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BOLOGNA
20-22 Febbraio 2023

Rilevanza clinica e preclinica dei fattori ambientali implicati nel disturbo dello spettro autistico

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DIPARTIMENTO DI NEUROSCIENZE, PSICOLOGIA, AREA DEL FARMACO E SALUTE DEL BAMBINO
ECCELLENZA 2023-27

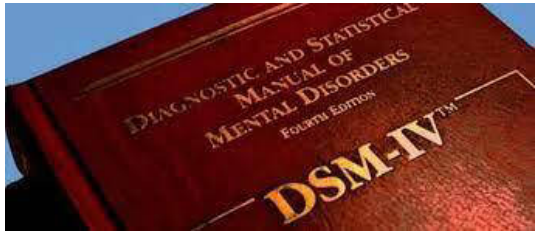
- Parte 1: concetti generali
- Parte 2: Ruolo dei fattori ambientali nella ezio-patogenesi del Disturbo dello Spettro Autistico (DSA)
- Parte 3: Valore predittivo dei modelli animali indotti da fattori ambientali (esposizione prenatale ad acido valproico)

Disturbo dello Spettro Autistico (DSA): concetti generali

Sintomi:

1. Deficit di socialità
2. Comportamento stereotipato, ripetitività
3. Difficoltà nella comunicazione verbale e non verbale

< 2013



1. Disturbo autistico
2. Disturbo disintegrativo dell'infanzia
3. Asperger
4. Sindrome di Rett

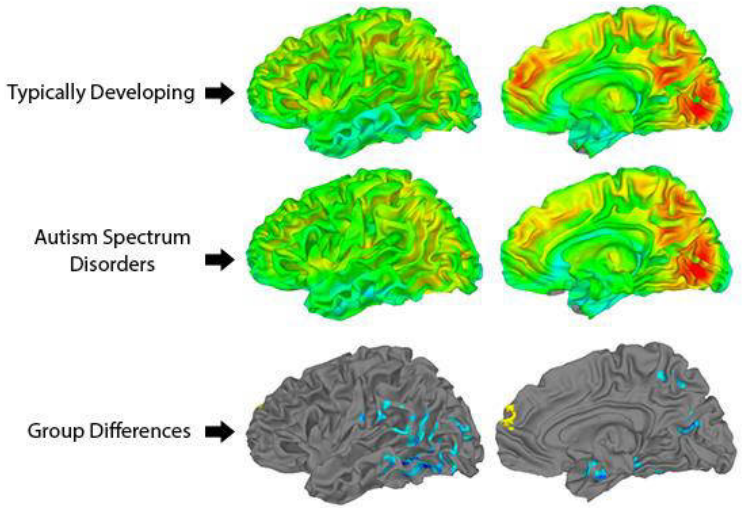
> 2013

DSA

Disturbo dello Spettro Autistico (DSA): concetti generali

Fisiopatologia

- Alterazioni diffuse nella sinaptogenesi e nella connettività strutturale e funzionale
- Alterazioni diffuse nella densità neuronale
- Alterazioni nelle proprietà elettriche intrinseche dei neuroni



Lee Keown et al., Cell Rep 2013

Disturbo dello Spettro Autistico (DSA): concetti generali

Sintomi associati:

- Cognitivi (deficit intellettivo)
- Neurologici (epilessia)
- Emotivi (ansia, irritabilità)

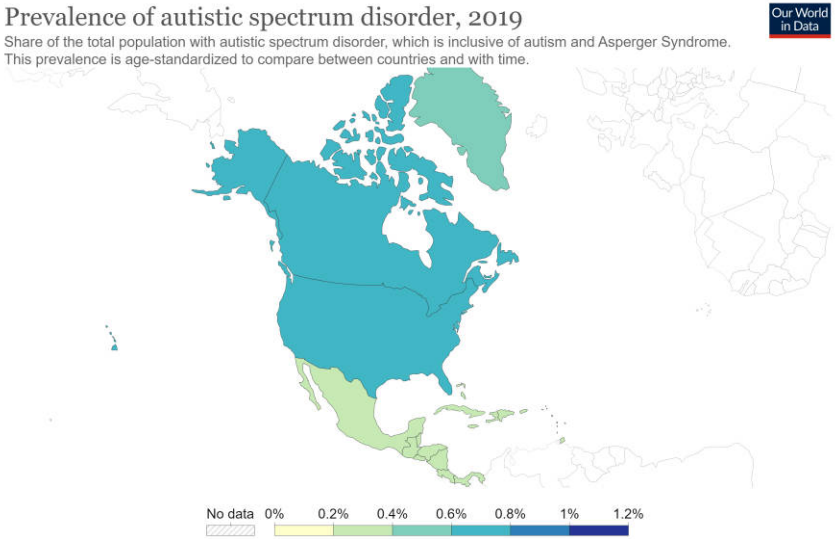
Autismo sindromico: malattie genetiche con presenza di fenotipo autistico

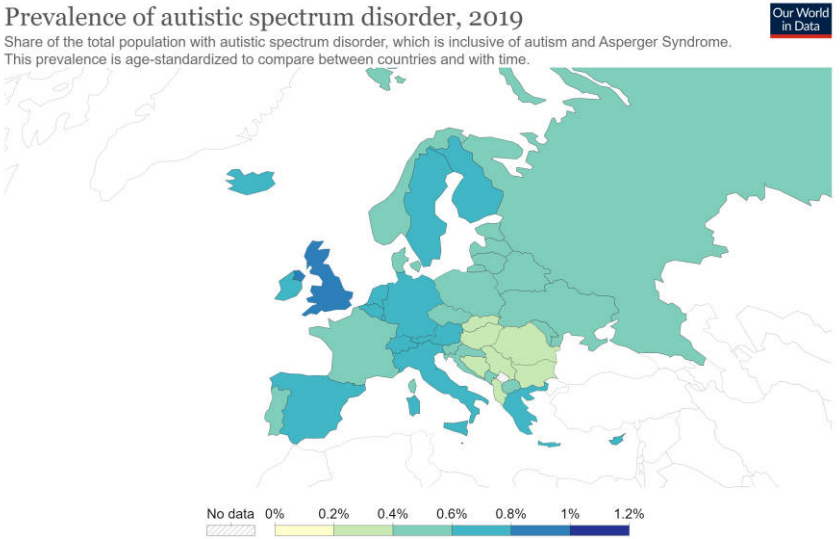
- Sindrome dell'X fragile
- Sindrome di Down
- Complesso della Sclerosi Tuberosa
- Sindrome di Dravet
- …

PARTE 2

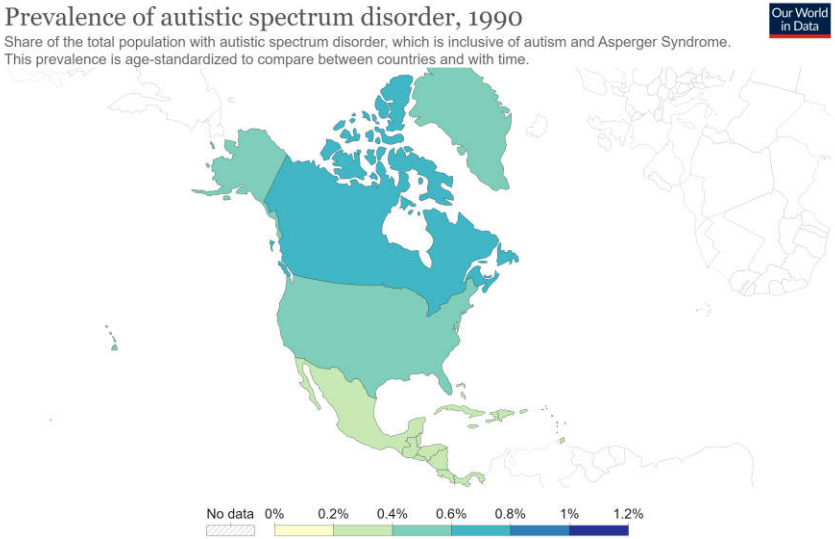
I fattori ambientali nella ezio-patogenesi del DSA

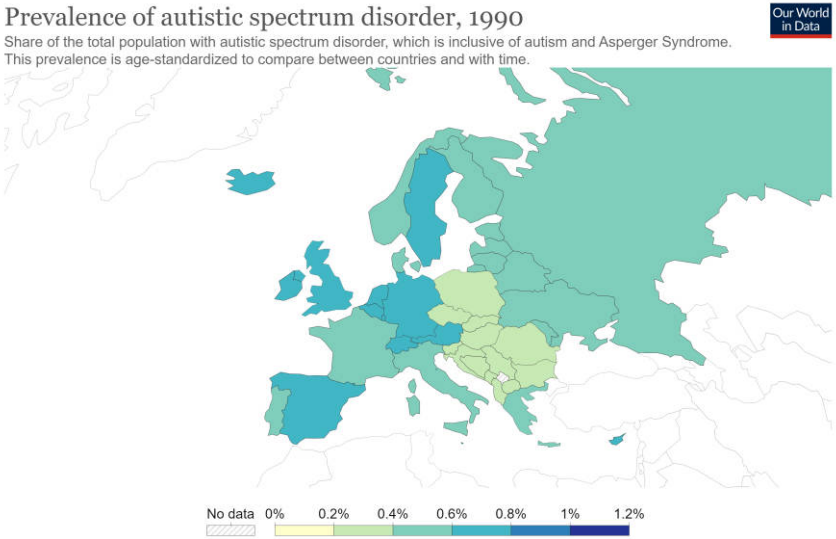
Prevalenza (2019)



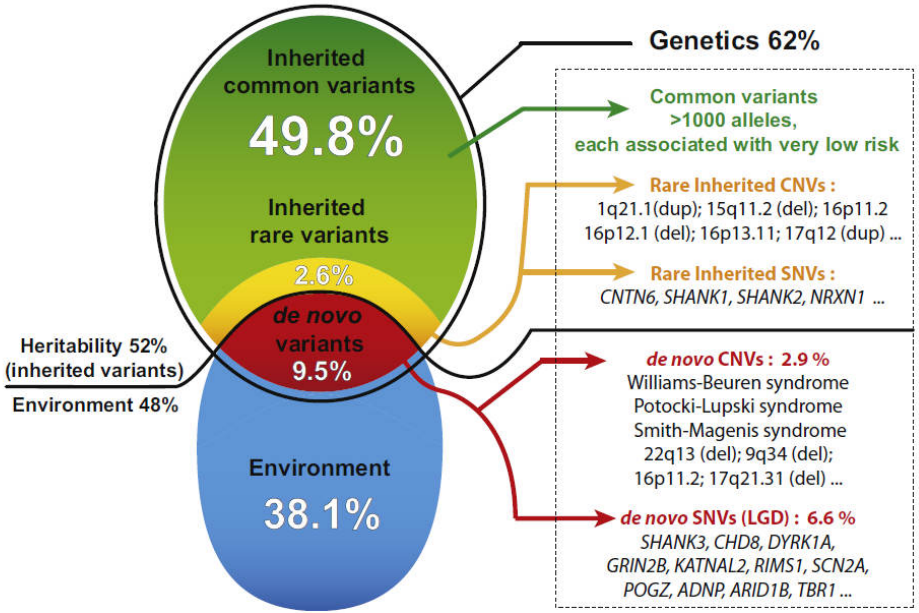


Prevalenza (1990)





DSA: fattori genetici ed ambientali



Relative contributions of genetics and environment in ASD

Based on twin and familial studies, it is estimated that the genetic and environmental contributions to ASD are approximately 50% and 50%.

Most of the inheritable part seems to be due to common variants observed in the general population, with a small contribution from rare variants.

Huguet e Bourgeron, 2016 «Genetic Causes of Autism Spectrum Disorders".

DSA: fattori ambientali

- Età parentale
- Parità
- Diabete ed obesità materna
- Infezioni e/o stati infiammatori durante la gravidanza
- Complicazioni durante il parto
- Farmaci in gravidanza (SSRI, antiepilettici)
- Inquinanti (pesticidi, additivi, particolato)
- Metalli pesanti (Hg, Cd)
- Vaccinazioni pediatriche

DSA: fattori ambientali

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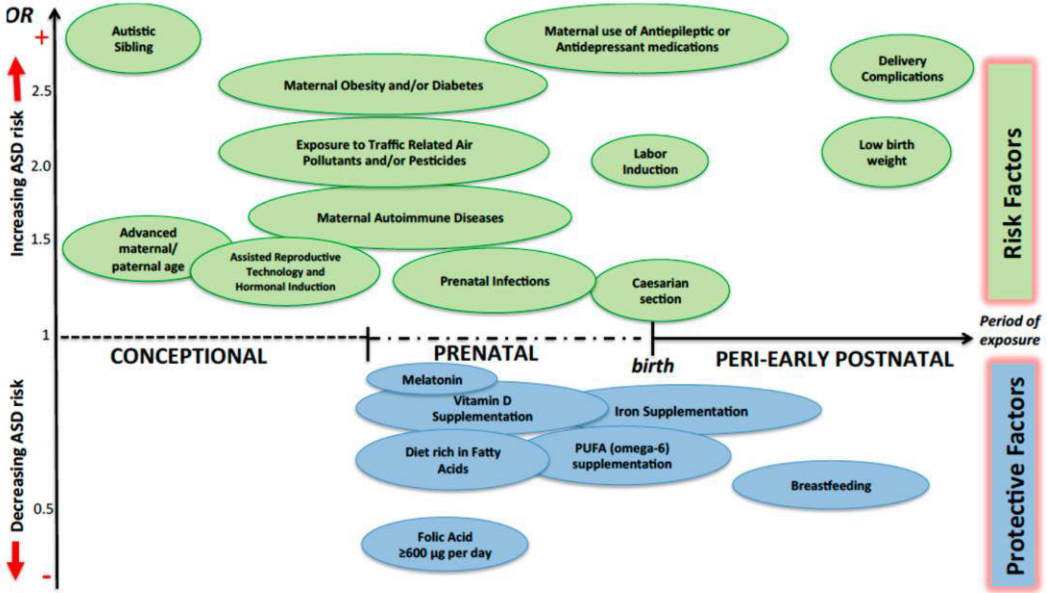
- ~~Vaccinazioni pediatriche~~

DSA: fattori ambientali



Note: Risk- and Protective factor areas have different scales

Gialloreti et al., *J. Clin. Med* 2019

DSA: fattori ambientali

Ma attenzione ai fattori confondenti!

Es: l'associazione tra DSA e SSRI in gravidanza è significativa in molti studi, ma la significatività si perde correggendo per il fattore «depressione materna», cioè l'indicazione stessa alla base della terapia.

Reproductive Toxicology 65 (2016) 170–178

Contents lists available at ScienceDirect

Reproductive Toxicology

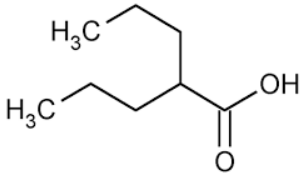
journal homepage: www.elsevier.com/locate/reprotox

Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis

Tohru Kobayashi (MD PhD)[a,b], Tasuku Matsuyama (MD)[a,c], Masanobu Takeuchi (MD)[a], Shinya Ito (MD)[a,d,*]

[a] Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Canada
[b] Division of Research Planning, Department of Development Strategy, Center for Clinical Research and Development, National Center for Child Health and Development, Japan
[c] Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Japan
[d] Motherisk Program, The Hospital for Sick Children, Canada

Valproic acid (VPA)



- Uso approvato come antiepilettico, stabilizzante dell'umore. Molto utilizzato perché efficace su tutte le forme di epilessia (assenze, crisi tonico-cloniche).
- Farmacodinamica complessa: agisce sui canali del sodio e del calcio voltaggio-dipendenti e sulla trasmissione GABA.
- Gli effetti teratogeni dovuti anche all'azione di inibizione dell'enzima istone deacetilasi (HDAC) che controlla la trascrizione ed è responsabile di effetti epigenetici.

Associazione tra esposizione prenatale a VPA e DSA

ORIGINAL CONTRIBUTION

Jakob Christensen, PhD
Therese Koops Grønborg, MSc
Merete Juul Sørensen, PhD
Diana Schendel, PhD
Erik Thorlund Parner, PhD
Lars Henning Pedersen, PhD
Mogens Vestergaard, PhD

Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Table 2. Association Between Any Maternal Use of Valproate During Pregnancy and Autism Spectrum Disorder and Childhood Autism

Valproate Exposure	Live Births, No.	Person-Years at Risk	No. With Disorder	Hazard Ratio (95% CI)		Absolute Risk Over 14 y, % (95% CI)
				Crude	Adjusted[a]	
			Autism Spectrum Disorder			
Yes	508	4880	14	3.0 (1.8-5.1)	2.9 (1.7-4.9)	4.42 (2.59-7.46)
No	655 107	5 793 387	5423	1 [Reference]	1 [Reference]	1.52 (1.47-1.58)
			Childhood Autism			
Yes	508	4891	9	5.4 (2.8-10.4)	5.2 (2.7-10.0)	2.50 (1.30-4.81)
No	655 107	5 803 842	2058	1 [Reference]	1 [Reference]	0.48 (0.45-0.51)

[a] Adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity.

Associazione tra esposizione prenatale a VPA e DSA

Linee guida EMA su VPA in gravidanza

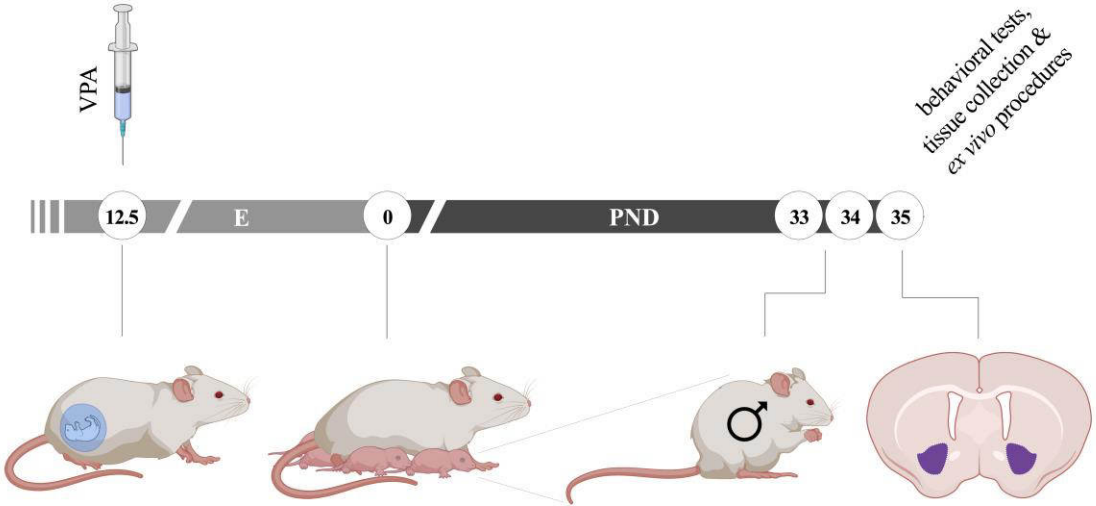
- If possible, an alternative to valproic acid should be used in women of reproductive age.
- If valproic acid is the only option, women should use effective contraception and should be closely supervised.
- Women taking valproic acid should also take 4mg of folic acid daily to reduce the risk of birth defects in the setting of unplanned pregnancy.

Pharmacovigilance Risk Assessment Committee (PRAC)

PARTE *3*

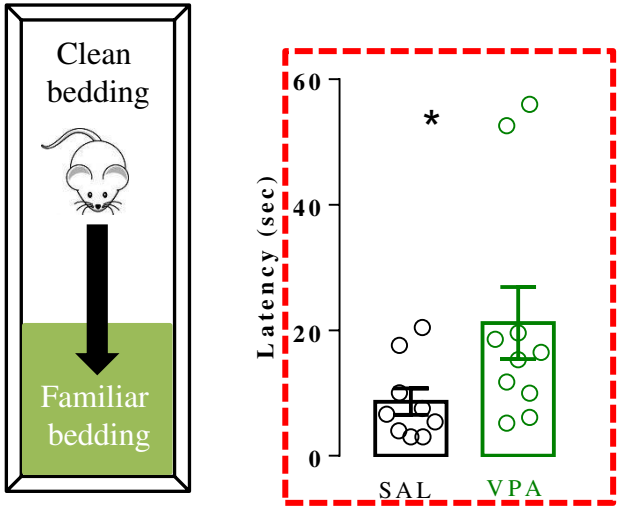
Valore predittivo dei modelli animali indotti da fattori ambientali (esposizione prenatale ad acido valproico)

Modello animale (ratto) da esposizione prenatale a VPA

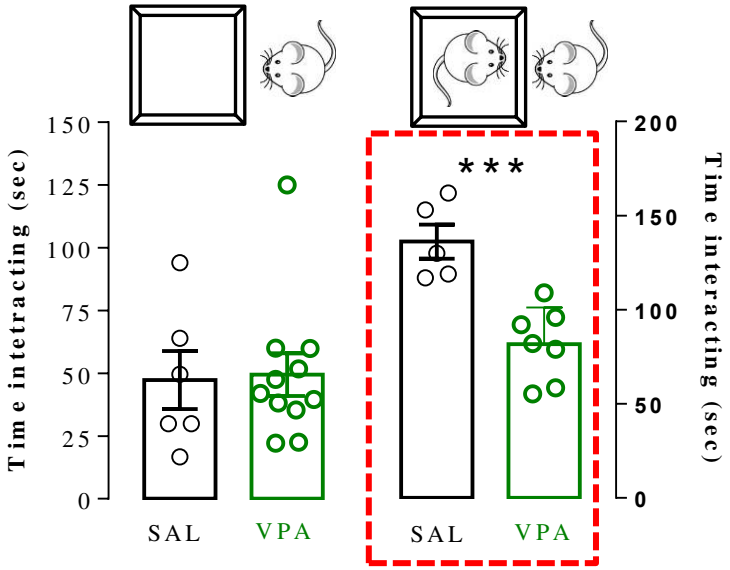


Caratterizzazione comportamentale: «face validity»

Homing behavior test (P13)



Social interaction test (P30-35)



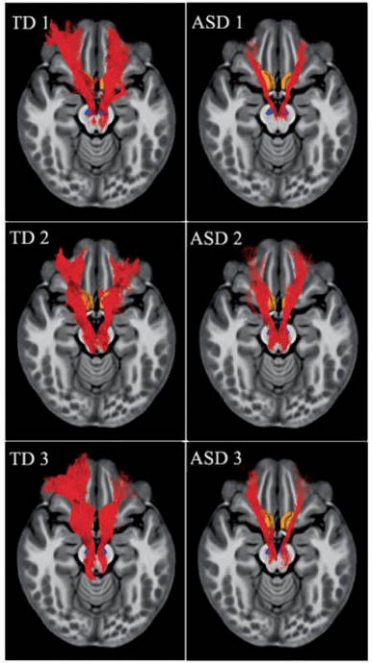
Il sistema meso-limbico nel social deficit del DSA

doi:10.1093/brain/awy191 BRAIN 2018: 141; 2795–2805 | 2795
BRAIN
A JOURNAL OF NEUROLOGY

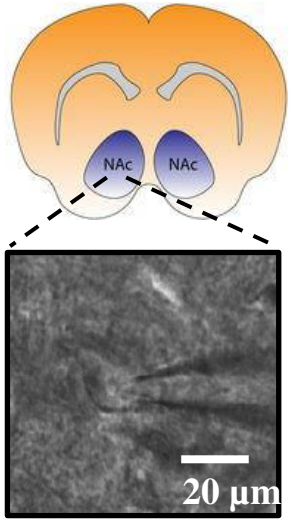
Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism

Kaustubh Supekar,[1,*] John Kochalka,[1,*] Marie Schaer,[1,2] Holly Wakeman,[1] Shaozheng Qin,[1,3] Aarthi Padmanabhan[1] and Vinod Menon[1,4,5]

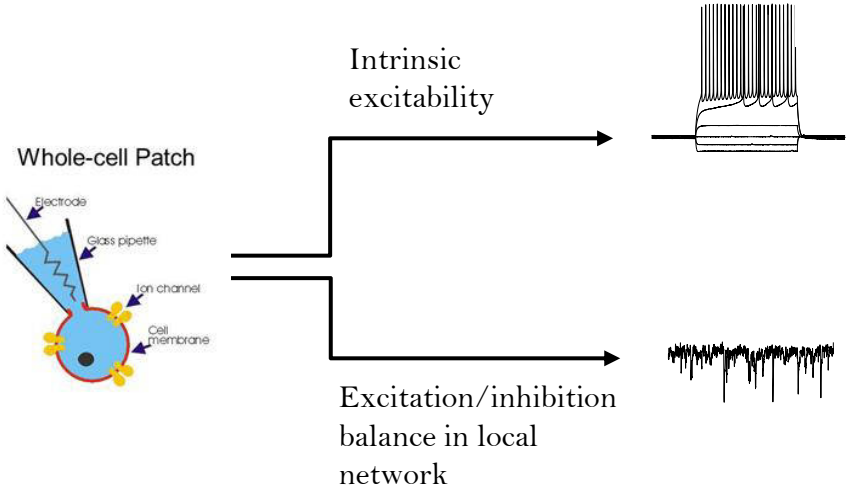
The fMRI study was performed on 82 children aged 7–13 years with autism spectrum disorder and age-, gender-, and intelligence quotient-matched typically developing children.
…evidence **for structural aberrations** in **white matter tracts linking the nucleus accumbens and the ventral tegmental area** in children with autism spectrum disorder



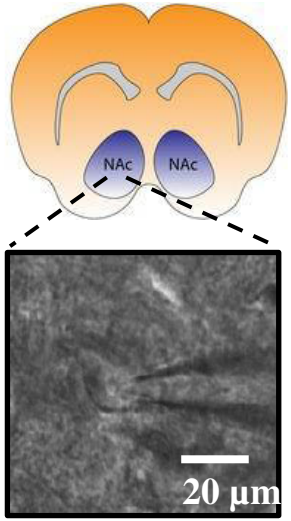
Caratterizzazione elettrofisiologica su tessuto cerebrale *ex vivo*



Neuroni spinosi medi (MSN)



Effetti di VPA prenatale sull'eccitabilità dei MSN del *nucleus accumbens*



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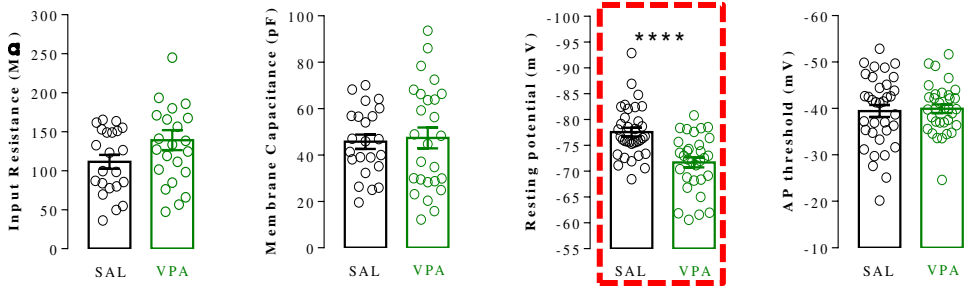
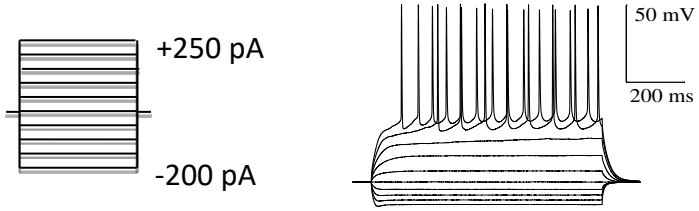
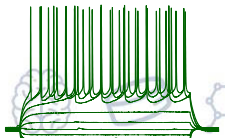


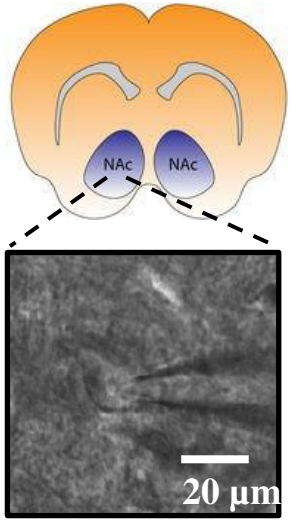


SAL

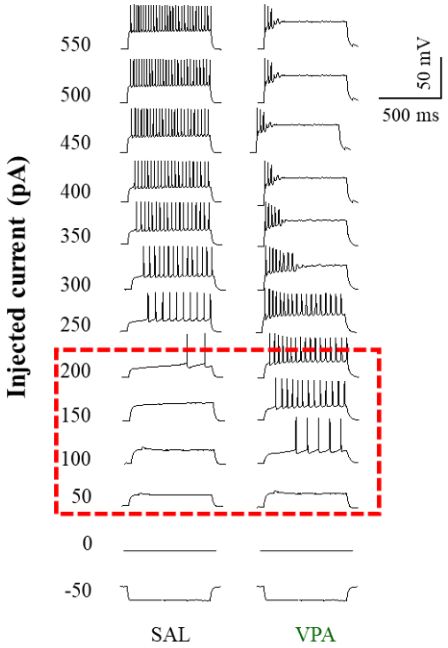
VPA

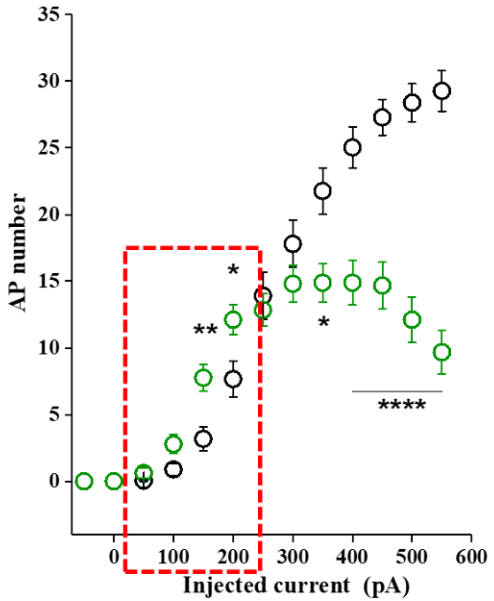


Effetti di VPA prenatale sull'eccitabilità dei MSN del *nucleus accumbens*



Neuroni spinosi medi (MSN)





Effetti di VPA prenatale sull'eccitabilità dei MSN del *nucleus accumbens*

1) Quali sono i pathway cellulari responsabili del fenotipo?

2) Esiste una relazione tra questo fenotipo neuronale ed il fenotipo comportamentale presente nel modello?

Il pathway mTOR nei disturbi del neurosviluppo

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-26131-z OPEN

mTOR-related synaptic pathology causes autism spectrum disorder-associated functional hyperconnectivity

Marco Pagani[1,2], Noemi Barsotti[3], Alice Bertero[1,3], Stavros Trakoshis[4,5], Laura Ulysse[6], Andrea Locarno[7], Ieva Miseviciute[7], Alessia De Felice[1], Carola Canella[1], Kaustubh Supekar[8], Alberto Galbusera[1], Vinod Menon[8], Raffaella Tonini[7], Gustavo Deco[6,9], Michael V. Lombardo[5,10,11], Massimo Pasqualetti[1,3,11] & Alessandro Gozzi[1,11✉]

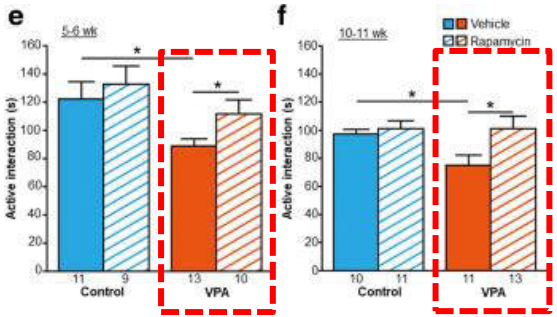
Kotajima-Murakami et al. Molecular Brain (2019) 12:3
https://doi.org/10.1186/s13041-018-0423-2

Molecular Brain

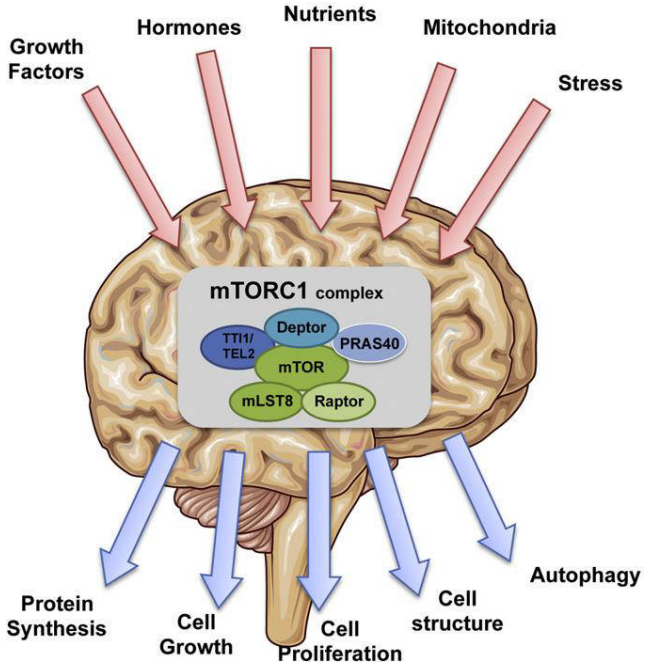
RESEARCH Open Access

Effects of rapamycin on social interaction deficits and gene expression in mice exposed to valproic acid in utero

Hiroko Kotajima-Murakami[1,2], Toshiyuki Kobayashi[3], Hirofumi Kashii[1,4], Atsushi Sato[1,5], Yoko Hagino[1], Miho Tanaka[1,6], Yasumasa Nishito[7], Yukio Takamatsu[7], Shigeo Uchino[1,2] and Kazutaka Ikeda[1*]

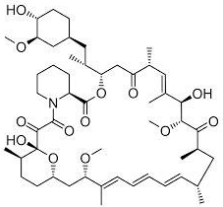


Il pathway mTOR nei disturbi del neurosviluppo



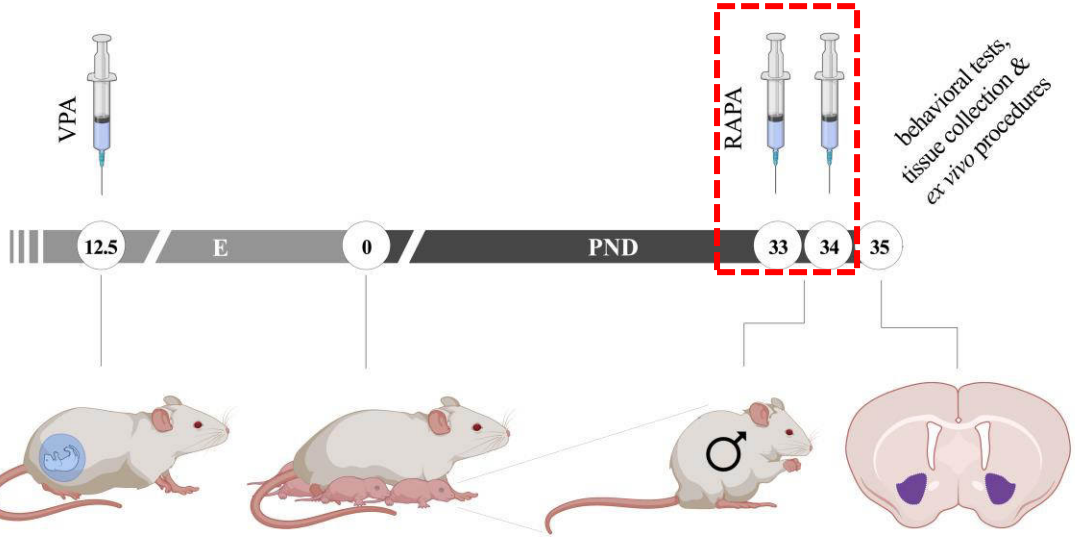
(Perluigi et al., *Neurobiol Dis.*, 2015)

Il pathway mTOR nei disturbi del neurosviluppo

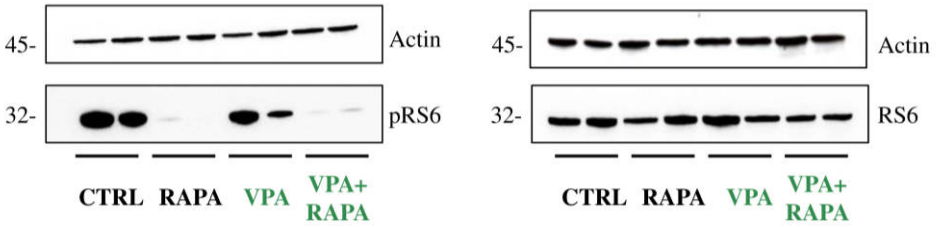


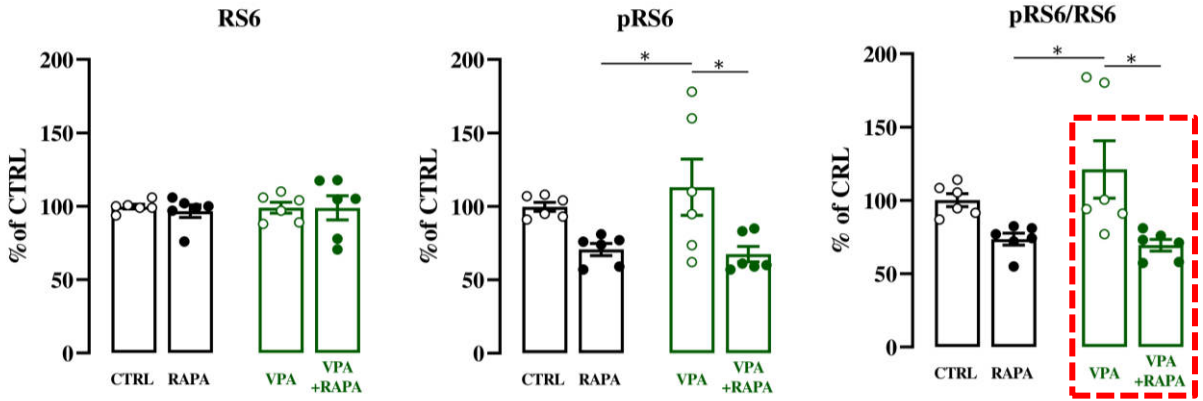
Rapamicina (Rapamune, Everolimus, Sirolimus) è un antibiotico macrolide ricavato dal batterio *Streptomyces Hygroscopicus*, endemico dell'isola di Pasqua (Rapa Nui).
Immunosoppressore, utilizzato per prevenire le crisi di rigetto nei trapianti d'organo.
I suoi effetti farmacologici sono dovuti all'inibizione di mTOR (mammalian/mechanistic Target Of Rapamycin).

Trattamento acuto post-natale con rapamicina

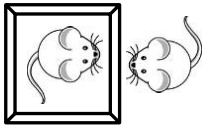


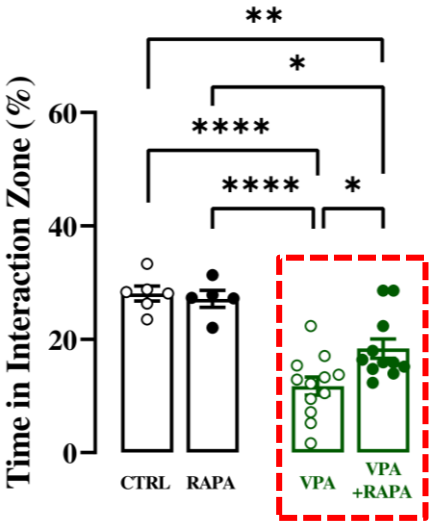
Trattamento acuto post-natale con rapamicina

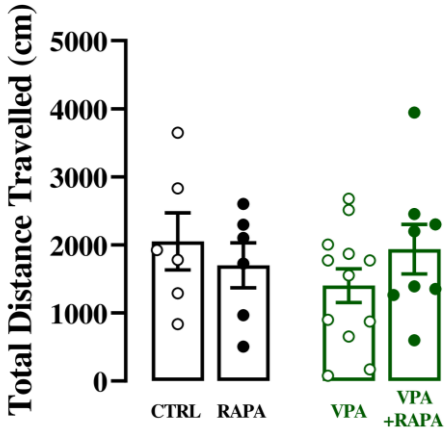


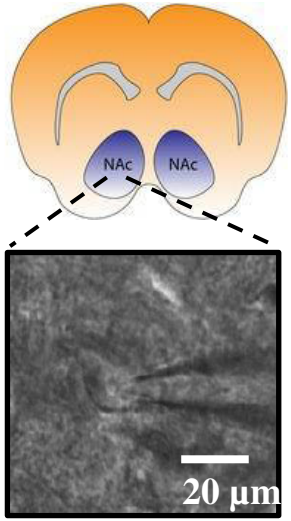


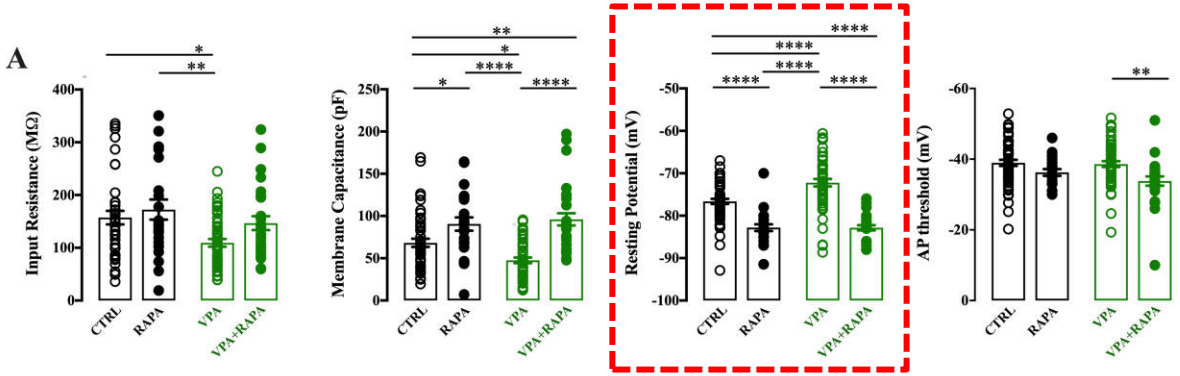
Trattamento acuto post-natale con rapamicina



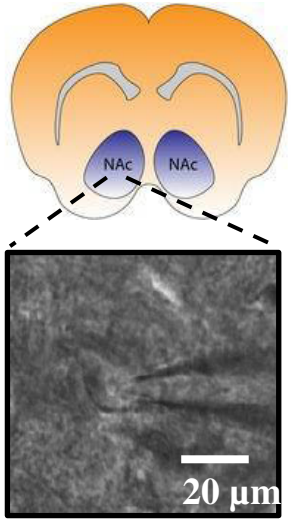








Neuroni spinosi medi (MSN)



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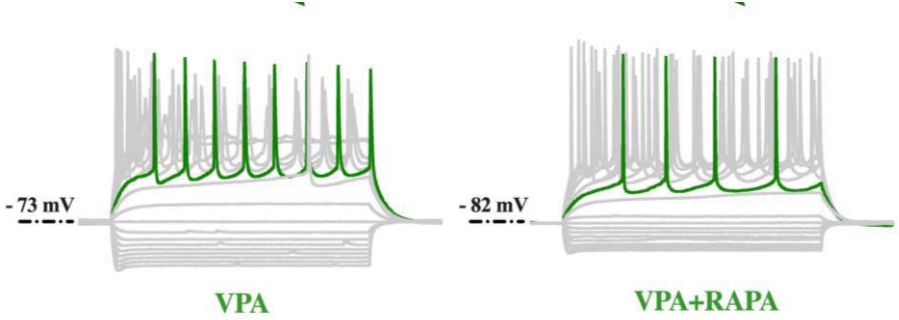

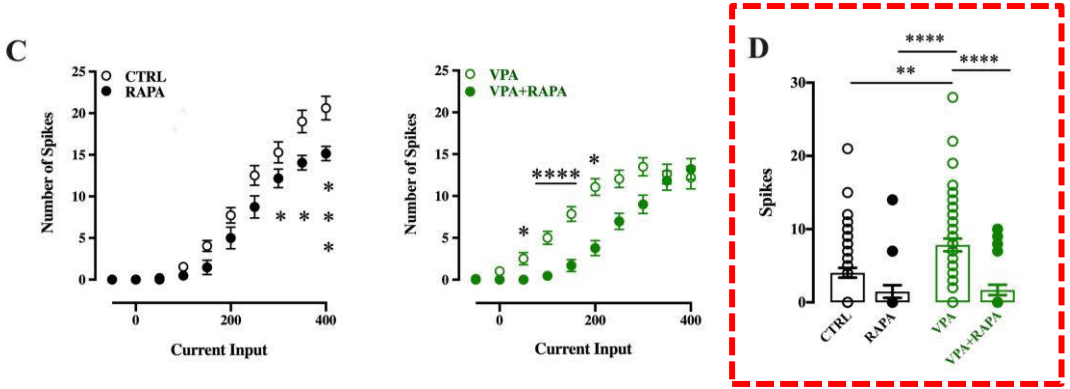

Trattamento acuto post-natale con rapamicina

Pharmacological Research 183 (2022) 106401

Contents lists available at ScienceDirect

Pharmacological Research

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

Acute rapamycin rescues the hyperexcitable phenotype of accumbal medium spiny neurons in the valproic acid rat model of autism spectrum disorder

D. Iezzi [a,b,1], L. Curti [a,1], G. Ranieri [a], E. Gerace [a], A. Costa [e], A. Ilari [a], A. La Rocca [a], C. Luceri [a], M. D'Ambrosio [a], L. Silvestri [c,d], M. Scardigli [c,d], G. Mannaioni [a,1], A. Masi [a,*,1]

Brain & Development 41 (2019) 1–10

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Everolimus for epilepsy and autism spectrum disorder in tuberous sclerosis complex: EXIST-3 substudy in Japan

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Results: Overall, 35 Japanese patients were randomized to everolimus low-exposure (LE; n = 10), everolimus high-exposure (HE; n = 14), or placebo (n = 11). The response rate was 30.0% and 28.6% versus 0% with the everolimus LE and HE versus placebo arm, respectively. Similarly, the median percentage reduction in seizure frequency was 6.88% and 38.06% versus −6.67%. Stomatitis was the most frequently reported adverse event (everolimus LE, 100%; HE, 78.6%; placebo, 9.1%). Four of 11 patients with ASD in the everolimus arms and 1 of 8 patients with ASD in the placebo arm showed ≥5 point decrease in PARS scores.

Conclusions: Adjunctive everolimus treatment improved seizure frequency with a tolerable safety relative to placebo among 35 Japanese patients with TSC-associated refractory seizures, consistent with the results of overall EXIST-3 study involving 366 patients. A favorable trend towards the improvement of ASD symptoms was observed.

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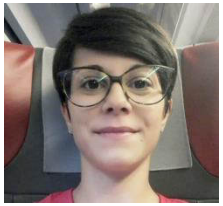
Conclusioni

1) Con il costante aumento delle diagnosi di DSA, i fattori di rischio ambientali meritano di essere valutati e studiati con attenzione

2) Le evidenze tossico-epidemiologiche forniscono un valido razionale per lo sviluppo di modelli preclinici con validità predittiva e costruttiva

Ringraziamenti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