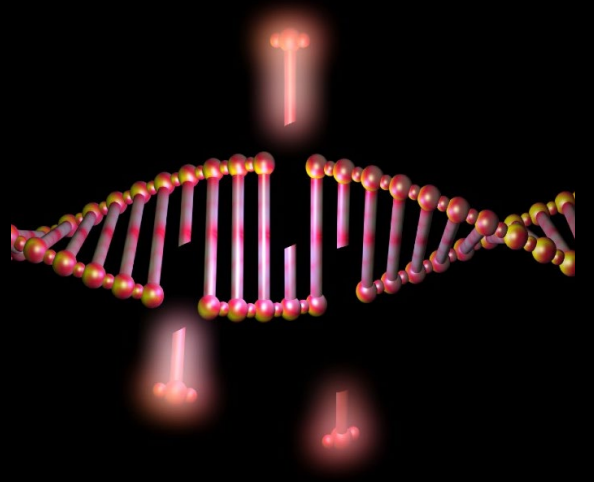
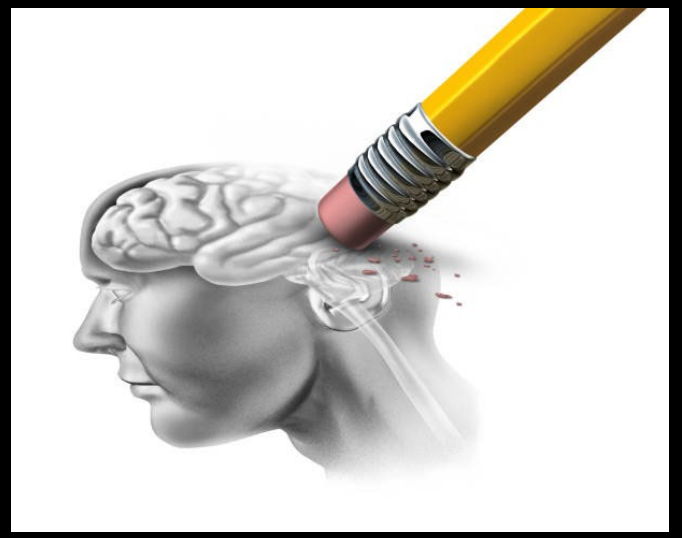




Etats internes et maladies neuropsychatriques

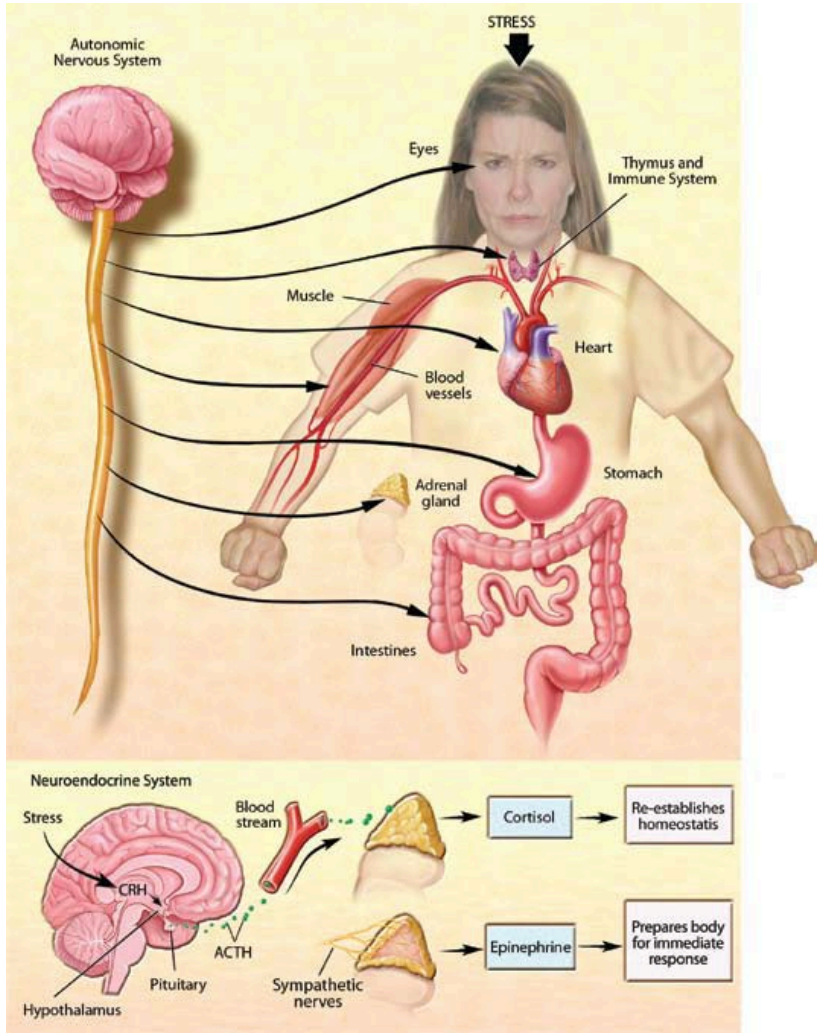
Prof. Alan Carleton et Prof. Denis Jabaudon

Département de Neurosciences Fondamentales

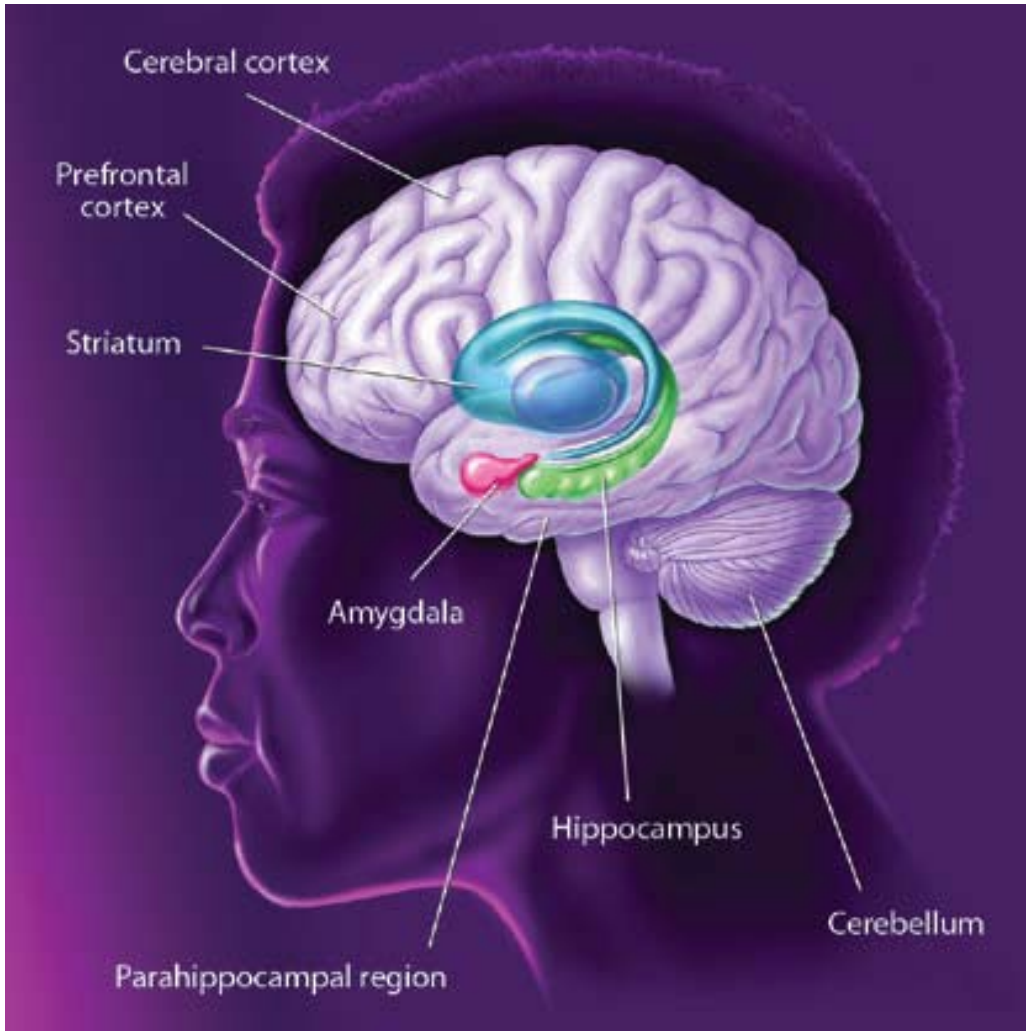
…et nous au milieu!

Cours 10

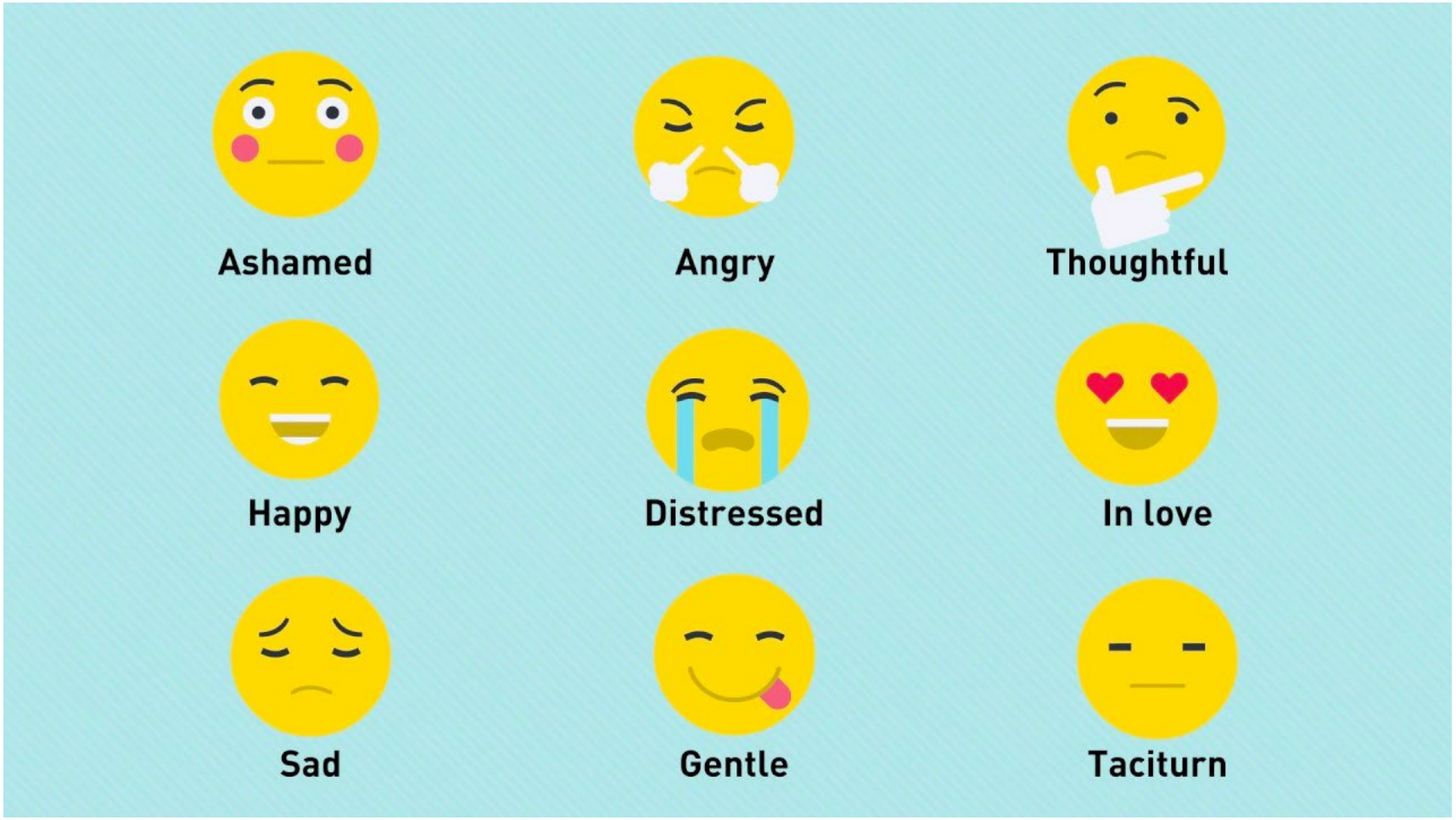
Emotions



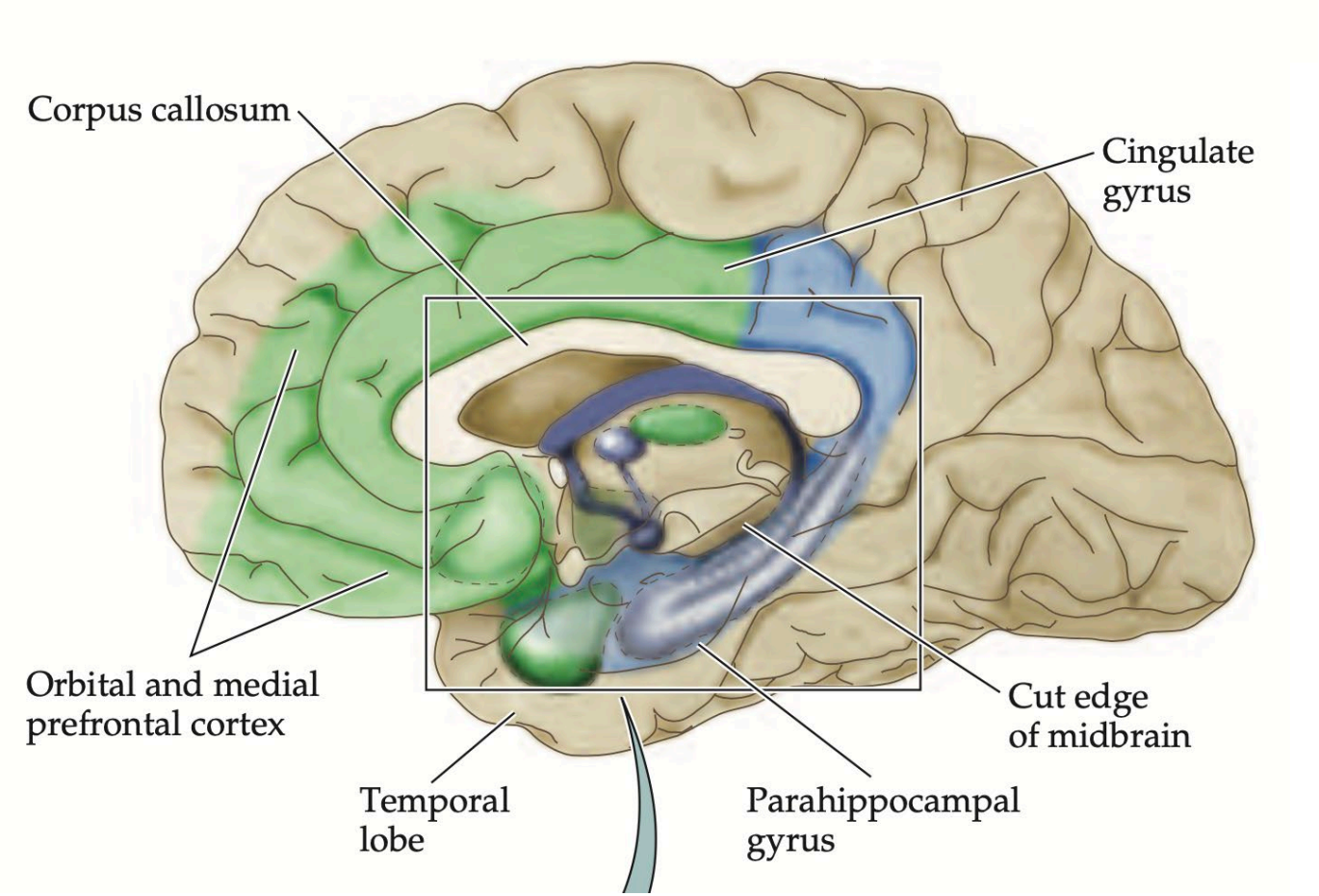
Cognition

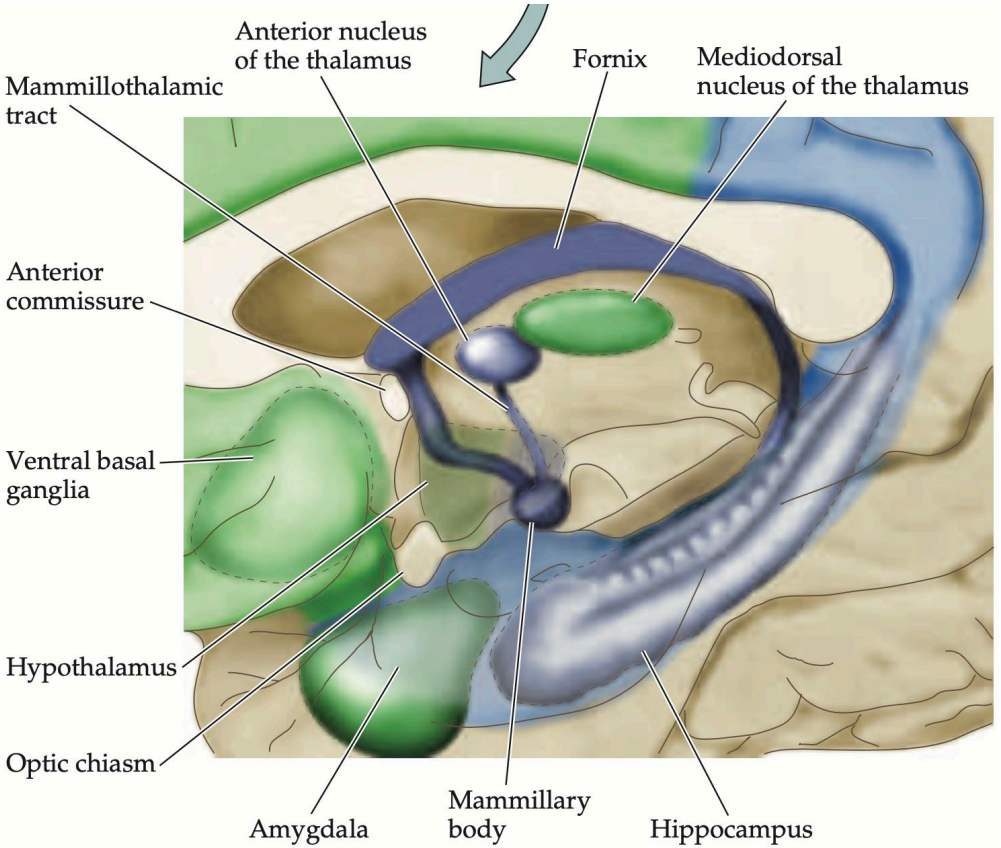


Les émotions

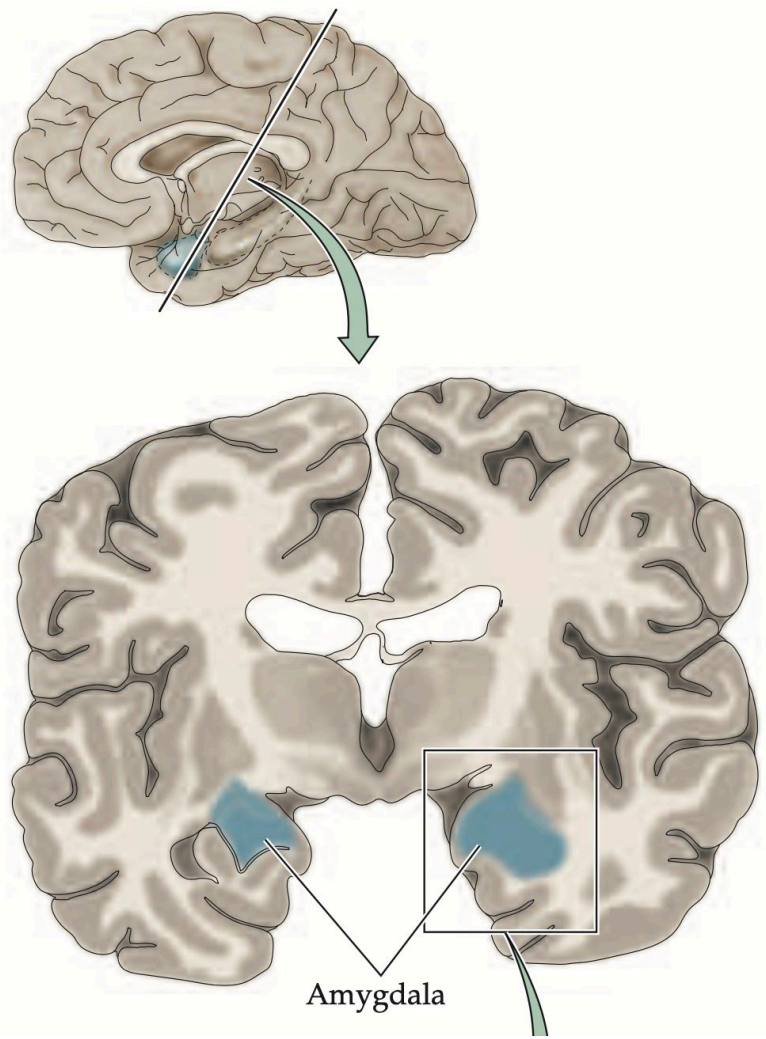


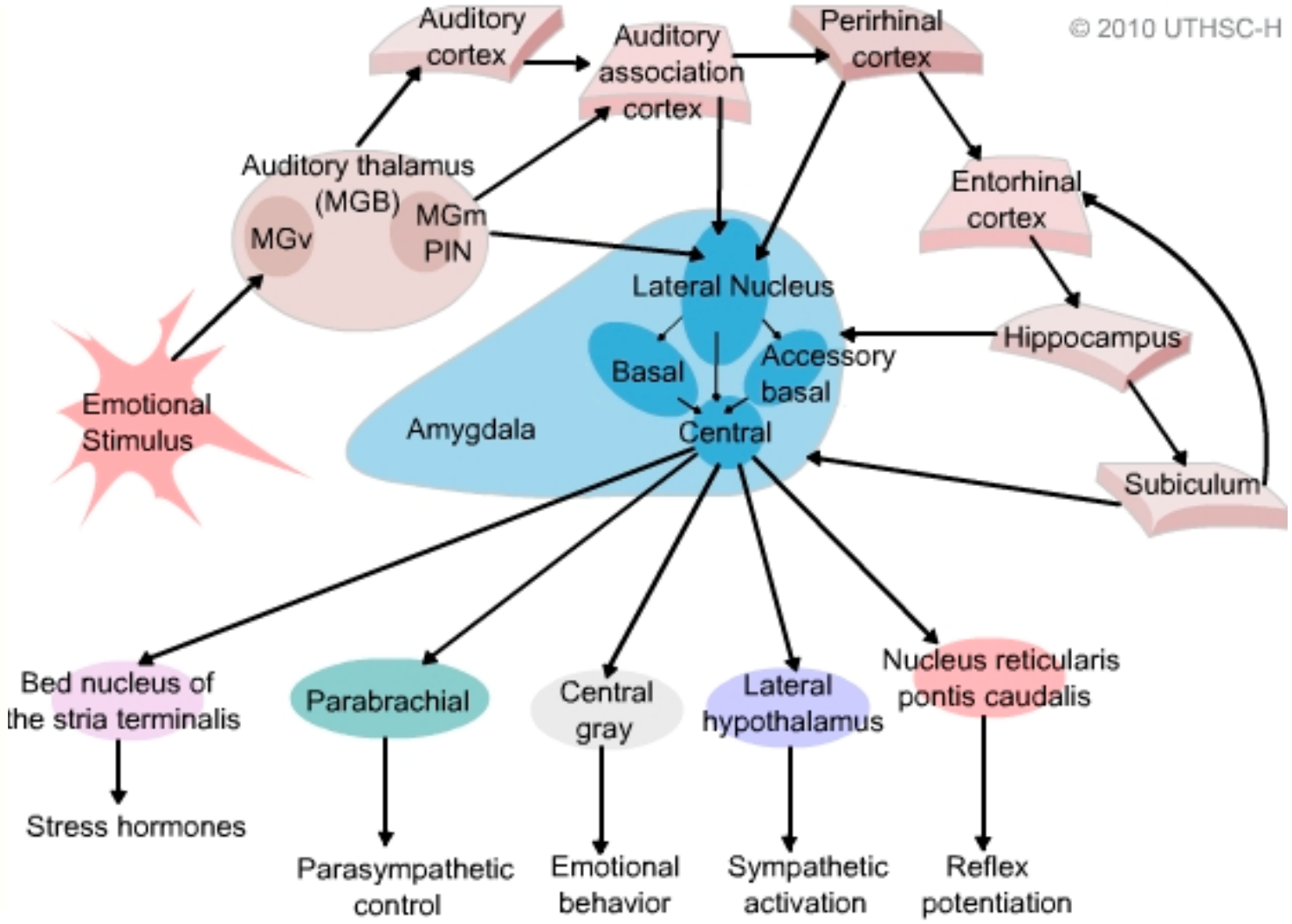
Système limbique et émotions





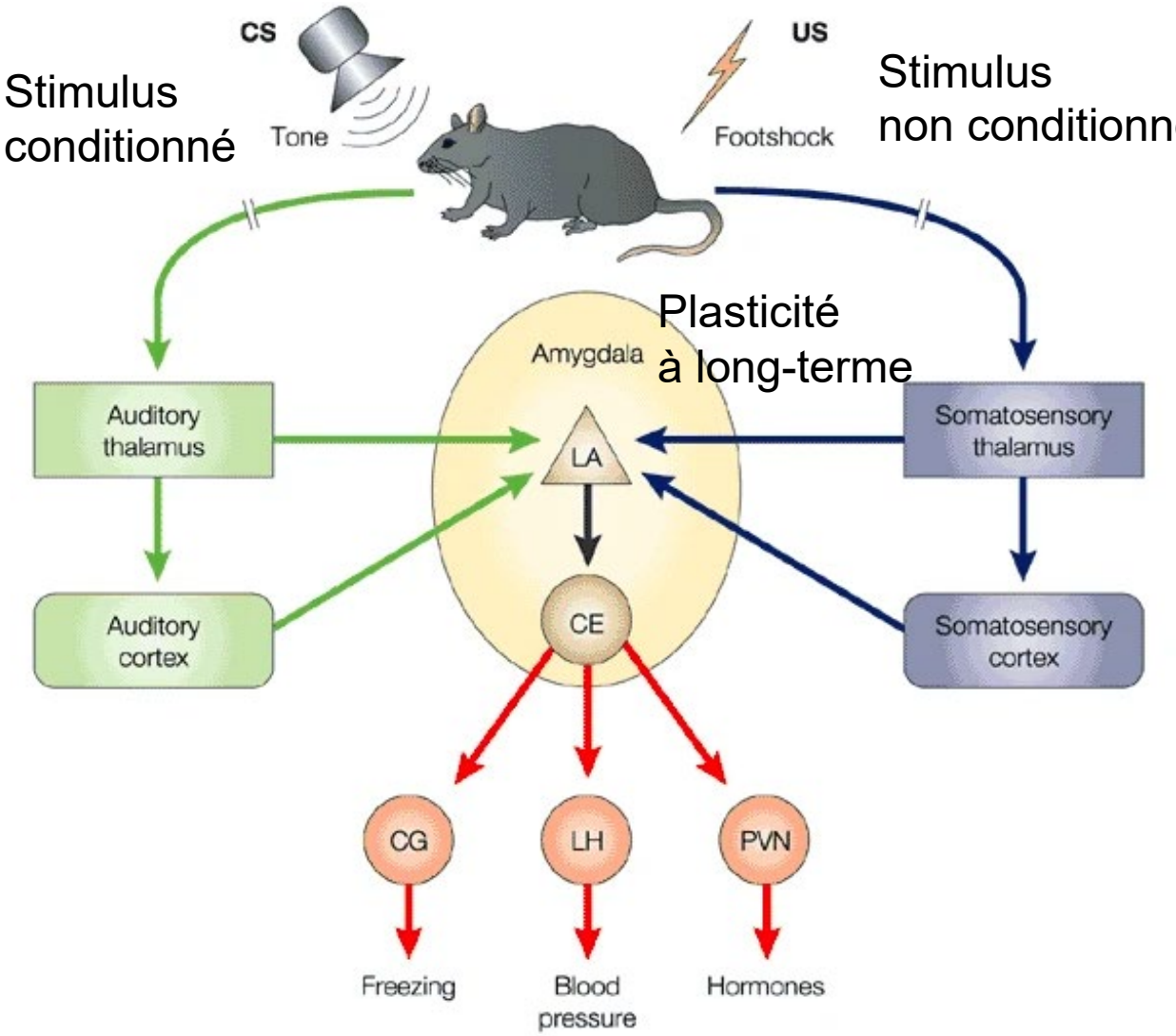
L’amygdale et les circuits de la peur





Amygdale et conditionnement à la peur

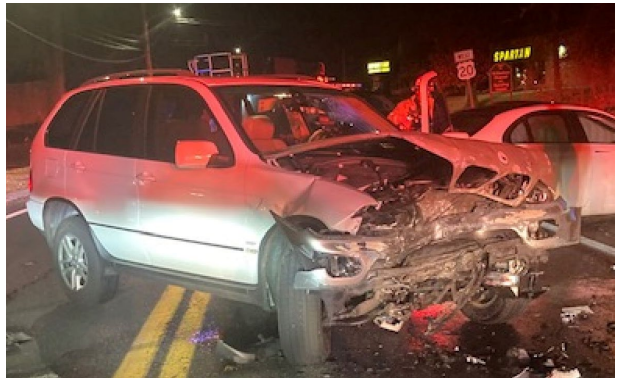
Stimulus conditionné



Stimulus non conditionné

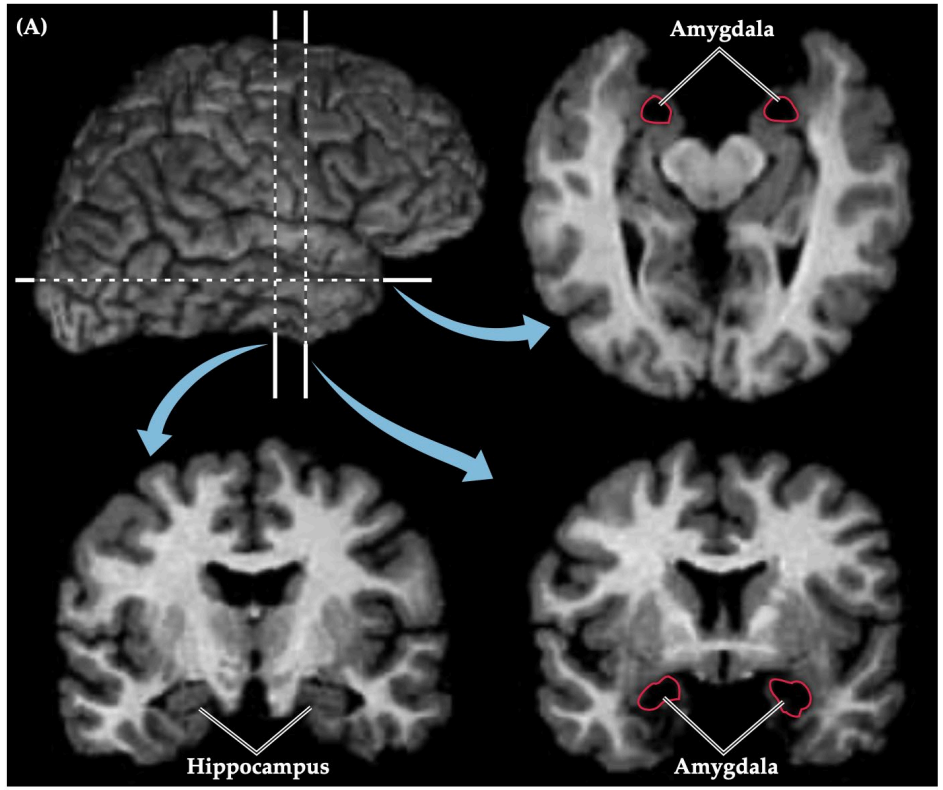
Plasticité à long-terme

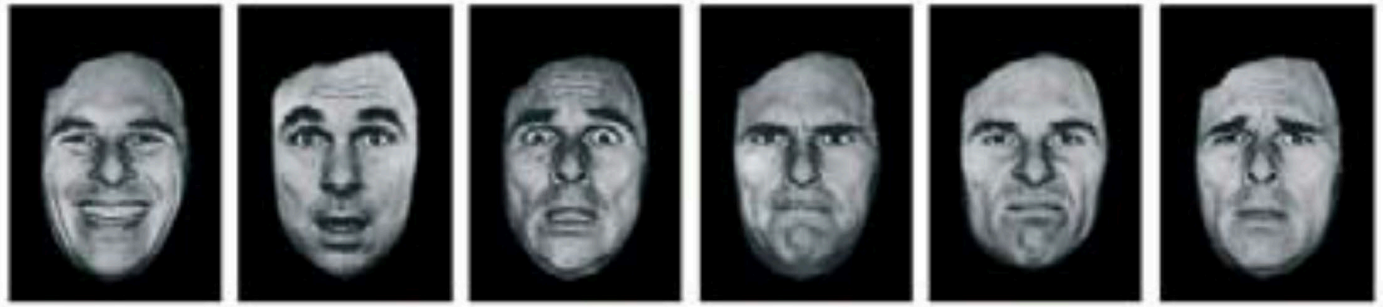
https://youtu.be/mi2gqhHw1N0

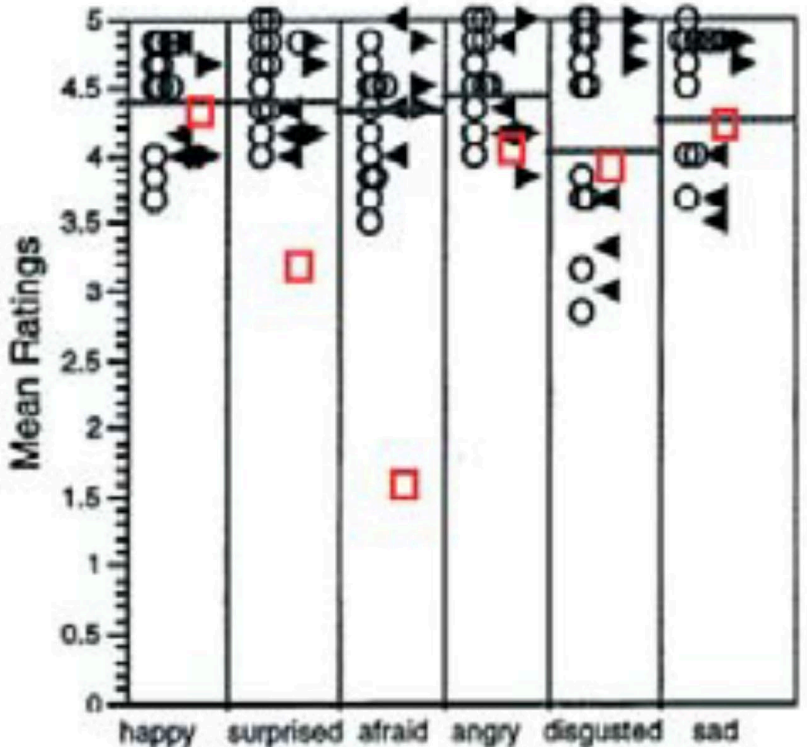


Syndrome de Stress post-traumatique (PTSD)

Amygdale et reconnaissance des émotions

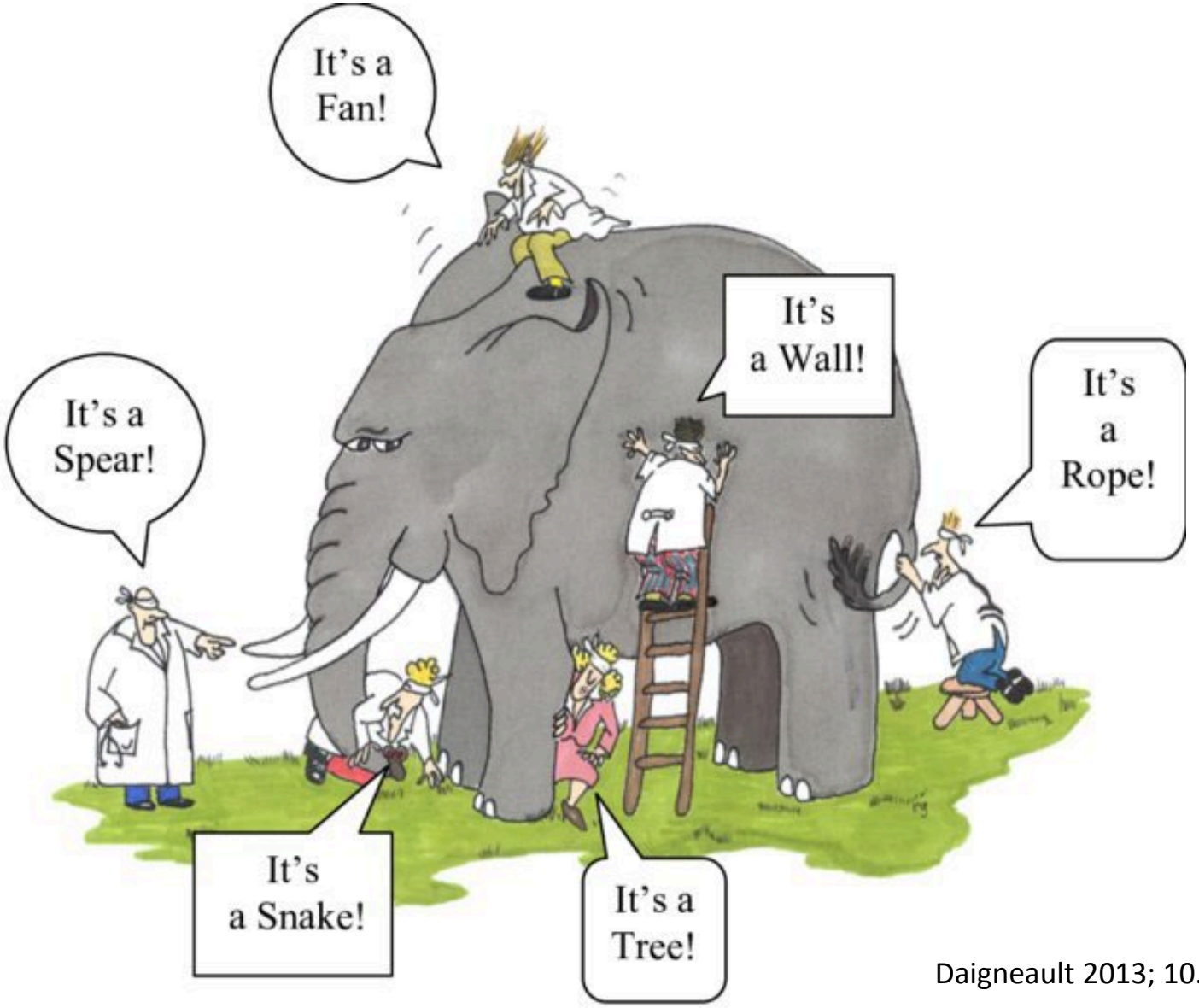






Brain-damaged controls
Normal controls
Left Amygdala damage
Right Amygdala damage
Patient SM: Bilateral damage

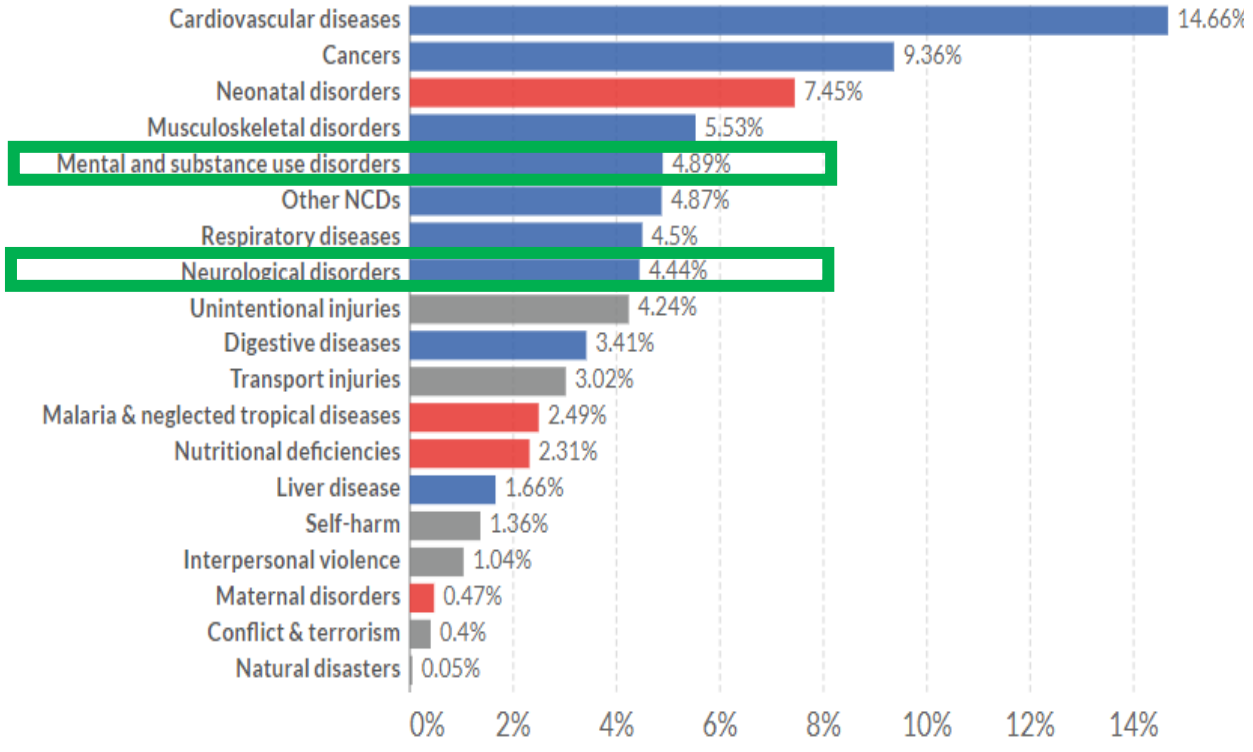
Comment étudier les maladies du cerveau?



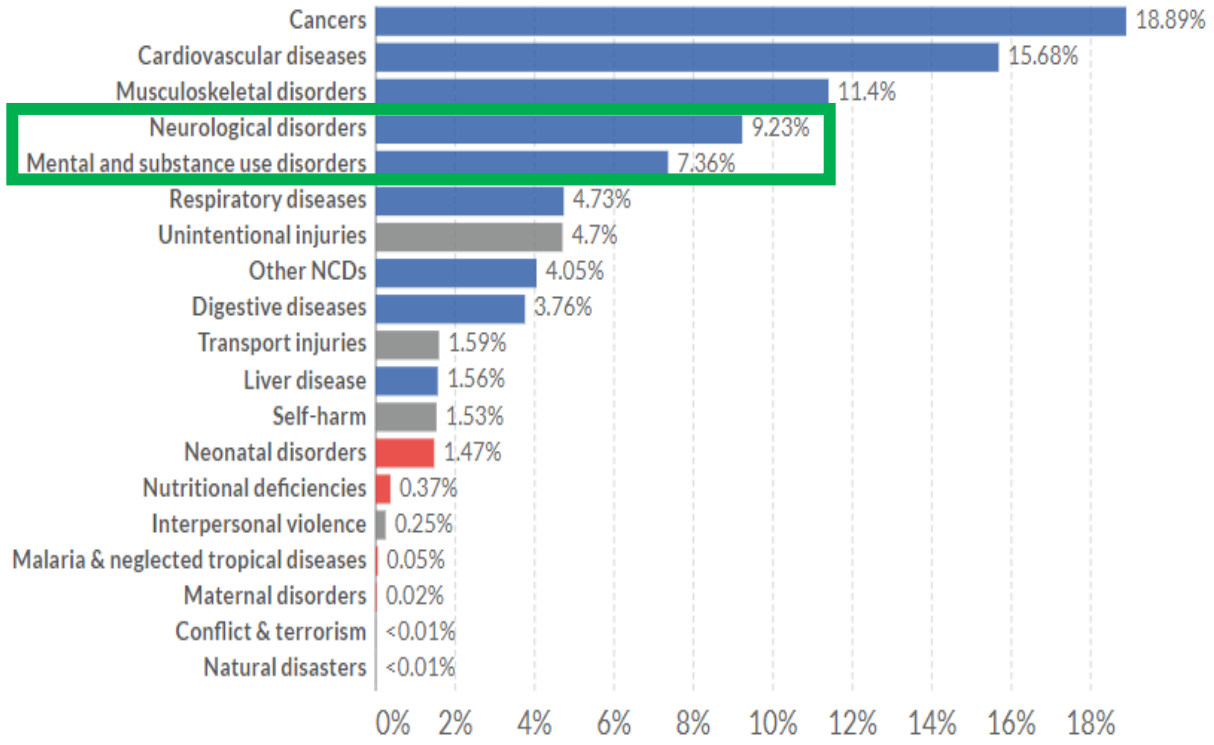
Daigneault 2013; 10.4256/mio.2013.015

Les maladies et leur impact sur l'espérance de vie corrigée

Monde (2017)



Europe de l'ouest (2017)

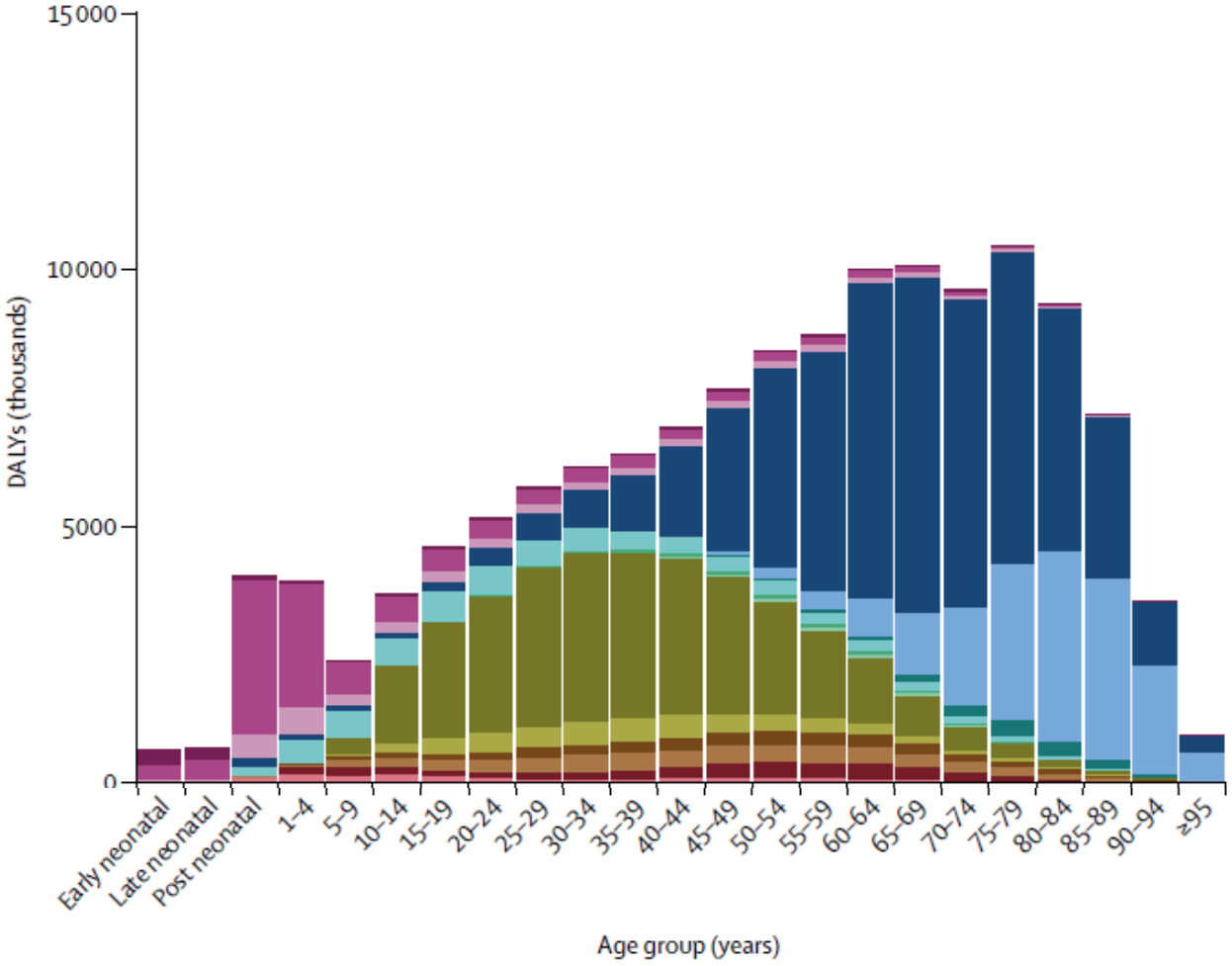


https://ourworldindata.org/burden-of-disease

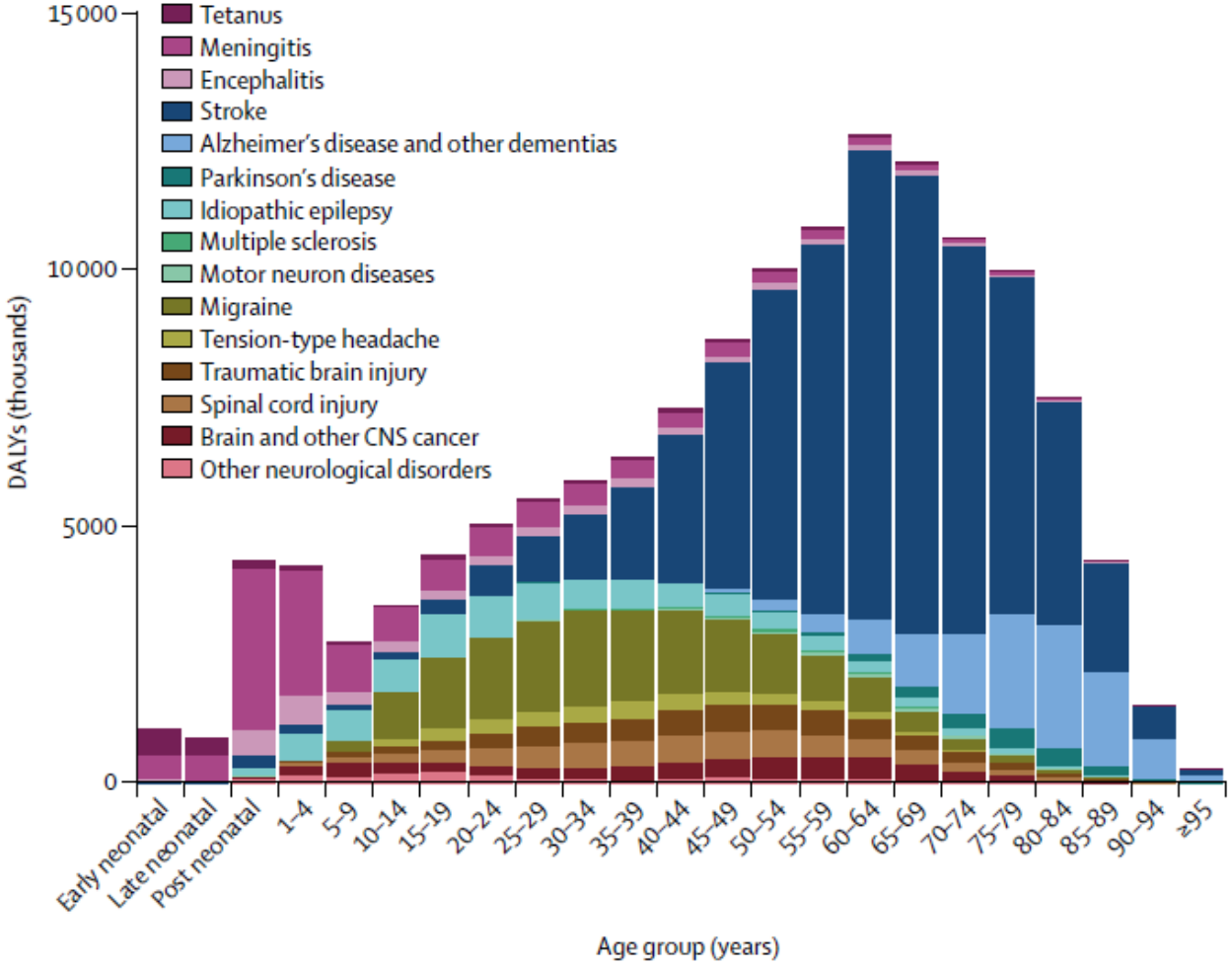
« L'**espérance de vie corrigée de l'incapacité** (**EVCI**) est un mode d'évaluation du coût des maladies mesurant l'espérance de vie en bonne santé, c'est-à-dire en soustrayant à l'espérance de vie le nombre d'années « perdues » à cause de la maladie, du handicap ou d'une mort précoce (**DALY en anglais)**. »
1 DALY = 1 année de vie en bonne santé perdue

Les maladies neurologiques

FEMME



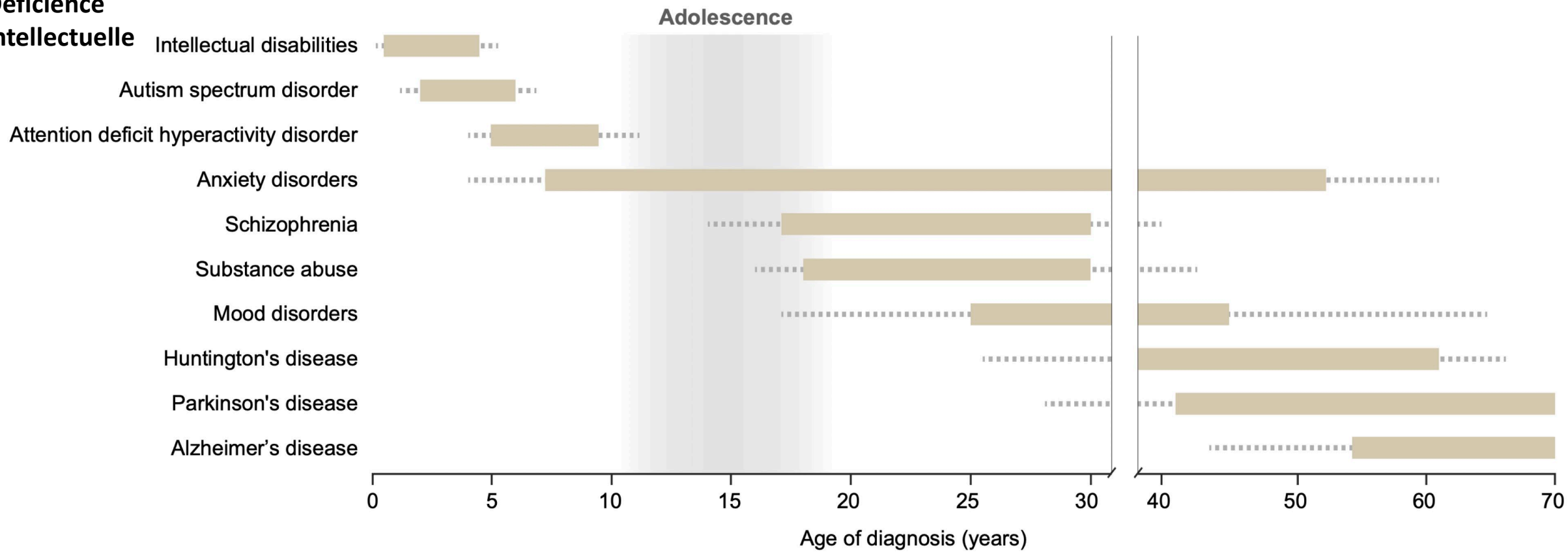
HOMME



Lancet Neurol 2019; 18: 459–80; http://dx.doi.org/10.1016/ S1474-4422(18)30499-X

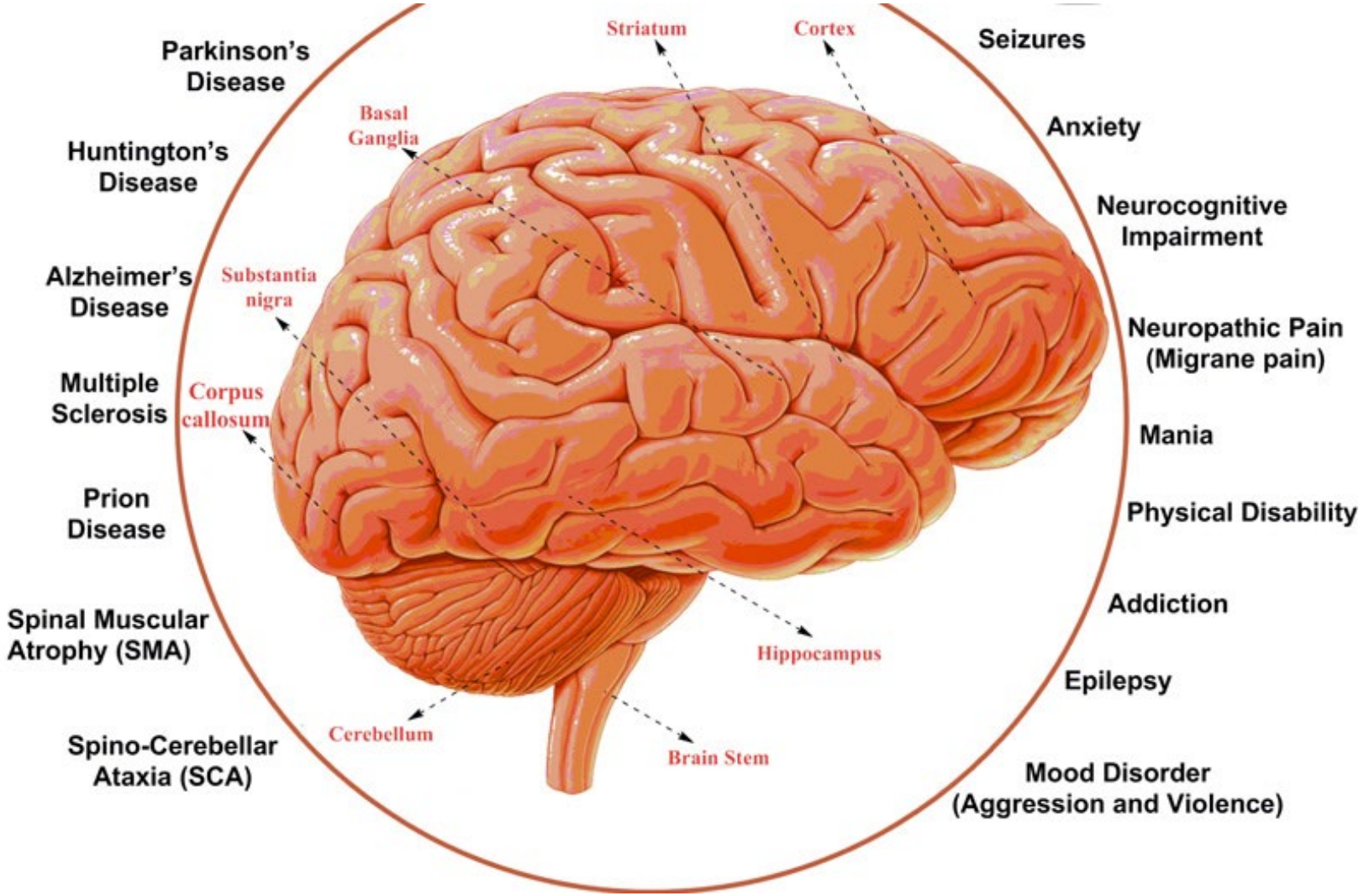
Les maladies neuropsychiatriques

Déficience intellectuelle

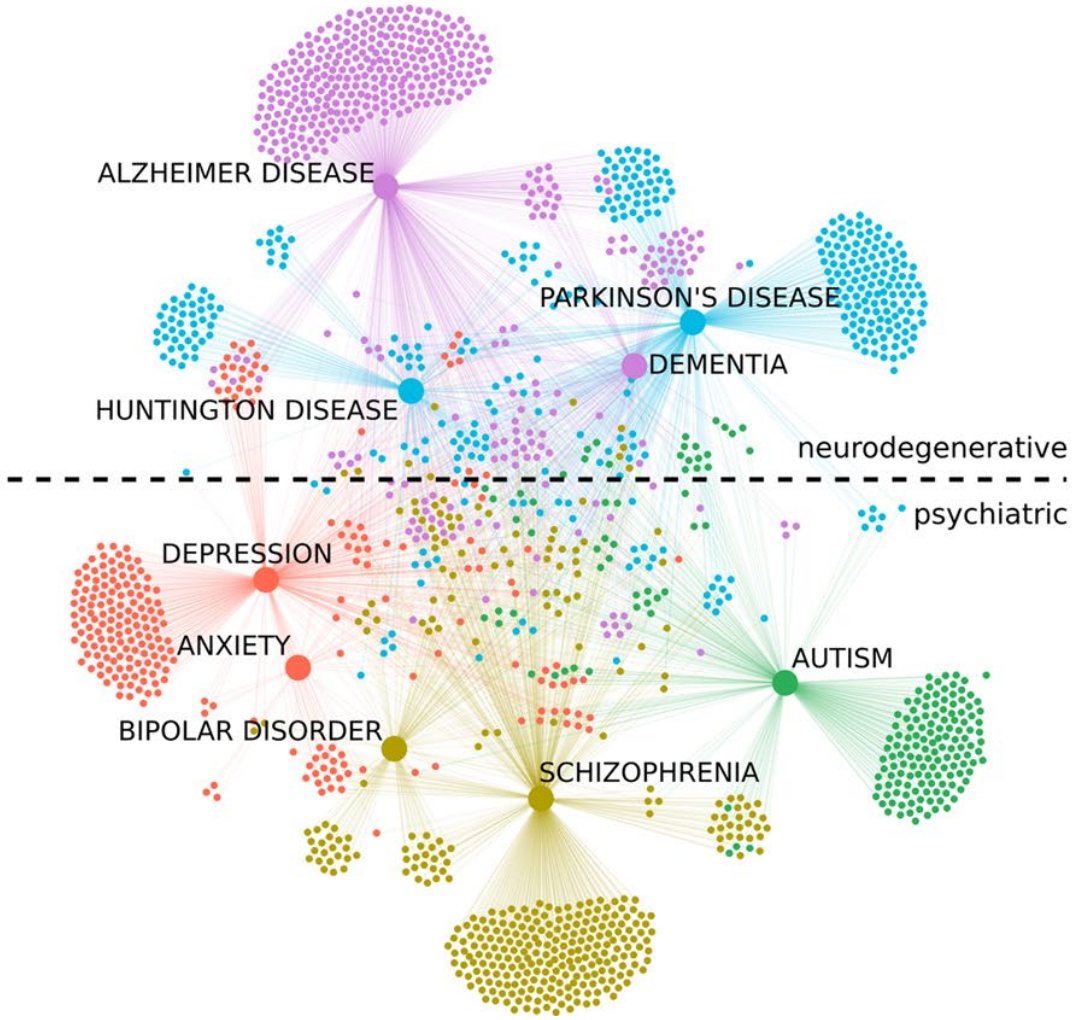


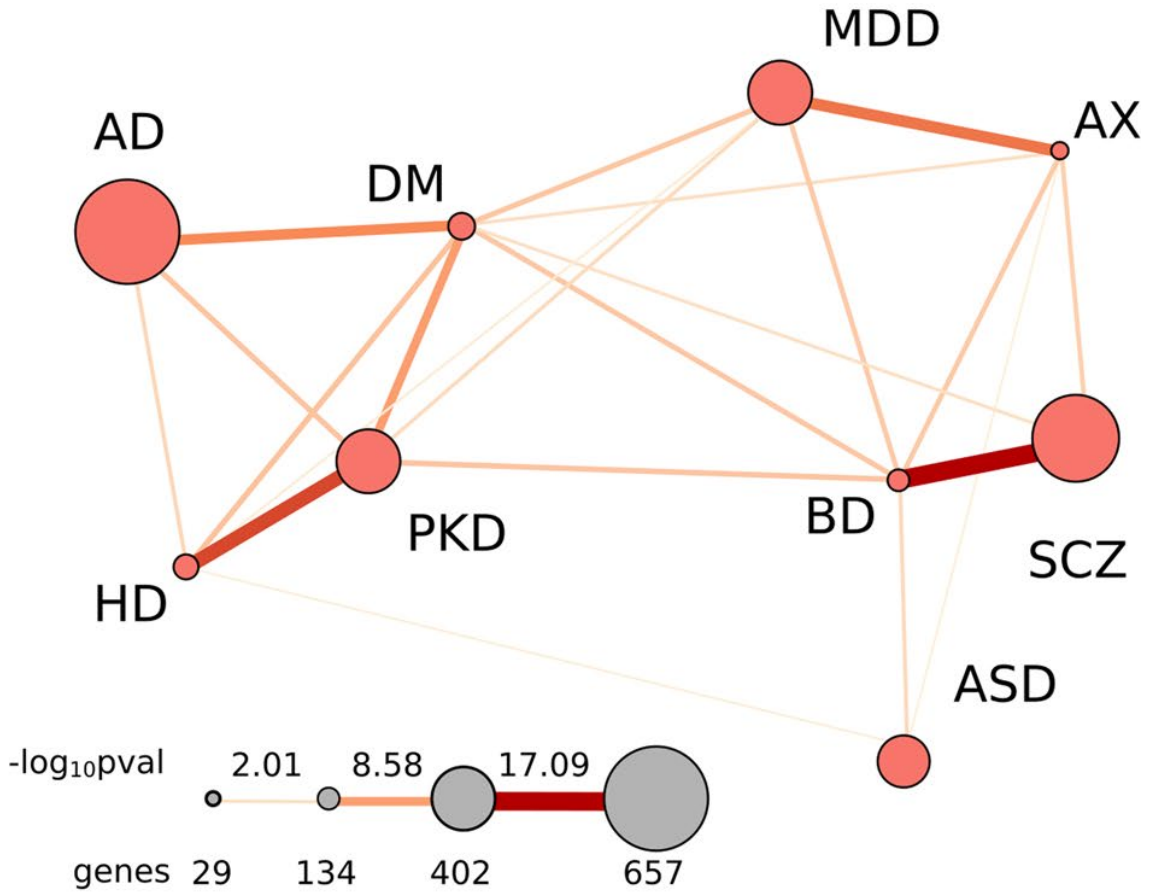
Silbereis et al. 2016, Neuron

Les maladies neurologiques et psychiatriques



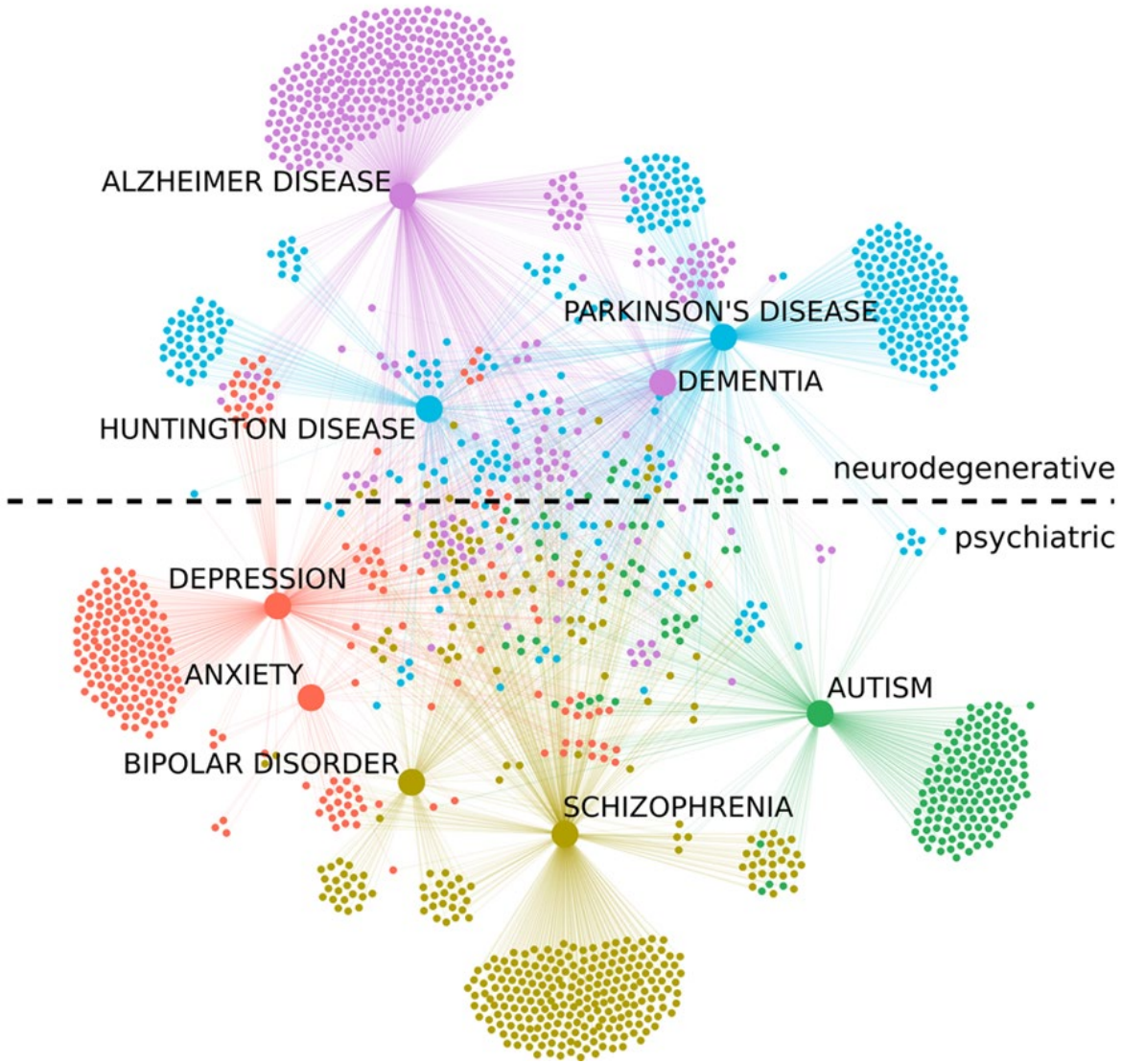
Les maladies neurologiques et psychiatriques: une génétique partiellement commune

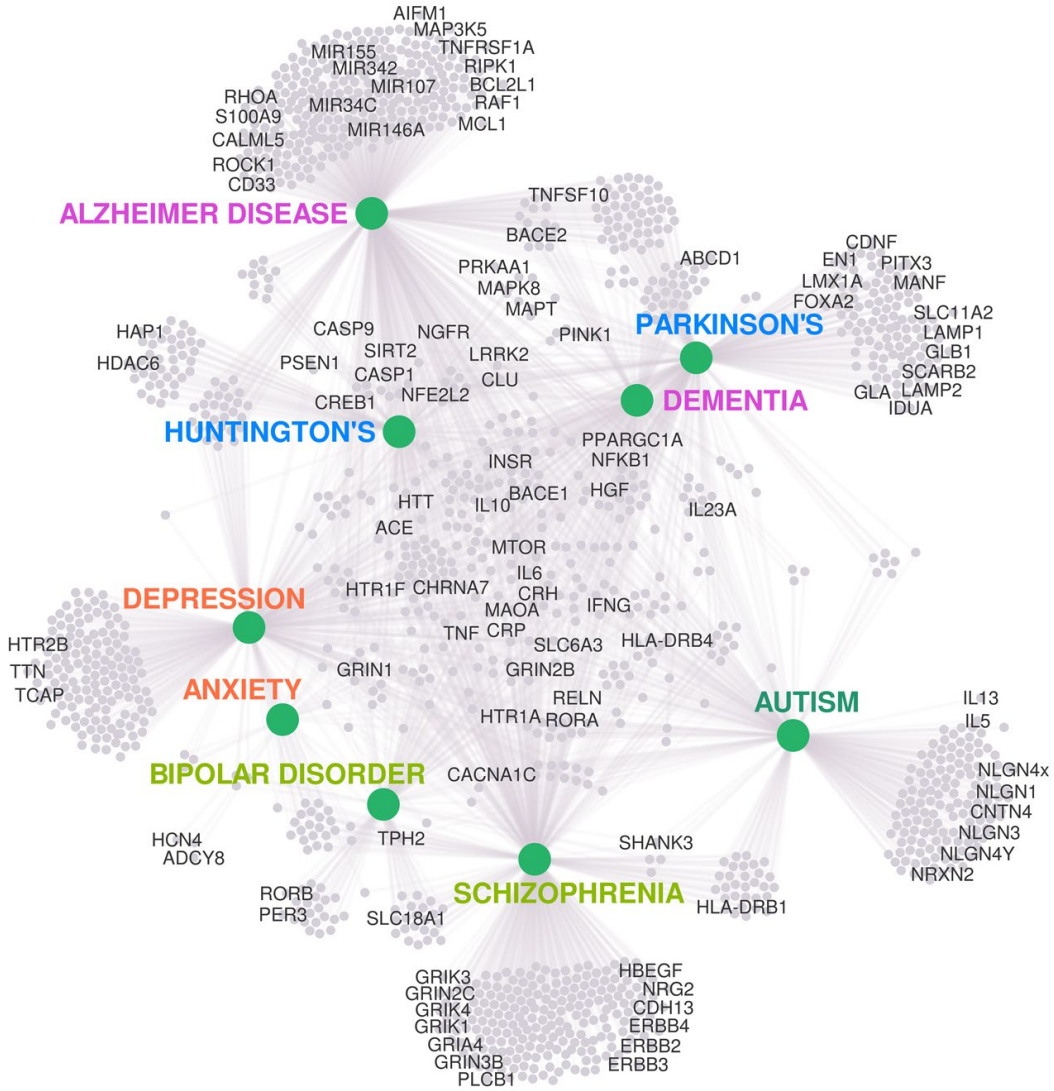




Lüscher Dias et al. Translational Psychiatry (2020) 10:141 https://doi.org/10.1038/s41398-020-0827-5

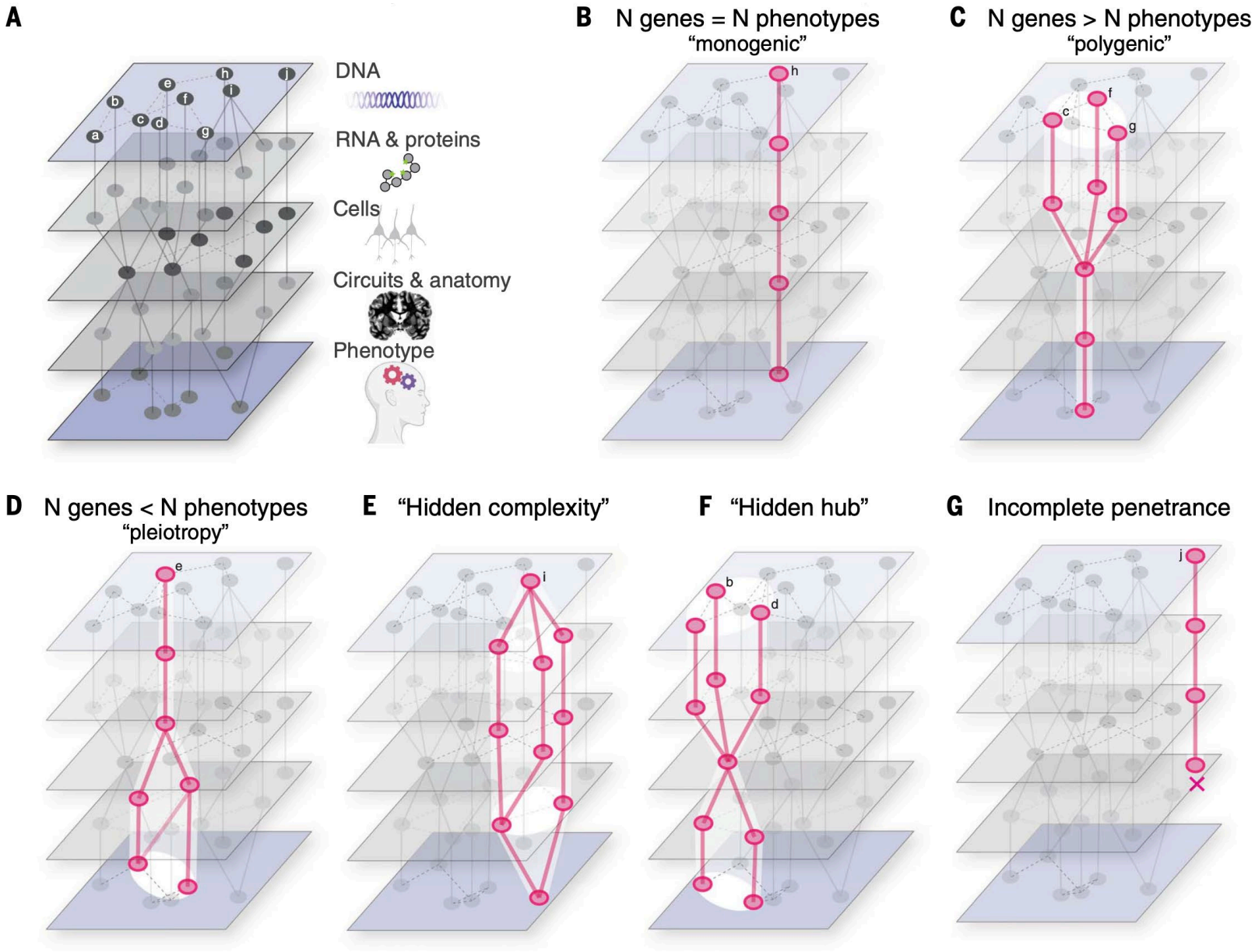
Les maladies neurologiques et psychiatriques: une génétique partiellement commune



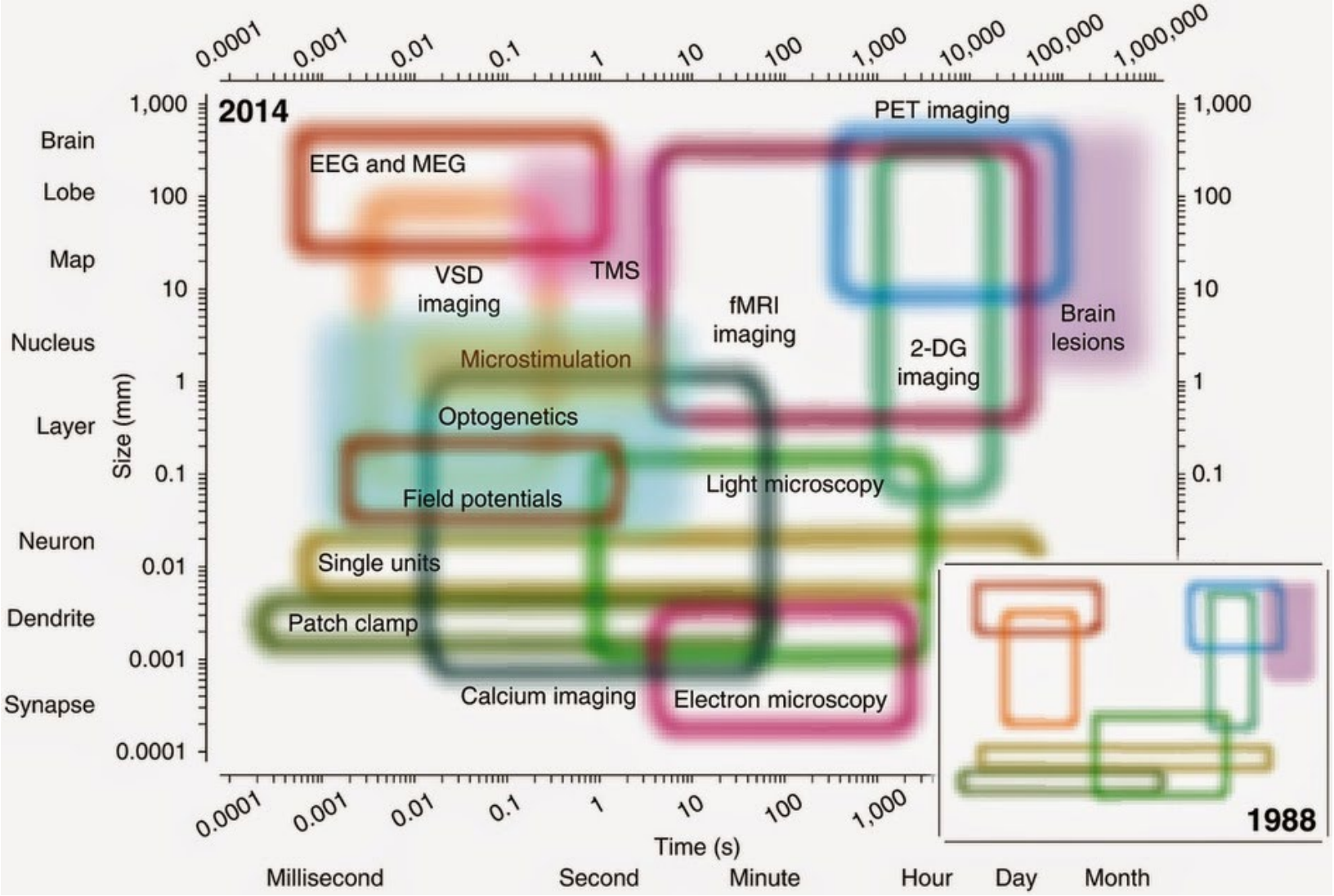


Lüscher Dias et al. Translational Psychiatry (2020) 10:141 https://doi.org/10.1038/s41398-020-0827-5

Comment relier gènes, cellules, circuits et phenotype?

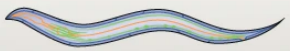


L’arsenal des techniques



Sejnowski, Churchland and Movshon, 2014, Nature Neuroscience

L’arsenal de modèles expérimentaux

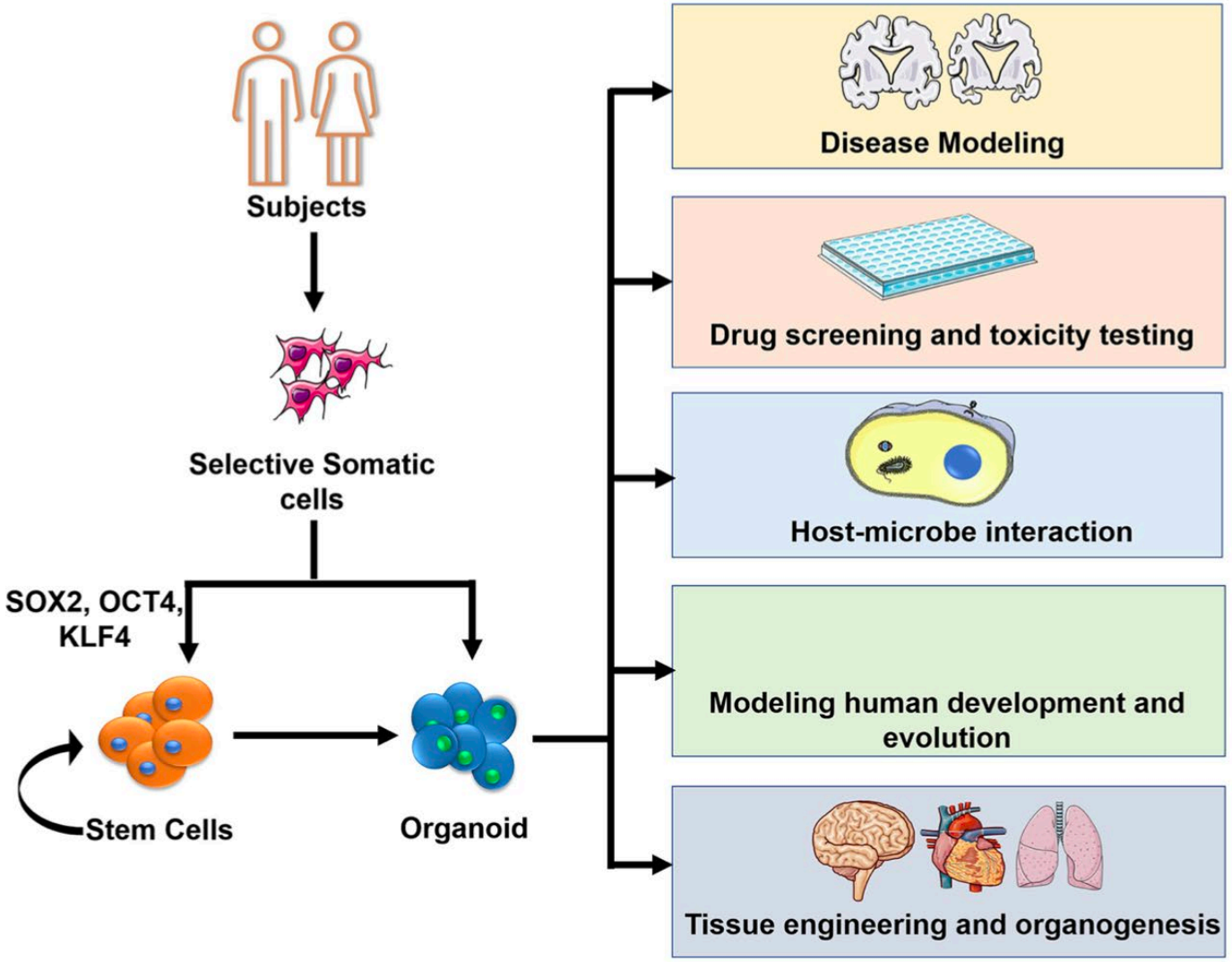
	 2D cell culture	 *C.elegans*	 *D. melanogaster*	 *D. rerio*	 *M. musculus*	 PDX	 Human organoids
Ease of establishing system	✓/✗	✓	✓	✓	✓	✓	✓
Ease of maintenance	✓	✓	✓	✓	✓	✓	✓
Recapitulation of developmental biology	✗	✓	✓	✓	✓	✗	✓
Duration of experiments	✓	✓	✓	✓	✓	✓	✓
Genetic manipulation	✓	✓	✓	✓	✓	✗	✓
Genome-wide screening	✓	✓	✓	✓	✗	✗	✓
Physiological complexity	✗	✓	✓	✓	✓	✓	✓
Relative cost	✓	✓	✓	✓	✓	✓	✓
Recapitulation of human physiology	✓	✓	✓	✓	✓	✓	✓

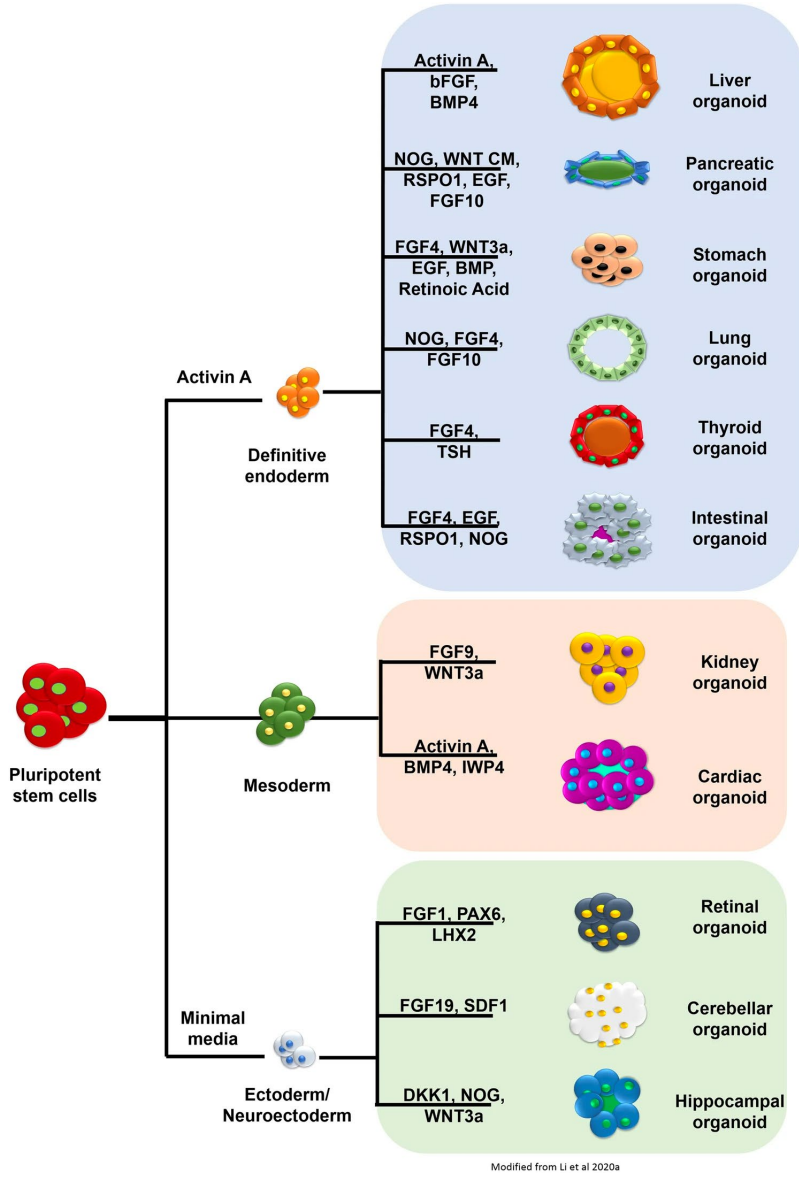
✓ Best ✓ Good ✓ Partly suitable ✗ Not suitable

MAIS
Impossibilité d’analyser du comportement !

Kim et al., Nat Rev Molec Cell Bio, 2022

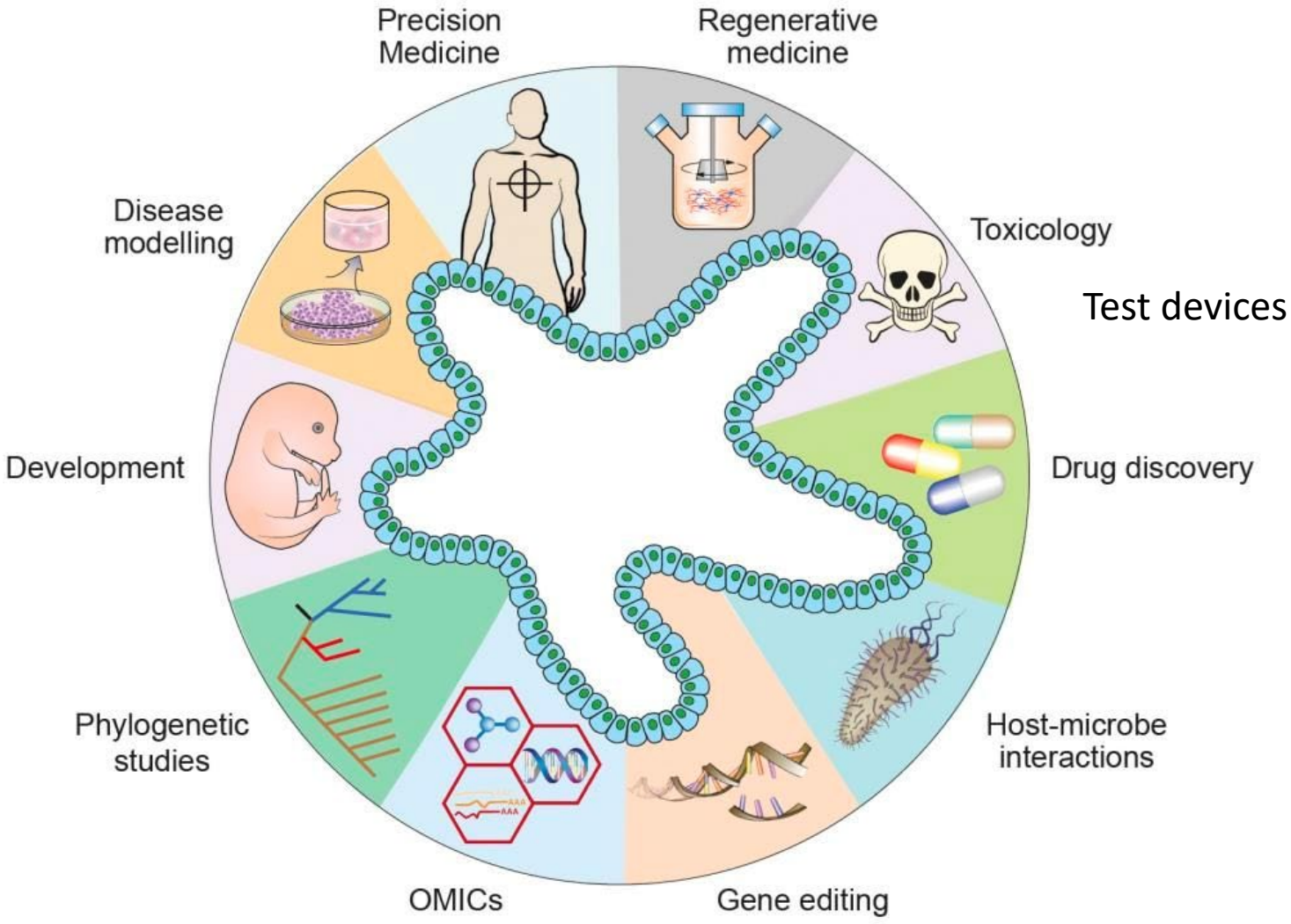
Répliquer le développement in vitro en 3D avec les organoïdes





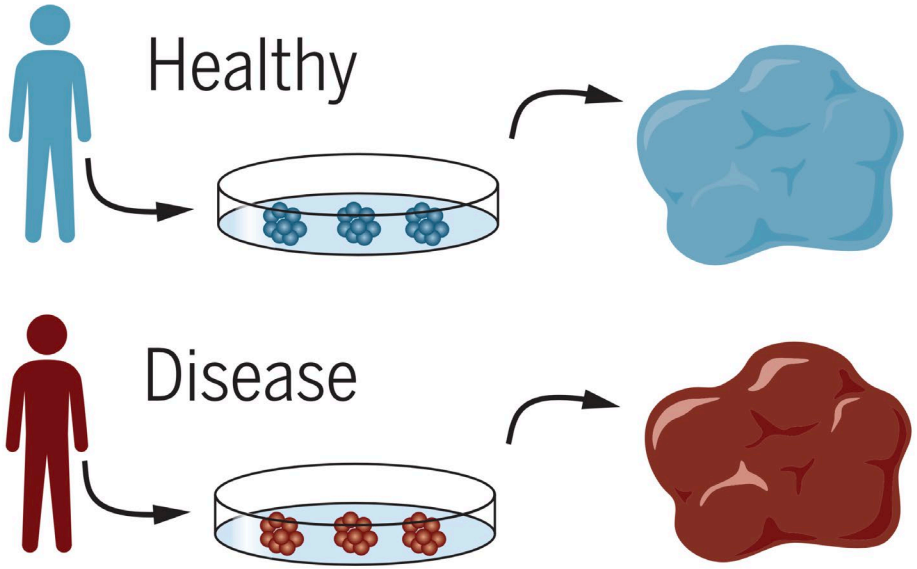
Modified from Li et al 2020a

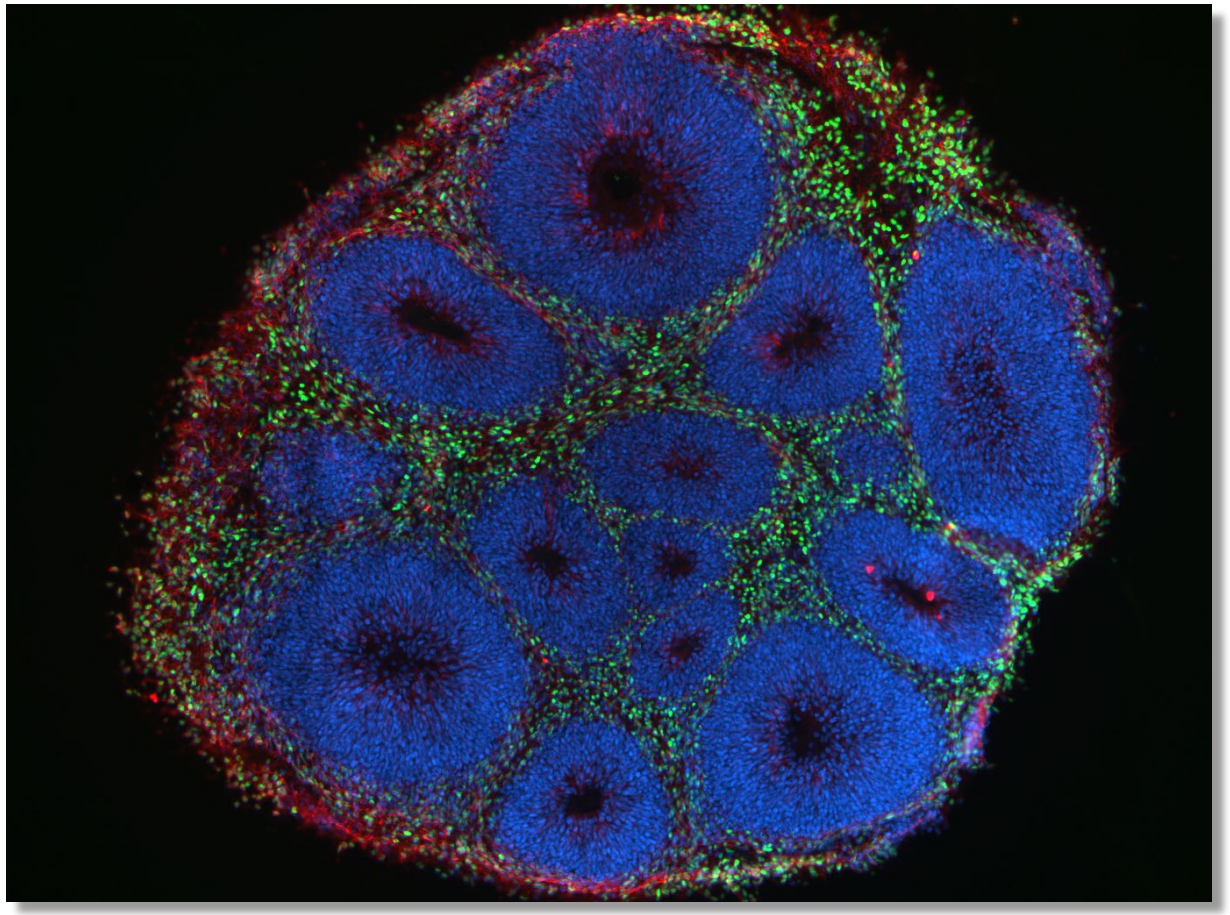
Application potentielles des organoïdes



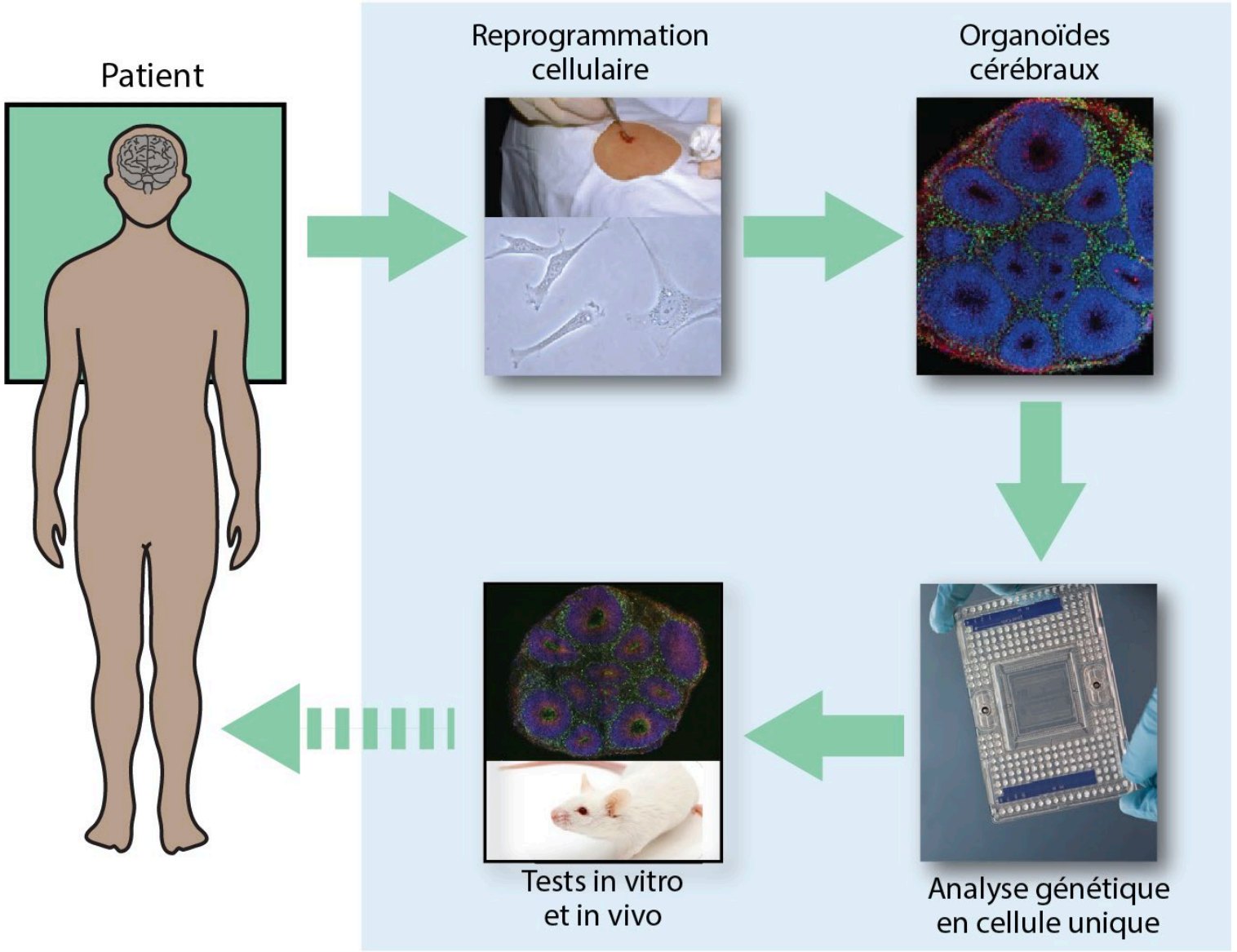
Corro et al., Am J Physiol, 2020

Les organoïdes permettent d'étudier des mécanismes cellulaires de maladies





Du patient à la cellule, et retour!



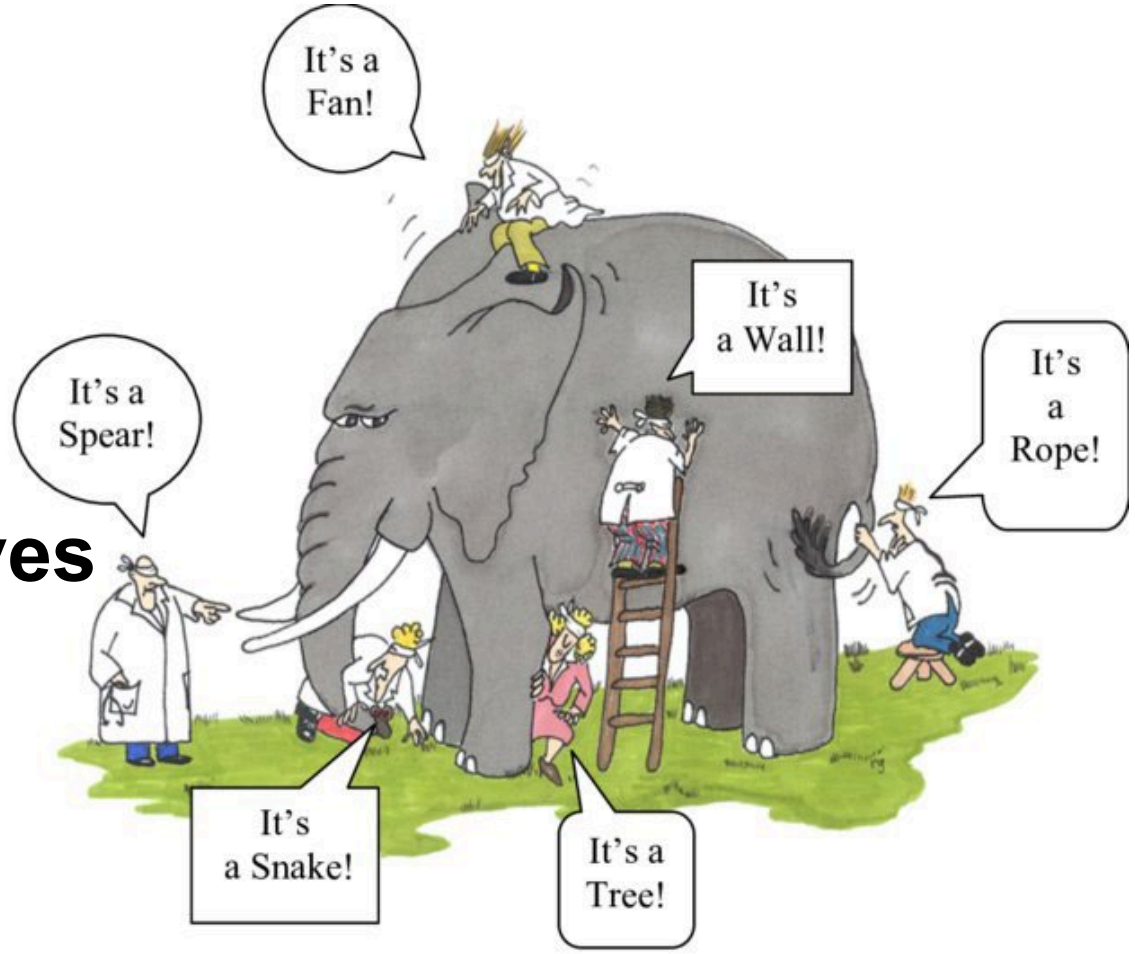
Exemples de pathologies du cerveau

Epilepsies

Schizophrénie

Alzheimer et maladies dégénératives

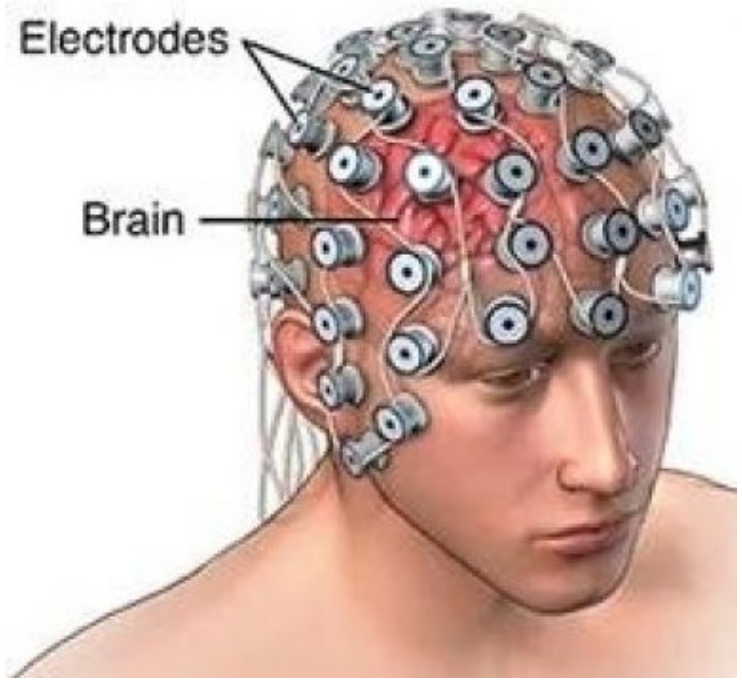
Maladies neuroimmunes

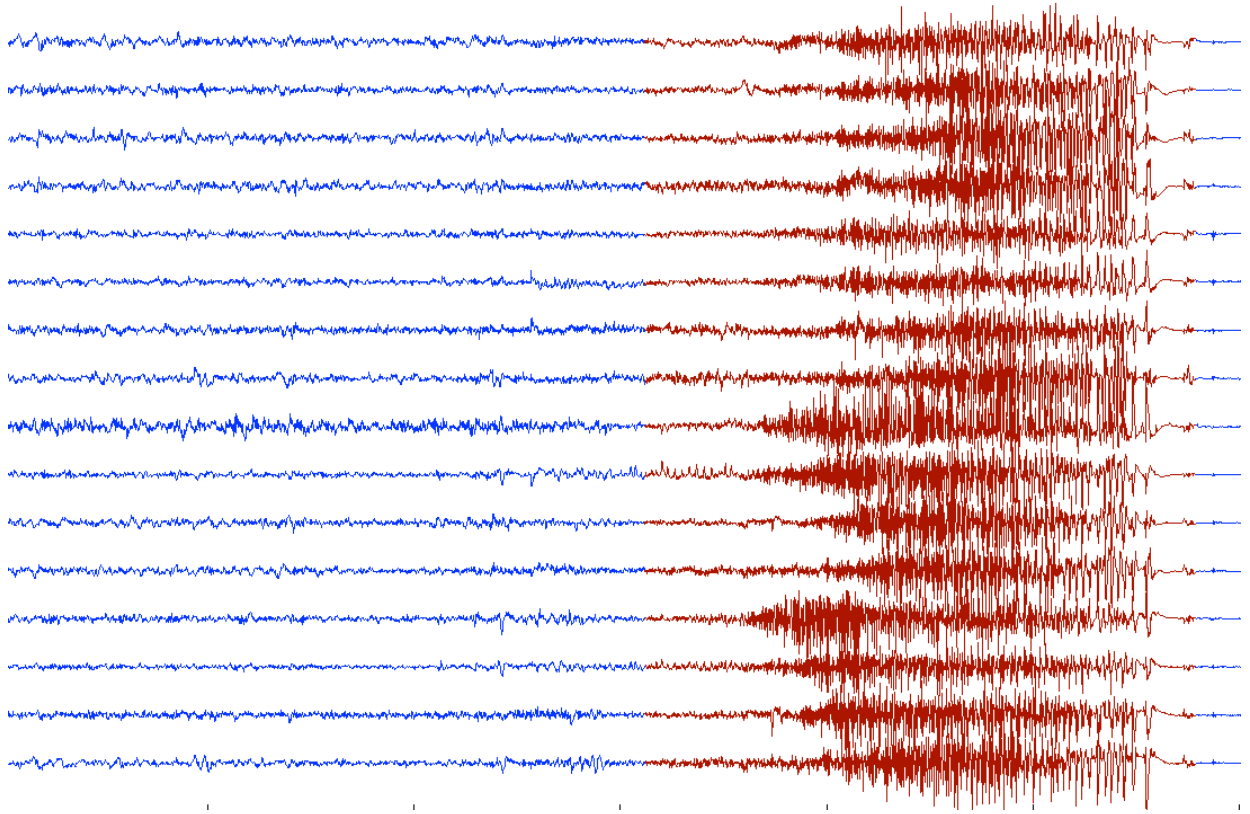


Epilepsie

« **Une crise d'épilepsie** est une manifestation clinique transitoire, liée à une activité électrique anormale des cellules nerveuses. On peut distinguer schématiquement les **crises généralisées**, liées à des décharges étendues à l'ensemble du cerveau et des **crises partielles** ou focales qui trouvent leur origine dans une zone localisée du cerveau. »

https://www.ffn-neurologie.fr





https://www.brightbraincentre.co.uk/electroencephalogram-eeg-brainwaves/

https://www.kaggle.com/c/seizure-detection

Différents types d'épilepsies

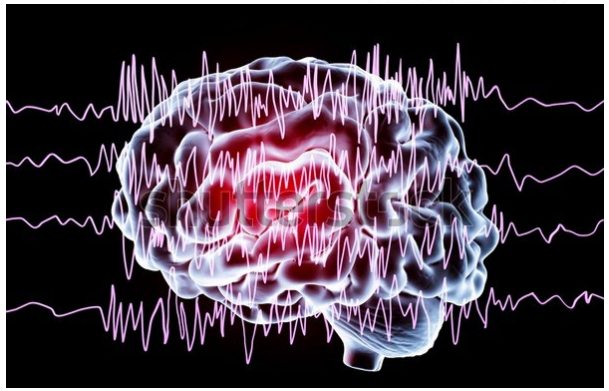
Epilepsy (based on prevalence)

Common Epilepsies (~95%)
(prevalence 3.8-9.5 in 1,000 patients)
(ILAE classification 2017, based on etiology)

Rare Epilepsy (~5%)
(prevalence 20-50 in 10,000 patients)
(ILAE classification 2017, based on etiology)

International League Against Epilepsy (ILAE)

Genetic	Structural	Unknown
GGE	TLE	Cryptogenic
CAE		Focal epilepsy
JAE		
JME		

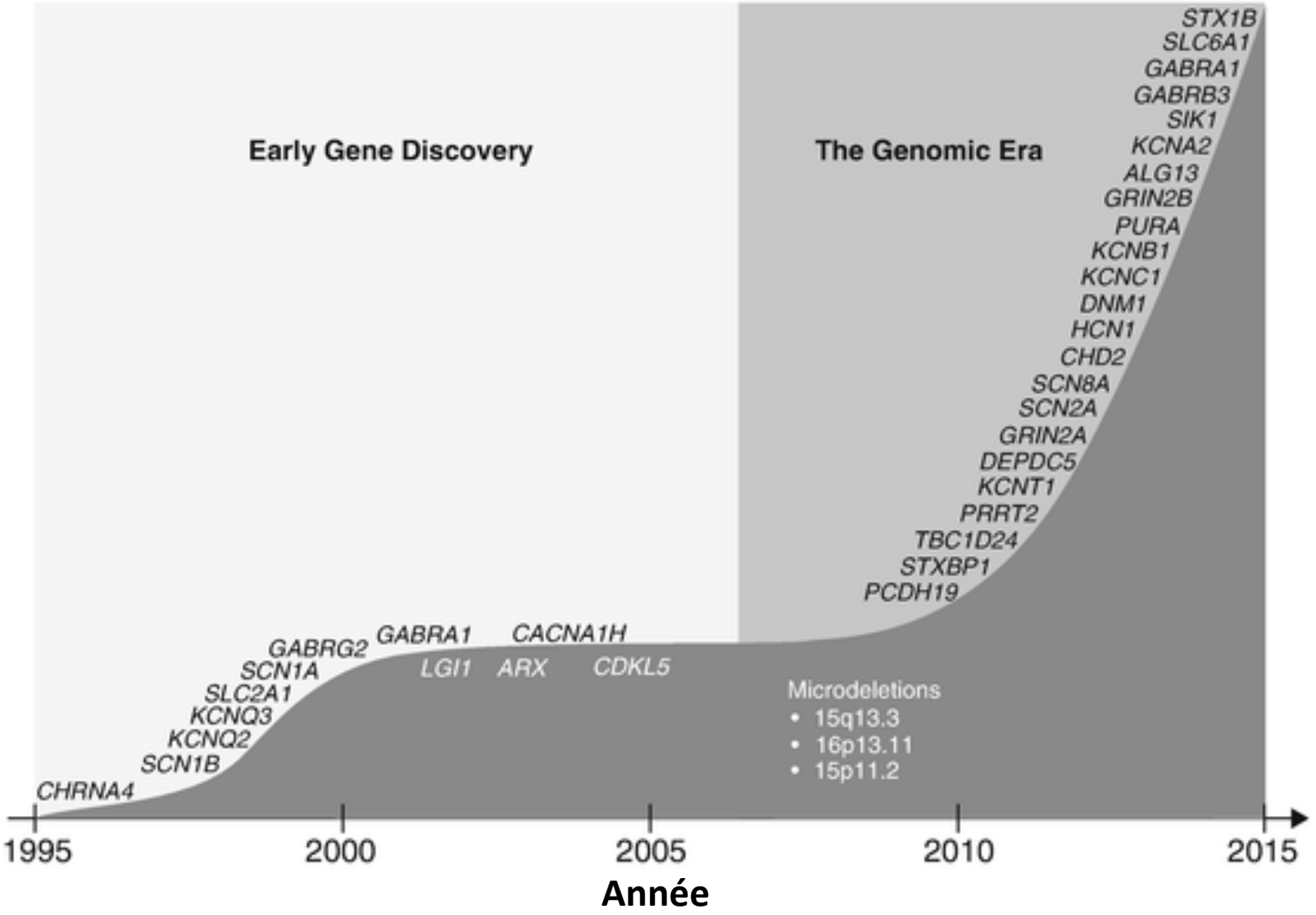


Genetic	Structural	Infectious	Metabolic	Immune	Unknown
Dravet syndrome	Gelastic Epilepsy	Viral encephalitis	Cerebral folate deficiency	Limbic encephalitis	Doose syndrome
Lafora Rett syndrome	Sturge-weber syndrome		Pyrodoxine-dependent epilepsy		Landau Kleffner syndrome

GGE: Genetic generalized epilepsy
CAE: Childhood absence epilepsy
JAE: Juvenile absence epilepsy
JME: Juvenile myoclonic epilepsy
TLE: Temporal lobe epilepsy.

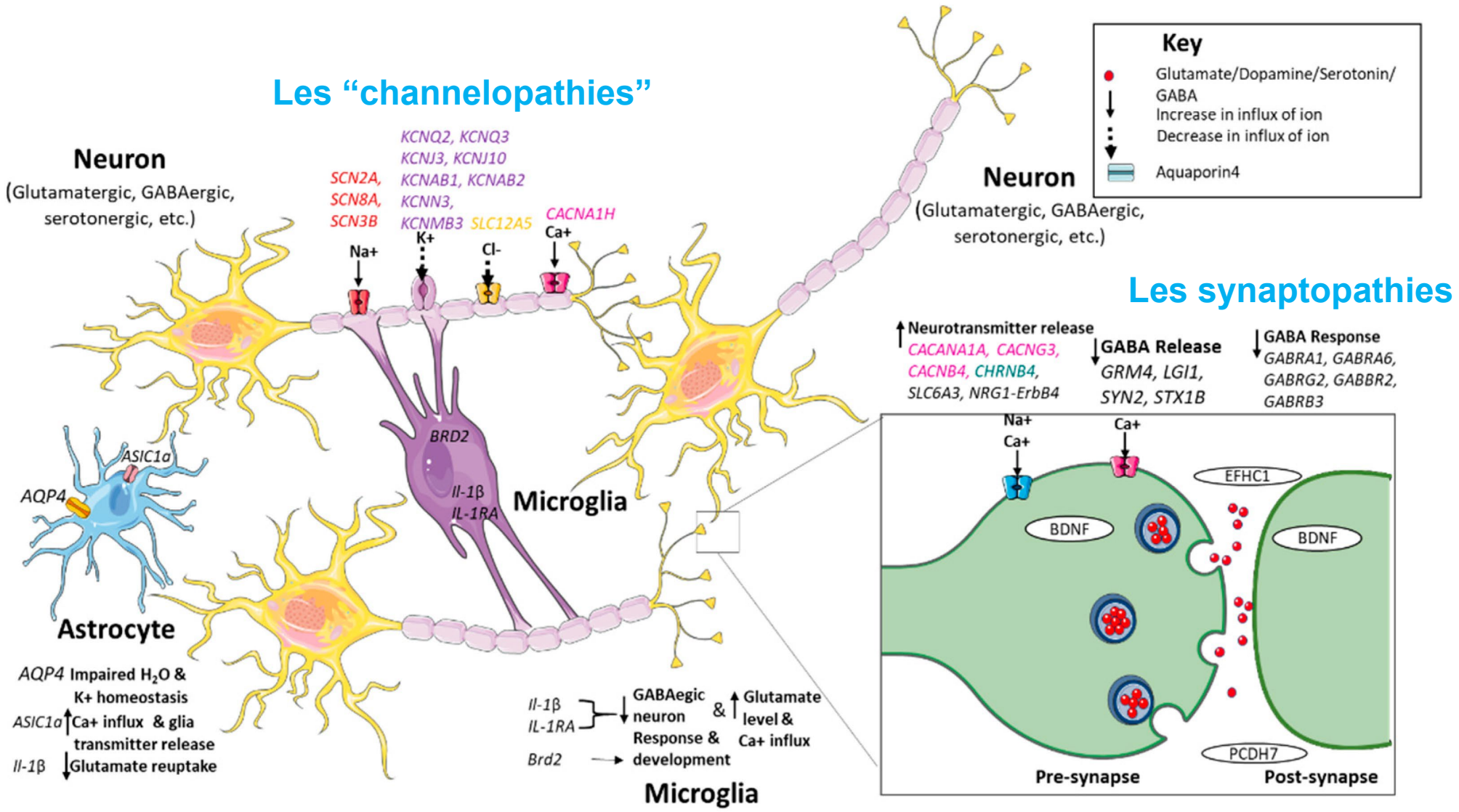
Thakran et al. *Int. J. Mol. Sci.* 2020, *21*(20), 7784; https://doi.org/10.3390/ijms21207784

Gènes impliqués dans les épilepsies



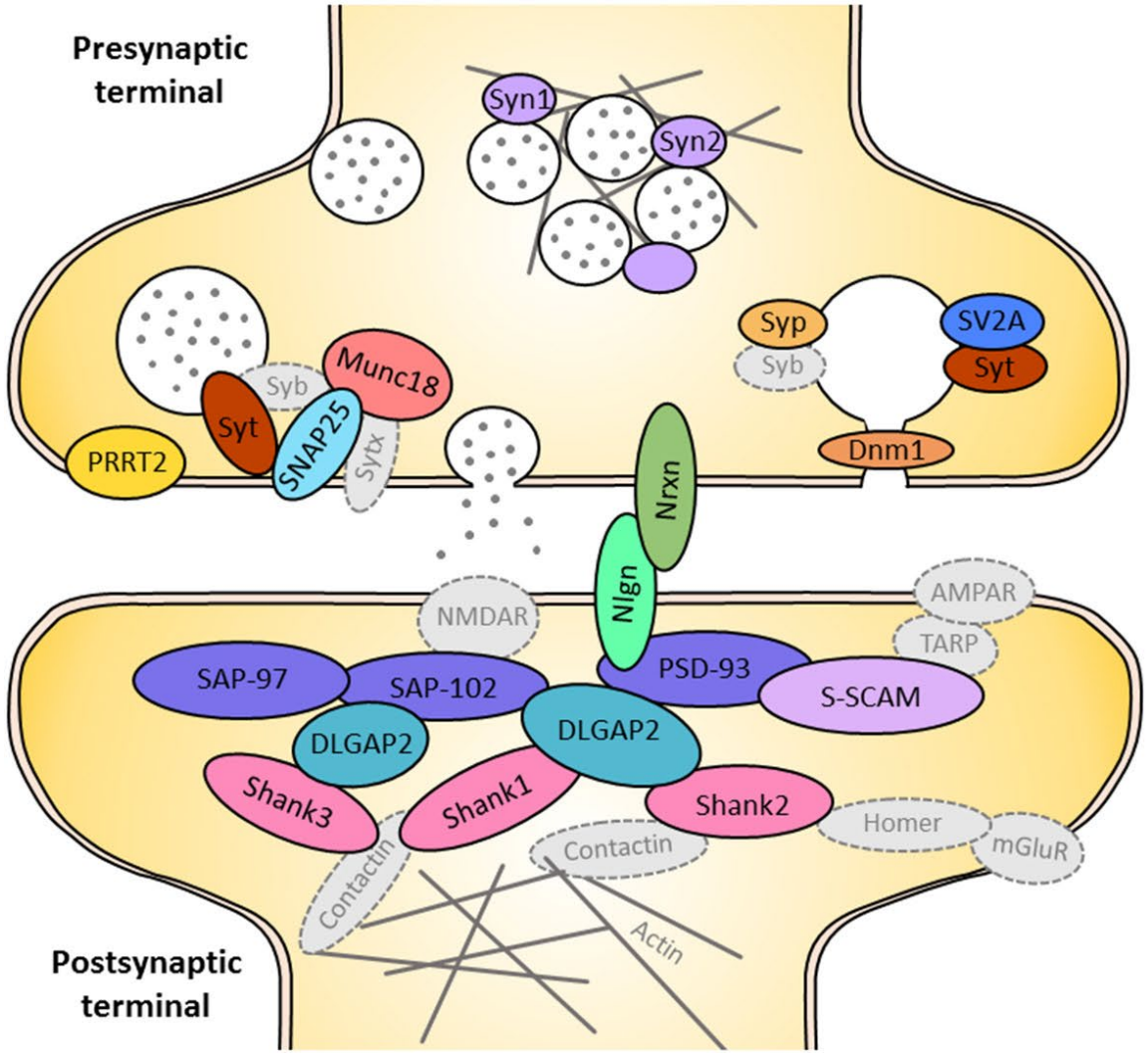
Helbig I et al. (2017) Epileptic Encephalopathies as Neurodegenerative Disorders. https://doi.org/10.1007/978-3-319-57193-5_11

Epilepsies: atteintes de divers mécanismes cellulaires



Thakran et al. *Int. J. Mol. Sci.* 2020, *21*(20), 7784; https://doi.org/10.3390/ijms21207784

Les synaptopathies



Developmental disorder	Presynaptic genes (proteins)	Postsynaptic genes (proteins)
Epilepsy	STXBP1 (Munc18) DNM1 (Dynamin 1) SNAP-25 PRRT2 SYN1 (Synapsin 1) SV2A SYP (Synaptophysin)	DLG1 (SAP-97) MAGI2 (S-SCAM) SHANK3
Intellectual disability **Déficience intellectuelle**	SNAP-25 SYT1 (Synaptotagmin 1) SV2A SYP (Synaptophysin) DMN1 (Dynamin 1)	NLGN4 (Neuroligin 4) DLG2 (PSD-93) DLG3 (SAP-102) SHANK3
Autism Spectrum Disorder	SYN1 (Synapsin 1) SYN2 (Synapsin 2) NRXN1 (Neurexin 1)	NLGN1 (Neuroligin 1) NLGN3 (Neuroligin 3) NLGN4 (Neuroligin 4) DLG1 (SAP-97) DLG2 (PSD-93) DLGAP2 SHANK1 SHANK2 SHANK3
Schizophrenia	NRXN1 (Neurexin 1)	NLGN2 (Neuroligin 2) DLG2 (PSD-93) MAGI2 (S-SCAM)

Luo et al. (2018); [10.1016/j.pnpbp.2017.12.001](https://doi.org/10.1016/j.pnpbp.2017.12.001)

La schizophrénie

« La schizophrénie est une pathologie psychiatrique chronique complexe qui se traduit par une perception perturbée de la réalité, des manifestations productives, comme des idées délirantes ou des hallucinations, et des manifestations passives, comme un isolement social et relationnel. »

Alberto Ruggieri / Getty Images

Symptômes positifs

Excès ou distorsion des fonctions normales[2]

- Délires[1]
- Hallucinations[1]
- Pensée/parole désorganisée[1]
- Comportement très désorganisé ou catatonique[1]

Symptômes négatifs

Déclin ou perte des fonctions normales[2]

- Alogie[1] (pauvreté du discours)
- Avolition[1] (manque de motivation)
- Anhédonie[1] (incapacité à ressentir du plaisir)
- Asocialité[1] (absence de désir de nouer des relations)
- Réduction de l'expression des émotions[1]

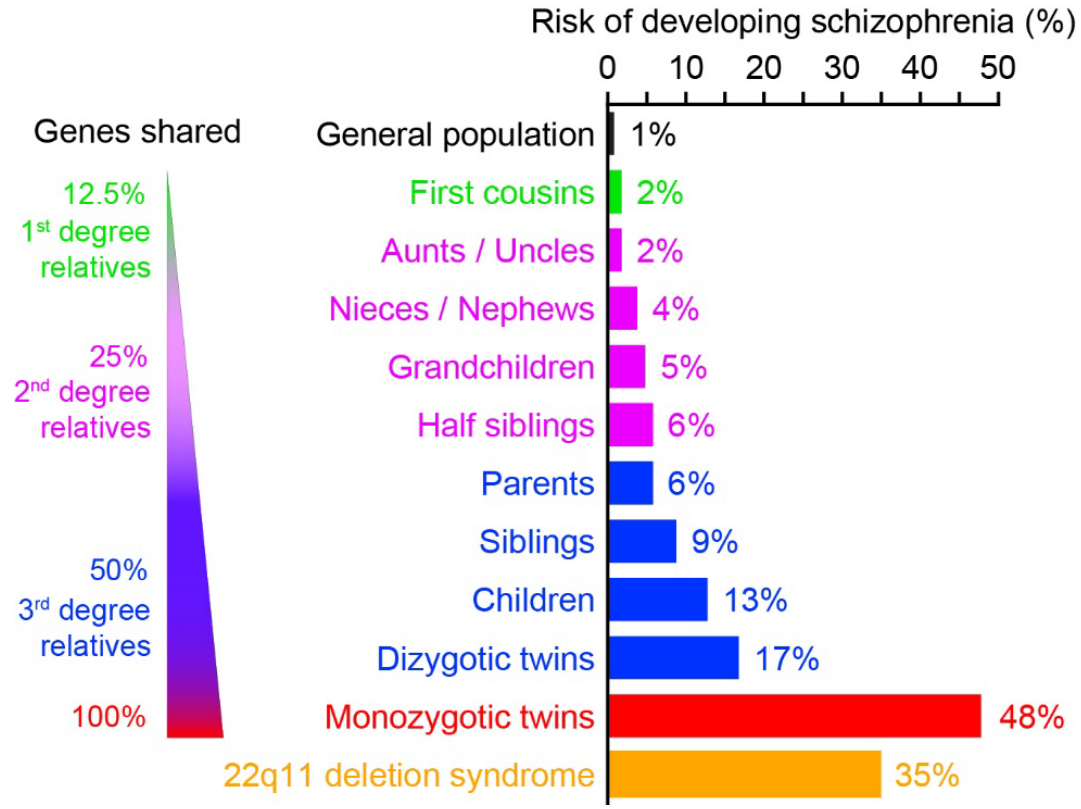
Symptômes cognitifs

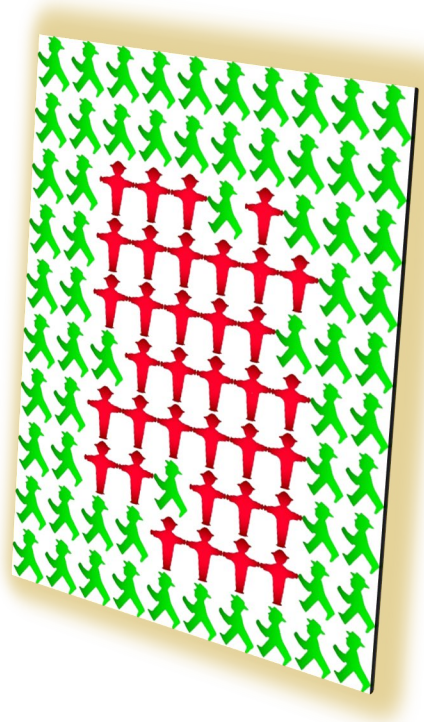
Composante clé de la schizophrénie[3]

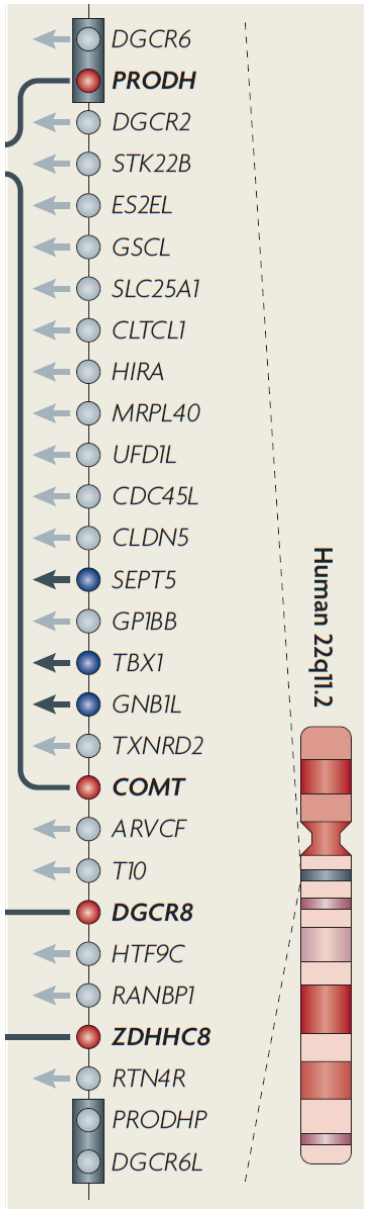
- Attention[1]
- Mémoire épisodique[1]
- Fonctions exécutives (dont la fonction du langage)[1]
- Mémoire de travail[1]
- Vitesse de traitement[1]
- Affect inapproprié[1]
- Capacité d'inhibition[1]

https://institute.progress.im/fr/content/evolution-histoire-naturelle-et-pronostic-1

La schizophrénie et le syndrome de la délétion 22q11.2



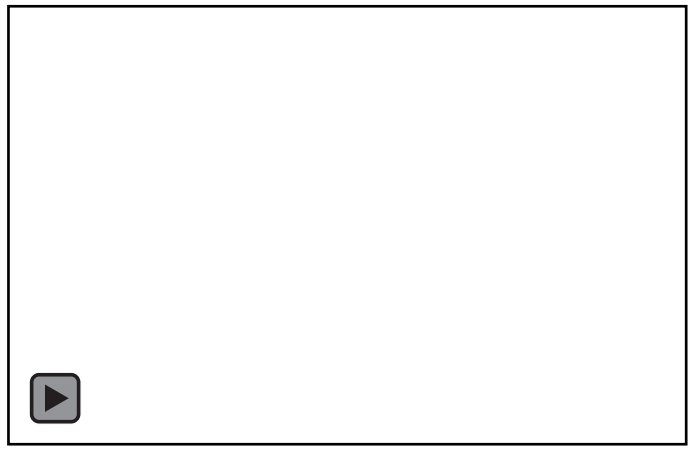


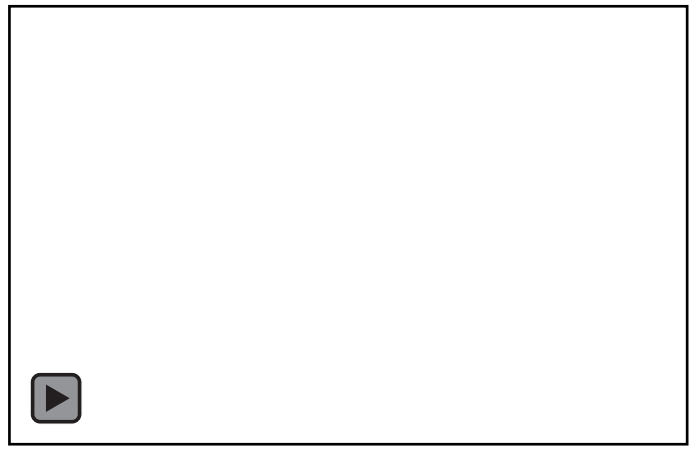


Modified from Gottesman (1991) Schizophrenia Genesis: The Origins of Madness.

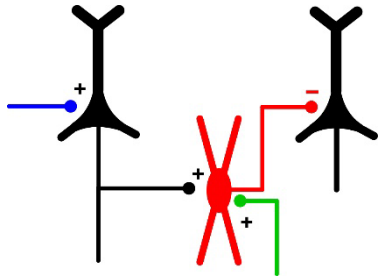
- **Incidence de la deletion (1/2000-4000)**
- **Haploinsuffisance des gènes de la deletion (entre 1.5 et 3 Mpb, 20-60 genes)**

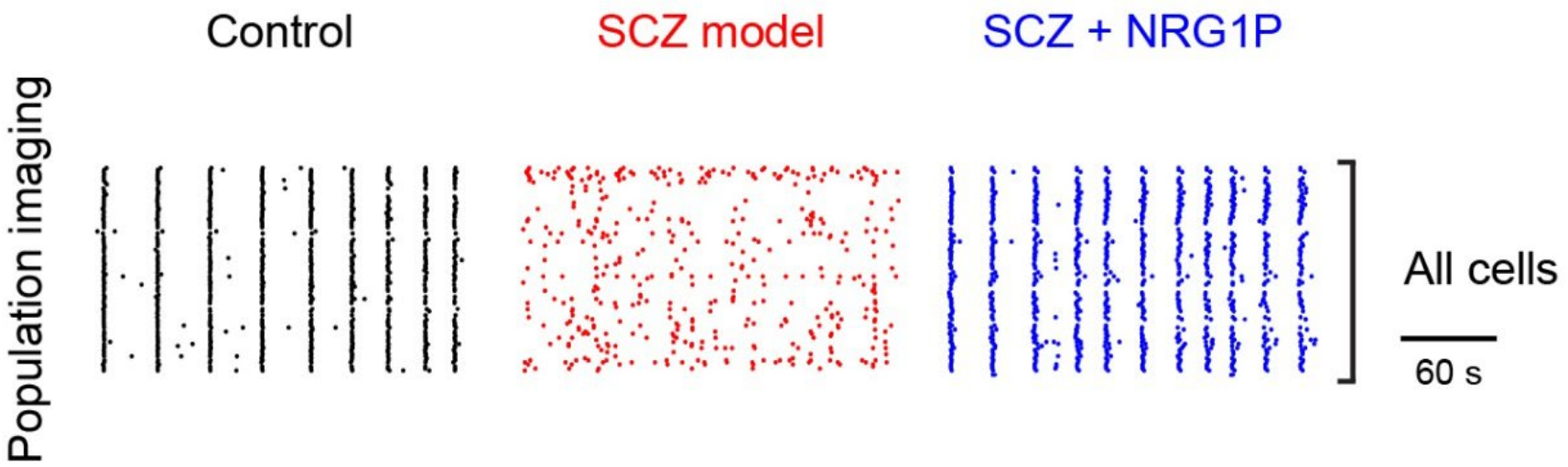
Modèle murin de la deletion 22q11.2

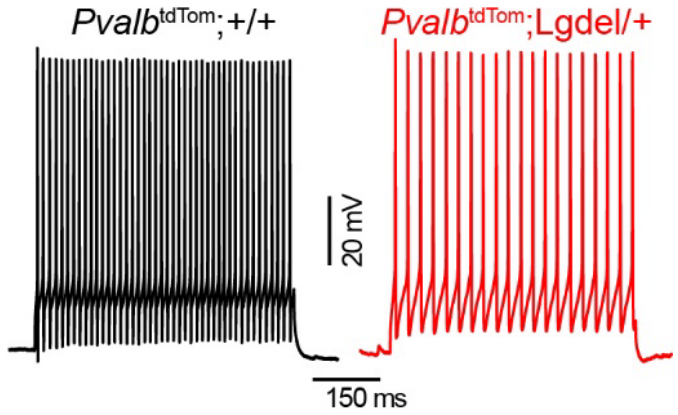




Control mouse **Animal model of schizophrenia**

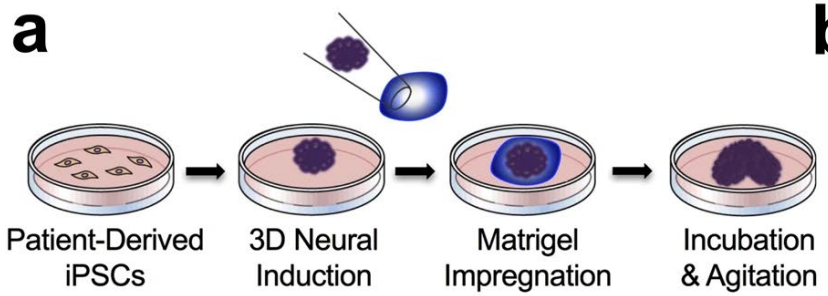


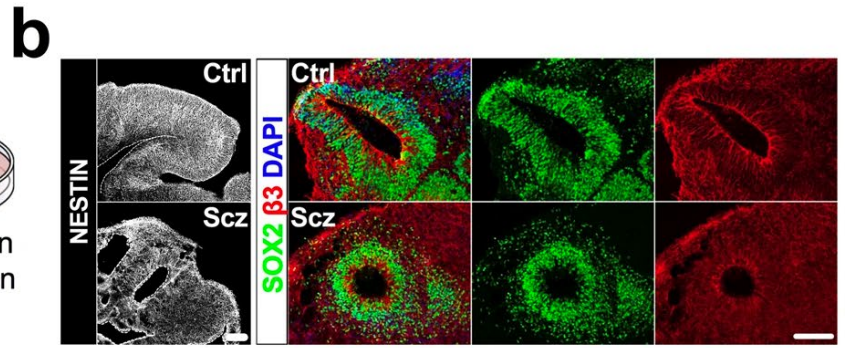


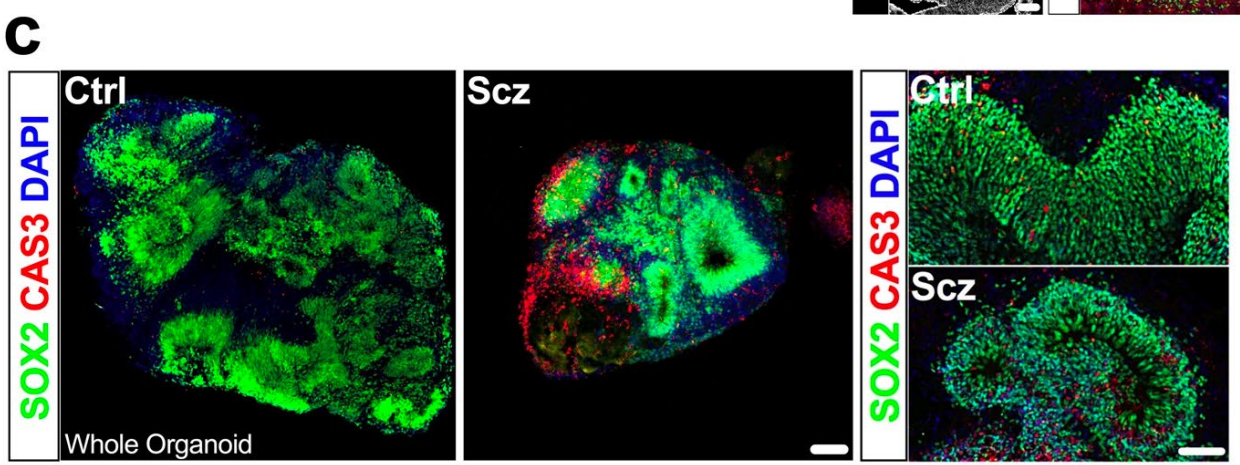


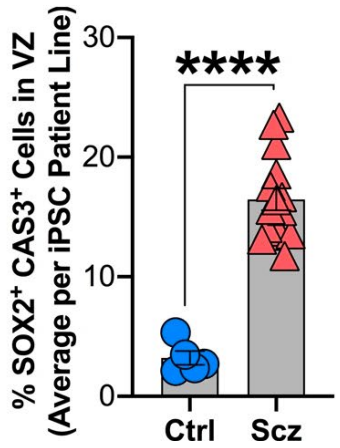
Marissal et al. (2018) Nature Neuroscience, 21:1412-1420

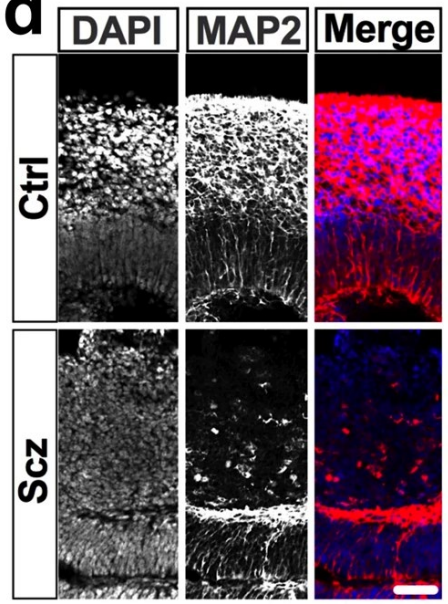
Les organoïdes dérivés de patients schizophrènes révèlent des anomalies développementales précoces

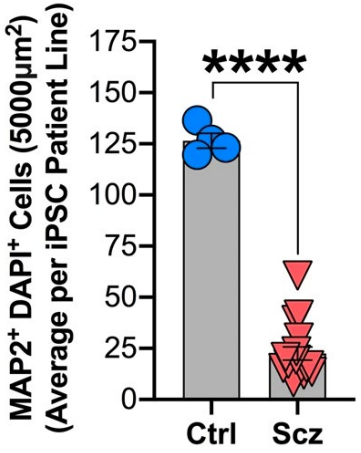






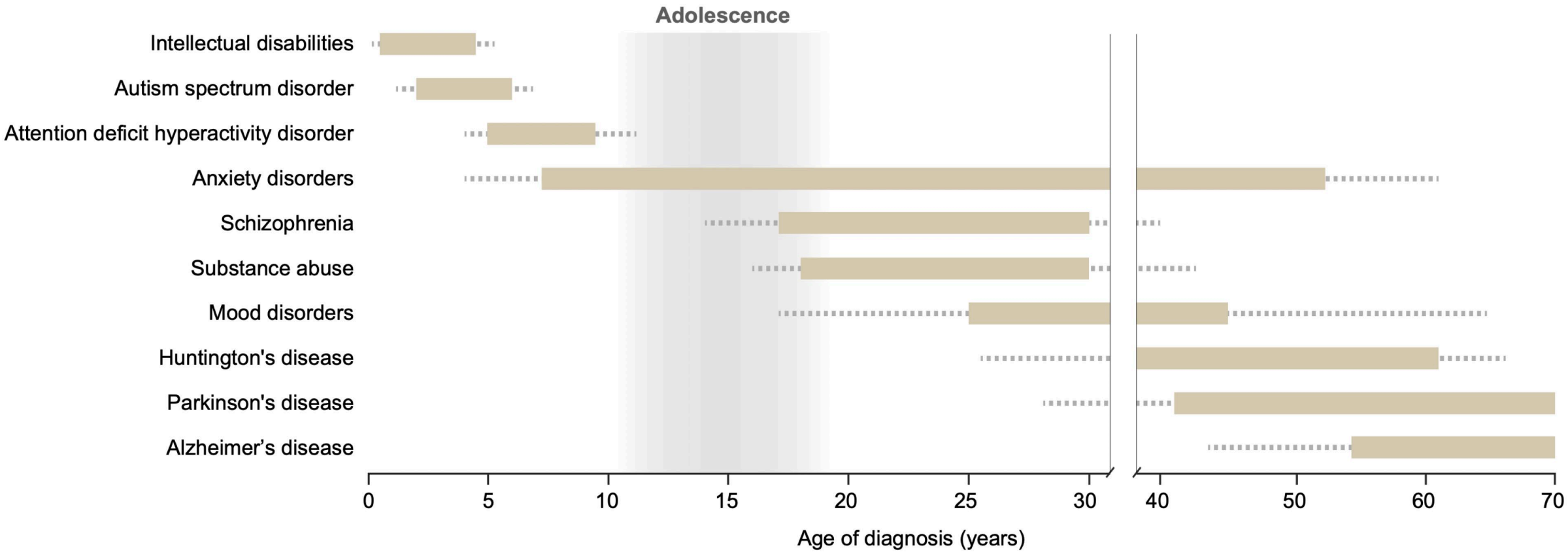






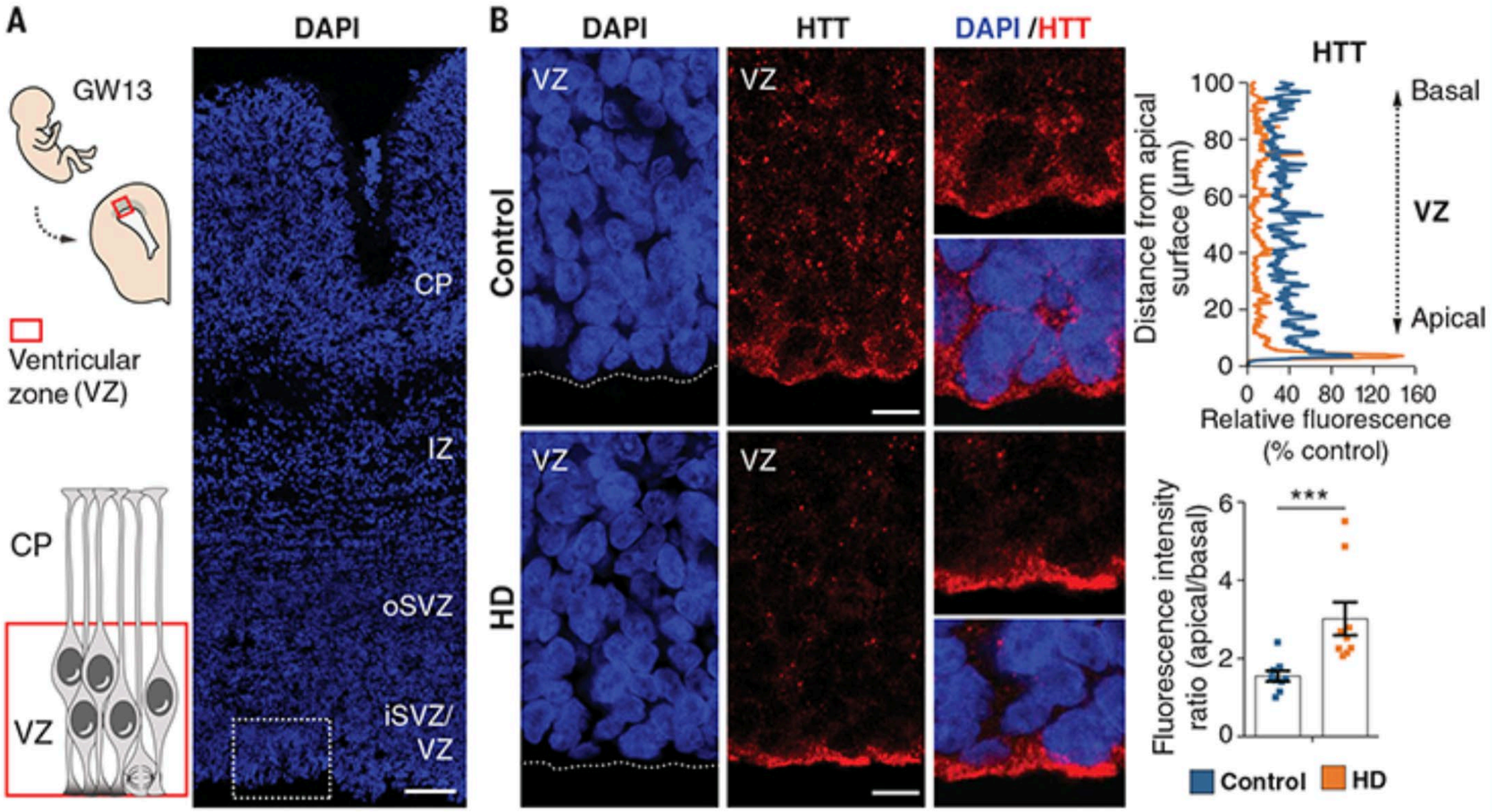
Notaras et al., Molec Psy 2021

Les maladies neuropsychiatriques



Silbereis et al. 2016, Neuron

La Huntingtin a un rôle dans le développement cérébral



Barnat et al., Science 2020

Maladie d'Alzheimer: par où commencer?

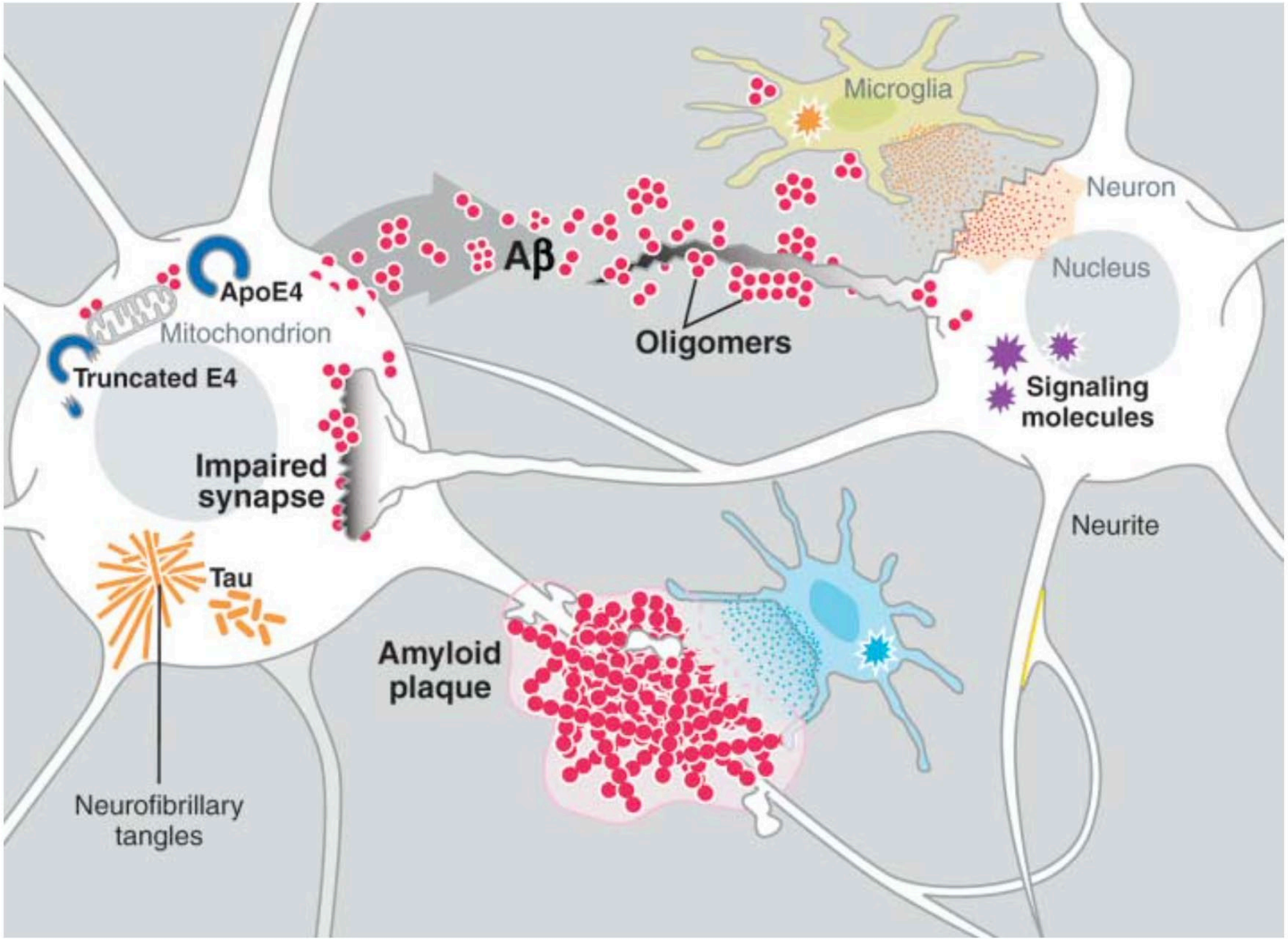


Fig. 1. Molecular and cellular processes presumed to participate in AD pathogenesis. Ab peptides produced by neurons and other brain cells aggregate into a variety of assemblies, some of which impair synapses and neuronal dendrites, either directly or through the engagement of glial loops. Build-up of pathogenic Ab assemblies could result from increased production or aggregation or from deficient clearance mechanisms. ApoE4 and tau promote Ab-induced neuronal injury and also have independent adverse effects. Microglia could be beneficial or harmful, depending on which of their signaling cascades and functions are engaged. This multifactorial scenario leads to progressive disintegration of neural circuits, isolation and loss of neurons, network failure, and neurological decline.

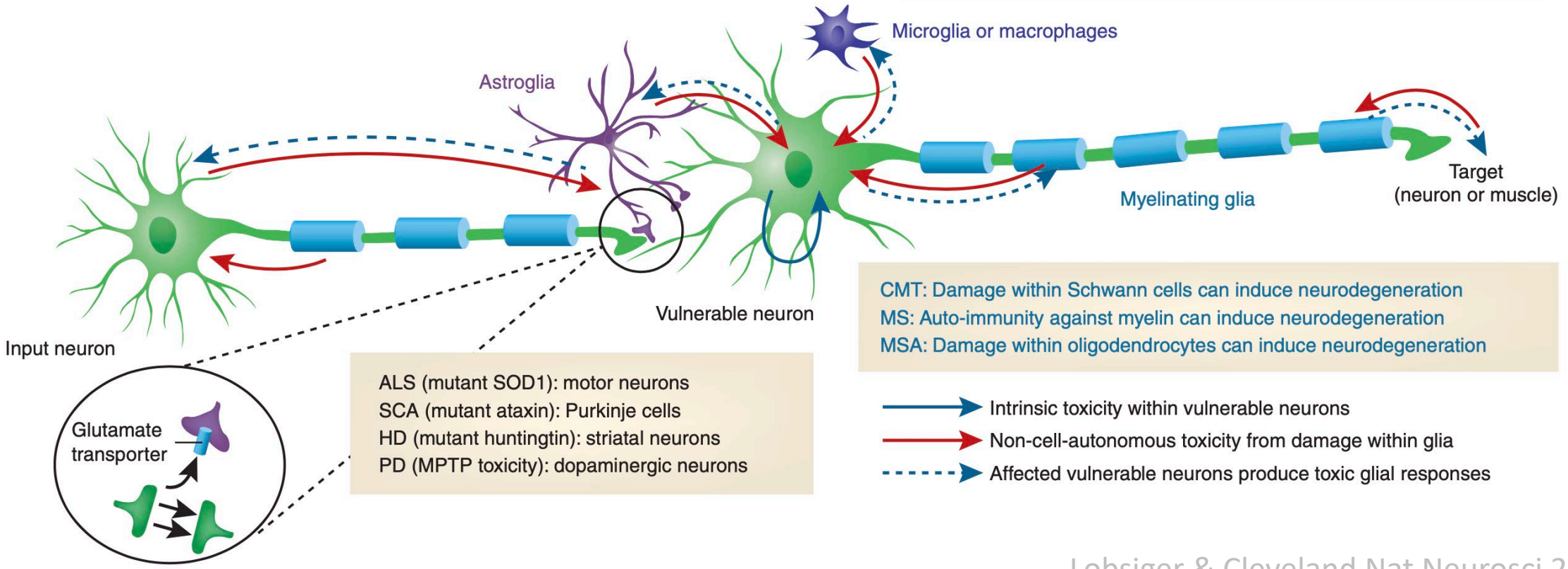
100 Years and Counting: Prospects for Defeating Alzheimer's Disease

Robertson & Mucke, Science 2006

Importance des interactions cellulaires dans les maladies neurodégénératives

ALS: Mutant SOD1–expressing astrocytes are toxic for cultured motor neurons
SCA: Mutant ataxin–expressing Bergman glia can induce Purkinje cell degeneration
HD: Mutant huntingtin–expressing astrocytes are toxic for cultured striatal neurons
PD: Astrocytes are essential to convert MPTP to its neurotoxic MPP^+ form

ALS: Microglial mutant SOD1 drives rapid disease progression
PD: Microglia are involved in MPTP-induced neurodegeneration



CMT: Damage within Schwann cells can induce neurodegeneration
MS: Auto-immunity against myelin can induce neurodegeneration
MSA: Damage within oligodendrocytes can induce neurodegeneration

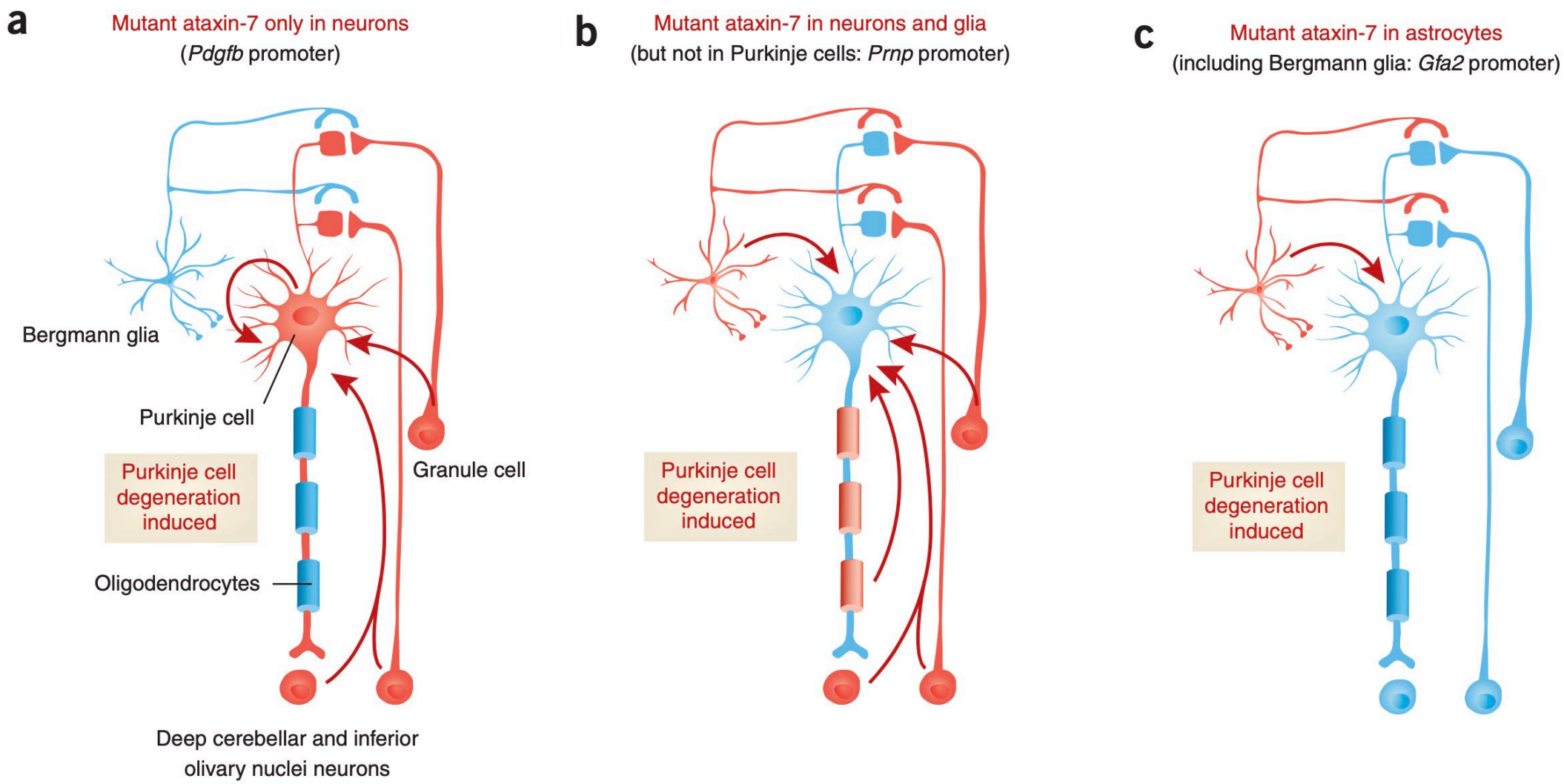
ALS (mutant SOD1): motor neurons
SCA (mutant ataxin): Purkinje cells
HD (mutant huntingtin): striatal neurons
PD (MPTP toxicity): dopaminergic neurons

Intrinsic toxicity within vulnerable neurons
Non-cell-autonomous toxicity from damage within glia
Affected vulnerable neurons produce toxic glial responses

Lobsiger & Cleveland Nat Neurosci 2007

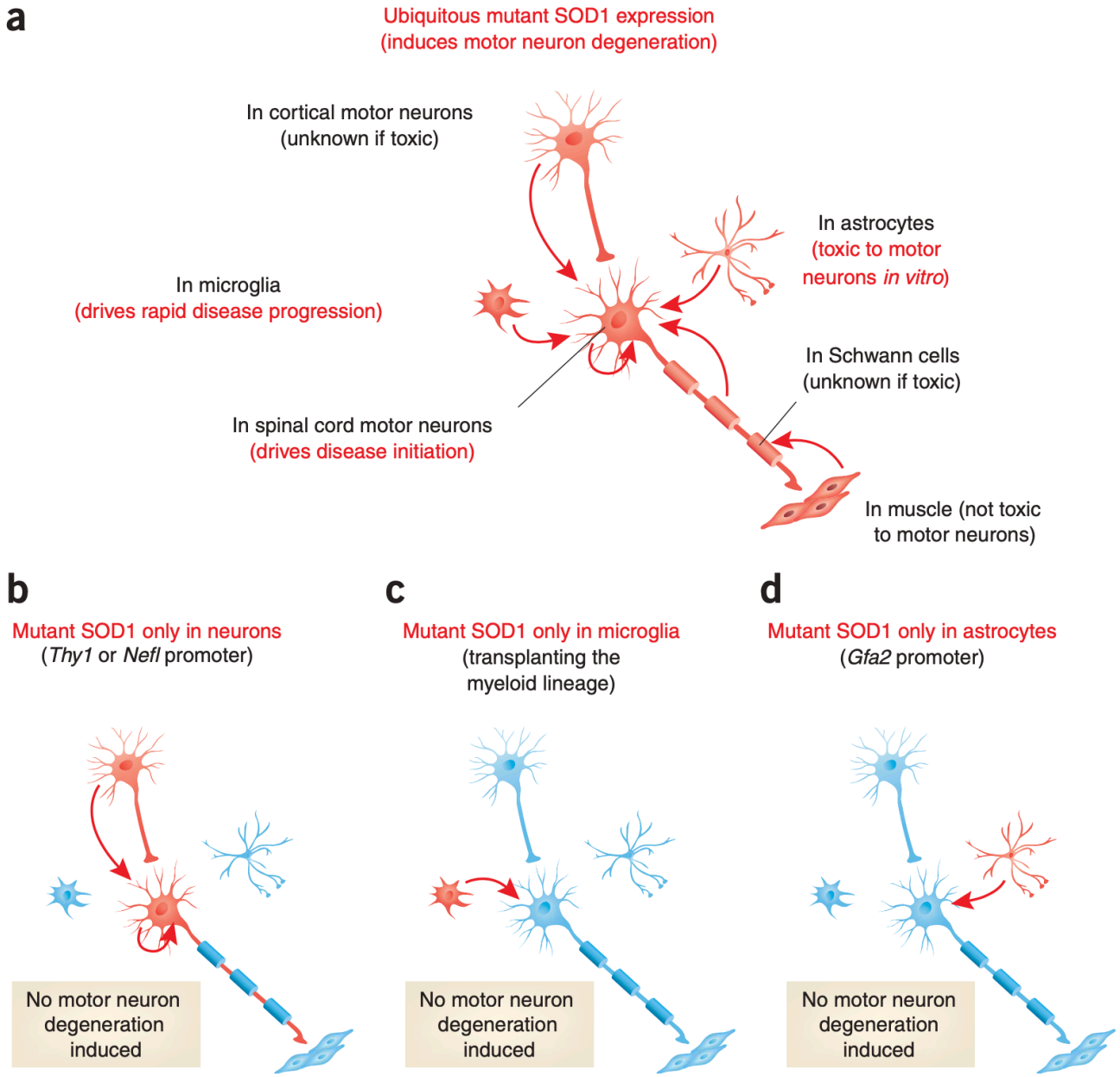
Exemples de spécificité d'atteinte cellulaire

Atrophie spino-cerebelleuse



Lobsiger & Cleveland Nat Neurosci 2007

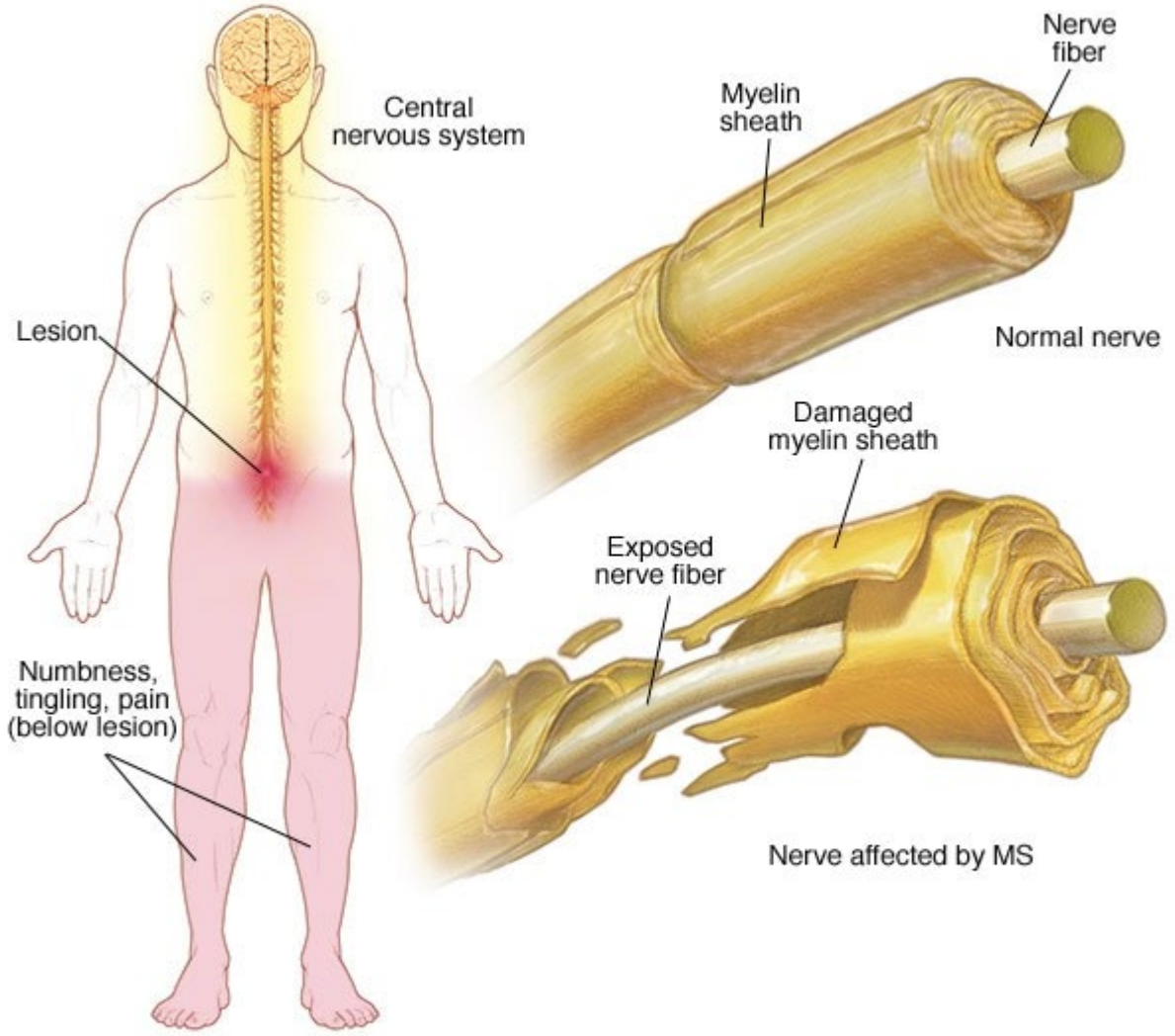
Exemples de spécificité d'atteinte cellulaire



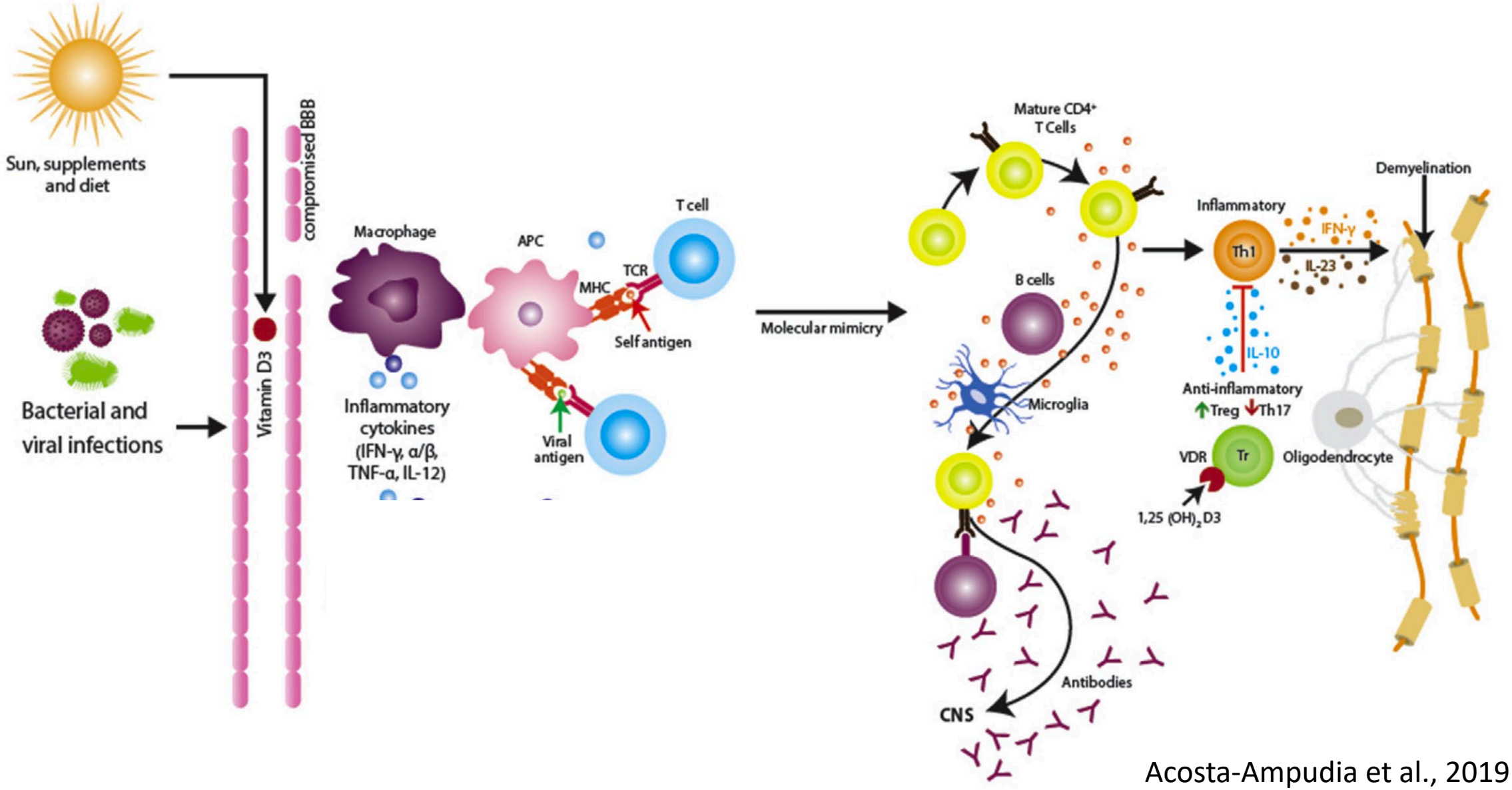
Sclérose latérale amyotrophique

Lobsiger & Cleveland Nat Neurosci 2007

La sclérose en plaque

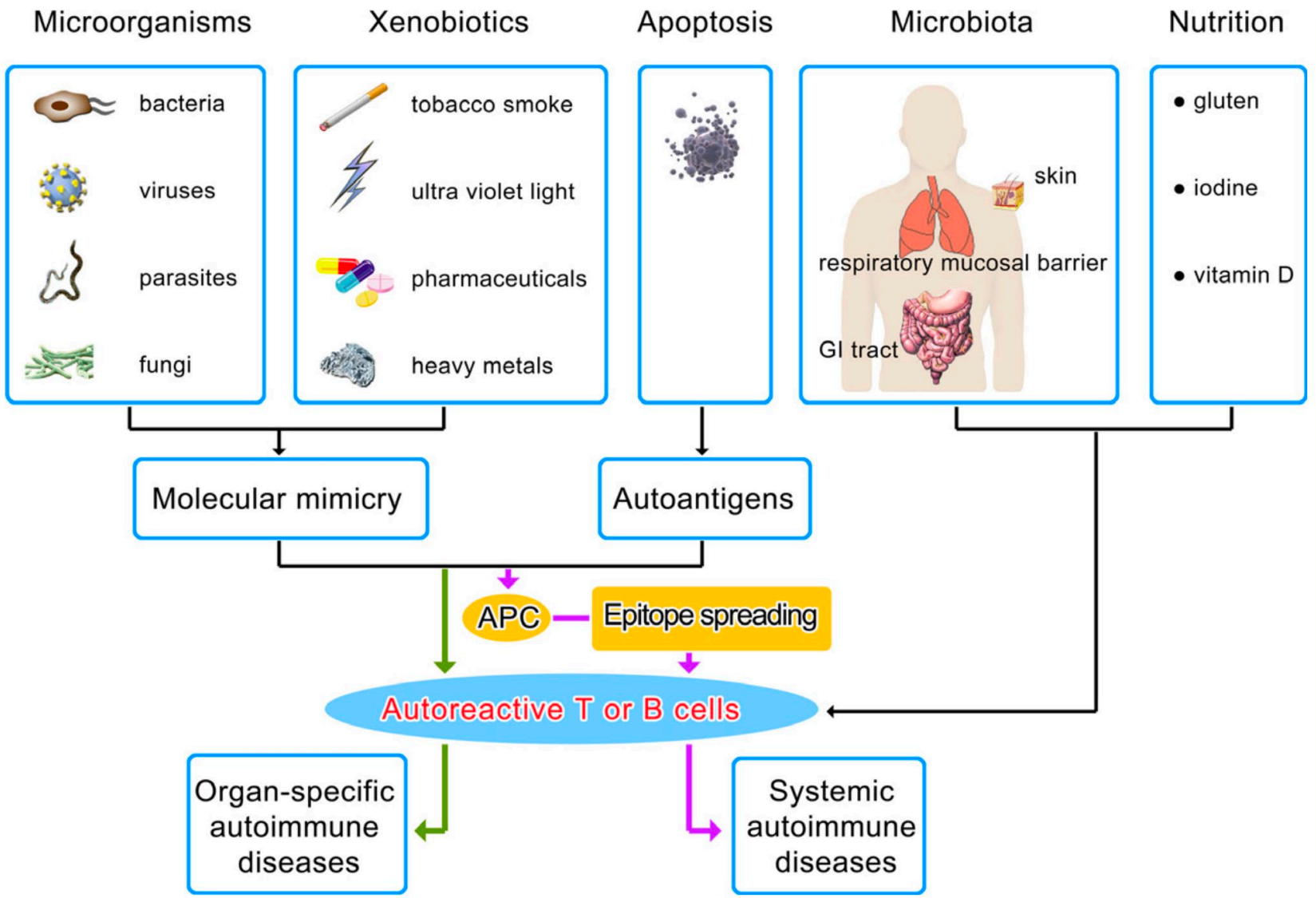


Mécanismes des maladies autoimmunes



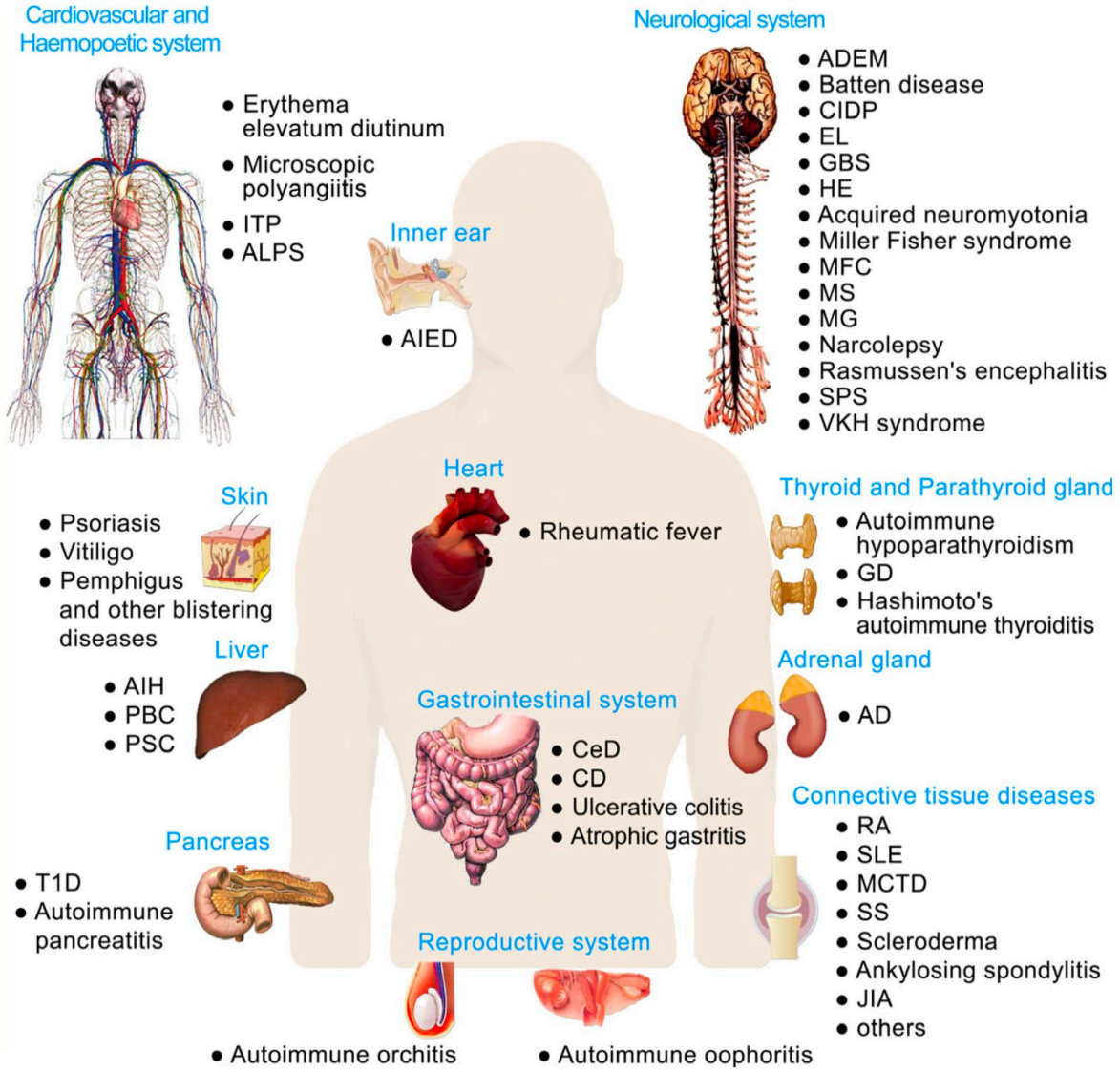
Acosta-Ampudia et al., 2019

Environnement et maladies autoimmunes

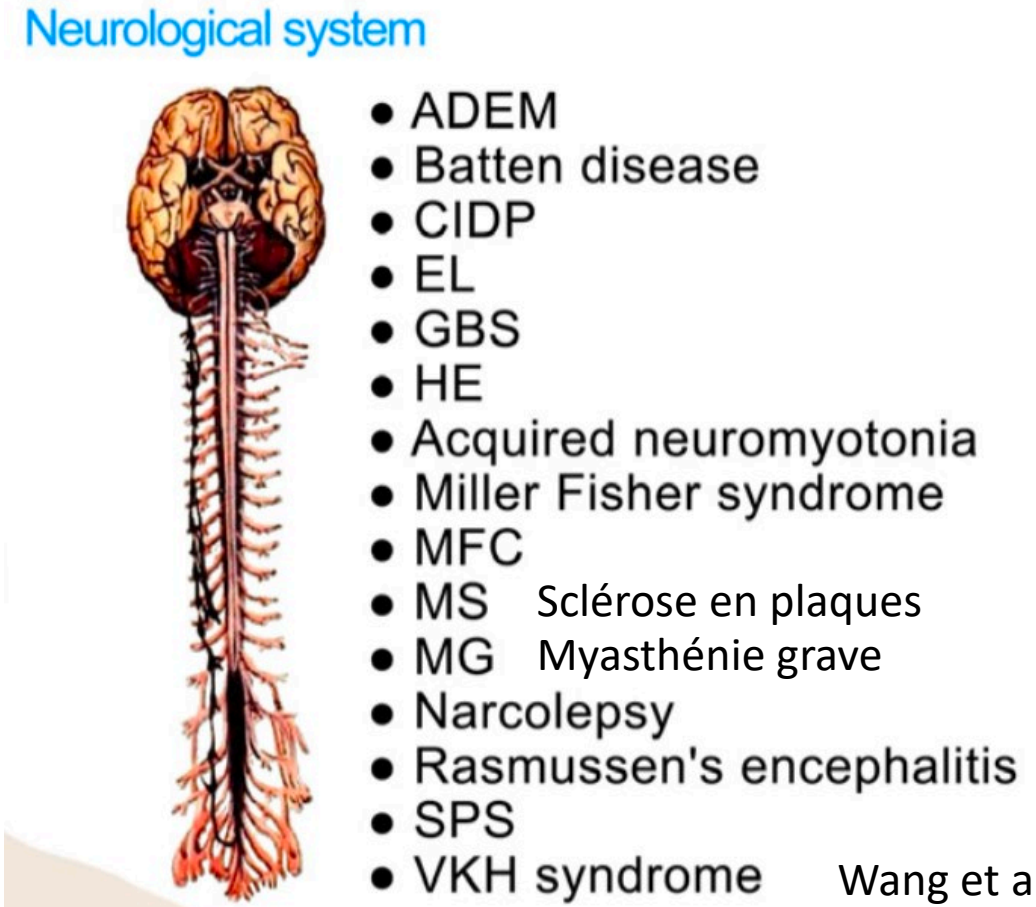


Wang et al., 2015

Types de maladies neuroimmunes



Cibles = myéline, neurones, récepteurs synaptiques ou de la junction neuromusculaire



Wang et al., 2015