THE NEUROARCHEOLOGY OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS
Environment & genes in autism

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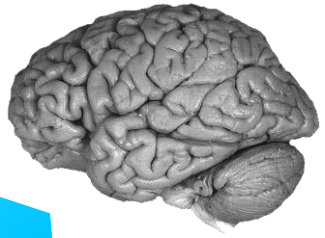
1

Brain development is associated with unique essential processes and activity

Genes and environment in brain construction

Genes

Environment



10 ^{15} synapses

Funtional neuronal assemblies

IV

Network Formation

III

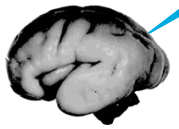
Synapse Formation

II

Migration

I

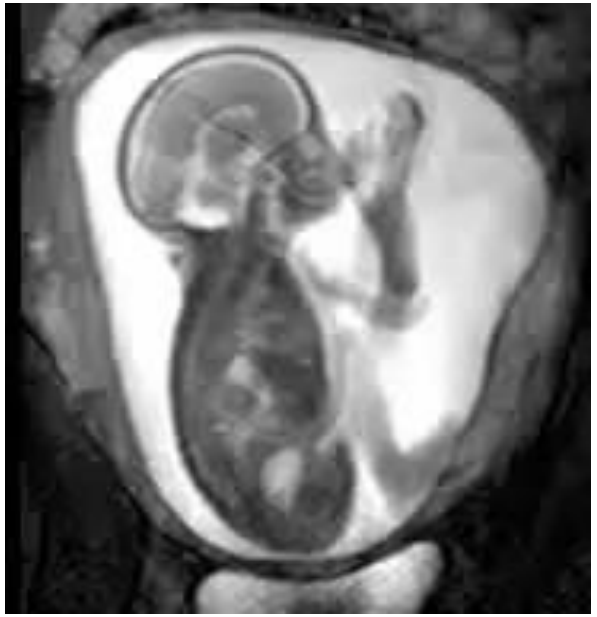
Proliferation

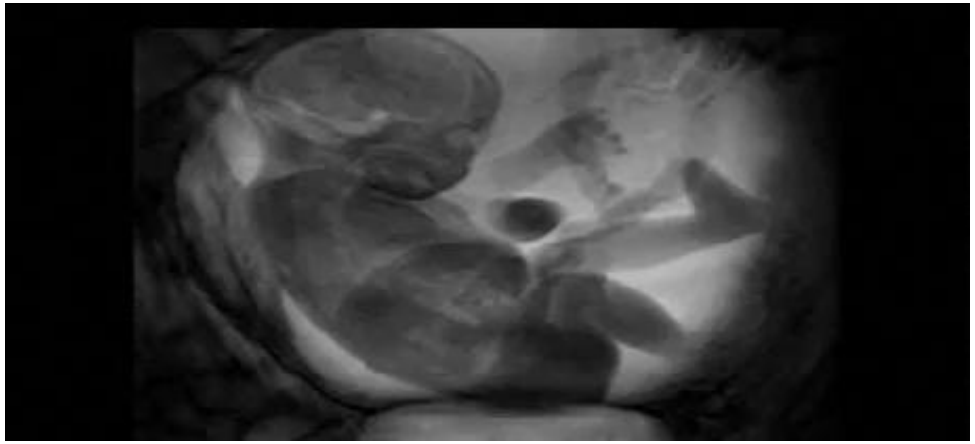


0 synapses

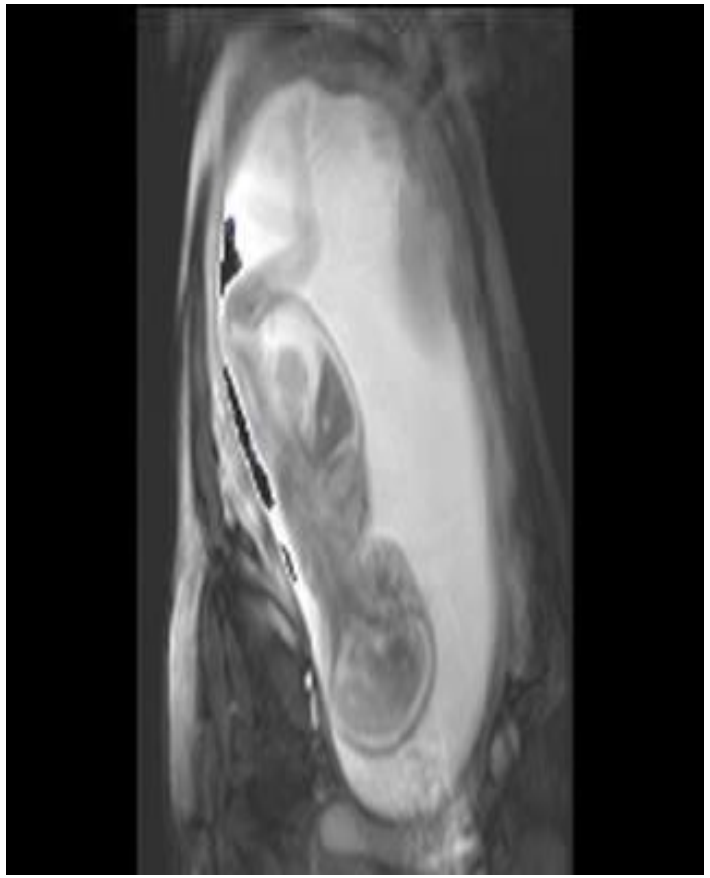
Genetic or Epigenetic Insults

A lot of movements

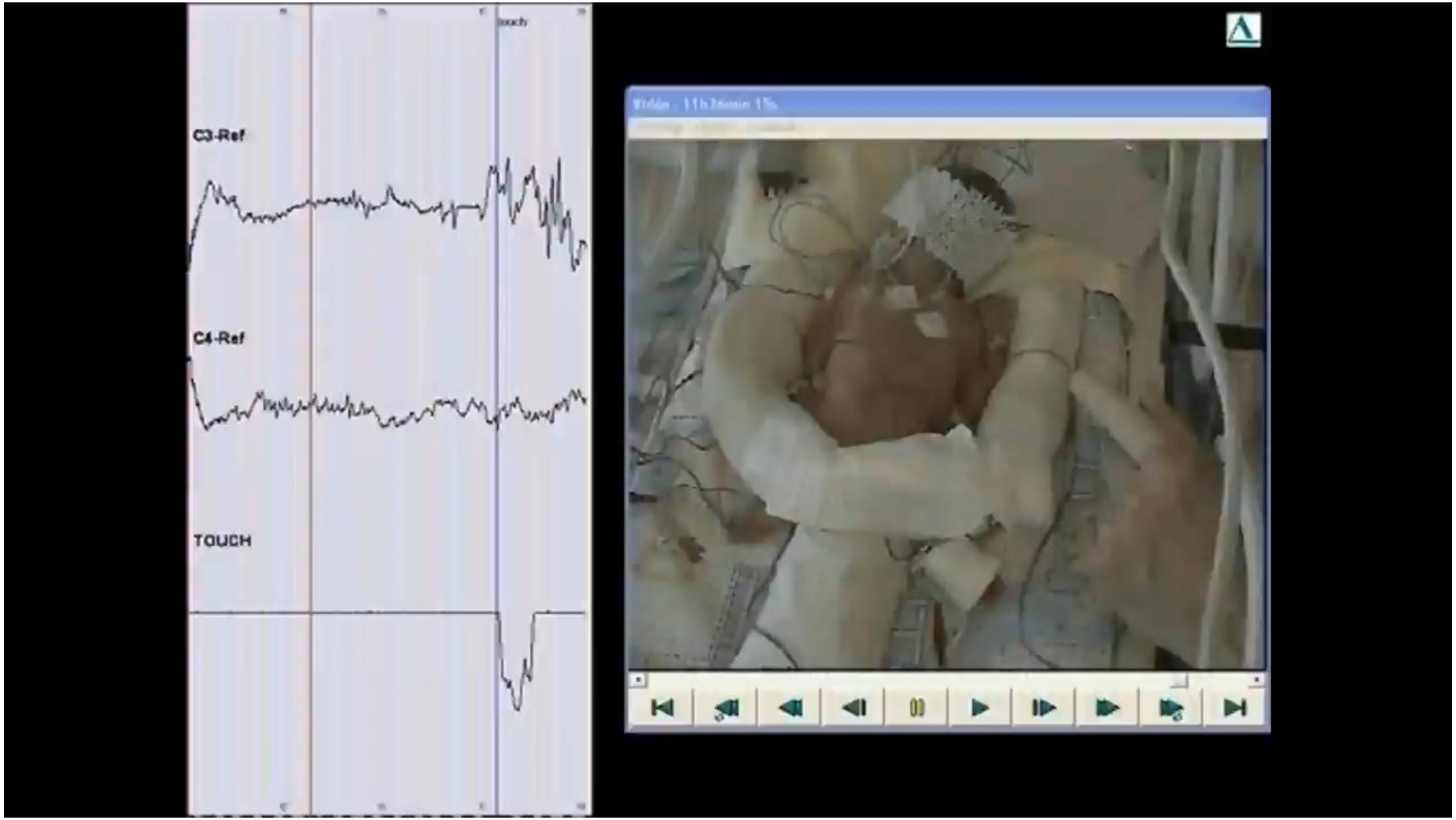




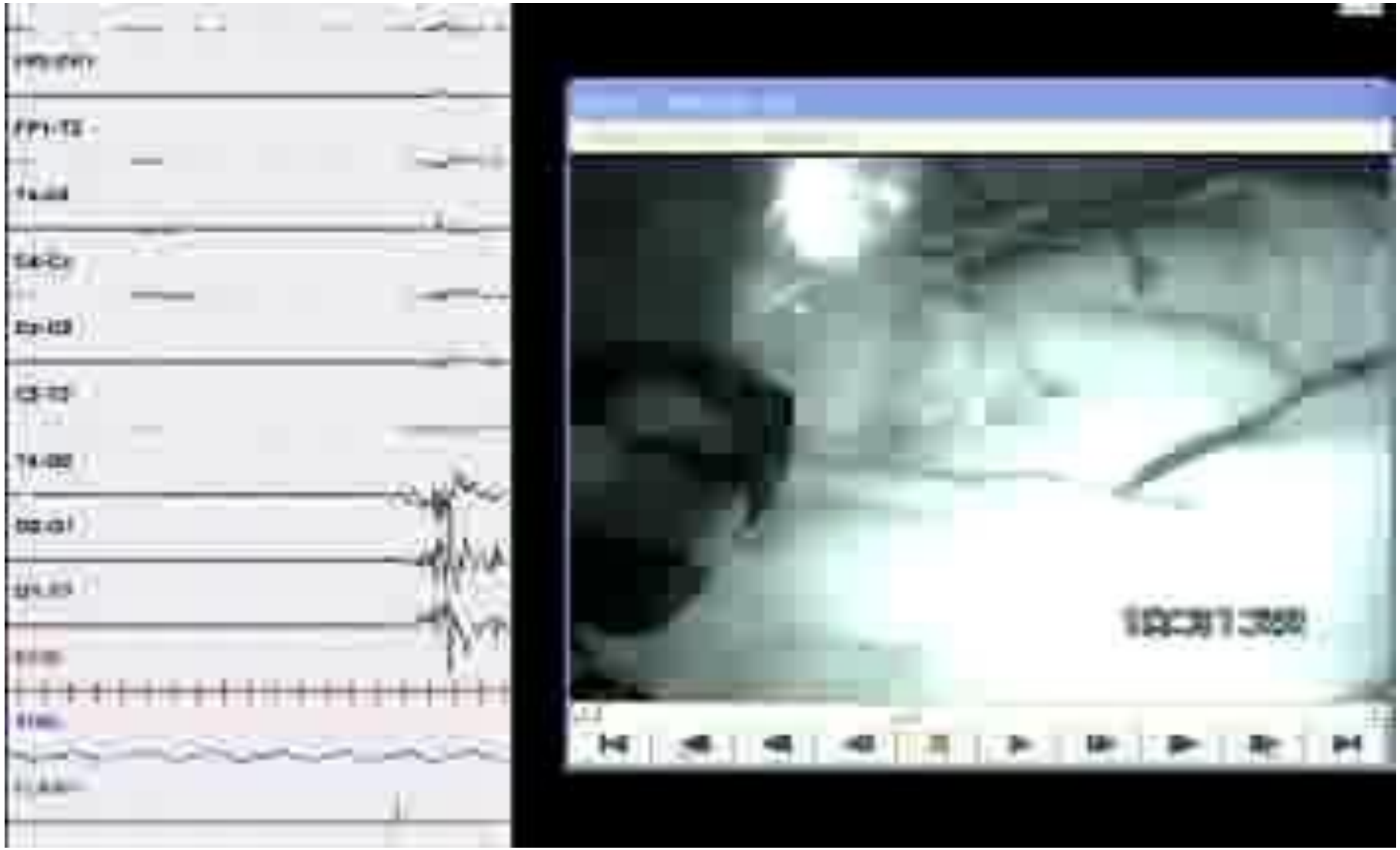
Dr. Daniela Prayer
(Medical University of Vienna)



Movements triggered by the periphery

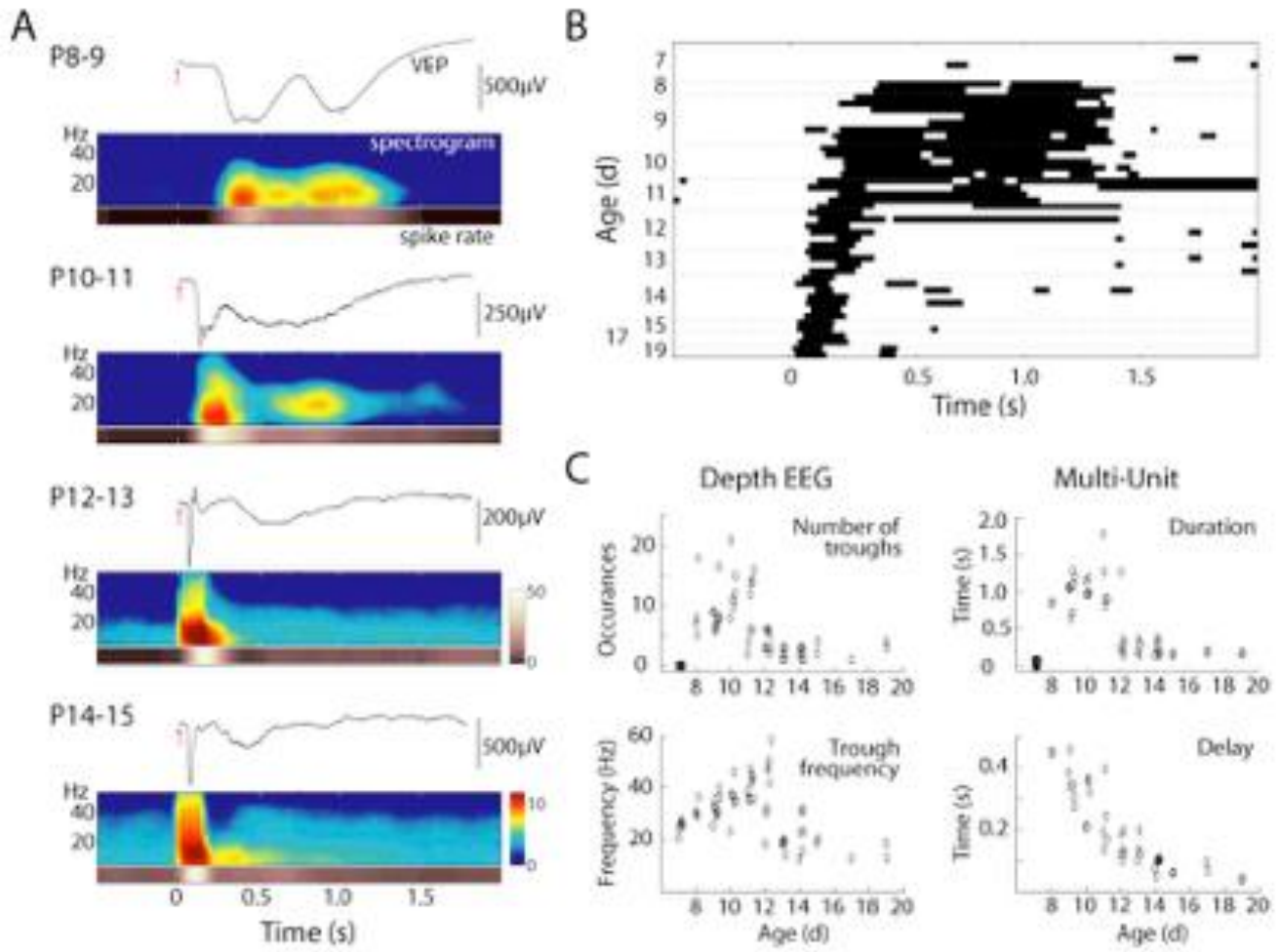


Retinal waves in preterm babies



Colonnese et al., Neuron, 2010; Colonnese and Khazipov, Neuroimage, 2012

Retinal waves shift progressively to adult responses in rodents

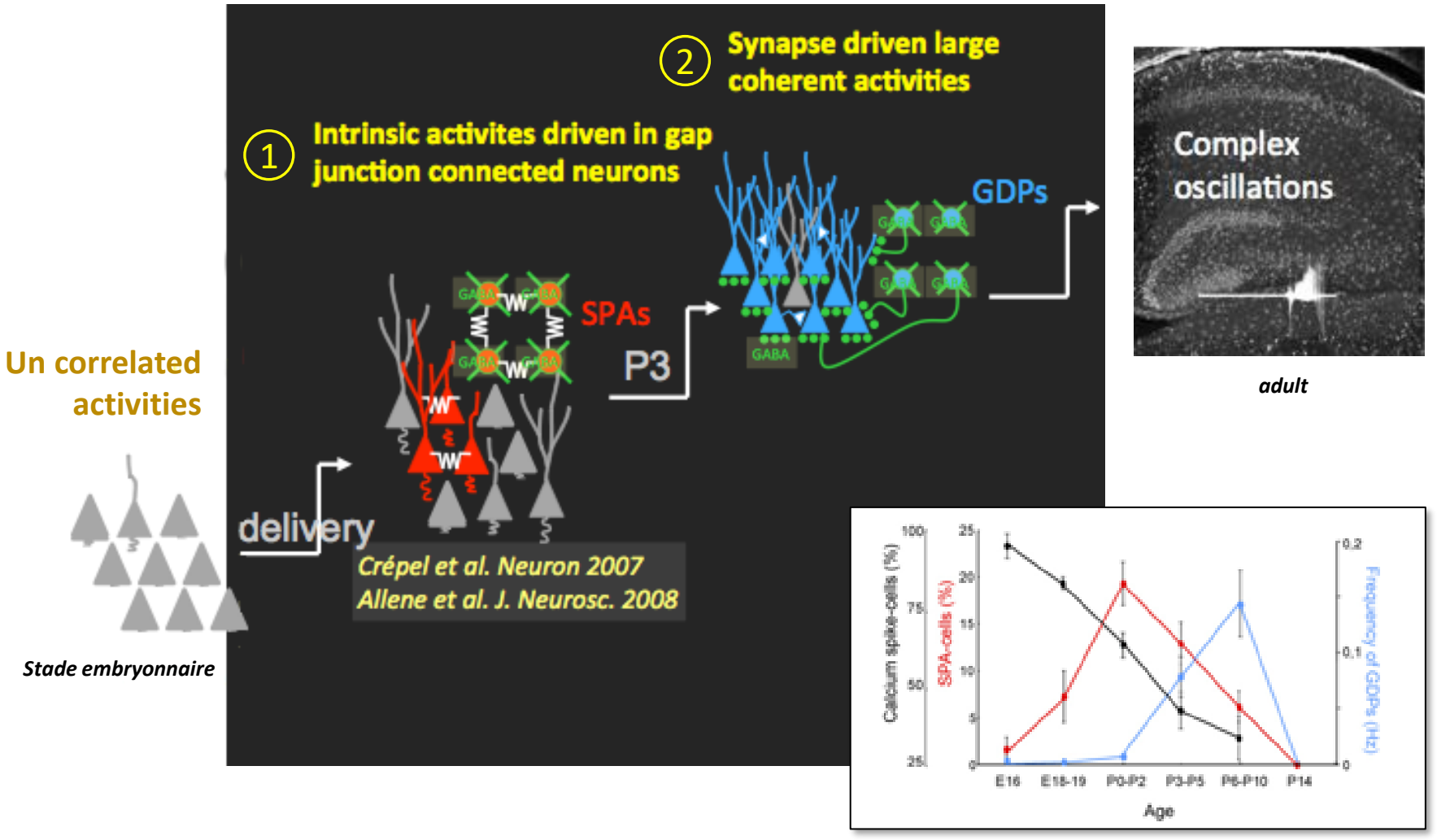


Colonnese et al., Neuron, 2010; Colonnese and Khazipov, Neuroimage, 2012

Therefore

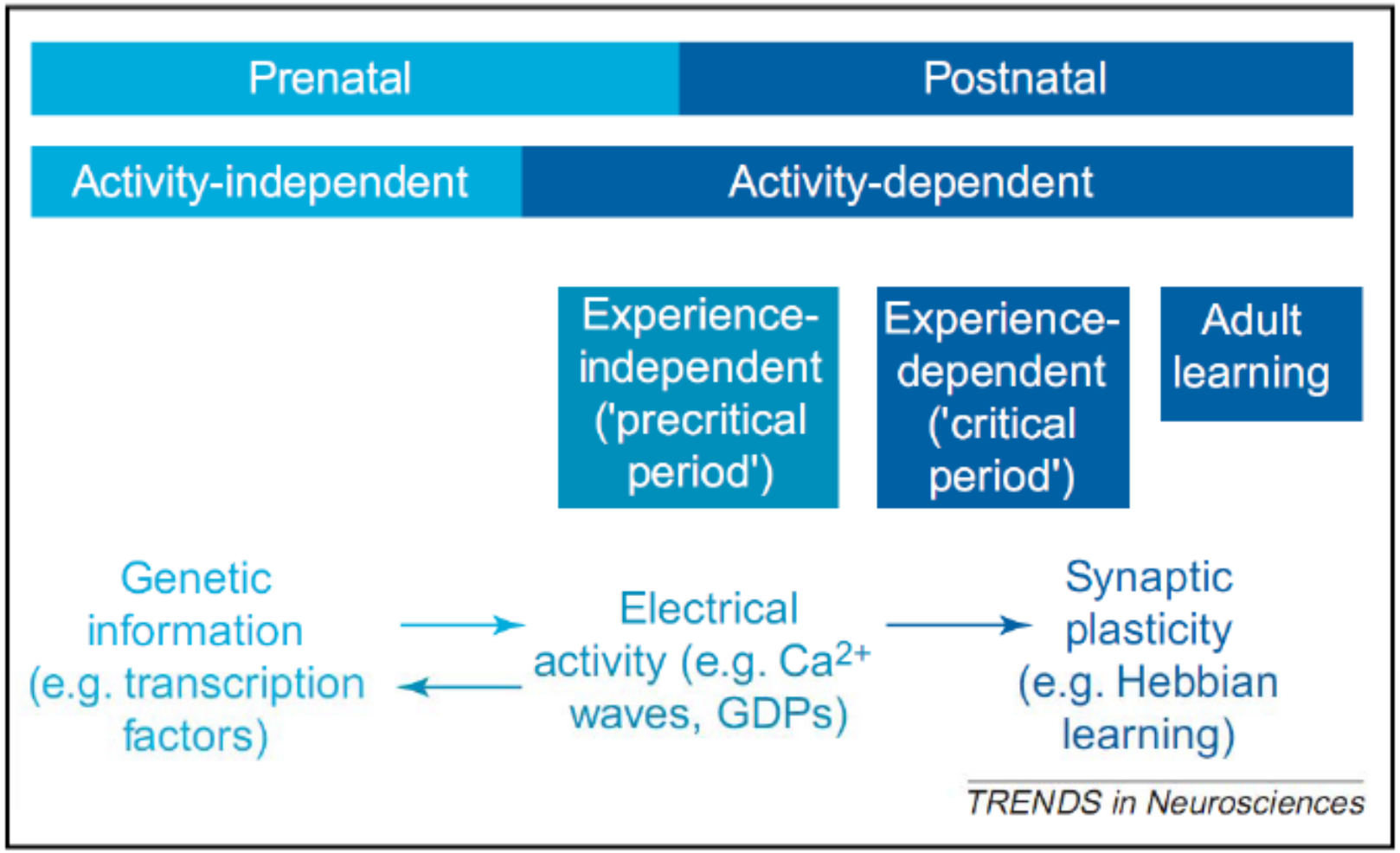
- The developing brain is not a small adult brain, it has its own patterns and properties
- These developmental sequences underlie the formation of correct neuronal ensembles

A triphasic sequence of brain patterns



Crepel et al Neuron 2007, Bonifazi et al Science 2009, Picardo et al Neuron 2011

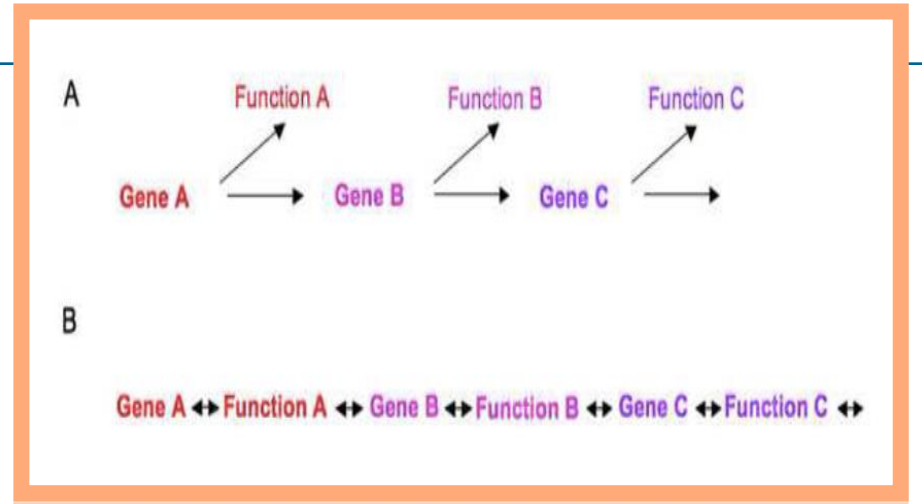
Genes and activity operate in series



2

The checkpoint and neuroarcheology concepts

The checkpoint concept



- Genes and activity operate in series not in parallel
- They play a different partition
- Ionic currents operate like a GPS providing the infos needed for correct connections

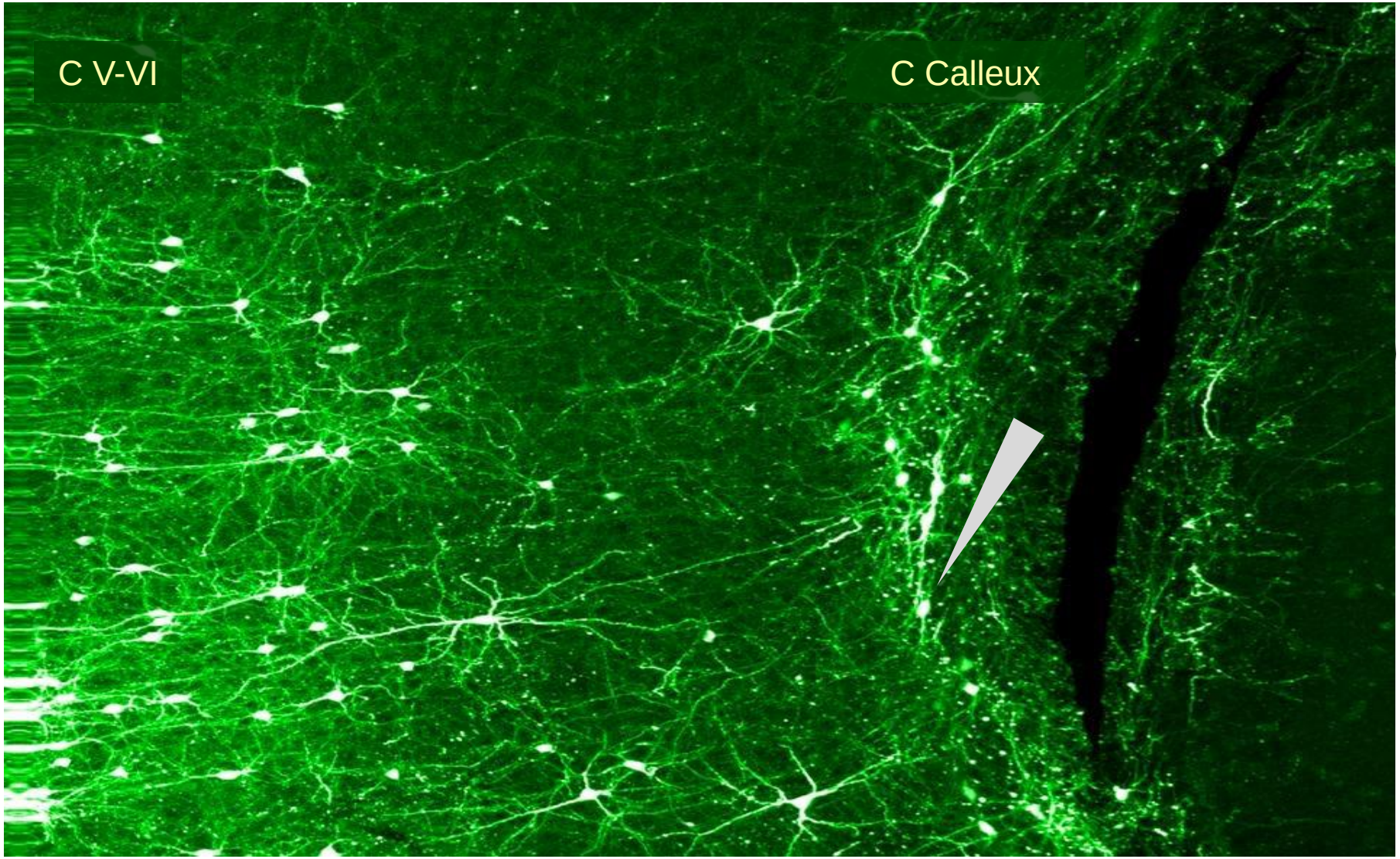
Neuroarcheology

- An in utero mutation will stop and deviate developmental sequences leading to immature currents/patterns in the adult brain that are the genuine direct cause of the disease
- Drugs that selectively block immature currents might provide novel therapeutic tools because they will act on "pathological" neurons
- Pathological conditions are a return to an "immature state"

IBEN

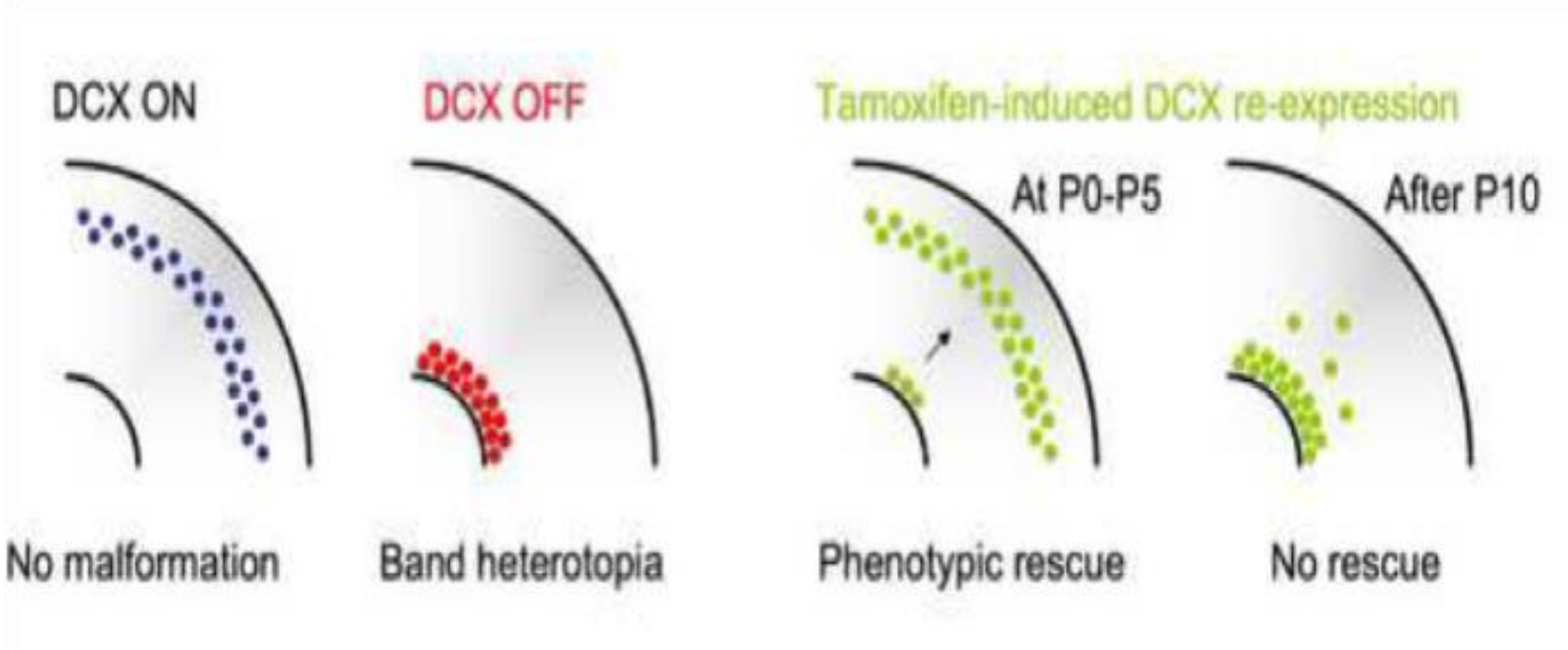
Ben-Ari,TINS, 2008; Ben-Ari, Nat Rev Neurosci, 2015; Ben-Ari, Neuroscience, 2015

Misplaced neurons are immature



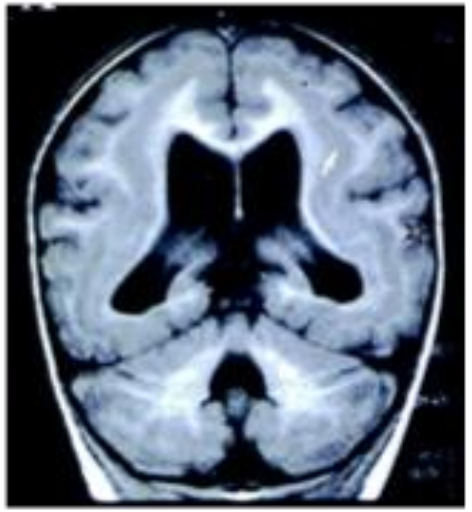
Ackmann et al J Neurosci. 2009

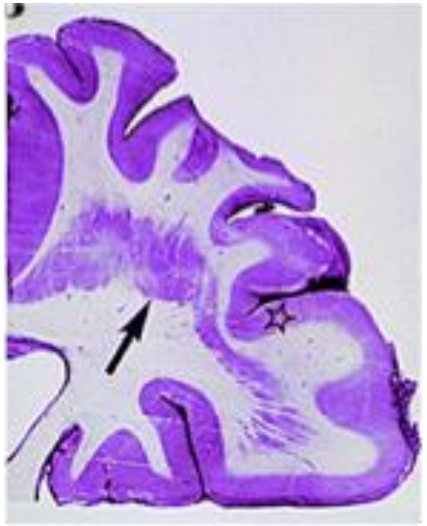
Gene therapy does not operate

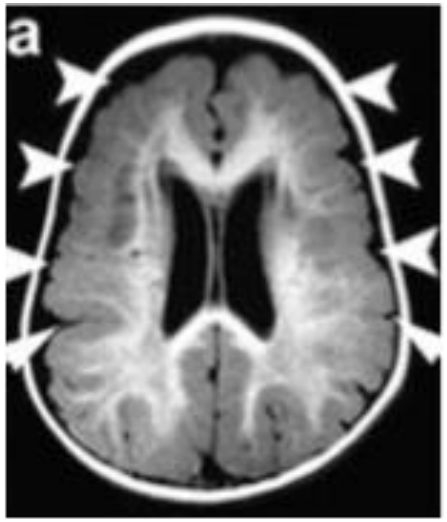


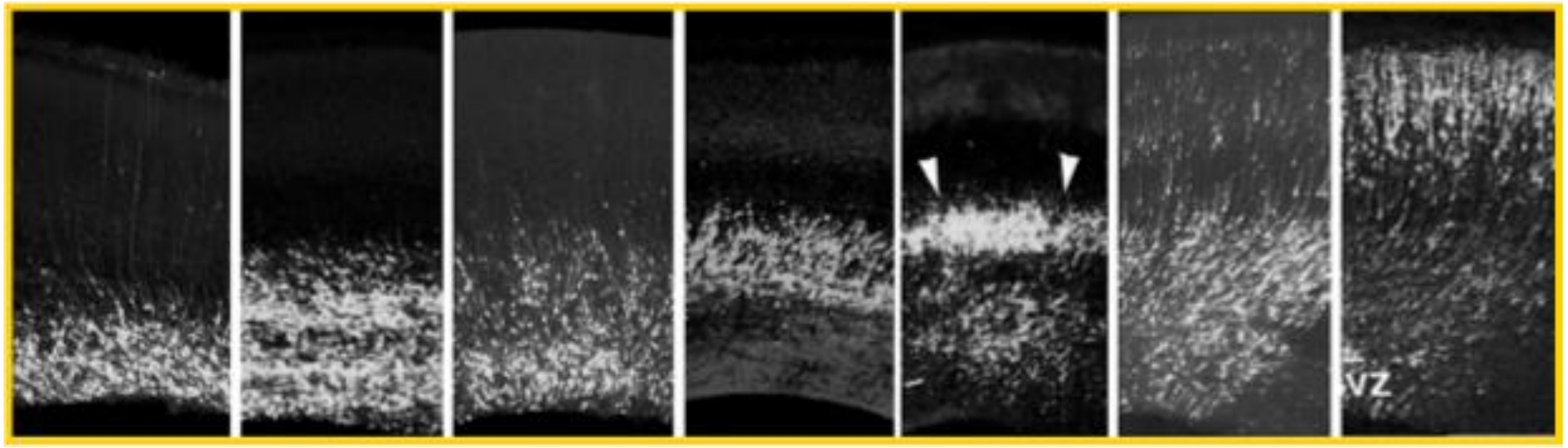
Manent, JJ LO Turco et al, Nature Meicine 2008

Migration disorders



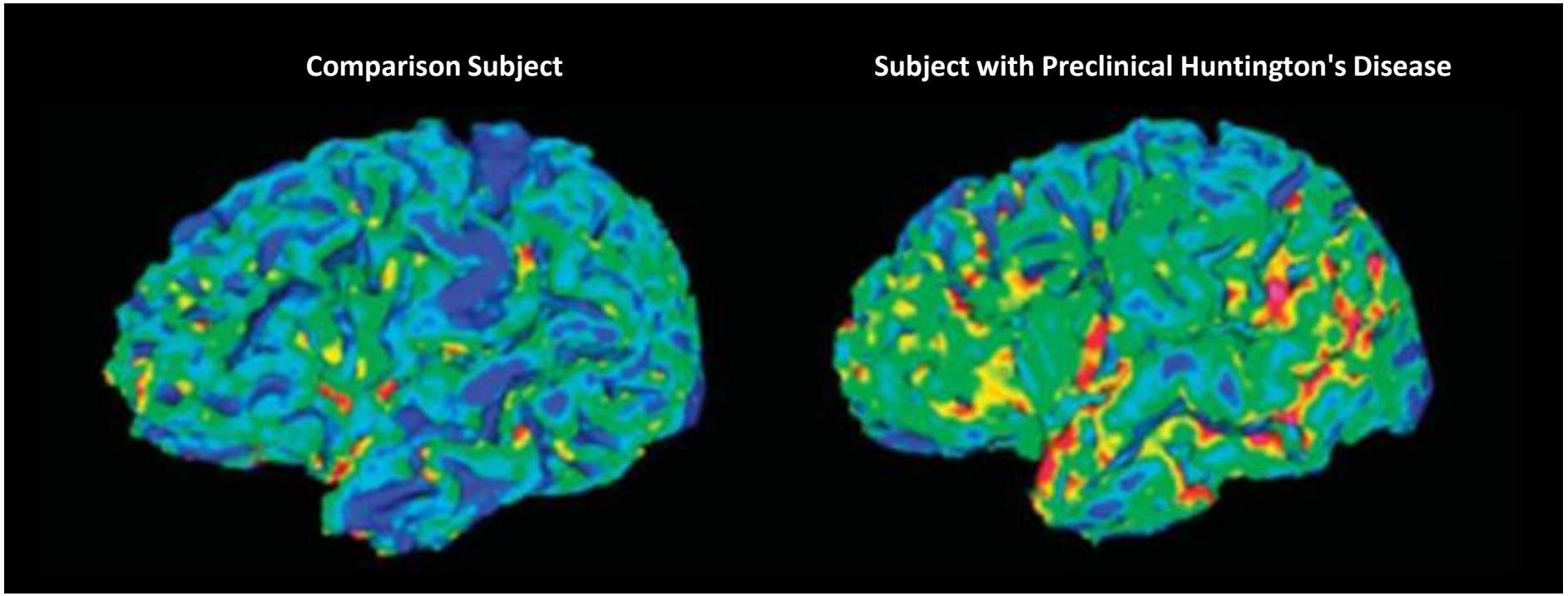






Early preclinical signs in Huntington disease

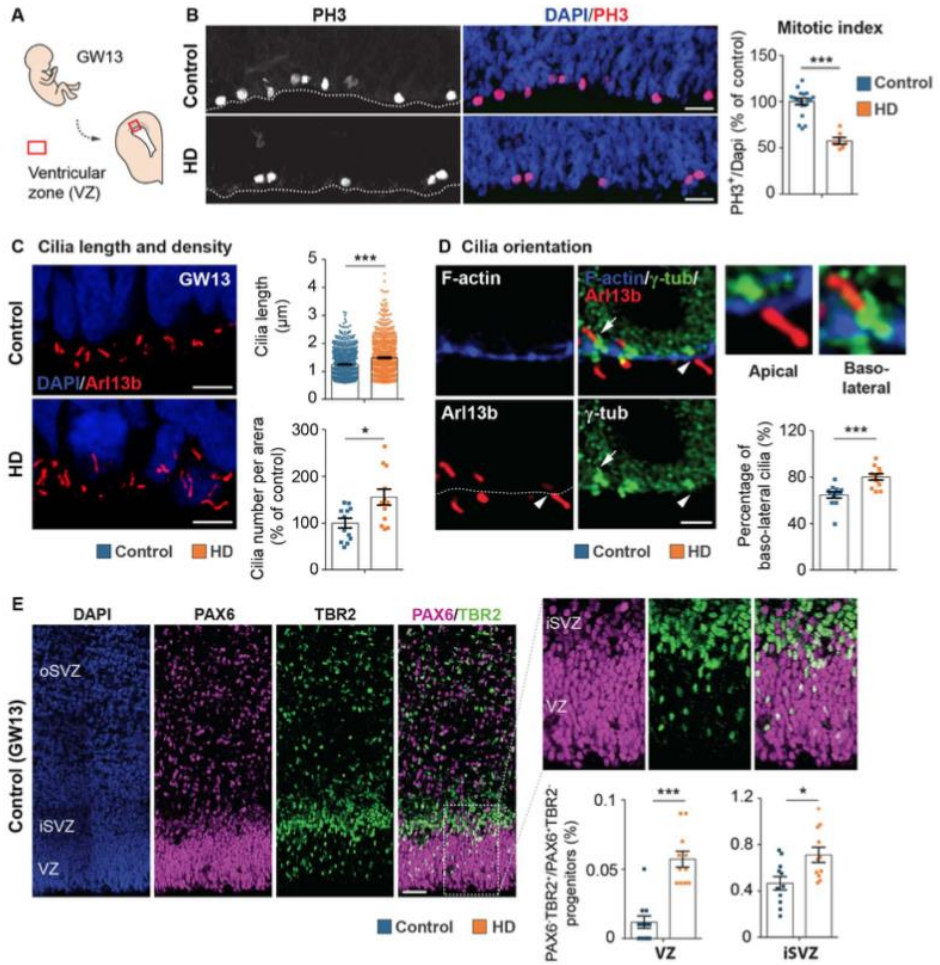
Three-Dimensional Images of the Cortical Surface in the Brains of a Healthy Comparison Subject and an Age-and Sex-Matched Subject with Preclinical Huntington's Disease*



* The color represents cortical thickness thin cortex is represented in hues of blue, and thicker cortex is represented by yellow and red

Nopoulos et al Americal journal of Psychiarrty 2007

Huntington's disease alters human neurodevelopment



Barbat et al Science 2020

Early born disorders

- Autism Spectrum Disorders,
- Fragile X, down syndrome, Rett syndrome etc. Infantile epilepsies
- Other Developmental disorders
- Huntington disease alters human bein development (Taubes etal science 2020)
- Mutation involved in Alzheimer impacts brain development
- Insults in utero

therefore

- Many disorders are born in utero
- They impact brain development leading to misplaced/misconnected neuronal ensembles
- These generate immature activity that perturbs the operation of networks
- They are responsible of the disorder
- This includes disorders thought to be late neurodegenerative ones

3

Identifying disorders by studying maternity

Contexte

Troubles du Spectre de l'Autisme (TSA)

Genèse in-utero

1 personne sur 100
En France est atteinte des TSA
(environ 700 000 personnes)

8 000 enfants
atteints naissent chaque année

Environs **67 millions**
de personnes dans le monde

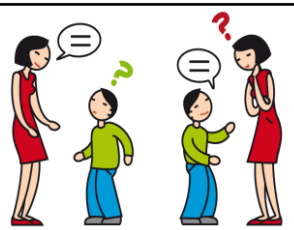
80 % des enfants autistes
en France ne sont pas scolarisés

4 garçons touchés pour **1** fille

85 à 95 % des autistes adultes
ne sont pas autonomes

Interactions
sociales restreintes

Communication
faible



Stéréotypes

Pelargos

Intelligence Artificielle & Maternité

Prédire l'autisme dès la naissance

B&A BIOMEDICAL

CHU Centre hospitalier universitaire Limoges

cra limousin Centre ressources autisme

EUROBIOMED

Contexte

Diagnostic de l'autisme

Diagnostic difficile

- Étiologie encore incertaine
- Forte variabilité interindividuelle des symptômes

Enjeu du pronostic précoce

Diagnostic tardif
Entre 4-5 ans

Amélioration des symptômes via

- Thérapie cognitivo-comportementale ABA, TEACCH …
- Plus efficace si commencée tôt

Aucun traitement curatif

Contexte

Un pronostic précoce est un enjeu majeur :

- Permettre un suivi clinique des patients à haut risque
- Avancer l'âge de diagnostic
- Mise en place précoce des interventions comportementales et éducationnelles et amélioration du pronostic clinique à long terme du patient

✗ **Pas de solution approuvée existante !!**

Objectifs

- Les TSA sont générés in-utero
- Les thérapies sont plus efficaces lorsqu'elles sont lancées tôt

D'où l'objet de Pelargos : identifier dès la naissance les bébés qui auront un diagnostic d'autisme plus tard en analysant les données recueillies pendant la grossesse et l'accouchement.

Références :

Granpeesheh, Doreen, et al. (2009) (https://doi.org/10.1016/j.rasd.2009.06.007)

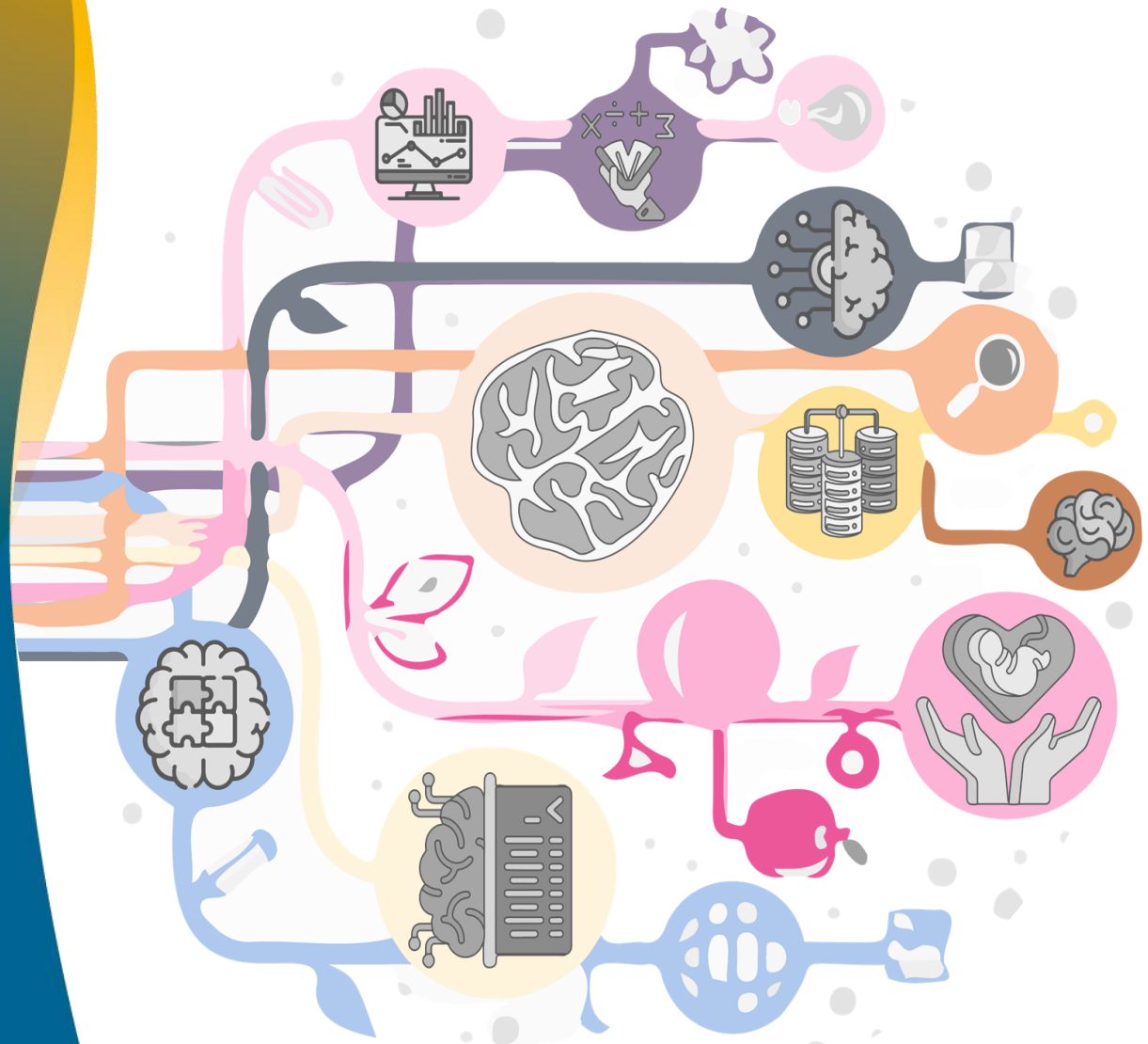
Bryson, Susan E., Sally J. Rogers, and Eric Fombonne. (2003) (https://journals.sagepub.com/doi/pdf/10.1177/070674370304800802)

Institut Pasteur. (2019) https://www.pasteur.fr/fr/centre-medical/fiches-maladies/autisme

Autisme Info Service https://www.autismeinfoservice.fr/accompagner/connaitre-therapies

Denoyelle, Francoise, et al. (2021) (10.1051/medsci/2021064)

Présentation de l'Equipe



Equipe
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Obstétricien gynécologue

Eric Lemonnier CHU Limoges
Consultant
Psychiatre, expert autisme

Résultats préliminaires - Première étude

- Pendant le suivi de **grossesse** et lors de **l'accouchement**, environ **200 paramètres** sont recueillis **en routine** en France :
  - Antécédents médicaux
  - Suivi de grossesse de la mère
  - Développement prénatal et naissance de l'enfant

- Nous nous sommes concentrés sur environ **116 paramètres** pertinents, sélectionnés en fonction des connaissances médicales du domaine :
  - 3 échographies
  - les paramètres biologiques et sanguins
  - les antécédents parentaux
  - les infections
  - les conditions de la naissance

- **La procédure rétrospective**

Diagnostic TSA

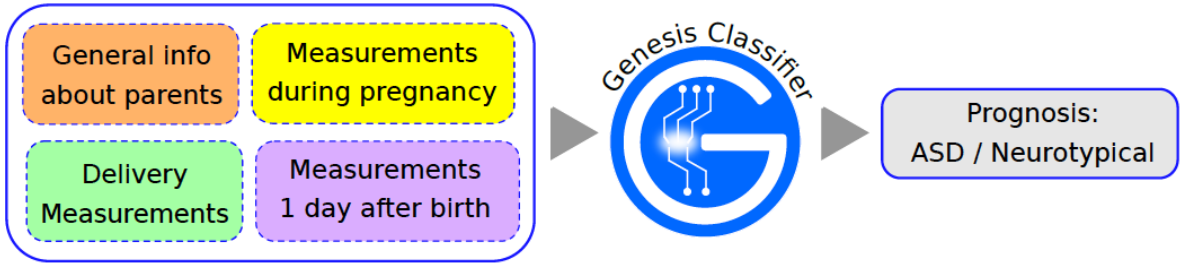
Recueillir les dossiers maternités

Analyse

Une première mondiale: identification à postériori des bébés qui ont eu un diagnostic d'autisme plus tard

H Rabiei

- Classification automatique des patients



E Lemonnier

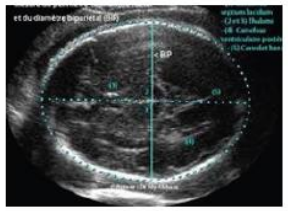
Classification

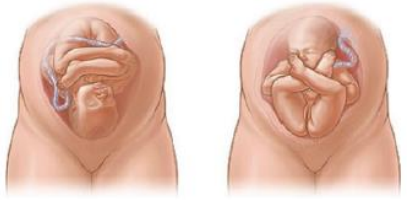
Bébés neurotypiques	96%
Bébés autistes	41%

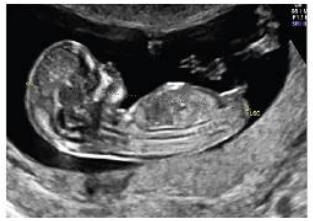
96% des futurs enfants qui ne seront pas autistes identifiés

41% des futurs autistes sont identifiés

Hughes Caly







- **Un essai plus large: recueillir dans 4-5 maternités des dossiers de 1000 /3000 autistes/non**
- **On espère avoir 70% de validation**
- **Ensuite faire essai prospectif**

Caly et al., Scientific Reports, 2021

Cas d'usage - Finalité de Pelargos

Accompagnement des parents

5

Explication des résultats aux parents via un discours médical adapté et des fiches d'informations.
Mise en place des stratégies de suivi de développement de l'enfant en fonction du risque et de l'avis du médecin.

Expertise médicale

4

Evaluation des résultats par le praticien.

Résultat pronostic

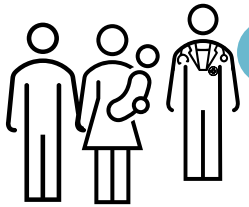
Transmission sécurisée des résultats au personnel de santé formé

Transmission sécurisée des données à B&A BIOMEDICAL

1

Maternité

Suivi de grossesse et recueil des données en routine (antécédents médicaux, grossesse, accouchement)



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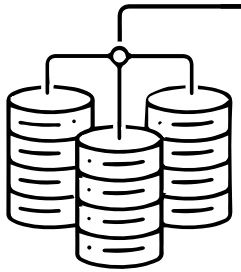
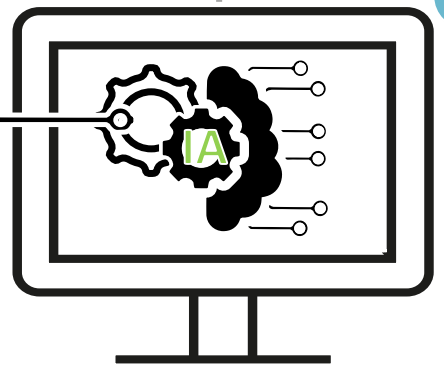
Naissance

Échanges entre le praticien et les parents : Présentation du test de pronostic TSA *Pelargos*.
Proposition de réalisation du pronostic.
Décision consentie et éclairée de réalisation du test.





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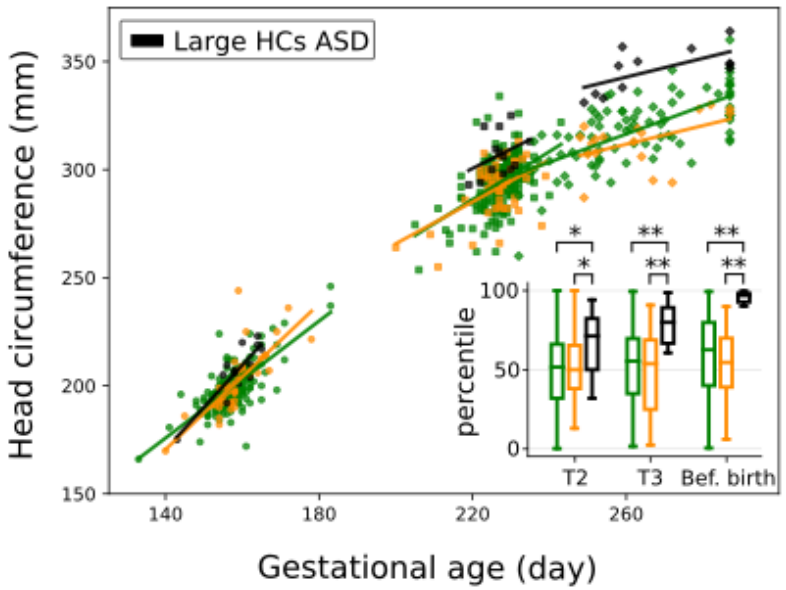
Pelargos CE

Traitement et analyse des données par Pelargos.

- **Non invasif**
- **Rapide** (analyse en quelques secondes)
- **Ethique** : Faux positifs faible
- **Apprentissage** continu **contrôlé**.

Bigger Head Circumference in autism in utero (ultrasound)



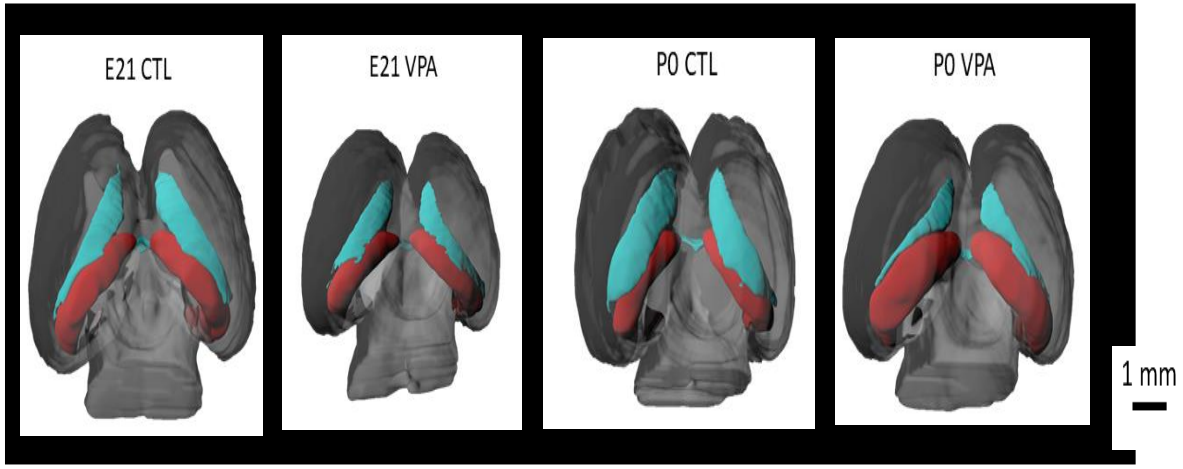
- 35% of infants and adolescents with ASD have a bigger brain
- Future infants with ASD have a bigger brain than NT shortly before birth
- A subpopulation of Future infants with ASD has bigger brains already 2nd trimester
- Therefore, brain growth is impacted in utero
- Is there a different preparation to birth?

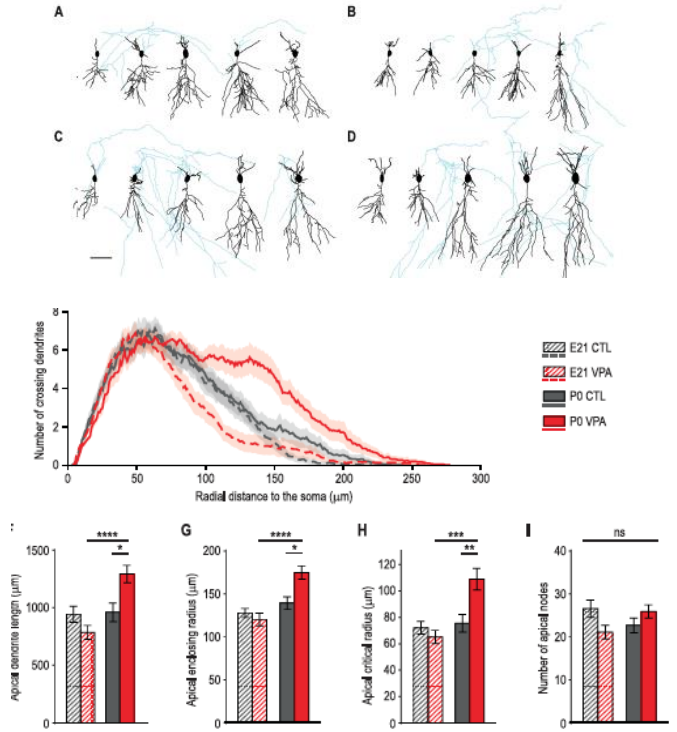
Caly et al., Scientific Reports, 2021

Courchesne et al J AM Med Association 2003; Amaral et al Autism res. 2017

SCIENCE ADVANCES | RESEARCH ARTICLE

Pyramidal neuron growth and increased hippocampal volume during labor and birth in autism

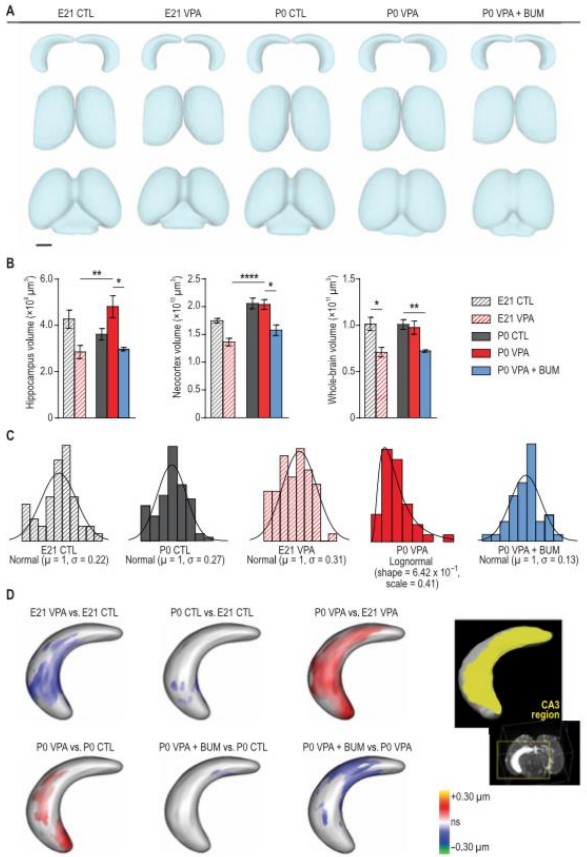


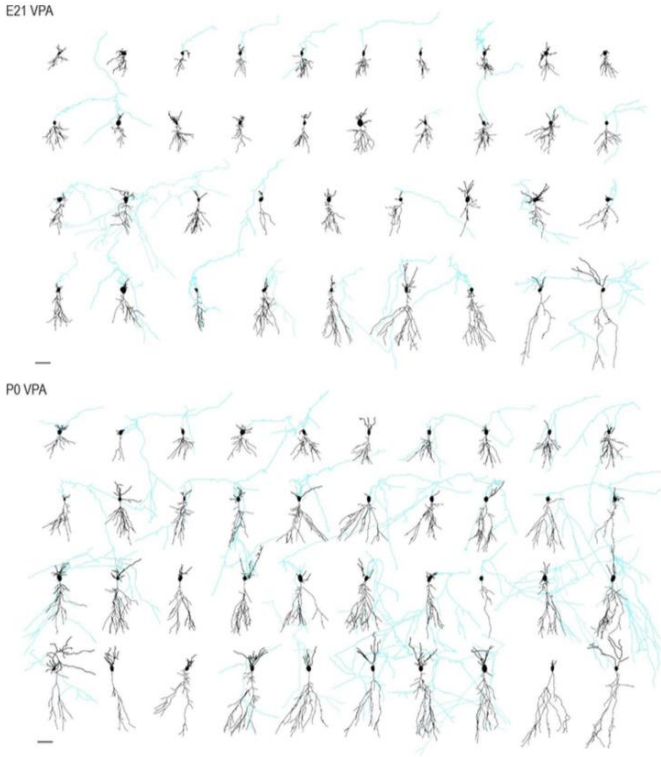


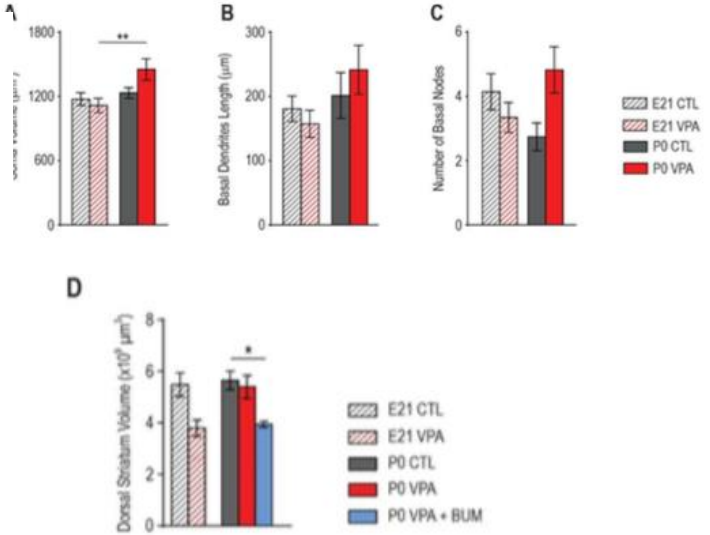
- The 3D brain, neocortex & hippocampus volumes increase during birth
- Bumetanide eliminates this growth
- Neurons grow DURING birth
- The first demonstration of growth during birth endowed with important implications

Cloarec et al , science Advances 2019

cellular and hippocampal volumes P0/E19







Cloarec et al , science Advances 2019

Therefore

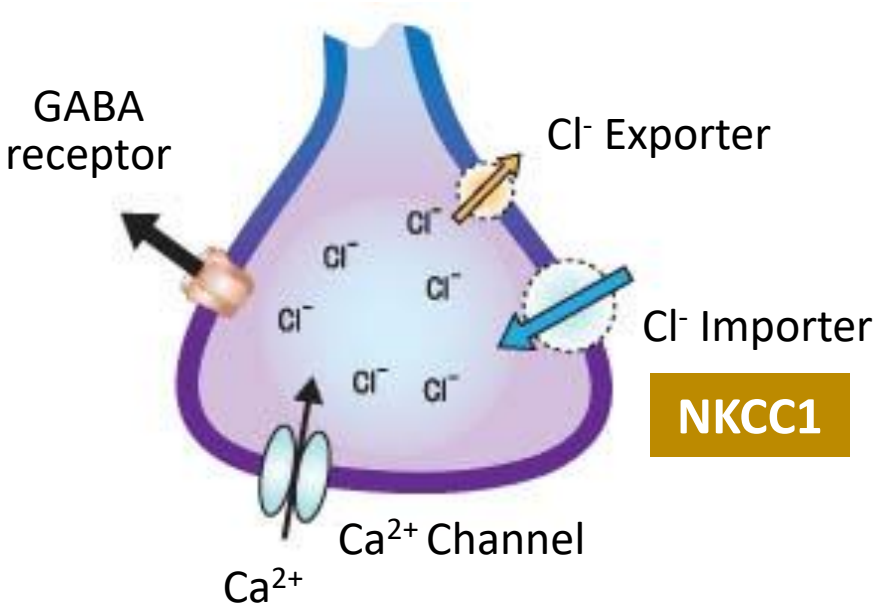
- ASD is born in utero
- Brain Growth is impacted already during the 2nd trimester
- It is possible to identify at birth babies who will have an Autism diagnostic later
- This is needed, prognosis cannot be made only relying on in utero data

Shelton et al environmental health perspect. 2014

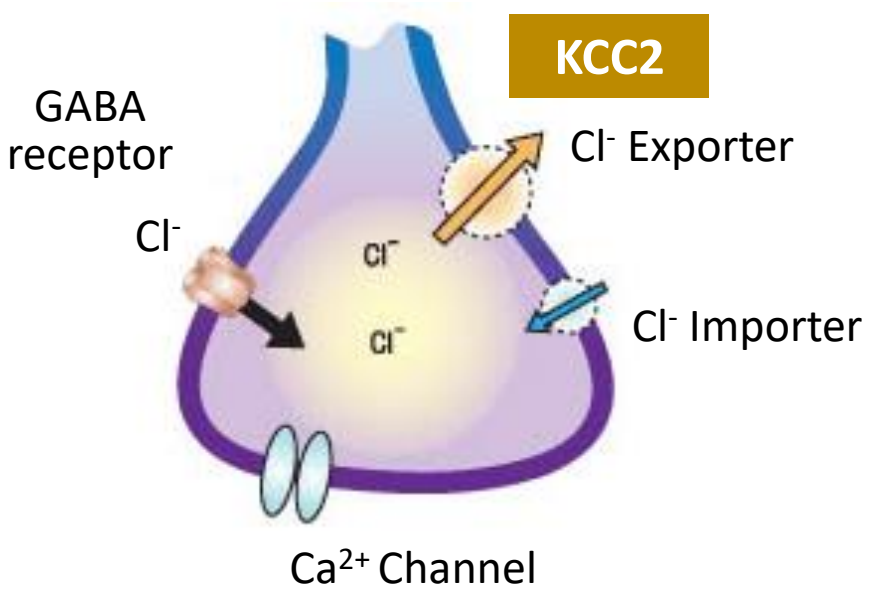
4

An example-
The GABA developmental sequence

The GABA E to I developmental sequence & chloride importer and an exporter



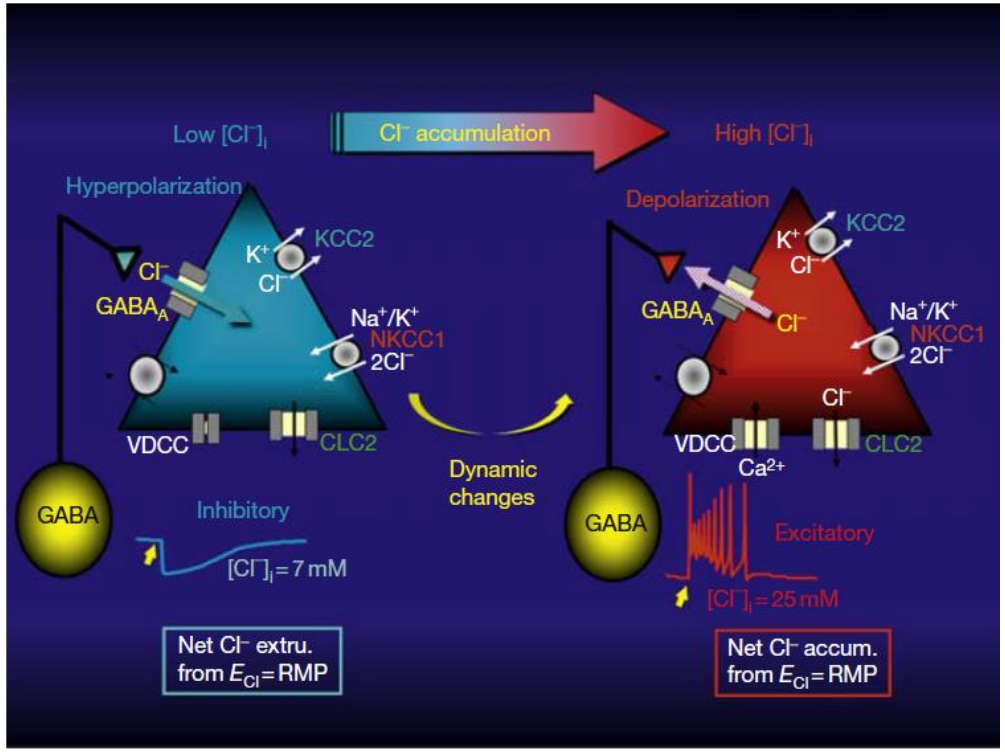
A - DEPOLARIZATION:
GABA is excitatory



B - HYPERPOLARIZATION:
GABA is inhibitory

Ben-Ari et al, 1989; Ben-Ari, Nat Rev Neurosci, 2002; Ben-Ari, Physiol Rev, 2007; Ben-Ari, Neuroscience commentary, 2014; Rivera et al, Nature 1999

An evolutionary conserved GABA polarity shift mediated by high $[Cl^-]_i$ levels



Atsuo Fukuda

GIANT SYNAPTIC POTENTIALS IN IMMATURE RAT CA3 HIPPOCAMPAL NEURONES

By YEHEZKEL BEN-ARI, ENRICO CHERUBINI, RENATO CORRADETTI AND JEAN-LUC GAIARSA

From the Unité 29, INSERM, Hôpital de Port-Royal, 123 Boulevard de Port-Royal, 75014 Paris, France

slices, cell cultures, intact preparations,

intact retina: chick, ferret, turtle, rat, mouse,

intact spinal cord: chick, rat, mouse, xenopus laevis

brain stem: rat, mice,

basal ganglia /hypothalamus: rat mouse

inferior colliculus: gerbil, rat, mouse

Hippocampus: kitten, rabbit, rat, mouse

neocortex, amygdala: rat, mouse, gerbil, guinea pig

human embryos

hippocampus in vivo rodent -

Ben-Ari, Nat Rev Neurosci, 2002; Ben-Ari, Physiol Rev, 2007; Ben-Ari, Neuroscience, 2014 Rivera et al Nature 1999, Crepel et al Neuron 2007, bonifazi et al Science 2009, Tyzio et al Science 2006 etc. + many papers by U29/INMED

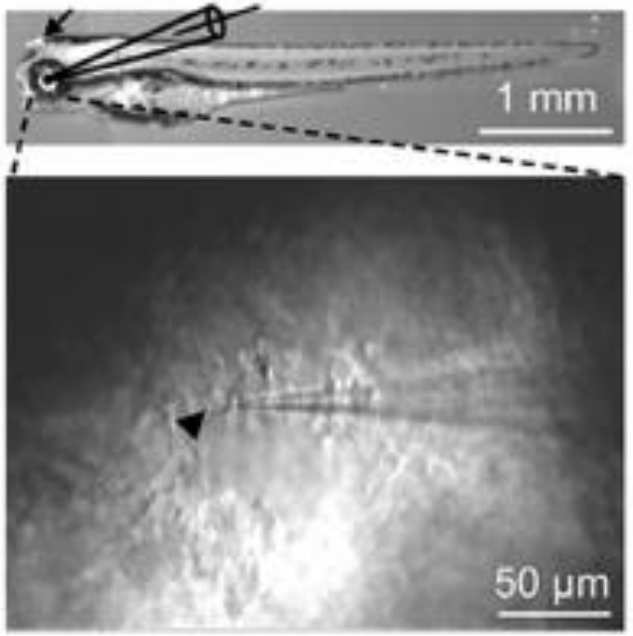
Multiple actions of GABA

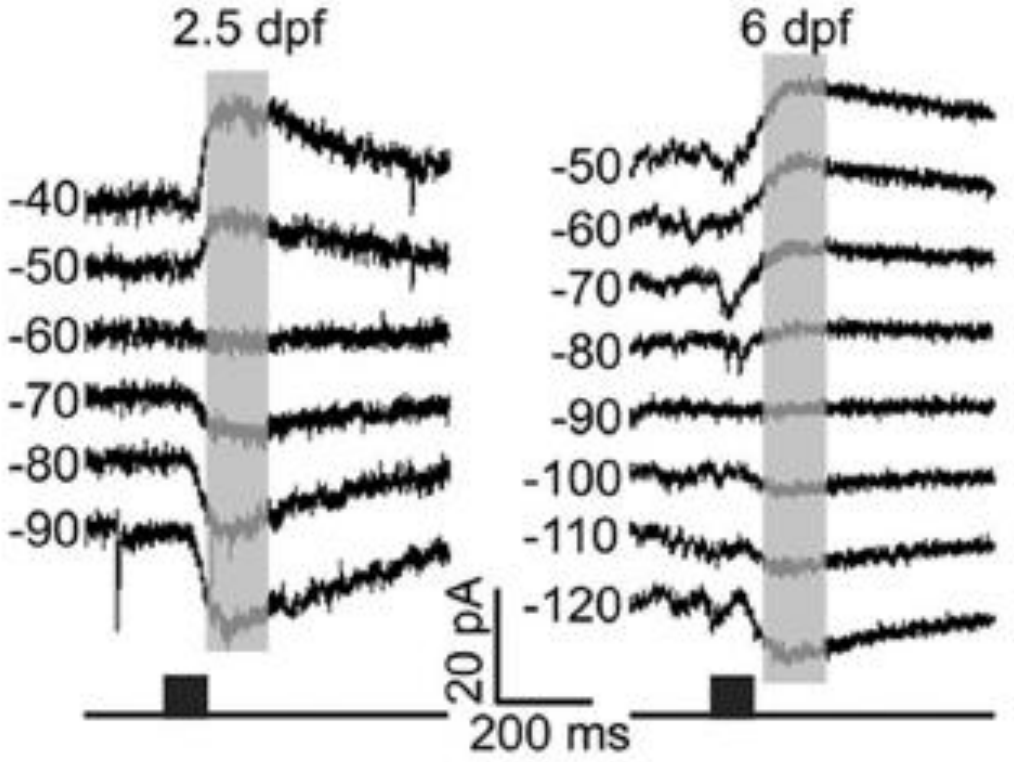
- Activates voltage gated calcium currents leading to a rise of calcium
- Removes the V-dependent Mg block of NMDA receptors channels leading to a rise of calcium
- GABA exerts a trophic role early, this is mediated by the large calcium influx that the excitation generates via voltage-dependent CA++ currents and NMDA receptors

IBEN

Ben-Ari et al, 1989; Ben-Ari, Nat Rev Neurosci, 2002; Ben-Ari, Physiol Rev, 2007; Ben-Ari, Neuroscience commentary, 2014; Rivera et al, Nature 1999

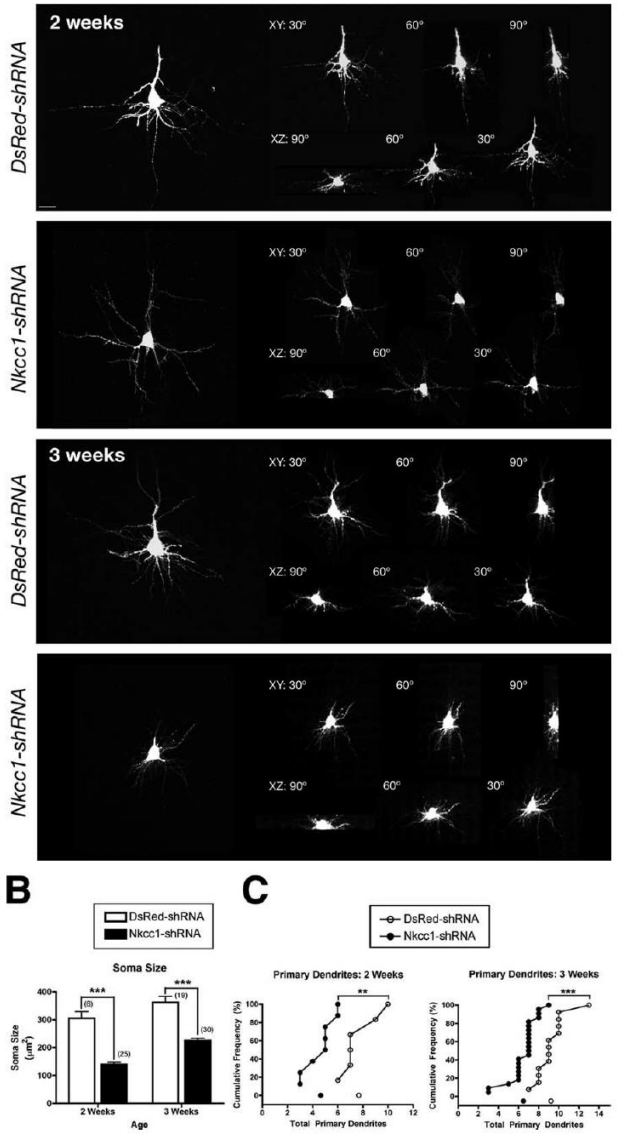
Sequential maturation in the intact zebra fish embryo and in vivo neocortex

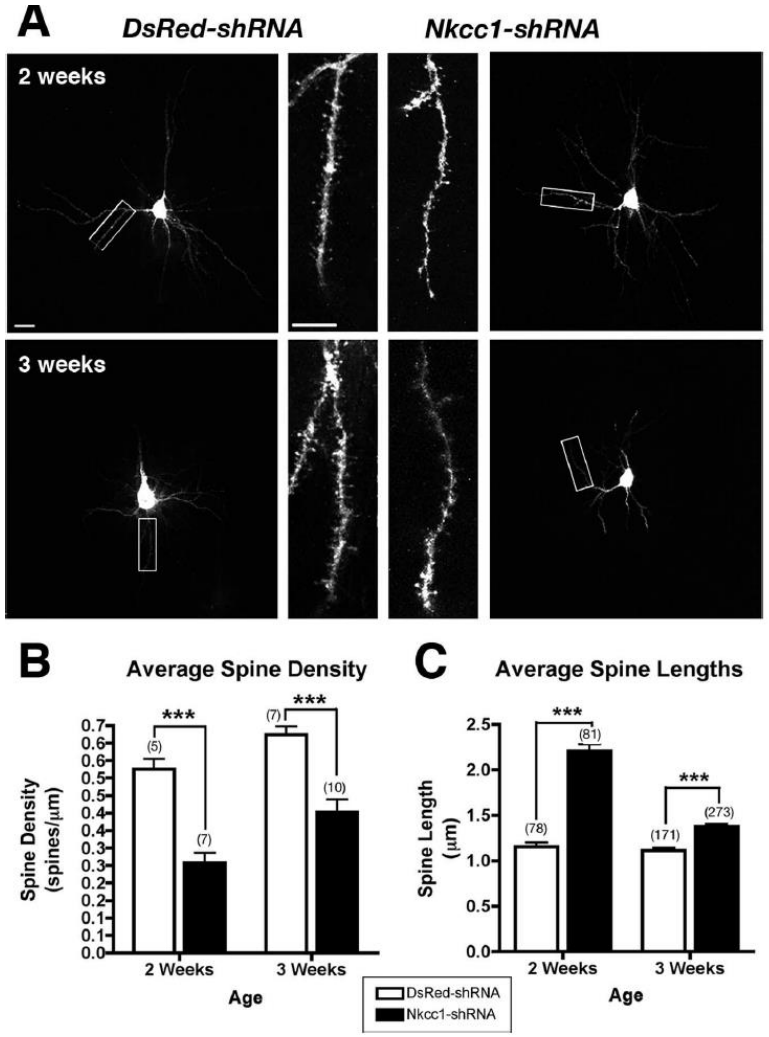




Zhang et al., J Physiol, 2010

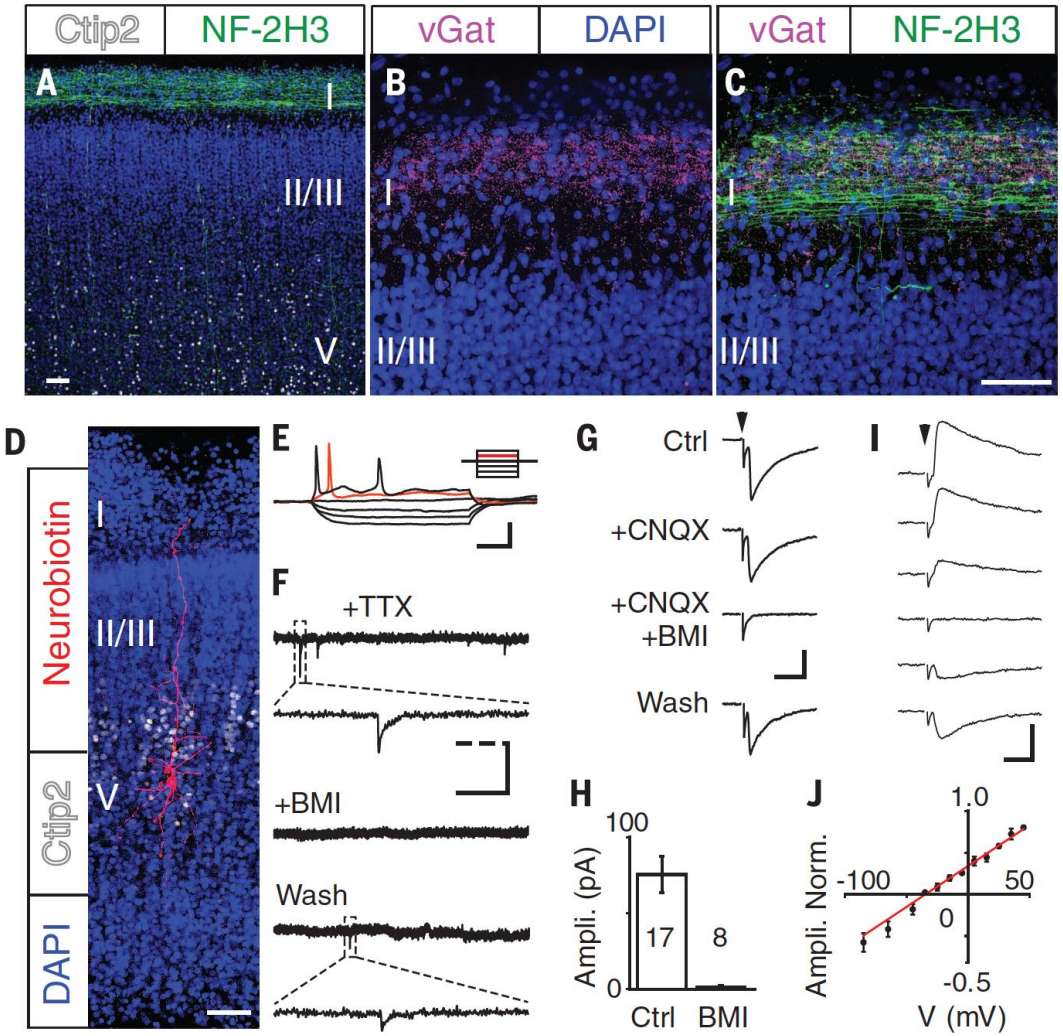
NKCC1 and E GABA control neuronal growth

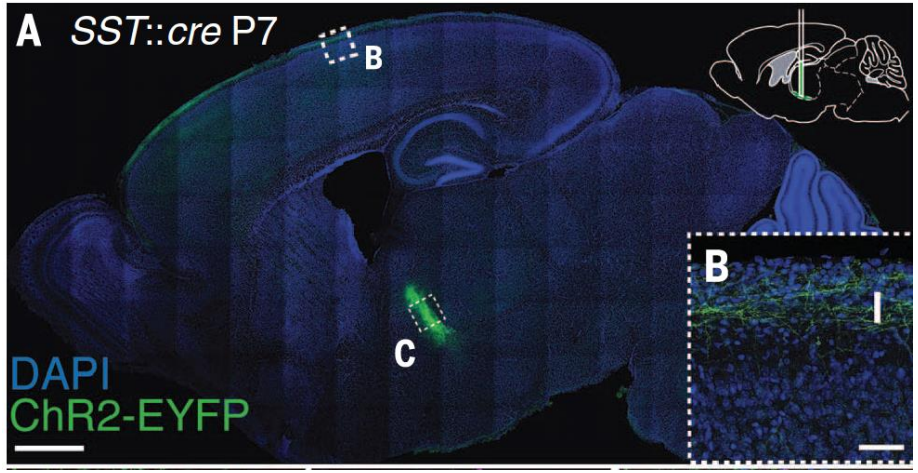




Wang & Kriegstein, J Neurosc, 2009

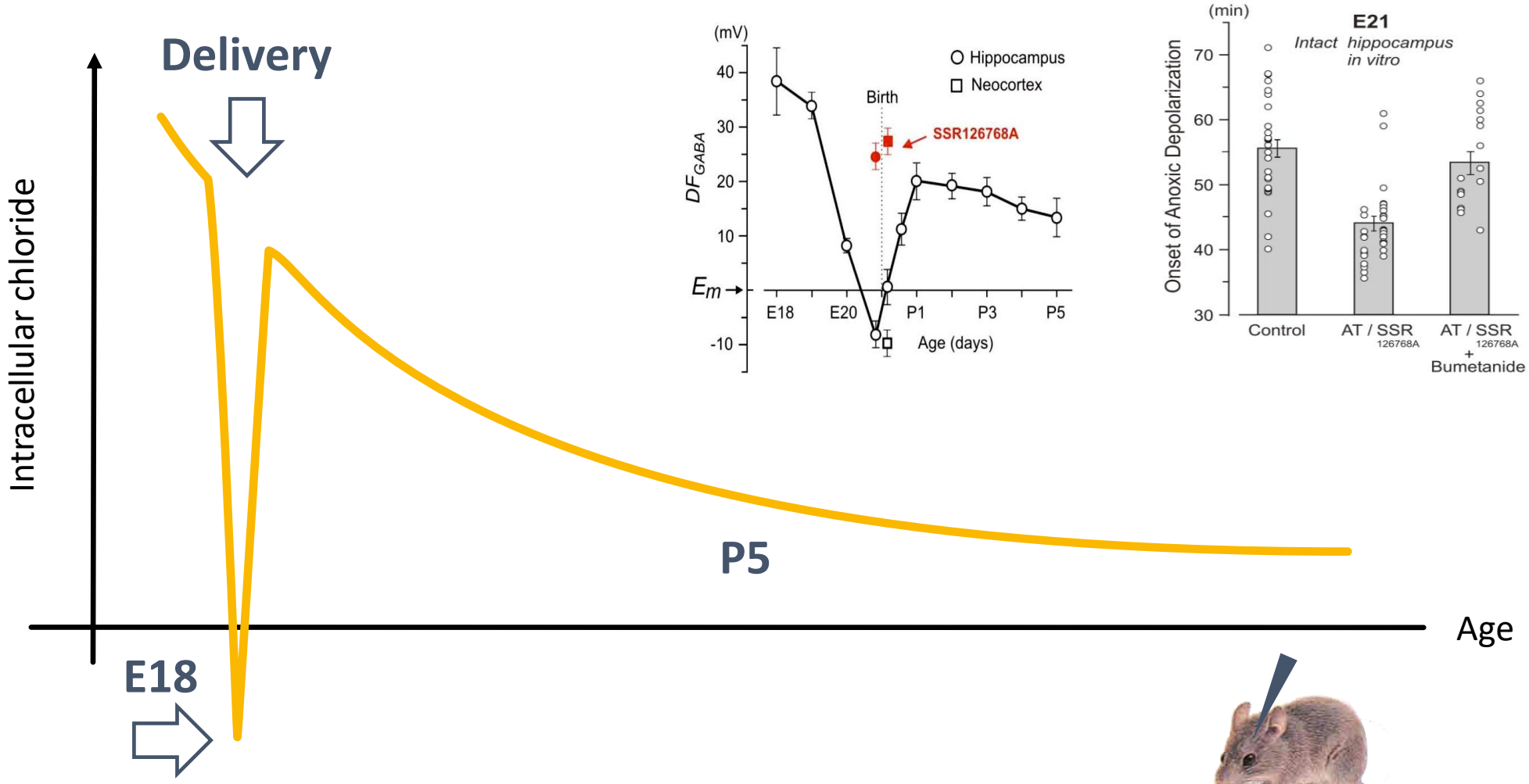
Excitatory GABAergic synapses in humans (22GW) and mice





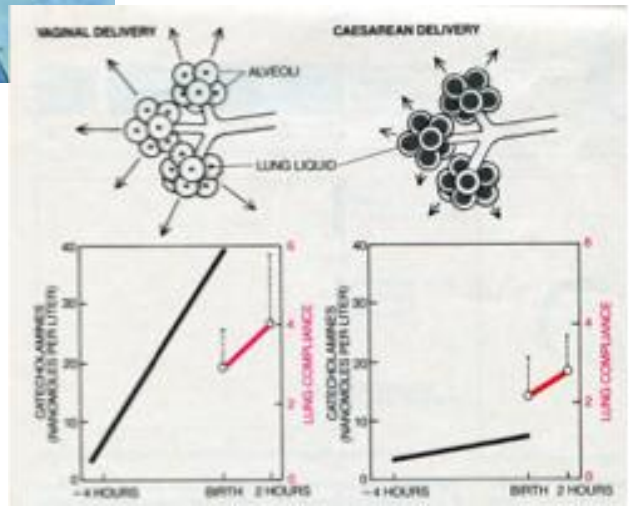
Chen and Kriegstein, Science 2015

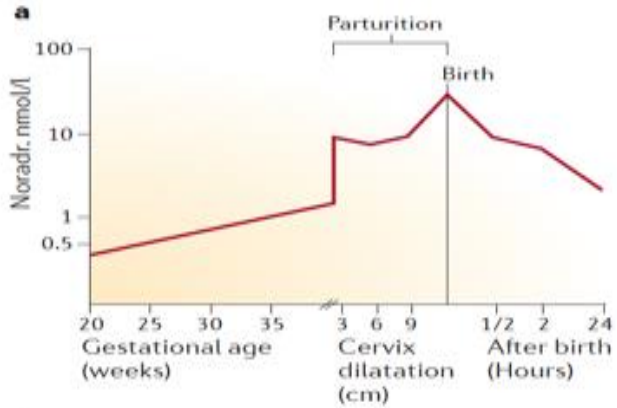
An oxytocin mediated neuroprotective action on GABA /Chloride

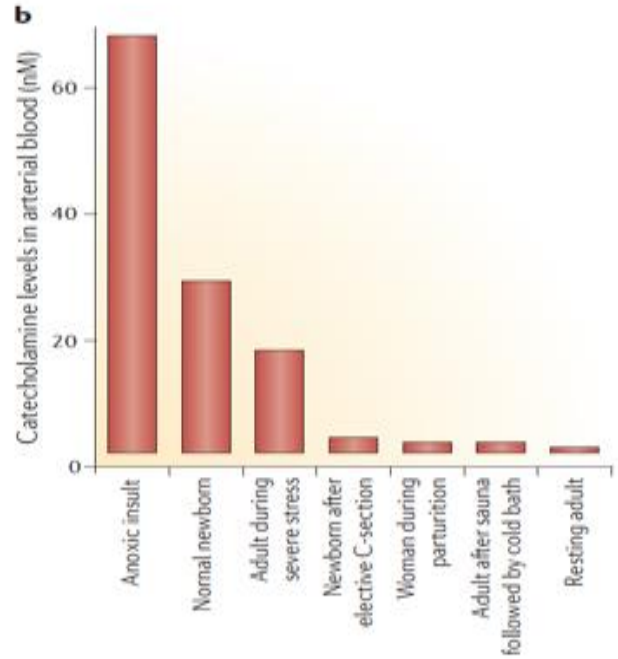


Tyzio et al., Science, 2006

Delivery is a a very stressful period







The "stress of being born" and the paradox of delivery

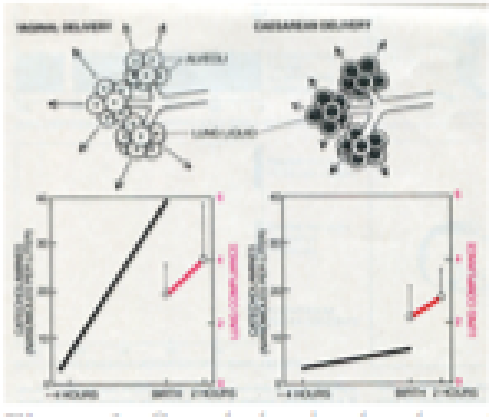
Lagercrantz and Bistoletti, Pediat Res., 1977

Lagercrantz and Slotkin, Scientific American, 1986

A much needed stress

Cesarean section delivery

1. Catecholamine levels are lower than for vaginal birth (Lagercrantz)



2. Increased respiratory distress

3. Increased TH activity and DAT binding in response to stress (Boksa, P. & Zhang, Y. *Psychopharmacology*,2008)

(b) NAcc - Repeated Mild Stress

	Vaginal birth	C-section
NE	1138.7 ± 135.5	1184.4 ± 130.8
E	1756.0 ± 171.8	708.3 ± 135.8**
DA	1202.7 ± 172.3	1974.1 ± 182.0*
DOPAC	1786.0 ± 131.9	1346.0 ± 158.2

4. Reduced plasma epinephrine at birth

C-sections

- The frequency of programmed C-sec is steadily increasing
- 18% in the world, 20% in Europe
- 50% Brazil, or Egypte)
- slightly increases the incidence of autism (Curran et al)
- The incidence of autism is increased also by preterm delivery and complications at birth

Curran et al JAMA 2015

Therefore

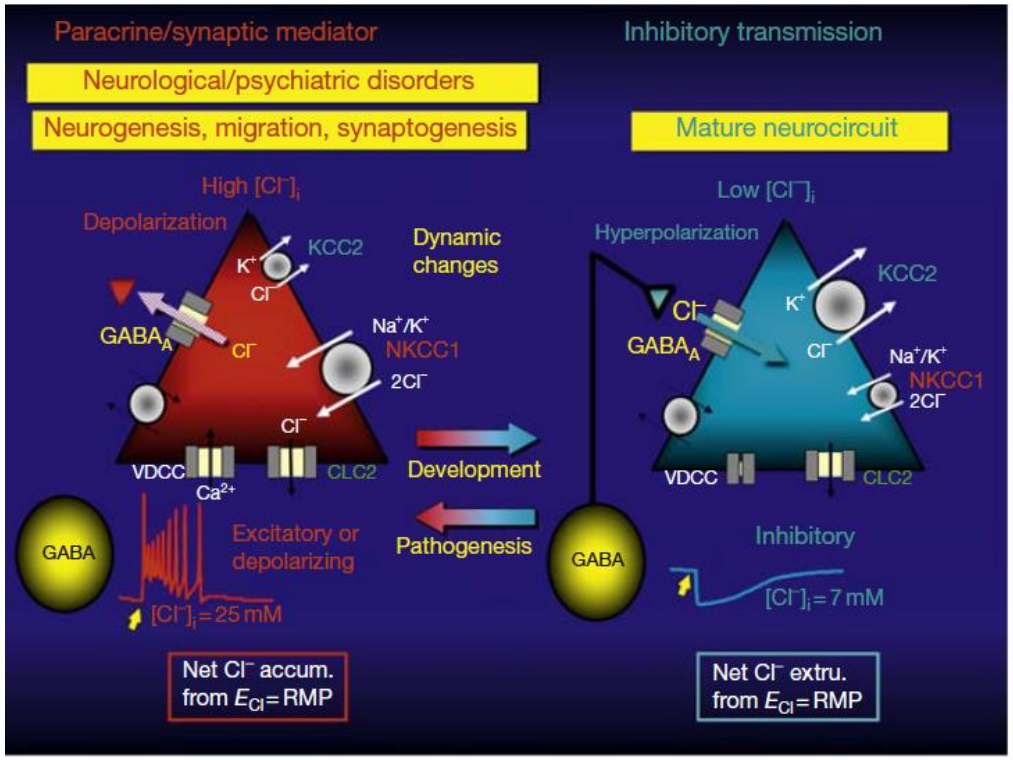
- High chloride initially is a feature that has been preserved throughout evolution
- GABA provides early excitation to very immature neurons endowed with little if any synapses
- There is a progressive reduction of chloride and shift from excitation to inhibition or more precisely a decrease of the E versus I actions
- Parturition and birth are complex episodes during which major alterations take place

5

The developmental GABA shift is “reversed” in brain Disorders potential treatments

GABA excites neurons in pathological conditions : a “return to immaturity”

- **Autism,** Rett, **Fragile X**, Down, **TSC**
- Brain damage, traumatic insults
- Spinal cord lesions
- Cerebrovascular infarcts
- Chronic pain
- Stress & PTSD
- Maternal Immune Activation
- Bacterial /viral infections during pregnancy
- **Parkinson disease**
- **Glioblastoma& many cancers**
- **Schizophrenia**



Atsuo Fukuda

Ben-Ari, TINS, 2017; *Fernandez et al., Cereb Cortex, 2019; Kourdougli et al., Ann Neurol, 2017; Lavertu et al., Brain, 2014; Dekonink, Cur. Opin. Pharmacol, 2007; Damier et al., Clinical Pharmacol, 2016,* Turner KL, Sontheimer PHIL SOC Trans 2014**, Savardi et al TIPS 2021**

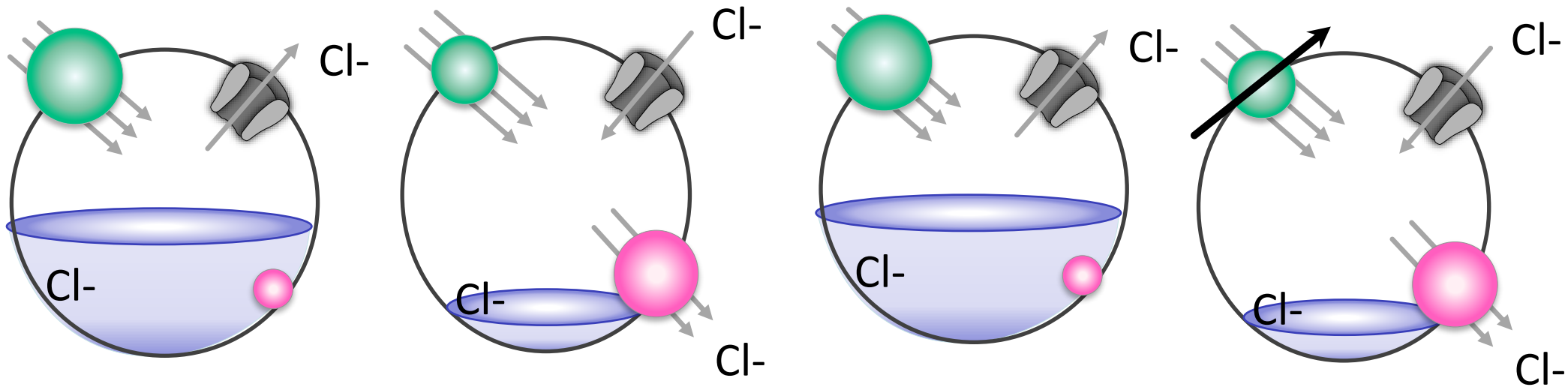
Traiter l’autisme en restaurant des taux bas de chlore

neurone jeune

Neurone adulte

Neurone autiste

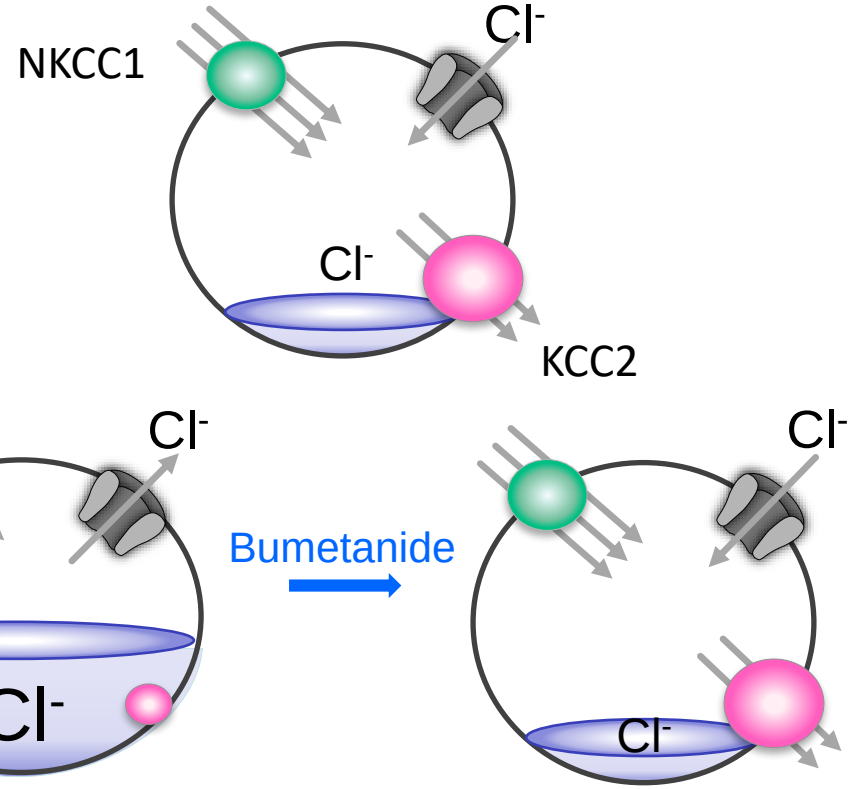
Neurone traité Bumétanide

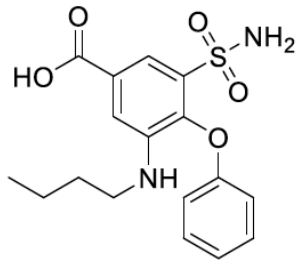


Repositoning Bumetanide to reduce $(Cl^-)_i$ and GABA Inhibition

- **Used for 4 decades to treat Hypertension brain edema**
- **Side effects well known and characterized**
- **Ad: “primum non nocere”**
- **Easy to obtain authorization**
- **A world wide PCT on a liquid formulation**

- **Limitations: Diuresis, low BBB permeability**
- **Poor financial return –pharmas are usually not interested**

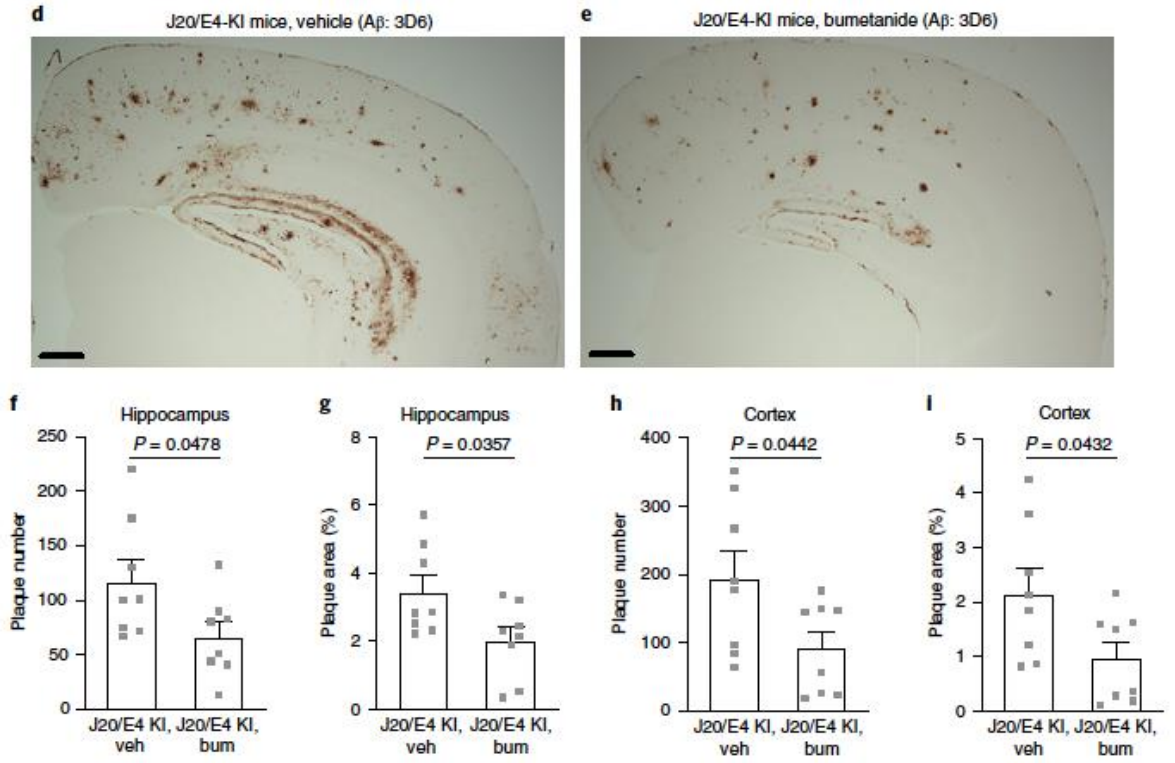




Bumetanide

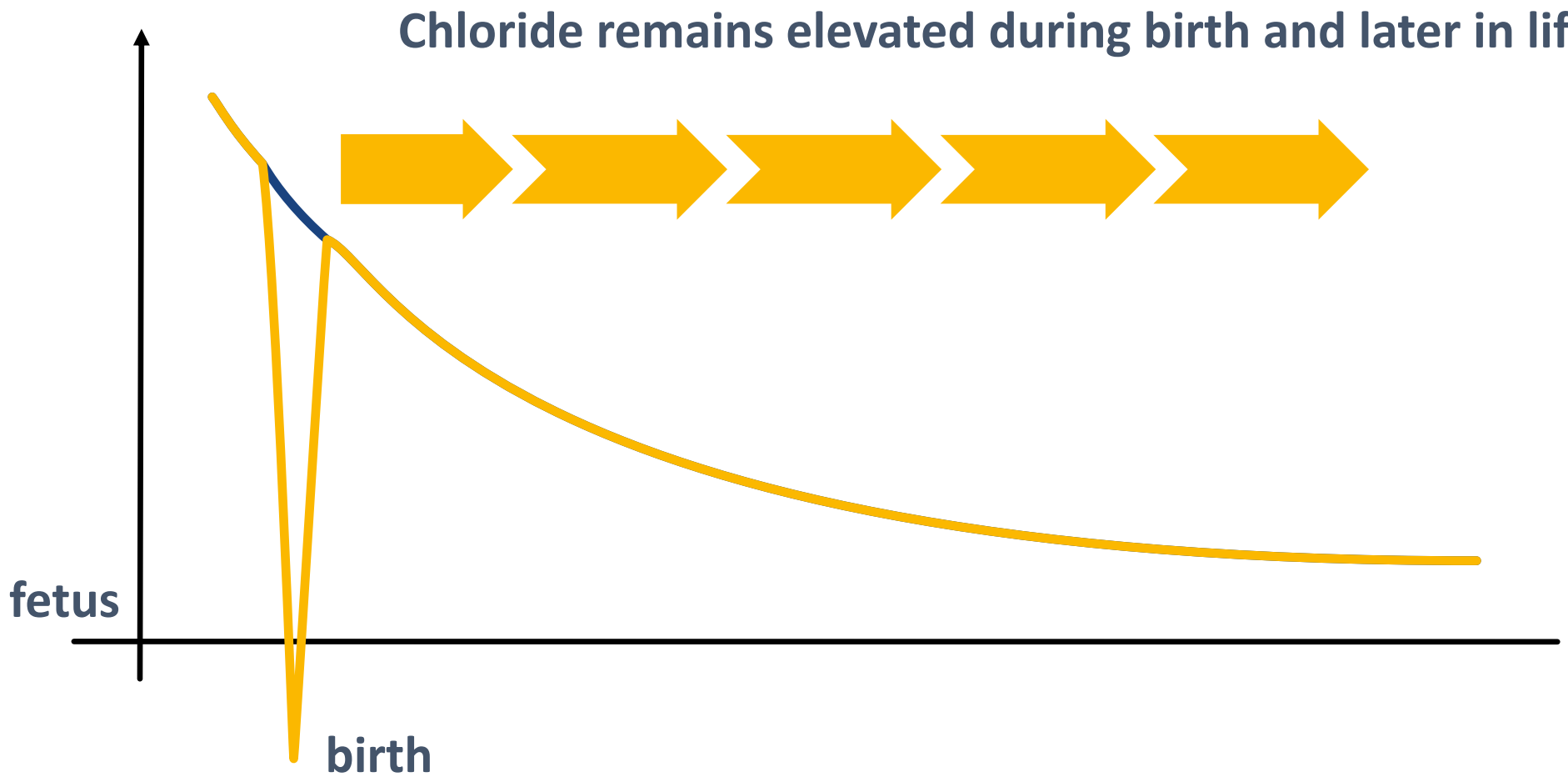
Experimental and real-world evidence supporting the computational repurposing of bumetanide for APOE- related Alzheimer's disease

- Of 1300 large consumption drugs used routinely, Bumetanide stemmed as the best to reverse APOE specific genetic signatures
- 30 to 70% reduction of Alzheimer incidence in aged people (>65) who have taken Bumetanide (4 Million people recruited) but not other diuretics
- Bumetanide attenuated behavioral features in an animal model and amyloid-β plaque loads



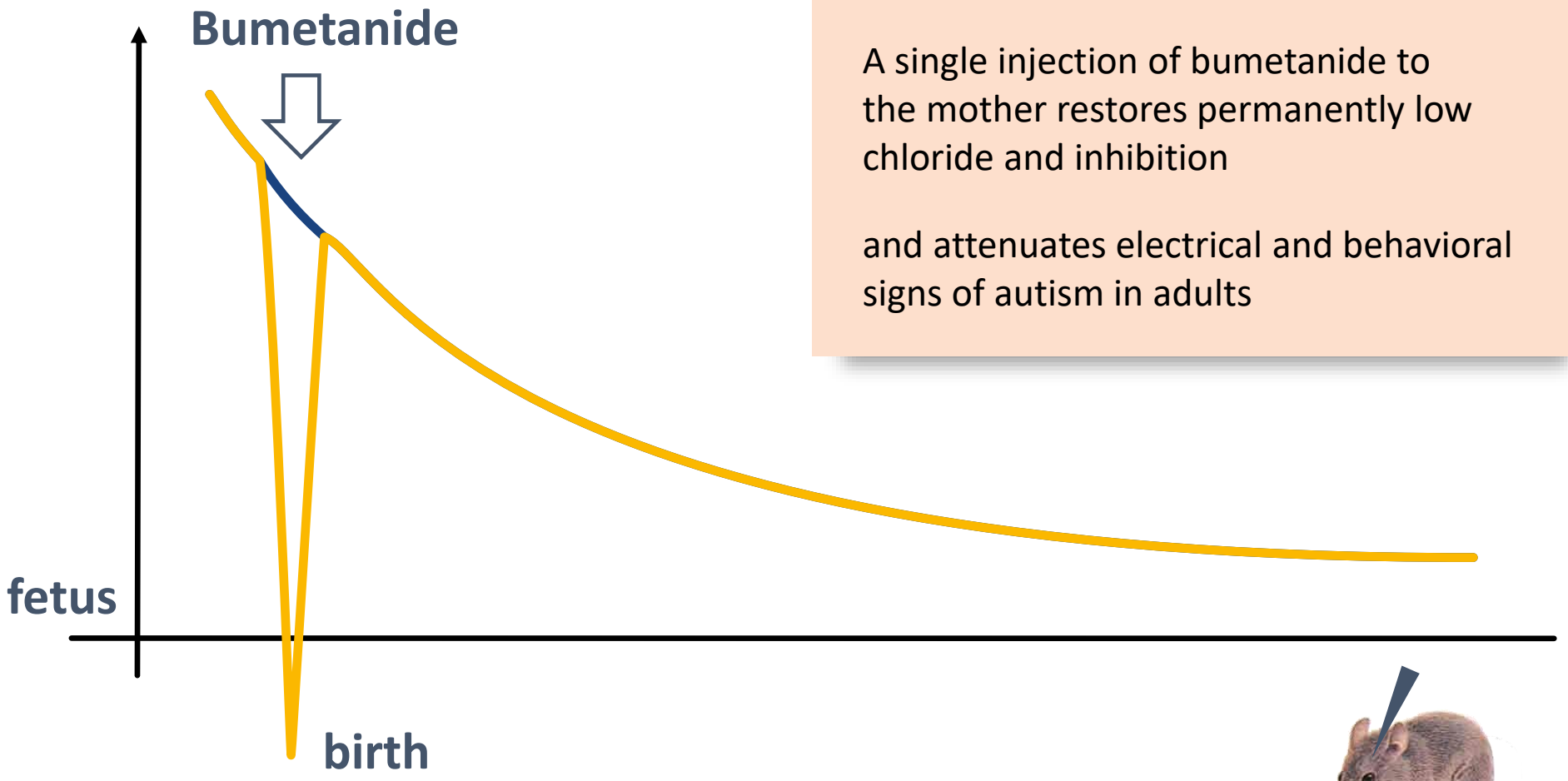
Taibes et al., Nature aging 2021

The fall of chloride is abolished in VPA and FRX



Tyzio et al., Science, 2014

Maternal bumetanide restores the shift and attenuates autism



A single injection of bumetanide to the mother restores permanently low chloride and inhibition

and attenuates electrical and behavioral signs of autism in adults

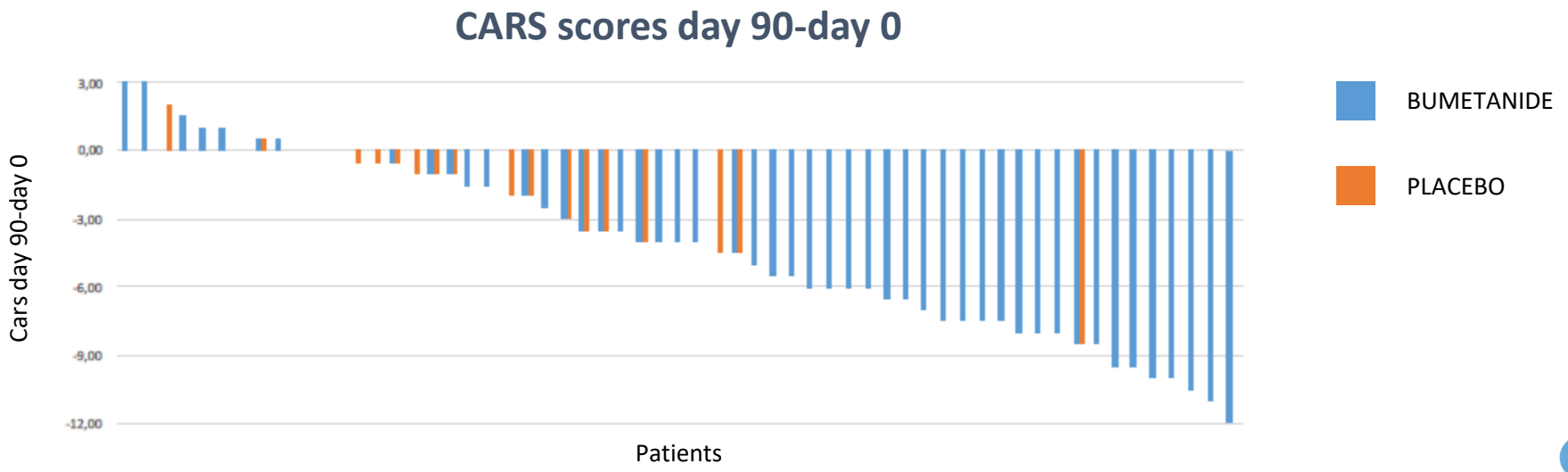
Tyzio et al., Science, 2014

Allan, before and after treatment

Lemmonier and Ben-Ari, Acta Pediatrica Scan, 2010; Lemonnier et al., Transl Psychiat, 2012

Amelioration with CARS scale: double blind randomized trial (74 children, 2-18yrs old)

Decrease in CARS score	BUM 0,5	BUM 1,0	BUM 2,0	PI
≥ 4,0	11 (58%)	10 (53%)	9 (69%)	5 (24%)
≥ 6,0	10 (50%)	6 (31%)	7 (54%)	1 (5%)
≥ 8,0	7 (35%)	3 (16%)	3 (23%)	1 (5%)



Lemmonier et al., Transl Psychiatry, 2012, 2017

Amelioration with SRSscale: double blind randomized trial (74 children, 2-18yrs old)

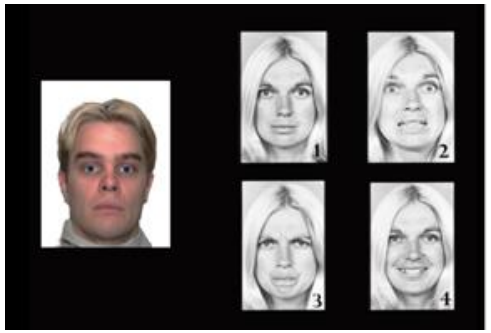
	0.5	1	2mg	Placebo	
SRS (total score)					
Screening					
N	20	23	22	22	
Mean (s.d.)	113.35 (17.48)	106.42 (23.95)	106.58 (25.09)	112.68 (20.65)	
Day 90					
N	20	18	13	21	
Mean (s.d.)	100.99 (23.70)	87.96 (19.89)	87.03 (22.03)	109.47 (26.07)	
Change					
Mean (s.d.)	−12.36 (23.57)	−13.17 (20.45)	−21.83 (19.78)	−1.55 (20.38)	
Median [range]	−13.00 [−86.0/14.0]	−6.00 [−52.0/18.0]	−27.00 [−47.0/8.0]	3.5 [−68.0/27.0]	
Kruskal–Wallis test					0.020

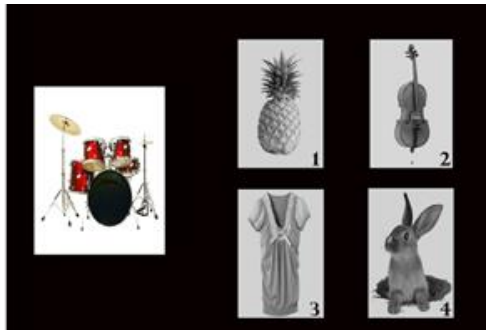
Lemmonier et al., Transl Psychiatry, 2012, 2017

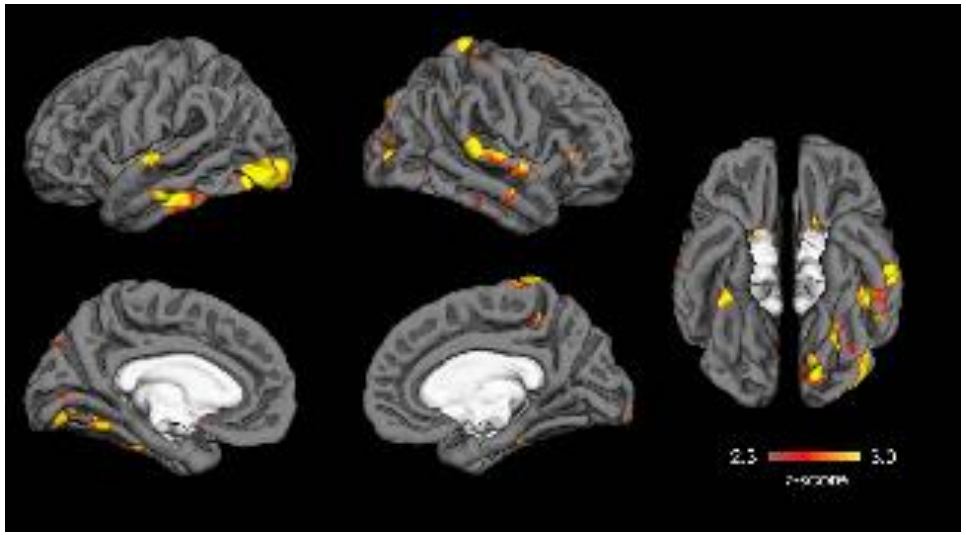
Country	N.	Age (y)	Rating scale	Dose	Duration	End points	Side effects	References
China	119	3-6	CARS, ADOS, CGI, SRS	0.5 mg twice/day	3 months	Improvement in CARS score	mild (polyuria, hypokalemia)	Dai Y. Et al. Science Bulletin, in press
Sweden	6	3-14	CARS	0.5 mg twice/day	4-12 weeks	Improvement in CARS score	mild (polyuria)	Fernell E. et al. Acta Paediatrica, 110, 1548-1553, 2021.
Netherland	92	7-15	CARS, ADOS, SRS	0.5 mg twice/day	3 months	Improvement in CARS and SRS score	Mild (hypokalemia)	Sprengers et al. J. Am Acad Child Adolesc Psych, 60,865-876,2021
China	83	3-6	CARS, ADOS, CGI	0.5 mg twice/day	3 months	Reduction in CARS score, CGI-I	mild (polyuria)	Zhang et al. Transl. Psych, 2020 Jan 27;10(1):9
Netherland	15	8-21	ABC-I (TSC)	0.5 mg twice/day	3 months	Improvement in ABC-I score EEG	mild (hypokalemia)	Van Andel et al. Molecular Autism, 2020 May 7;11(1):30
Tunisia	29	Average 7.9	ADI-R, CARS, CGI	0.1 mg/day	12 months	Improvement in CARS score	mild (hypokalemia)	Hajri et al. Tunis Medicine, 97,971-977, 2019
France	9	Average 21.4	Eye tracking	1 mg/day	10 months	fMRI	None	Hadjikhani et al. Sci Rep 2018 Feb 26;8(1):3602
France	88	2-18	CARS, SRS, CGI	0.5-2 mg twice/day	3 months	Improvement in CARS, CGI, SRS score	mild (hypokalemia)	Lemonnier et al. Transl. Psych 2017 Mar 14; 7(3):e1056
China	60	Average 4.5	ABC, CARS, CGI	0.5 mg twice/day	3 months	Improvement in ABC, CARS, CGI score	None	Du et al. J Child Adolesc Psychopharmacol 25,585-588, 2015
France	7	Average 19.3	ADOS, fMRI emotion recognition	1 mg/day	10 months	Improvement performance for emotion recognition	mild (polyuria)	Hadjikhani et al. Autism, 19, 149-157, 2015
France	60	3-11	CARS, SRS, ADOS	1 mg/day	3 months	Improvement in CARS, ADOS score	mild (hypokalemia)	Lemonnier et al. Transl. Psych. 2012 Dec 11;2(12):e202
France	5	3-11	CARS, ABC, CGI, RDEG, RRB	1mg/day	3months	Improvement in CARS, CGI,	None	Lemonnier & Ben-ari acta pediatrica 2010, 99(12):1885-8.

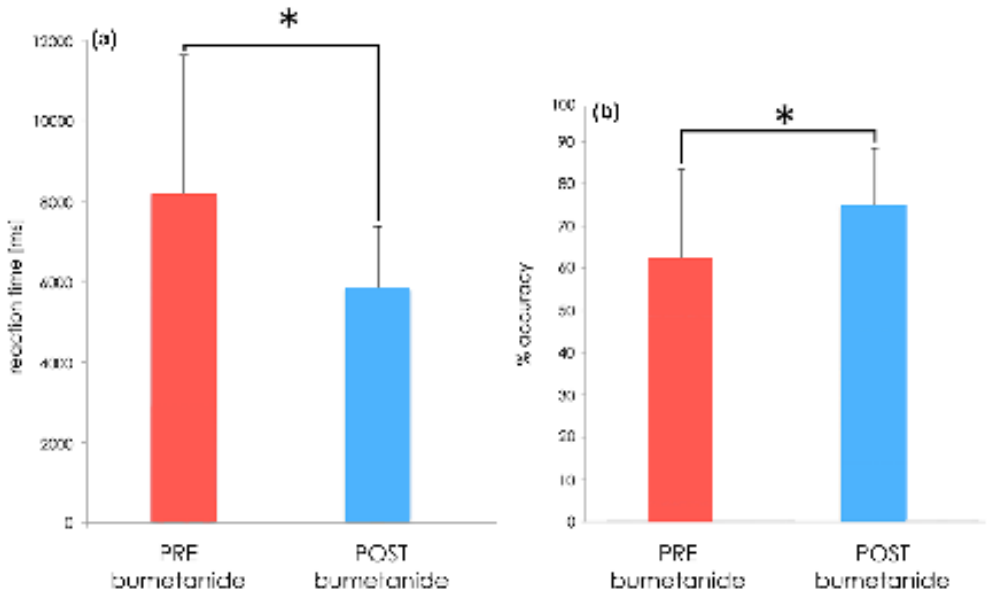
N. HADJIKANI
Assistant Professor
HARVARD & Goteborg

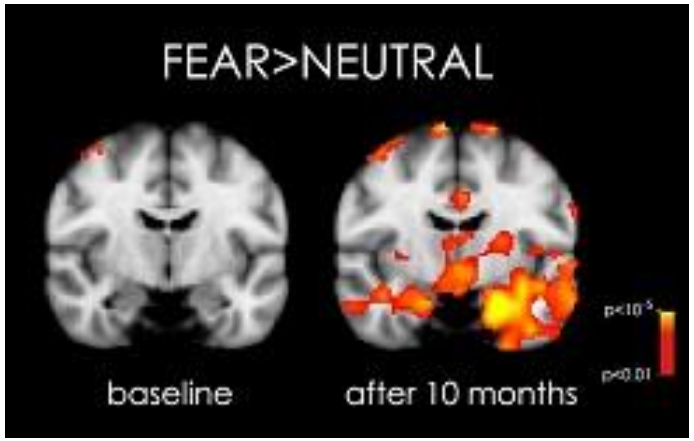
Bumetanide augments visual connections and attenuates activation of amygdala in functional MRI











Hadjikhani et al, Autism, 2015; Scientific Reports 2018

Brain treatments: a cemetery of trials & billions (over 90% failures)

Clinical needs

INNOVATION: basic research

preclinical research

Clinical trial I to III

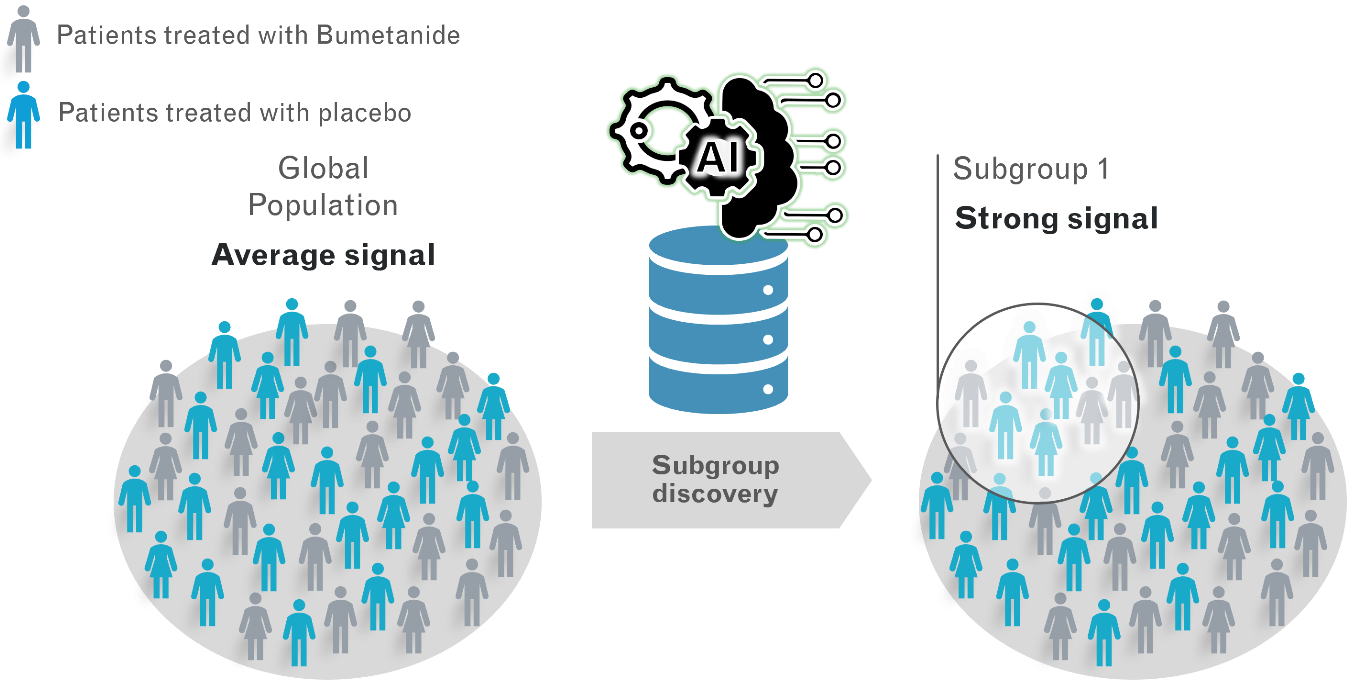
Medical validation
regulation
biocompatibility
industrialization

A contract with Servier for phase 3

- Licence for Europe acquired by Servier for phase III
- 2-18 years old, EU/Brazil/USA/Australia, 400 children /adolescents
- `but in spite of hundreds of children treated successfully ….it failed
- ***no significant difference between treated and placebo (placebo levels increased ++)***

- ***BUT results based on a single value –CARS – a mean of 15 different parameters or SRS – a mean of 65 different parameters***

Machine Learning identifies children who respond to bumetanide (20-40%)



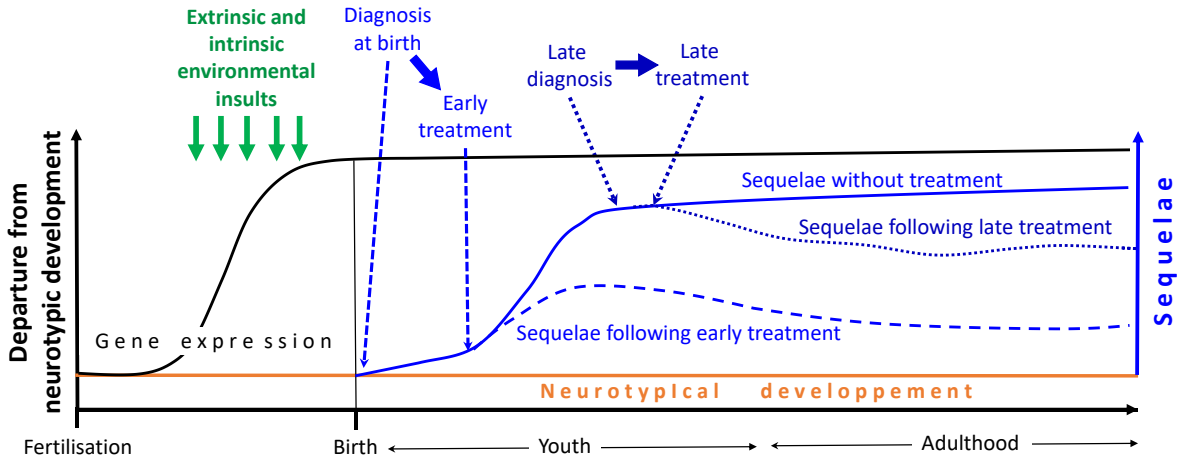
- BUT new trials in Holland suggest that bumetanide is efficient in sub-populations of children with autism, Bumetanide restores control EEG and clinical features
- EEG alterations enable to identify responders like immunological features
- **We identified subpopulations of children with autism having specific clinical features in various ITEMS of SRS CARS DSM5 etc. implying that a trial centered on these children will be successful**

Conclusions

- To treat brain disorders, it is instrumental to understand brain development and how developmental sequences are deviated by early insults
- Drugs capable of selectively blocking “immature-misplaced-misconnected” neurons are potential efficient treatments of many brain disorders
- Genetic tools will be inefficient when disorders are born in utero
- We shall not cure these disorders but attenuate them

IBEN

Early treatment –better outcome



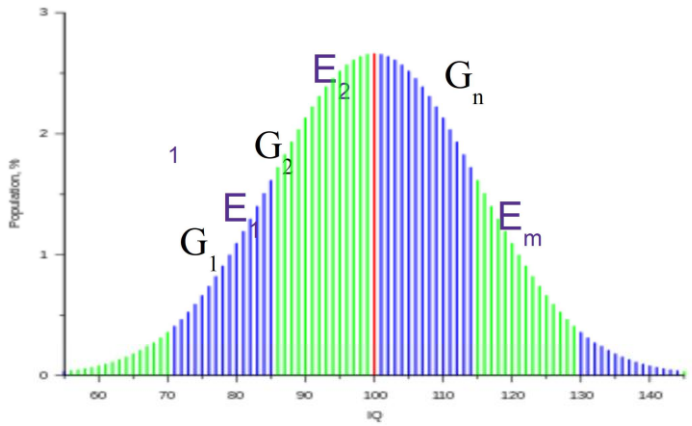
6

Et la génétique dans tout ca???

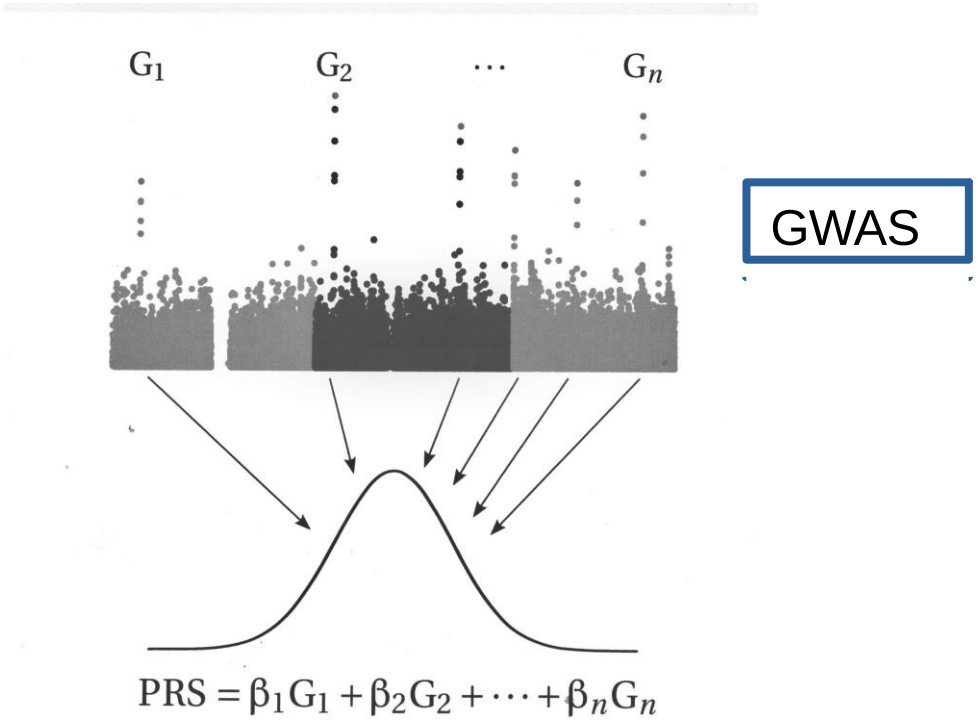
The unjustified attraction to genetic explanations of autism

- **We are not dealing here with monogenic disorders – that are readily identifiable and useful to determine underlying mechanisms**
- **These include Huntington chorea, Rett syndrome, tuberous Sclerosis etc**
- **But also a few genetic mutations clearly associated with ASD ---BUT they concern – very small % of children with ASD and in most cases are based on inappropriate assumptions**
- **2 widely used approaches – GWAS and Twins studies**
-

Genome Wide association study (GWAS)
Calcul du score polygénique



Modèle de Fisher



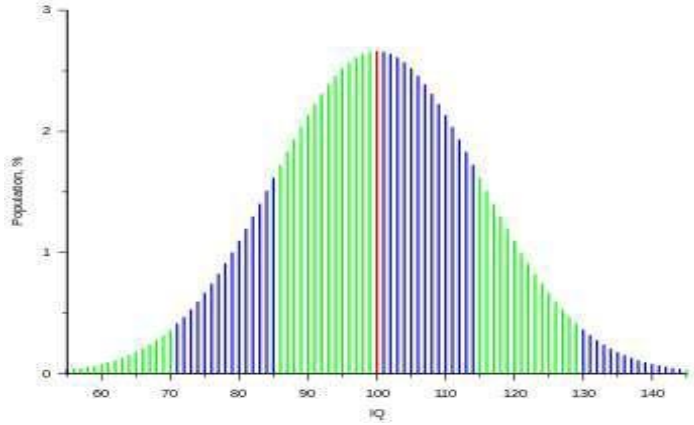
GWAS

On ajoute l'effet des facteurs détectés par association en supposant que tous ces facteurs sont génétiques et qu'il n'y a pas d'interaction

Genome-Wide Association studies - GWAS

Based on a polygenic model developed by Fisher (1919)

The major assumptions/ conditions required to use GWAS are never met in human studies: (*i*) the disease must be homogeneous, (*ii*) generated by many independent genetic factors, (*iii*) each endowed with small effects, and that (*iv*) must not interact with the environment. These conditions are never met in human studies casting serious doubt on their use in medicine [4].



Robette N, Génin E, Clerget-Darpoux F. Heritability: What's the point? What is it not for? A human genetics perspective. *Genetica* 2022;**150**(3-4):199-208.

Les études de jumeaux sur l'autisme

Frazier, T.W et coll. (2014) A twin study of heritable and shared environmental contributions to autism. J Autism Dev Disord

taux de concordance T_M des jumeaux MZ 76 %
taux de concordance T_D des jumeaux DZ 34 %

$$h2 = 2 (T_M - T_D) = 84\ \%$$

Si une mutation de novo est germinale ou se produit avant la division du zygote en deux embryons, elle sera présente chez les deux embryons.

En revanche, deux enfants d'une même fratrie, non issus d'un même zygote, n'ont quant à eux qu'une très faible probabilité de porter une même mutation de novo .

MZ twins are the result of a single fertilised egg, whereas DZ twins are the result of two eggs each fertilised by different sperms. A discordance for a trait in MZ twins is interpreted as resulting from different environmental factors, whereas a higher concordance rate in MZ twins than in DZ twins is interpreted as resulting from genes, ignoring environmental factors [13]. These methods make two major unmet assumptions, (*i*) **MZ twins are genetically identical, while DZ twins share 50% of their genome, and (*ii*) environmental exposure are equivalent for both throughout embryonic development. Assumption (*i*) that MZ twins share the same genetic composition is, however, challenged by the fact that 15% of *de novo* mutations are specific to one of the twins [14].** Furthermore, **MZ twins also share the same placenta, as well as friends, classes, parental care etc. to a larger extent than DZ twins, which can only increase their resemblance beyond their genetic similarity [4]. Thus, such assumptions ignore the impact of environmental factors [15, 16], which are often denied [10],** and leading to overestimated heritabilities. The many placenta mediated DNA methylation effects [17] should make epigenomes far more similar in MZ than DZ twins [18], and indeed the MZ genomes are identical early in life but become different as they grow older [19].Therefore, despite the large number of rare genetic mutations identified, most children with ASD lack specific genetic diagnosis, challenging their clinical relevance [20], and suggesting moderate genetic heritability with a substantial role of shared environmental components in twins [21].

Only a minority of *de novo* mutations are postzygotic. Generated by a single or several cell lineages, pre-twining mutations can increase the differences between germline genomes of MZ twins [14]. A large study of parental influence on the germline in Iceland describes an unexpectedly large level of sequence diversity linked to **complex interactions between age, sex, mutation type and genomic location** [12, 27], implying a large variety of interacting factors that cannot be readily included in a single genetic model [28]. Furthermore, heritability cannot be interpreted as revealing the proportion of DNA sharing when causal variants are *de novo* mutations [4] or involve inherited **epigenetic variants .**

Geier DA, Kern JK, Sykes LK, *et al. The Application of Clinical Genetics* 2016;**9**:121-9.
Jónsson H, Sulem P, Kehr B, *et al. Nature* 2017;**549**(7673):519--.

Many risk factors linking the environment and autism (>140)

Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses

Amirhossein Modabbernia1*, Eva Velthorst1,2 and Abraham Reichenberg1,2,3,4 Mol Autism 2017

Table 1 Summary of meta-analyses of environmental risk factors for autism spectrum disorders

Risk factor [ref], year	No. of studies	Study design	Estimates	Precision	Consistency	Directness	Publication bias
Advanced parental age [23], 2017							
• Highest paternal age category	20	4 cohort; 16 case-control	+	+	−	+	Absent
• Highest maternal age category	19	4 cohort; 15 case-control	+	+	−	+	Absent
Labor [25], 2011							
• Prolonged labor	9	NA	+/−	−	−	+	Absent
• Induced or augmented labor	8	NA	+/−	−	−	+	Absent
• Precipitous labor	5	NA	+/−	−	−	+	Absent
• Premature rupture of membranes	7	NA	+/−	−	+	+	Absent
Delivery options [25], 2011							
• Cesarean section [29], 2015	21	6 Cohort; 15 case-control	+	+	−	+	Absent
• Emergency cesarean	4	NA	+/−	−	−	+	Absent
• Elective cesarean	2	NA	+/−	−	−	+	Absent
• Delivery anesthesia	7	NA	+/−	−	+	+	Absent
• General anesthesia	3	NA	+/−	−	+	+	Absent
• Assisted vaginal delivery	14	NA	+/−	+	+	+	Absent
• Forceps	7	NA	+/−	−	+	+	Absent
• Vacuum extraction	2	NA	−/+	−	−	+	Absent
Conditions at birth [25], 2011							
• Abnormal presentation	15	NA	+	−	−	+	Absent
• Breech presentation	4	NA	+	−	+	+	Absent
• Cord complications	14	NA	+	−	+	+	Absent
• Fetal distress	4	NA	+	−	+	+	Absent
• Birth injury or trauma	6	NA	++	−	+	+	Absent
• Twins or multiple birth	10	NA	+	−	−	+	Absent
Maternal hemorrhage [25], 2011	4	NA	++	−	+	+	Absent
Timing of birth [25], 2011							
• January through March	4	NA	+/−	+	+	+	Absent
• April through June	4	NA	+/−	−	−	+	Absent
• July through September	4	NA	+/−	+	+	+	Absent
• October through December	4	NA	−/+	−	−	+	Absent[b]
• Fall	3	NA	−/+	−	−	+	Absent
• Winter	3	NA	−/+	−	−	+	Absent
• Spring	3	NA	−/+	−	−	+	Absent
• Summer	3	NA	+	+	+	+	Absent
Birth spacing (ref ≥36 m) [30], 2016	7	3 cohort; 3 cross-sectional; 1 case-control					
• <12 months	5	NA	+	−	−	+	NC
• 12–23 months	5	NA	+/−	−	−	+	NC
• 24–35 months	5	NA	−/+	−	−	+	NC
Birth spacing (ref 24–59 m) [30], 2016							
• <12 months	4	NA	+	−	−	−	NC
• 12–23 months	4	NA	+	−	−	−	NC
• >60 months	4	NA	+	−	−	−	NC

Environnemental insults

- Near Roadway Air pollution increases the incidence of autism
- Then the authors tested the effects of NO2 and particulate matter (PM 2,5 and 10) , ozone and near roadway air pollution during pregnancy on the children
- Among children with ASD, exposure during pregnancy (1st trimester) and first year post natal increases impairments in cognitive and adaptive skills & communication
- No effect on normotypic children

Kerin et al J of Autism dev disorders 2020, Volk et al Jama psychiatry 2013

Pesticides and autism/DDs

- mothers living, during pregnancy, within 1.5 km (just under 1 mile) of an agricultural pesticide application.
- Proximity to organophosphates during gestation was associated with a 60% increased risk for ASD, higher for third-trimester exposures (OR = 2.0; 95% CI: 1.1, 3.6), and second-trimester chlorpyrifos applications (OR = 3.3; 95% CI: 1.5, 7.4).
- Children of mothers residing near pyrethroid insecticide applications just before conception or during third trimester were at greater risk for both ASD and DD, with ORs ranging from 1.7 to 2.3.

Shelton et al environmental health perspect. 2014

Gestational impact of pesticides

Table 2. Mechanisms by which gestational exposure to certain classes of pesticides may induce observed pathophysiologic symptoms of autism.

Mechanism of action/ Route to autism pathophysiology	Observed effects	Specific pesticides	Class of pesticide	Reference
Developmental neurotoxicity				
Alteration of excitation/ inhibition mechanisms	Decrease in GABA receptors	Dieldrin (prenatal exposure in rats)	OCs	Brannen et al. 1998; Liu et al. 1998
	Inhibition of GABA	General function of OC, pyrethroid pesticides	OC, pyrethroid	
	Inhibition of AChE	General function of OP, CB pesticides	OPs, CBs	
Mitochondrial dysfunction				
Oxidative stress	Apoptosis of neuronal cells	Dichlorvos (rat brain)	OPs	
	Inhibition of mitochondrial respiration	Methoxychlor (mice brain)	OCs	Kaur et al. 2007; Schuh et al. 2005
Immune toxicity				
Immunosuppression	Decreased DTH and antibody production	Atrazine (gestational exposure to rats)	Triazine	Rooney et al. 2003
Neuroinflammation	Activation of human fetal astrocytes, increased expression of proinflammatory cytokines	Cyfluthrin, chlorpyrifos (primary human fetal astrocytes)	Pyrethroid, OPs	Mense et al. 2006
Maternal hypothyroxinemia				
Insufficient gestational thyroid hormones	Decreased T_4, inhibition of T_4 deiodination to T_3, prevention of iodine uptake	Acetochlor, alachlor, mancozeb, thiocyanates, 2,4-D, aminotriazole, endosulfan, malathion (multiple animal studies)	OCs, thiocyanates, OPs	Cheek et al. 1999; Colborn 2004; Goldner et al. 2010; Rathore et al. 2002

Shelton et al environmental health perspective 2012

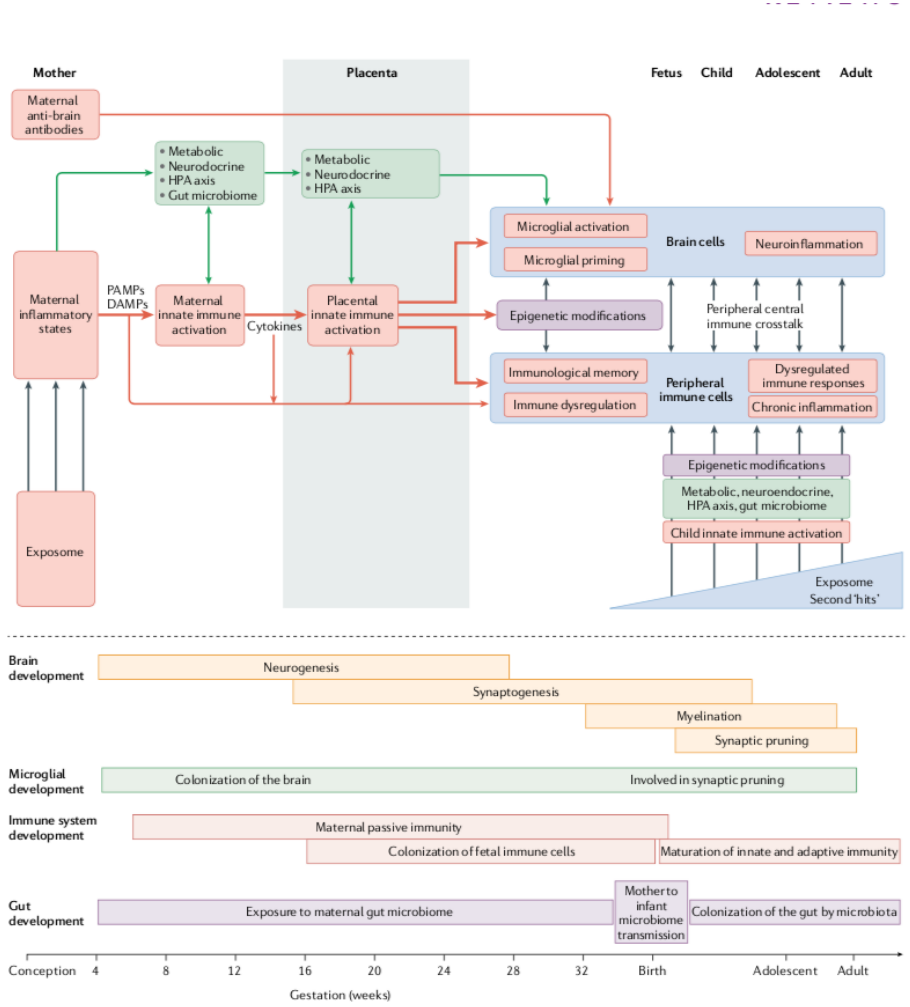
Infections and insults during maternity

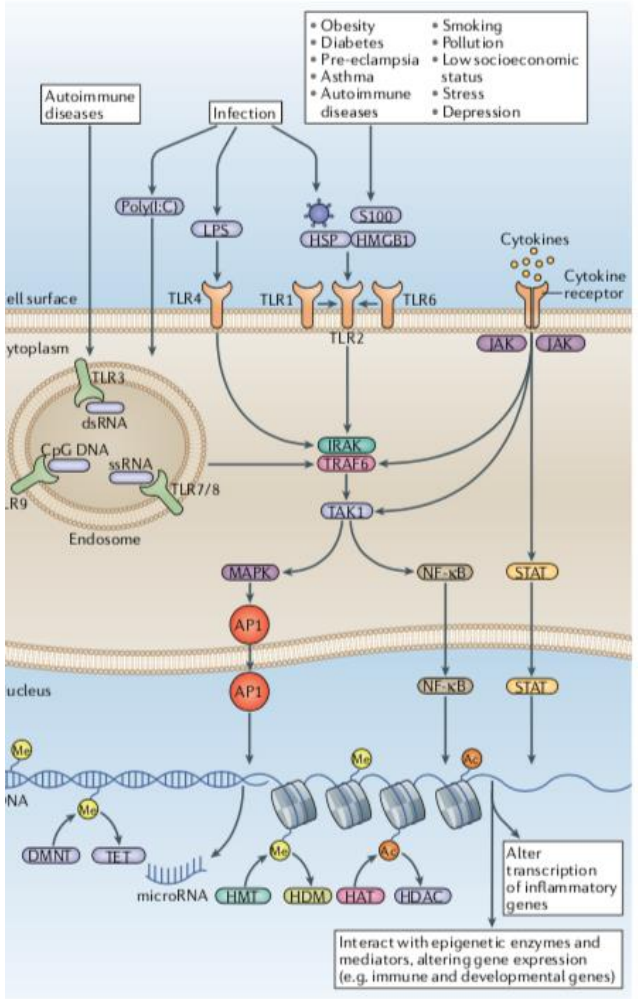
- Prenatal exposure to a wide range of insults –viral or bacterial infections- or simply severe inflammation alters subtly brain development leading to brain disorders including Autism and Developmental disorders
- Extensive experimental and clinical evidence is available
- Maternal immune activation and immunological insults etc
- Maternal influenza,
- Torch pathogens (Rubella, CMV etc).
- the timing of the insult might be instrumental in the pathogenesis of the disorder

- Une métanalyse liste environ 140 facteurs environnementaux impactant les TSAs

Al-Haddad et al American journal of Obstetrics & gynecology 2019, Patterson P curr opinion neurobiol. 2002, shi et al int j dev neurosci. 2005

Maternal immunity

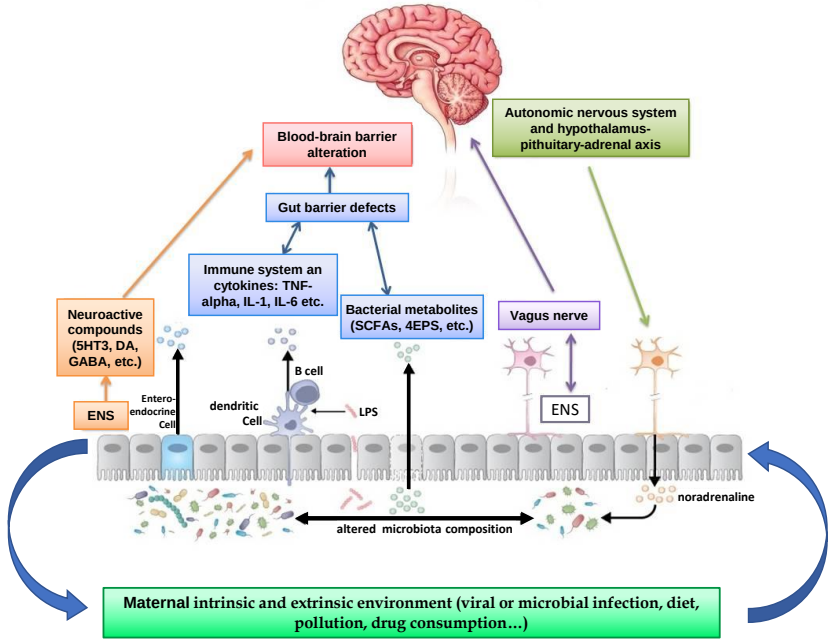




Han et al Nature Neuros. Rev 2021

Gut Brain interactions & microbiota

The contribution of the gut-brain-immune axis
In disorders like ASD that are born in the womb, many extrinsic and intrinsic environmental insults alter the normal developmental sequence. Among these many environmental insults *in utero,* gut-brain-immune interactions have been directly linked to ASD including pathogenesis and are often underestimated (**Figure 1,** and [11, 44]



Summary factors impacting pathogenesis of Neurodevelopmental disorders

- **Environmental insults**
- **The contribution of the gut-brain-immune axis**
- **Maternal viral/microbial infections**
- **Epigenetic alterations**
- **Inflammatory /immune activation**

In disorders like ASD that are born in the womb, many extrinsic and intrinsic environmental insults alter the normal developmental sequence. Among these many environmental insults *in utero,* gut-brain-immune interactions have been directly linked to ASD including pathogenesis and are often underestimated

Des associations discutables

Comparaison jumeaux HZ et DZ propriétaire d'un chien

- **35035 paires de jumeaux, plus grande concordance chez HZ que DZ**
- **Conclusion: être propriétaire d'un chien a une forte composante génétique**

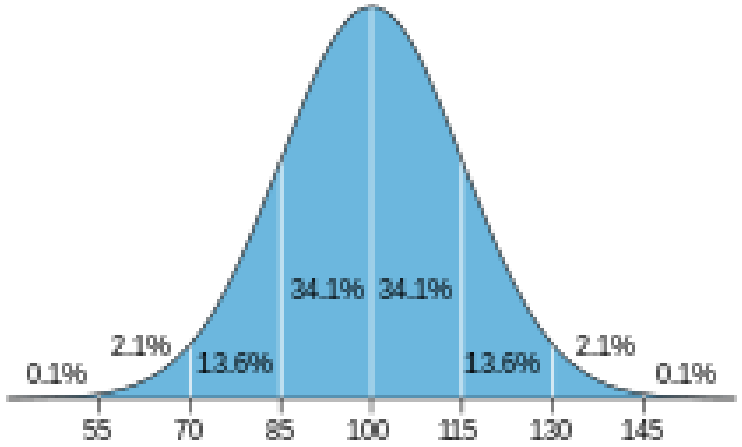
- **Héritabilité de la tuberculose estimée à 86% (différences HZ /DZ)**
- **Cela ne veut pas dire que génétique 86 et environnement 14%**

- **436 jumeaux avec un enfant adopté et l'autre élevé par les parents biologiques**
- **Enfants adoptés ont Qi 4,41 + élevé que biologiques (famille avec statut économique + élevé)**

- **« Familial Aggregation of Quantitative Autistic Traits in Multiplex versus Simplex Autism » , on observe des différences entre les paramètres de l'autisme selon que celui ci est familial et de novo**

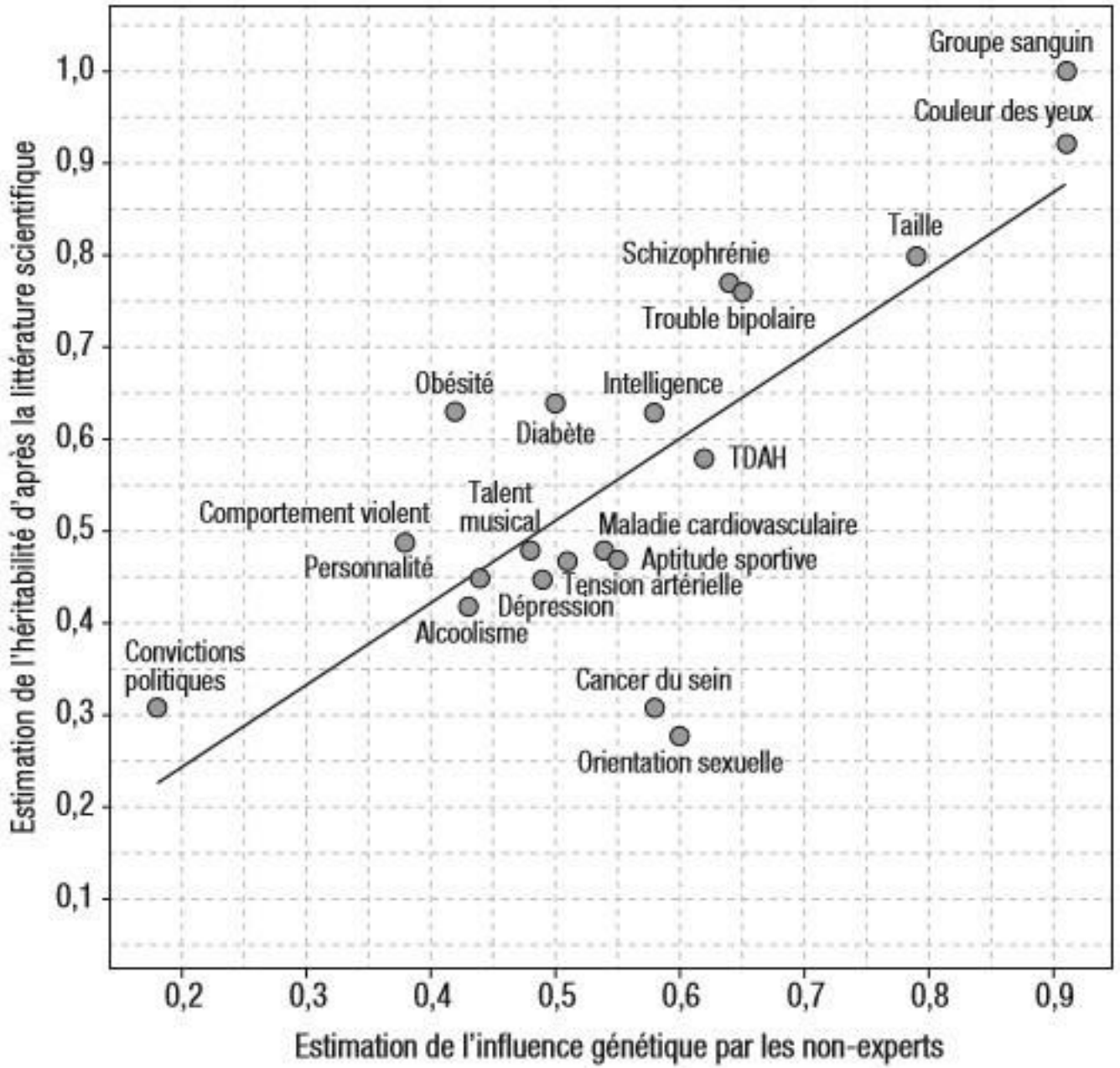
Narabanhai microbiol.spect.2016, fal et al sci.rep.2019, kendler et al PNAS 2015

Le quotient Intellectuel (QI)

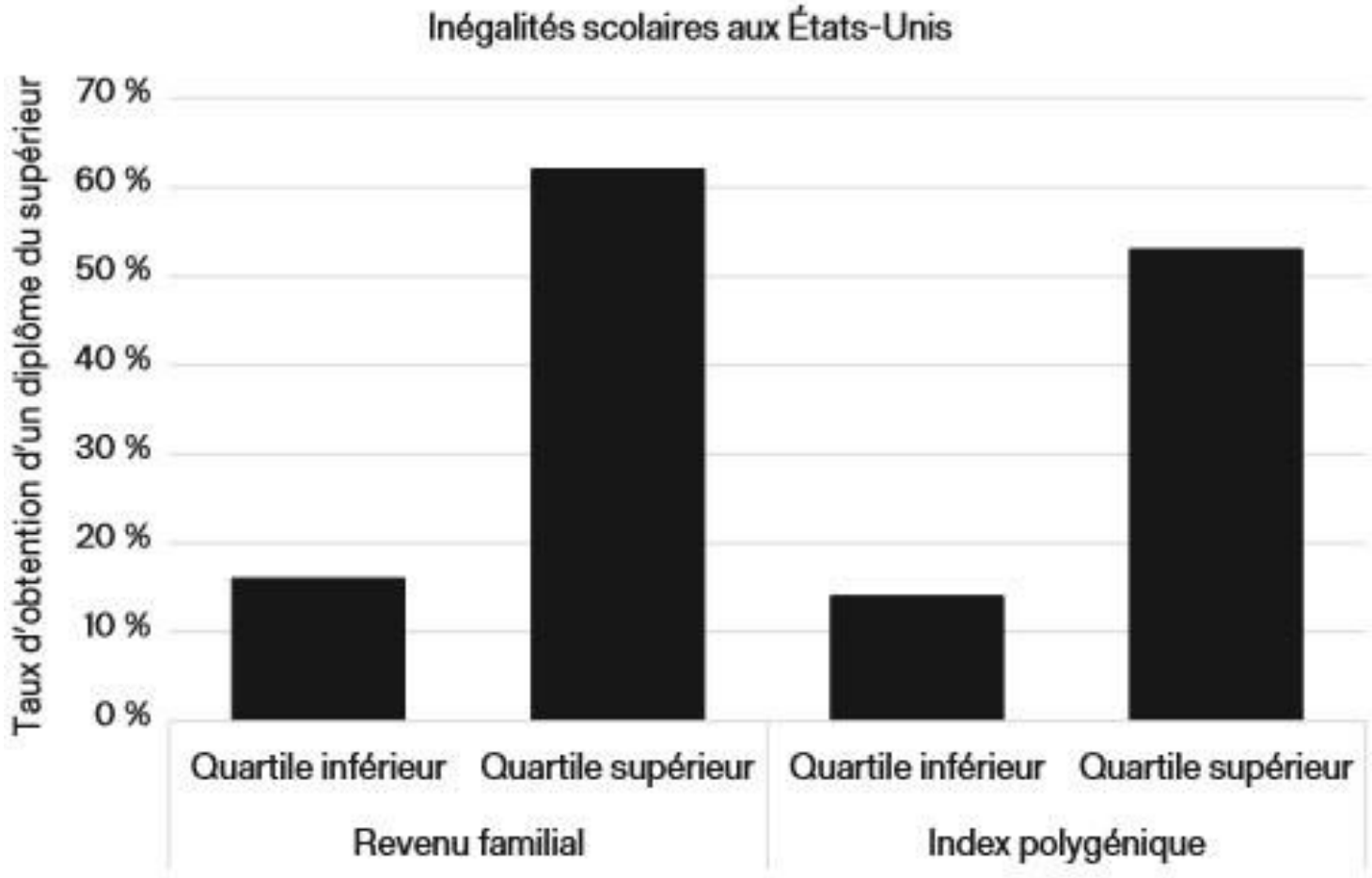


Test de Binet- Simon → QI → mesure d'aptitudes scolaires

Donner une valeur d'héritabilité du QI, c'est mesurer la contribution génétique à la variabilité du QI. C'est donc pouvoir séparer les effets de nos gènes de ceux de notre environnement familial, social, scolaire ...


Groupe sanguin
Couleur des yeux
Taille
Schizophrénie
Trouble bipolaire
Obésité
Intelligence
Diabète
TDAH
Talent musical
Comportement violent
Maladie cardiovasculaire
Personnalité
Aptitude sportive
Tension artérielle
Dépression
Alcoolisme
Convictions politiques
Cancer du sein
Orientation sexuelle
Estimation de l'héritabilité d'après la littérature scientifique
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
Estimation de l'influence génétique par les non-experts

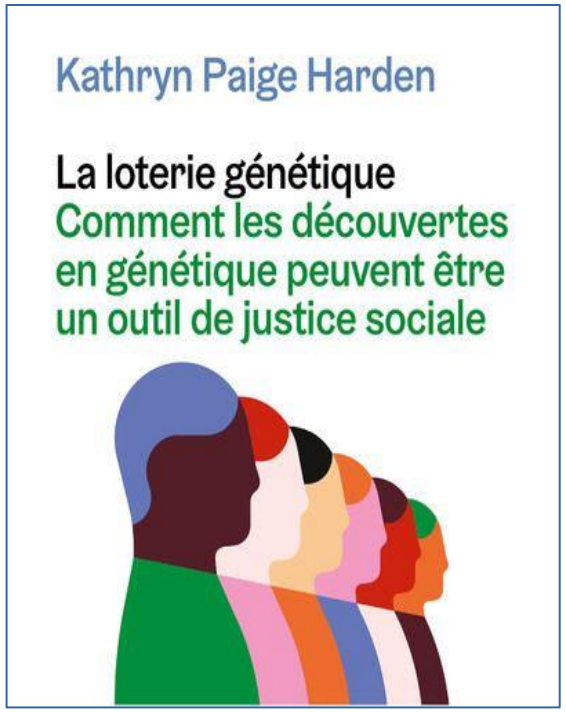
Index polygénique et inégalité sociale



Down tuning the exclusive roles of genetics

- Several hundreds mutations possibly involved in autism but none genuinely compellingly causally related .. probably many mutations are needed to be sure that autism will prevail
- Yet, to understand what the mutation does, it is crucial to determine whether and how it alters developmental sequences
- Therapeutic interventions will rely in the future on specific drugs that block immature currents in the neonatal/adult brain
- “Environment” cannot be ignored
- Therefore to understand and treat, all our efforts must be placed in pathophysiology of brain development

IBEN



Aider plus ceux qui ont eu peu de chance à la loterie génétique (ceux qui ont un mauvais score génétique)

Par exemple plus d'aide scolaire à ceux
qui ont un petit score génétique d'aptitude scolaire

Utiliser les données génétiques
pour créer plus d'équité

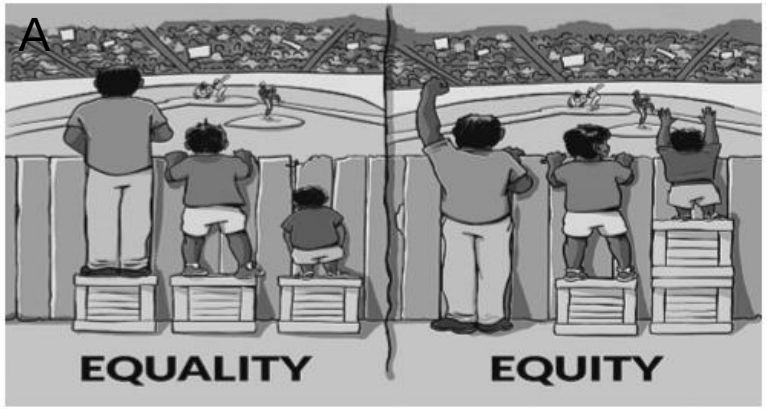


FIGURE 8.1. **Égalité *versus* équité.** Dessins de l'*Interaction Institute for Social Change*.

Pour les curieux qui veulent mieux comprendre les conditions et l'interprétation d'un calcul d'héritabilité et de l'autisme

Voir Wikipédia : Héritabilité (rédigé par F Ramus)

ou l'article : « Heritability: What's the point? What is it not for? A human genetics perspective » Genetica. 2022 Aug;150(3-4):199-208.

Le monde: https://www.lemonde.fr/sciences/article/2023/05/12/genomique-la-part-de-variabilite-liee-a-l-environnement-ne-peut-plus-etre-niee_6173078_1650684.html#xtor=AL-32280270-

https://leblogdebenari.com/

Y Ben-Ari - Les 1000 premiers jours; humensciences 2021

Y Ben-Ari, N Hadjikhani & E. Lemonnier
Traiter l'autisme au delà de la génétique et de la psychanalyse
De Boeck 2019

T Bourgeron , des gènes des synapses et des autismes
Odile jacob 2022