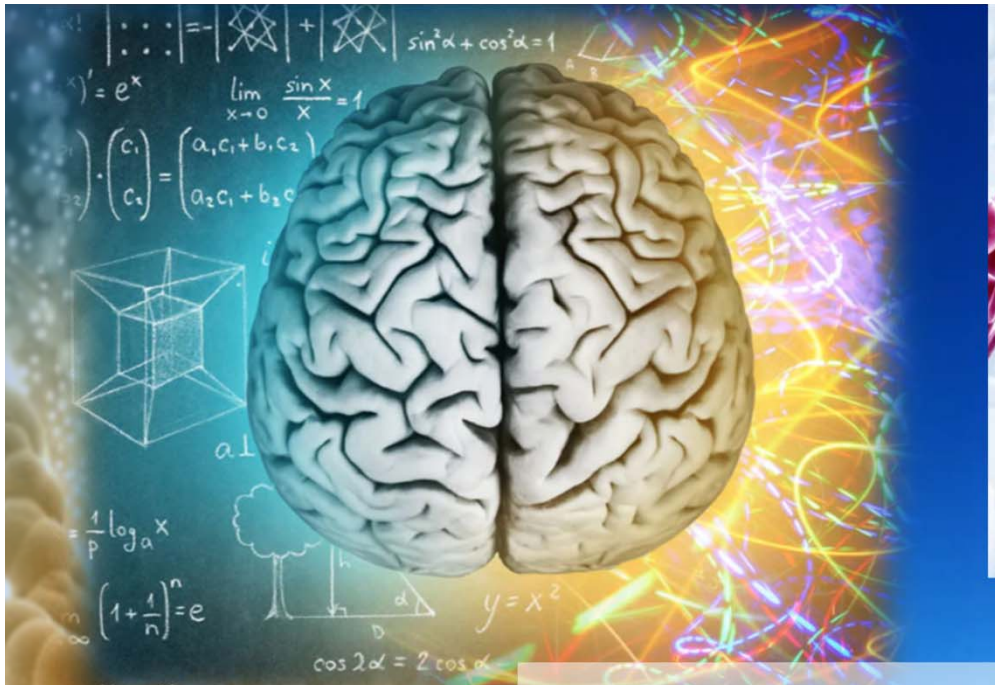


IL MITOCONDRIO:
IL SEGRETO DELLA LONGEVITA'

Energia per la vita

MILANO, 16 Febbraio 2020

Autismo … da una prospettiva sistemica

CRISTINA PANISI

Istituto Sacra Famiglia, Varese
SPAEE Università Cattolica, Milano

cristina.panisi@tin.it

FONDAZIONE SACRA FAMIGLIA ONLUS

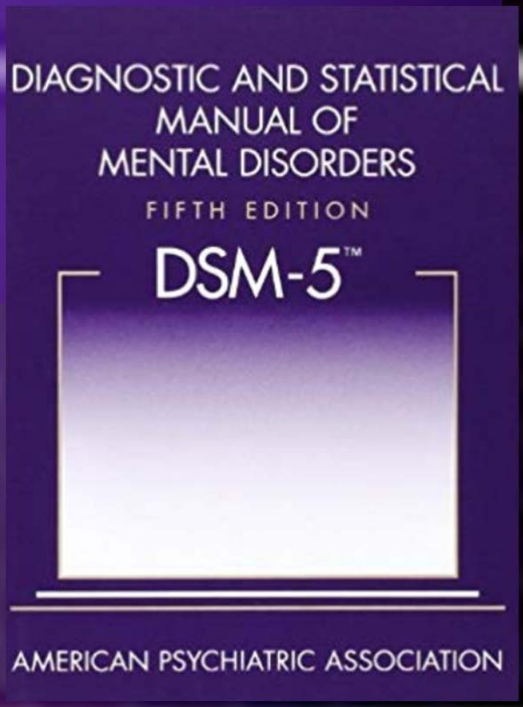
BLU LAB

SPAEE

SIMA
SOCIETÀ ITALIANA DI MEDICINA AMBIENTALE

Disturbo dello spettro autistico (ASD)

- Disturbo del neurosviluppo caratterizzato da
  - *Difficoltà nella comunicazione e nella interazione sociale*
  - *Interessi ristretti e comportamenti ripetitivi*
- 3 livelli di gravità
- Esordio nei primi anni di vita



AUTISM SPECRTUM DISORDER (ASD)

Grave disabilità intellettiva

AUTISMO CLASSICO

QI normale o elevato

HFA
SINDROME DI ASPERGER

EDITORIAL

Into, and Out of, the "Valley of Death": Research in Autism Spectrum Disorders

Peter Szatmari, M.D., Tony Charman, Ph.D., John N. Constantino, M.D.

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 51 NUMBER 11 NOVEMBER 2012

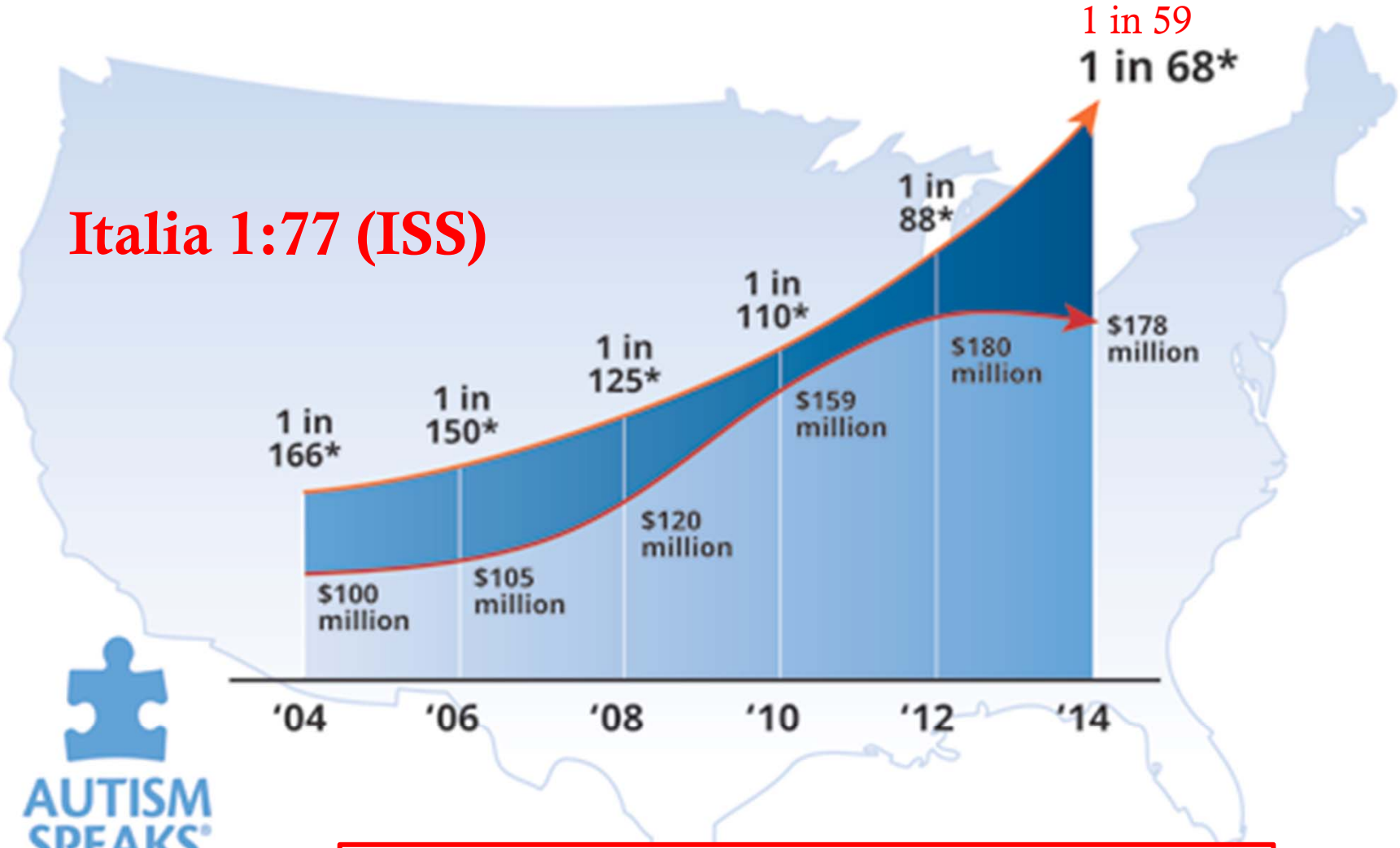
community setting. Granting agencies are now recognizing that the enormous investments they make in funding research have not always led to improved outcomes, and are requiring that applicants demonstrate plans for traversing the Valley of Death (although they may not phrase it that way) into their research proposals. As the pace of scientific discovery increases with re-

Medicina Coerente

Modelli sistemici per una medicina più efficace, umana, individualizzata

Autism on the Rise

Estimated Autism Prevalence and NIH Funding for Autism Research



AUTISM SPEAKS®

It's time to listen.

AutismSpeaks.org

15-20 % tra disabilità neuropsichica e/o disturbi psichici

* CDC prevalence estimates are for 4 years prior to the report date (e.g. 2014 figures are from 2010)

X CONGRESSO NAZIONALE FIMP 2016

1000 Giorni

29 SETTEMBRE
1 OTTOBRE 2016

CENTRO CONGRESSI
PISA

fimp
Federazione
Italiana Medici Pediatri

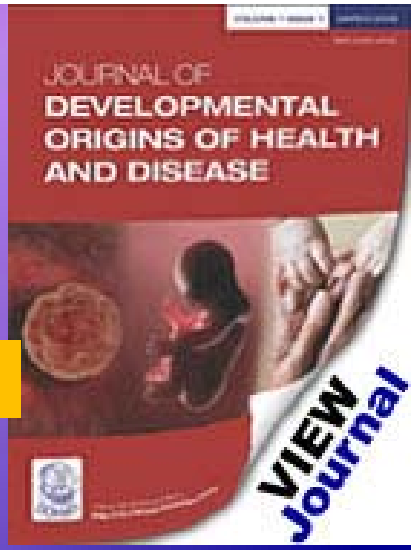
Aderente CONF PROFESSIONI confederazione italiana libere professioni

Member of EUROPEAN PAEDIATRIC ASSOCIATION UEPA / UNEPSAF

..recently, the ***fetal programming mismatch theory*** has been transformed into the **key-moodel theory of DOHAD..**

Obesity/Metabolic Syndrome

Cardiovascular Diseases



Obesogens

Multiorgan Effects of Endocrine Disruptors

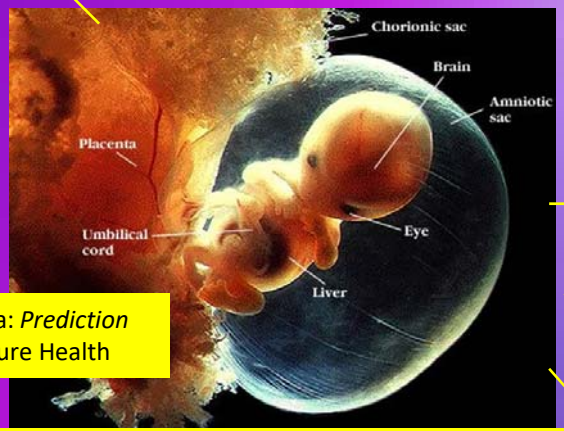
Pesticides

In Vitro Fertilization

Materno Fetal Stress

DOHAD

Ipertension



Placenta: *Prediction* of Future Health

OBESITY DIABESITY PANDEMICS

Asthma and allergies

Lung Development ⇩

Developmental Time Windows of Vulnerability

Reproductive Diseases/Dysfunctions

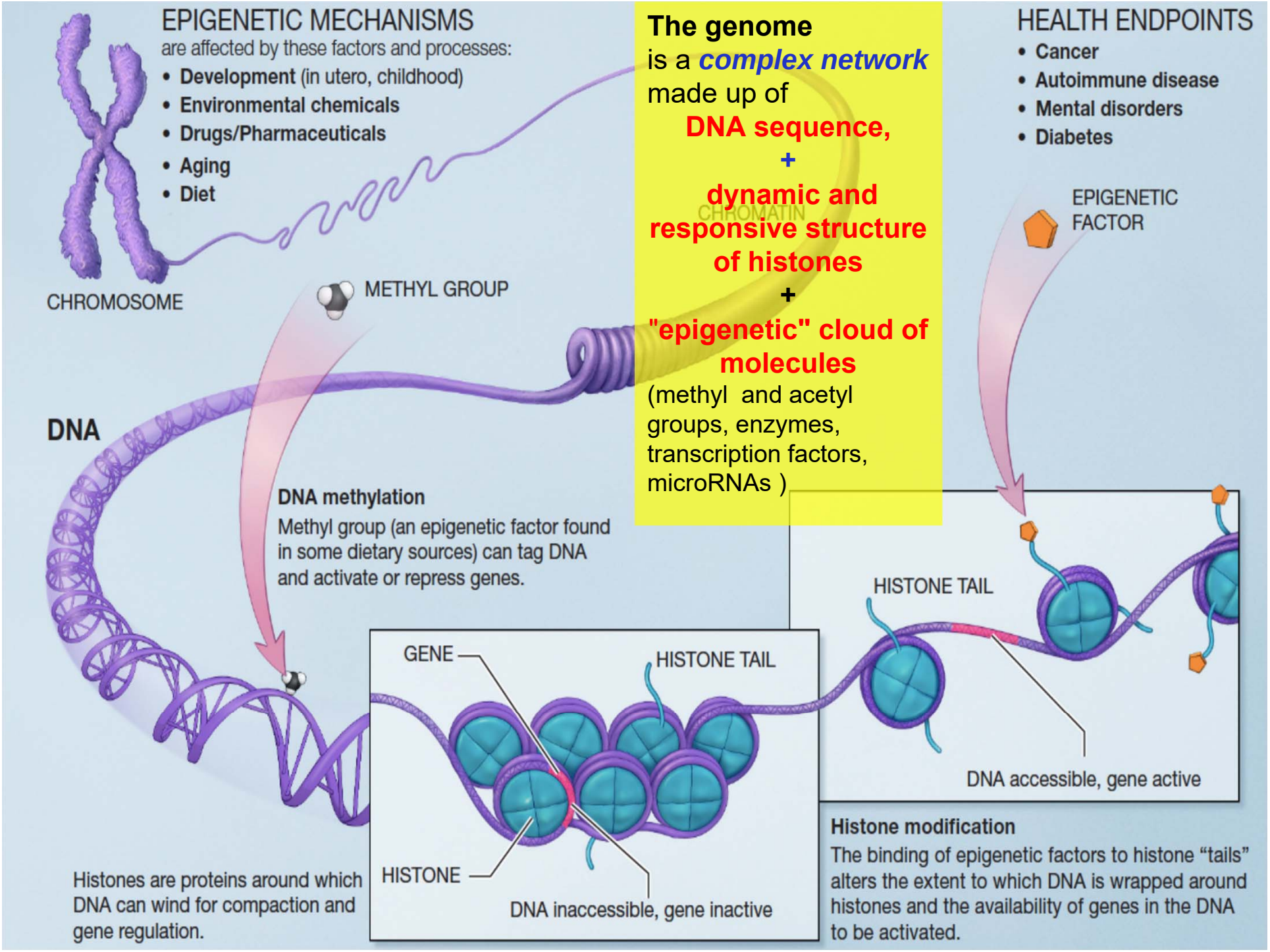
Semen Abnormalities

CANCER

Neurobehavioral Deficits and Diseases

Psychiatric Diseases

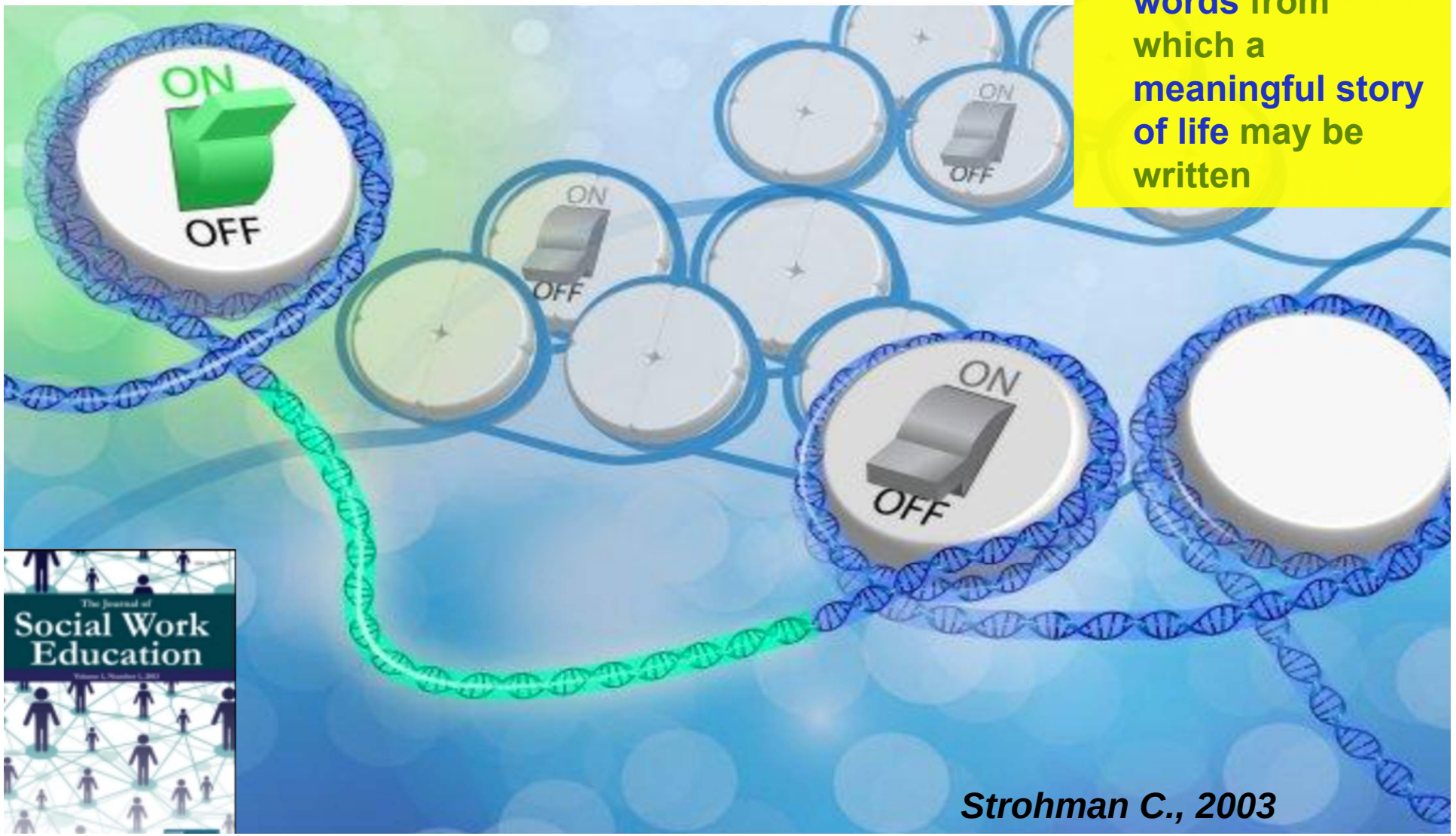
E. Burgio
erburg@libero.it


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
CHROMOSOME
METHYL GROUP
CHROMATIN
DNA
The genome
is a complex network
made up of
DNA sequence,
+
dynamic and
responsive structure
of histones
+
"epigenetic" cloud of
molecules
(methyl and acetyl
groups, enzymes,
transcription factors,
microRNAs)
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
EPIGENETIC
FACTOR
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
HISTONE TAIL
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Genetic Determinism as a Failing Paradigm in Biology and Medicine

Richard C. Strohman

- Genes need to be told to switch **OFF** and **ON**
- DNA is a **random collection of words** from which a **meaningful story of life** may be written

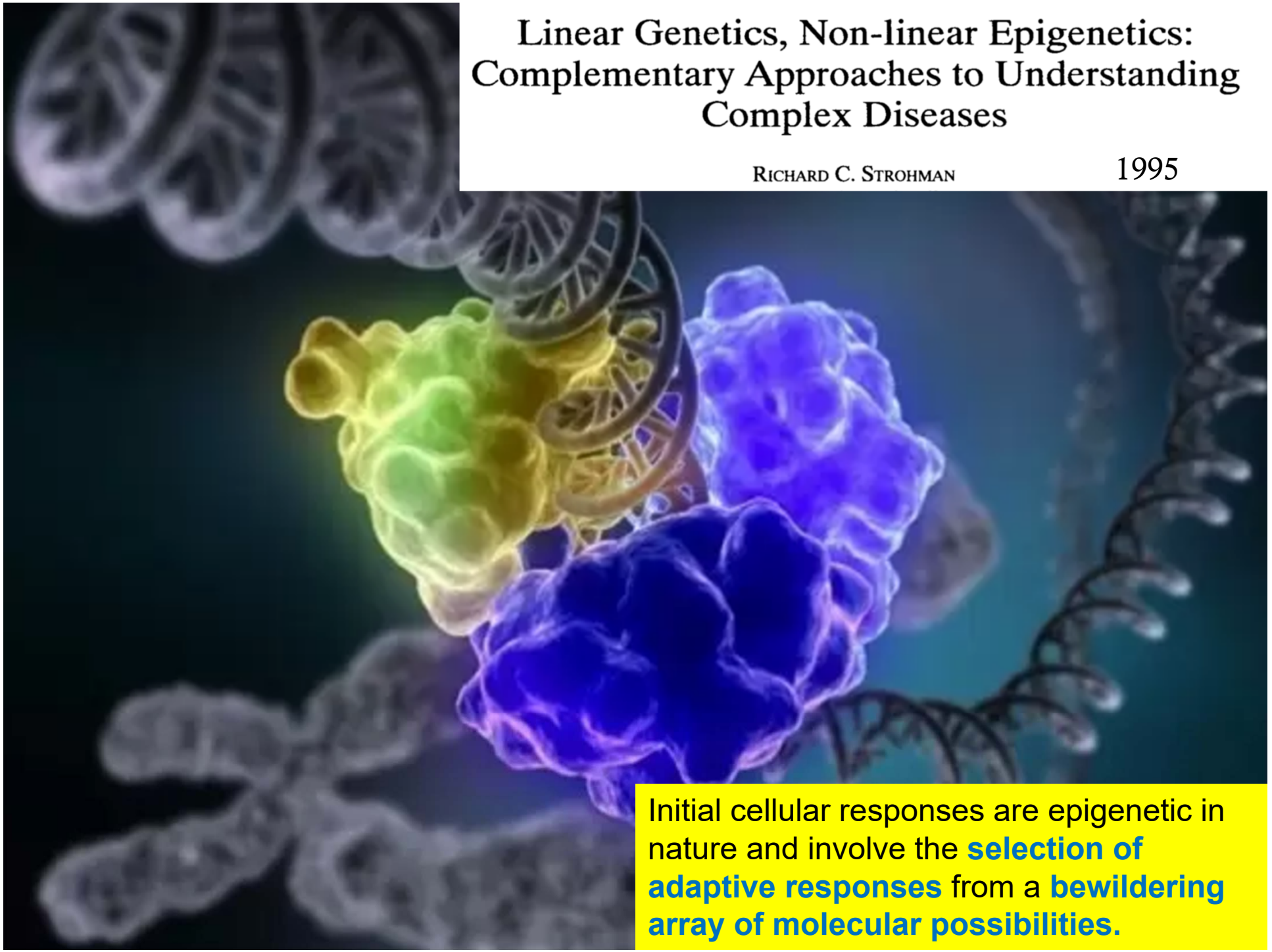


Strohman C., 2003

Linear Genetics, Non-linear Epigenetics: Complementary Approaches to Understanding Complex Diseases

RICHARD C. STROHMAN

1995



Initial cellular responses are epigenetic in nature and involve the **selection of adaptive responses** from a **bewildering array of molecular possibilities.**

- DIET
- DRUGS
- MICROBIOTA
- SOCIAL INTERACTIONS
- STRESS (HORMONES)

ENDOCRINE DISRUPTORS

ULTRAFINE PARTICLES

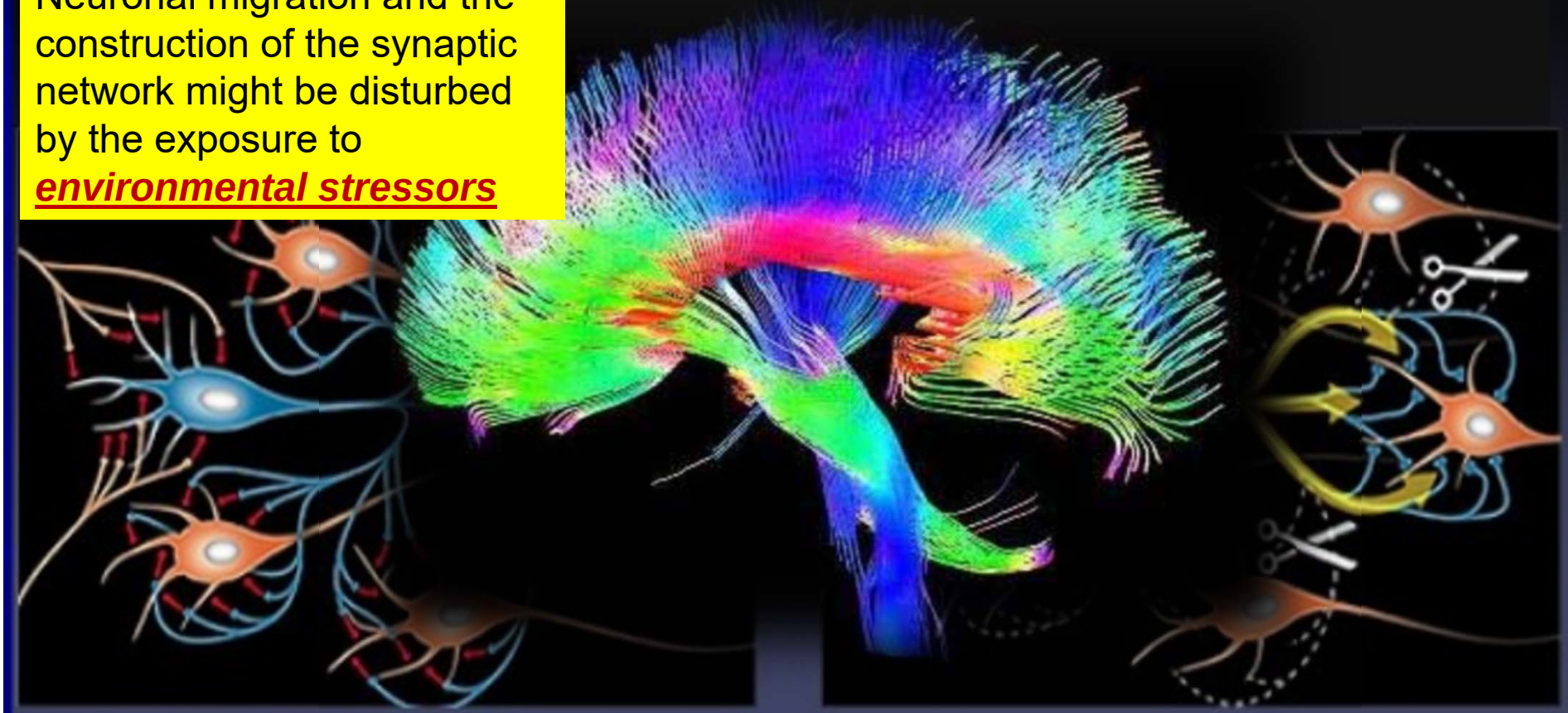
HEAVY METALS

genetics.

ENVIRONMENT is as a restless stream of **information interacting** with cells [***membrane /transmembrane receptors, signal transduction proteins, nuclear receptors, genome (DNA + Epigenome)]*** **forcing them to adapt**

Nerve Proliferation... ...and Pruning

Neuronal migration and the construction of the synaptic network might be disturbed by the exposure to ***environmental stressors***



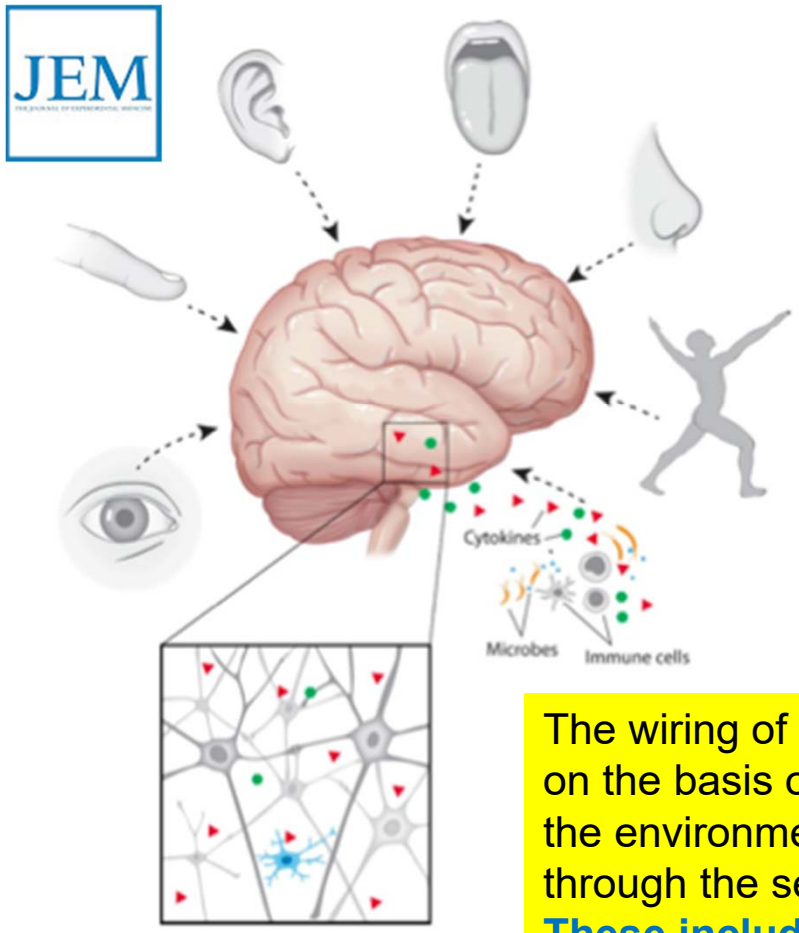
The ***Individual*** wiring

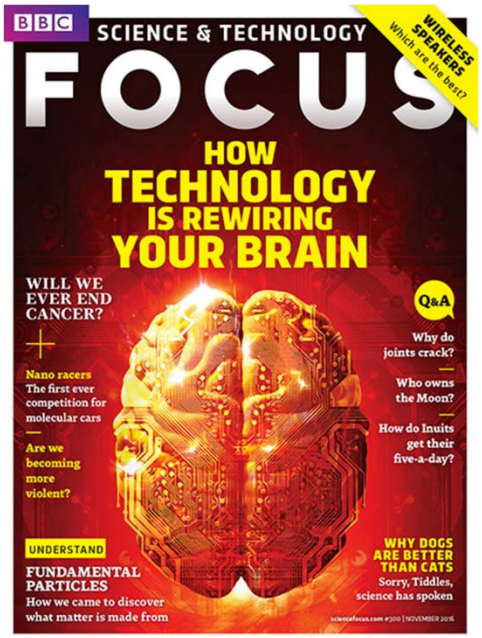

TIME
SPECIAL REPORT
HOW A CHILD'S BRAIN DEVELOPS
And what it means for child care and welfare reform

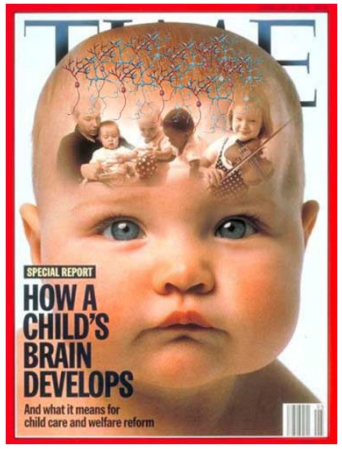
Immune system: The "seventh sense"

Jonathan Kipnis

The Rockefeller University Press
J. Exp. Med. 2018 Vol. 215 No. 2 397–398
https://doi.org/10.1084/jem.20172295





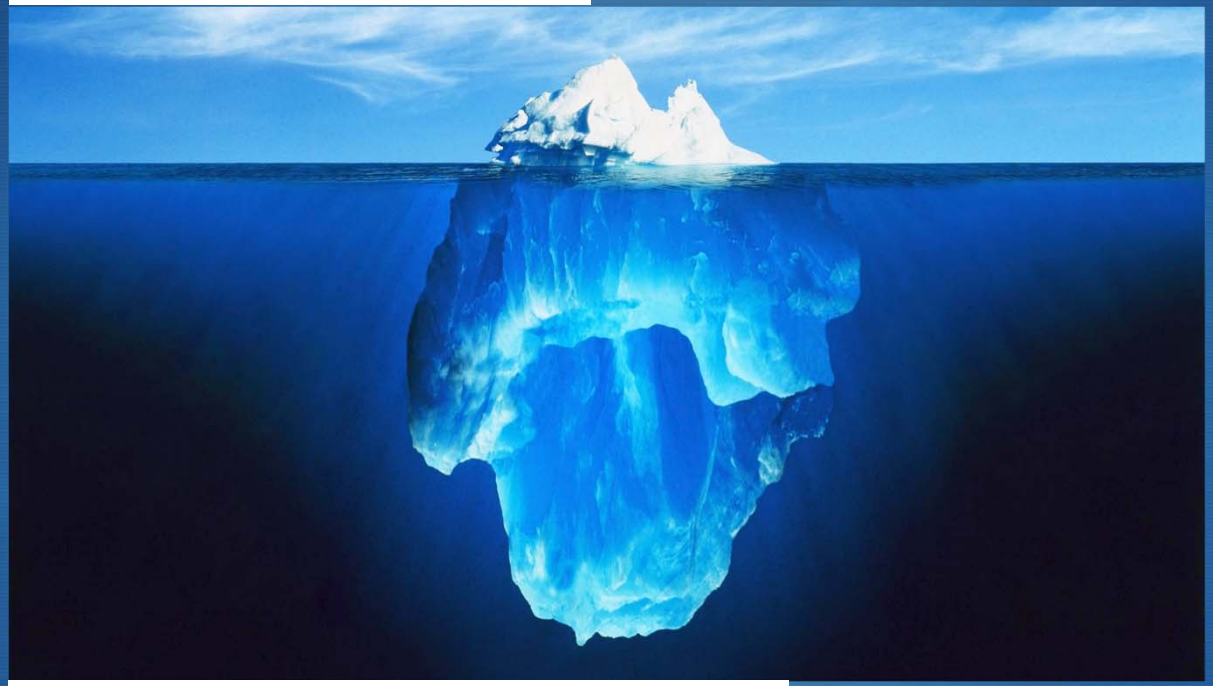


The wiring of the nervous system takes place on the basis of the experiences provided by the environment, which reach the brain through the senses.
These include the immune system.

The brain is our computing machine that integrates stimuli from the environment and orchestrates responses to these stimuli. Here, I propose that the defining role of the immune system is to sense microorganisms and to inform the brain about them.

From AUTISM …

BEHAVIOR

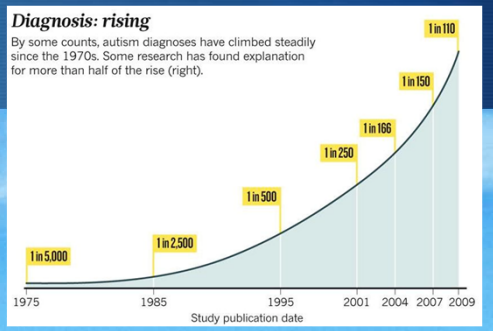


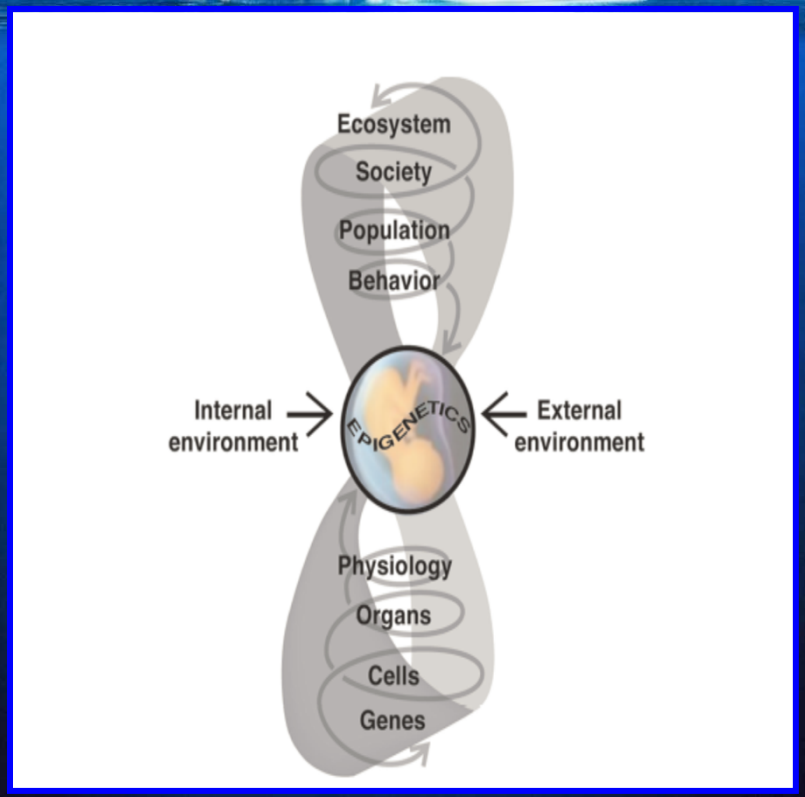
GENETICS

… to AUTISM SPECTRUM DISORDERS

BEHAVIOR

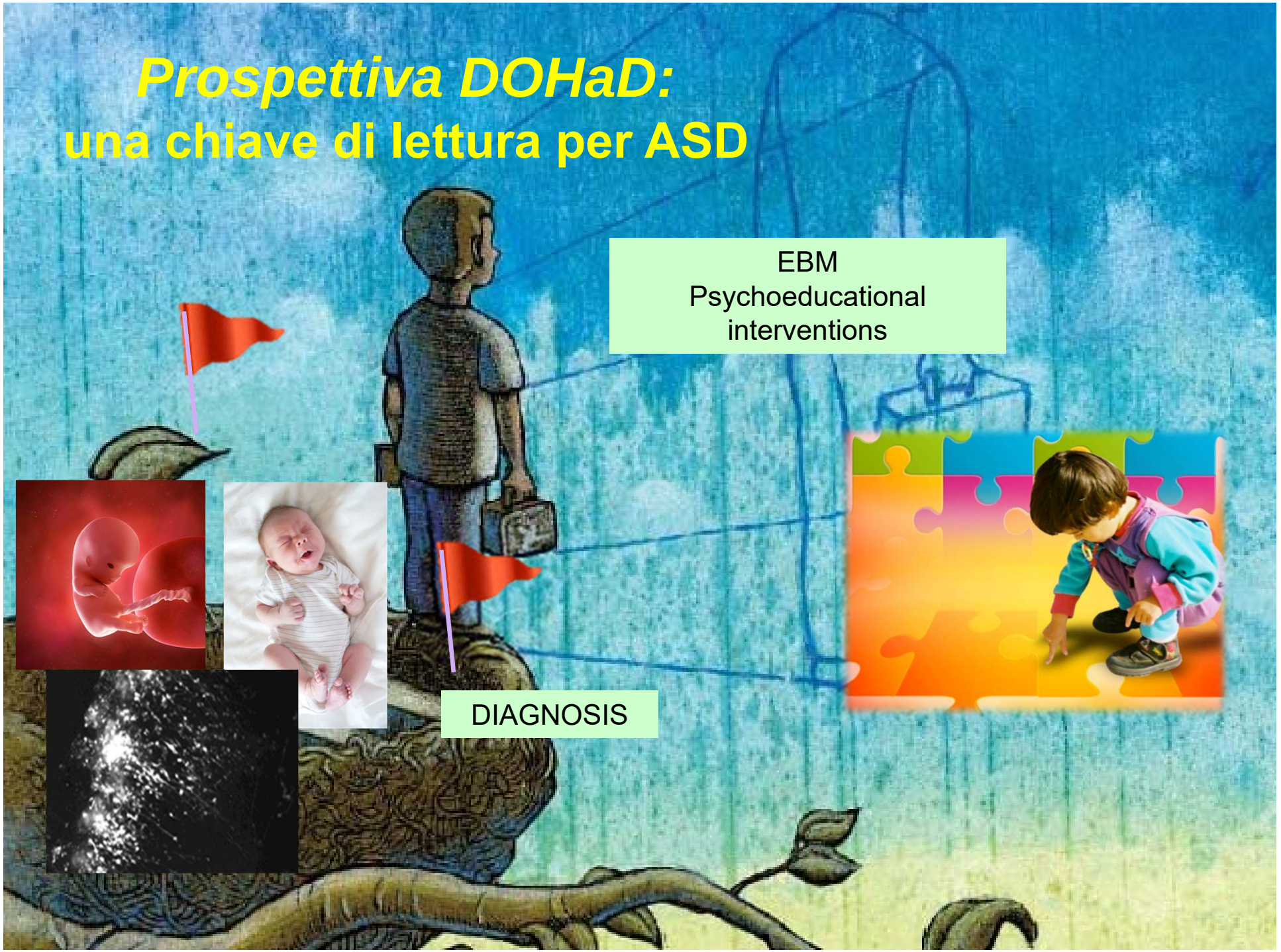
COMORBIDITIES





FLUID NETWORK

Prospettiva DOHaD:
una chiave di lettura per ASD



OBSTETRICS

Extremely low gestational age and very low birthweight for gestational age are risk factors for autism spectrum disorder in a large cohort study of 10-year-old children born at 23-27 weeks' gestation

Robert M. Joseph, PhD; Steven J. Korzeniewski, PhD; Elizabeth N. Allred, MS; T. Michael O'Shea, MD; Tim Heeren, PhD; Jean A. Frazier, MD; Janice Ware, PhD; Deborah Hirtz, MD; Alan Leviton, MD; Karl Kuban, MD; for the ELGAN Study Investigators

CONCLUSION: Our study confirms that low gestational age is associated with increased risk for autism spectrum disorder irrespective of intellectual ability, whereas severe fetal growth restriction is strongly associated with autism spectrum disorder without intellectual disability. Maternal report of cervical-vaginal infection is associated with increased risk of autism spectrum disorder with intellectual disability, and peripartum maternal fever is associated with increased risk for intellectual disability without autism spectrum disorder.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2018) **60**, 517–522 doi: 10.1111/ped.13565

Original Article

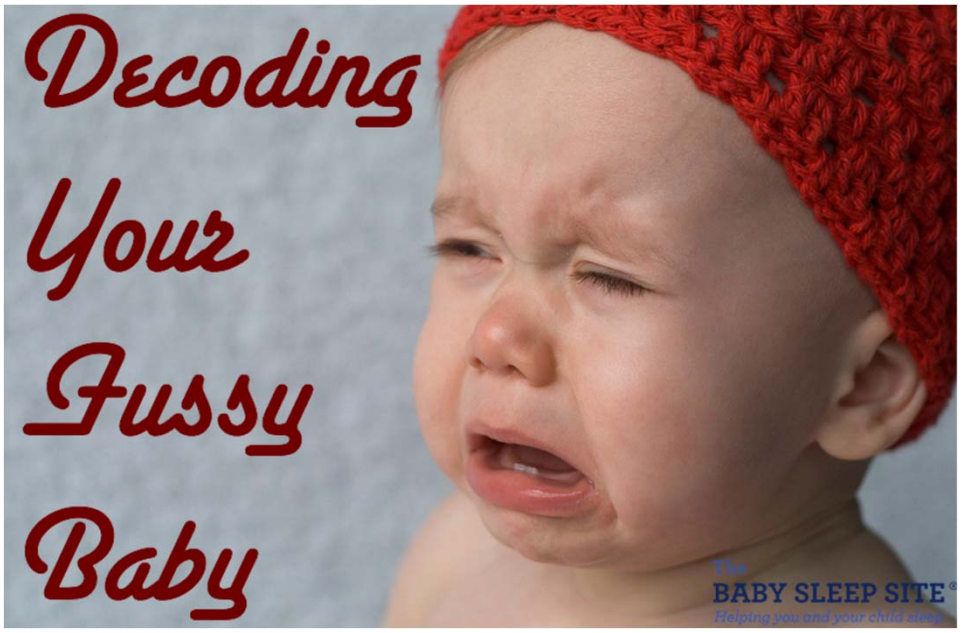
Infant colic or early symptom of autism spectrum disorder?

Özlem Bağ,[1] Sevay Alşen Güney,[3] Nagihan Cevher Binici,[3] Tuba Tuncel,[5] Aslıhan Şahin,[2] Emel Berksoy[6] and Çiğdem Ecevit[4]

The rate of persistent crying was significantly higher in the ASD group than in the control group (32% vs 9%, **P < 0.001**). The **relative risk** of persistent crying was **4.40 in ASD**. The likelihood of being **misdiagnosed with IC** in this group was **78%.**

Conclusion: Infants with excessive crying should be very thoroughly evaluated before being diagnosed with IC. In particular, persistent crying in infants (i.e. excessive crying with late onset and long duration) **may be an early symptom of ASD.**

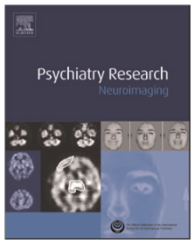
?



Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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



Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis

Roberto Sacco [a,*], Stefano Gabriele [a], Antonio M. Persico [a,b]

[a] Unit of Chi
[b] Mafalda Lu

ABSTRACT

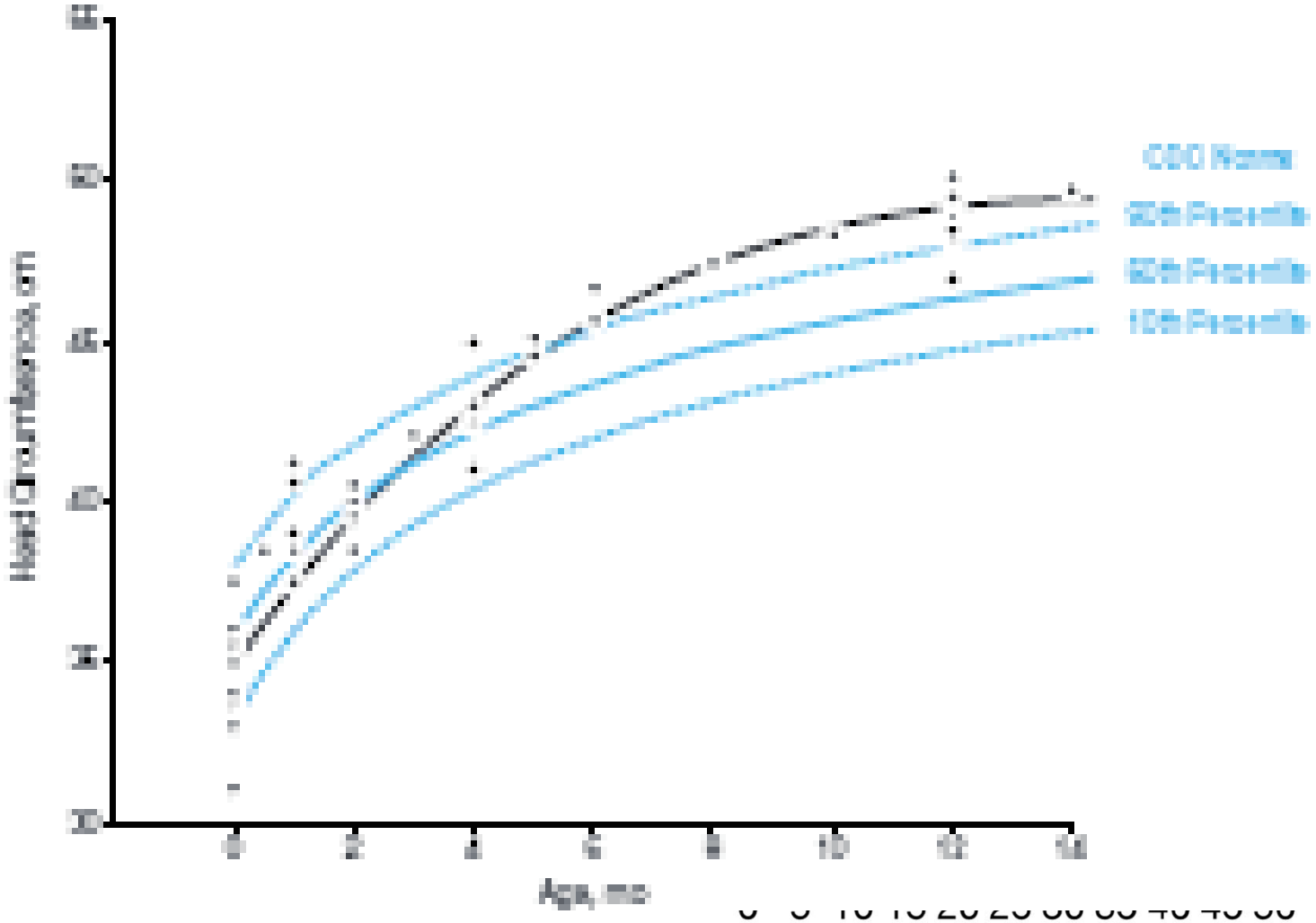
Macrocephaly and brain overgrowth have been associated with autism spectrum disorder. We performed a systematic review and meta-analysis to provide an overall estimate of effect size and statistical significance for both head circumference and total brain volume in autism. Our literature search strategy identified 261 and 391 records, respectively; 27 studies defining percentages of macrocephalic patients and 44 structural brain imaging studies providing total brain volumes for patients and controls were included in our meta-analyses. Head circumference was significantly larger in autistic compared to control individuals, with 822/5225 (15.7%) autistic individuals displaying macrocephaly. Structural brain imaging studies measuring brain volume estimated effect size. The effect size is higher in low functioning autistics compared to high functioning and ASD individuals. Brain overgrowth was recorded in 142/1558 (9.1%) autistic patients. Finally, we found a significant interaction between age and total brain volume, resulting in larger head circumference and brain size during early childhood. Our results provide conclusive effect sizes and prevalence rates for macrocephaly and brain overgrowth in autism, confirm the variation of abnormal brain growth with age, and support the inclusion of this endophenotype in multi-biomarker diagnostic panels for clinical use.

348 | NATURE | VOL 542 | 16 FEBRUARY 2017

LETTER

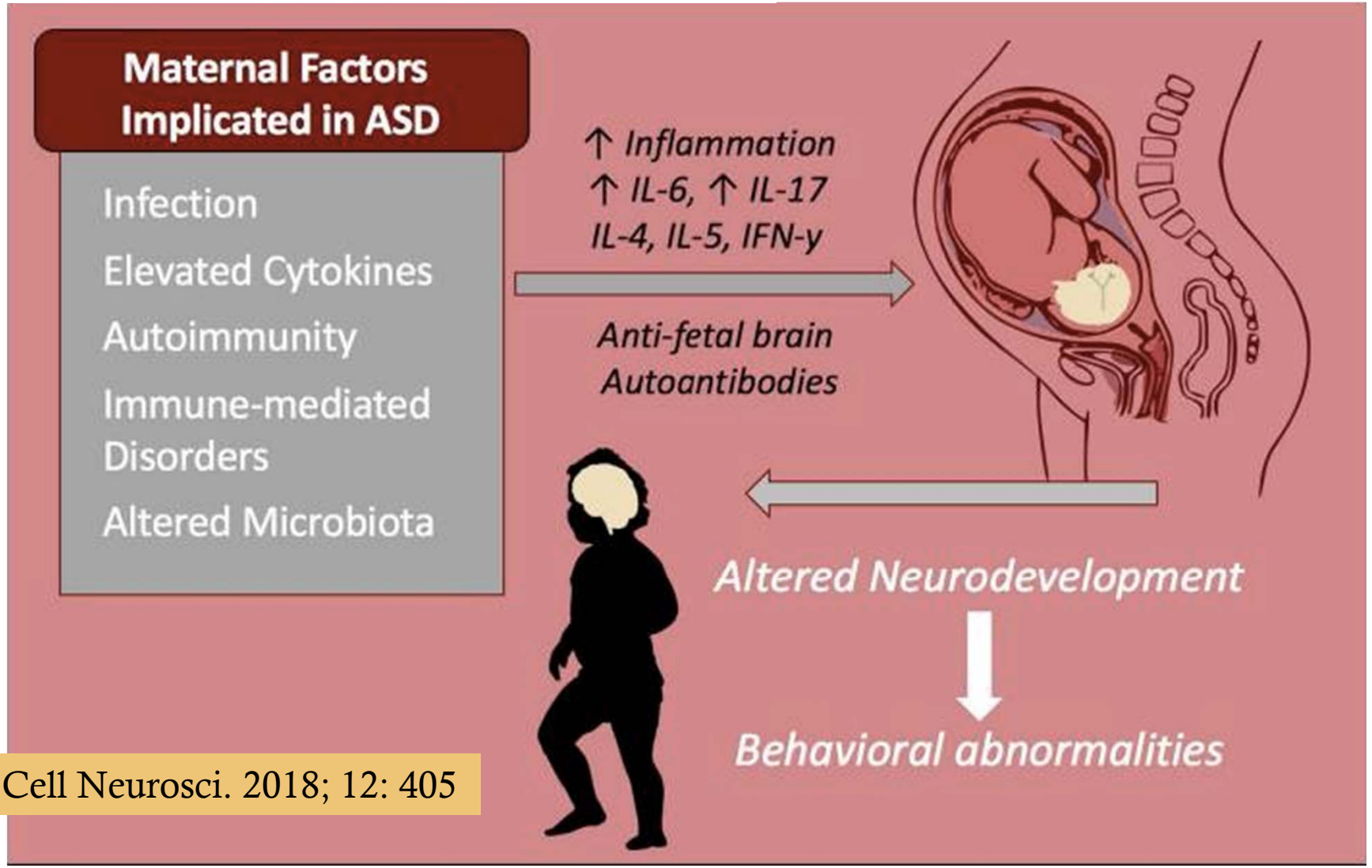
doi:10.1038/nature21369

nature
International weekly journal of science



Immune Dysfunction and Autoimmunity as Pathological Mechanisms in Autism Spectrum Disorders

Heather K. Hughes [1,2], Emily Mills Ko [1,2], Destanie Rose [1,2] and Paul Ashwood [1,2]*



Front Cell Neurosci. 2018; 12: 405

Placental adaptive responses and fetal programming

Leslie Myatt

The metabolic activity of placental mitochondria leads to oxidative stress even in normal pregnancy which is exacerbated further in IUGR, diabetic and pre-eclamptic pregnancies and may also give nitrative stress known to lead to covalent modification and hence altered activity of proteins. **Hypoxia, oxidative and nitrative stress all alter placenta development** and may be a general underlying mechanism that links altered placental function to fetal programming.

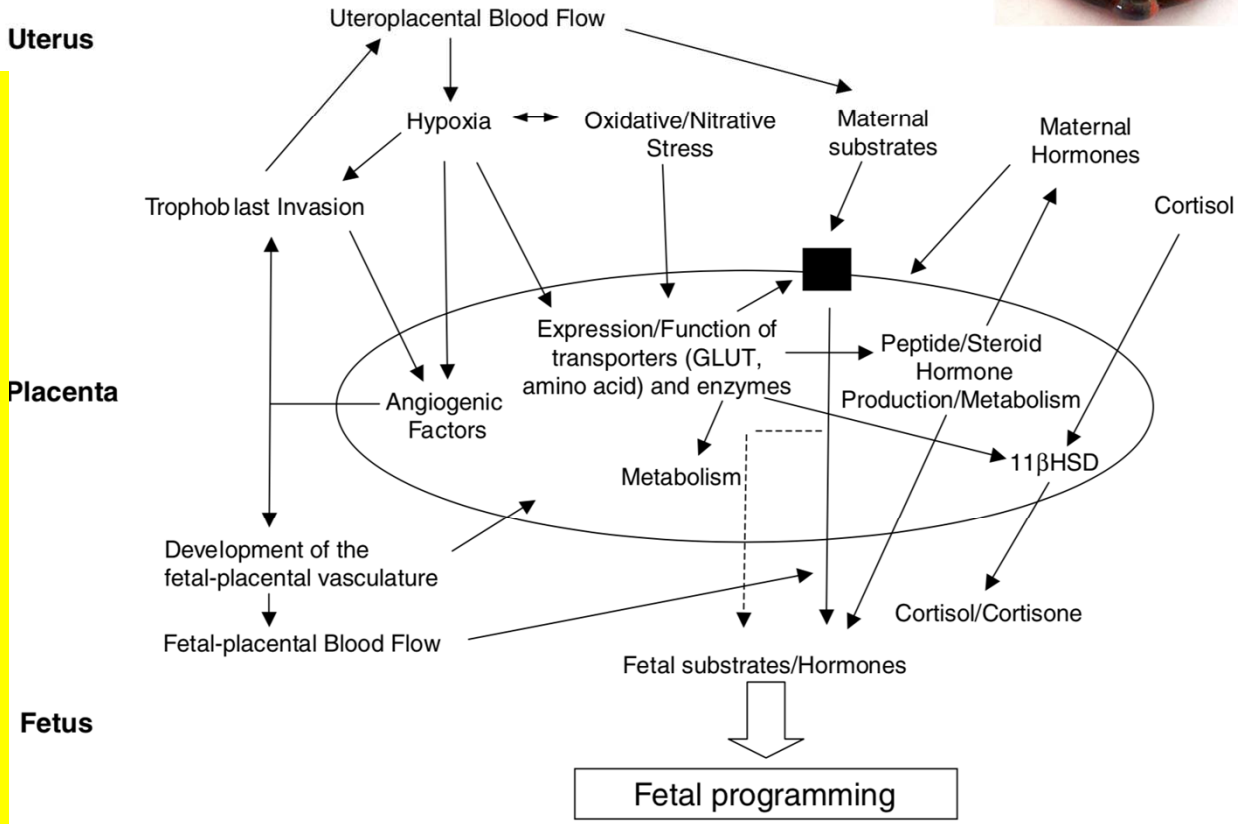


Figure 1
Placental adaptive responses and fetal programming.

J Physiol 572.1 (2006) pp 25–30

International Journal of *Molecular Sciences*

Int. J. Mol. Sci. **2019**, *20*, 2757

MDPI

Review

The Role of Nitric Oxide, ADMA, and Homocysteine in The Etiopathogenesis of Preeclampsia—Review

Weronika Dymara-Konopka * and Marzena Laskowska

• NO PATHWAY ROLE	STAGES OF PE
•confers autocrine/paracrine effects in the placenta •regulates feto-placental vascular reactivity •main vasodilator in the placenta •involved in trophoblast invasion and apoptosis, platelet adhesion in the intervillous space •promotes embryo survival and tissue remodeling •regulates vasculo and angiogenesis •downstream mediator of VEGR, FGF and angiopoietin-1 and possibly upstream regulator via HIF-1	**1. Abnormal placental invasion** incomplete, restricted to superficial layers of decidua inadequate access to oxygen and nutrients for placenta and fetus reduction in uteroplacental perfussion pressure placental ischemia/hypoxia
•maintains endothelial cell barrier integrity •a key transmitter for endothelium-dependent regulation of vascular tone •inhibits tha adhesion and activation of platelet aggregation •acts as an anticoagulant •contributes to decrease in vascular resistance observed during early pregnancy in response to expended blood volume •supports growing need of organ perfusion during pregnancy •abolishes toxic activity of superoxide ions •correlates with concentrations of anti and proangiogenic molecules	**2. Maternal endothelial dysfunction** endotheliosis endothelial dysfunction generalised multisystem vasospasm reduced plasma volume oxidative stress hyperinflammatory and antiangiogenic state

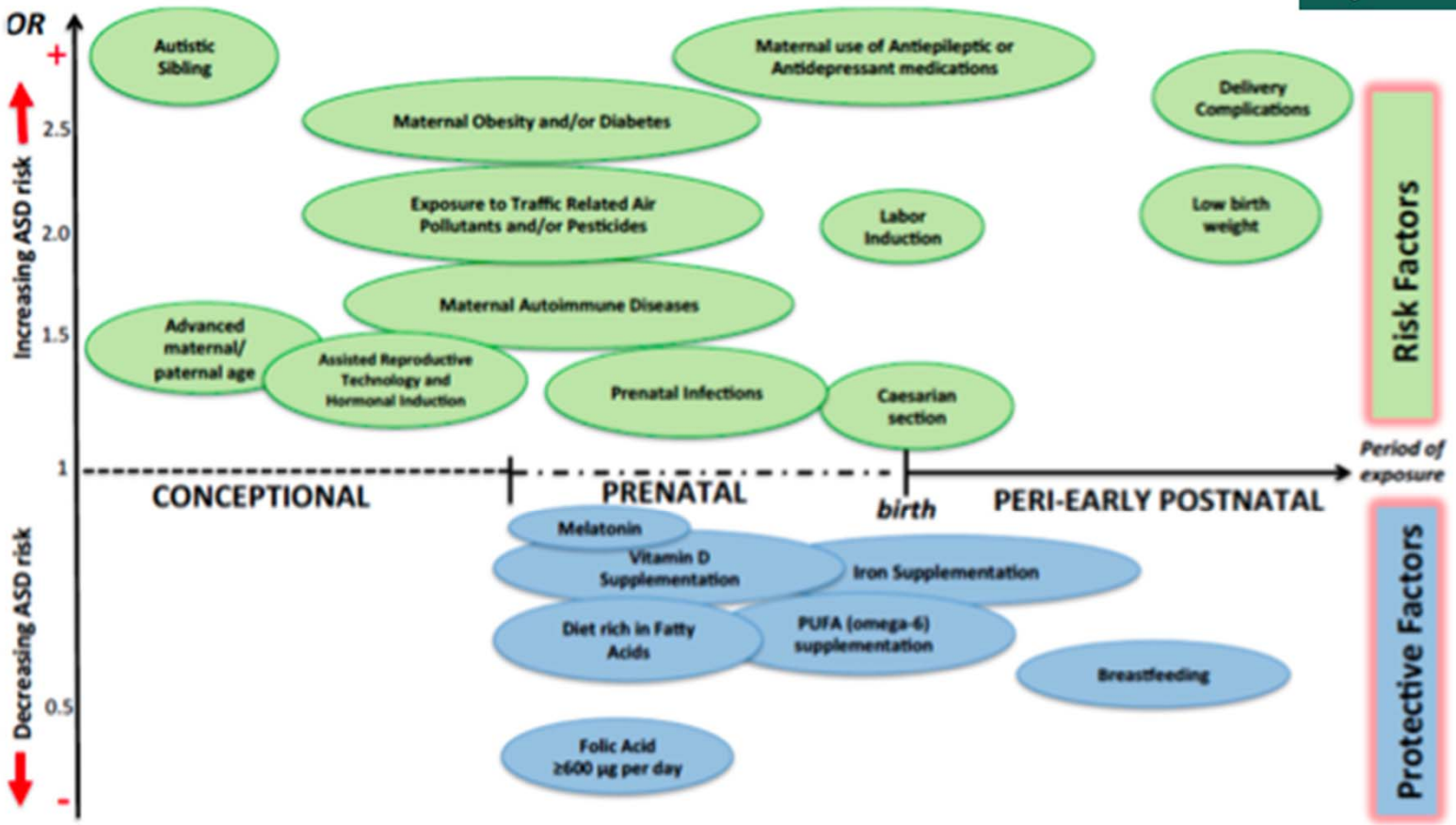
Journal of Clinical Medicine

J. Clin. Med. 2019, 8, 217; doi:10.3390/jcm8020217

Review

Risk and Protective Environmental Factors Associated with Autism Spectrum Disorder: Evidence-Based Principles and Recommendations

Leonardo Emberti Gialloreti [1,*], Luigi Mazzone [2], Arianna Benvenuto [2], Alessio Fasano [3], Alicia Garcia Alcon [4], Aletta Kraneveld [5], Romina Moavero [2,6], Raanan Raz [7], Maria Pia Riccio [8], Martina Siracusano [1,9], Ditza A. Zachor [10], Marina Marini [11] and Paolo Curatolo [2]



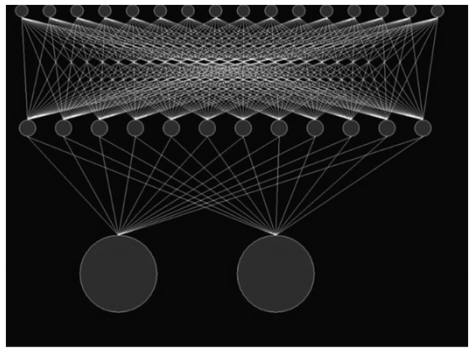
Journal of Developmental Origins of Health and Disease

2018

cambridge.org/doh

Pregnancy risk factors related to autism: an Italian case–control study in mothers of children with autism spectrum disorders (ASD), their siblings and of typically developing children

E. Grossi[1], L. Migliore[2] and F. Muratori[3,4]



Original Article

Cite this article: Grossi E, Migliore L, Muratori F. (2018) Pregnancy risk factors

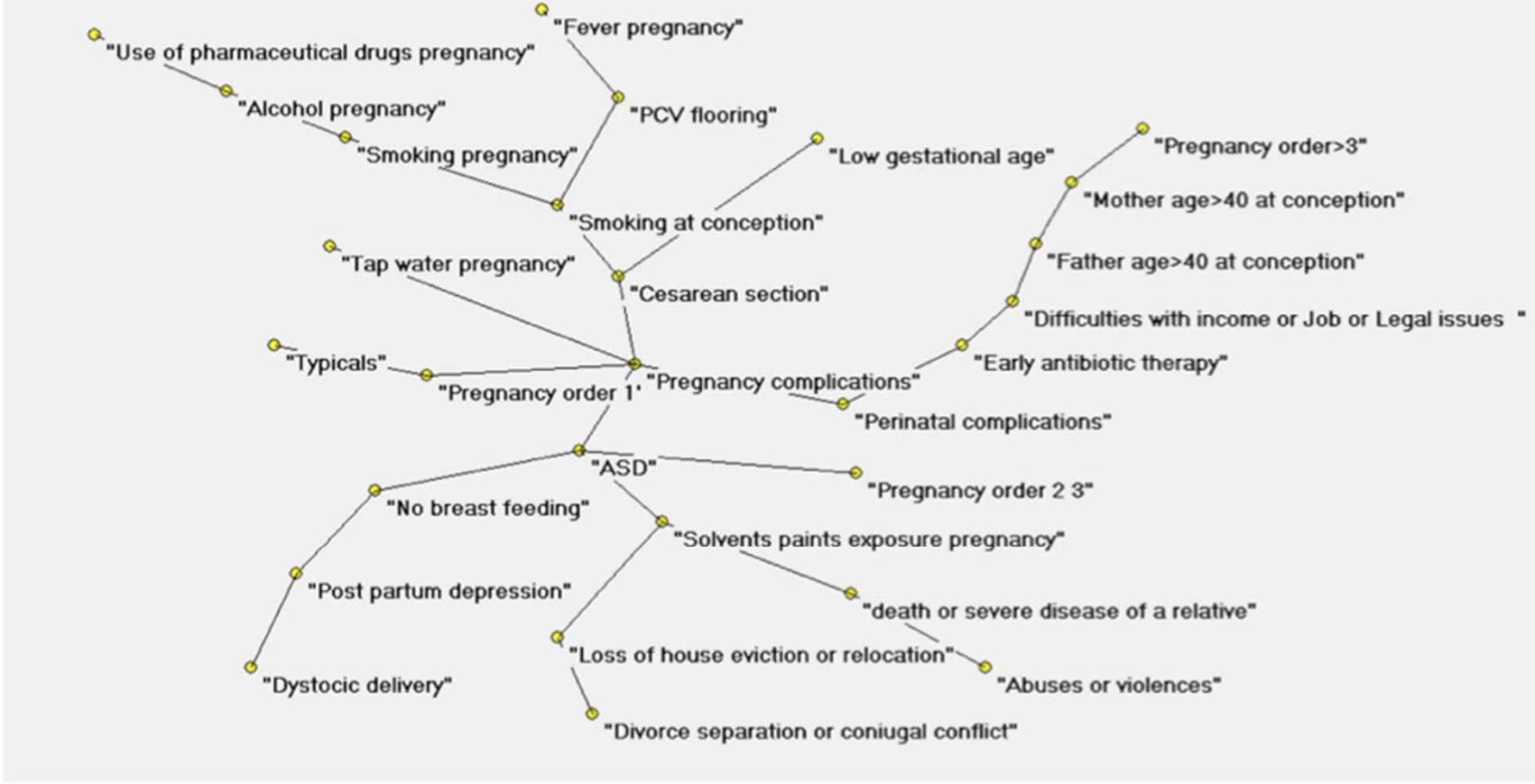


Fig. 3. Semantic connectivity map of factors on study. See text for areas description.

REVIEW

Maternal immune activation: Implications for neuropsychiatric disorders

Myka L. Estes, A. Kimberley McAllister*

Science
Vol 353, Issue 6301
19 August 2016

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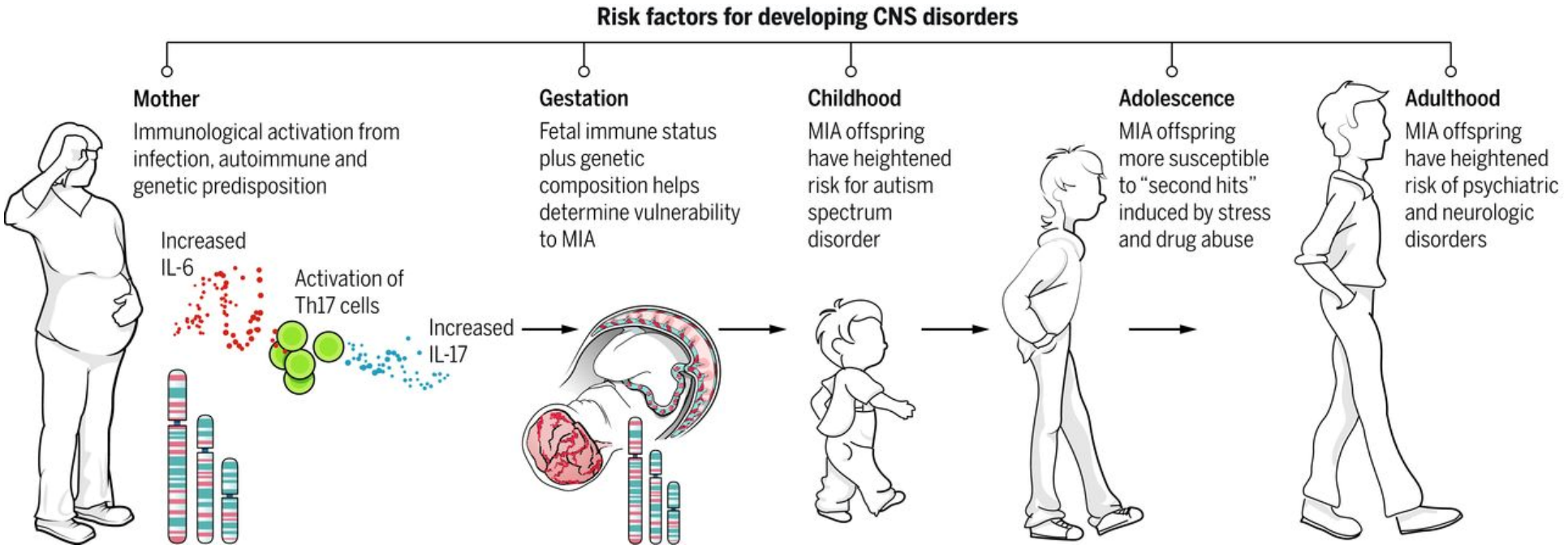
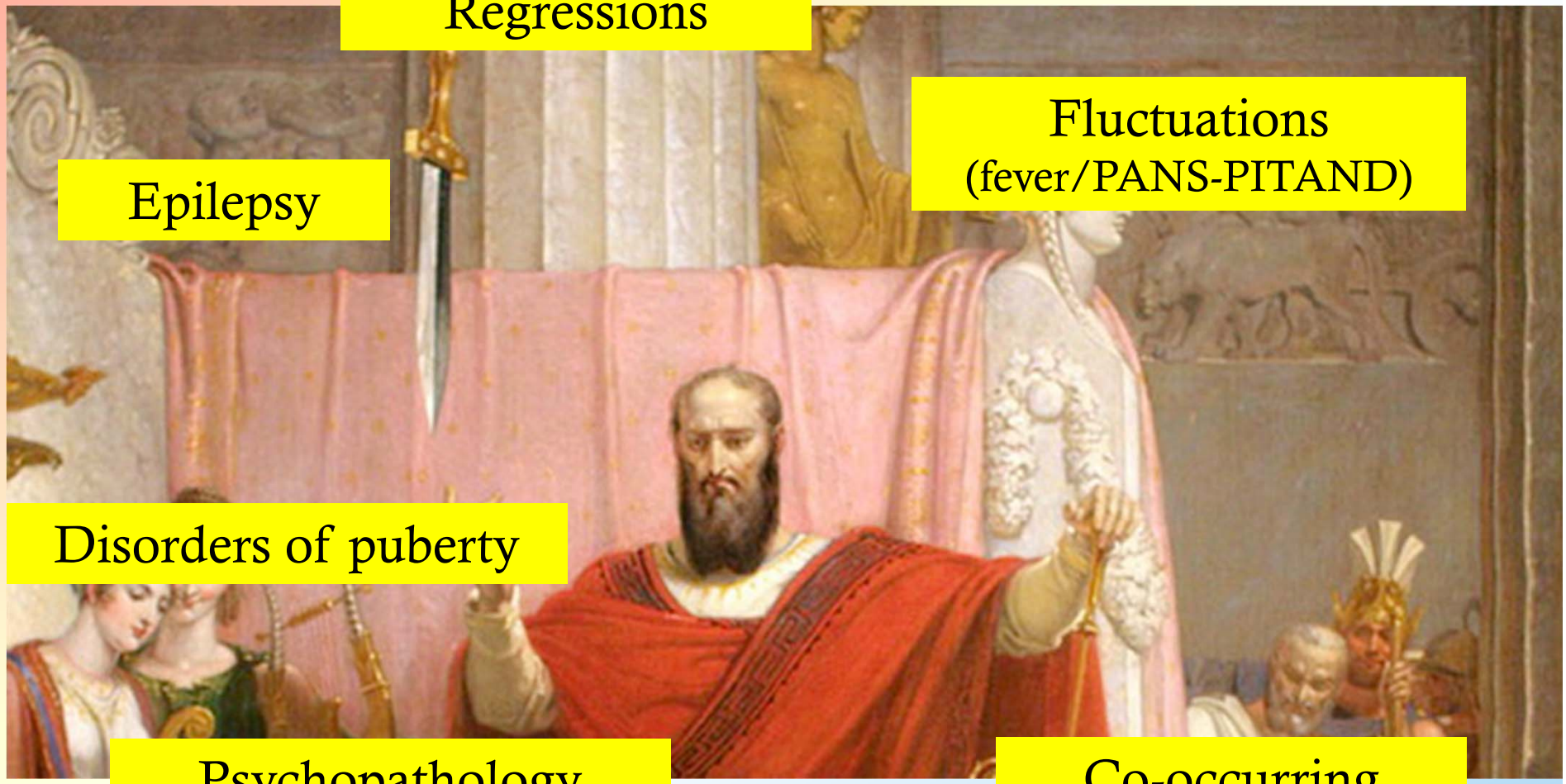
Advertising (PDF)
Classified (PDF)
Masthead (PDF)

traiettoria di fragilità possibile VS fotografia di un danno inevitabile e irreversibile



An open issue:



GENETIC/GENOMICS

EPIGENETIC/EPIGENOMICS

ENVIRONMENTAL FACTORS

NEUROINFLAMMATION

IMMUNE RESPONSE

OXIDATIVE STRESS

GUT-BRAIN AXIS

MITOCHONDRIAL IMPAIRMENT

Research in ASD: WHAT TOPICS?

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
Explore this journal >

Original Article

Neuroglial activation and neuroinflammation in the brain of patients with autism

Diana L. Vargas MD, Caterina Nascimbene MD, Chitra Krishnan MHS, Andrew W. Zimmerman MD, Carlos A. Pardo MD

*"…**We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients**. Immunocytochemical studies showed **marked activation of microglia and astroglia, and cytokine profiling** indicated that macrophage chemoattractant protein (MCP)–1 and tumor growth factor–β1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a **marked increase in MCP-1**. Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that **future therapies might involve modifying neuroglial responses** in the brain"*

Vargas et al, 2005; 57 (1): 67-81

ASD and immune dysfunction

Genetic associations with immune-related genes

Family history of autoimmune diseases

Maternal infections, inflammation and autoimmunity infection during pregnancy

Autoantibodies directed toward CNS proteins

Elevated serum titres of antibodies

Inadequate quantity and quality of serum immunoglobulins

Alterations of mitogen-induced proliferation

Reduced number of total lymphocytes

Impairments of the CD4/CD8 T cells ratio

Defective T cell activation

Reduced NK cytotoxicity

Alterations in the Th1/Th2 cytokine balance

Dysregulation in apoptosis mechanisms

BIOL PSYCHIATRY 2009;66:978–984

Brain, Behavior, and Immunity 57 (2016) 125–133

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Full-length Article

Multiple inflammasome complexes are activated in autistic spectrum disorders

Marina Saresella [a,*], Federica Piancone [a], Ivana Marventano [a], Martina Zoppis [a], Ambra Hernis [a], Michela Zanette [a], Daria Trabattoni [b], Matteo Chiappedi [e], Alessandro Ghezzo [f], Maria Paola Canevini [d], Francesca la Rosa [a], Susanna Esposito [c], Mario Clerici [a,c]

ABSTRACT

Background: Inflammasomes are multimeric protein platforms involved in the regulation of inflammatory responses whose activity results in the production of proinflammatory cytokines. Because neuroinflammation is observed in autistic spectrum disorders (ASD), a neurologic condition of childhood resulting in a complex behavioural impairment, we analyzed the inflammasomes activity in ASD. Additionally we verified whether alterations of the gastrointestinal (GI) barriers might play a role in inflammasomes activation.

Methods: The activity of the inflammasomes, the concentration of the inflammasomes-derived proinflammatory cytokines interleukin (IL)-1β and IL-18, and serum parameters of GI damage were analyzed in 25 ASD children, 23 healthy siblings (HS) and 30 unrelated age-matched healthy controls (HC).

Results: A significant upregulation of the AIM2 and the NLRP3 inflammasomes and an increased production of IL-1β and IL-18 that was associated with a consistent reduction of IL-33, an anti inflammation cytokine were observed in ASD alone. Notably, in a possible immune-mediated attempt to dampen inflammation, IL-37, a suppressor of innate inflammatory responses, was significantly augmented in these same children. Finally, intestinal fatty acid binding protein (IFABP), an index of altered GI permeability, was significantly increased in serum of ASD and HS.

Conclusions: These results show that the inflammasomes are activated in ASD and shed light on the molecular mechanisms responsible for ASD-associated neuroinflammation. The observation that GI alterations could be present as well in ASD offers a possible link between such alterations and neuroinflammation. Therapeutic strategies targeting inflammasome activation could be useful in ASD.

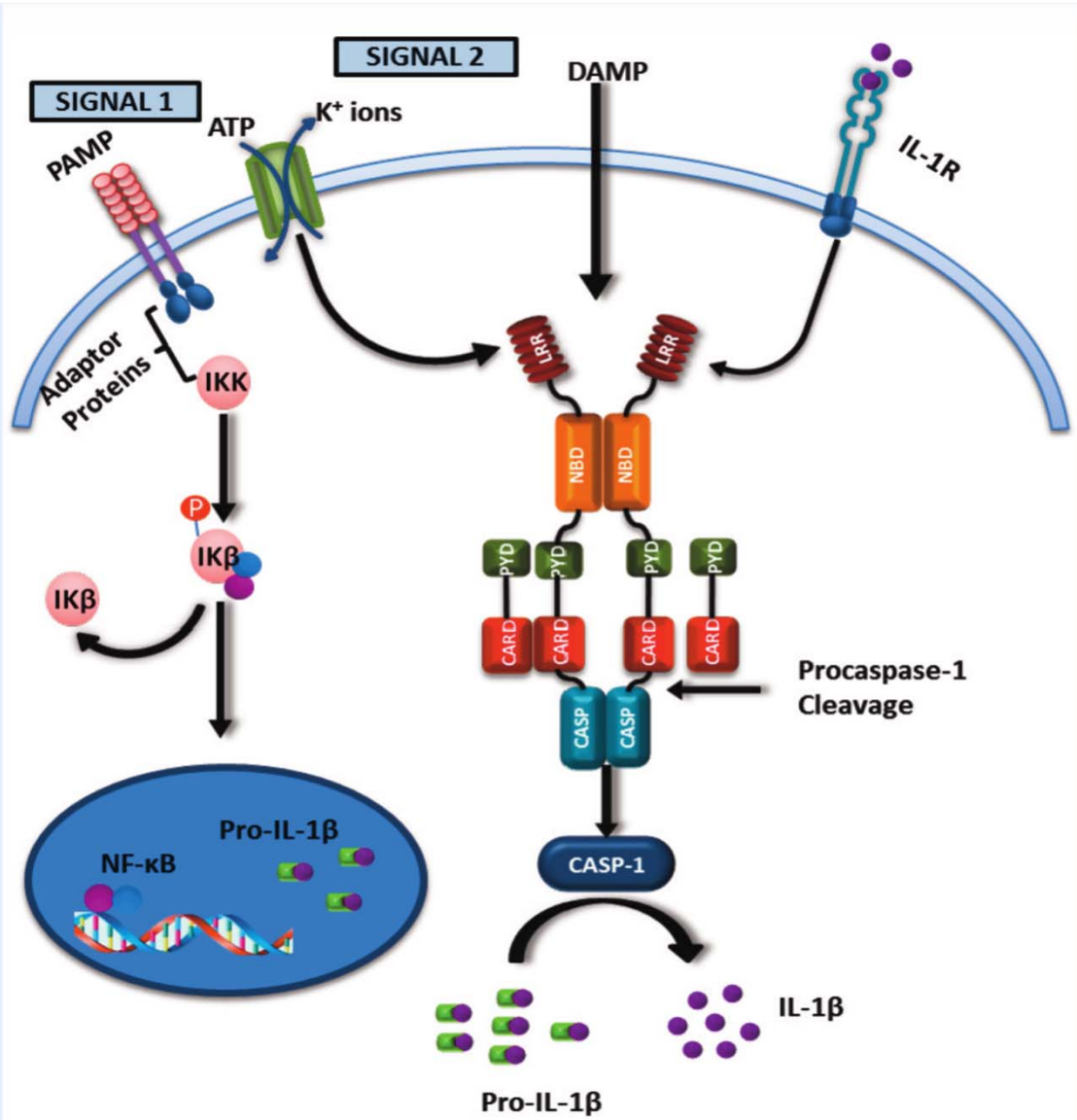
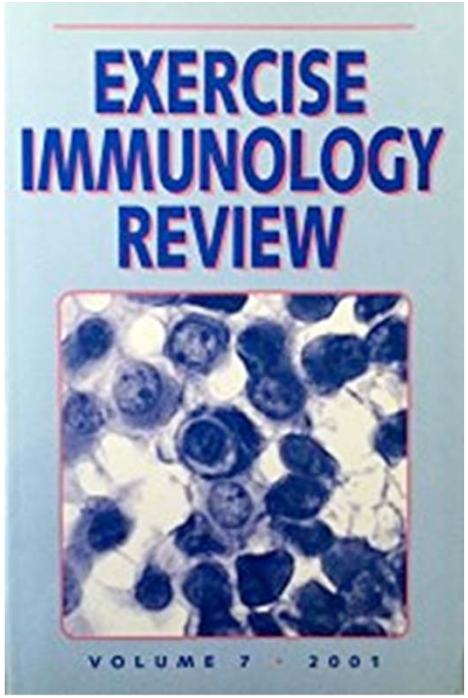
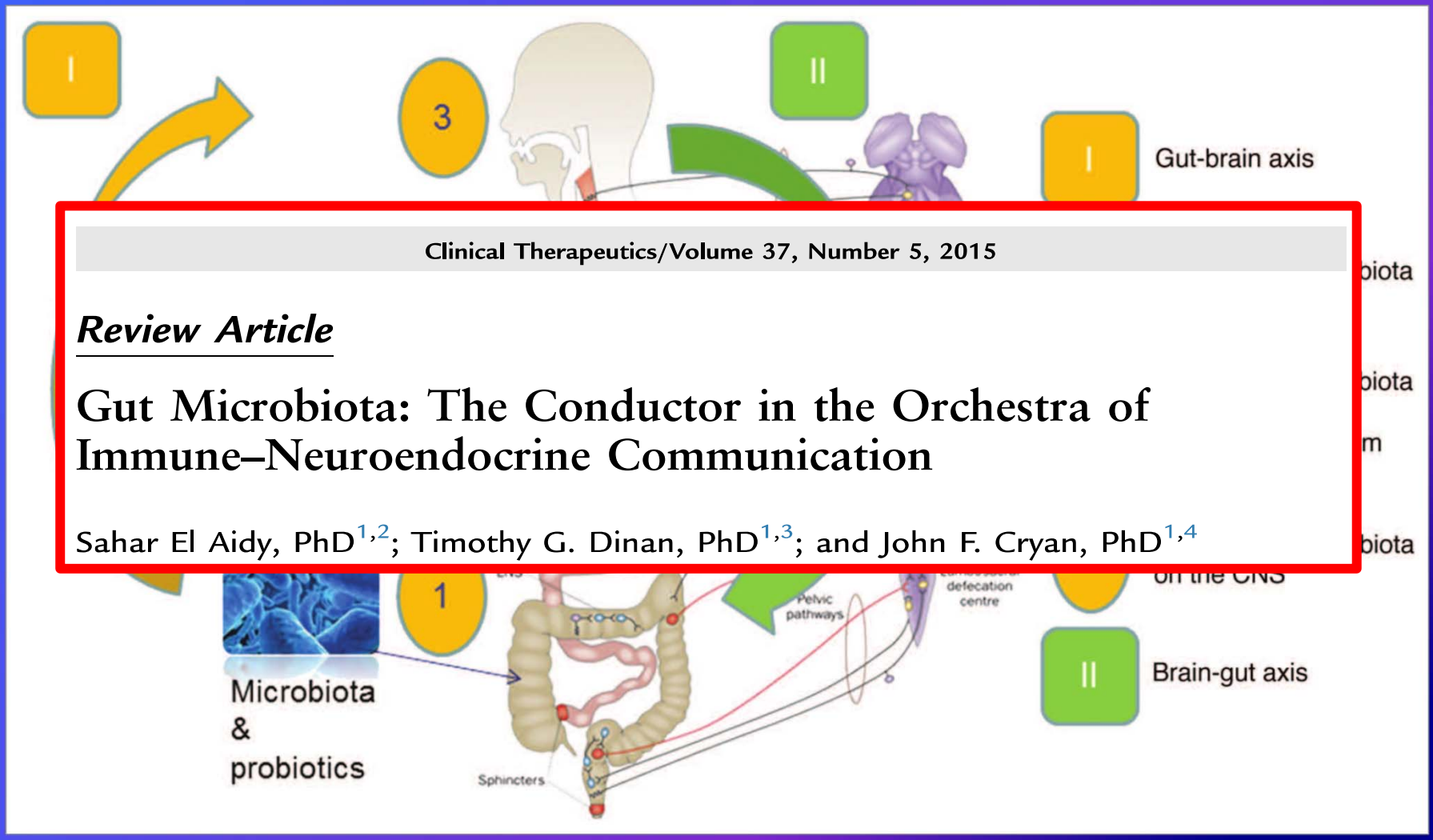


Figure 5 - Schematic illustration of NLRP3 inflammasome activation and subsequent intracellular signalling that produces a pro-inflammatory outcome.



S. Horsburgh et al, 2015

The Relationship Between Microbiome, Gut, and Brain



Clinical Therapeutics/Volume 37, Number 5, 2015

Review Article

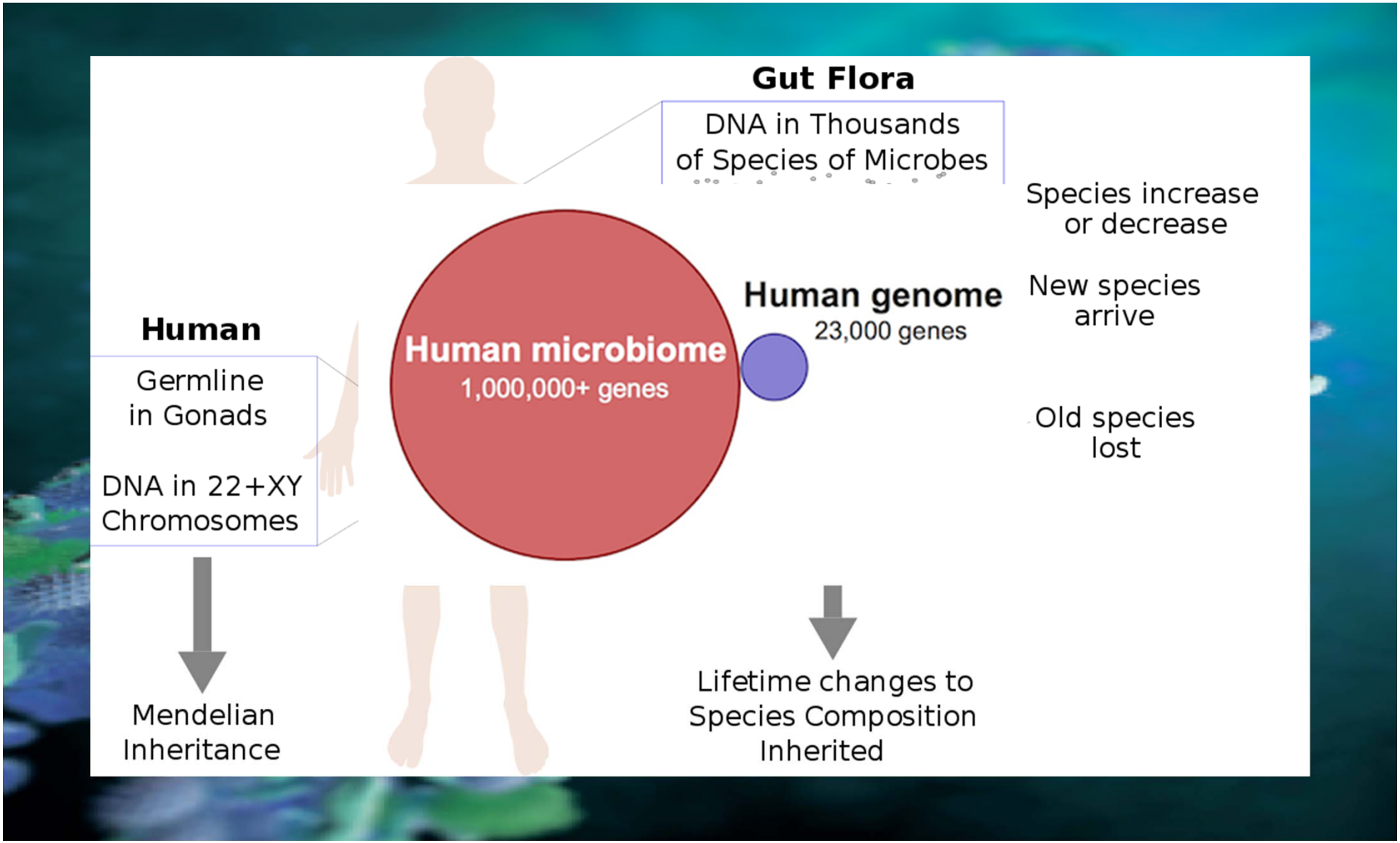
Gut Microbiota: The Conductor in the Orchestra of Immune–Neuroendocrine Communication

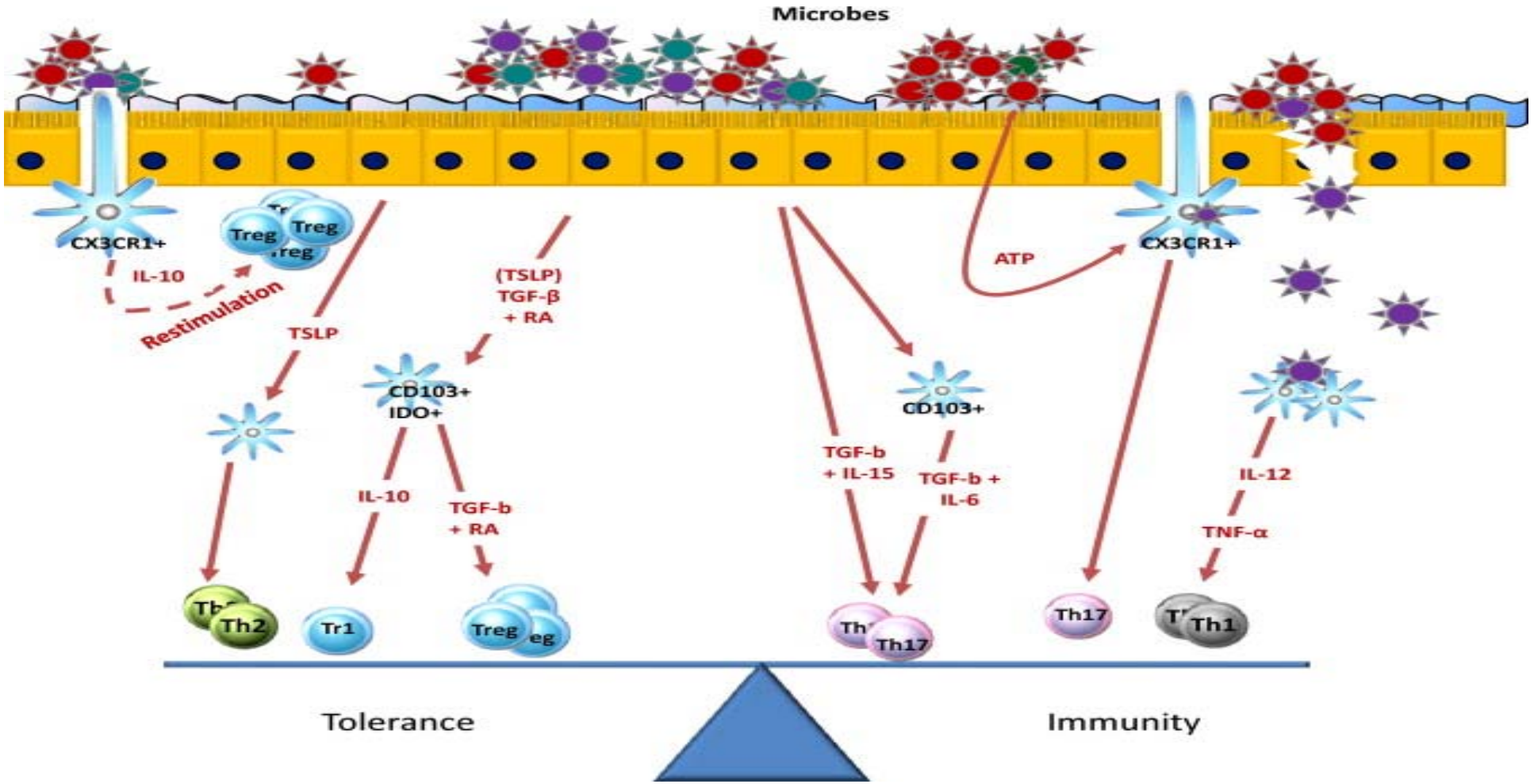
Sahar El Aidy, PhD[1,2]; Timothy G. Dinan, PhD[1,3]; and John F. Cryan, PhD[1,4]

Saulnier et al, 2013

Gut Microbes 4:1, 17–27; January/February 2013

Hologenome → Holobiont

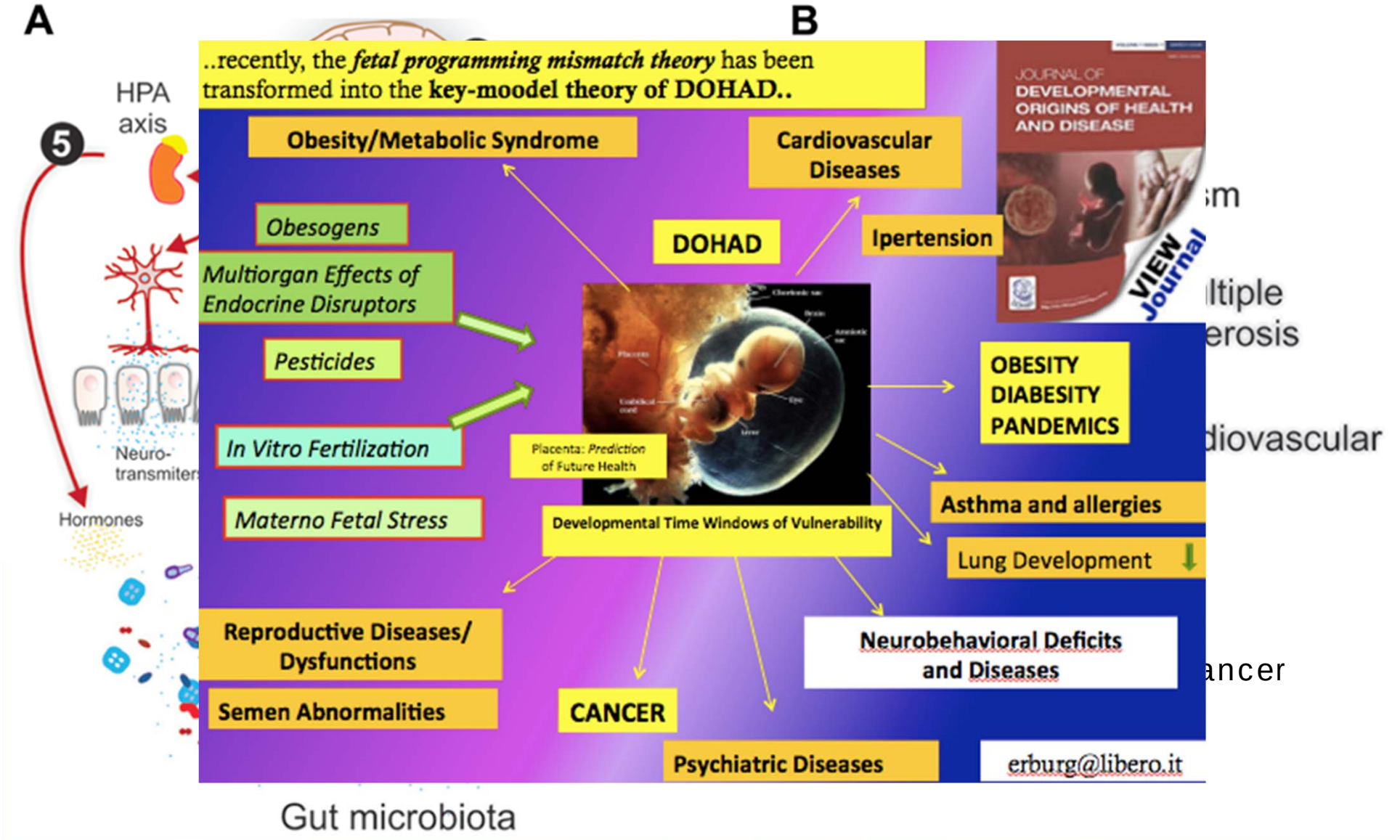


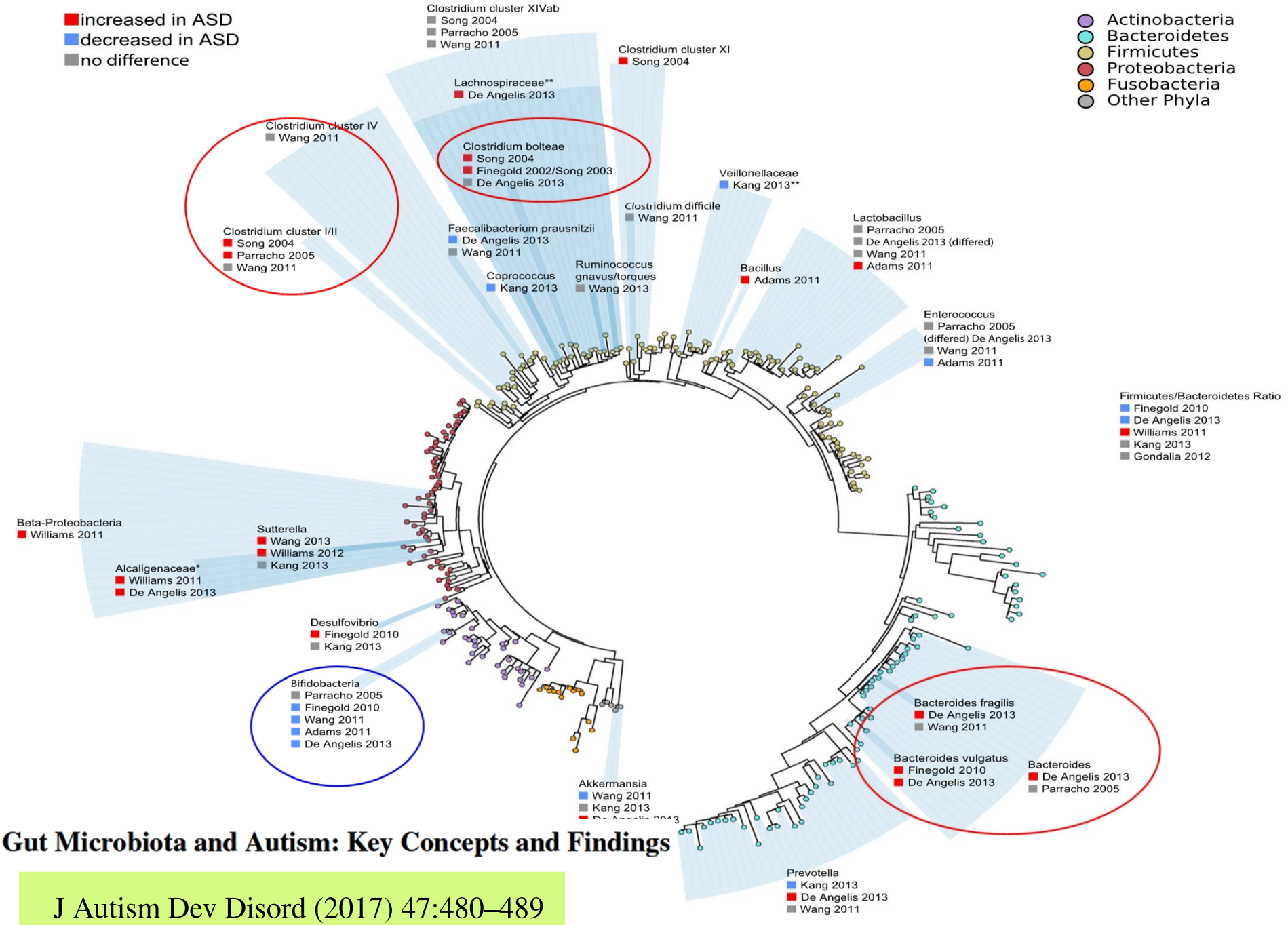


Rescigno M

How the interplay between antigen presenting cells and microbiota tunes host immune responses in the gut

Seminars in Immunology, Volume 24, Issue 1, 2012, 43 - 49

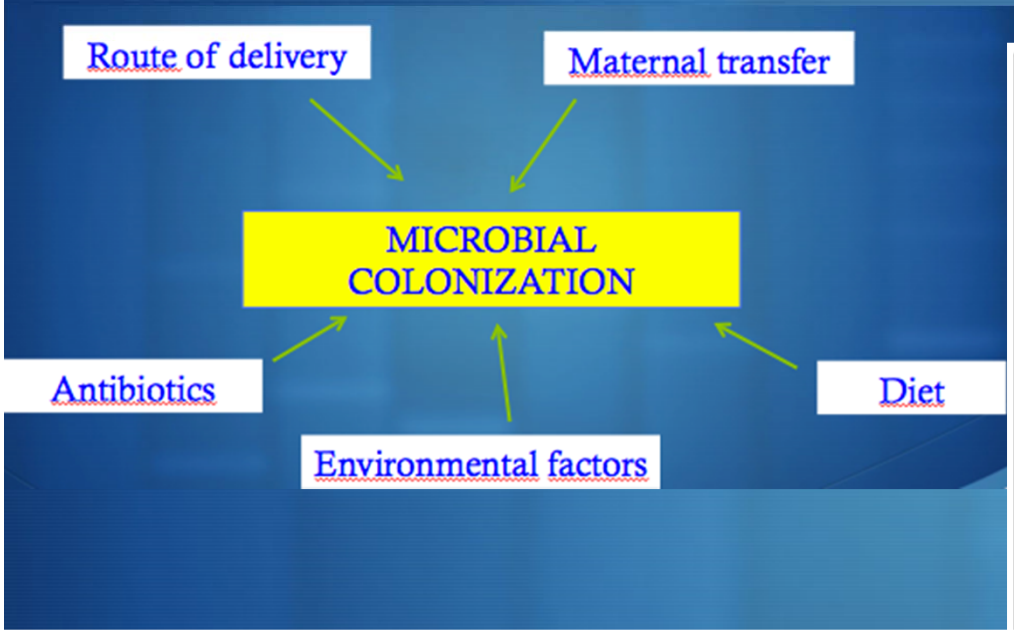

A
B
HPA axis
5
Neuro-transmiters
Hormones
Gut microbiota
..recently, the fetal programming mismatch theory has been transformed into the key-moodel theory of DOHAD..
Obesity/Metabolic Syndrome
Cardiovascular Diseases
Obesogens
DOHAD
Ipertension
Multiorgan Effects of Endocrine Disruptors
Pesticides
In Vitro Fertilization
Materno Fetal Stress
Placenta: Prediction of Future Health
Developmental Time Windows of Vulnerability
OBESITY
DIABESITY
PANDEMICS
Asthma and allergies
Lung Development
Reproductive Diseases/ Dysfunctions
Neurobehavioral Deficits and Diseases
Semen Abnormalities
CANCER
Psychiatric Diseases
erburg@libero.it
JOURNAL OF DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE
VIEW Journal

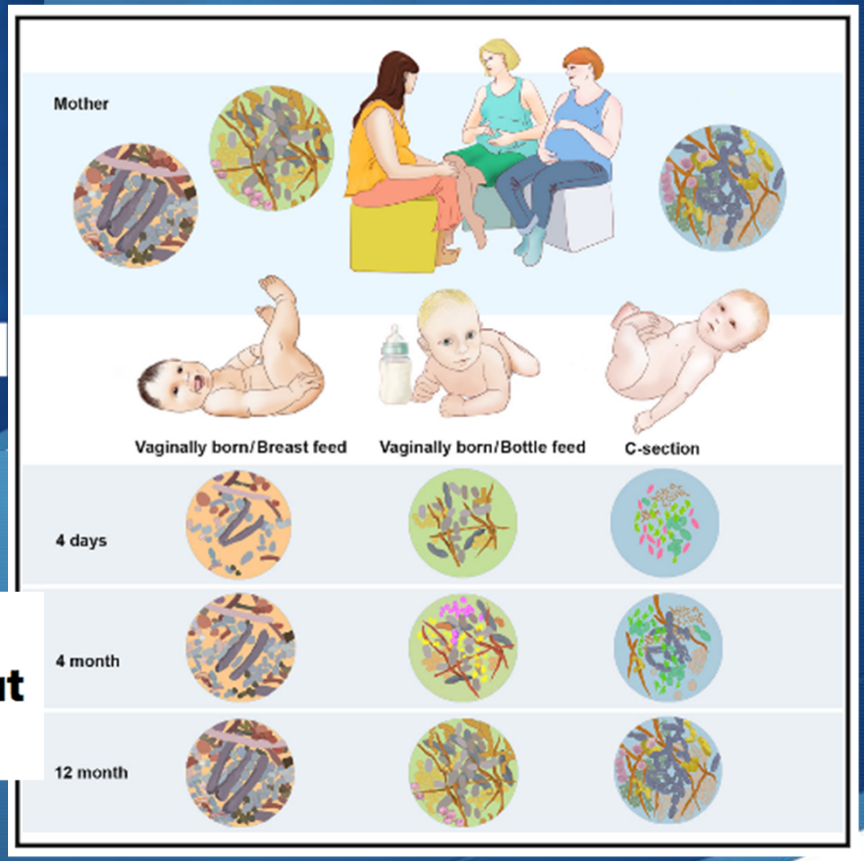


Gut Microbiota and Autism: Key Concepts and Findings

J Autism Dev Disord (2017) 47:480–489

The gut microbiota is shaped in early infancy



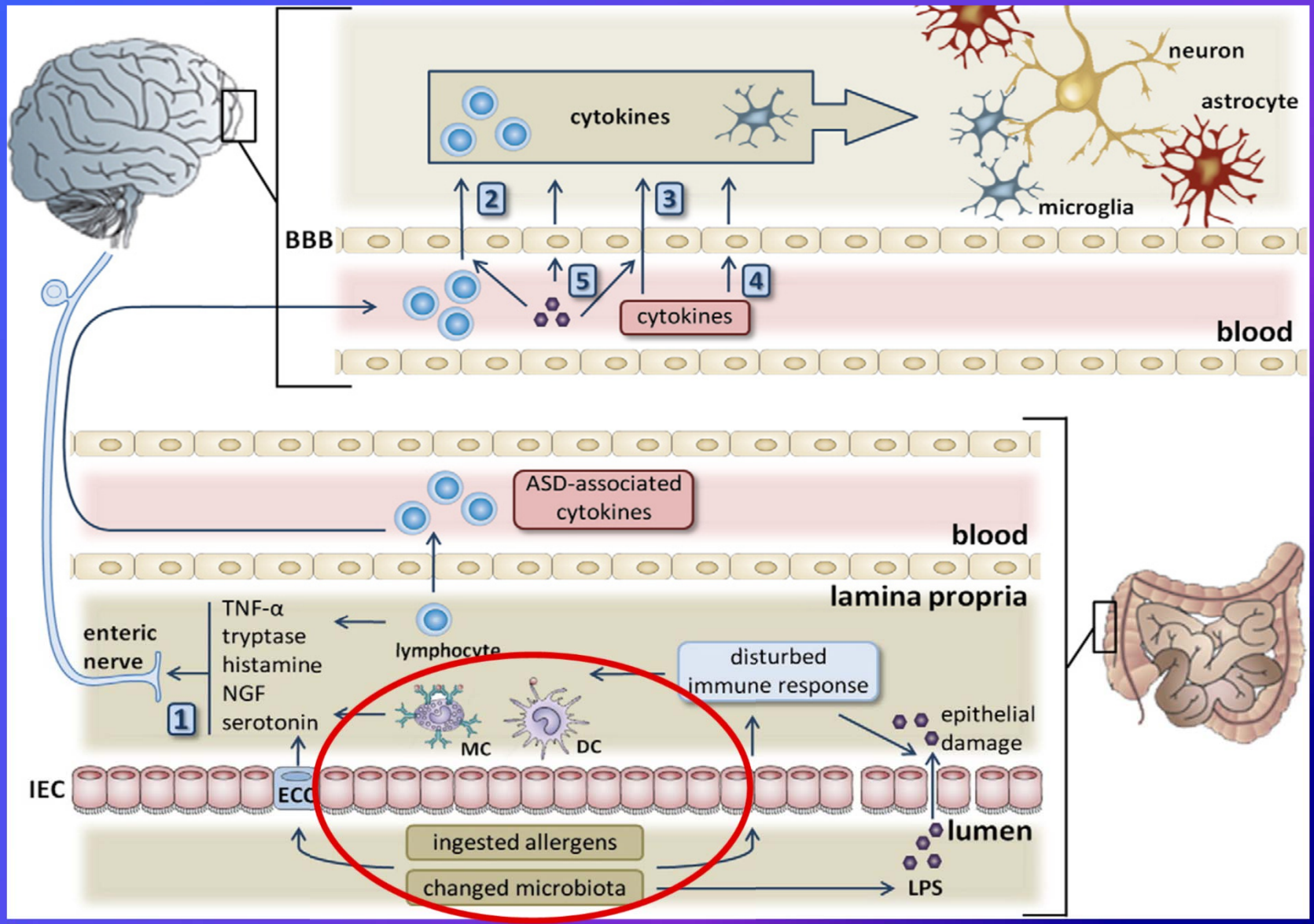


Cell Host & Microbe

Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life

Bäckhed et al., 2015, Cell Host & Microbe *17*, 690–703
May 13, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.chom.2015.04.004

Gut-brain axis



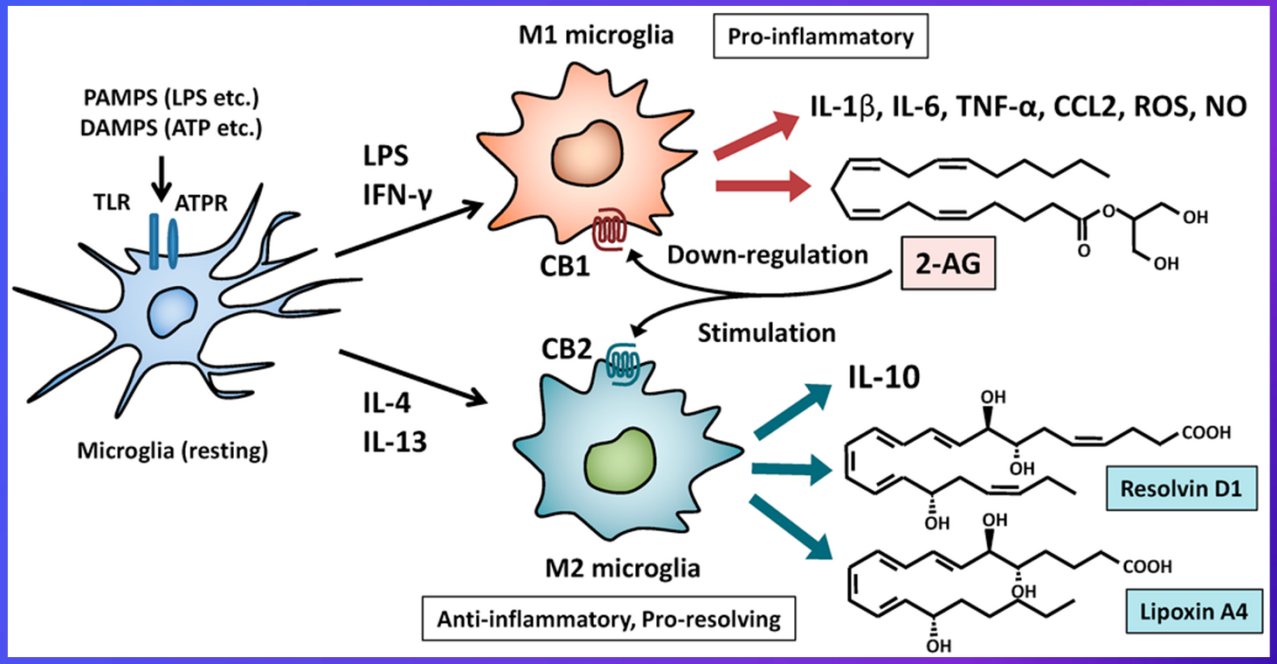
De Theije et al Eur J Pharmacol. 2011 Sep;668 Suppl 1:S70-80

Review

Role of Microglial M1/M2 Polarization in Relapse and Remission of Psychiatric Disorders and Diseases

Yutaka Nakagawa [1] and Kenji Chiba [2,*]

Pharmaceuticals **2014**, *7*, 1028-1048; doi:10.3390/ph7121028



Microglia are nervous system-specific immune cells serving as tissue-resident macrophages influencing brain development, homeostasis, response to injury and repair.

As influenced by their environment, microglia assume different phenotypes and shift functions to maintain tissue homeostasis

nutrients

MDPI

Article

Effects of *Lactobacillus plantarum* PS128 on Children with Autism Spectrum Disorder in Taiwan: A Randomized, Double-Blind, Placebo-Controlled Trial

Yen-Wenn Liu [1,2], Min Tze Liong [3], Yu-Chu Ella Chung [4], Hui-Yi Huang [5], Wu-Shun Peng [1], Yun-Fang Cheng [1], Yu-Siou Lin [6], Yu-Yu Wu [7,*] and Ying-Chieh Tsai [1,2,*]

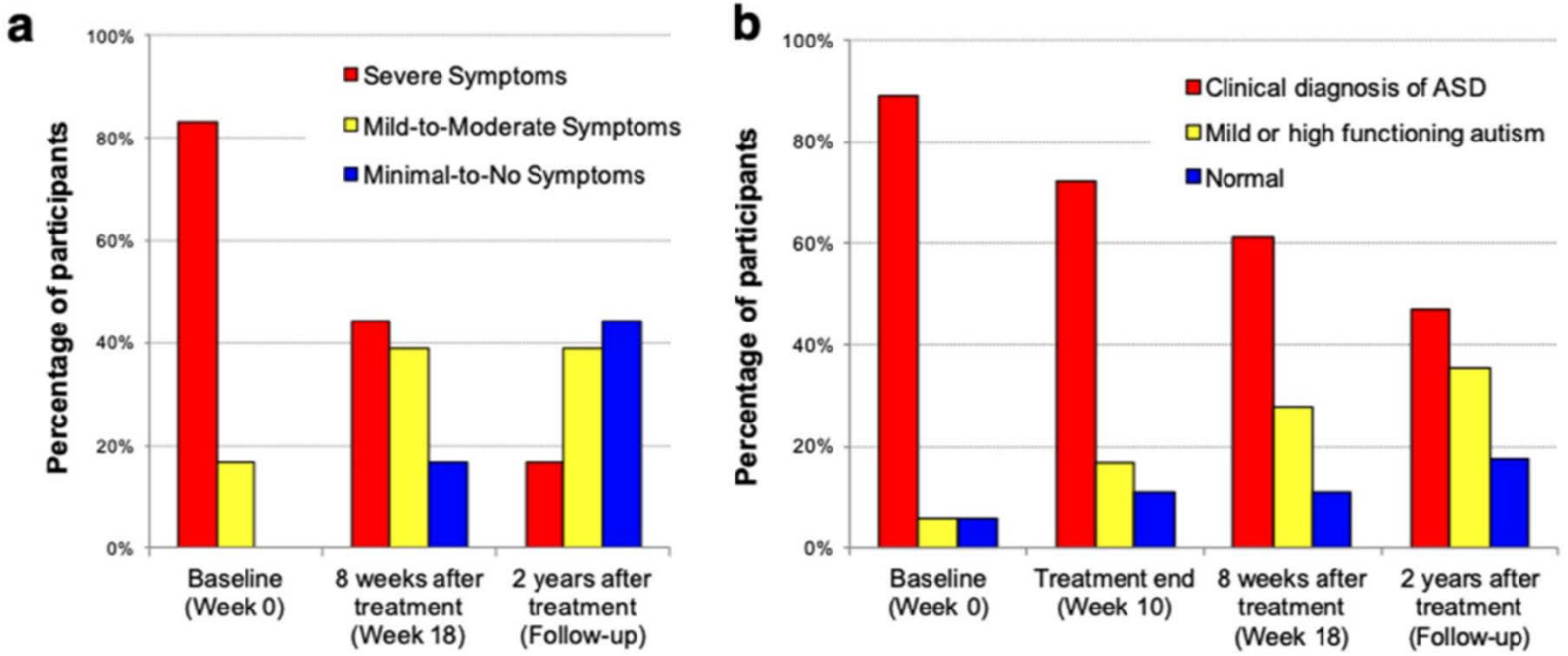
Abstract: This four-week, randomized, double-blind, placebo-controlled study investigated the effects of *Lactobacillus plantarum* PS128 (PS128) on boys with autism spectrum disorder (ASD) aged 7–15 in Taiwan. All subjects fulfilled the criteria for ASD diagnosis of DSM-V and the Autism Diagnostic Interview-Revised (ADI-R). Questionnaires used for the primary outcome measure include the Autism Behavior Checklist-Taiwan version (ABC-T), the Social Responsiveness Scale (SRS) and the Child Behavior Checklist (CBCL). The Swanson, Nolan, and Pelham-IV-Taiwan version (SNAP-IV) and the Clinical Global Impression-improvement (CGI-I) were used for the secondary outcome measure. The results showed that PS128 ameliorated opposition/defiance behaviors, and that the total score of SNAP-IV for younger children (aged 7−12) improved significantly compared with the placebo group. Additionally, several elements were also notably improved in the PS128 group after 28-day consumption of PS128. Further studies are needed to better clarify the effects of PS128 for younger children with ASD on broader symptoms.

SCIENTIFIC REPORTS

Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota

Dae-Wook Kang, 2018

Two years after treatment was completed, most improvements in GI symptoms were maintained, and autism-related symptoms improved even more after the end of treatment. Important changes in gut microbiota at the end of treatment remained at follow-up, including significant increases in bacterial diversity and relative abundances of *Bifidobacteria* and *Prevotella*. Our observations demonstrate the long-term safety and efficacy of MTT as a potential therapy to treat children with ASD who have GI problems, and warrant a double-blind, placebo- controlled trial in the future.



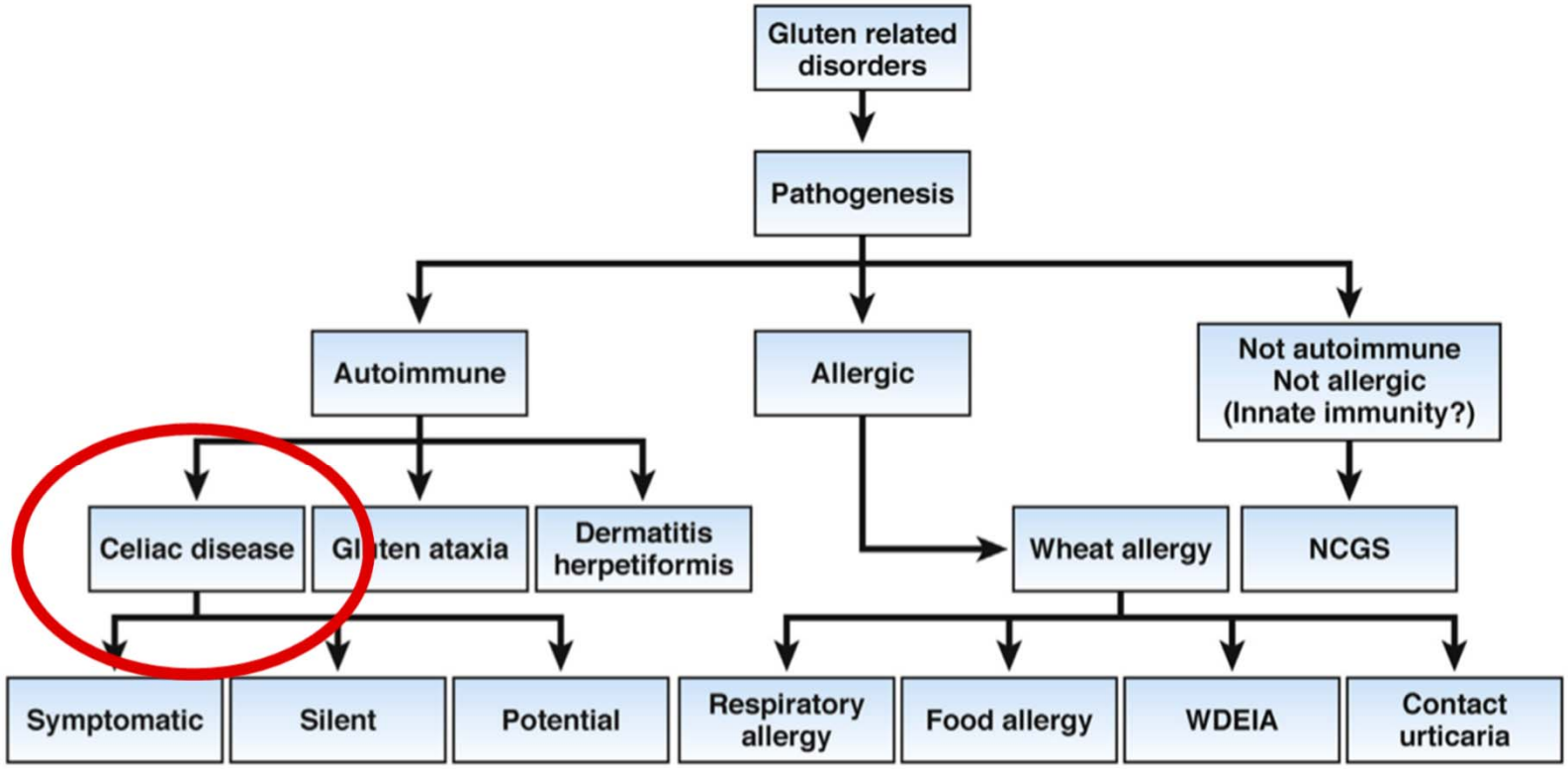
Gastroenterology 2015;148:1195–1204

NONCELIAC GLUTEN AND WHEAT SENSITIVITY

Nonceliac Gluten Sensitivity




Alessio Fasano[1] *Anna Sapone*[1,2] *Victor Zevallos*[3] *Detlef Schuppan*[2,3]



OPEN ACCESS

Review

nutrients

Non-Celiac Gluten Sensitivity: The New Frontier of Gluten Related Disorders

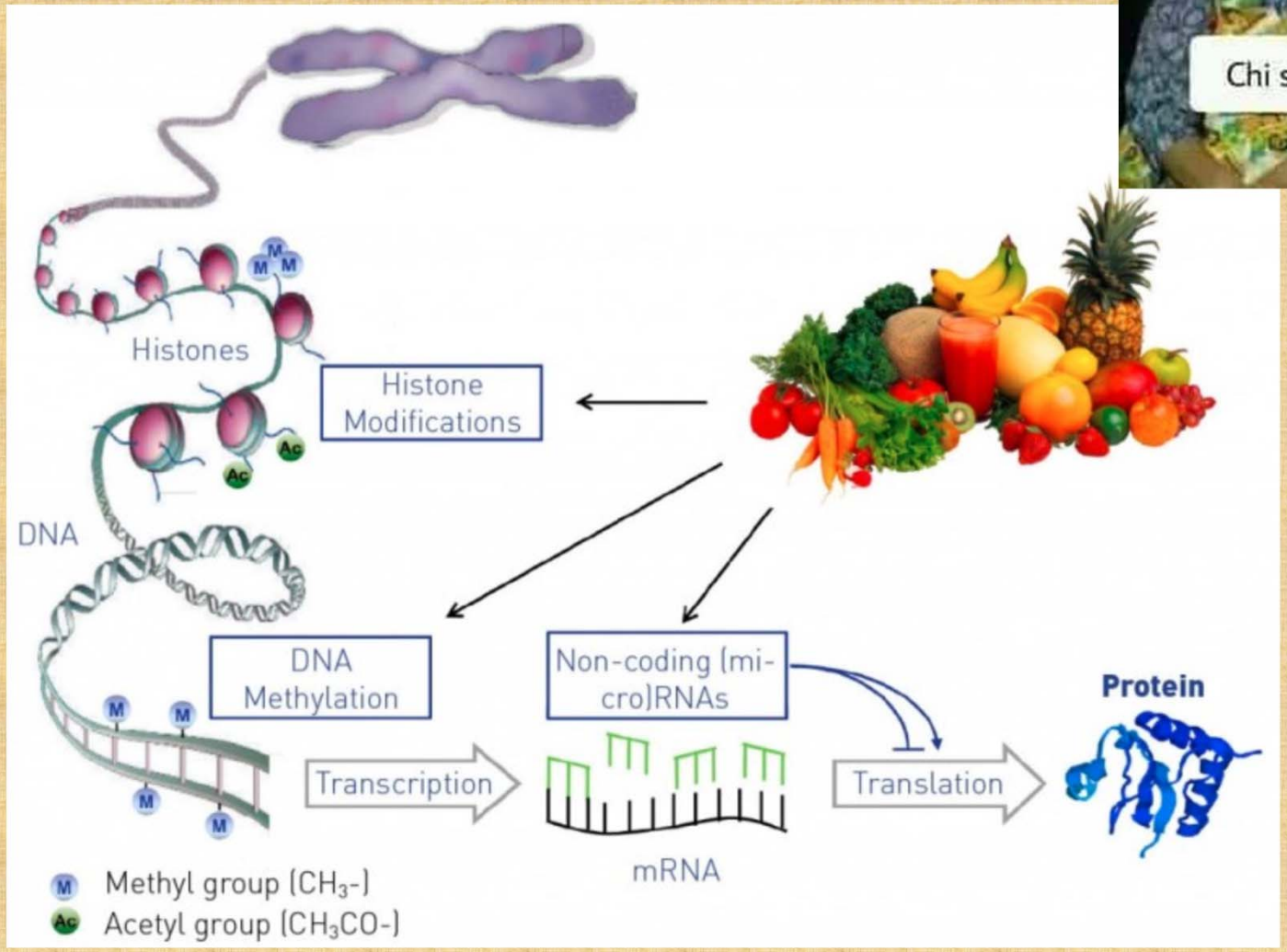
Trends in publication on celiac disease (CD) and non-celiac gluten sensitivity (NCGS) during the last decades.

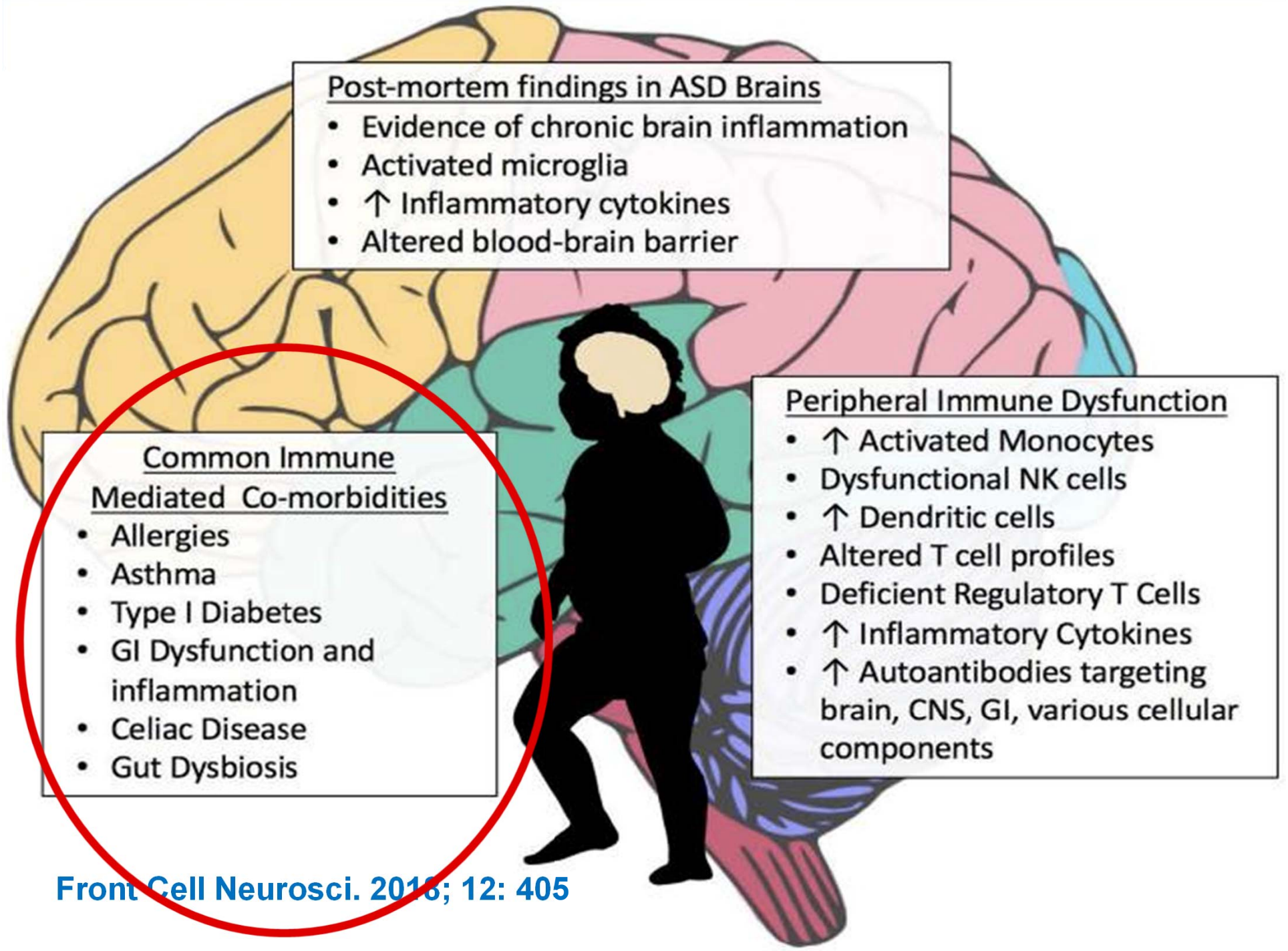
Timeline	CD	NCGS	NCGS/CD ratio
1950–1970	2632	6	1:438
1971–1990	4915	118	1:43
1991–2010	9498	733	1:13
2011–2013	2014	188	1:10

Catassi et al

Nutrients **2013**, *5*, 3839-3853; doi:10.3390/nu5103839

Diet and Lifestyle Before, During Pregnancy and in Early Years





Front Cell Neurosci. 2018; 12: 405

PATHOLOGY

To understand and measure emotional qualities is very difficult. Psychologists and educators have been struggling with that problem for years but we are still unable to measure emotional and personality traits with the exactness with which we can measure intelligence.

—Rose Zeligs in *Glimpses into Child Life**

AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

By Leo Kanner

SINCE 1 whose
conditi ted so
far, th etailed
consideration neces-
sarily impose terial.
For the sam of the
children of th ust be
considered a older
and further

; 217-250

Patterns of Risk for Multiple Co-Occurring Medical Conditions Replicate Across Distinct Cohorts of Children with Autism Spectrum Disorder

Kimberly A. Aldinger, Christianne J. Lane, Jeremy Veenstra-VanderWeele, and Pat Levitt

Children with autism spectrum disorder (ASD) may present with multiple medical conditions in addition to ASD symptoms. This study investigated whether there are predictive patterns of medical conditions that co-occur with ASD, which could inform medical evaluation and treatment in ASD, as well as potentially identify etiologically meaningful subgroups. Medical history data were queried in the multiplex family Autism Genetic Resource Exchange (AGRE). Fourteen medical conditions were analyzed. Replication in the Simons Simplex Collection (SSC) was attempted using available m (GID), sleep problems, allergy and epilepsy. In the AGRE coho conditions. GID and seizures were enriched in unaffected famil epresented in both AGRE and SSC. Further analysis of these me tterns in both samples. For a child with ASD, the presence of (approximately 2-fold odds ratio in each direction. These risk pa dition, there was increased risk for seizures and sleep problems t vas not predictive of the other conditions co-occurring, but beh of co-occurring medical symptoms increased. These findings inc with ASD will benefit from evaluation for specific patterns of r ily members. ***Autism Res*** *2015, 8: 771–781*. © 2015 The Autho . on behalf of International Society for Autism Research.

Keywords: gastrointestinal di

Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis

PEDIATRICS Volume 133, Number 5, May 2014

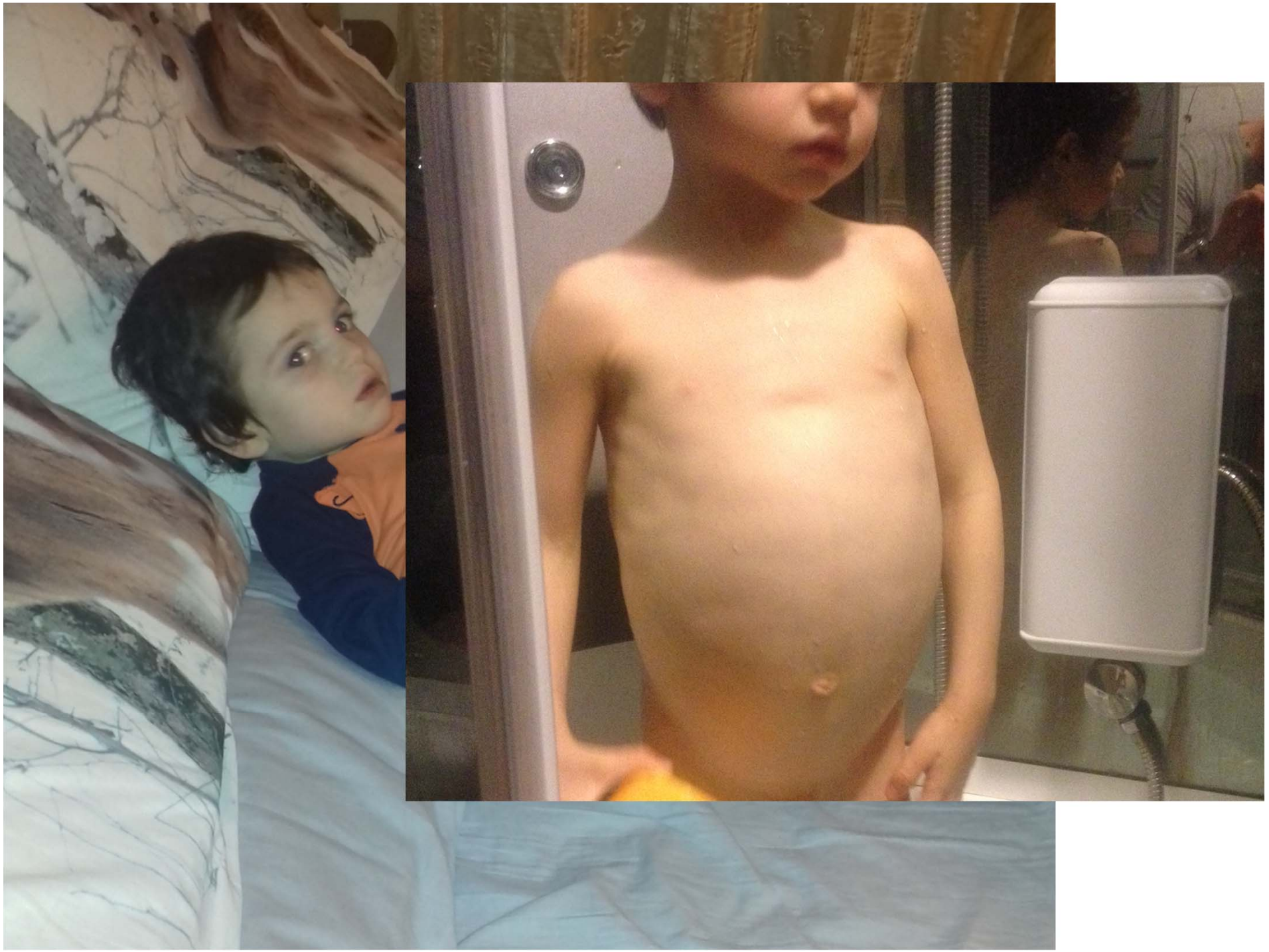
AUTHORS: Barbara O. McElhanon, MD,[a] Courtney McCracken, PhD,[a] Saul Karpen, MD, PhD,[a] and William G. Sharp, PhD[a,b]

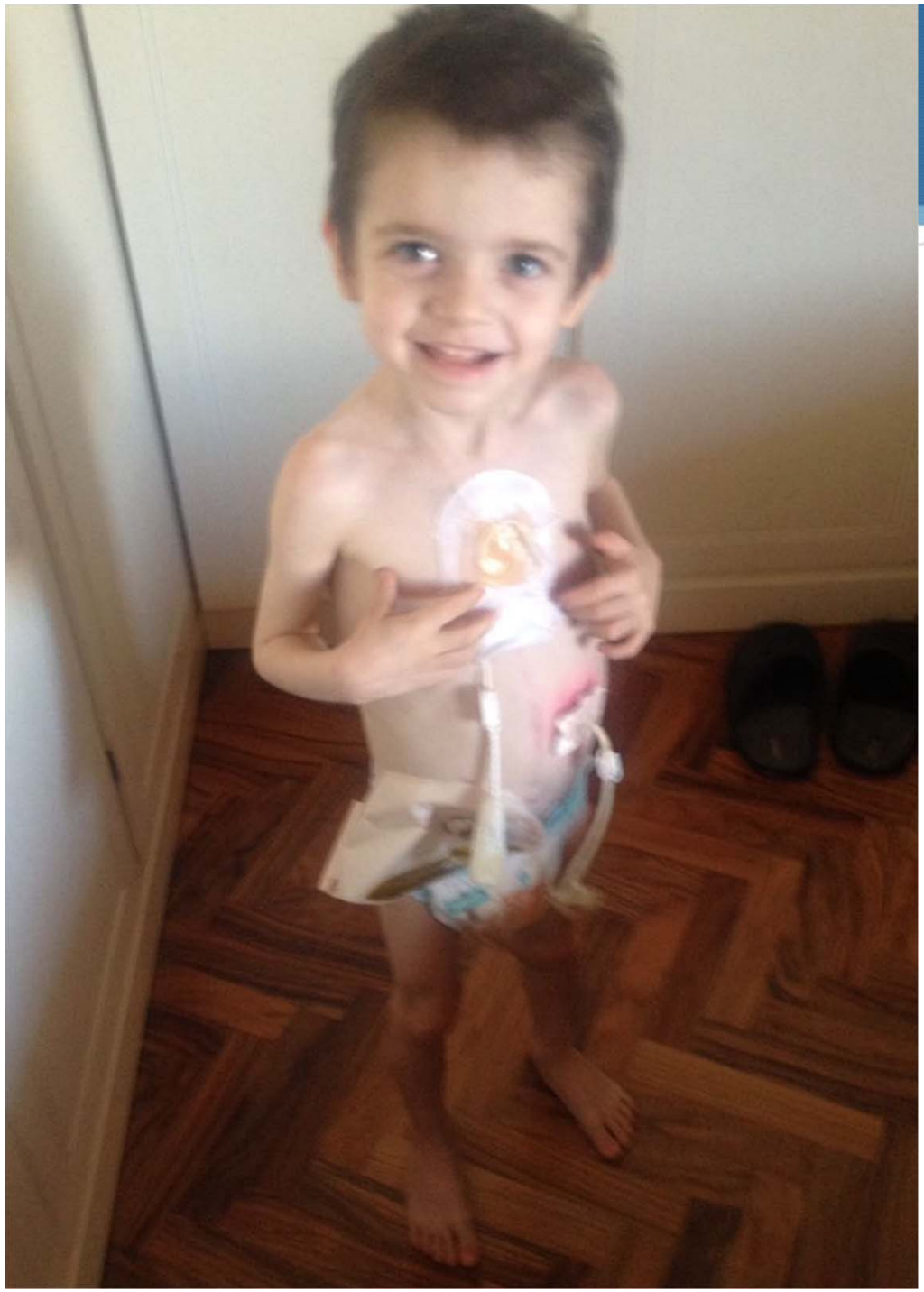
[a]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia; and [b]Marcus Autism Center, Atlanta, Georgia

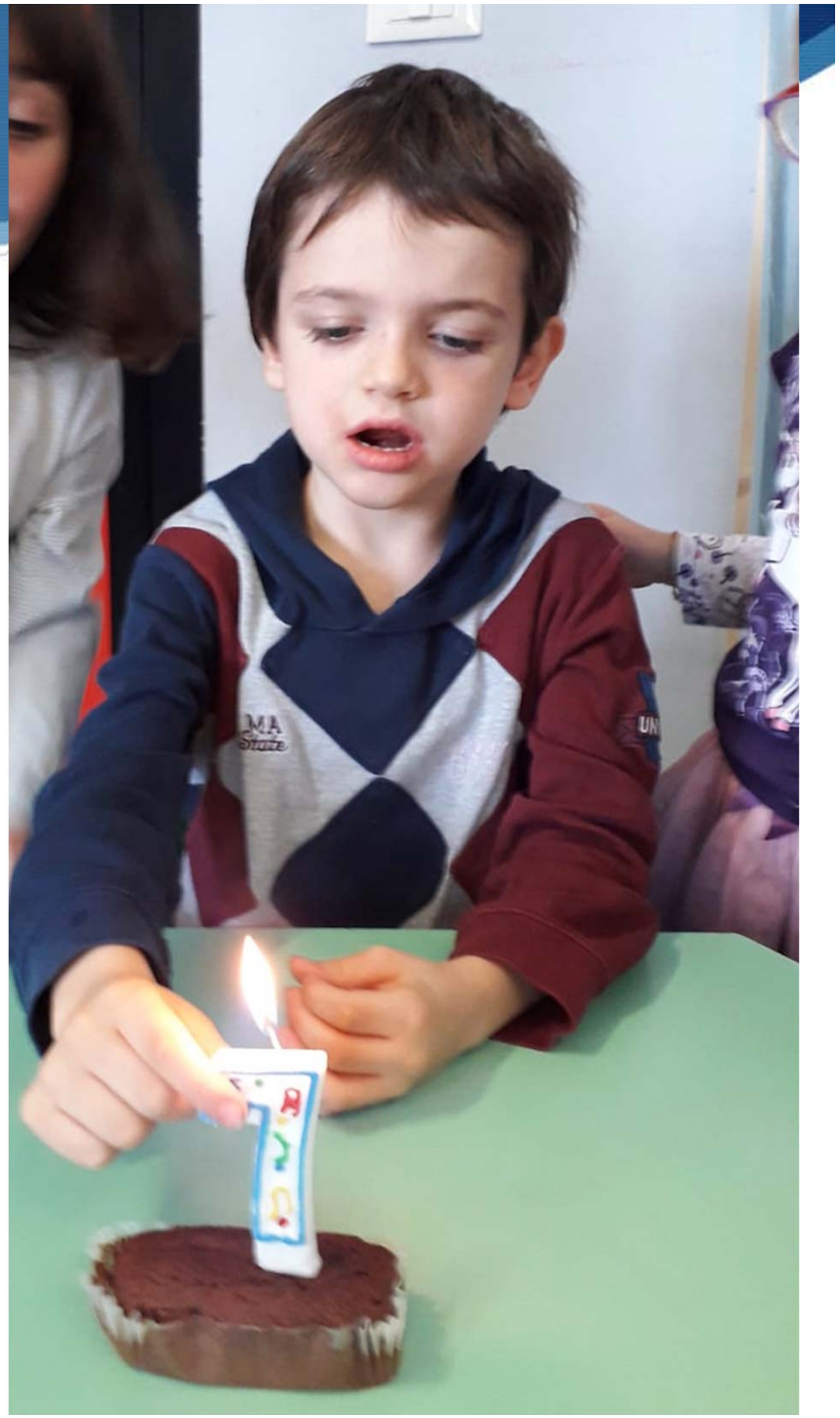
KEY WORDS

autism spectrum disorder, constipation, digestive disorders, GI

- Sintomi GI **4X**
- Diarrea **>3X**
- Stipsi **>3X**
- Dolore addominale**>2X**







Research Letter

ONLINE FIRST

October 28, 2019

National Prevalence of Pain Among Children and Adolescents With Autism Spectrum Disorders

Daniel G. Whitney, PhD[1]; Danielle N. Shapiro, PhD[1]

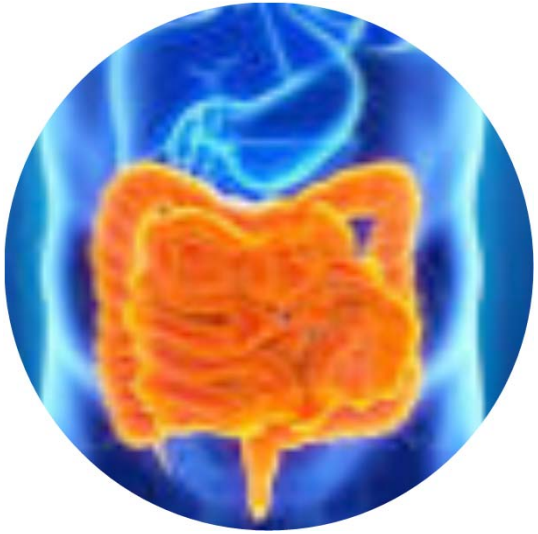
» Author Affiliations

JAMA Pediatr. Published online October 28, 2019. doi:10.1001/jamapediatrics.2019.3826

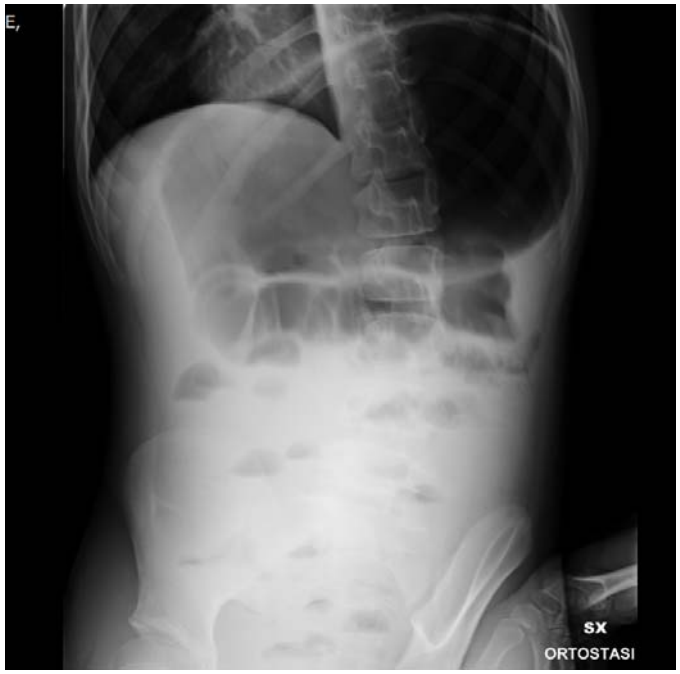
Pain is a leading contributor to the global morbidity and disability burden.[1] Pediatric pain is especially problematic, as it may impede healthful development into and throughout adulthood.[2] For children with autism spectrum disorders (ASD), pain is a highly understudied area, perhaps owing to the misguided historical impression that children with ASD have lower pain sensitivity.[3] However, recent evidence has contradicted this perspective[4] and indicates that pain may be implicated in pathogenesis of poor health outcomes in children with ASD.[5] Therefore, this study sought to provide recent national estimates of the prevalence of pain among children and adolescents with ASD.

Sintomi gastrointestinali in ASD

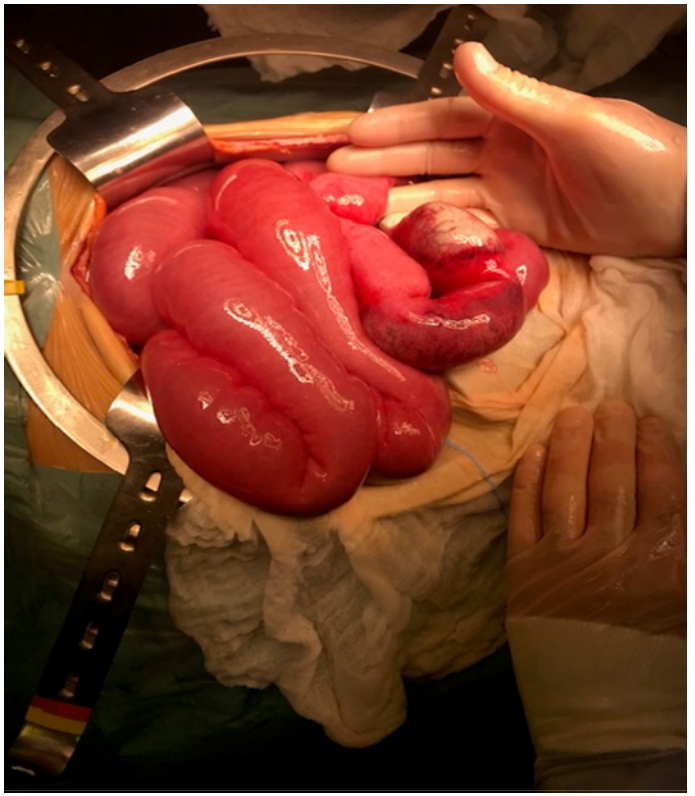
- ASD **GI +** : maggiore ansia, irritabilità e ritiro sociale (Nikolov et al. 2009).
- I problemi comportamentali (comportamenti autolesivi, aggressività, irritabilità, disturbi del sonno) potrebbero essere **manifestazioni di fastidio o dolore** ad origine gastrointestinale (Buie et al. 2010).
- Elevata **correlazione** tra la disfunzione/patologia intestinale e la **severità dell'autismo** per i domini di linguaggio, comportamenti e interazione sociale. (Adams et al. 2011).



G.A. 15 a
Paziente autistico con storia di stipsi moderata con un alvo ogni due giorni, non precedenti interventi chirurgici né ricoveri per patologie organiche.
Trasferito in data **24.12.18** da altro nosocomio per occlusione intestinale.

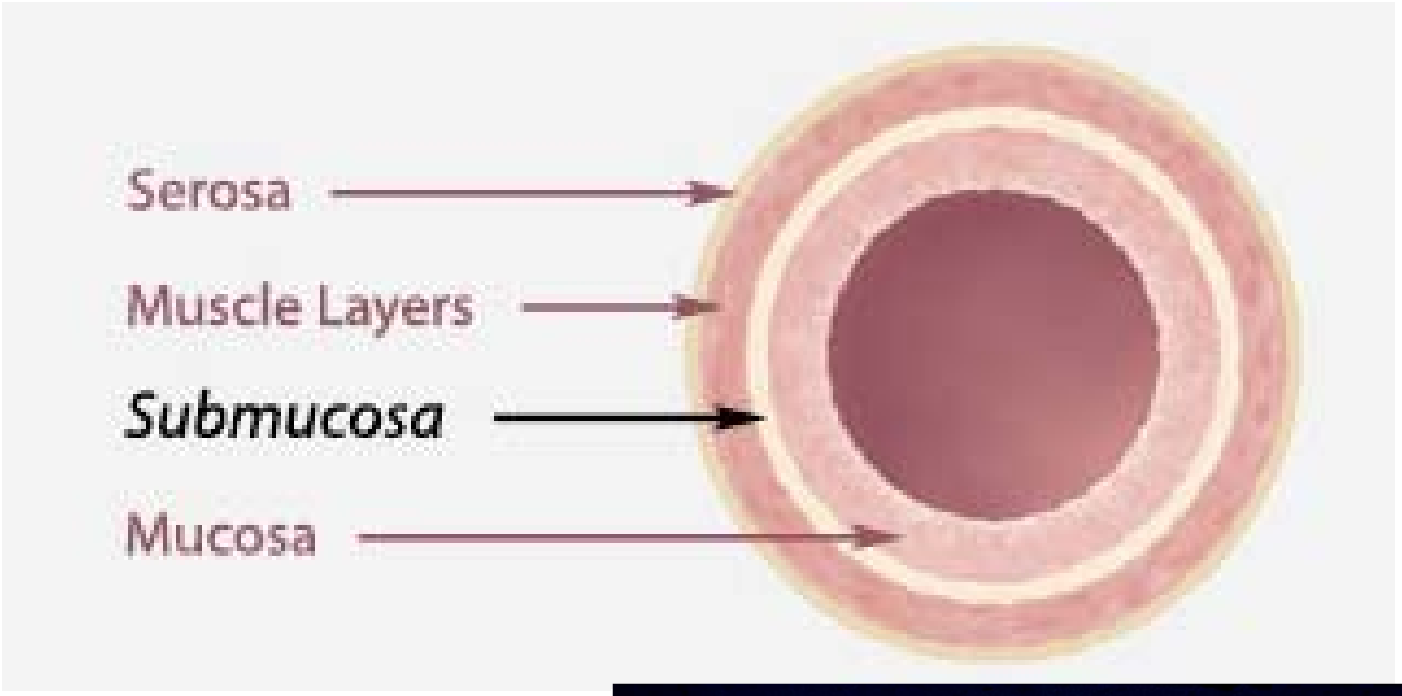


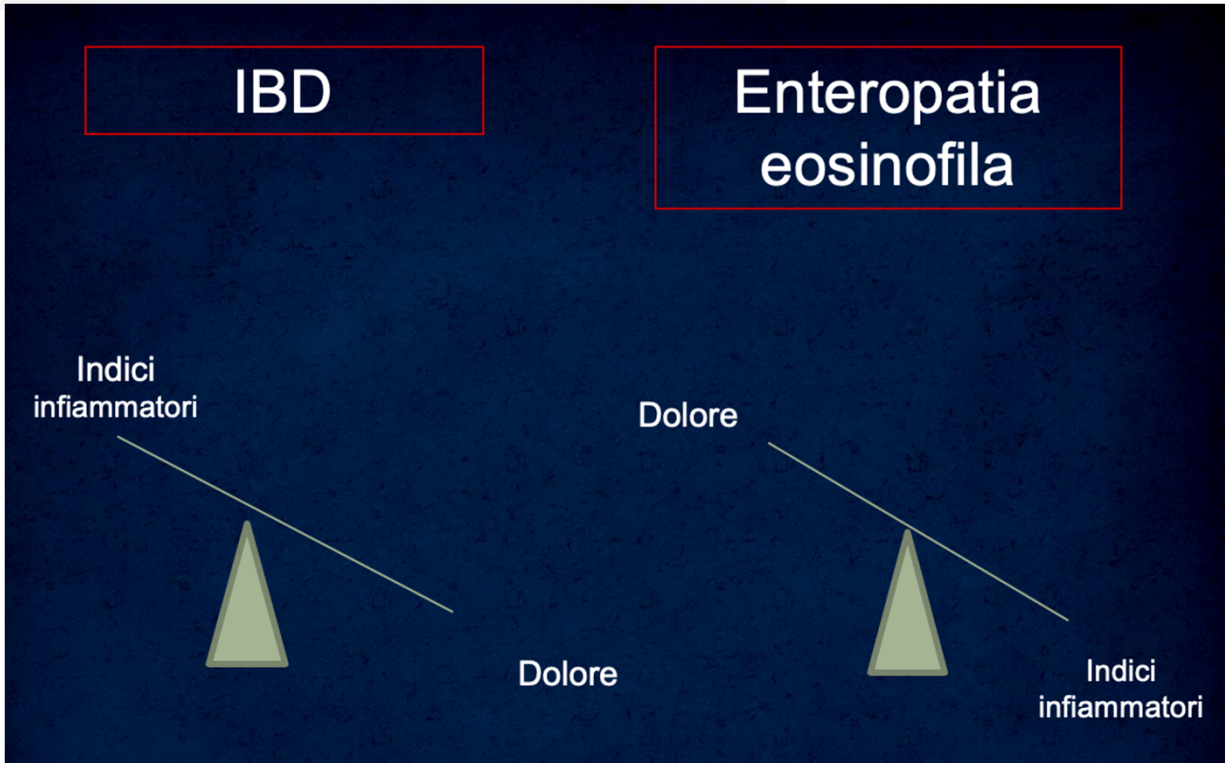
Si osserva sovradistensione delle anse intestinali, con diffuso ispessimento delle pareti dell'intestino tenue e del colon, cui si associa pneumatosi parietale in sede digiunoileale medio-distale e del tratto prossimale del colon discendente



Intervento chirurgico in urgenza di laparotomia esplorativa
Riscontro di necrosi transmurale di circa 150 cm.
Eseguita resezione parziale leale ,
confezionamento di stomia Ileale a stomi separati

Dott G Selvaggio, Ospedale Buzzi, Milano


Serosa
Muscle Layers
Submucosa
Mucosa


IBD
Enteropatia eosinofila
Indici infiammatori
Dolore
Dolore
Indici infiammatori

Esofagite ed Enterocolite

Materiale inviato

A Biopsia duodeno
B Biopsia stomaco
C Biopsia esofago distale

Materiale inviato

A Biopsia cieco
B Biopsia colon destro
C Biopsia colon trasverso
D Biopsia colon sinistro
E Biopsia sigma
F Biopsia retto

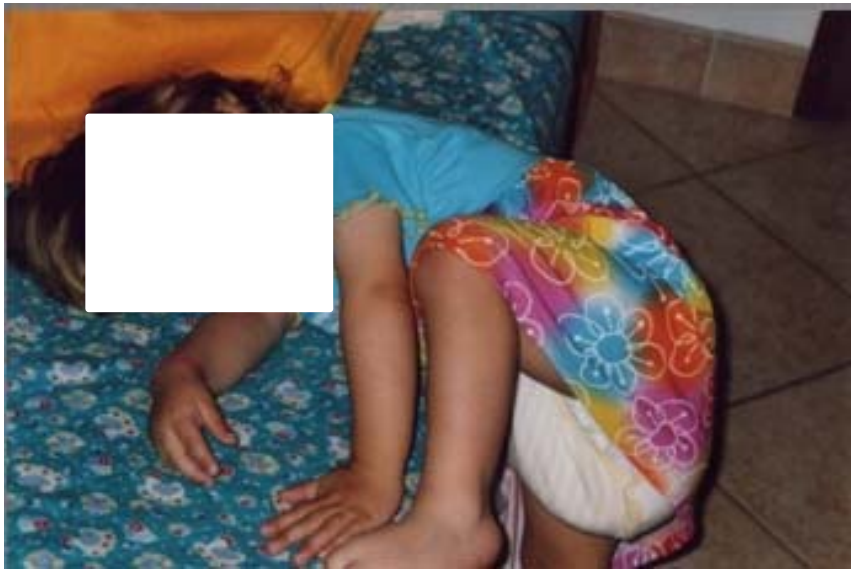
Diagnosi

A) Due campioni di mucosa del grosso intestino sede di flogosi cronica interstiziale, con componente eosinofila (141 eosinofili nel campo più densamente infiltrato, 40x) e microaggregati linfoidi dotati talora di centro germinativo.
Linfociti T CD3+ intraepiteliali: 15/100 cellule epiteliali.
B) Due campioni di mucosa del grosso intestino in frammenti con caratteri analoghi ad A) (138 eosinofili nel campo più densamente infiltrato, 40x).
Linfociti T CD3+ intraepiteliali: 18/100 cellule epiteliali.
C) Due campioni di mucosa del grosso intestino in frammenti con caratteri analoghi ad A) (90 eosinofili nel campo più densamente infiltrato, 40x).
Linfociti T CD3+ intraepiteliali: 18/100 cellule epiteliali.
D) Due campioni di mucosa del grosso intestino in frammenti con caratteri analoghi ad A) (143 eosinofili nel campo più densamente infiltrato, 40x).
Linfociti T CD3+ intraepiteliali: 15/100 cellule epiteliali.
E) Perviene un campione di mucosa del grosso intestino con caratteri analoghi ad A) (73 eosinofili nel campo più densamente infiltrato, 40x).
Linfociti T CD3+ intraepiteliali: 15/100 cellule epiteliali.
F) Due campioni di mucosa del grosso intestino in frammenti con caratteri analoghi ad A) (124 eosinofili nel campo più densamente infiltrato, 40x).
Linfociti T CD3+ intraepiteliali: 14/100 cellule epiteliali.

Pain

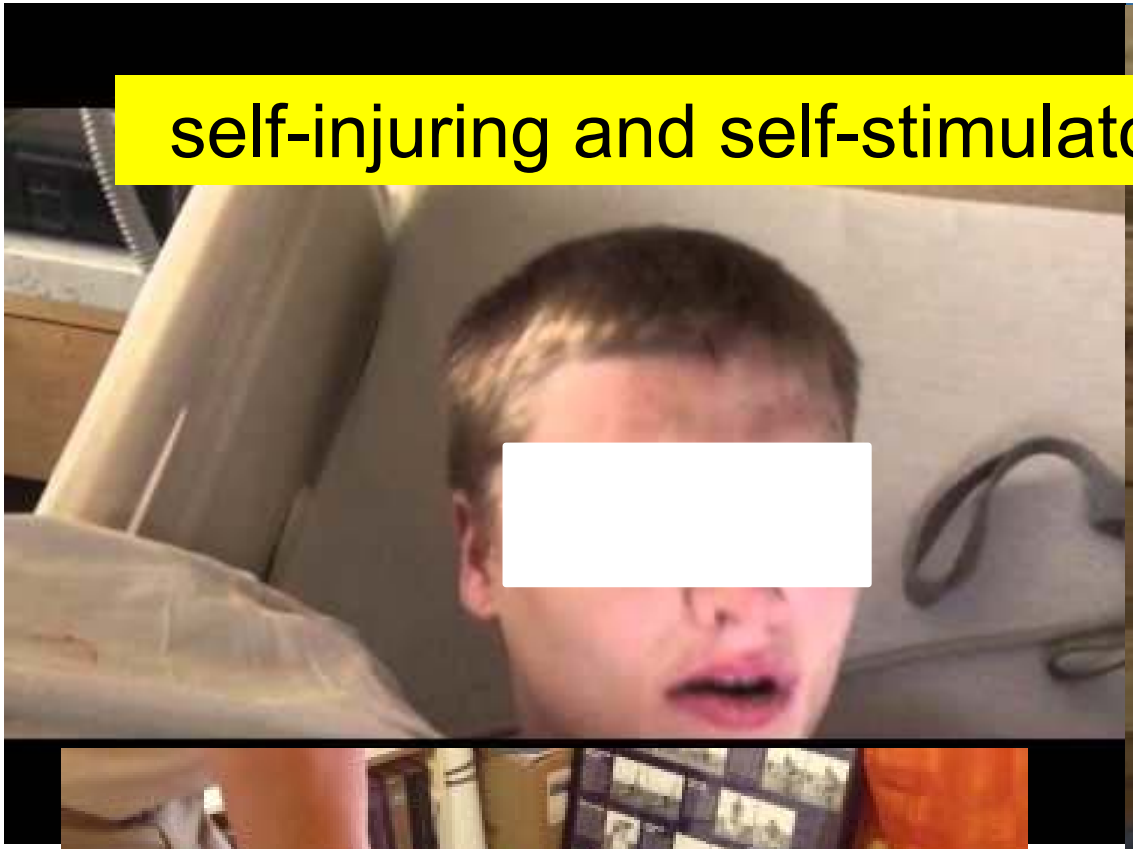
F. Balzola

Pain



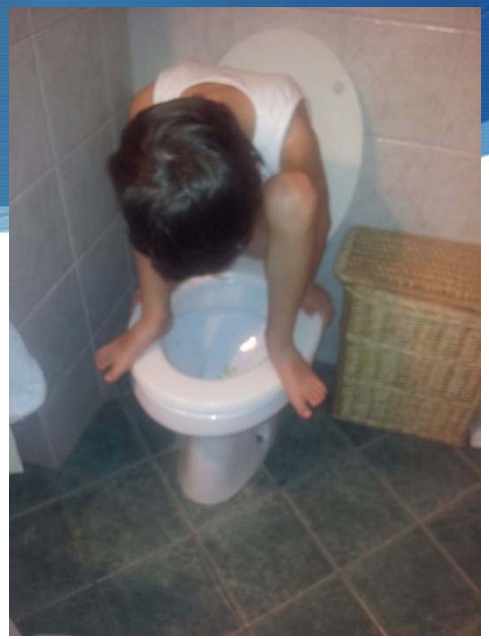
F. Balzola

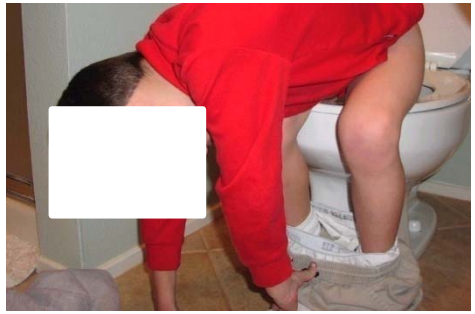
self-injuring and self-stimulatory behaviors

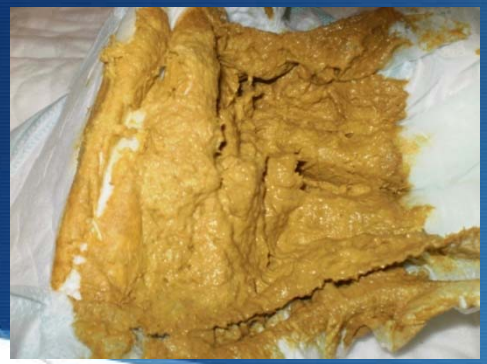
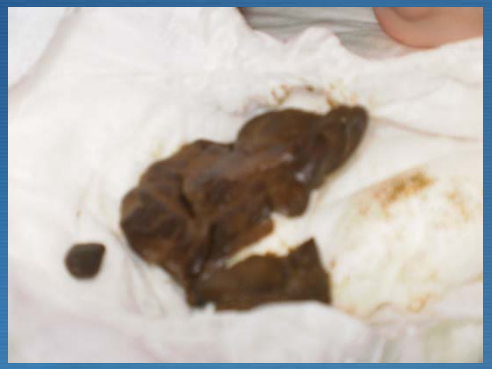
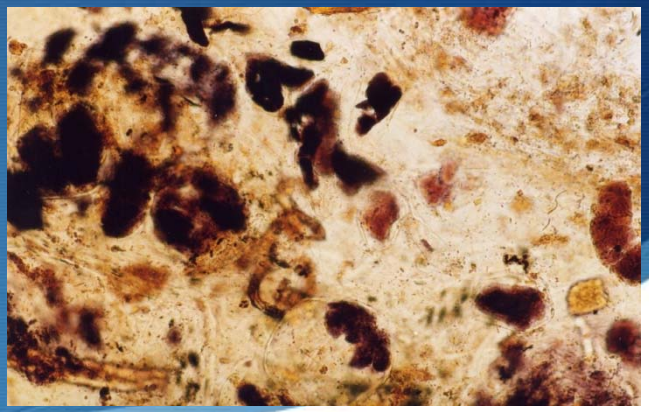
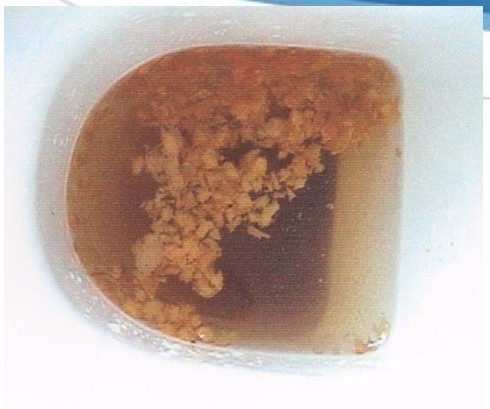


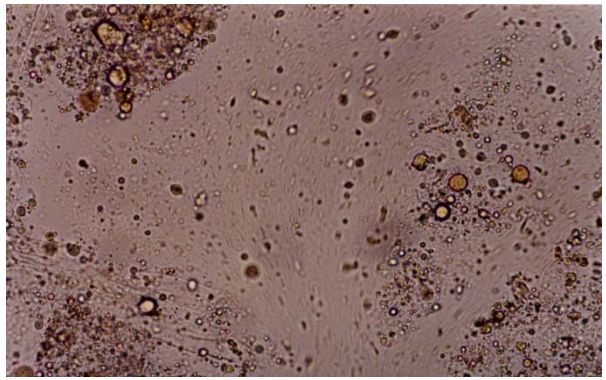
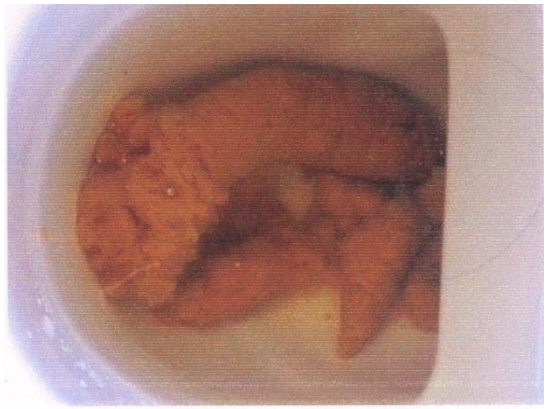
F. Balzola

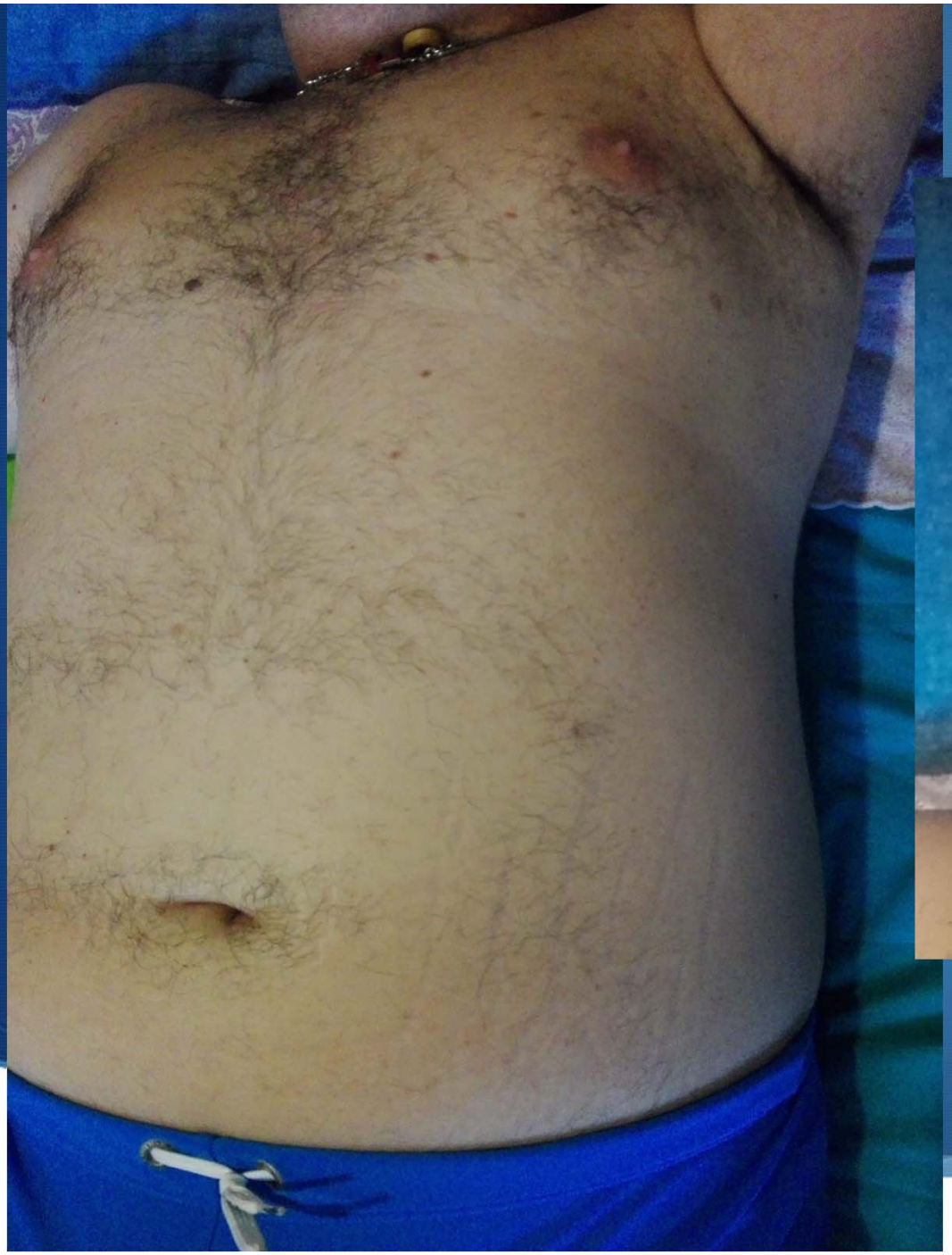
Increase in the abdominal press

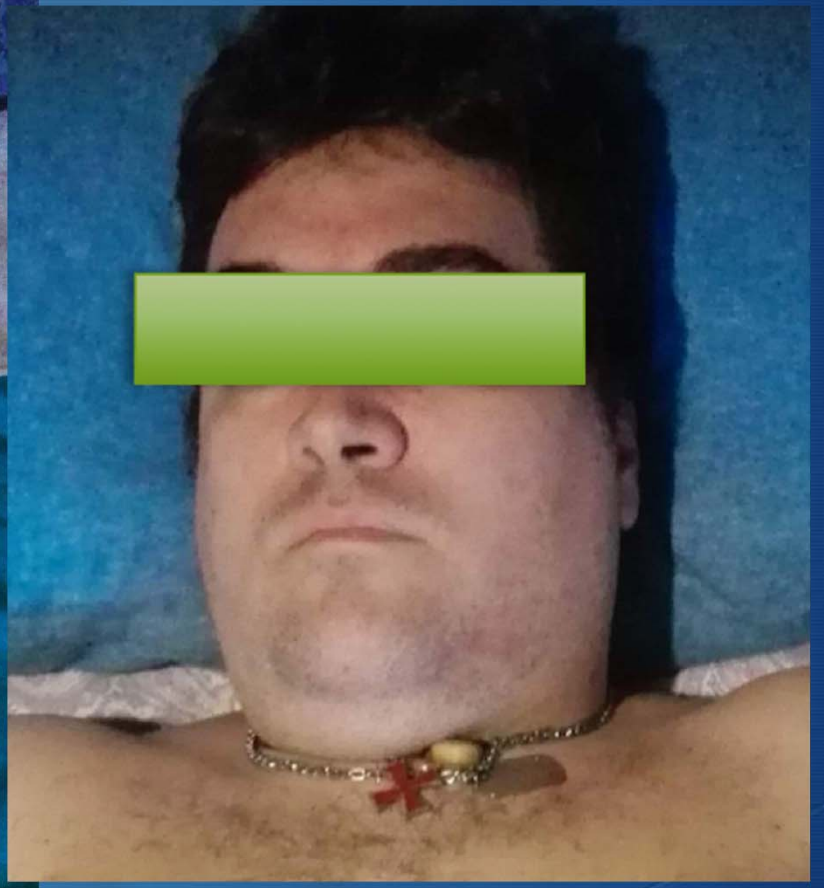


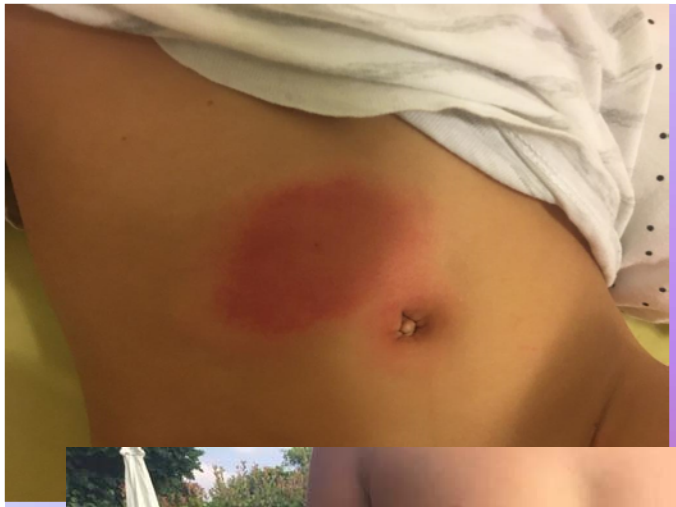


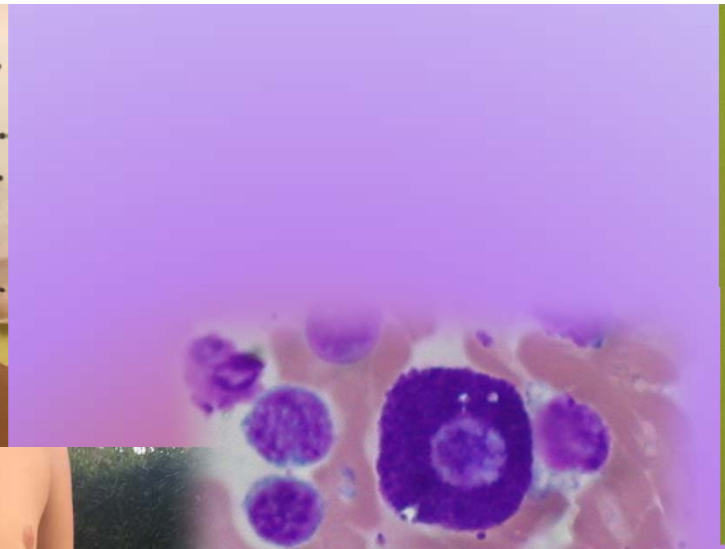





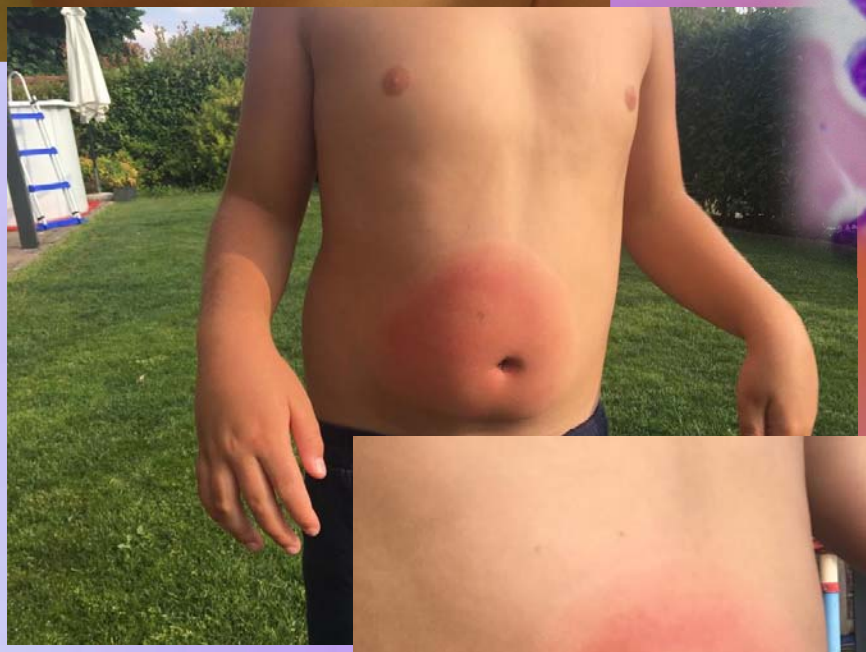



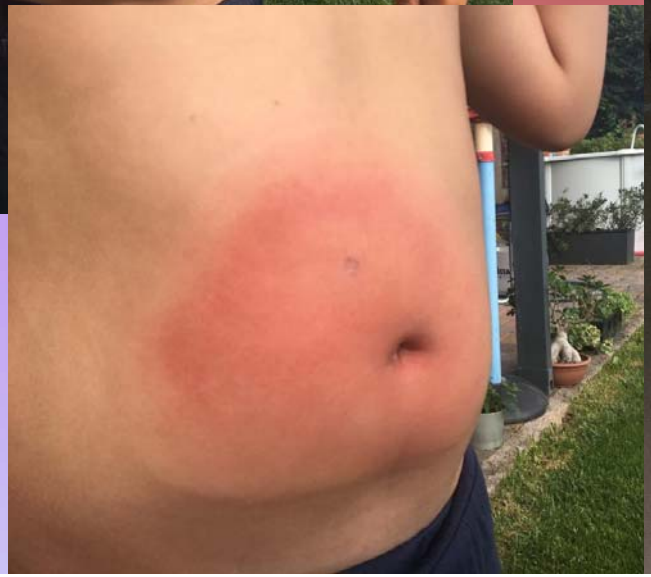


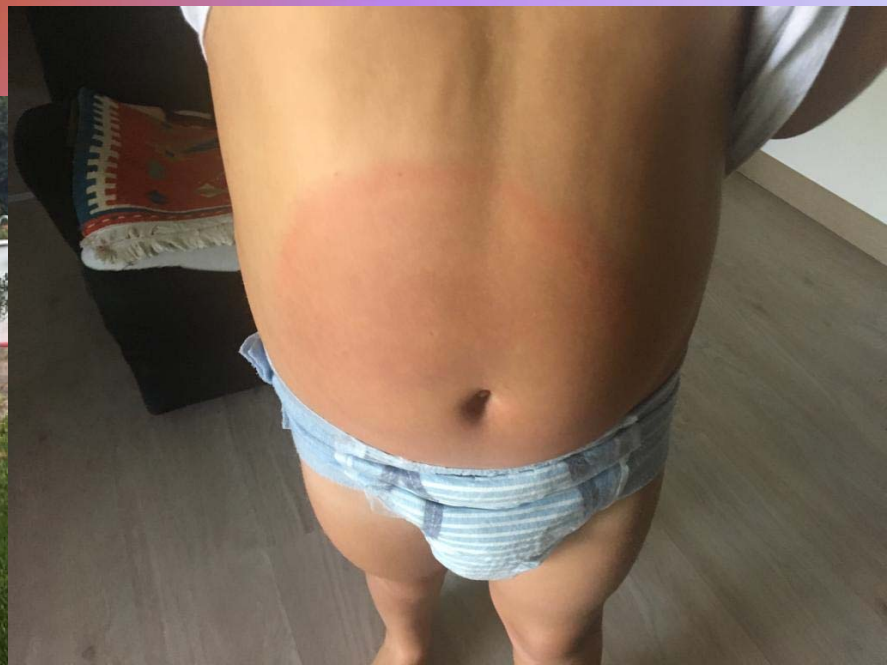






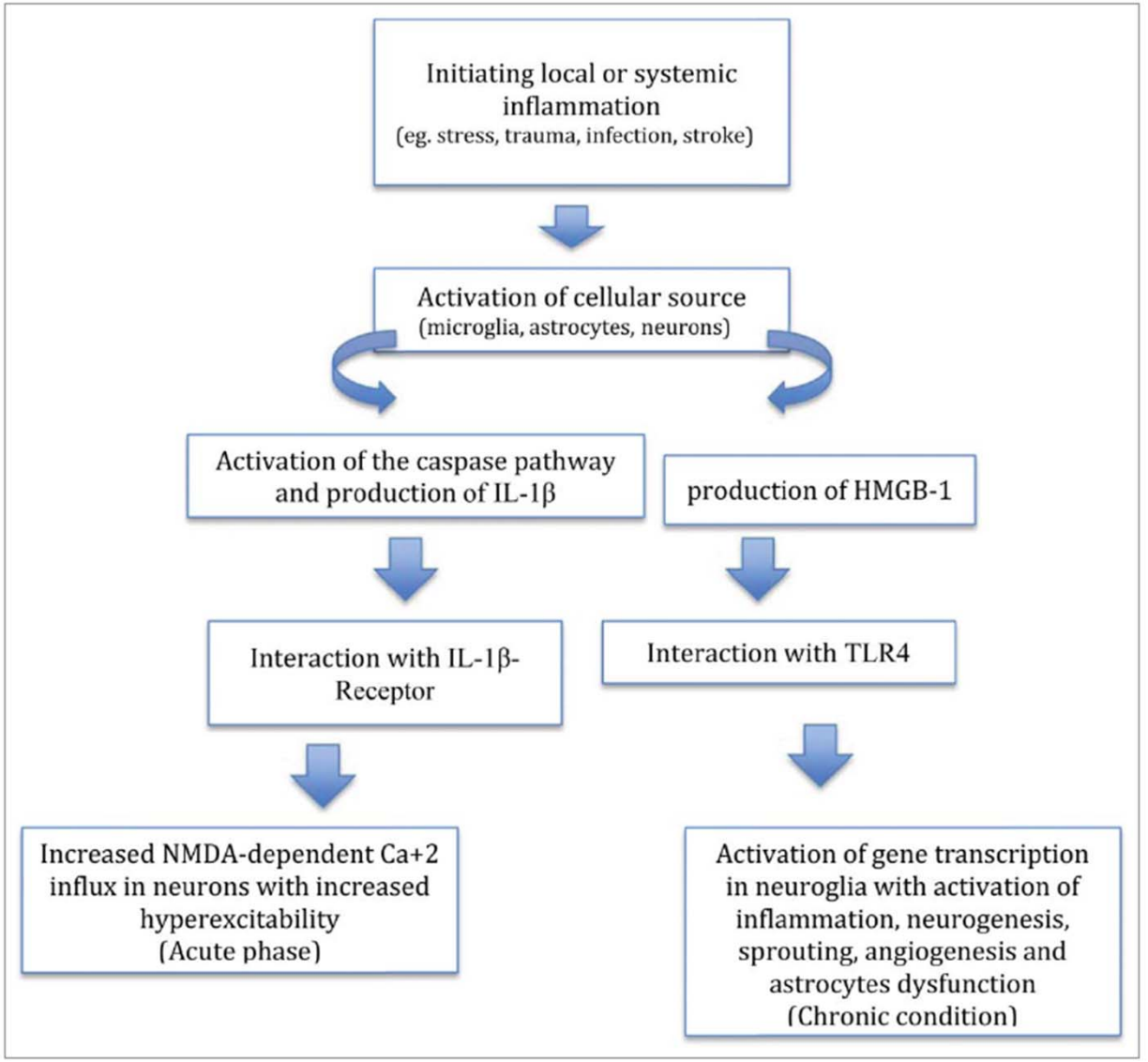






Epilepsy and innate immune system: A possible immunogenic predisposition and related therapeutic implications

Nassim Matin, Omidreza Tabatabaie, Raffaele Falsaperla, Riccardo Lubrano, Piero Pavone, Fahad Mahmood, Melissa Gullotta, Agostino Serra, Paola Di Mauro, Salvatore Cocuzza & Giovanna Vitaliti



Martin N., 2015

ARTICLE

PEDIATRICS Volume 120, Number 6, December 2007

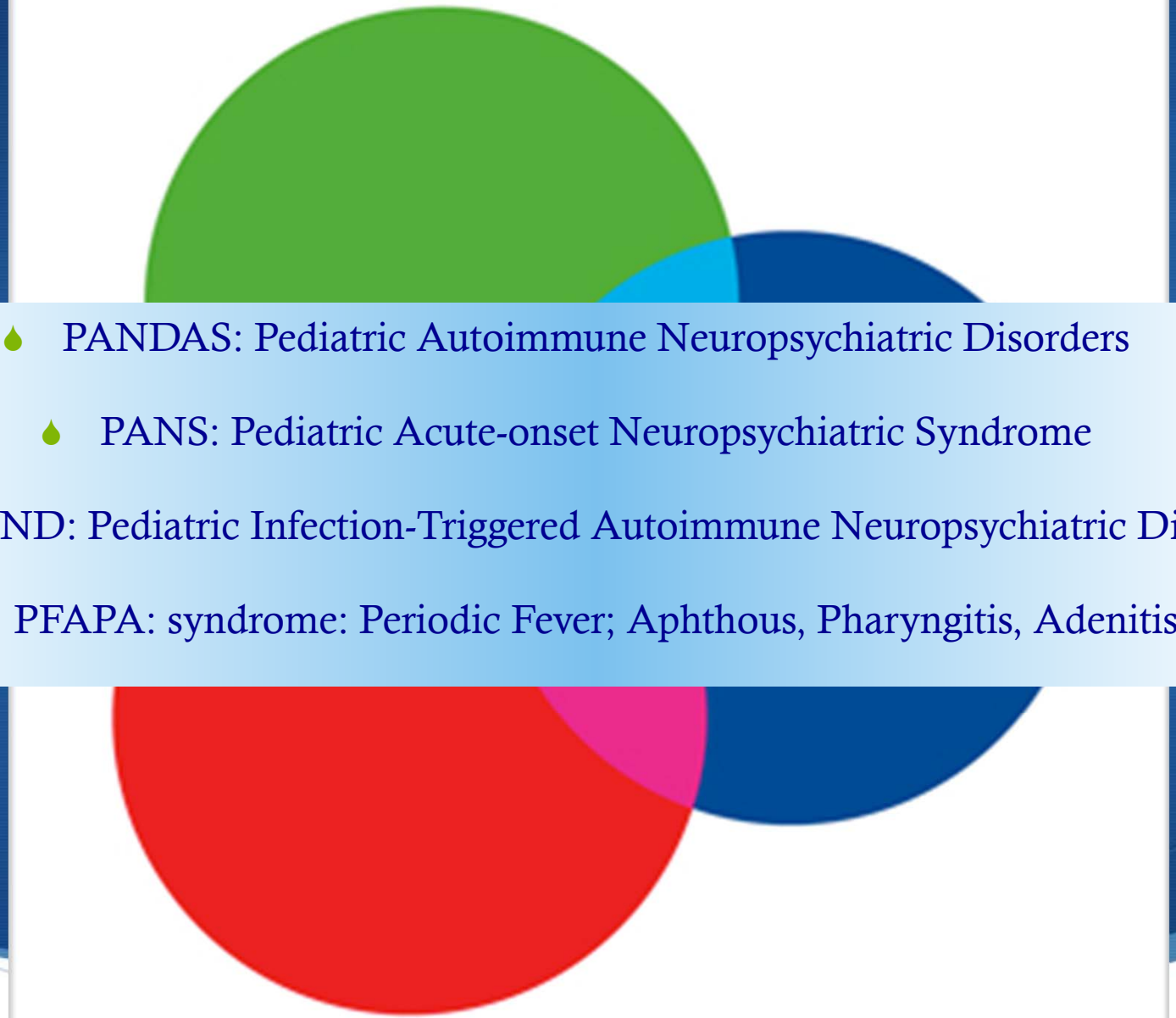
Behaviors Associated With Fever in Children With Autism Spectrum Disorders

Laura K. Curran, PhD[a,b], Craig J. Newschaffer, PhD[c], Li-Ching Lee, PhD[a], Stephen O. Crawford, MHS[a], Michael V. Johnston, MD[b], Andrew W. Zimmerman, MD[b]

[a]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [b]Department of Neurology and Developmental Medicine, Kennedy Krieger Institute, Baltimore, Maryland; [c]Department of Epidemiology and Biostatistics, Drexel University School of Public Health, Philadelphia, Pennsylvania

The authors have indicated they have no financial relationships relevant to this article to disclose.

… more research is needed to prove conclusively fever-specific effects and elucidate their underlying biological mechanisms (possibly involving immunologic and neurobiological pathways, intracellular signaling, and synaptic plasticity).



- PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders
- PANS: Pediatric Acute-onset Neuropsychiatric Syndrome
- PITAND: Pediatric Infection-Triggered Autoimmune Neuropsychiatric Disorder
- PFAPA: syndrome: Periodic Fever; Aphthous, Pharyngitis, Adenitis

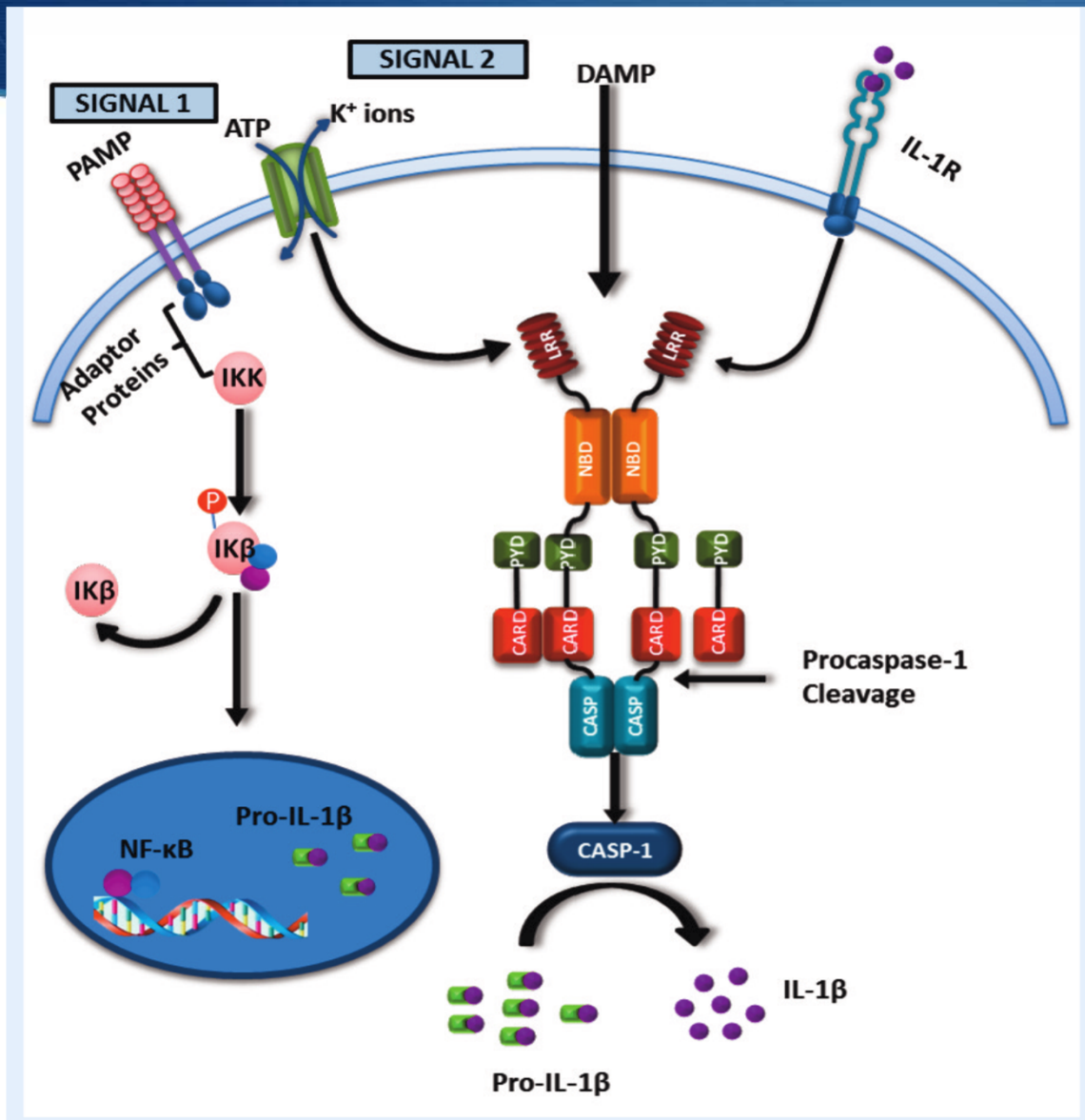
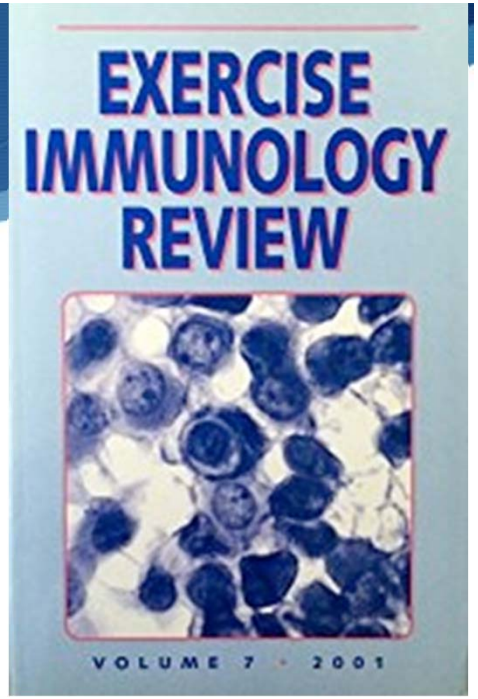
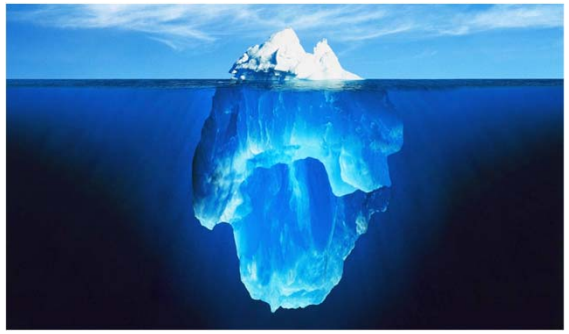


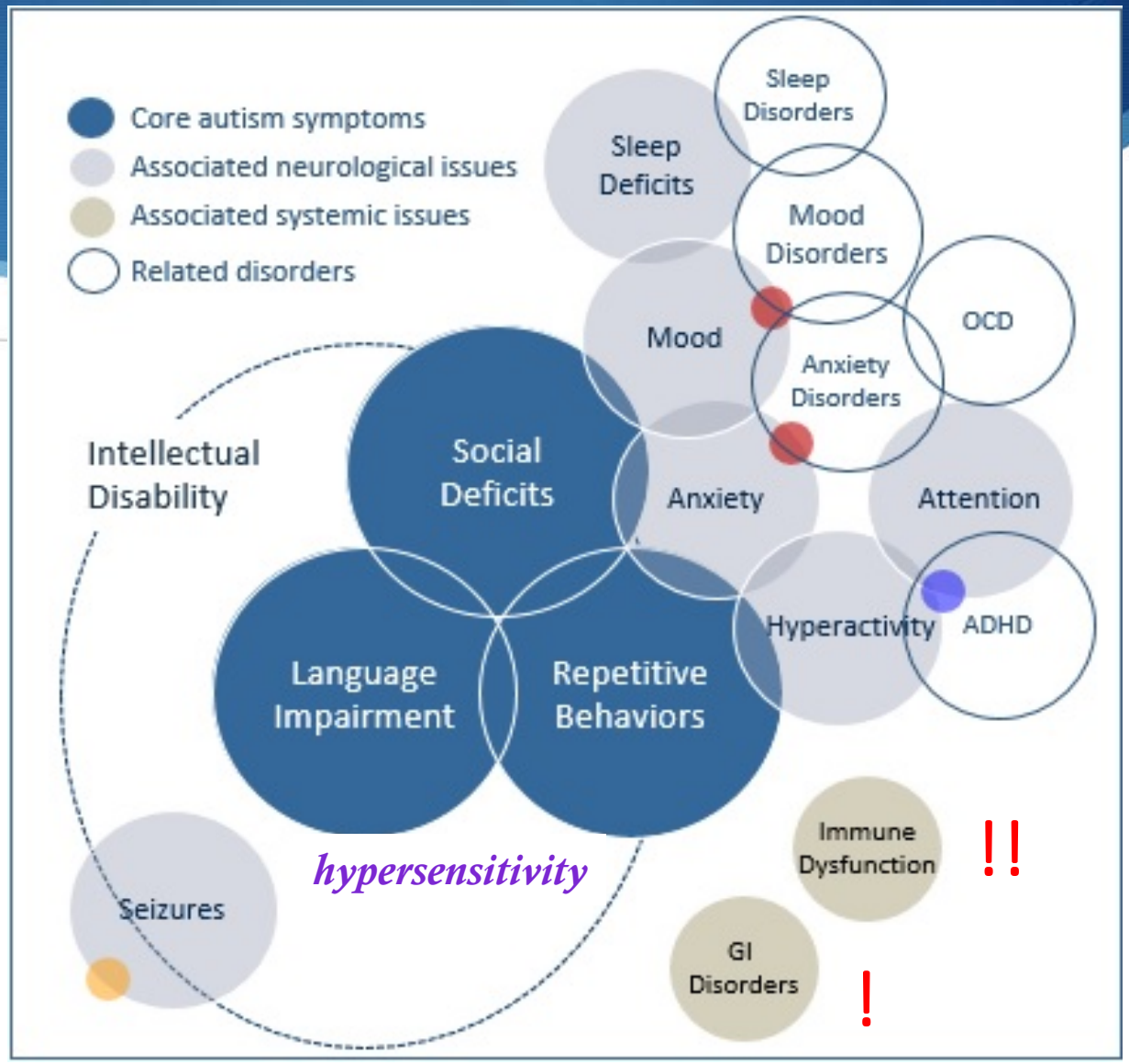
Figure 5 - Schematic illustration of NLRP3 inflammasome activation and subsequent intracellular signalling that produces a pro-inflammatory outcome.

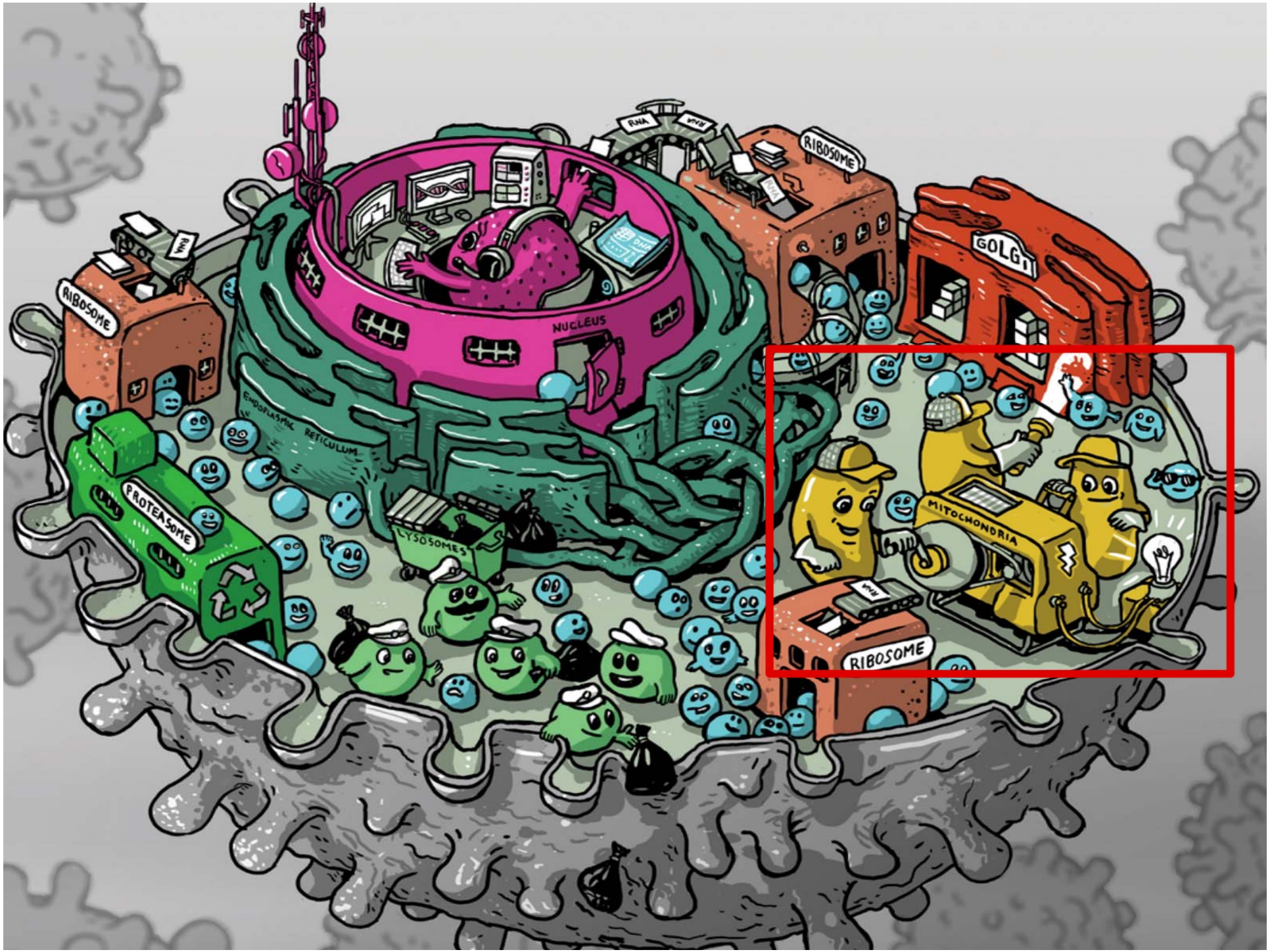


S. Horsburgh et al, 2015

People with ASD have an **early** and **systemic** (whole body) disorder






RIBOSOME
RNA
NUCLEUS
RIBOSOME
GOLGI
ENDOPLASMIC RETICULUM
PROTEASOME
LYSOSOMES
MITOCHONDRIA
RIBOSOME

CASE REPORT

My Experience Learning About Autism

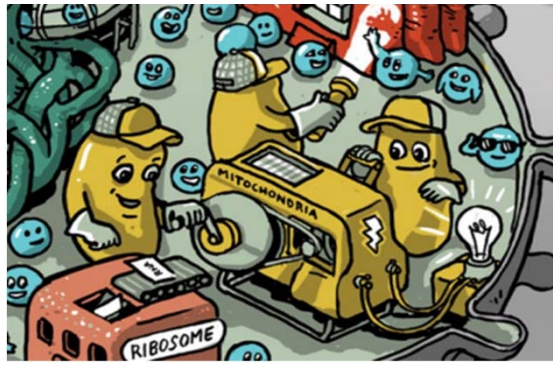
我对自闭症的认识经历

Mi experiencia de aprendizaje sobre el autismo

Daniel A. Rossignol, MD, *United States*

Volume 2, Number 6 • November 2013 • www.gahmj.com

I remember the first time I heard the word "autistic." I was 10 years old, and my mom mentioned that someone had a child who was autistic. I was confused because I mistook her description as "artistic."

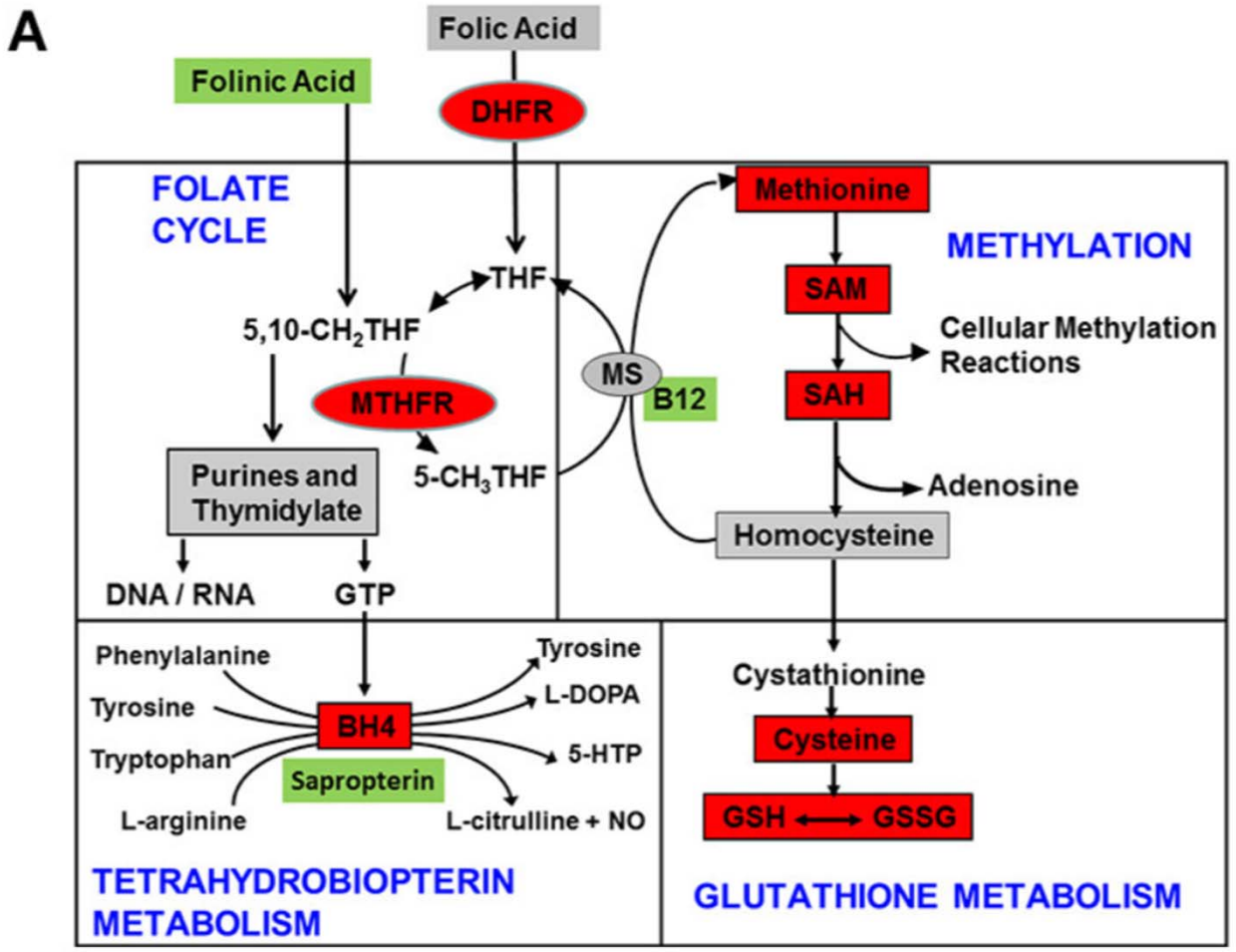


Isaiah & Joshua

My research interest is now focused on metabolic and other problems that may contribute to autism symptoms and that are also treatable.[63] These conditions include mitochondrial dysfunction,[64-67] inflammation,[68] oxidative stress,[68] environmental toxicant exposures,[68] and seizures.[69] A great deal of information has been learned about autism since my children were diagnosed. Every day, more and more studies concerning autism are appearing in the literature. Several recent studies have reported "recovery" or the loss of autism in some children.[56,70-73] These factors as well as reports of recovery in some children give me a great deal of hope for the future concerning autism.

frontiers in Neuroscience

Metabolic pathways disrupted in ASD



Metabolites

THF	TetraHydroFolate
SAM	*S*-Adenosyl methionine
SAH	*S*-Adenosyl homocysteine
GSH	Reduced Glutathione
GSSG	Oxidized Glutathione
NO	Nitric Oxide
BH4	Tetrahydrobiopterin

Enzymes

DHFR	Dihydrofolate Reductase
MS	Methionine Synthase
MTHFR	Methylenetetrahydrofolate Reductase

Figure Key

Blue text outlines one of the four pathways related to folate metabolism
Ovals represent enzymes
Boxes represent metabolites
Red indicates metabolites and enzymes repeatedly noted to be abnormal in autism
Green highlights important metabolites

M.L.Delhey 2018

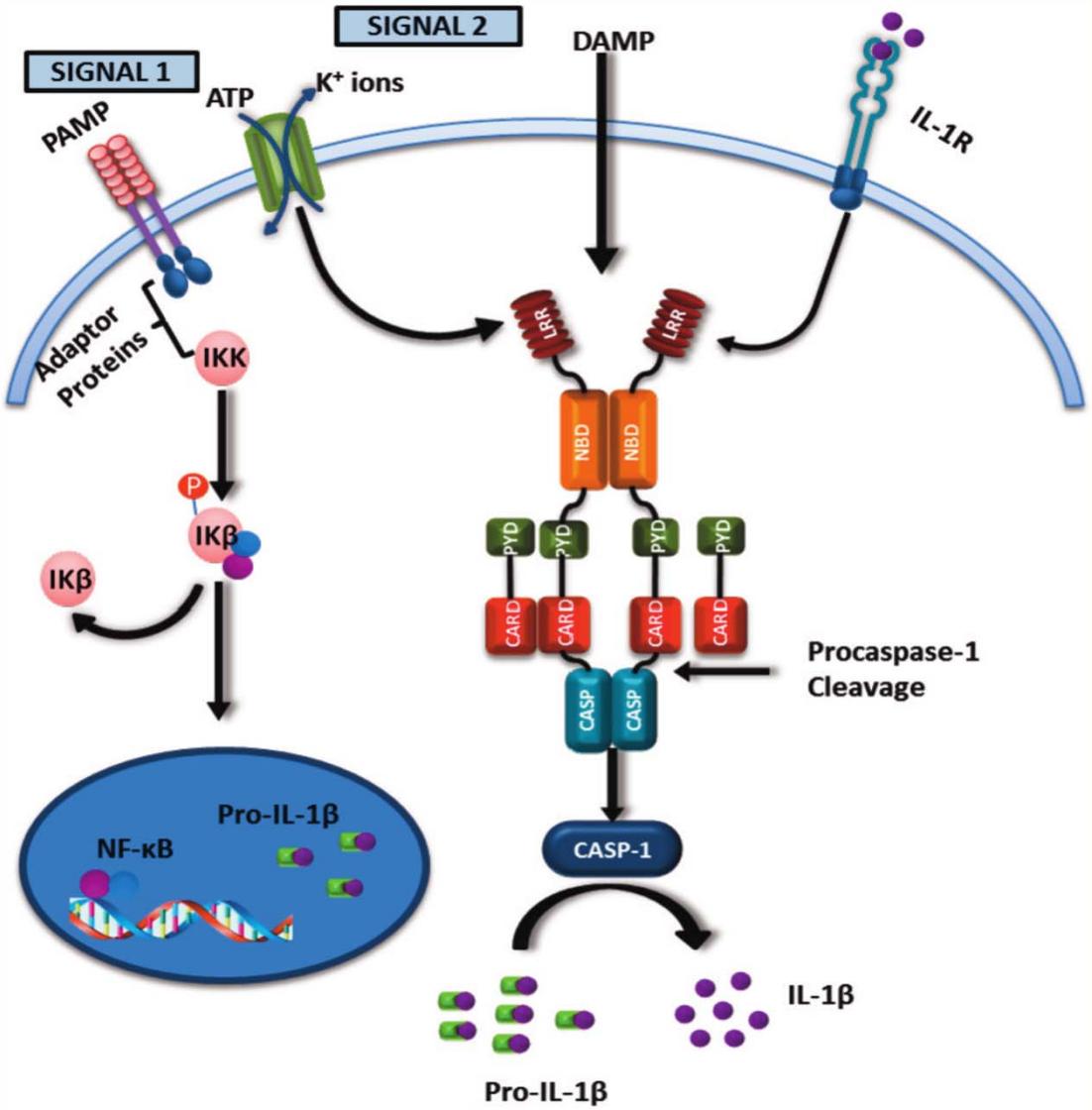
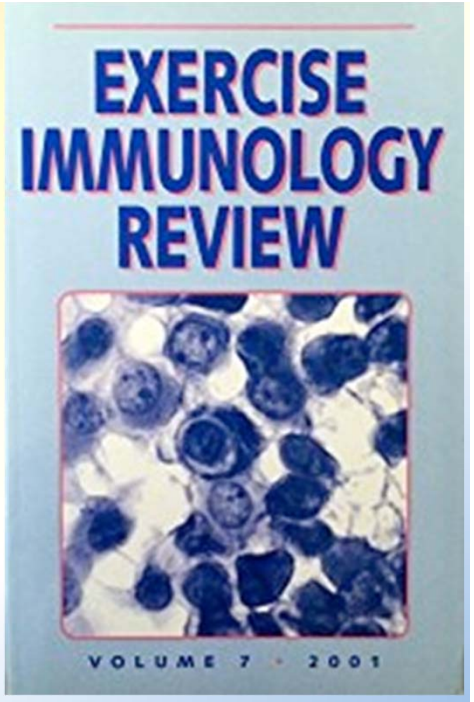
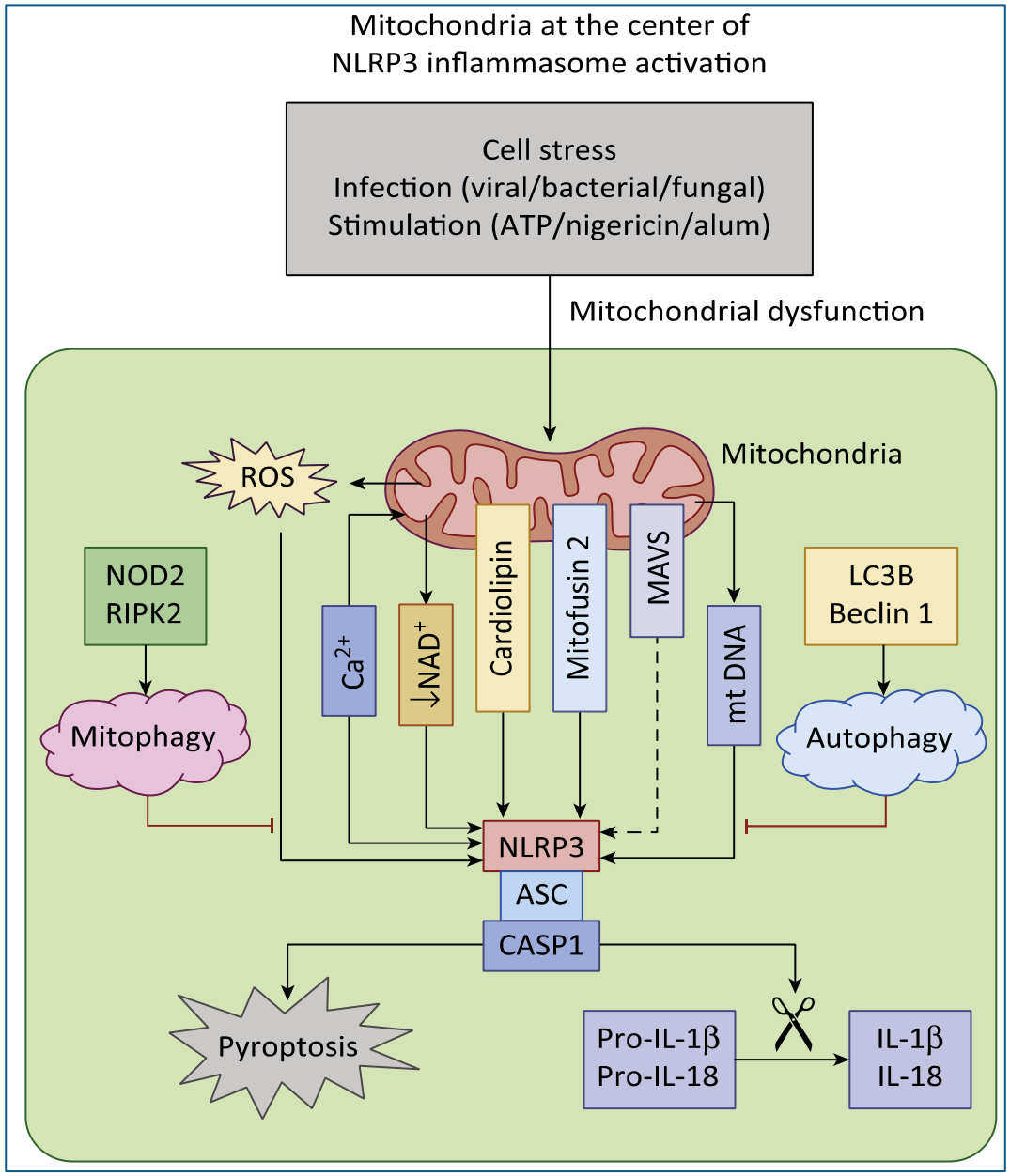
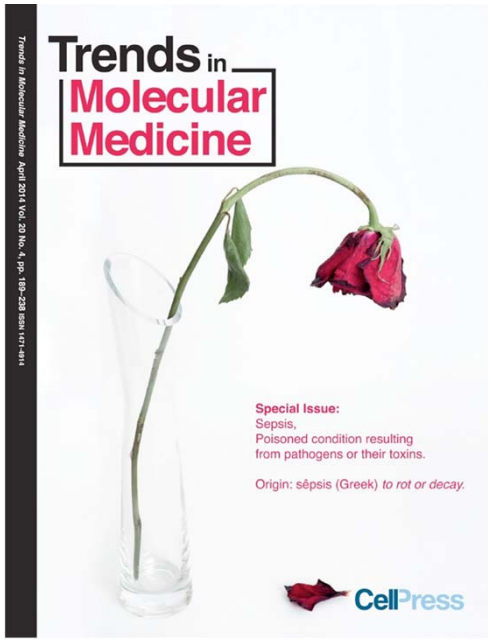


Figure 5 - Schematic illustration of NLRP3 inflammasome activation and subsequent intracellular signalling that produces a pro-inflammatory outcome.



S. Horsburgh et al, 2015



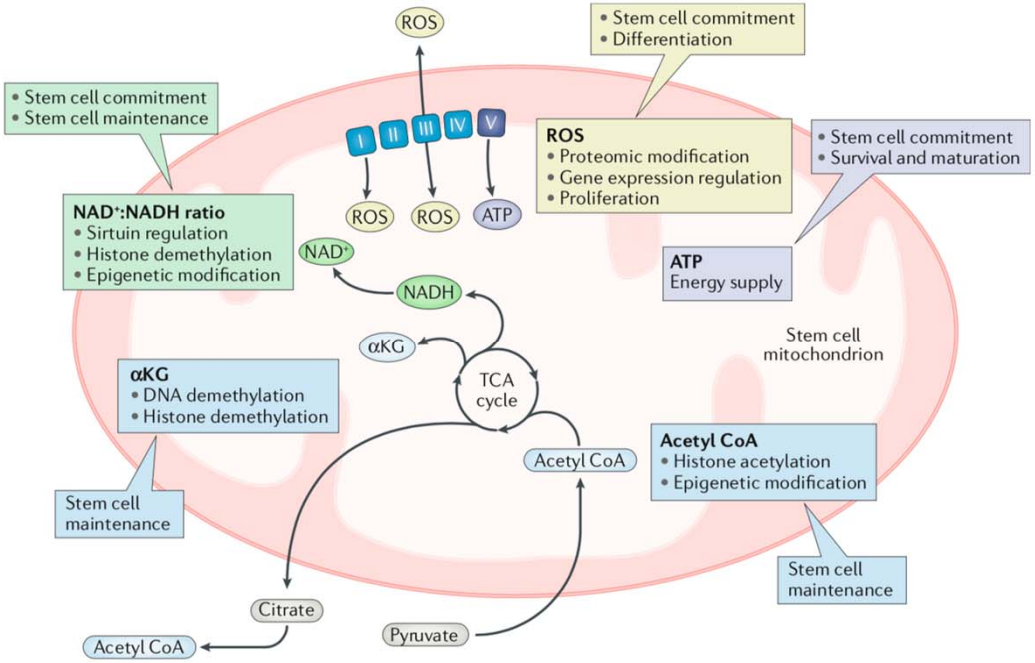


Gurung et al, 2015

Mitochondria as central regulators of neural stem cell fate and cognitive function

*Mireille Khacho[1], Richard Harris[2] and Ruth S. Slack[2]**

Abstract | Emerging evidence now indicates that mitochondria are central regulators of neural stem cell (NSC) fate decisions and are crucial for both neurodevelopment and adult neurogenesis, which in turn contribute to cognitive processes in the mature brain. Inherited mutations and accumulated damage to mitochondria over the course of ageing serve as key factors underlying cognitive defects in neurodevelopmental disorders and neurodegenerative diseases, respectively. In this Review, we explore the recent findings that implicate mitochondria as crucial regulators of NSC function and cognition. In this respect, mitochondria may serve as targets for stem-cell-based therapies and interventions for cognitive defects.



NATURE REVIEWS | NEUROSCIENCE

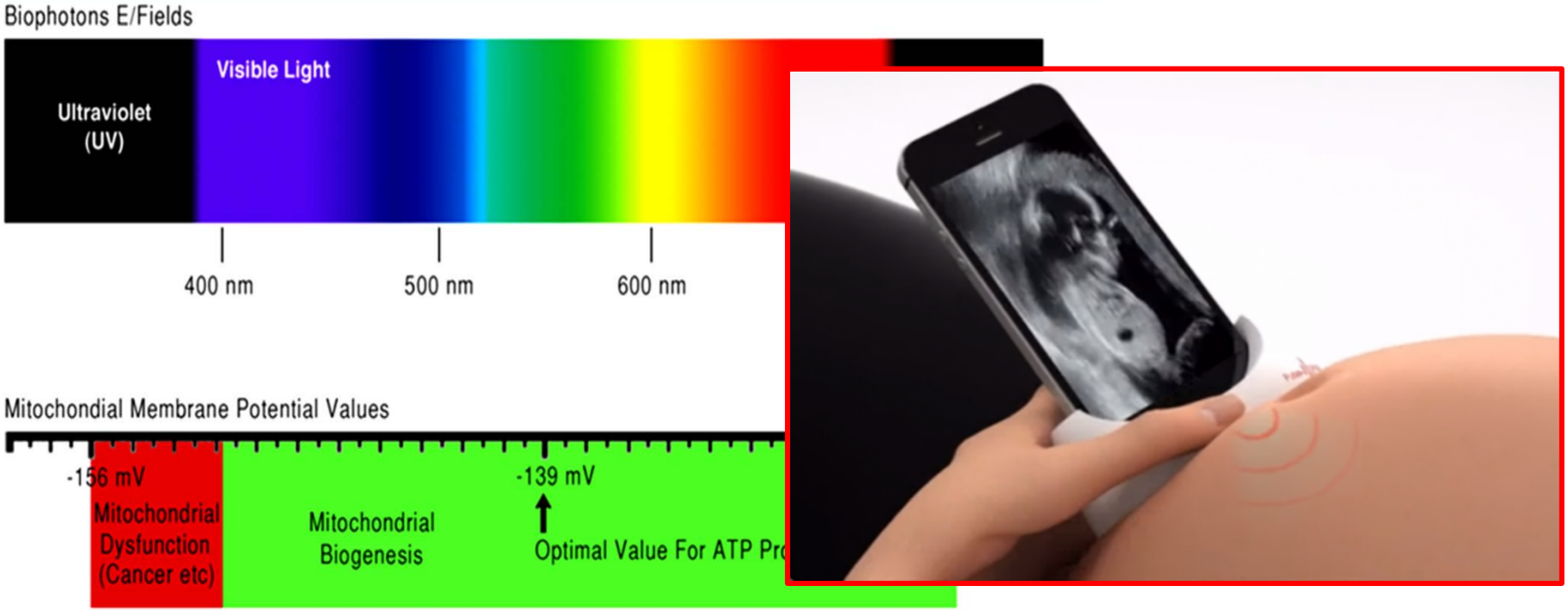
Medical Hypotheses 85 (2015) 810–818

Mitochondrial emitted electromagnetic signals mediate retrograde signaling

Georgios Bagkos, Kostas Koufopoulos, Christina Piperi *

Department of Biological Chemistry, University of Athens Medical School, Athens, Greece

Mitochondrial membrane potential (**MMP**) and the accompanied strong electromagnetic field (**EF**) **might be a key regulatory factors of nuclear activity**. Mitochondrial emitted EFs extend in long distance and affect the function of nuclear membrane receptors. Depending on their frequencies, EFs can directly **activate or deactivate different groups of nuclear receptors and so determine nuclear gene expression.** One of the key features of the above hypothesis is that nuclear membrane receptors, besides their own endoge-nous or chemical ligands (hormones, lipids, etc.), can also be activated by electromagnetic signals.

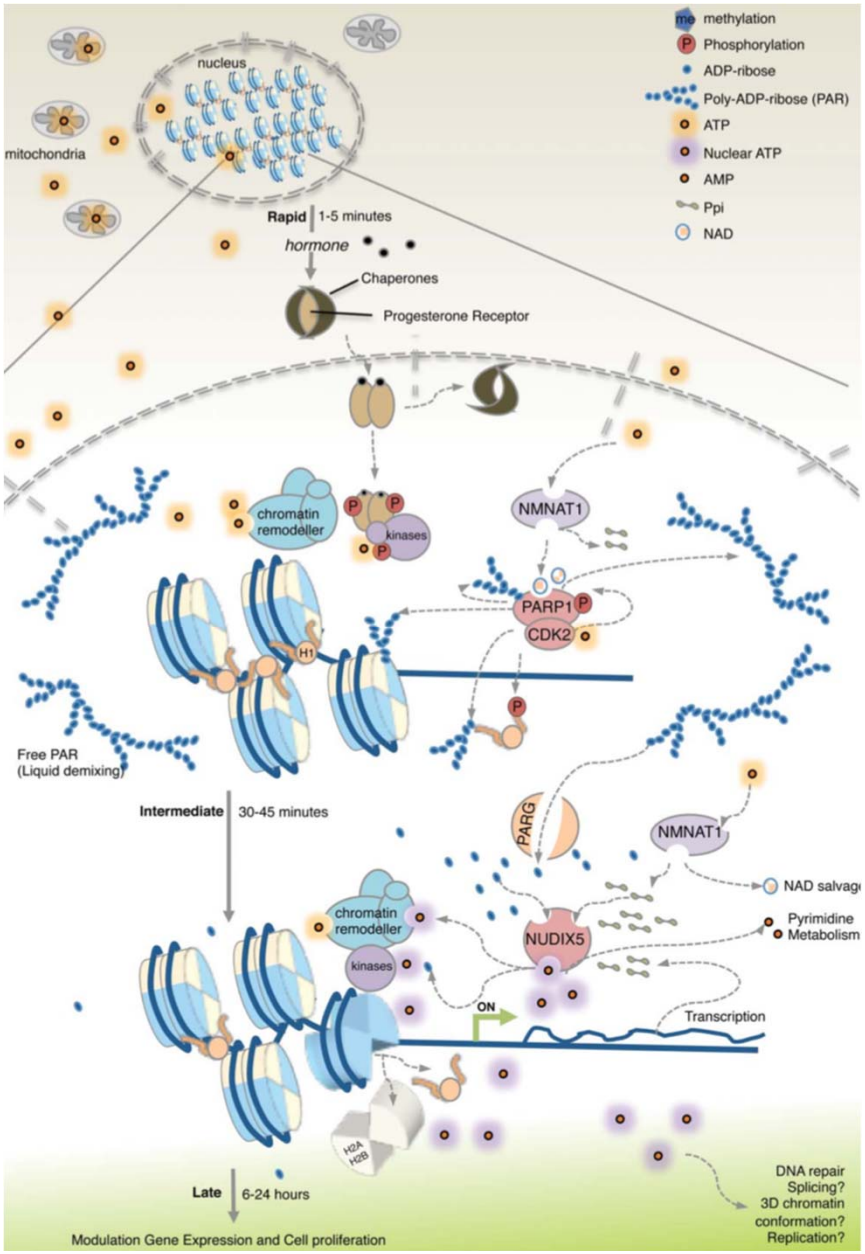


Insight into the machinery that oils chromatin dynamics

NUCLEUS
2016, VOL. 7, NO. 6, 532–539
http://dx.doi.org/10.1080/19491034.2016.1255392

Roni H. G. Wright [a,b], Narcis Fernandez-Fuentes [c], Baldomero Oliva [b], and Miguel Beato [a,b]

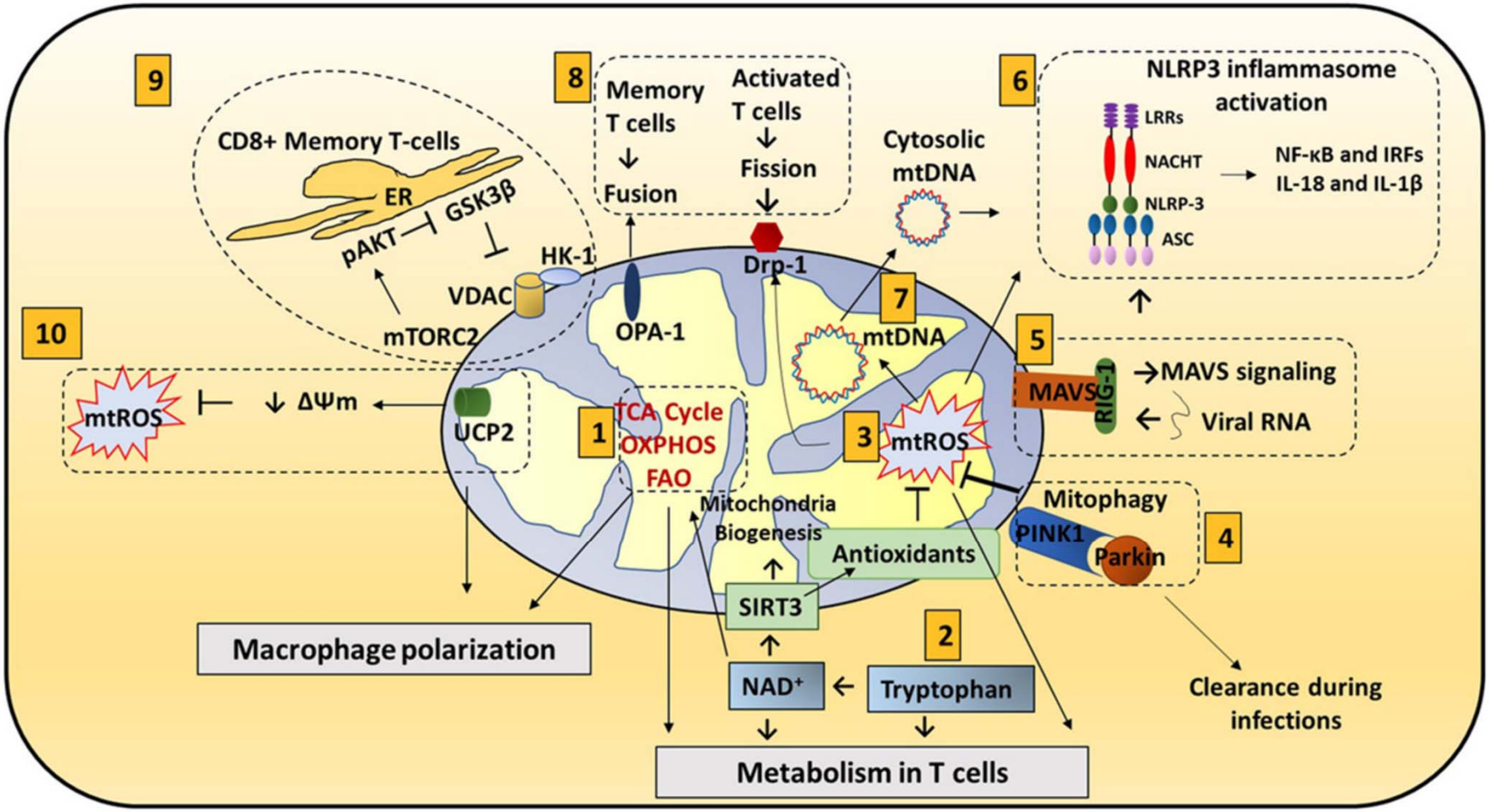
Storing information within chromatin allows selective access to specific DNA sequences by regulating the various levels of chromatin structure from nucleosomes, to chromatin fibers, loops and topological associating domains (TADs) using mechanisms that are being progressively unravelled. However, **a relatively unexplored aspect is the energetic cost of changing the chromatin configuration to gain access to DNA information.**



Diverse Roles of Mitochondria in Immune Responses: Novel Insights Into Immuno-Metabolism

frontiers in Immunology

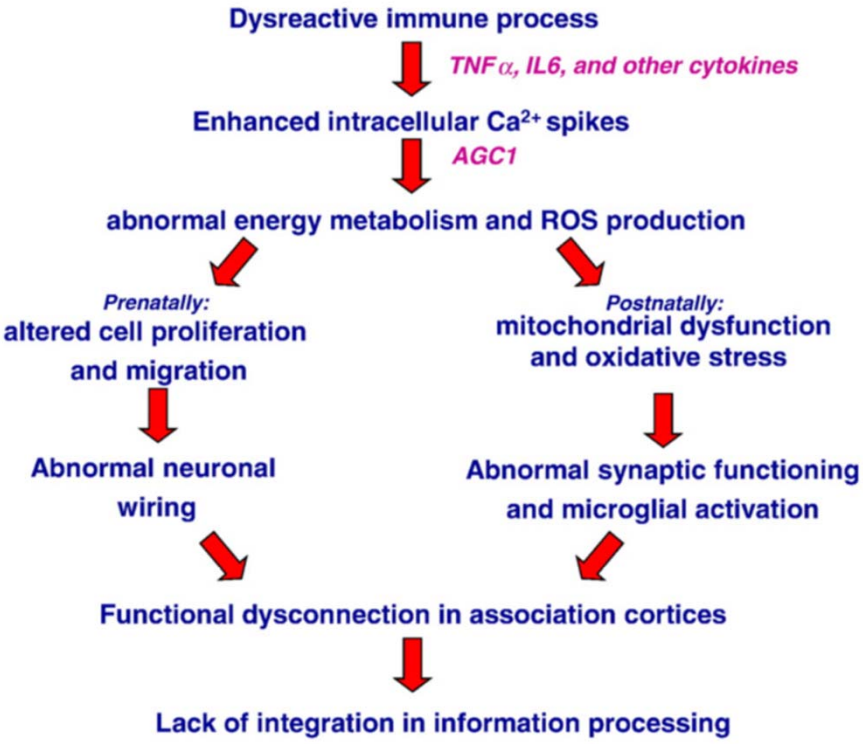
Angajala et al, 2018



Clinical and Molecular Characteristics of Mitochondrial Dysfunction in Autism Spectrum Disorder

Shannon Rose[1] · Dmitriy M. Niyazov[2] · Daniel A. Rossignol[3] · Michael Goldenthal[4] · Stephen G. Kahler[1] · Richard E. Frye[5,6]

Two major metabolic abnormalities associated with ASD are mitochondrial dysfunction and oxidative stress. The inter-connection between these two metabolic abnormalities is well known: **oxidative stress causes mitochondrial dysfunction and dysfunctional mitochondria produce ROS.**
Both intrinsic and extrinsic stressors can cause detrimental effects by increasing ROS and/or reducing mitochondrial function.
In children with ASD, the reduced form of GSH, the major intracellular antioxidant responsible for maintaining redox homeostasis and reducing ROS in the cytosol and mitochondria, **is usually deficient**



OPEN ACCESS Freely available online

PLOS | ONE

Oxidative Stress and Erythrocyte Membrane Alterations in Children with Autism: Correlation with Clinical Features

Alessandro Ghezzo[1☯], Paola Visconti[2], Provvidenza M. Abruzzo[1,3☯], Alessandra Bolotta[1,3], Carla Ferreri[4], Giuseppe Gobbi[2], Gemma Malisardi[5], Stefano Manfredini[5], Marina Marini[1,3]*, Laura Nanetti[6], Emanuela Pipitone[7], Francesca Raffaelli[6], Federica Resca[2], Arianna Vignini[6☯], Laura Mazzanti[6]

June 2013 | Volume 8 | Issue 6 | e66418

Research Article

Oxidative Stress in Autistic Children Alters Erythrocyte Shape in the Absence of Quantitative Protein Alterations and of Loss of Membrane Phospholipid Asymmetry

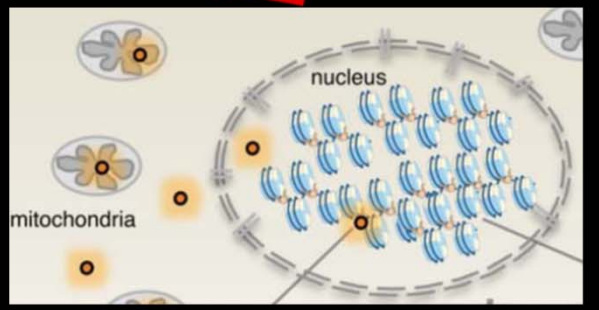
Alessandra Bolotta,[1,2] Michela Battistelli,[3] Elisabetta Falcieri,[3] Alessandro Ghezzo,[1] Maria Cristina Manara,[4] Stefano Manfredini,[5] Marina Marini,[1,2] Annio Posar,[6,7] Paola Visconti,[7] and Provvidenza Maria Abruzzo[1,2]

Oxidative Medicine and Cellular Longevity
Volume 2018, Article ID 6430601, 11 pages
https://doi.org/10.1155/2018/6430601

EVERY BREATH YOU TAKE

Modulazione della disponibilità di ossigeno nella persona con autismo:

dalla prevenzione primaria alla disabilità grave

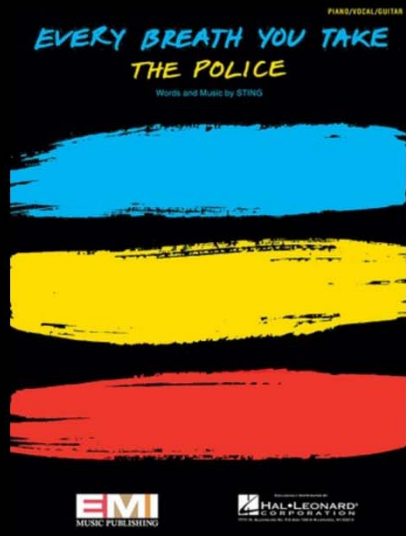


Insight into the machinery that oils chromatin dynamics

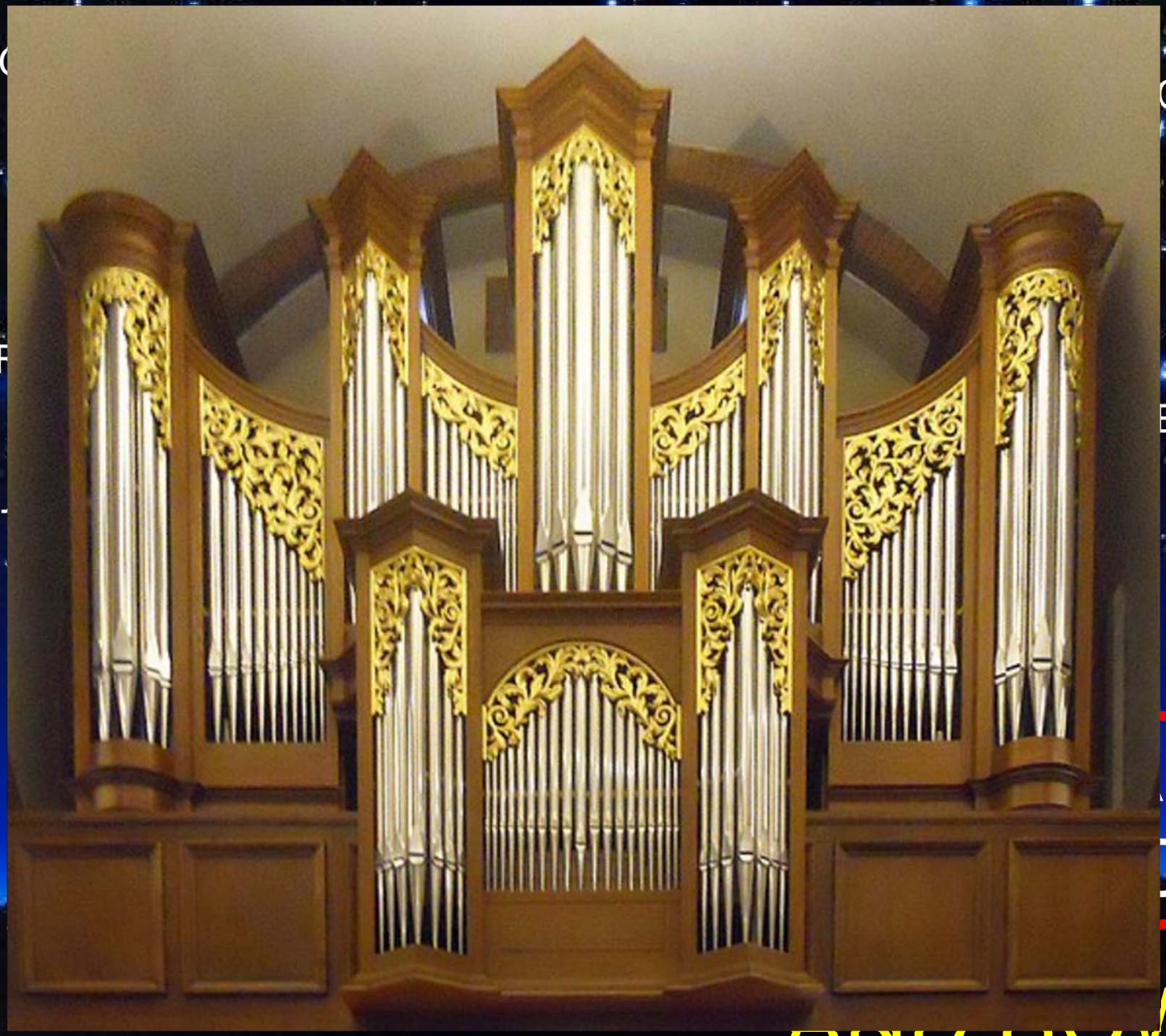
Gravidanza

Neonato e lattante a rischio

Persone con autismo




RESPIRA!
Gabriele T.



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JPNIM

SYSTEMIC PERSPECTIVE FOR THE FRAMING OF THE NEURODEVELOPMENTAL DISORDERS: GLIA (GRUPPO DI LAVORO INTERDISCIPLINARE PER L'AUTISMO, MEANING "THE INTERDISCIPLINARY GROUP FOR AUTISM")

C. Panisi[1], E. Burgio[2], R. Pintus[3], S. Vendemmia[4], E. Grossi[5], V. Fanos[3]

The interpretation of the ASD according to the pathogenetic key of DOHaD is the precondition for the building of GLIA (Gruppo di Lavoro Interdisciplinary per l'Autismo, meaning "the interdisciplinary workgroup for autism") in the SIPO. Among the main objectives, there is the beginning of effective strategies of primary prevention and the individuation of biomarkers for early diagnosis.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2018) **60**, 517–522 doi: 10.1111/ped.13565

Original Article

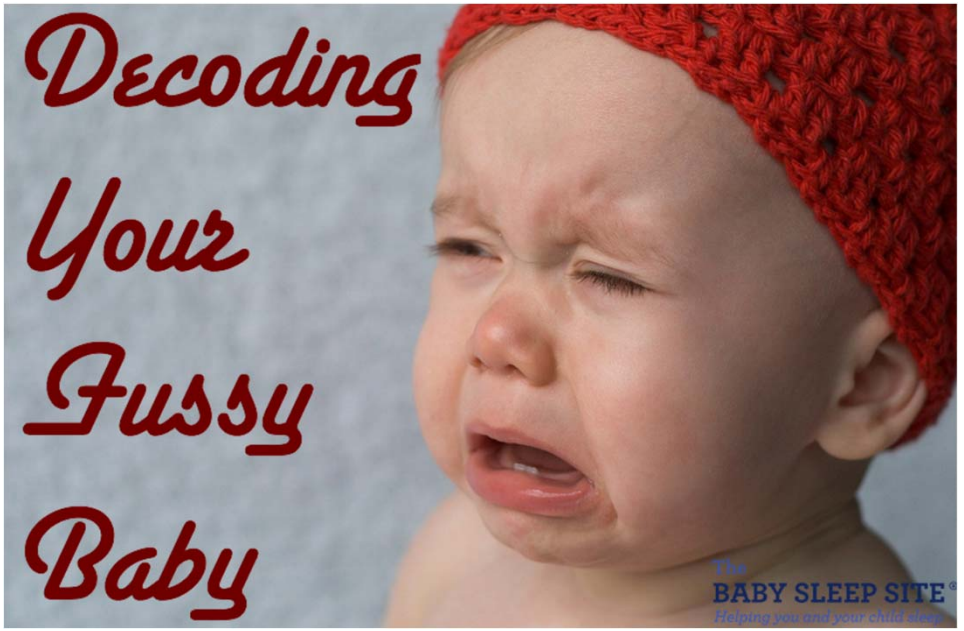
Infant colic or early symptom of autism spectrum disorder?

Özlem Bağ,[1] Sevay Alşen Güney,[3] Nagihan Cevher Binici,[3] Tuba Tuncel,[5] Aslıhan Şahin,[2] Emel Berksoy[6] and Çiğdem Ecevit[4]

The rate of persistent crying was significantly higher in the ASD group than in the control group (32% vs 9%, **P < 0.001**). The **relative risk** of persistent crying was **4.40 in ASD**. The likelihood of being **misdiagnosed with IC** in this group was **78%.**

Conclusion: Infants with excessive crying should be very thoroughly evaluated before being diagnosed with IC. In particular, persistent crying in infants (i.e. excessive crying with late onset and long duration) **may be an early symptom of ASD.**

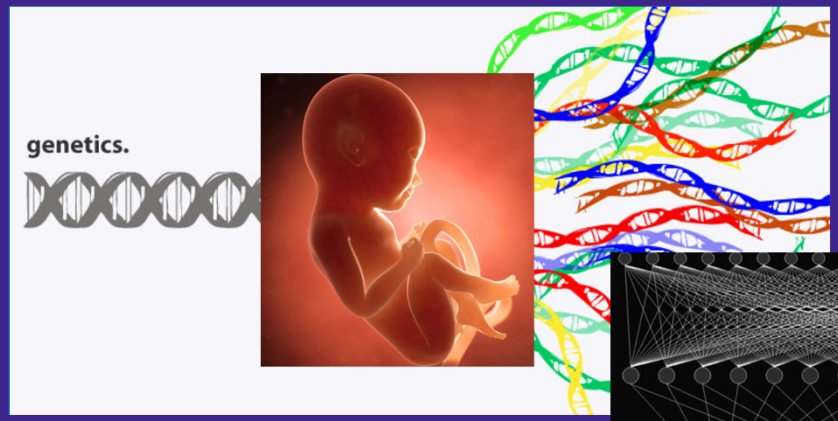
?

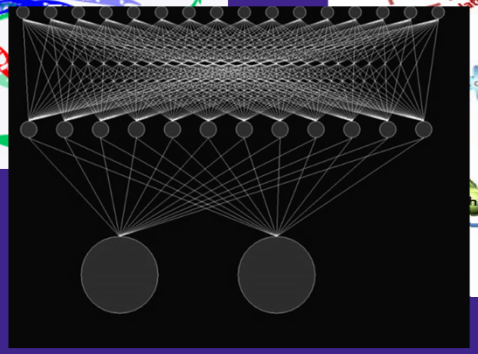


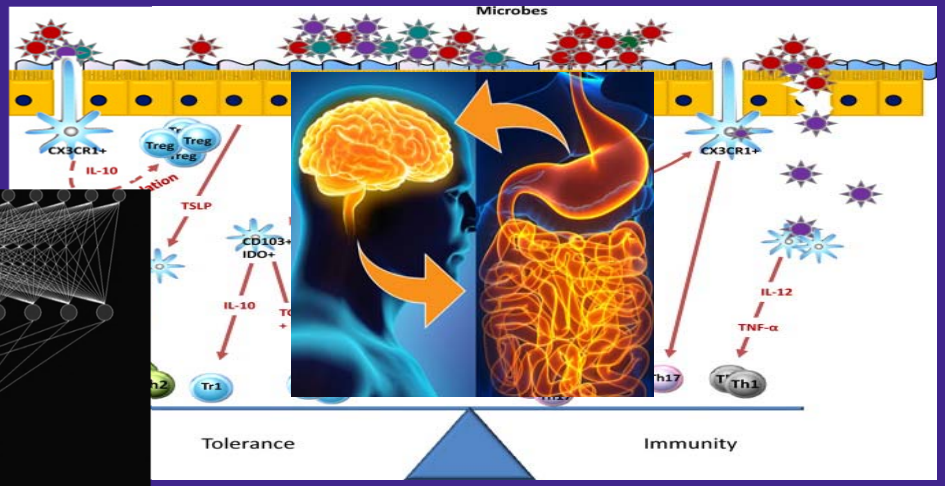
Autism Spectrum Disorder: suggestions for a paradigm shift

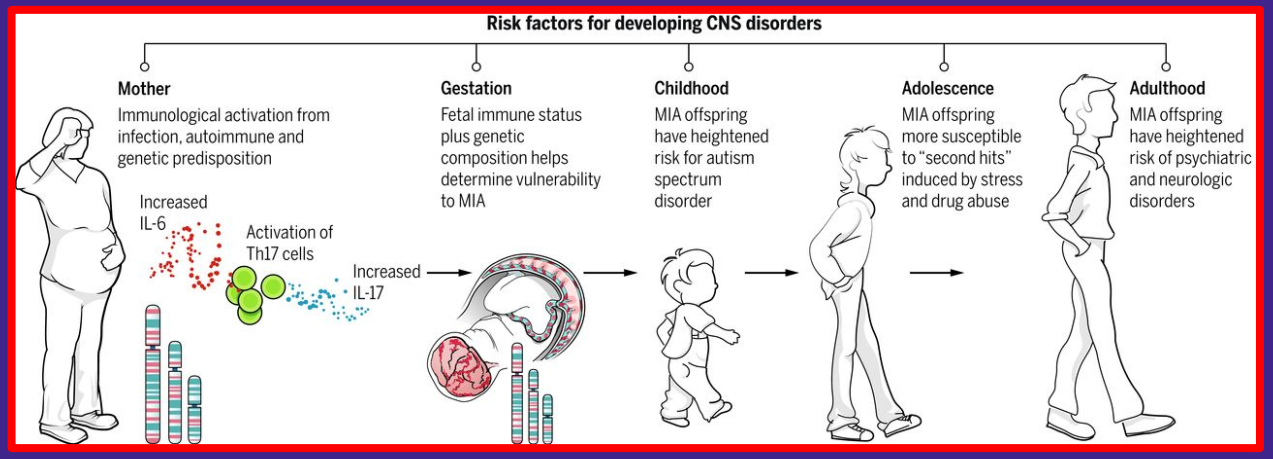
Panisi C, Burgio E, Ghezzo A, Grossi E, Guerini F, Marini M, Migliore L, Saresella M, Fanos V

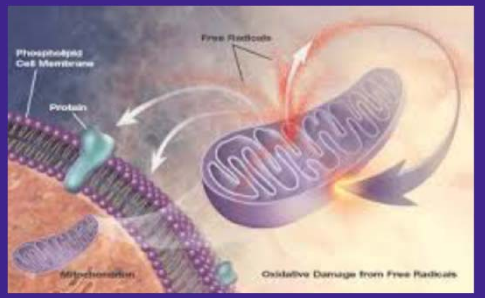
Working Paper

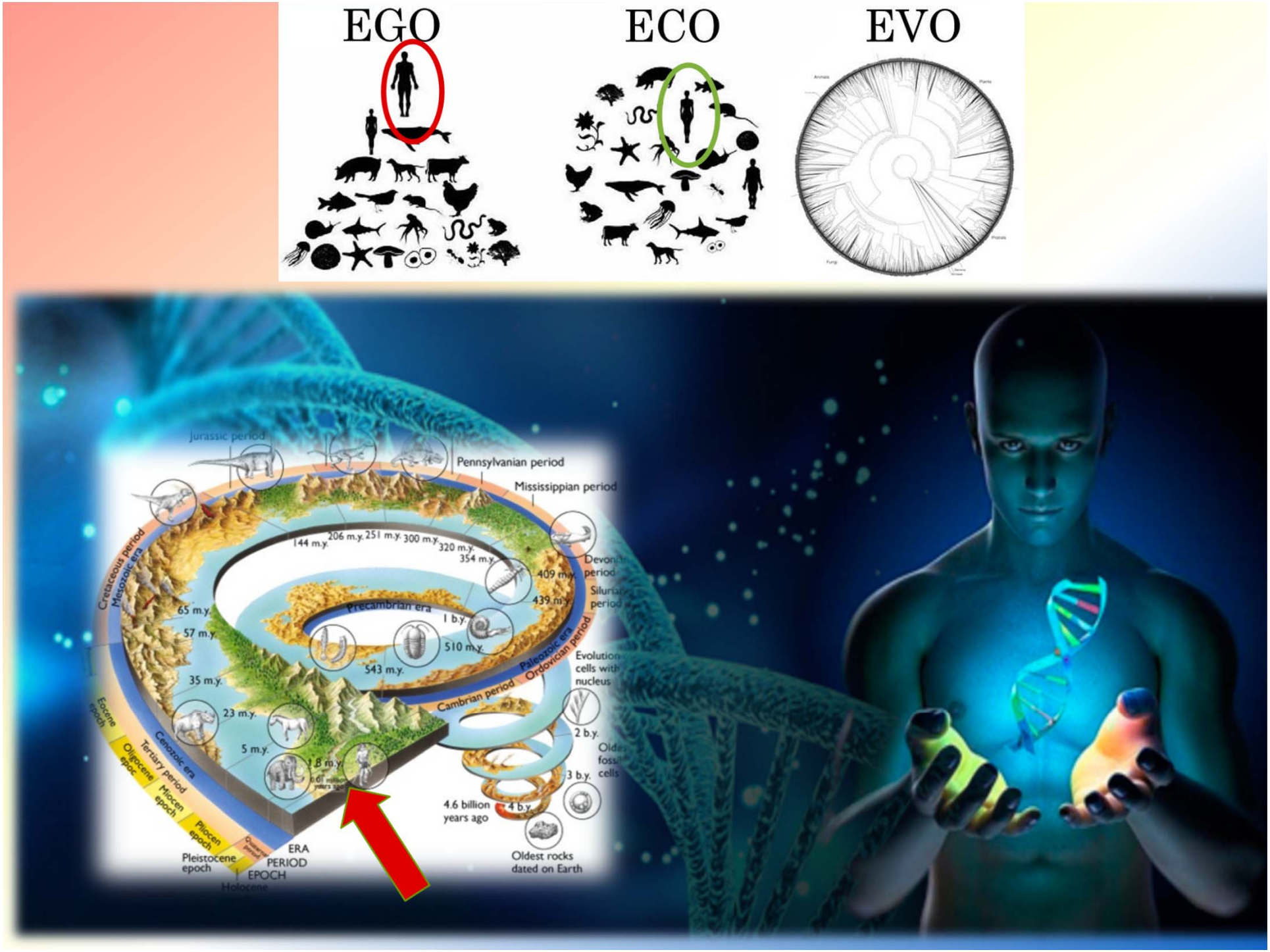


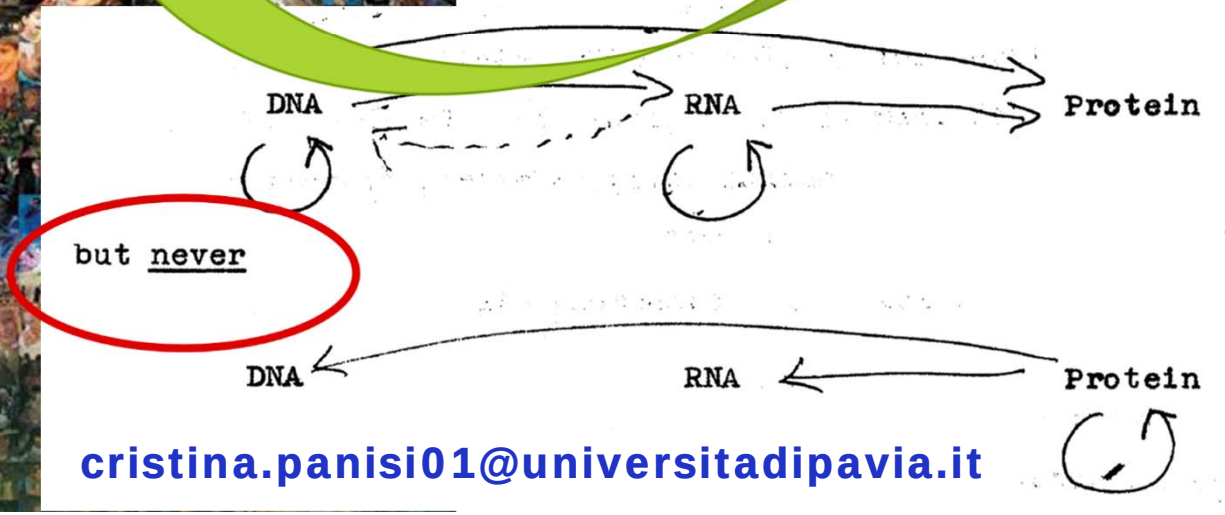









EGO
ECO
EVO
Jurassic period
Pennsylvanian period
Mississippian period
144 m.y.
206 m.y.
251 m.y.
300 m.y.
320 m.y.
354 m.y.
409 m.y.
439 m.y.
Precambrian era
1 b.y.
510 m.y.
543 m.y.
Paleozoic era
Ordovician period
Cambrian period
Cretaceous period
Mesozoic era
65 m.y.
57 m.y.
35 m.y.
23 m.y.
5 m.y.
1.8 m.y.
Eocene epoch
Oligocene epoch
Miocen epoch
Pliocen epoch
Pleistocene epoch
Holocene
Tertiary period
Cenozoic era
ERA
PERIOD
EPOCH
2 b.y.
3 b.y.
4 b.y.
4.6 billion years ago
Oldest rocks dated on Earth



cristina.panisi01@universitadipavia.it