L'importanza della via del reward nel modello sperimentale di autismo indotto da acido valproico

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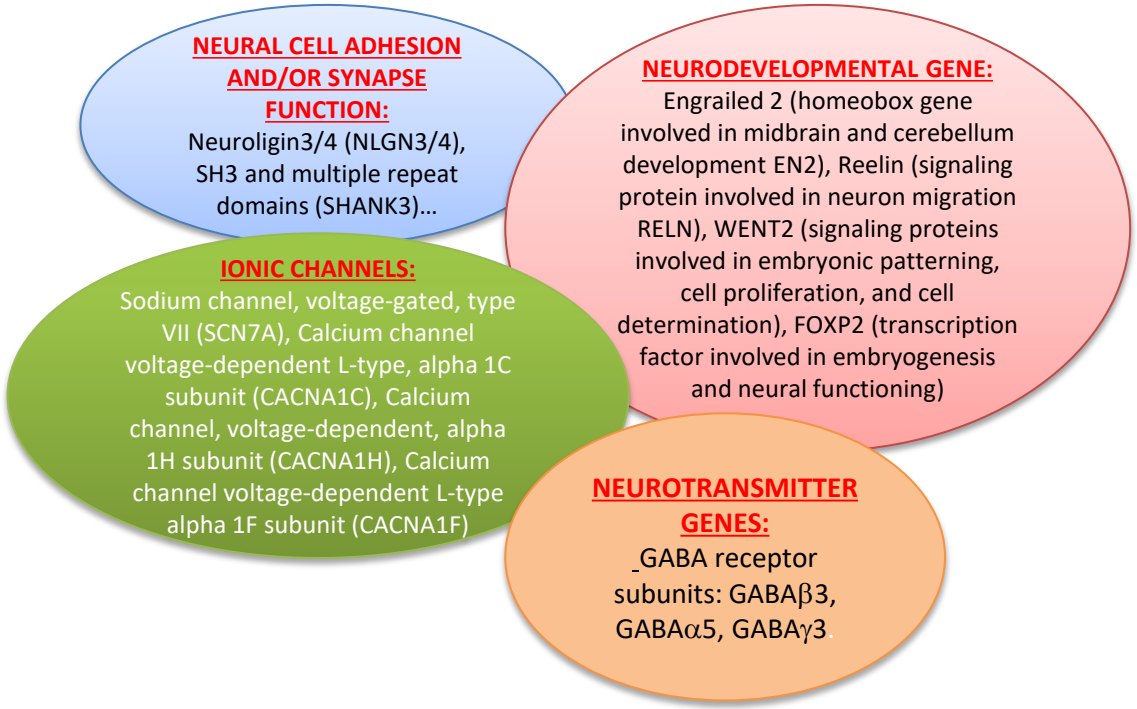
&

SOD Tossicologia Medica e Centro Antiveleni

Azienda Ospedaliero Universitaria Careggi

ETIOLOGY OF ASD

GENETIC FACTORS

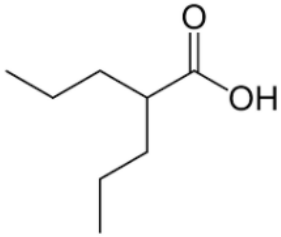


ENVIROMENTAL FACTORS

PRENATAL VIRAL INFECTION
ZINC DEFICIENCY
ABNOLMAL MELATONIN SYNTHESIS
MATERNAL DIABETES
PRENATAL AND PERINATAL STRESS
TOXINS (VALPROIC ACID)

Park et al., 2016

VALPROIC ACID (VPA)



- **Valproic acid is commonly used for the treatment of bipolar disorder and epilepsy;**

- **VPA is also a potent teratogen and prenatal exposure increases the risk of congenital malformations and neural tube defects, and more recently increased risk of autism (8,9% of the studied children exposed to VPA developed either autism or Asperger's syndrome)[*Roullent and Foster 2013*];**

- ***In utero* injection of VPA during neural tube closure in rats and mice results in progeny that model some of the neurodevelopmental changes found in humans. There is an increase in autistic like behaviors (repetitive behaviors, reduced social interaction and hypersensitivity) [*Trezza et al., 2014*];**

- **VPA is also an histone deacetylase (HDAC) inhibitor [*Gottlicher et al., 2001; Servadio et al., 2018*].**

TOPIC AIMS

1. Illustrate the data of the Teratology Information Service (TIS) of AOUC in Firenze. Just numbers but they can underline the problem!

2. 

Pavăl, 2017

STUDY THE POSSIBLE CONSEQUENCE OF VPA PRENATAL EXPOSURE ON REWARD SYSTEM

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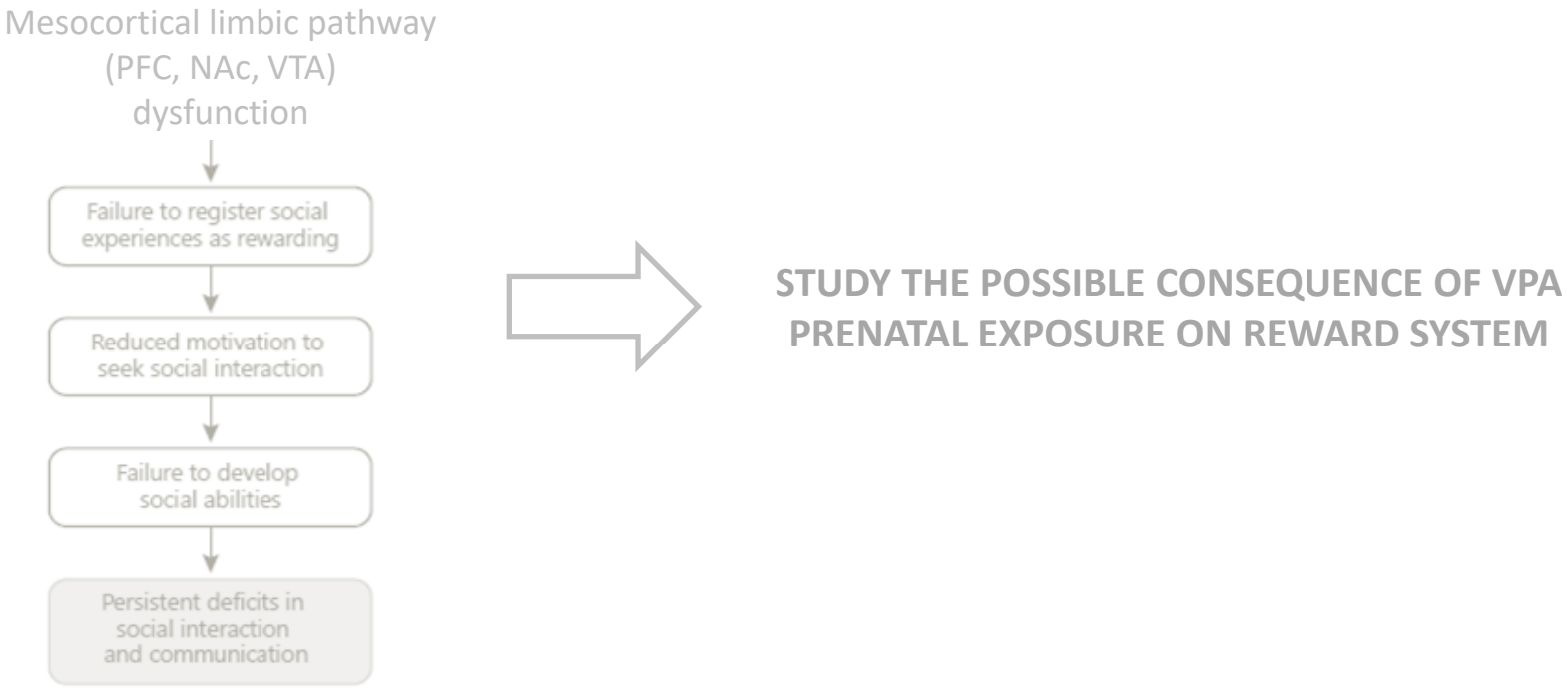
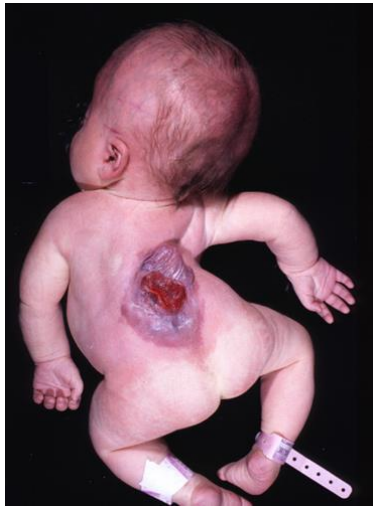
2. 

Pavăl, 2017

U.S Food and Drug Administration

Information for Healthcare Professionals: Risk of Neural Tube Birth Defects following prenatal exposure to Valproate (**December 3, 2009**)

The FDA is reminding health care professionals about **the increased risk of neural tube defects and other major birth defects**, such as craniofacial defects and cardiovascular malformations, in babies exposed to valproate sodium and related products during pregnancy



The benefits and the risks of valproate sodium and related products should be carefully weighed when prescribing these drugs to women of childbearing age, particularly for conditions not usually associated with permanent injury or death

If the use of valproate is not essential, alternative medications that have a lower risk to the fetus of birth defects and adverse cognitive effects should be considered in pregnant women and women of childbearing age. If the decision is made to use valproate in women of childbearing age, effective birth control should be used

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Valproate and related substances

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CURRENT STATUS:
European Commission final decision

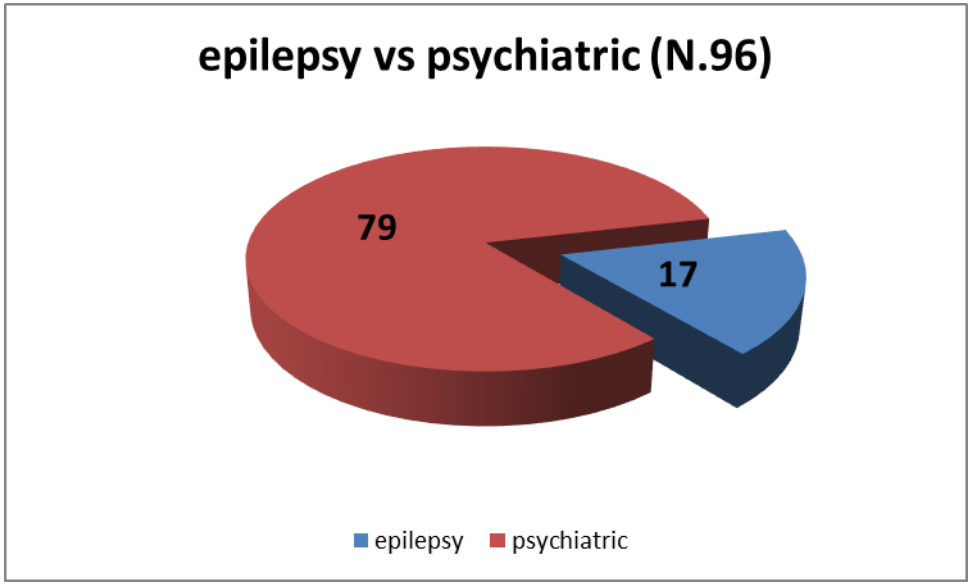
Procedure started → Under evaluation → PRAC recommendation → CMDh position → European Commission final decision

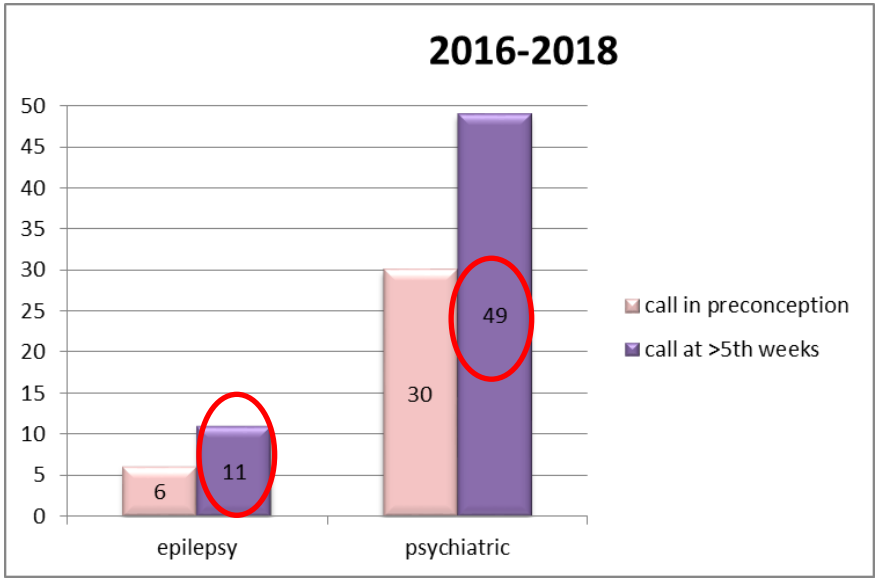
- On 21 March 2018 the European Commission endorsed **new measures** to avoid exposure of babies to valproate medicines in the womb, because exposed babies are at high risk of malformations and developmental problems.

- The new measures include a **BAN** on the use of such medicines for migraine or bipolar disorder during pregnancy, and a **BAN** on treating epilepsy during pregnancy unless there is no other effective treatment available.

- Further, the medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention program are met.

data of the Teratology Information Service (TIS) of AOUC in Firenze (2016-2018)





TOPIC AIMS

1. Illustrate the data of the Teratology Information Service (TIS) of AOUC in Firenze. Just numbers but they can underline the problem!

2.

Mesocortical limbic pathway (PFC, NAc, VTA) dysfunction

- Failure to register social experiences as rewarding
- Reduced motivation to seek social interaction
- Failure to develop social abilities
- Persistent deficits in social interaction and communication

Pavăl, 2017

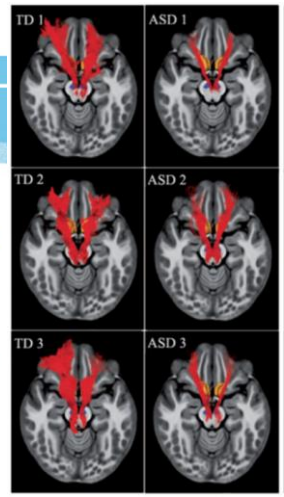
STUDY THE POSSIBLE CONSEQUENCE OF VPA PRENATAL EXPOSURE ON REWARD SYSTEM

doi:10.1093/brain/awy191 BRAIN 2018: 141; 2795–2805 | 2795

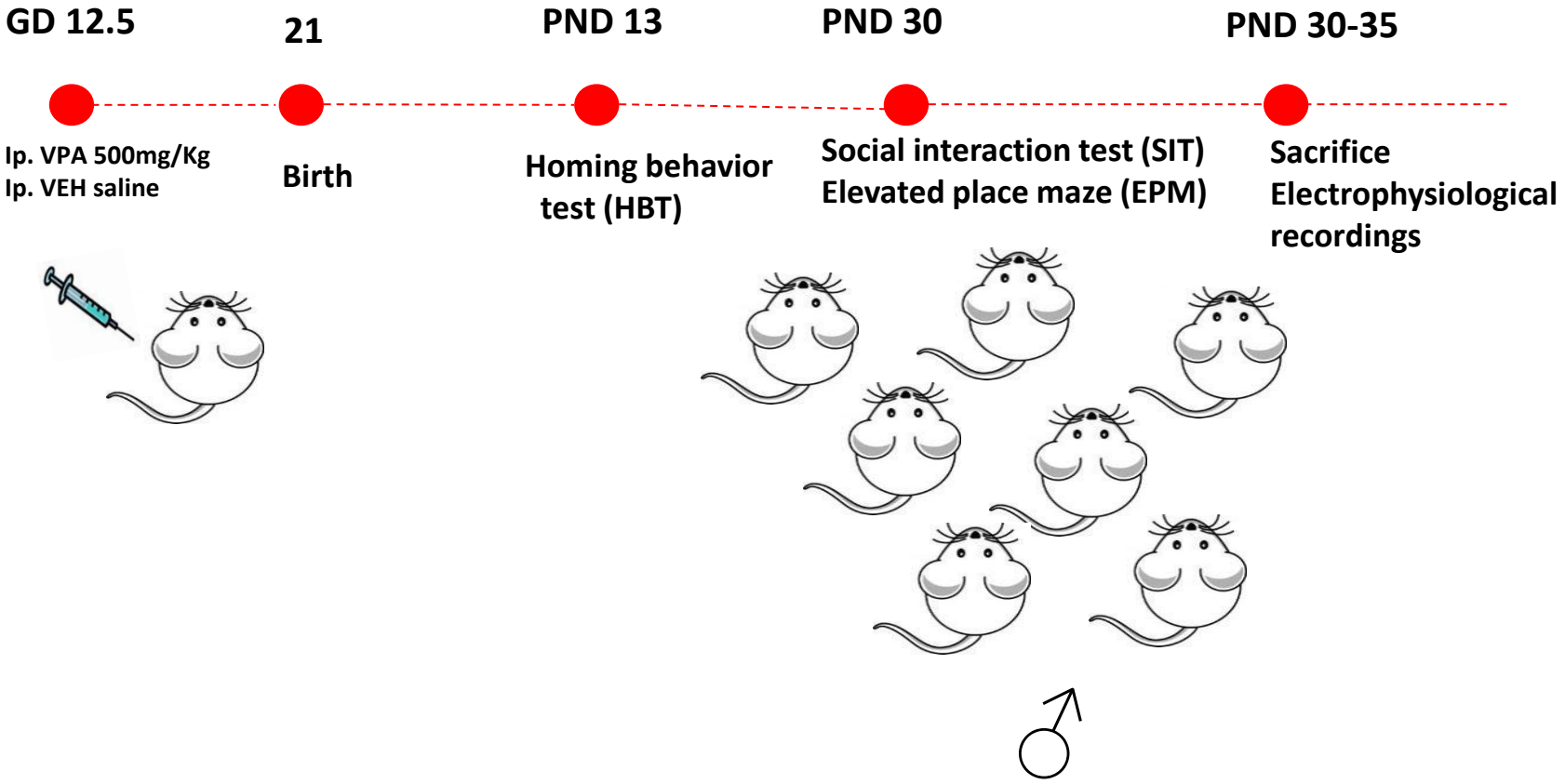
BRAIN
A JOURNAL OF NEUROLOGY

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

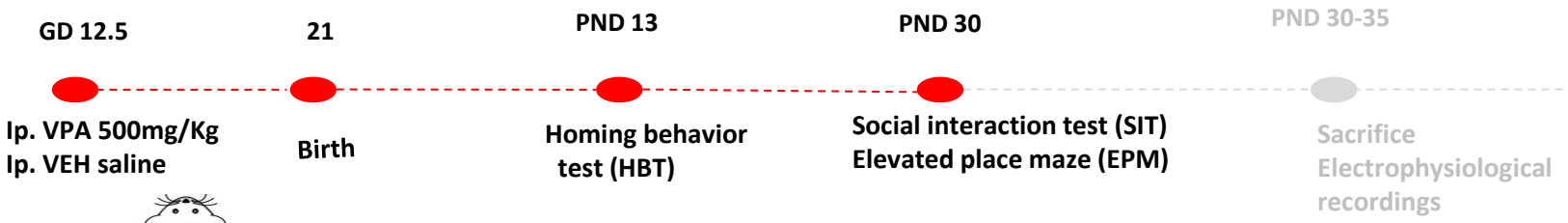
Kaustubh Supekar,[1,*] John Kochalka,[1,*] Marie Schaer,[1,2] Holly Wakeman,[1] Shaozheng Qin,[1,3] Aarthi Padmanabhan[1] and Vinod Menon[1,4,5]

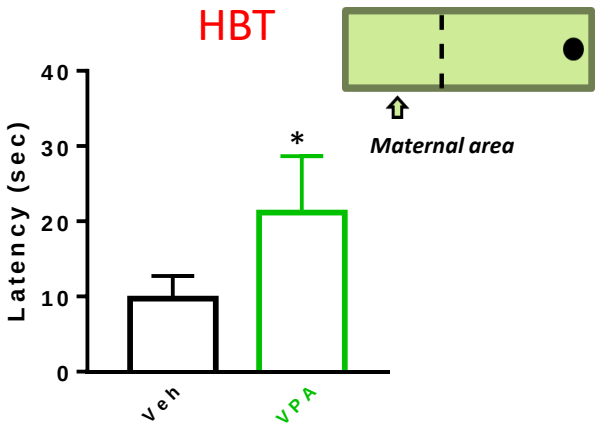


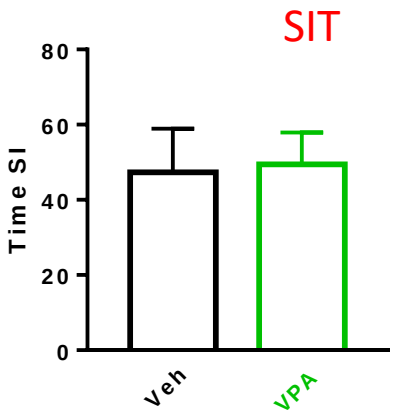
MATERIALS AND METHODS

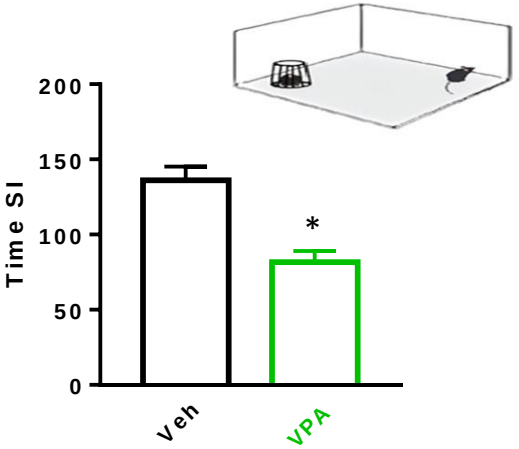


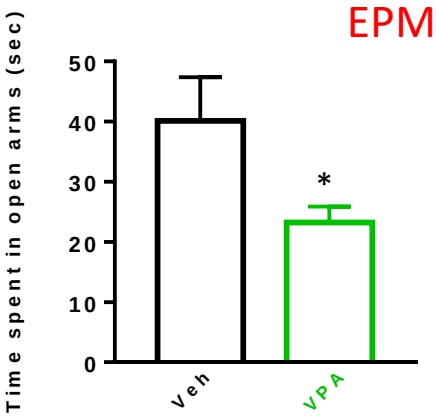
BEHAVIORAL PHENOTYPING OF VPA-TREATED RATS

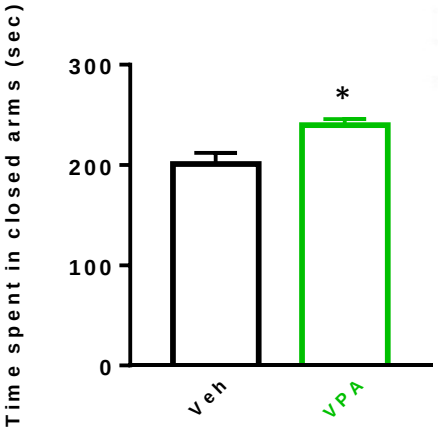


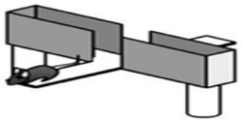






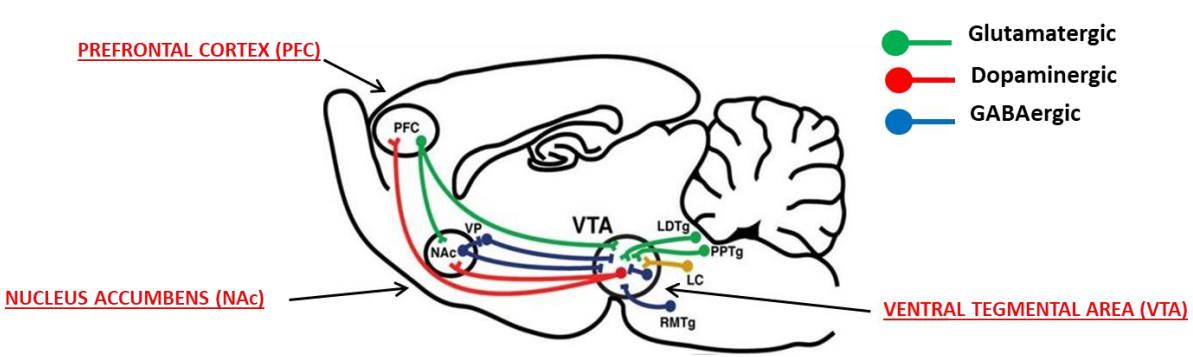


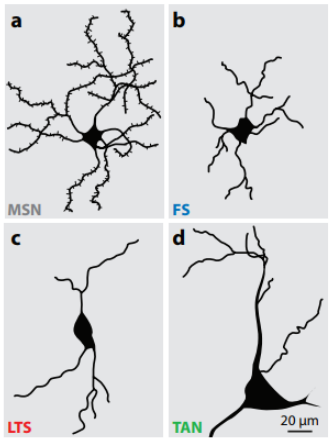




PRENATAL VPA EXPOSURE REDUCES MATERNAL ATTACHMENT, SOCIAL INTERACTION BEHAVIOR AND INDUCES ANXIOUS-LIKE PHENOTYPE IN ADOLESCENT RATS.

VENTRAL STRIATUM (NUCLEUS ACCUMBENS)



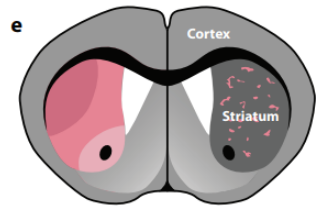


SPINY PROJECTION NEURON

(GABAergic Interneurons)

MEDIUM SPINY NEURON (MSN)>95 %

Large and extensive dendritic trees



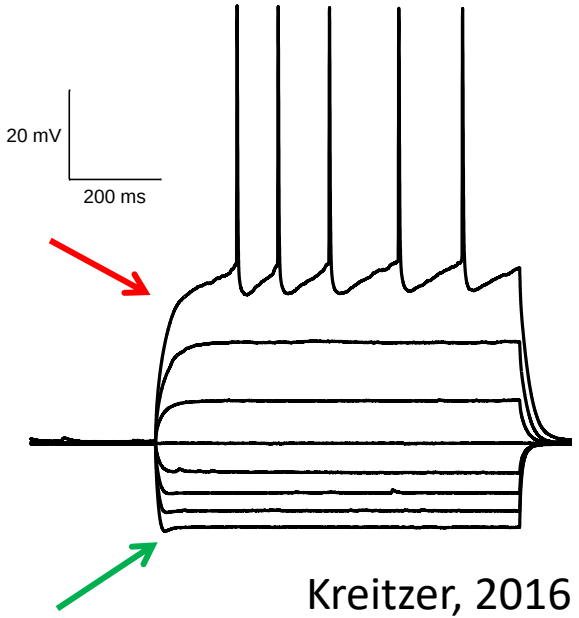
Hyperpolarized resting membrane potential (-80/-90 mV)

Low input resistance

Different type potassium conduttance:

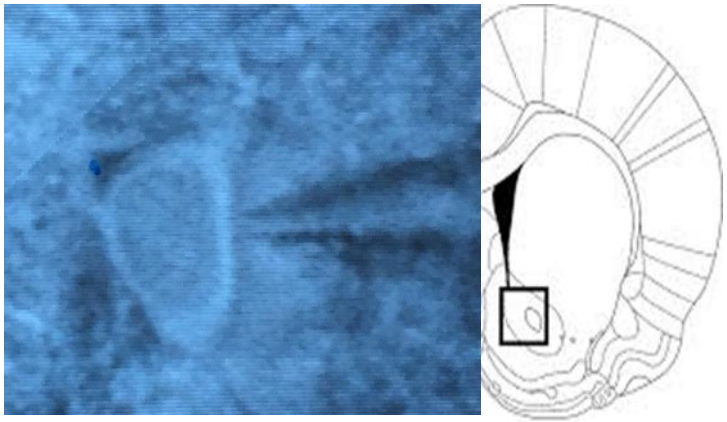
- **at rest, inwardly rectifying potassium channels (Kirs 2.1 and 2.3) that contribute to their negative resting potential and form the small voltage sag in responses to hyperpolarizing currents (green arrow)**
- **fast- (Kv4.2) and slow inactivating (Kv1.2) A-type potassium currents**

Slow depolarization and delay to the initial spike (red arrow).

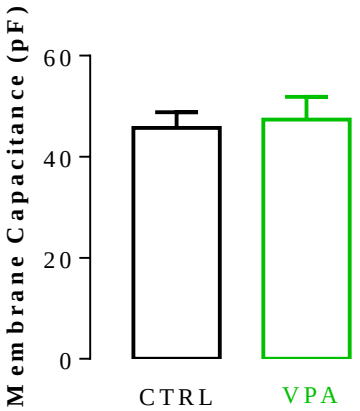


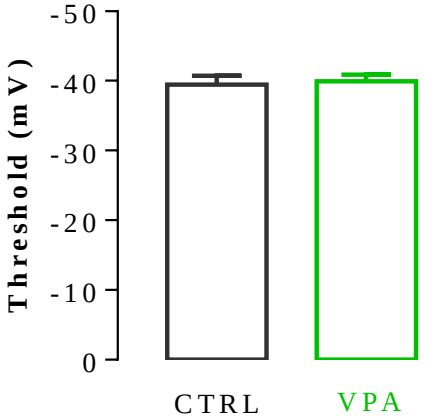
Kreitzer, 2016

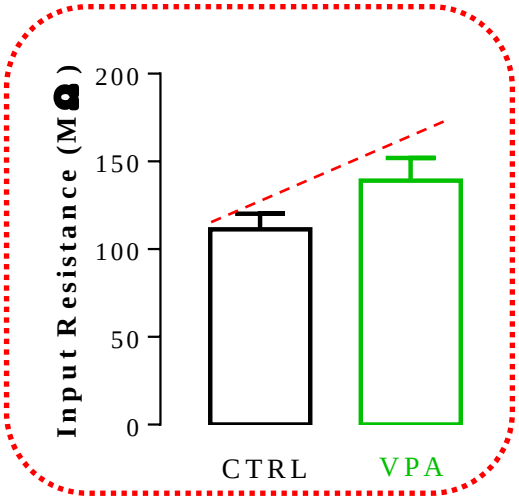
MEMBRANE PROPERTIES OF NAc-MSNs

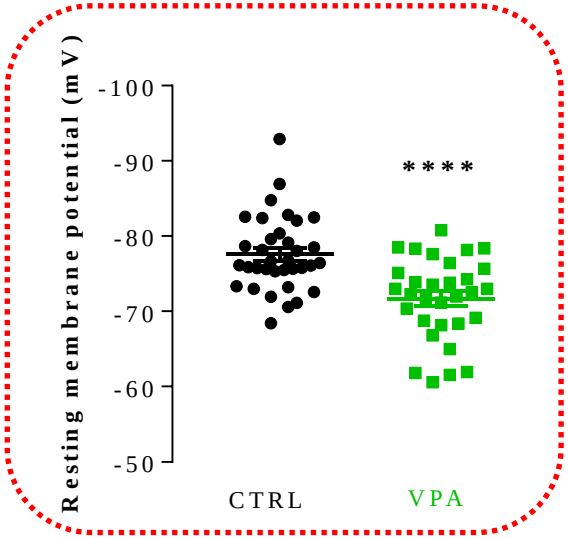


Coronal brain slices (300µm)



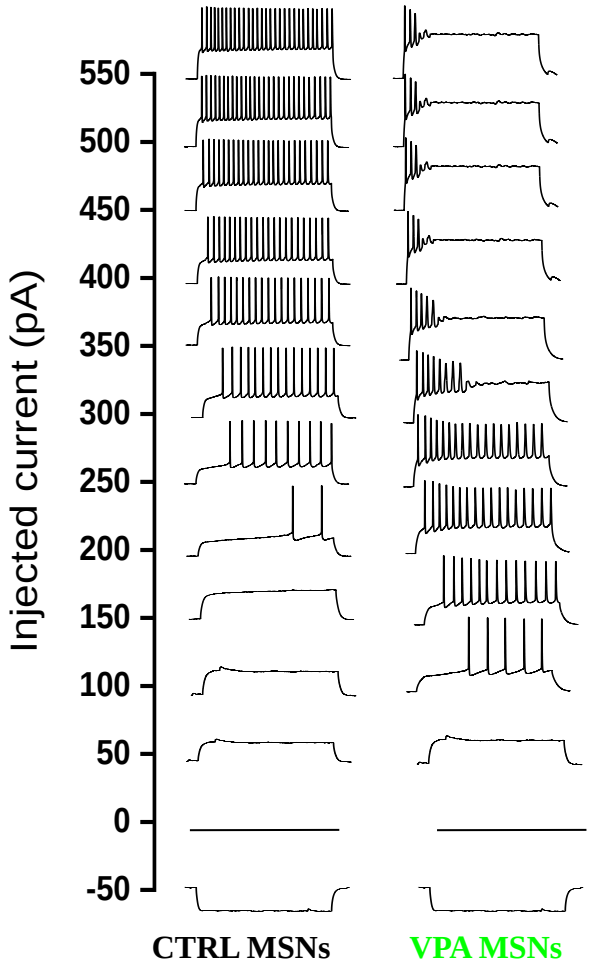


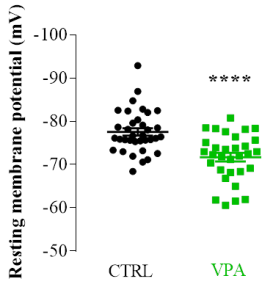


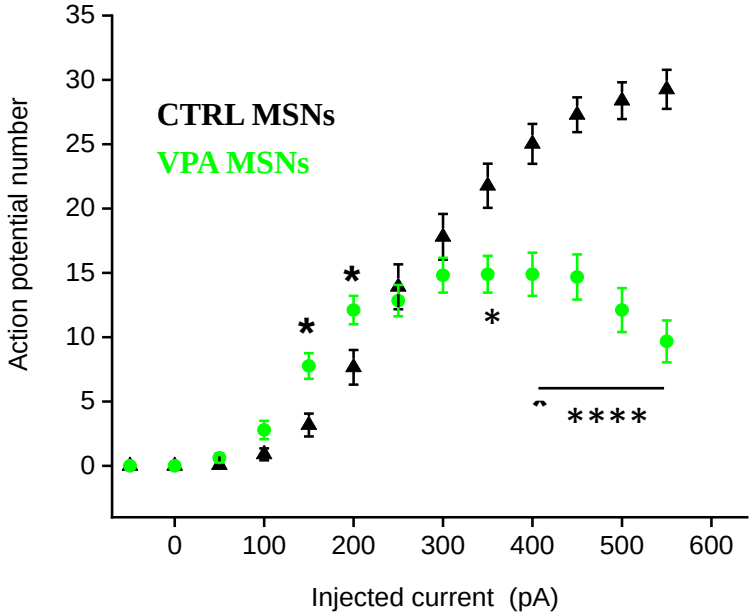


Iezzi, Schiavi et al., Front Cell Neurosci. 2019

INTRINSIC EXCITABILITY OF NAc-MSNs







Iezzi, Schiavi et al., Front Cell Neurosci. 2019

INWARDLY RECTIFYING POTASSIUM (K_{IR}) CHANNEL

KIR 2.1 ARE MOST PROMINENT IN **SOMATODENDRITIC** COMPARTMENT OF ACCUMBAL **MEDIUM SPINY NEURONS**

Püss et al., 2003

Life Sciences 213 (2018) 183–189

Contents lists available at ScienceDirect

Life Sciences

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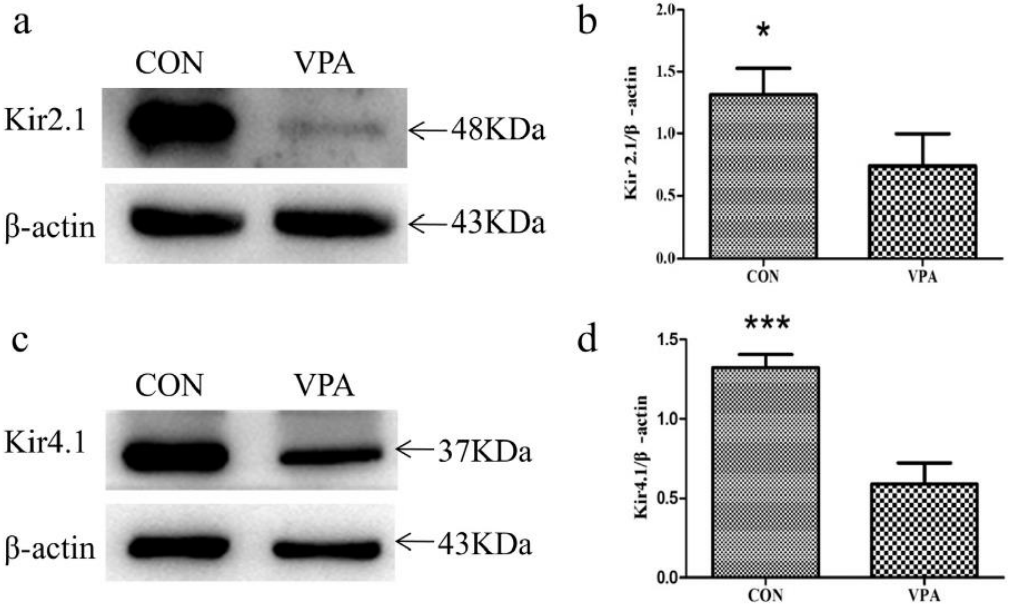
Association study between inwardly rectifying potassium channels 2.1 and 4.1 and autism spectrum disorders

Caihong Sun[a,1], Mingyang Zou[a,1], Ling Li[a], Dexin Li[a], Yongjuan Ma[a], Wei Xia[a], Lijie Wu[a,*], Huan Ren[b,*]

[a] Department of Children's and Adolescent Health, Public Health College, Harbin Medical University, Harbin 150081, China
[b] Department of Immunology, Harbin Medical University, Harbin 150081, China



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Püss et al., 2003

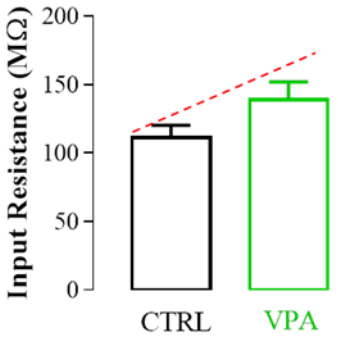
OPEN ACCESS Freely available online

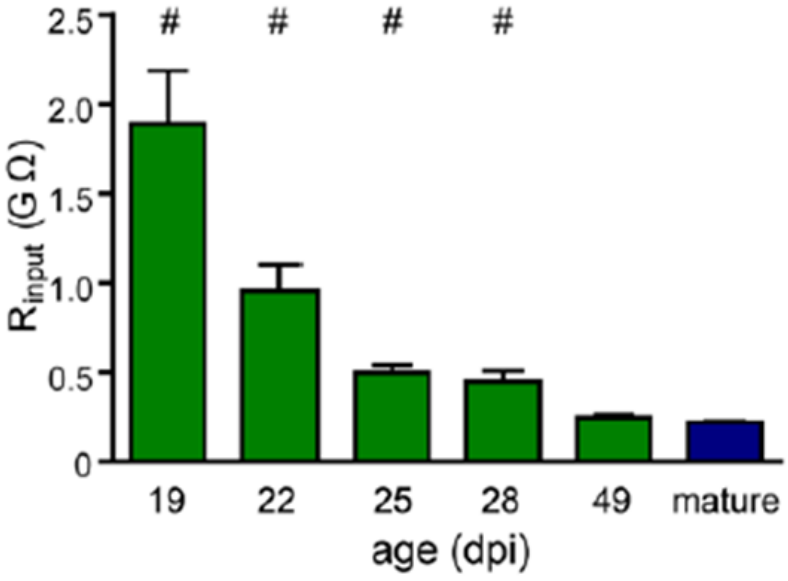
PLoS one

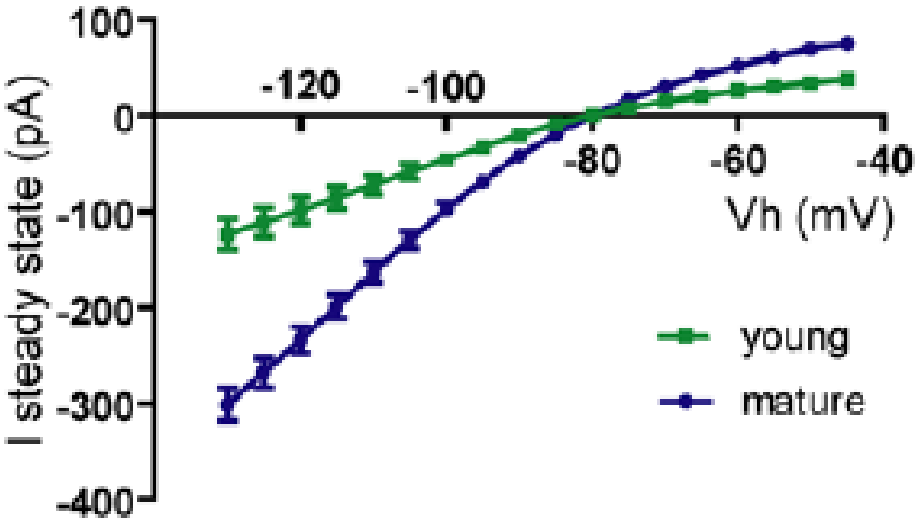
Reliable Activation of Immature Neurons in the Adult Hippocampus

Lucas A. Mongiat, M. Soledad Espósito, Gabriela Lombardi, Alejandro F. Schinder*

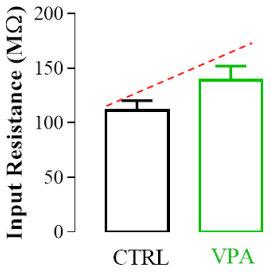
Laboratory of Neuronal Plasticity, Leloir Institute – CONICET, Buenos Aires, Argentina







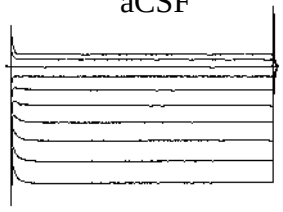
I_{kir} IN NAc-MSNs



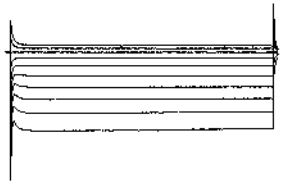
CTRL MSNs

VPA MSNs

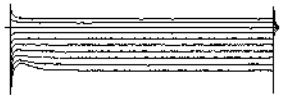
I_{aCSF}



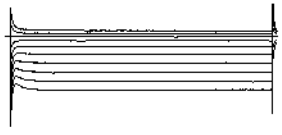
I_{aCSF}



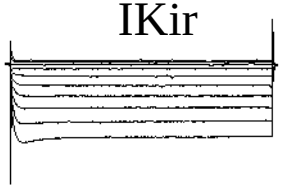
I_{Cs+}



I_{Cs+}



IKir



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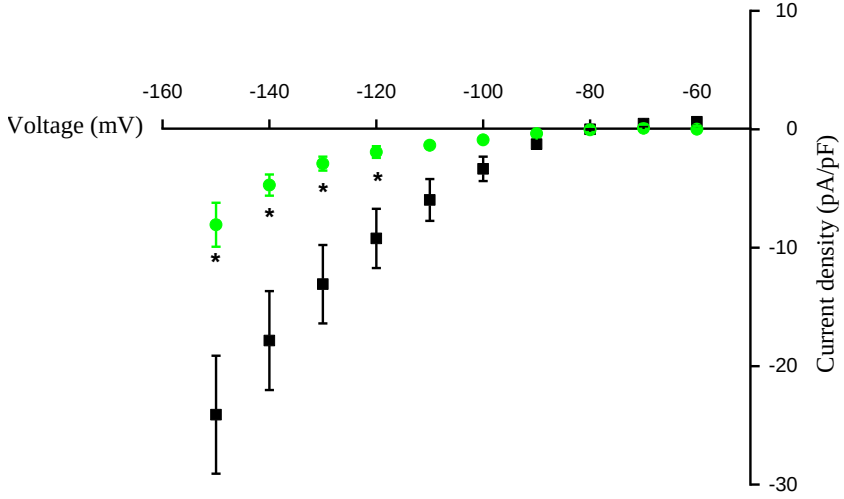
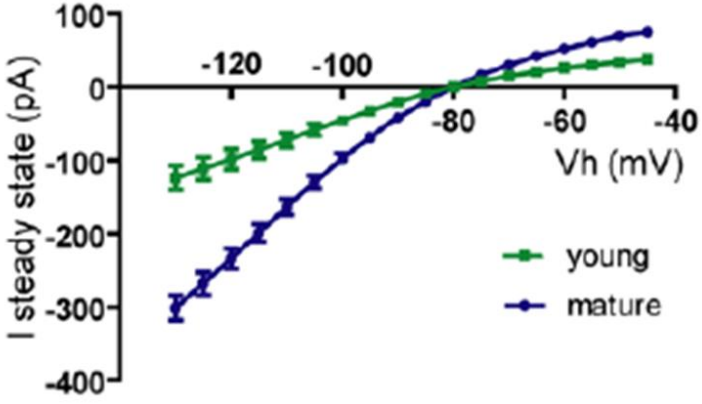
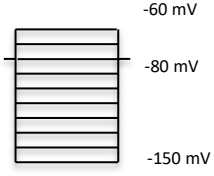


CTRL MSNs (MATURE)

VPA MSNs (YOUNG)





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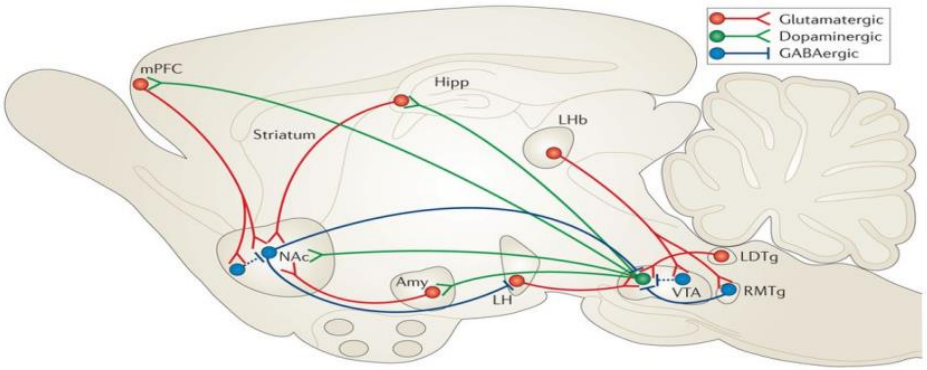
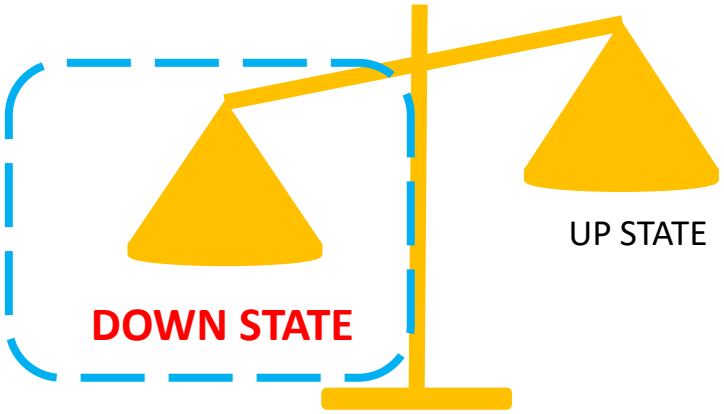
Striatal D2 receptors regulate dendritic morphology of medium spiny neurons via Kir2 channels

Maxime Cazorla[1,2], Mariya Shegda[1,2], Bhavani Ramesh[1,2], Neil L. Harrison[2,3], and Christoph Kellendonk[1,2]

GRAPHICAL HYPOTESIS OF VPA PRENATAL EXPOSURE EFFECTS



NAc-MSN



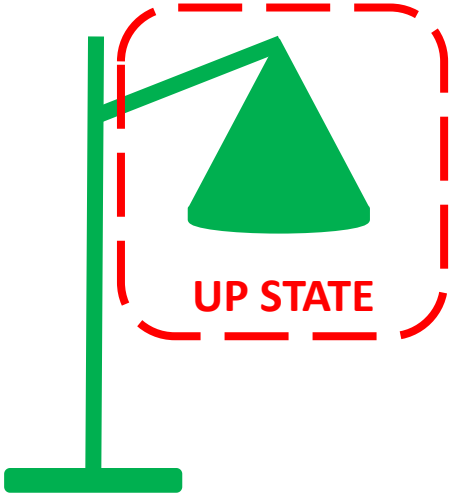
Hyperpolarizing RMP
Low Input Resistence

FILTER IRRELEVANT INPUTS

Depolarizing RMP
High Input Resistence

CORRECT BEHAVIORAL RESPONSE

VPA NAc-MSN



LOSE THE ABILITY TO DISCRIMINATE BETWEEN IRRELEVANT AND RELEVANT REWARD STIMULI

CONCLUSIONS

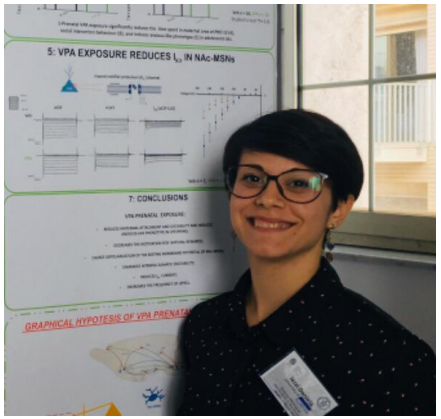
VPA PRENATAL EXPOSURE:

- **INDUCES ASD IN ANIMAL MODEL;**
- **DEPOLARIZES THE RESTING MEMBRANE POTENTIAL OF NAc-MSNs;**
- **ENHANCES INTRINSIC SOMATIC EXCITABILITY OF NAc-MSNs;**
- **REDUCES IK_{IR} IN NAc-MSNs.**

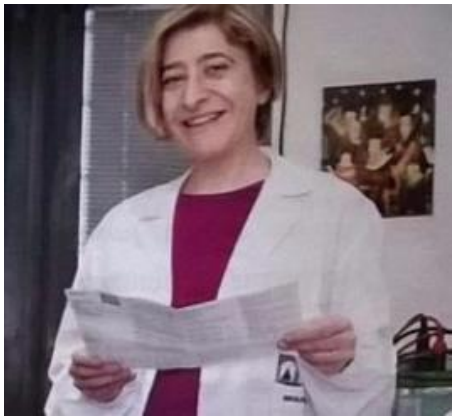
- **INVESTIGATE SYNAPTIC TRANSMISSION AND PLASTICITY IN NAc TO VERIFY IF VPA-PRENATAL EXPOSURE COULD LEAD TO CHANGE IN SYNAPTIC TRANSMISSION.**
- **TEST SMALL-MOLECULE MODULATORS OF Kir 2.1 CHANNELS TO UNDERSTAND THE THERAPEUTIC VALUE OF THESE CHANNELS IN THE TREATMENT OF ASD? Or GM1/NGF?**

MANY THANKS TO:

Alessio Masi



Daniela Iezzi



Viviana Trezza

Alessandra Pistelli

Ministero della Salute

Fondazione Umberto Veronesi
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