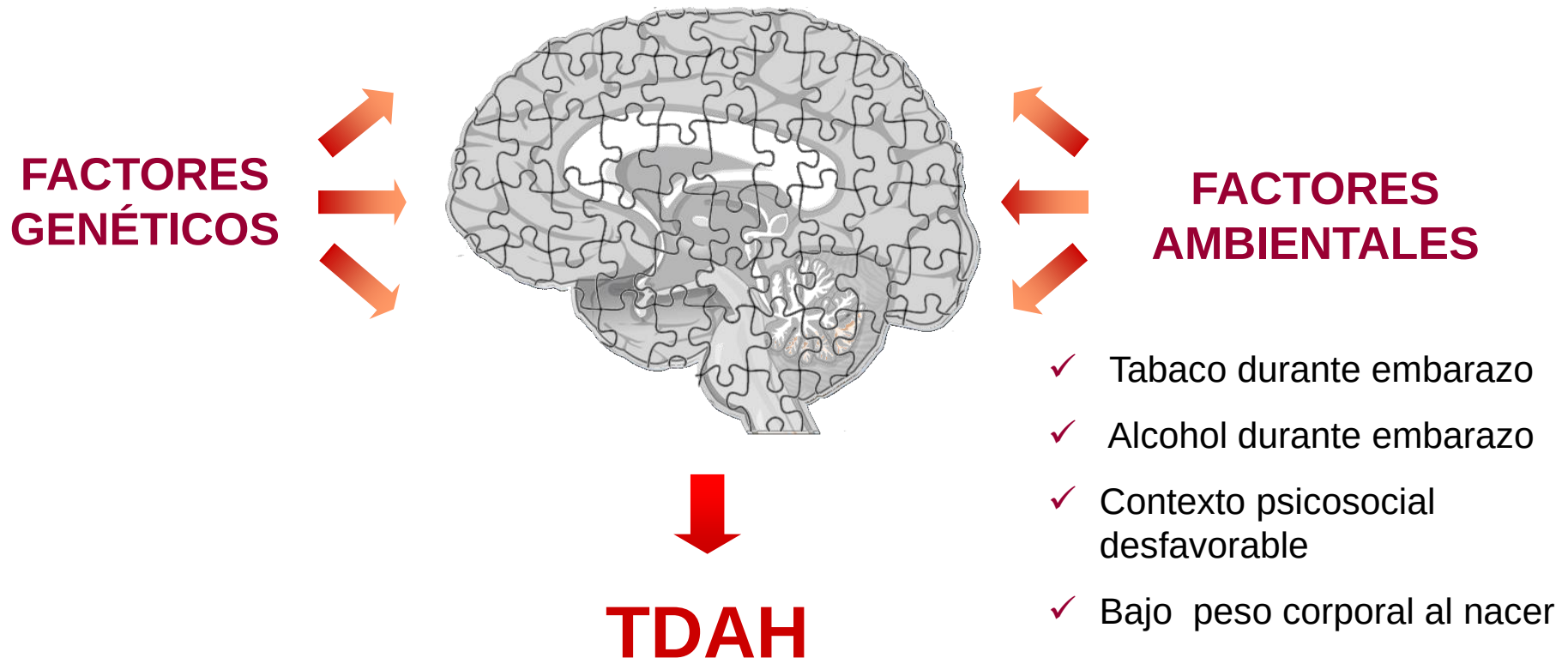
ESTRUCTURAS SUBCORTICALES



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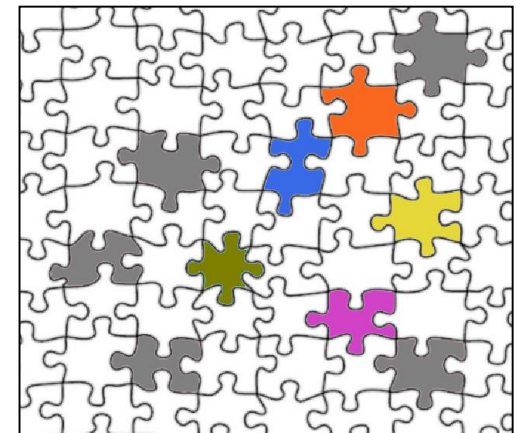
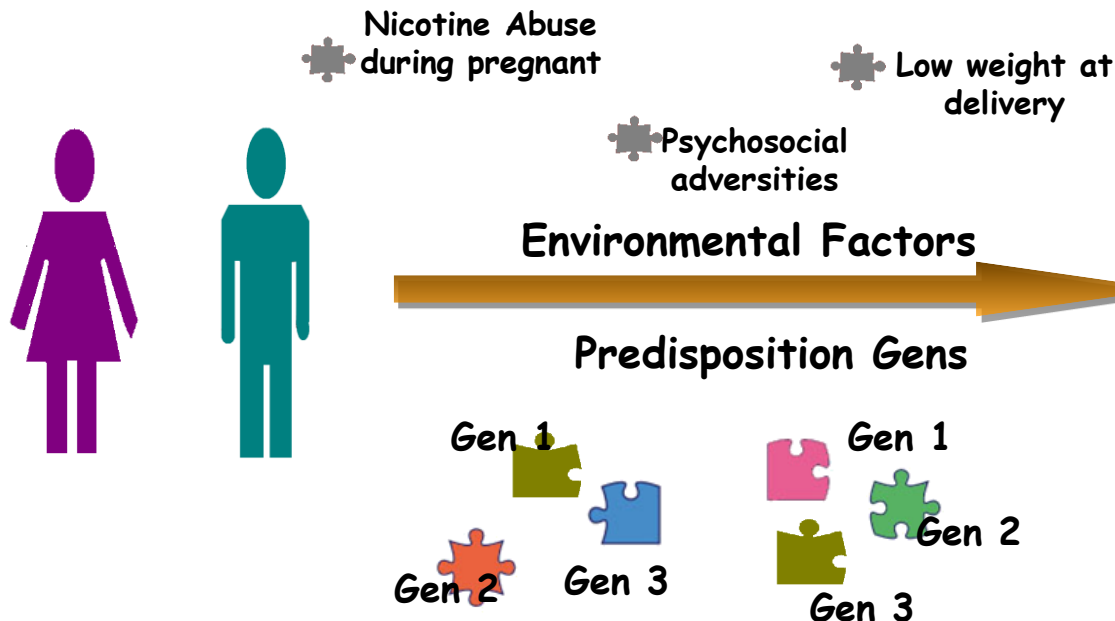
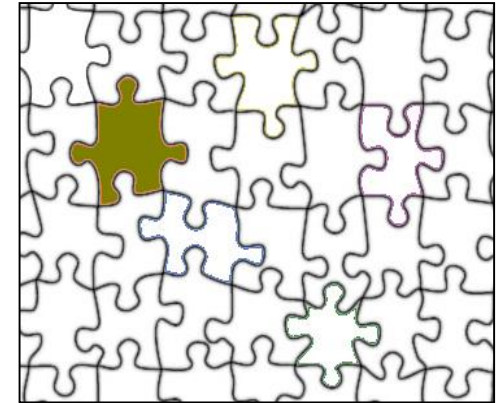
ETIOLOGIA MULTIFACTORIAL



COMPLEJO Y MULTIFACTORIAL



MENDELIAN ILLNESS



COMPLEX DISORDER

EMBARAZO

0 - 12 Meses

> 12 Meses

Factores pre/perinatales

Tabaquismo
Alcohol
Sustancias
Estrés
Bajo peso nacimiento
Prematuridad

Tóxicos medioambientales

Plaguicidas / Biphényls / Plomo

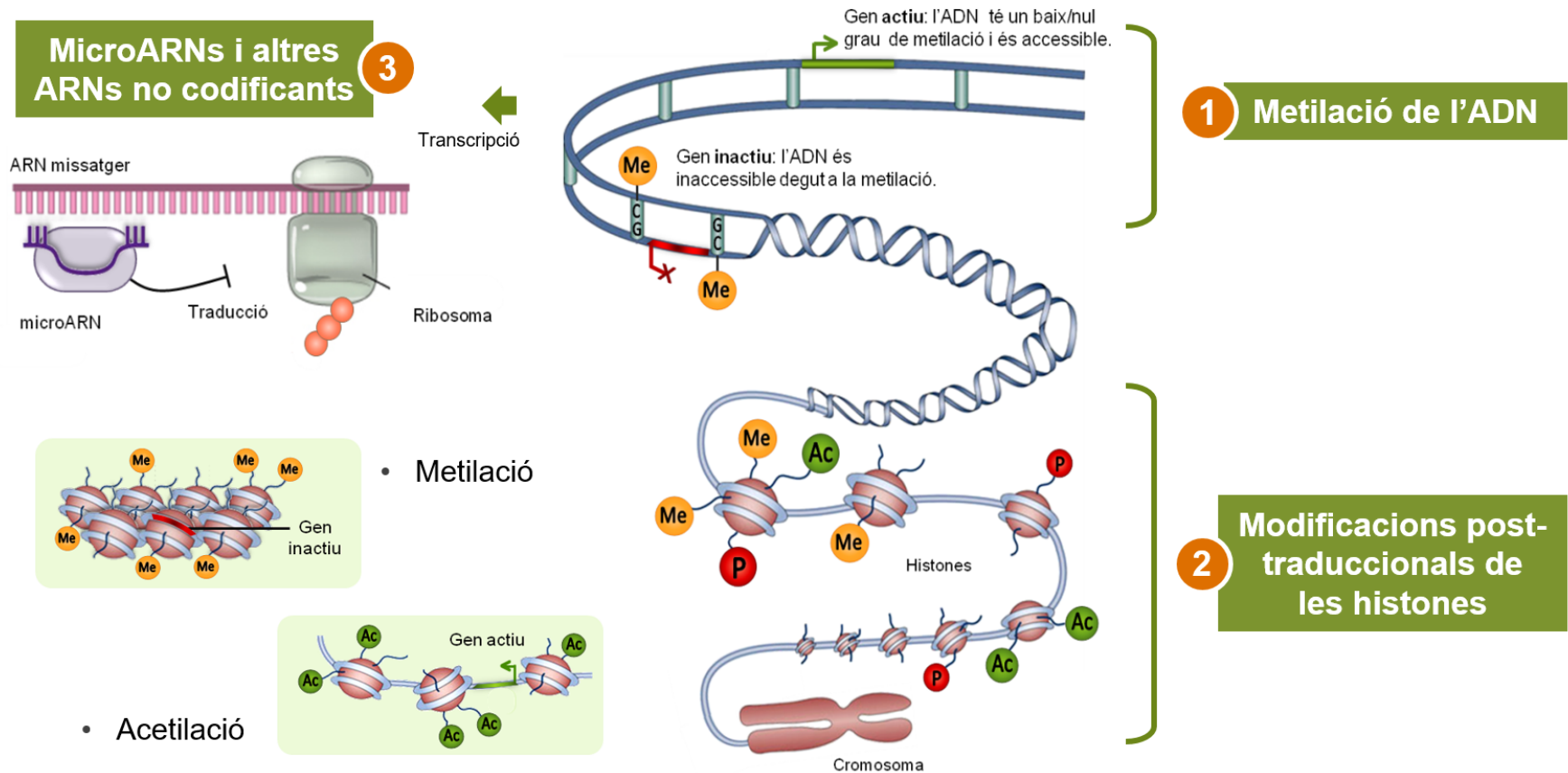
Adversidad social

Bajo NSE / Conflictos padres / Coerción / privaciones severas

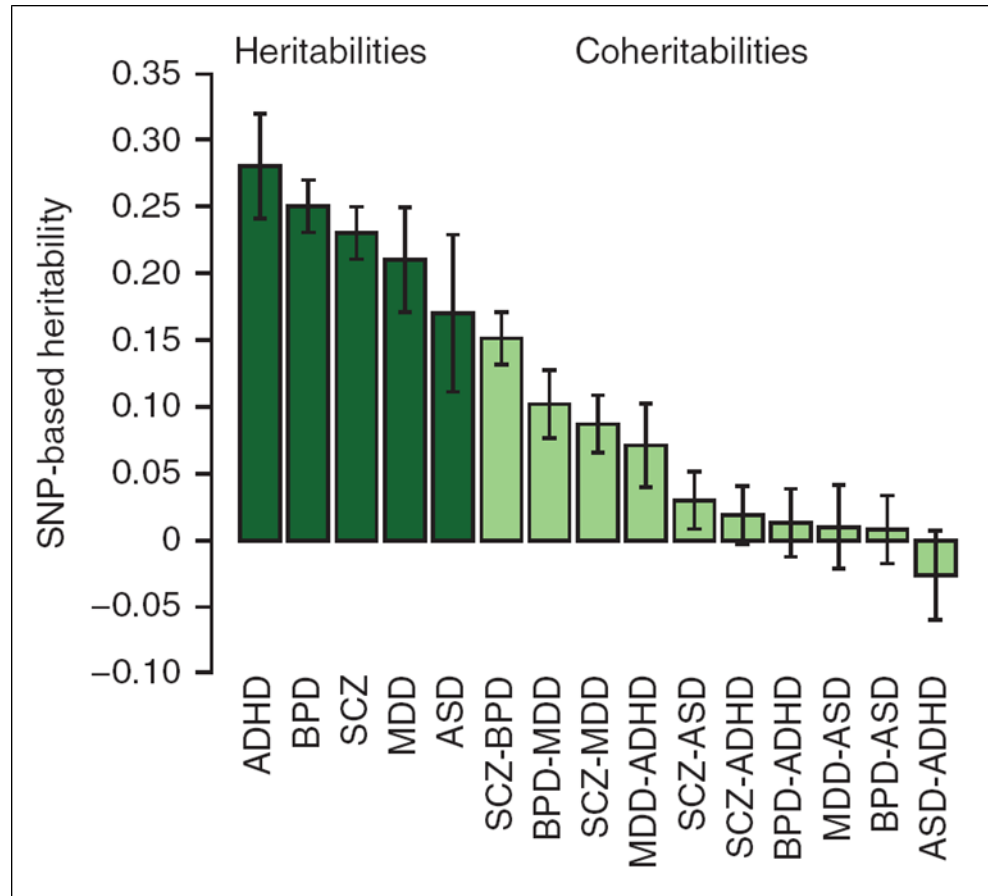
Factores dietéticos

Deficiencia Zn, Mg, Fe, AG / Colorantes / Azúcar / Low-High IgG foods

TDAH: EPIGENÈTICA



TDAH: componente genético



ADHD
Bipolar Disorder
Schizophrenia
Major Depression
Autism

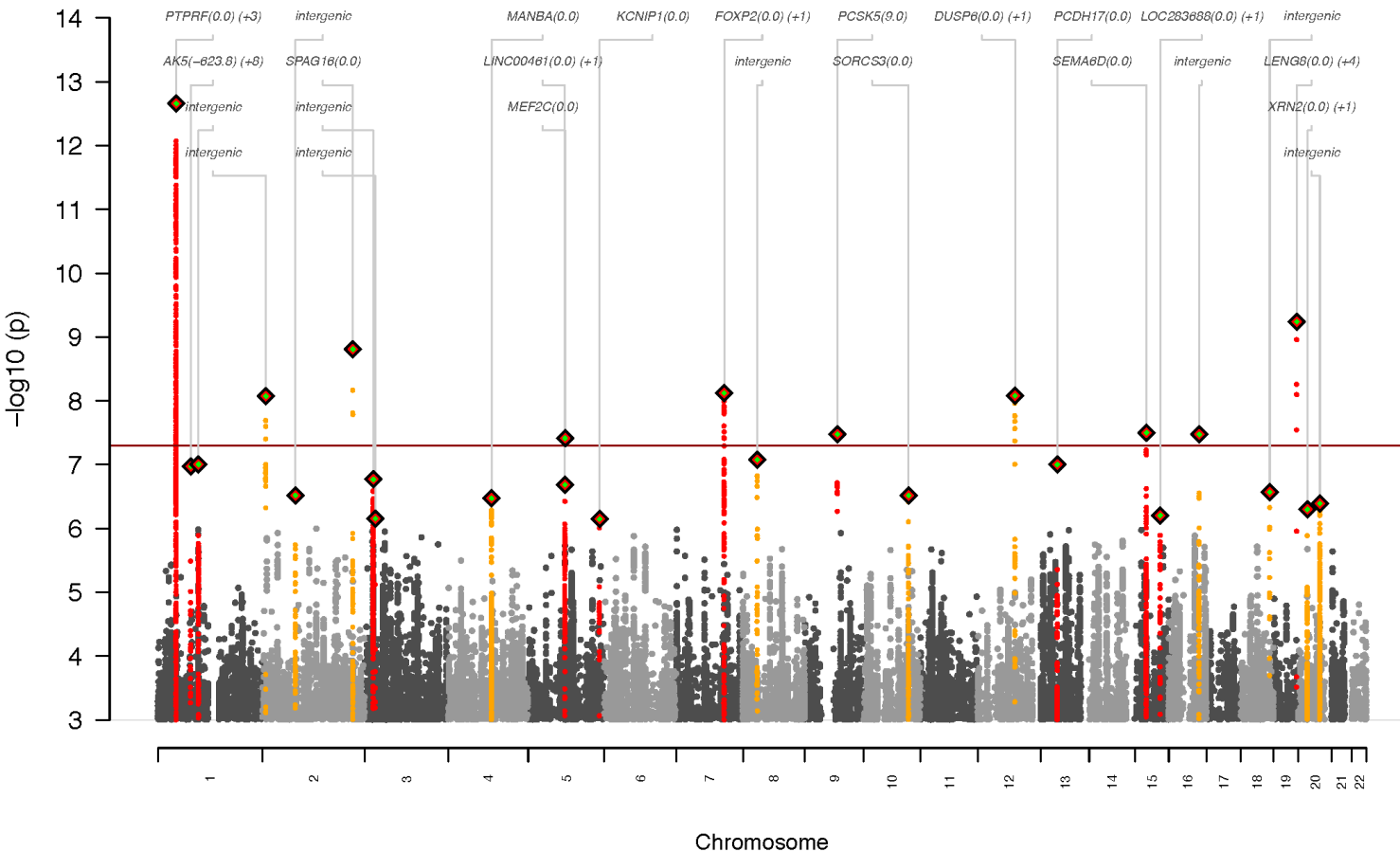
$$h^2_{\text{SNP}} = 28\%$$

$$\lambda_{\text{SNP}} = 1.71$$

Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

Cross-Disorder Group of the Psychiatric Genomics Consortium. Nature Genetics;45(9):984-94(2013)

GWAS:... EUREKA!!!!



**10 loci
8 look robust
On the path!**



New ADHD meta-analysis
18.284 cases 33.836 controls

EJE INTestino-CEREBRO



Molecular Psychiatry (2016) 21, 738–748

OPEN

www.nature.com/mp

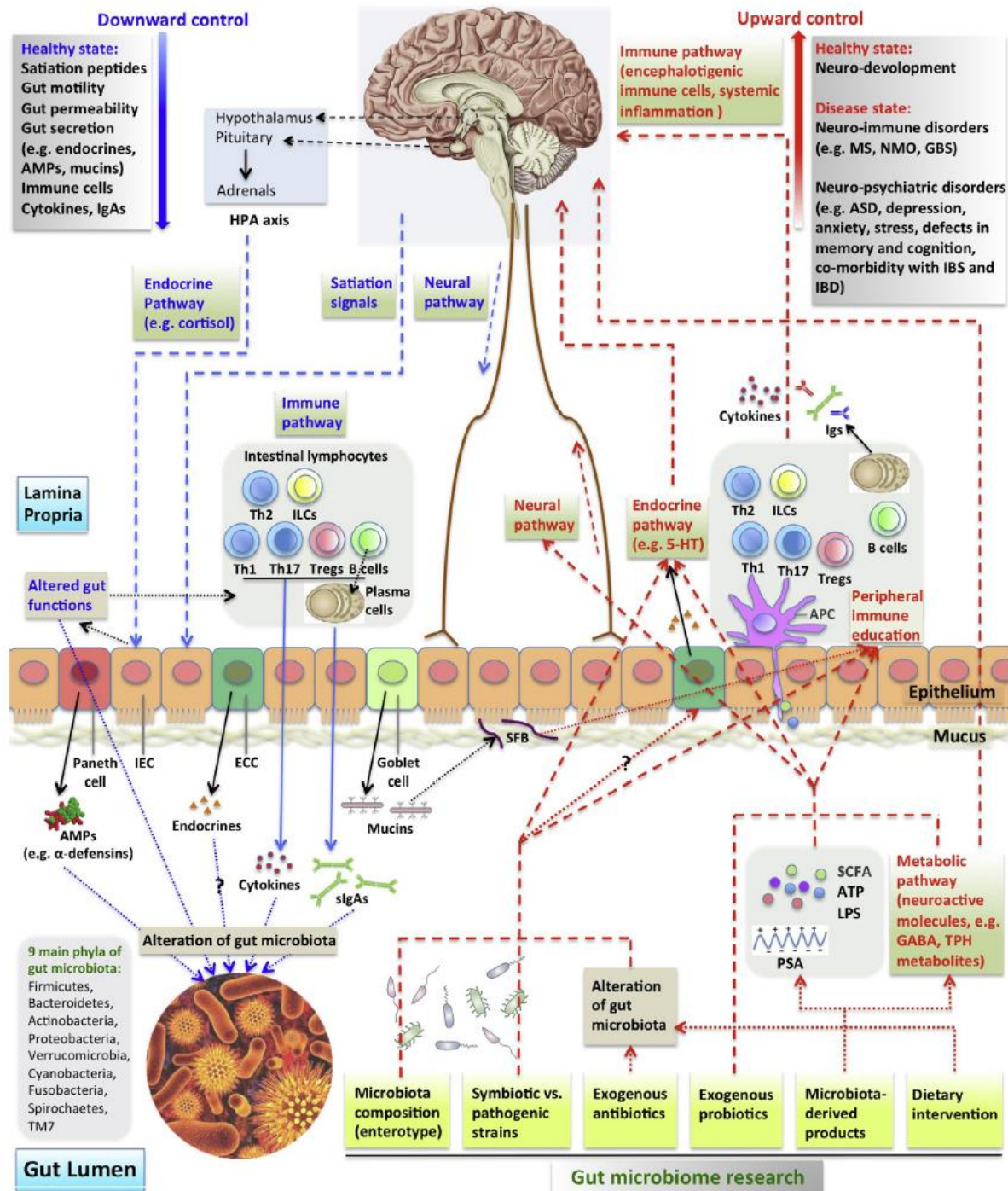
EXPERT REVIEW

From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways

GB Rogers¹, DJ Keating², RL Young³, M-L Wong⁴, J Licinio⁴ and S Wesselingh¹

The human body hosts an enormous abundance and diversity of microbes, which perform a range of essential and beneficial functions. Our appreciation of the importance of these microbial communities to many aspects of human physiology has grown dramatically in recent years. We know, for example, that animals raised in a germ-free environment exhibit substantially altered immune and metabolic function, while the disruption of commensal microbiota in humans is associated with the development of a growing number of diseases. Evidence is now emerging that, through interactions with the gut–brain axis, the bidirectional communication system between the central nervous system and the gastrointestinal tract, the gut microbiome can also influence neural development, cognition and behaviour, with recent evidence that changes in behaviour alter gut microbiota composition, while modifications of the microbiome can induce depressive-like behaviours. Although an association between enteropathy and certain psychiatric conditions has long been recognized, it now appears that gut microbes represent direct mediators of psychopathology. Here, we examine roles of gut microbiome in shaping brain development and neurological function, and the mechanisms by which it can contribute to mental illness. Further, we discuss how the insight provided by this new and exciting field of research can inform care and provide a basis for the design of novel, microbiota-targeted, therapies.

Molecular Psychiatry (2016) **21**, 738–748; doi:10.1038/mp.2016.50; published online 19 April 2016



IMPACTO DEL MICROBIOMA TDAH

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-017-0969-z



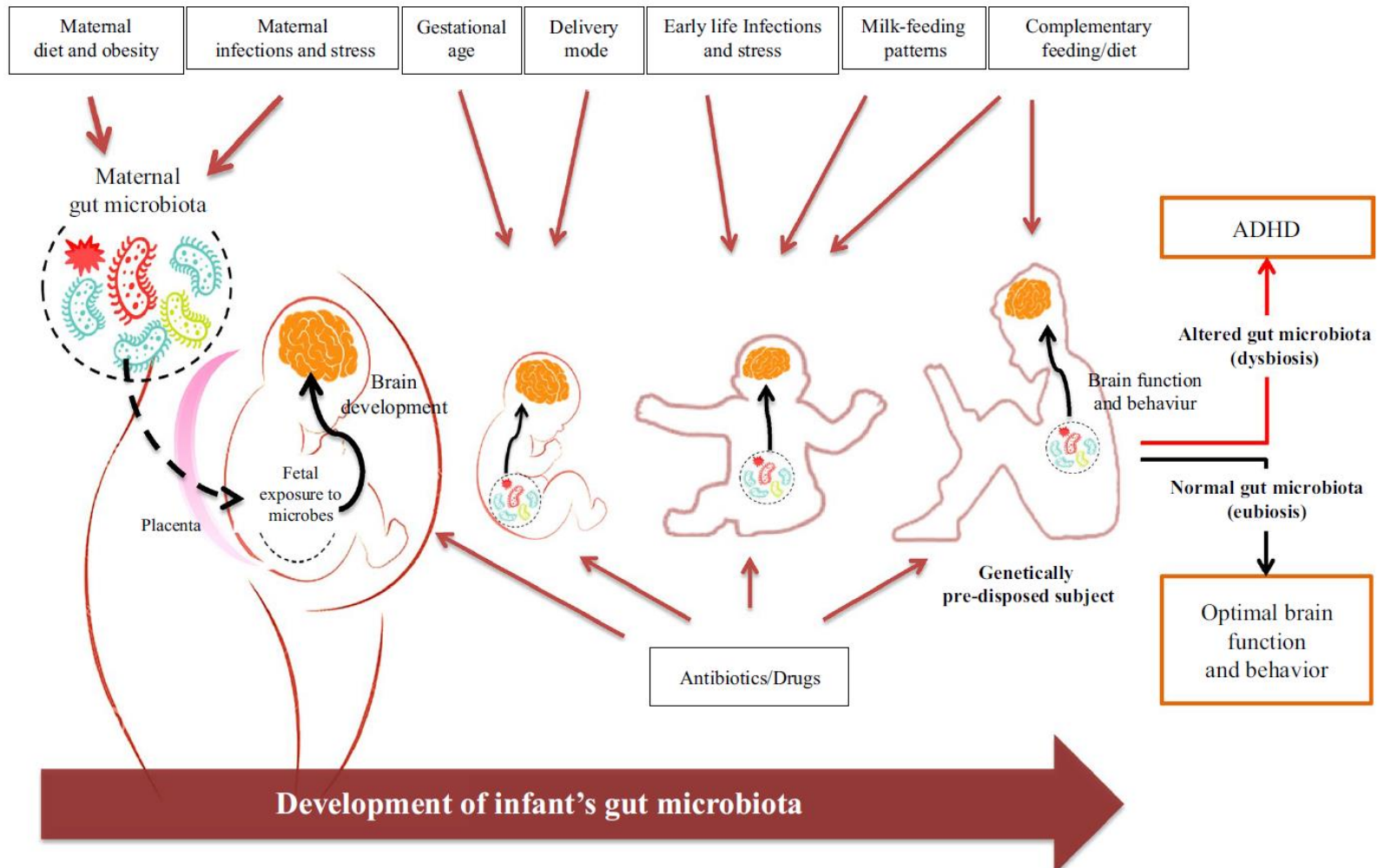
REVIEW

Gut microbiota and attention deficit hyperactivity disorder: new perspectives for a challenging condition

María Carmen Cenit^{1,2} · Isabel Campillo Nuevo¹ · Pilar Codoñer-Franch^{2,3} ·
Timothy G. Dinan^{4,5} · Yolanda Sanz¹

IMPACTO DEL MICROBIOMA TDAH

Eur Child Adolesc Psychiatry



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MANEJO DEL TDAH

MEDICINA BASADA EN PRUEBAS:

- Las decisiones corresponden a un uso racional, explícito, juicioso y actualizado de los mejores datos objetivos aplicados al tratamiento de cada paciente.
- El objetivo primordial de la MBP es el de que la actividad médica cotidiana se fundamente en datos científicos y no en suposiciones o creencias.

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Augusto Vidal Perera

Metilfenidato

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1907

1957

1902

1937

1967

2017...

George Still

Charles Bradley
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Repercusiones
Tratamientos



TDAH Y CRIMINALIDAD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Medication for Attention Deficit– Hyperactivity Disorder and Criminality

Paul Lichtenstein, Ph.D., Linda Halldner, M.D., Ph.D., Johan Zetterqvist, M.Ed.,
Arvid Sjölander, Ph.D., Eva Serlachius, M.D., Ph.D.,
Seena Fazel, M.B., Ch.B., M.D., Niklas Långström, M.D., Ph.D.,
and Henrik Larsson, M.D., Ph.D.

N Engl J Med 367;21 november 22, 2012

TDAH Y CRIMINALIDAD

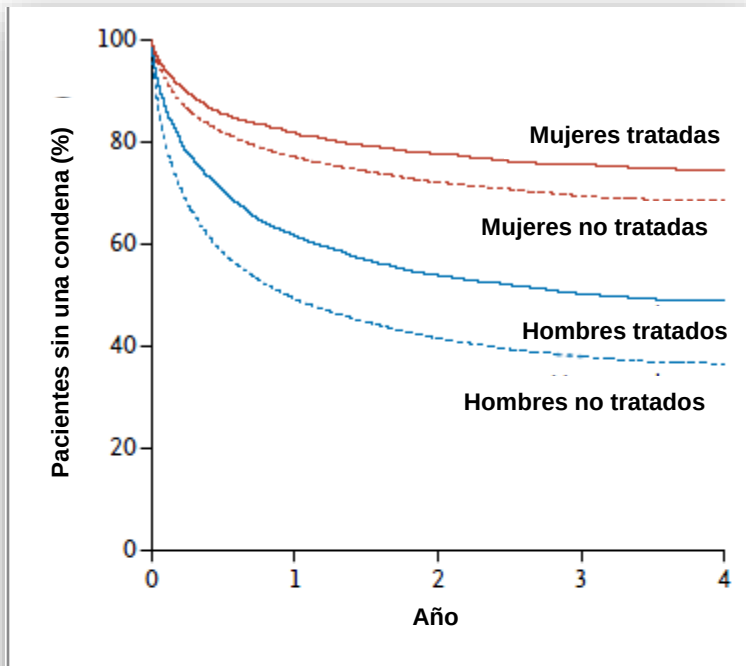


Figura 1. Curvas extendidas de Kaplan-Meier para pacientes del Registro Sueco de Pacientes con un diagnóstico de TDAH que habían nacido no más tarde de 1990, según género y estado de medicación.

Este análisis se basó en 56.227 periodos de tratamiento o no tratamiento y 23.693 condenas que afectaron a 16.087 varones (en promedio 3,5 periodos de tratamiento o no tratamiento y 1,5 condenas) y 23.533 periodos de tratamiento o no tratamiento y 4.112 condenas que afectaron a 9.569 mujeres (en promedio 2,5 periodos de tratamiento o no tratamiento y 0,4 condenas).

Se produjeron crímenes con menor frecuencia durante los periodos en que los pacientes con TDAH estaban tomando medicación:

- **Varones: 32% reducción**
- **Mujeres: 41% reducción**

EFECTO BENEFICIOSO DEL TRATAMIENTO

Research

Original Investigation

Serious Transport Accidents in Adults With Attention-Deficit/Hyperactivity Disorder and the Effect of Medication A Population-Based Study

Zheng Chang, PhD; Paul Lichtenstein, PhD; Brian M. D'Onofrio, PhD; Arvid Sjölander, PhD; Henrik Larsson, PhD

Chang et al., 2014

EFEECTO BENEFICIOSO DEL TRATAMIENTO

Articles

Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study



Søren Dalsgaard, James F Leckman, Preben Bo Mortensen, Helena Skyt Nielsen, Marianne Simonsen

Summary

Background Injuries represent the largest disease burden and most common cause of death in children. Attention deficit hyperactivity disorder (ADHD) is associated with increased mortality, with accidents being the most common cause of death in ADHD. However, it is not known whether pharmacological treatment has any modifying effect on the risk of injuries in children and adolescents with ADHD.

Methods Using Danish national registers, we followed a cohort of 710 120 individuals, including 4557 individuals diagnosed with ADHD before age 10 years. Using a quasi-experimental, difference-in-difference design, we estimated the odds ratios (ORs) for injuries and the mean change in prevalence rates of injuries and emergency ward visits before and after treatment, with matched untreated children with ADHD at the same age serving as controls.

Findings Children with ADHD were more likely to sustain injuries, compared with children without ADHD, at age 10 years (adjusted OR=1.29, 95% CI 1.22–1.37) and at age 12 years (adjusted OR=1.30, 1.23–1.37). From age 5 to 10 years, the prevalence of injuries in children with ADHD who were treated with ADHD drugs decreased from 19% to 14%, compared with a prevalence of about 17% in non-treated children with ADHD. This corresponded to an adjusted difference-in-difference reduction in prevalence of injuries at age 10 years of 31.5% (8.2–54.8) and 43.5% (18.1–69.0) at age 12 years due to treatment. Pharmacological treatment also reduced the prevalence of emergency ward visits at age 10 years (28.2%, 6.3–50.1) and age 12 years (45.7%, 25.8–65.7).

Interpretation Children with ADHD had an increased risk of injuries compared with other children. Treatment with ADHD drugs reduced the risk of injuries by up to 43% and emergency ward visits by up to 45% in children with ADHD. Taken together with previous findings of accidents being the most common cause of death in individuals with ADHD, these results are of major public health importance.

Lancet Psychiatry 2015

Published Online

July 22, 2015

[http://dx.doi.org/10.1016/S2215-0366\(15\)00271-0](http://dx.doi.org/10.1016/S2215-0366(15)00271-0)

See Online/Comment

[http://dx.doi.org/10.1016/S2215-0366\(15\)00321-1](http://dx.doi.org/10.1016/S2215-0366(15)00321-1)

National Centre for Register-based Research (S Dalsgaard PhD, Prof P B Mortensen Dr Med Sc), Department of Economics and Business (H S Nielsen PhD, M Simonsen PhD), School of Business and Social Sciences, Aarhus University, Aarhus, Denmark; The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark (S Dalsgaard, Prof P B Mortensen); Department for Child and Adolescent Psychiatry, Hospital of Telemark, Kragerø, Norway (S Dalsgaard); and Child

TDAH & TUS: MPH

THE JOURNAL OF CHILD
PSYCHOLOGY AND PSYCHIATRY



THE ASSOCIATION FOR
CHILD AND ADOLESCENT
MENTAL HEALTH

Journal of Child Psychology and Psychiatry 55:8 (2014), pp 878–885

doi:10.1111/jcpp.12164

Stimulant ADHD medication and risk for substance abuse

**Zheng Chang,¹ Paul Lichtenstein,¹ Linda Halldner,^{1,2} Brian D'Onofrio,³ Eva Serlachius,⁴
Seena Fazel,⁵ Niklas Langstrom,¹ and Henrik Larsson¹**

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ²Karolinska Institutet Center of Neurodevelopmental Disorders (KIND), Stockholm, Sweden; ³Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA; ⁴Department of Clinical Neuroscience, Centre for Psychiatric Research and Education, Karolinska Institutet, Stockholm, Sweden; ⁵Department of Psychiatry, University of Oxford, Oxford, UK

Virtual Reality with ADHD

 **mindfulness**

Mindfulness Applied
through virtual reality



- Reduction of treatment time
- Improve patient adherence
- Improving Symptoms of ADHD

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CONCLUSIONES

- El TDAH es un trastorno de neurodesarrollo, con elevada prevalencia en la población general y con evolución crónica.
- Conocemos que existen alteraciones en la estructura y en el funcionamiento del cerebro .
- El TDAH es un trastorno con una alta carga genética.
- Existen tratamientos eficaces y seguros a lo largo de la vida.

CONCLUSIÓN

**EL TDAH
NO EXISTE,
ES UNA
INVENCIÓN...**



AGRADECIMIENTOS



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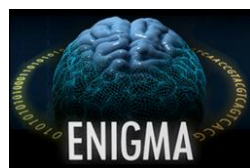
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