

Etude des altérations moléculaires, cellulaires et vasculaires induites par l'apnée du prématûré dans le cervelet de la souris.

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Equipe 4, *Epigénétique et Physiopathologie des troubles du neurodéveloppement* – Dr. Bruno Gonzalez

1 L'apnée du prématuré: généralités

L'AdP

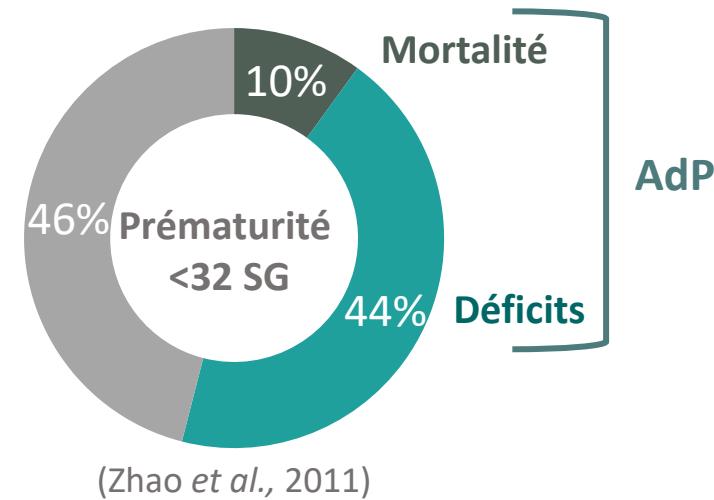
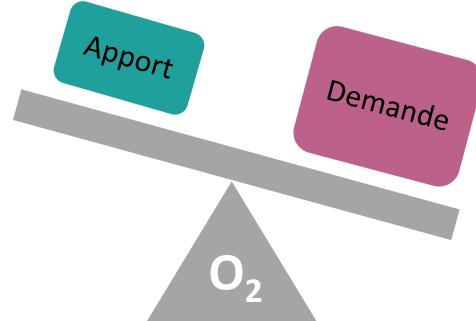
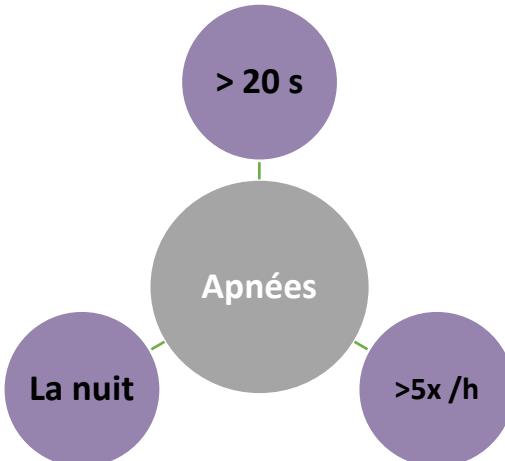
- Période périnatale
- Apnée du sommeil

L'hypoxie

- Déséquilibre d'oxygénation
- Hypoxie intermittente

Epidémiologie

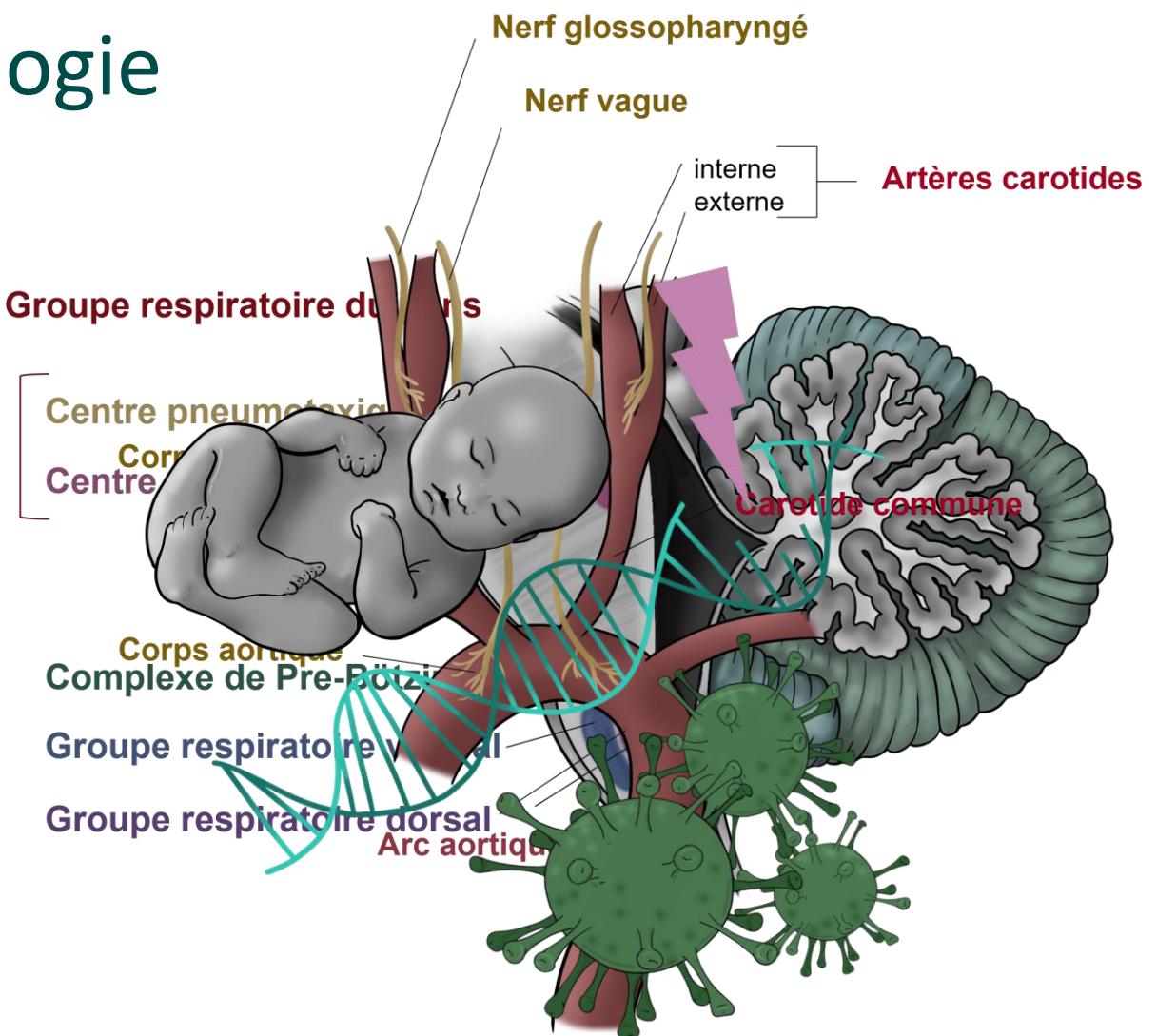
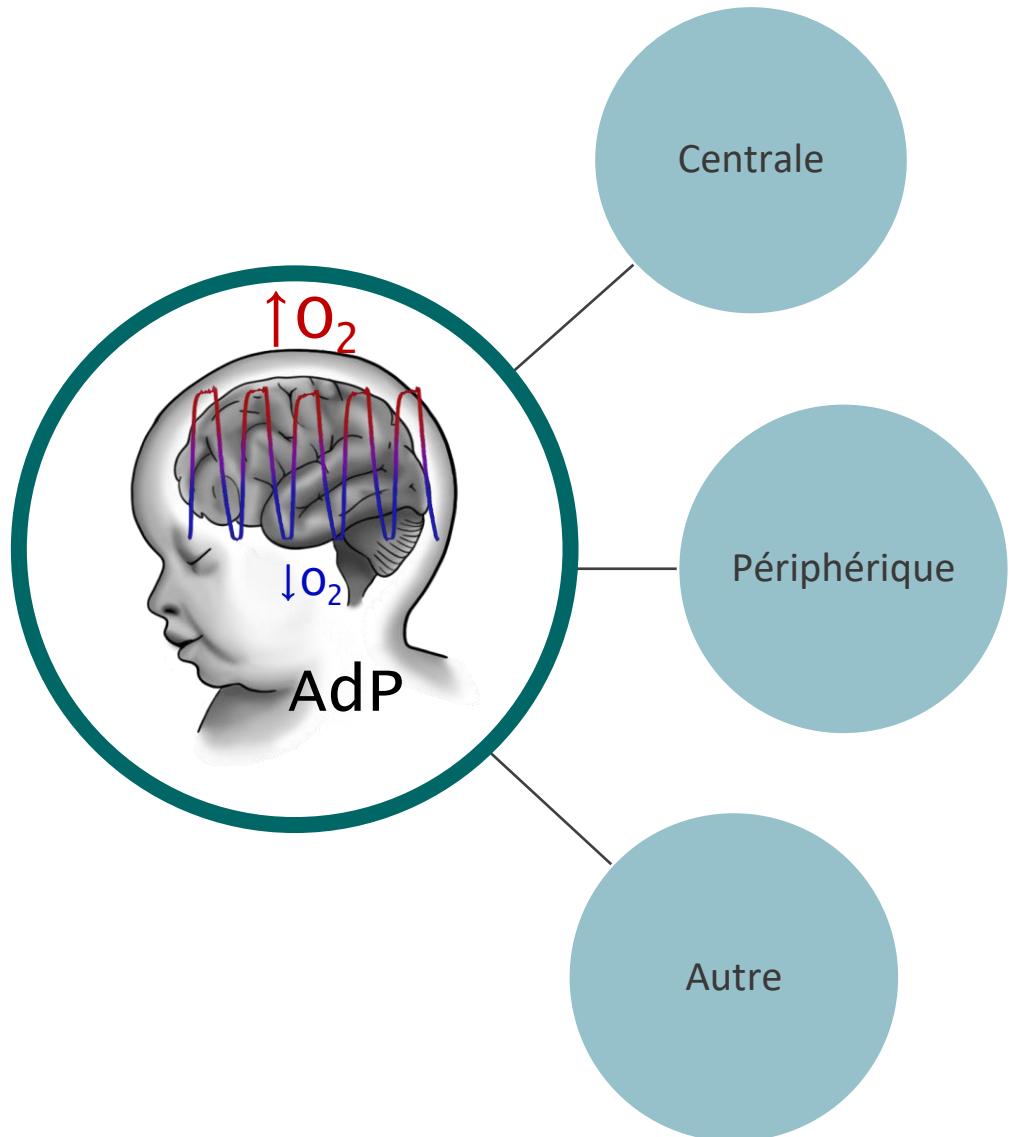
- >50% des prématurés
- Troubles développementaux



L'ADP EST UNE PATHOLOGIE FRÉQUENTE ET AUX RÉPERCUSSIONS SÉVÈRES.

2

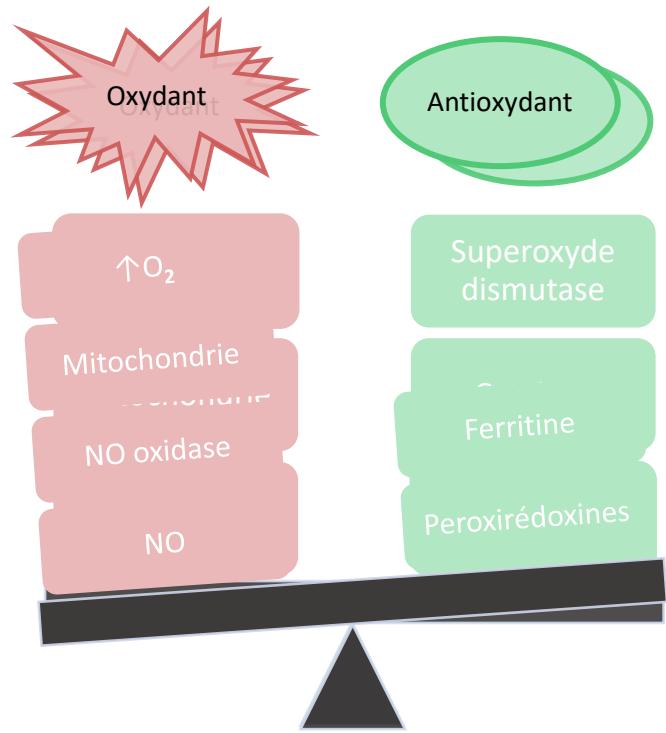
L'apnée du prématuré: étiologie



L'ADP A UNE ÉTIOLOGIE MULTIPLE.

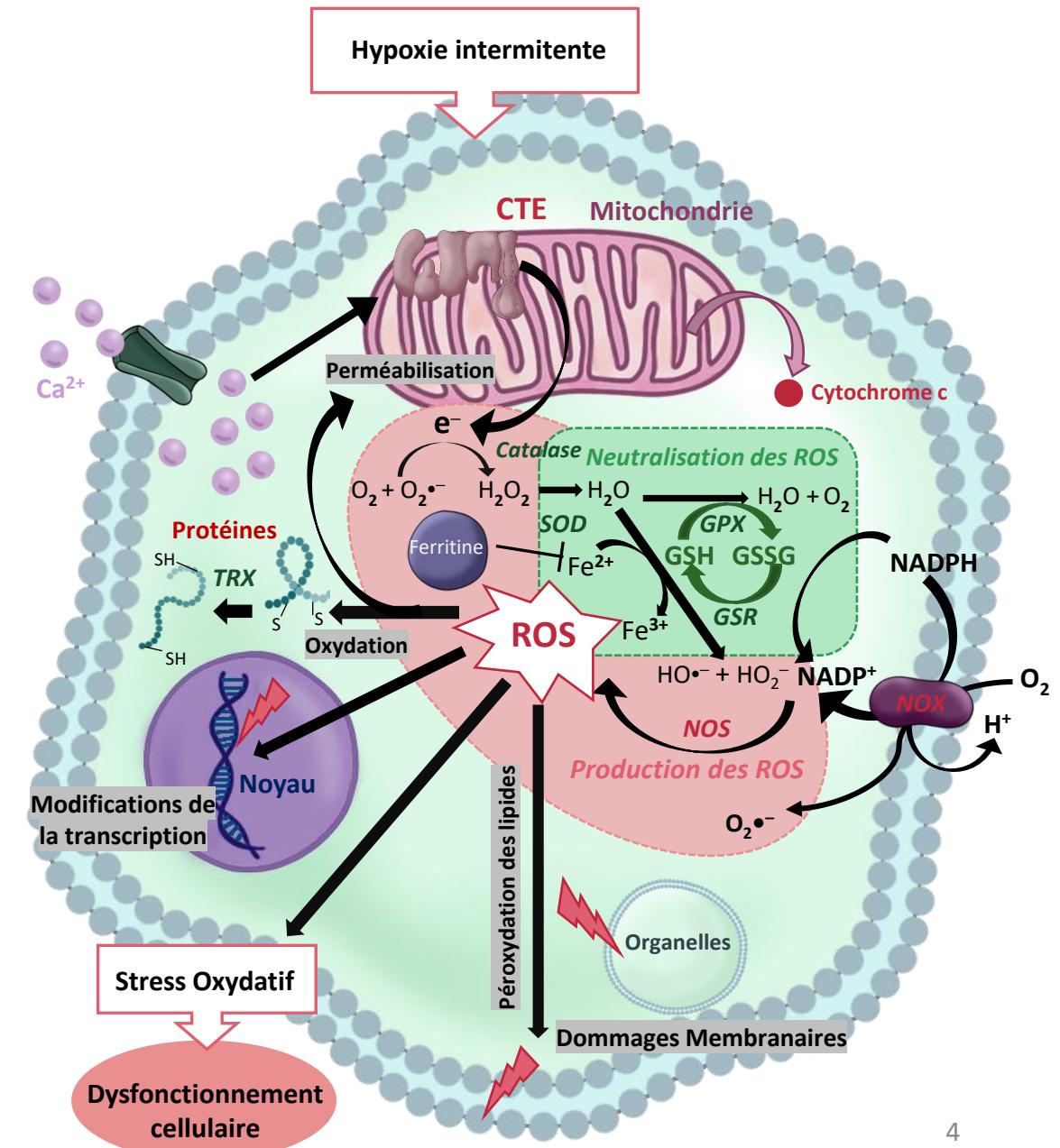
1

Mécanismes cellulaires



- Pas compensé car:
 - Stress chronique
 - Immaturité du système redox

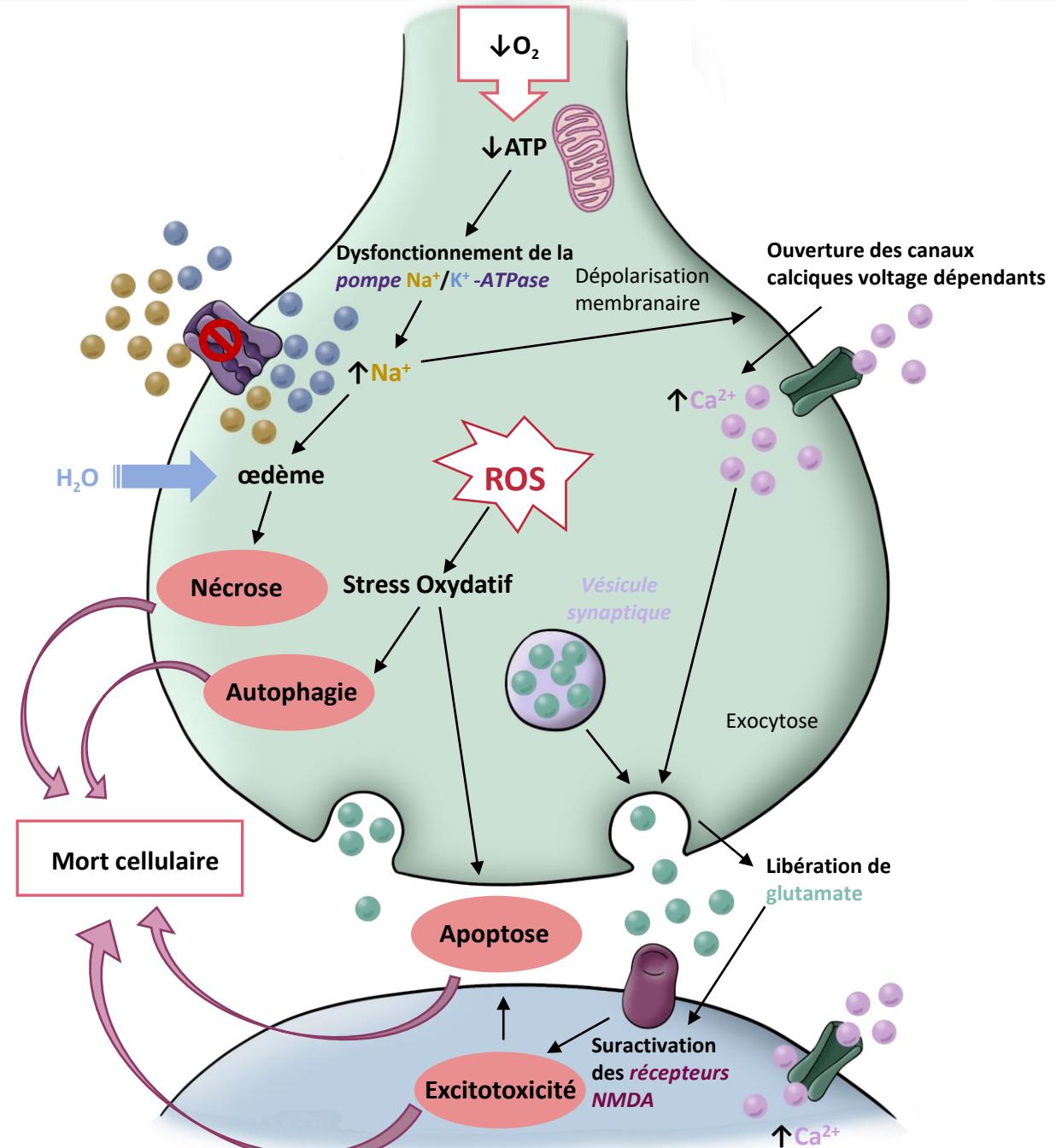
→ L'HI INDUIT UN ÉTAT DE STRESS OXYDATIF (SO).



2 Mécanismes cellulaires

- Neurones:
 - Haute demande métabolique → vulnérabilité
 - Activation de plusieurs voies de mort cellulaire

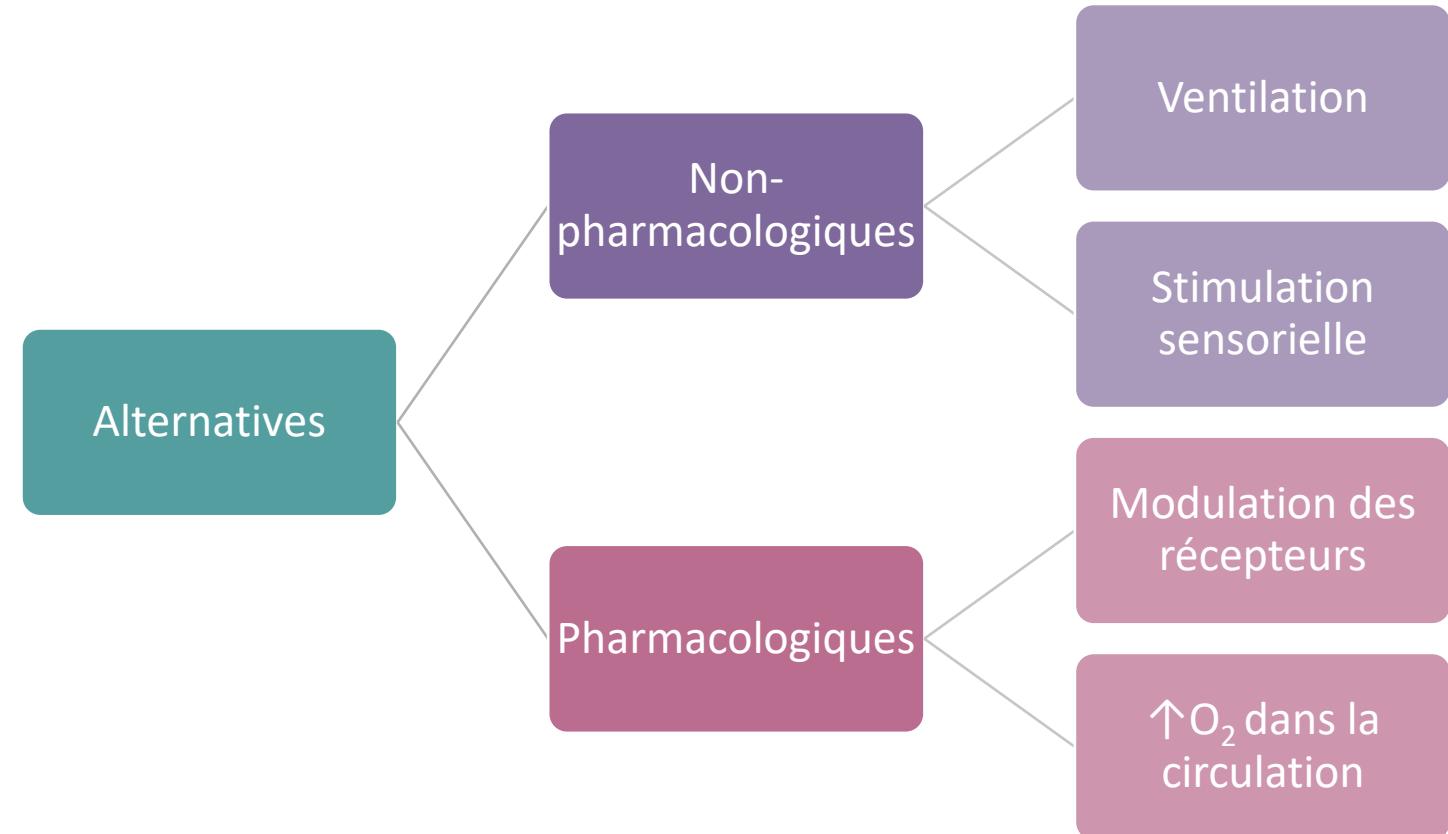
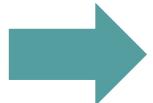
→ L'HI CAUSE UNE MORT CELLULAIRE.



3

L'apnée du prématûré: prise en charge

- Standard:
 - **Caféine** (methylxanthine)
 - Mais ... effets secondaires



→ LA CAFÉINE EST LE TRAITEMENT PAR EXCELLENCE MAIS LES SÉQUELLES PERSISTENT.

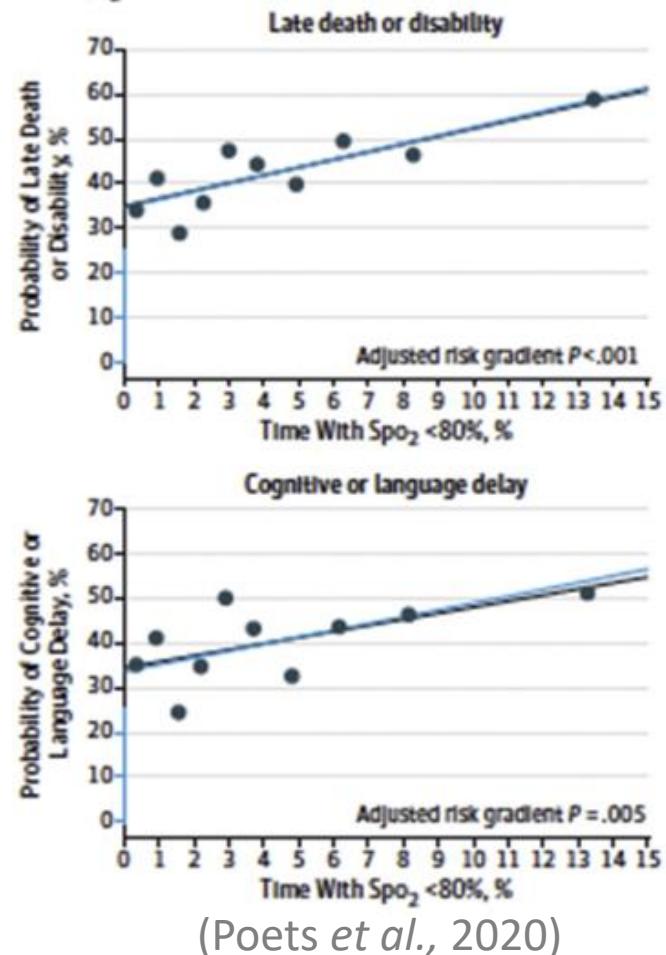
4

L'apnée du prématuré: effets à long terme

- Étude sur 11 ans → scolarisation
(Schmidt *et al.*, 2017)

Outcome	Group, No./Total No. (%)	
	Placebo	
Composite		
Functional impairment, No. (%)	174/463 (37.6)	
Components ^b		
Poor academic performance		
One or more of 4 subtests	61/462 (13.2)	
Sentence comprehension	11/454 (2.4)	
Word reading	14/461 (3.0)	
Spelling	21/461 (4.6)	
Math computation	50/472 (10.6)	
Motor impairment	130/473 (27.5)	
Behavior problem	40/481 (8.3)	

- Durée de l'apnée ↔ troubles neurodéveloppementaux (Janvier *et al.*, 2004)
- Nombre d'événements ↔ troubles cognitifs et académiques (Poets *et al.*, 2020)

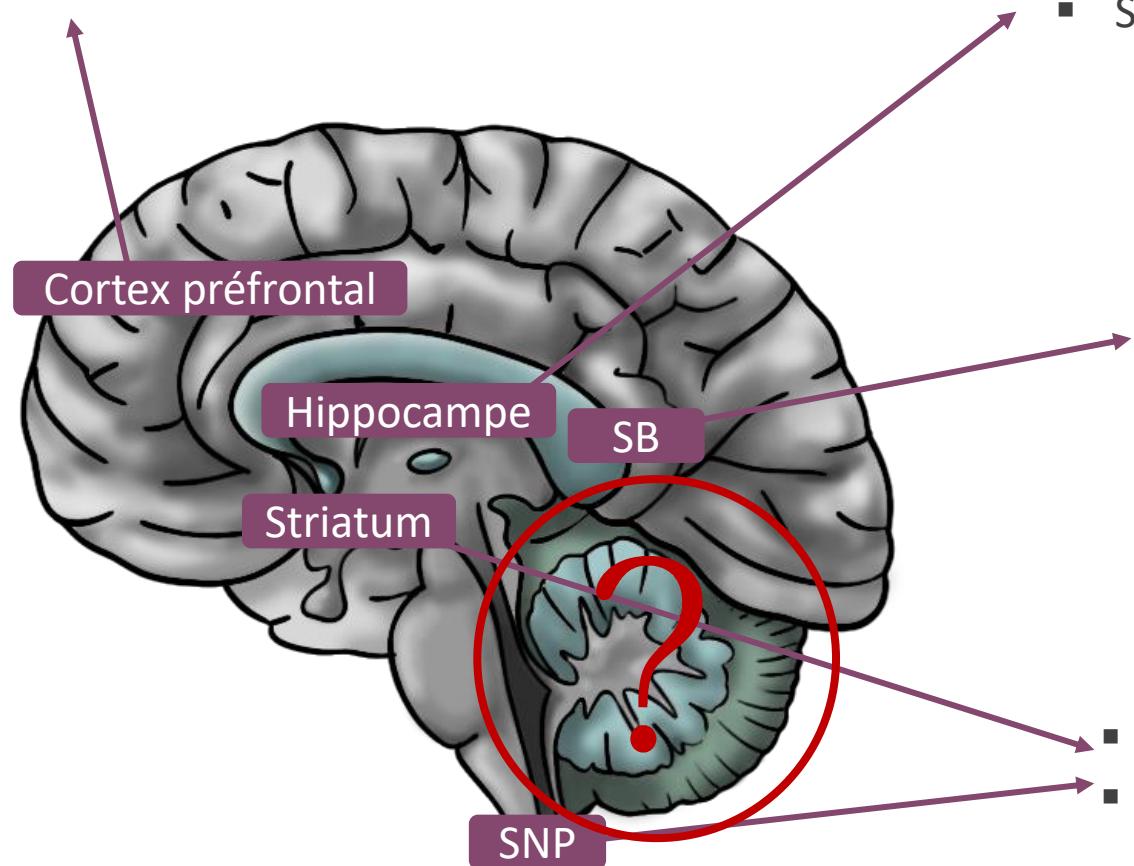


→ L'ADP AFFECTE DIVERSES FONCTIONS COGNITIVES → QUELLES ZONES SONT IMPLIQUÉES?

5

L'apnée du prématuré: implication du SNC

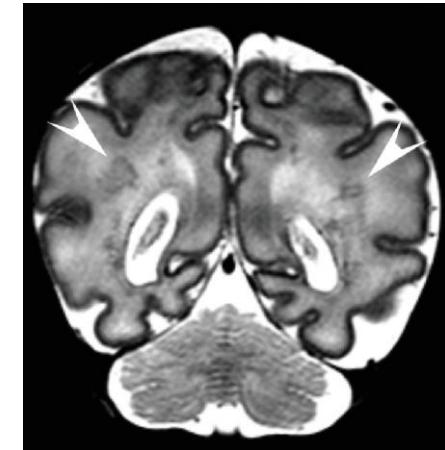
- ↓ Mémoire de travail
- Rat (Decker *et al.* 2003; Kheirandish *et al.* 2005)



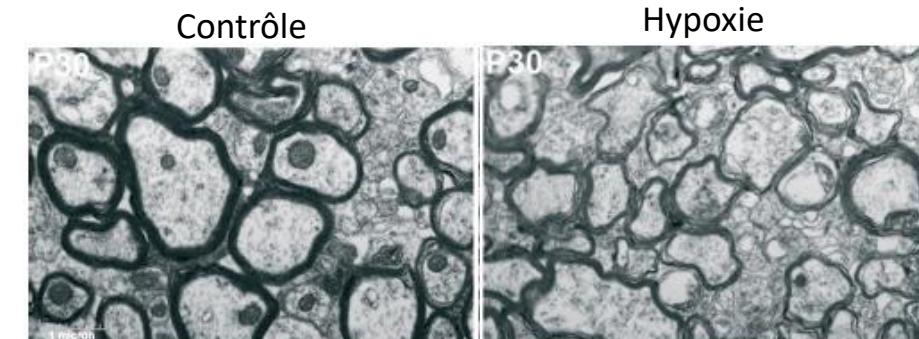
- ↓ plasticité synaptique
- Souris (Goussakov *et al.*, 2019)

- Lésion de la substance blanche périventriculaire
- Enfant prématuré (Van Bel *et al.*, 2019)

- Hypomyélinisation
- Souris (Cai *et al.*, 2012)



(Van Bel *et al.*, 2019)



(Striatum - Cai *et al.*, 2012)

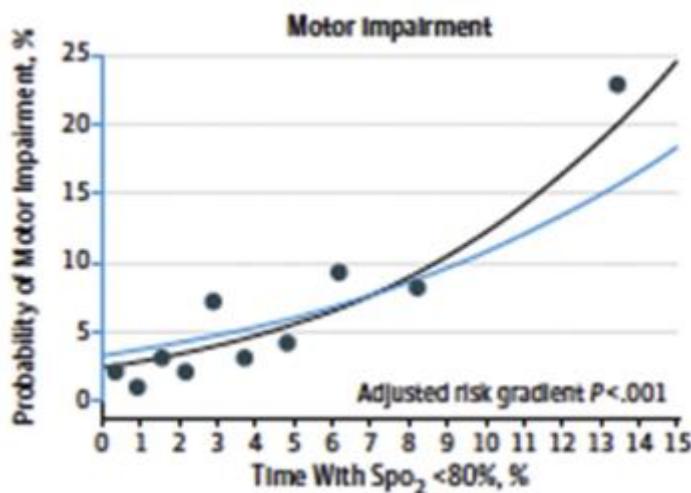
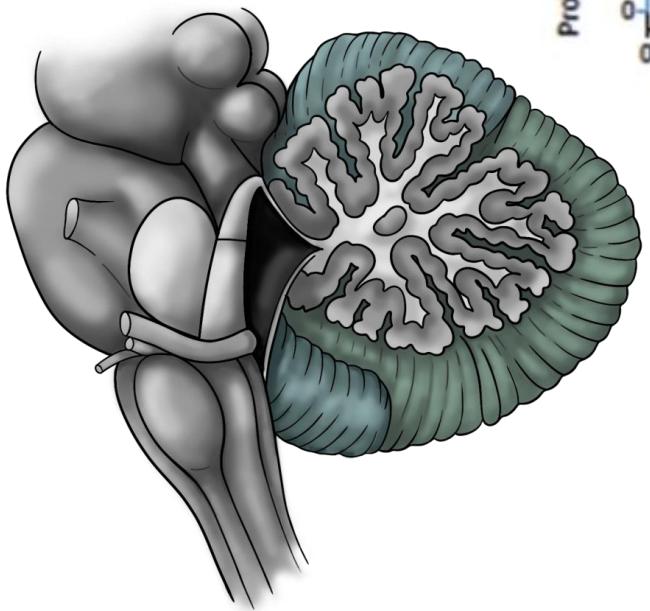


LE CERVELET EST PEU ÉTUDIÉ.

1

Le cervelet: impliqué dans l'AdP

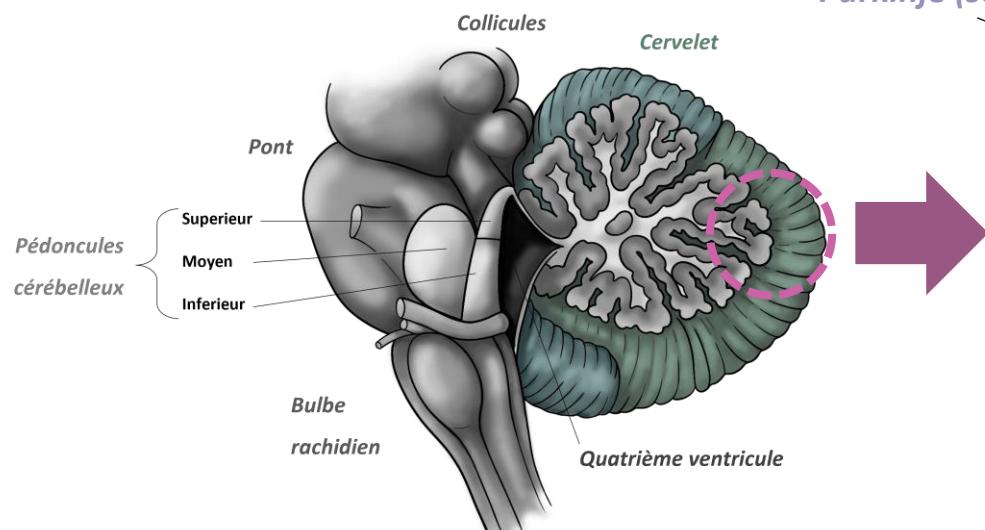
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(Schmidt *et al.*, 2017)(Poets *et al.*, 2020)

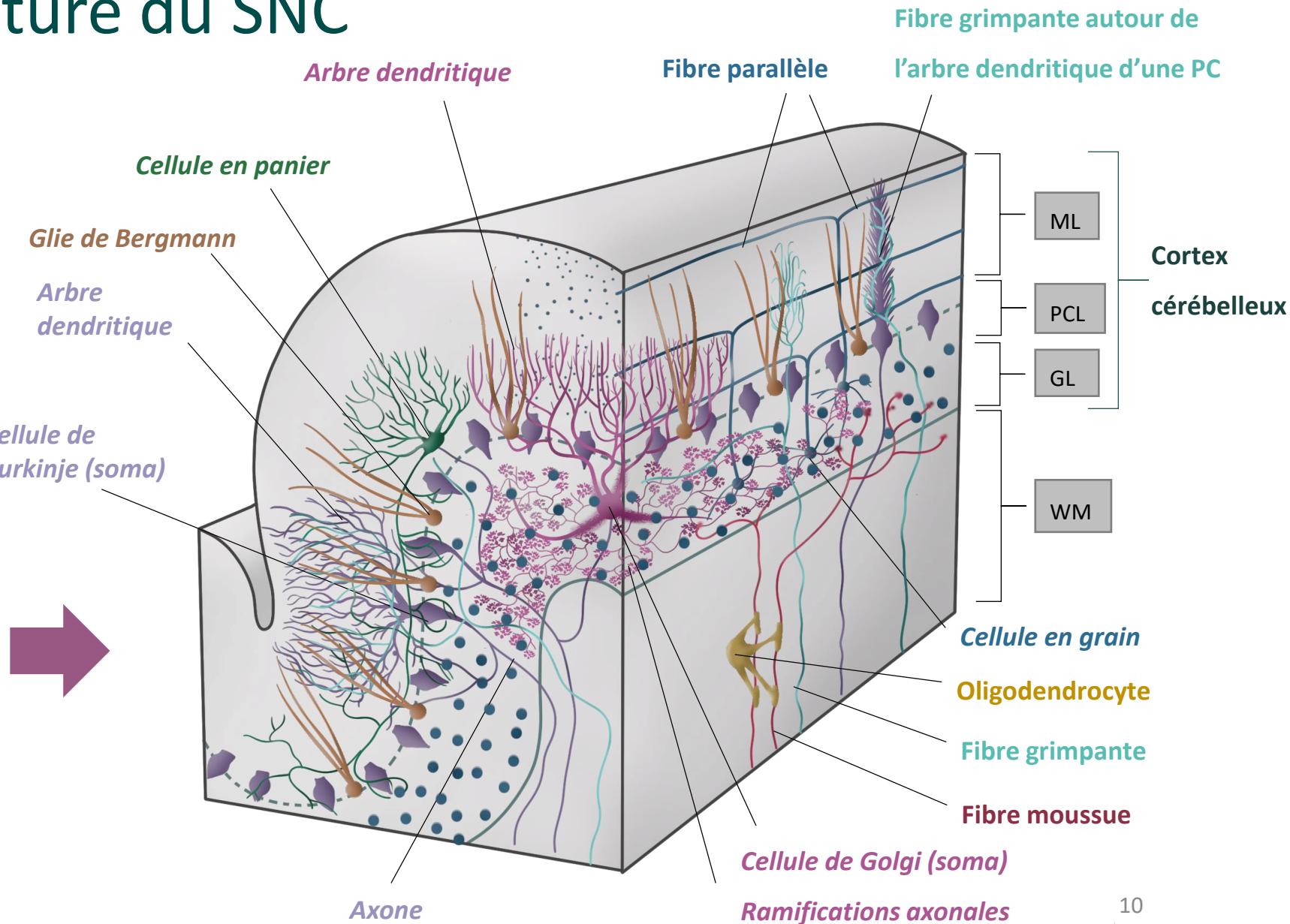
→ LES SYMPTÔMES CORRESPONDENT À DES FONCTIONS PARTIELLEMENT CÉRÉBELLEUSES.

2 Le cervelet: structure du SNC

- “Petit cerveau” dans la fosse postérieure
- Généralités:
 - Aspect lobulé
 - 15% de la masse cérébrale
 - 70% des neurones



(Herculano-Houzel et al. 2006)

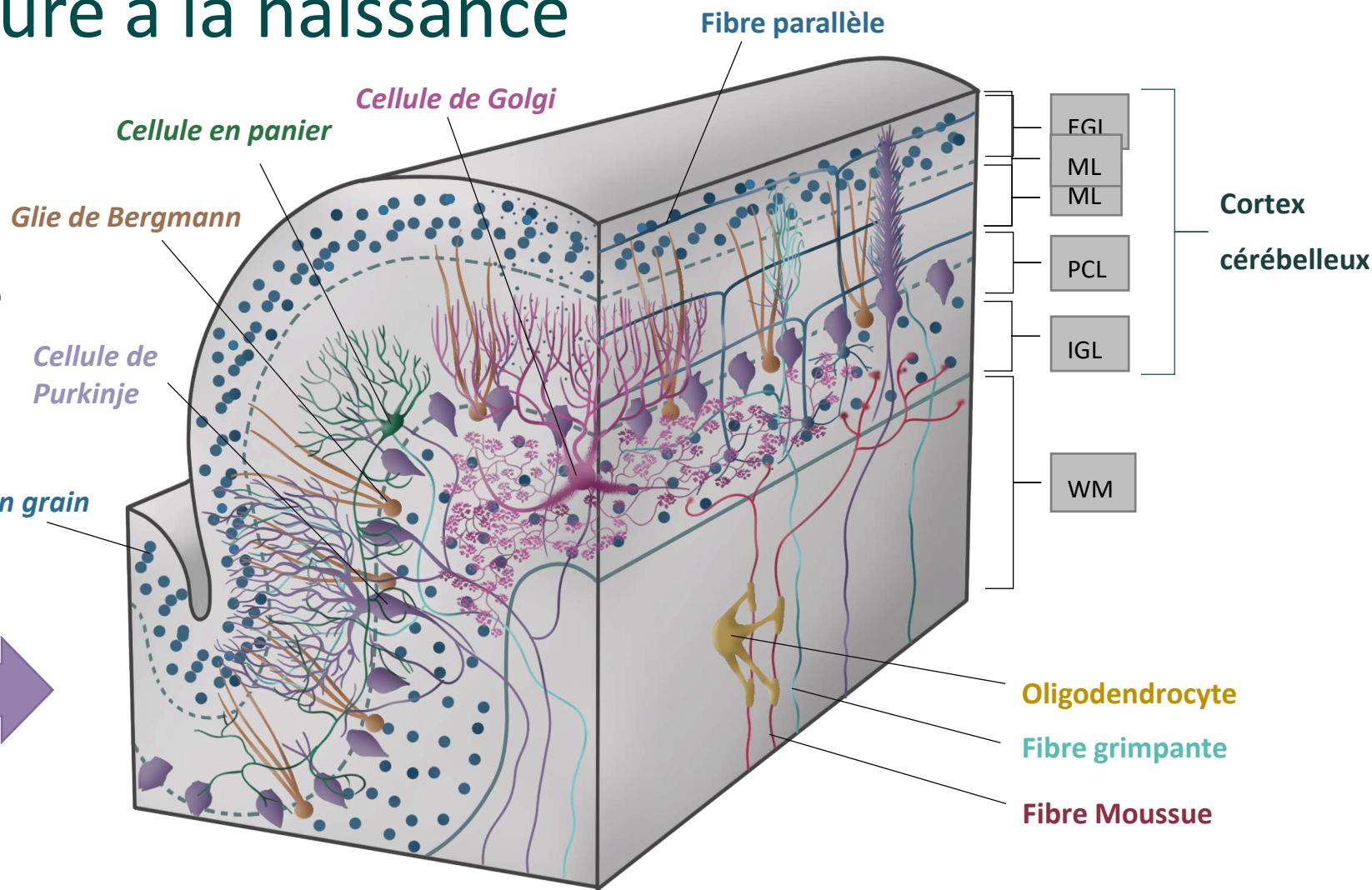
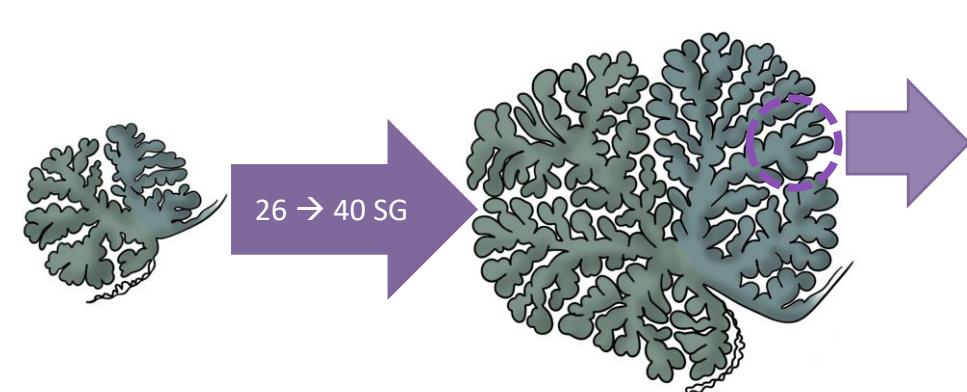


3

Le cervelet: immature à la naissance

- Immaturité à la naissance
- Période périnatale :

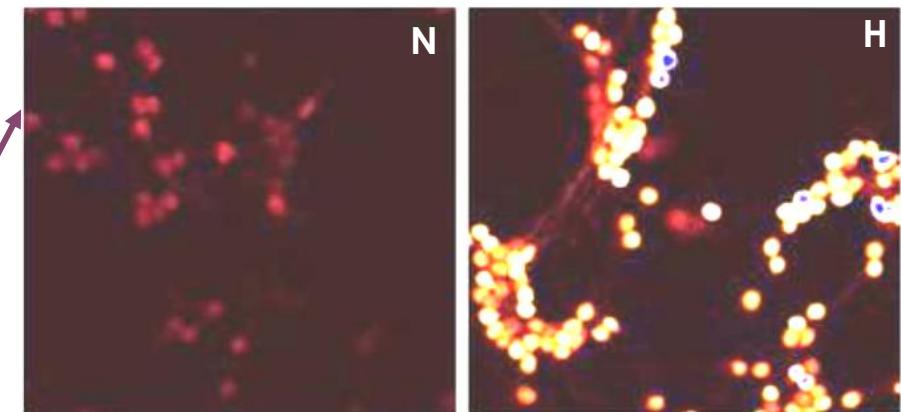
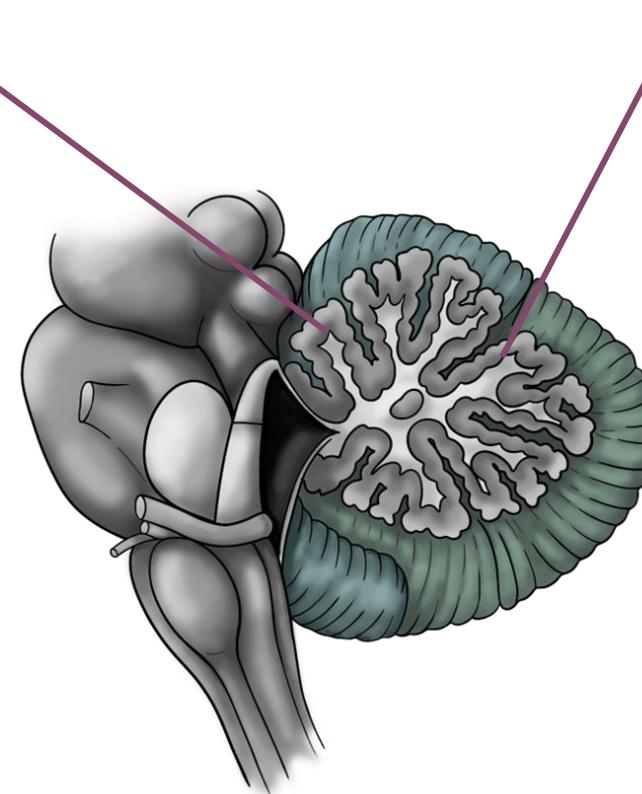
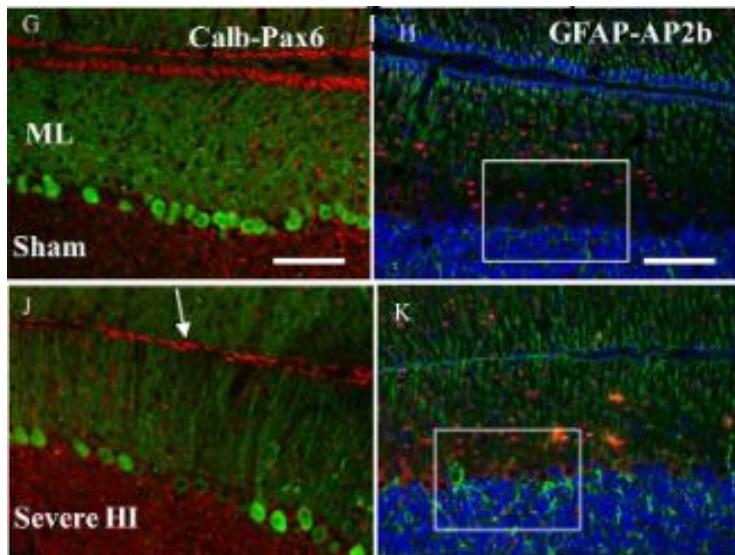
- Volume x4
- ↗ foliation
- Surface x30



4

Le cervelet: sensibilité à l'hypoxie

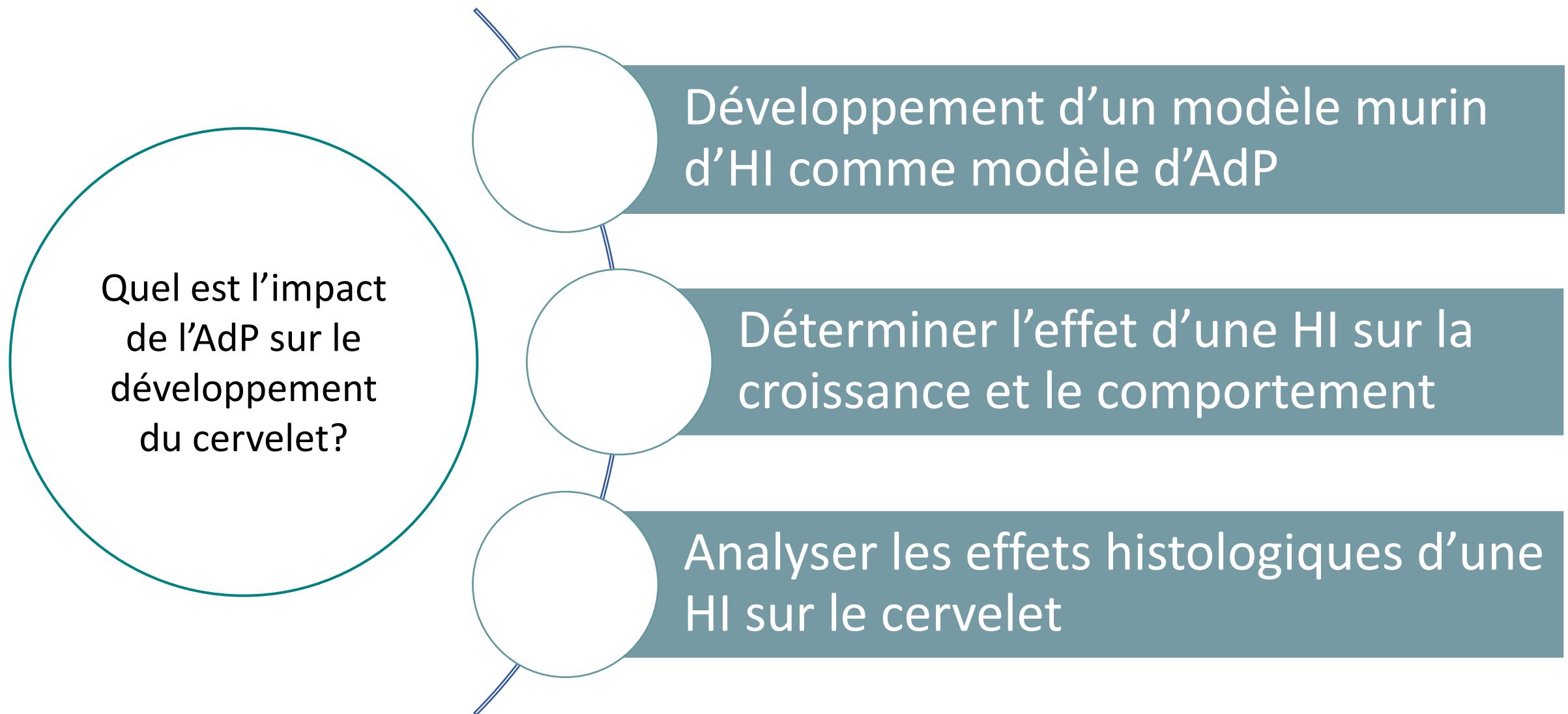
- Altération des PCs et interneurones en hypoxie continue et hypoxie-ischémie.
(Scheuer *et al.*, 2017, Biran *et al.*, 2011)



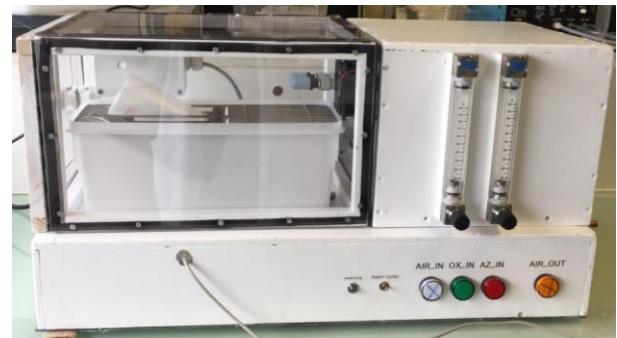
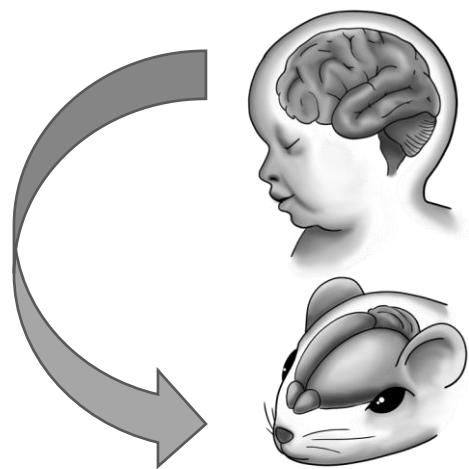
(Chiu *et al.*, 2012)

- In vitro*: culture de cellules en grain
 - Rats P7 ↑ROS (Chiu *et al.*, 2012)
 - Rats → activation NOS et excitotoxicité (Ferriero 2001)

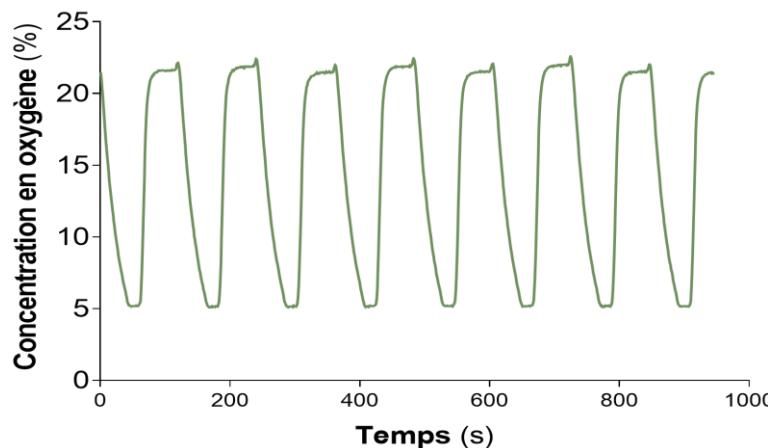
(Biran *et al.*, 2011)



L'hypoxie intermittente comme modèle d'AdP



Chambre d'hypoxie validée par Dr. Sarah Leroux



- Répétition de cycles d'hypoxie/réoxygénéation
- 2 minutes dont 20s à 5% d'O₂ pendant 6h/jour
- A partir de P2 durant 10 jours

1

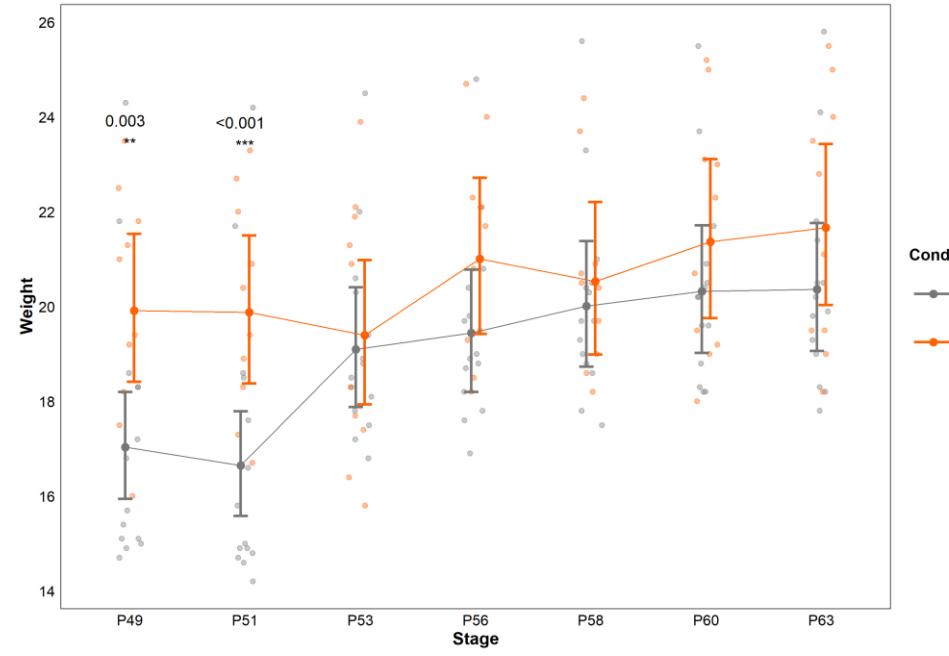
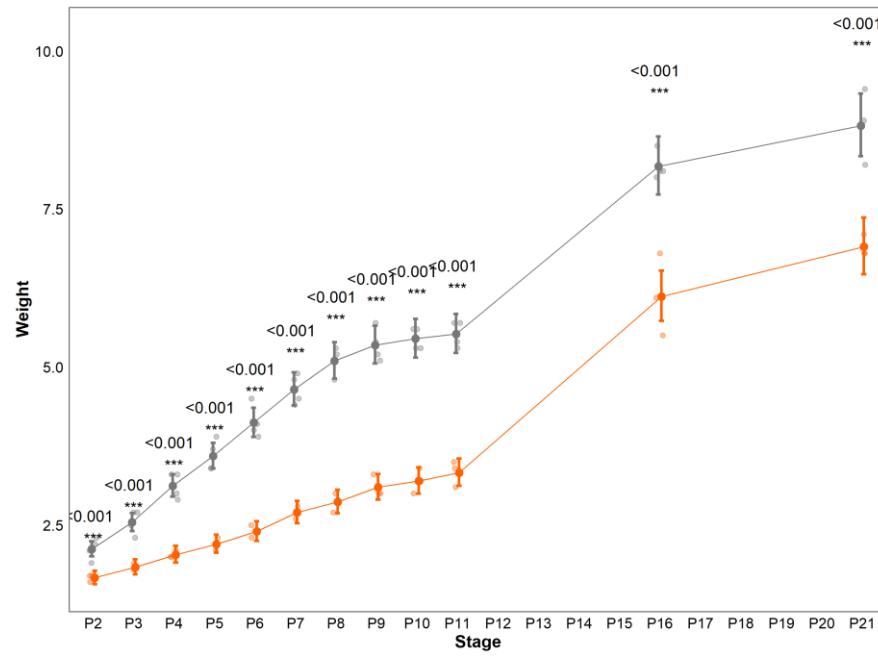
Croissance

Pas de différence à la naissance

Retard pendant le protocole

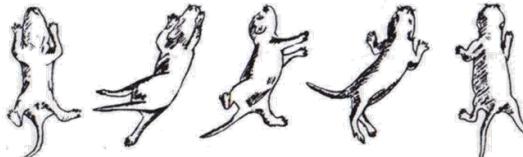
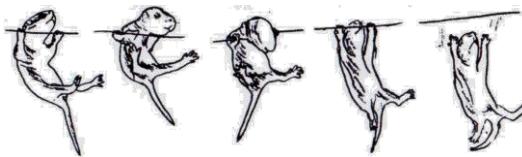
Stabilisation après le protocole

Compensation à l'âge adulte

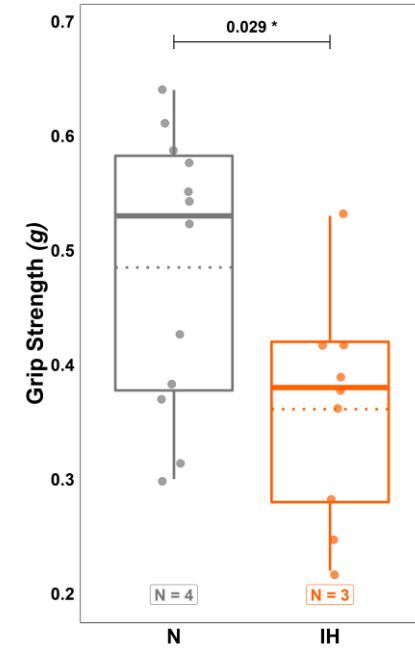
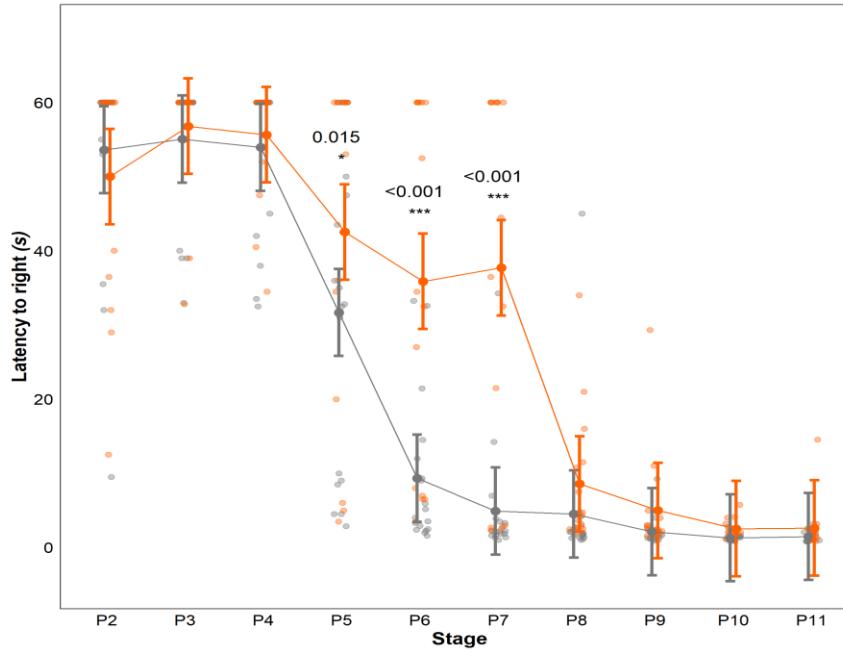
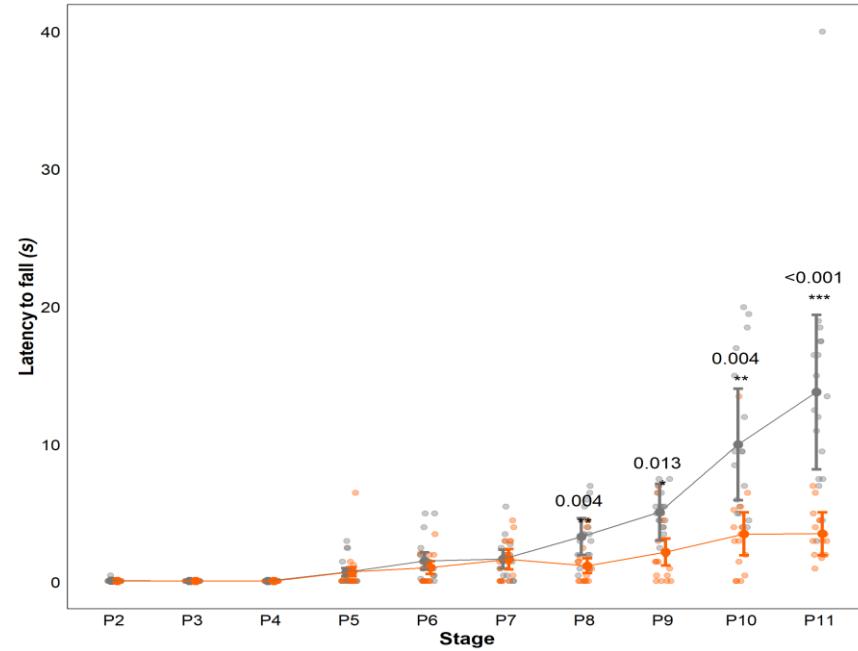


→ NOTRE PROTOCOLE D'HI INDUIT UN RETARD DE CROISSANCE QUI EST COMPENSÉ DANS LE LONG TERME.

2 Développement moteur



P21

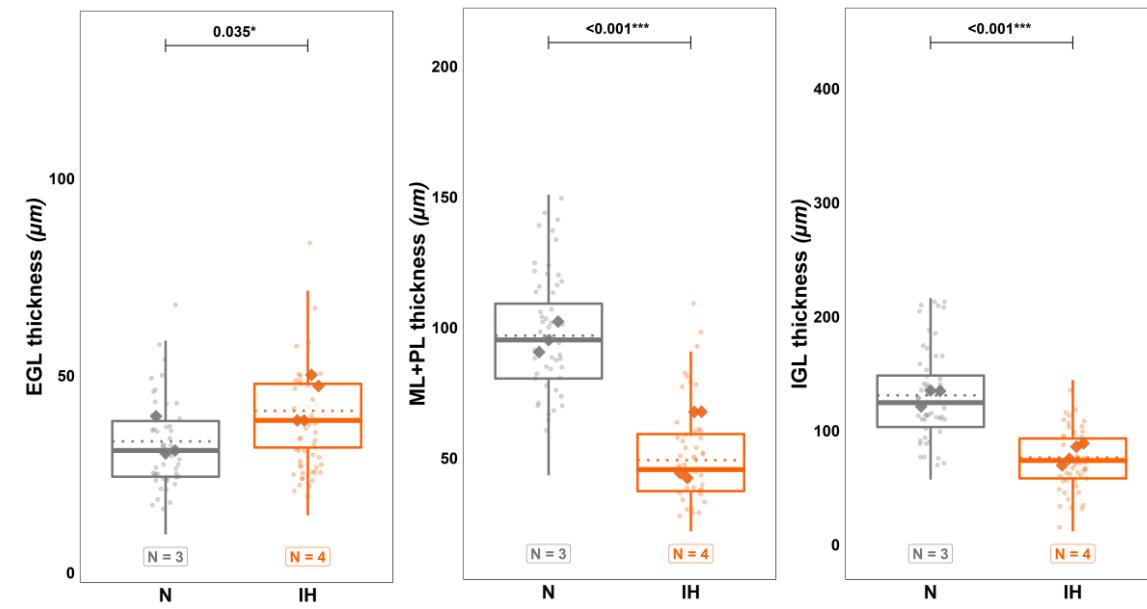
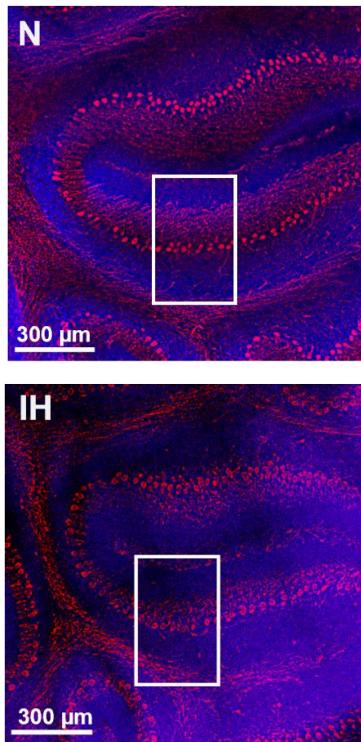
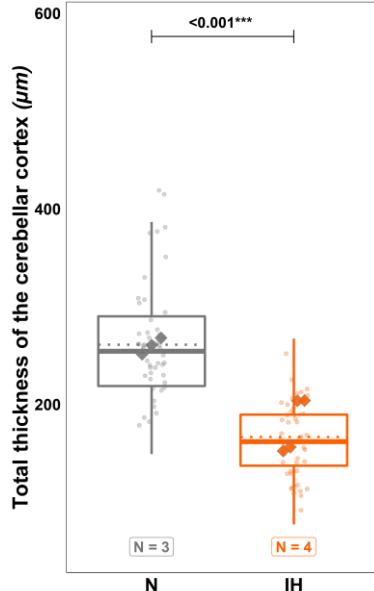


→ L'HI INDUIT UN DÉFICIT DES FONCTIONS MOTRICES ET DE LA COORDINATION.

3

Histologie

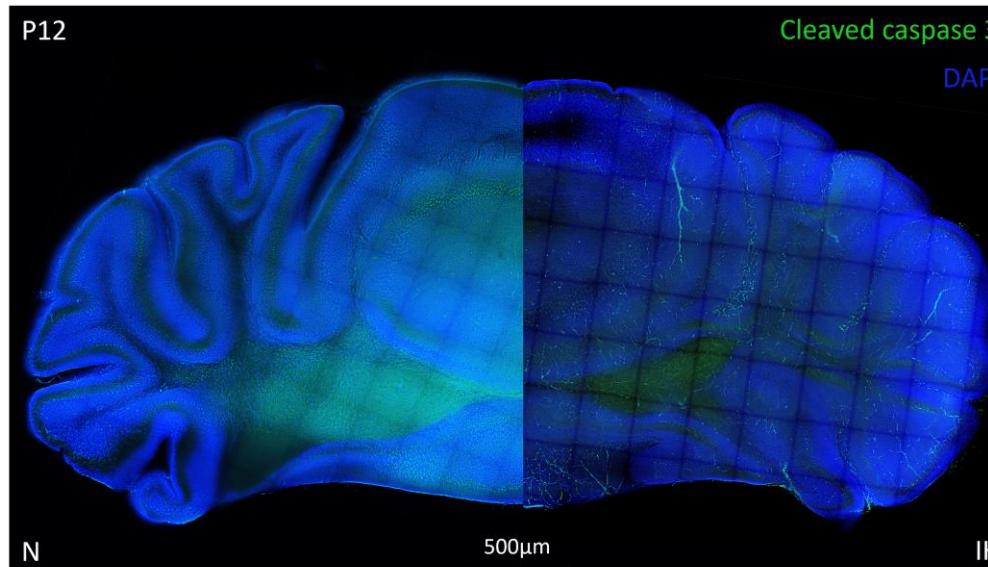
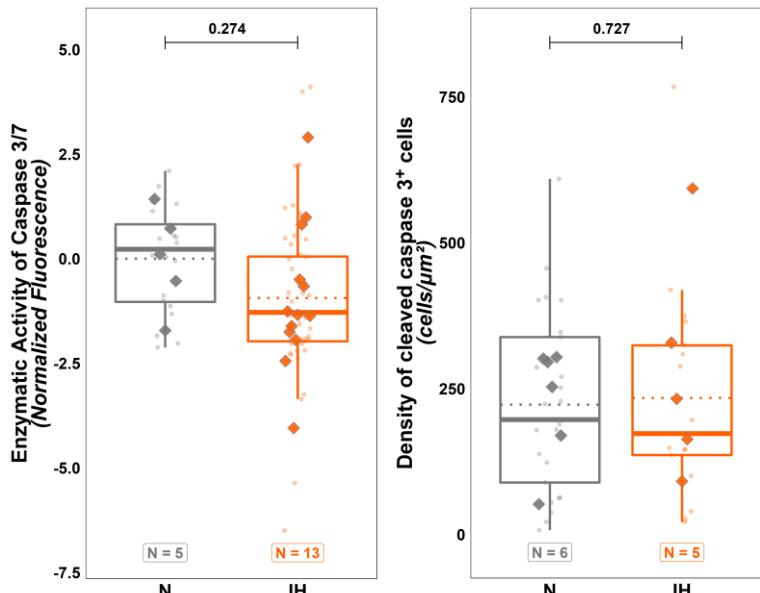
Quels sont les effets à la fin du protocole?



→ L'HI INDUIT UNE DIMINUTION DE LA TAILLE DU CERVELET ET UN RETARD DE MATURATION À P12.

Histologie

Est-ce que la diminution d'épaisseur du cortex est due à la caspase?



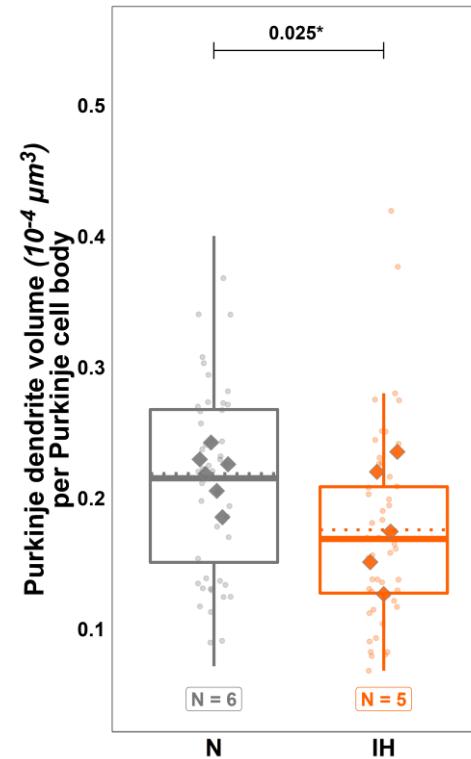
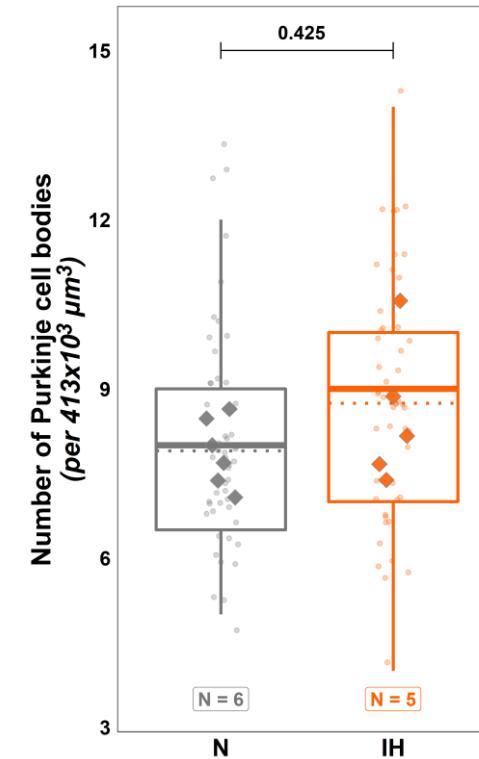
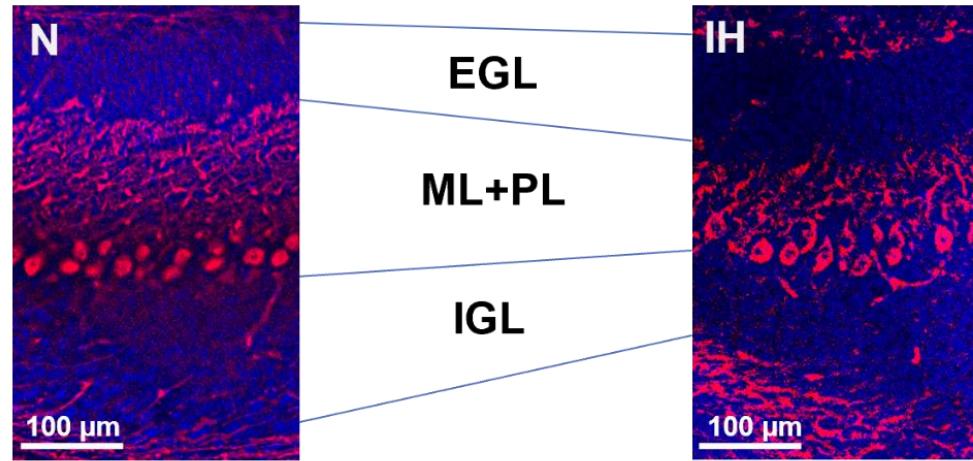
- Autre moment?
- Autre mécanisme?

→ L'HI N'INDUIT PAS DE MORT CELLULAIRE CASPASE-DÉPENDANTE À P12.

Histologie

Quels sont les effets sur les cellules de Purkinje?

- Nombre de corps cellulaires équivalents
- Volume réduit de l'arbre dendritique

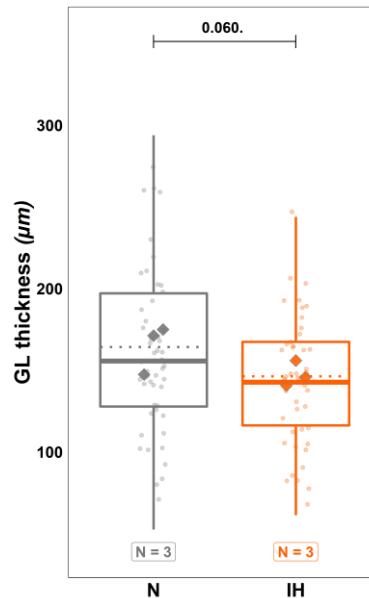
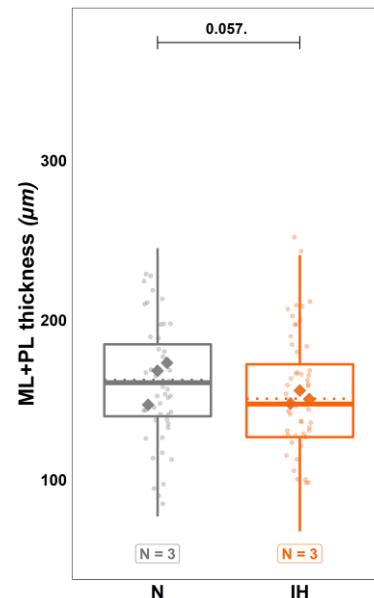
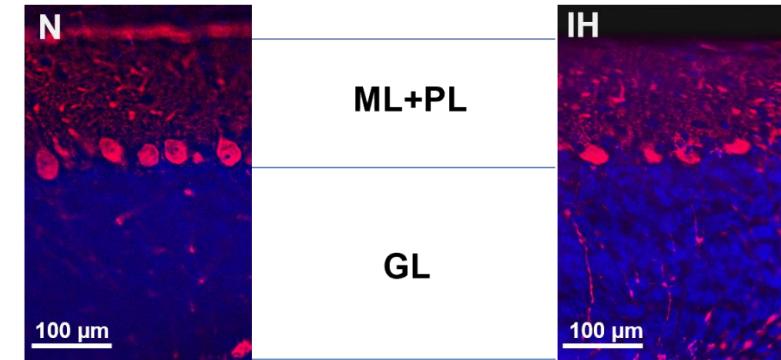
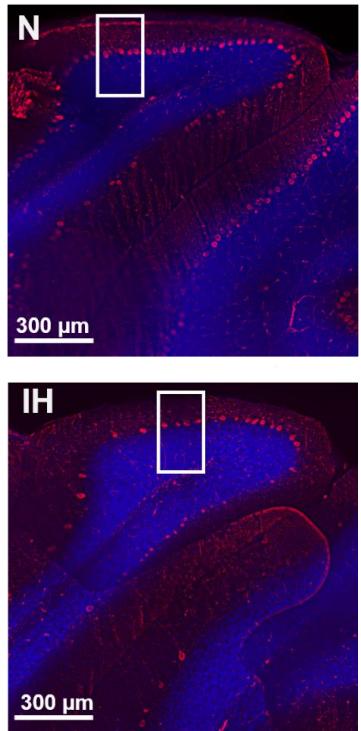
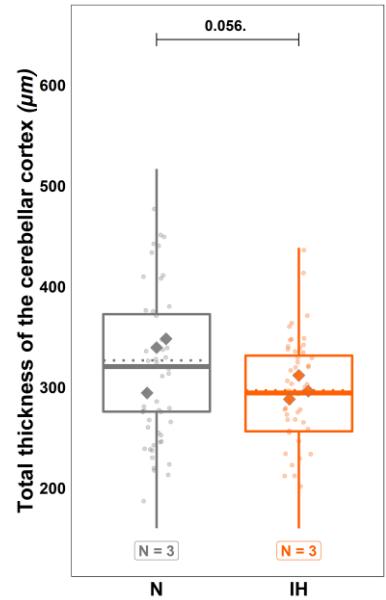


→ L'HI INDUIT UN RETARD DE DIFFÉRENCIATION DES PC À P12.

6

Histologie

Est-ce que les altérations perdurent à P21?

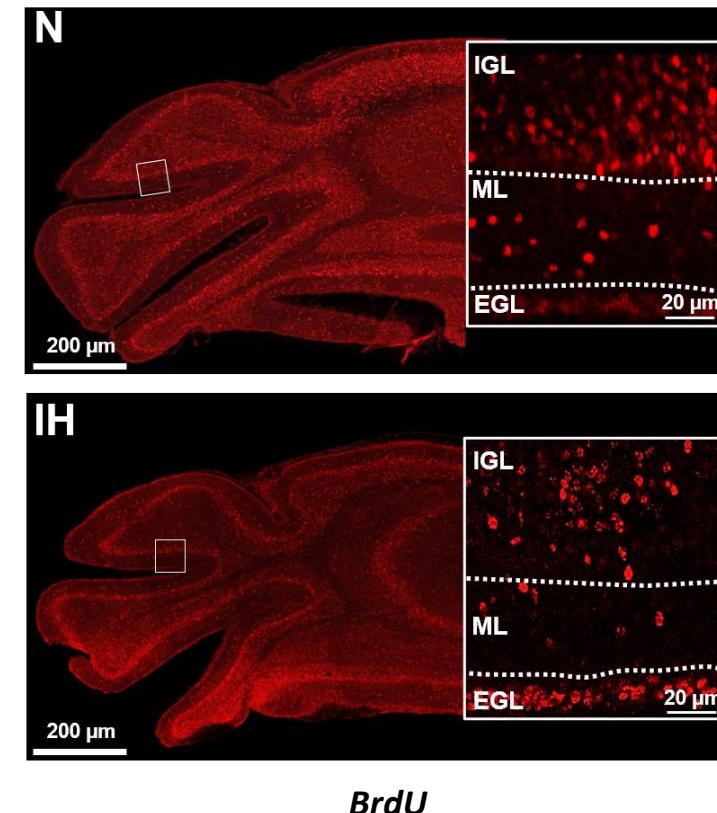
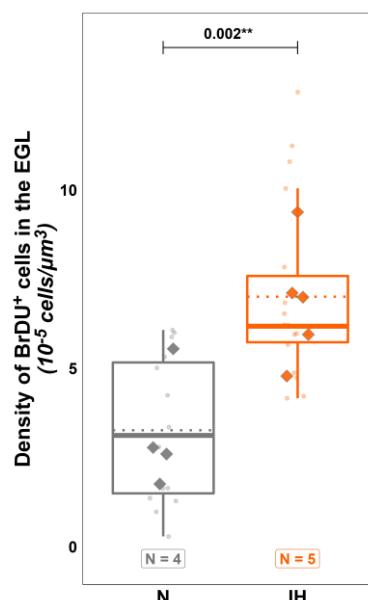
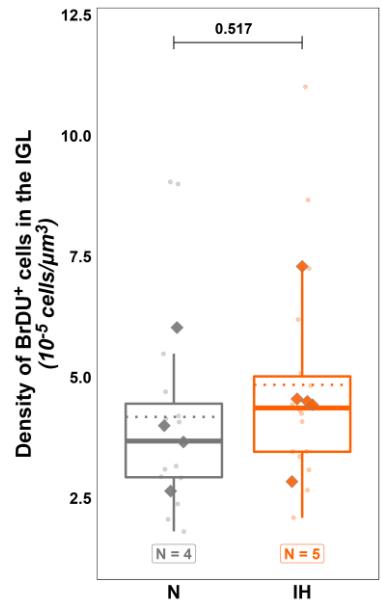


→ LES EFFETS HISTOLOGIQUES DE L'HI SEMBLENT SE COMPENSER À P21.

Histologie

Quelle peut être cette compensation?

- BrdU: injection P6 → pas de déficit de migration
- BrdU: injection P12 → augmentation de la prolifération



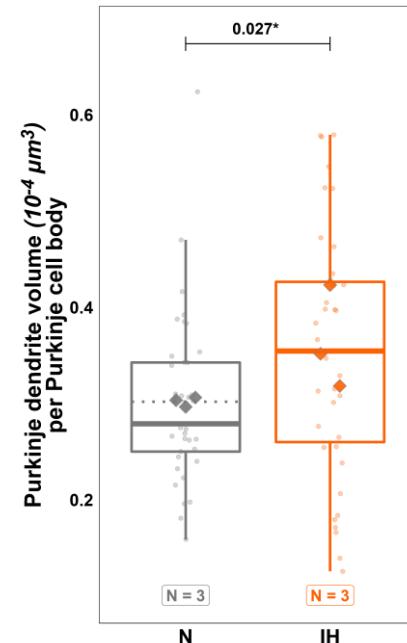
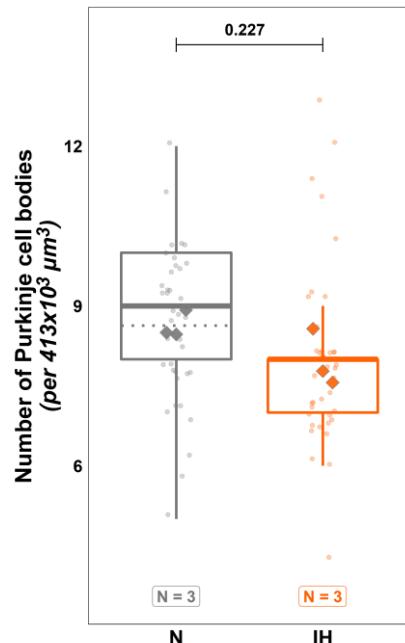
BrdU

LA COMPENSATION IMPLIQUE UNE AUGMENTATION DE LA PROLIFÉRATION DES GCs.

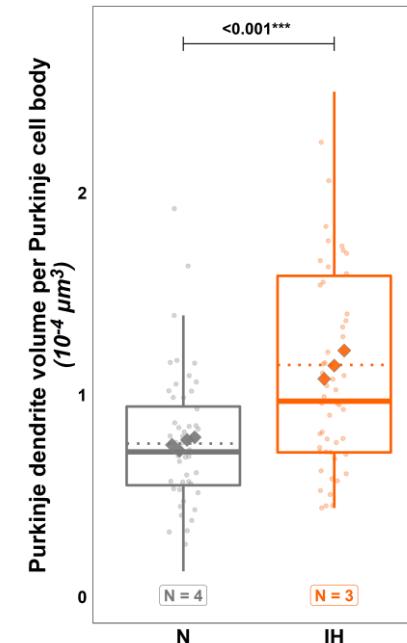
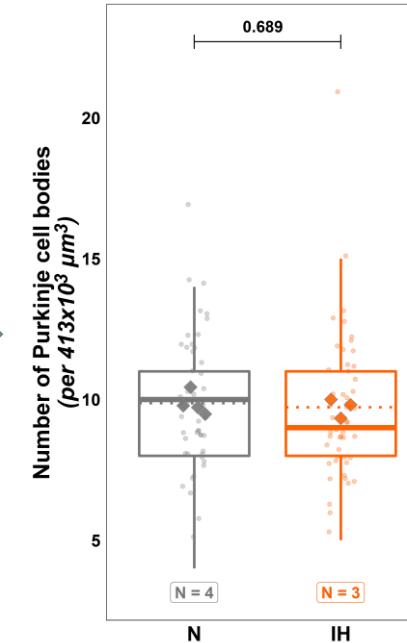
Histologie

Quels sont les effets sur les cellules de Purkinje à long terme?

- Nombre de corps cellulaires équivalents
- Volume accru de l'arbre dendritique



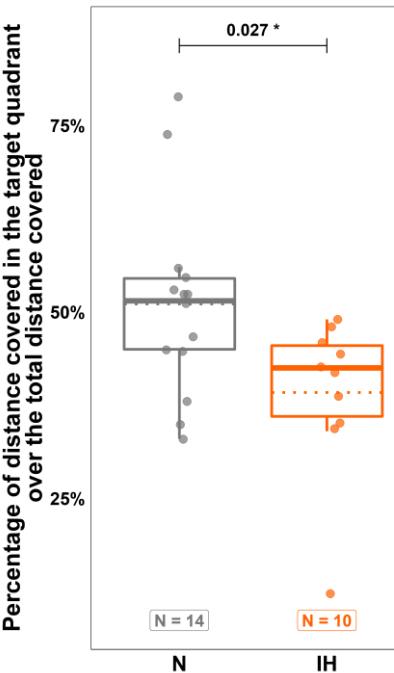
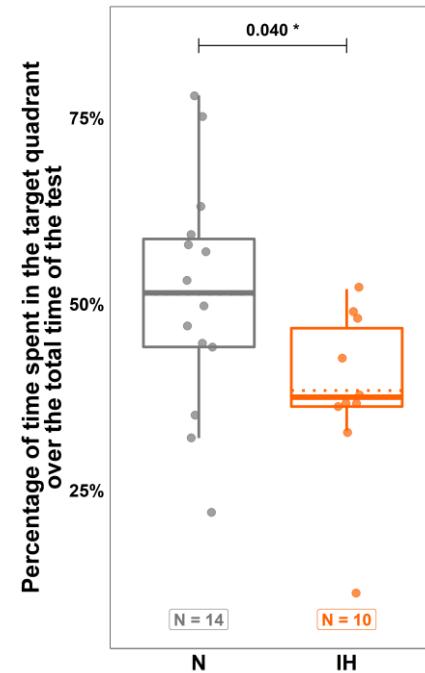
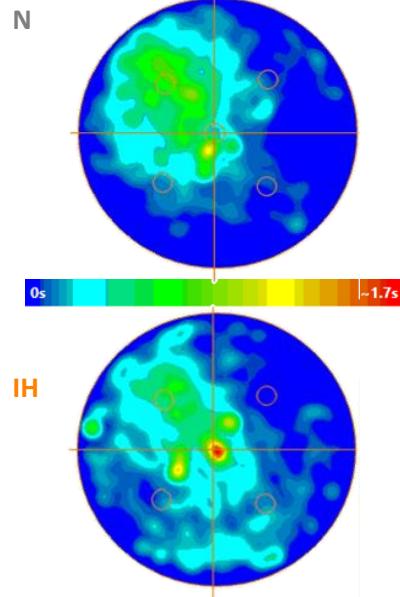
P21- adulte



→ L'HI SEMBLE INDUIRE UNE SUR-COMPENSATION DES PCs À LONG TERME.

1

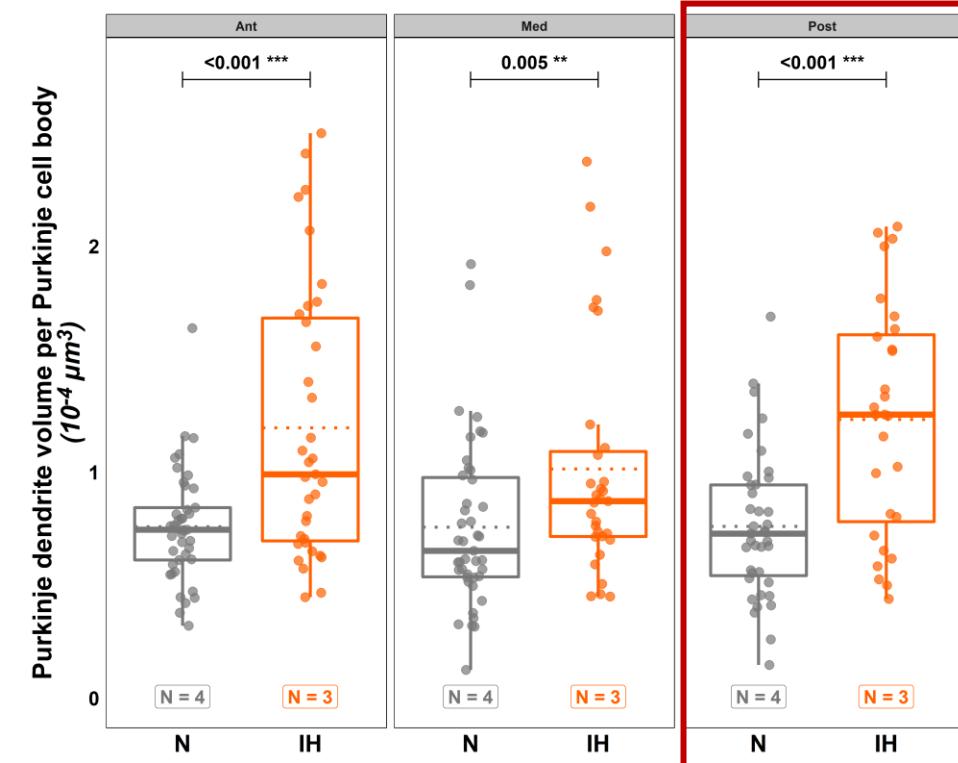
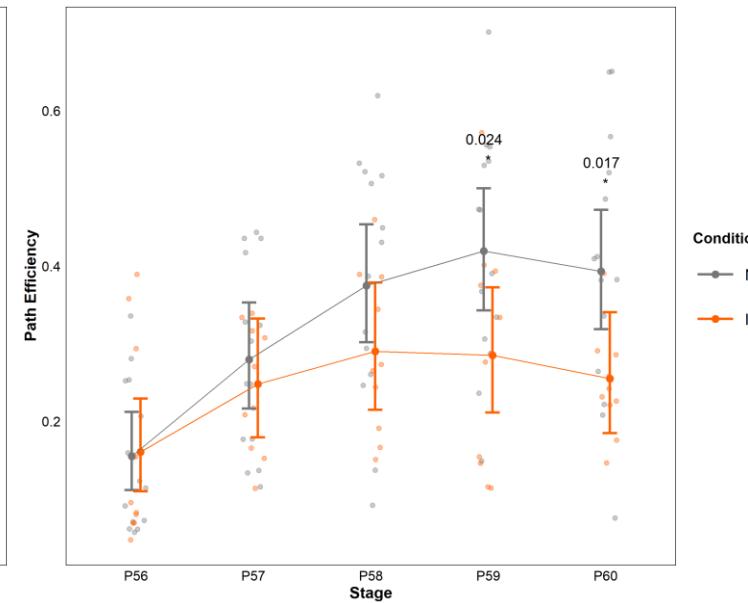
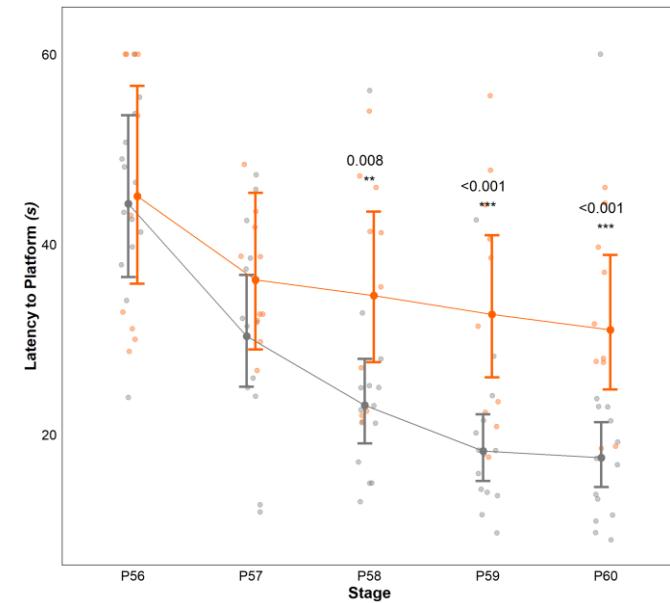
Comportement: piscine de Morris



→ L'HI INDUIT DES PROBLÈMES D'ORIENTATION SPATIALE.

2

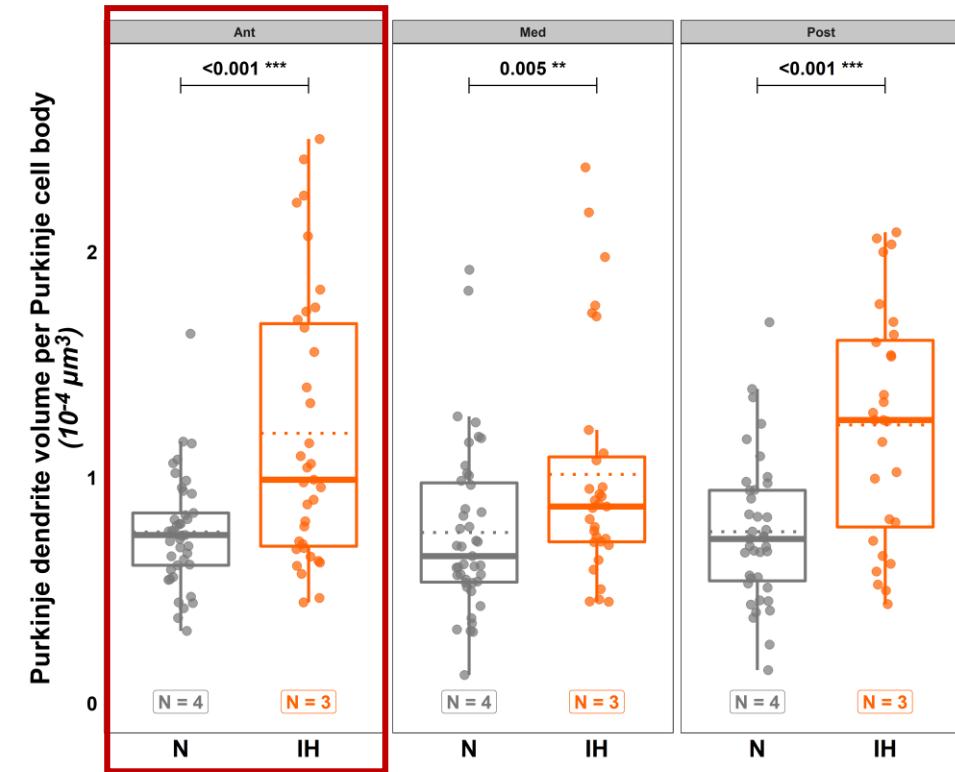
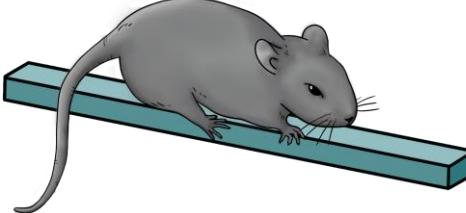
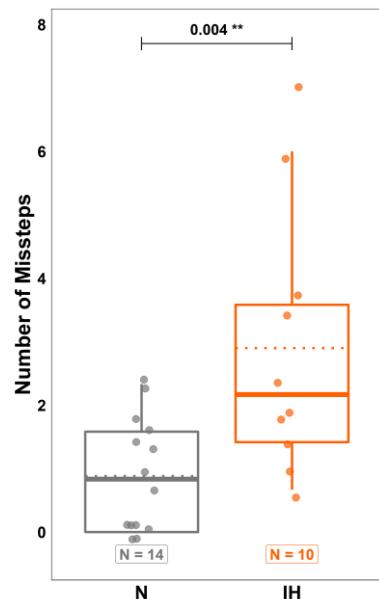
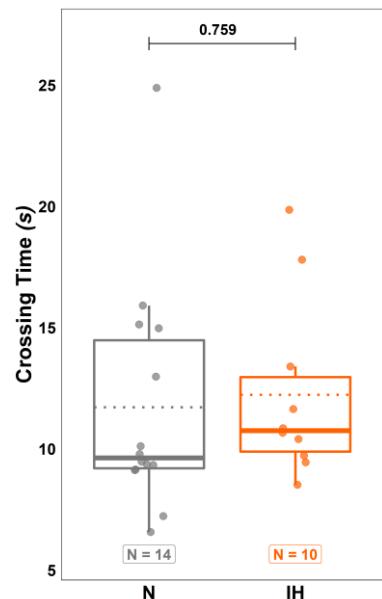
Comportement: piscine de Morris



→ L'HI INDUIT DES TROUBLES DE L'APPRENTISSAGE SPATIAL.

4

Comportement: coordination

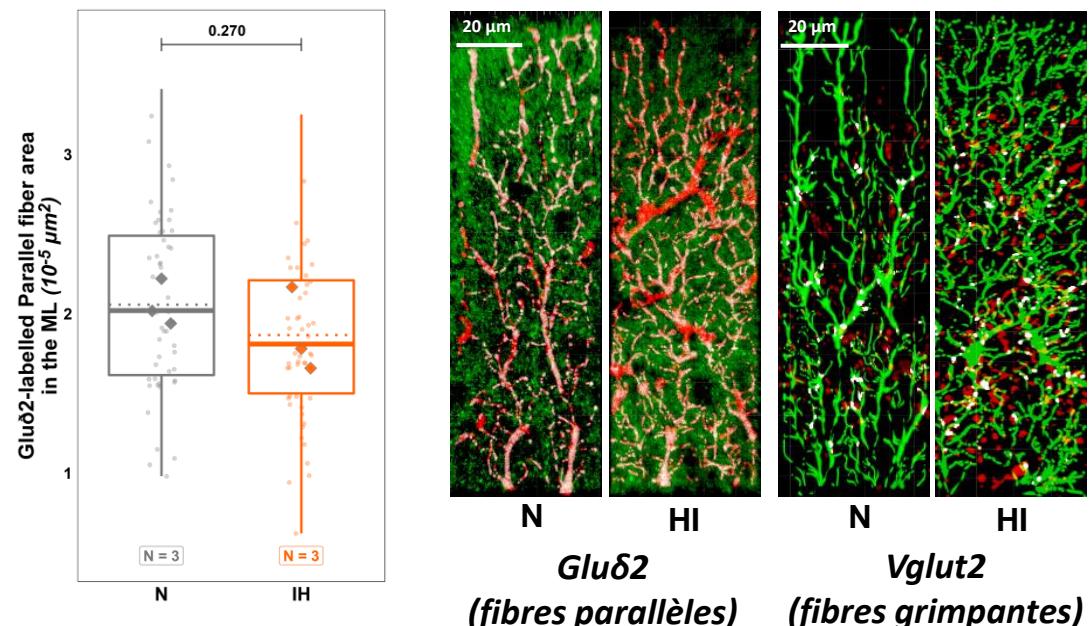


→ L'HI SEMBLE AFFECTER LA COORDINATION MOTRICE.

1 Afférences cérébelleuses

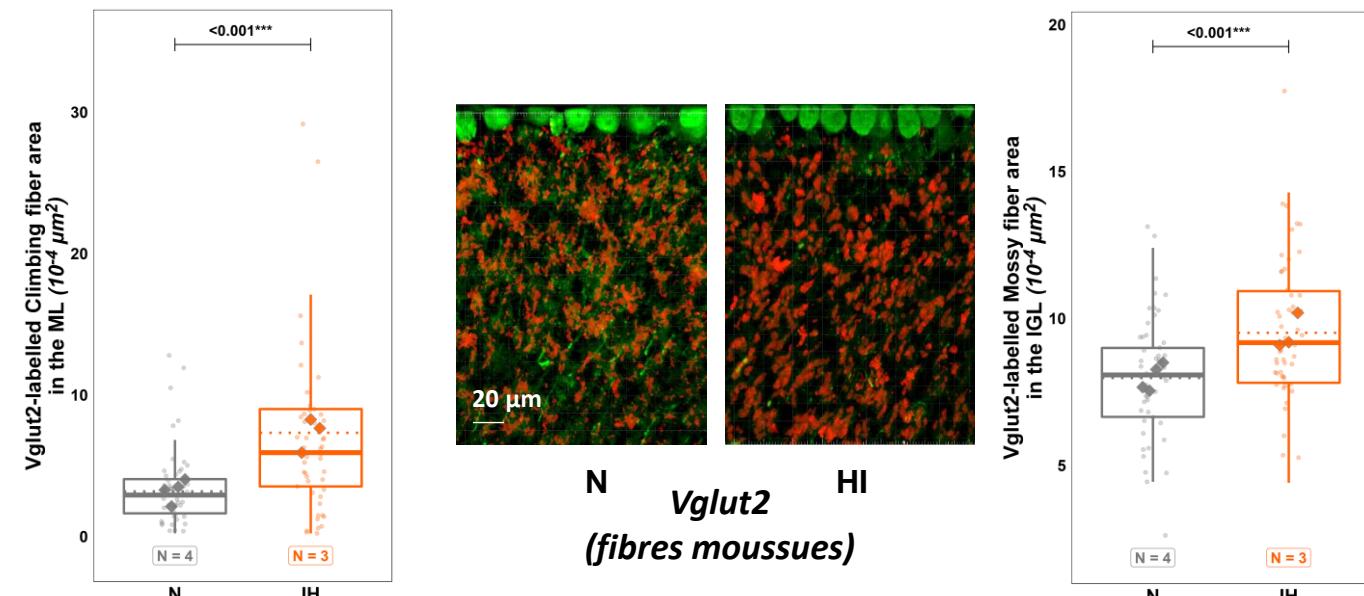
- **Glu δ 2 :**

- pas de différence dans l'innervation par les fibres parallèles



- **Vglut2 :**

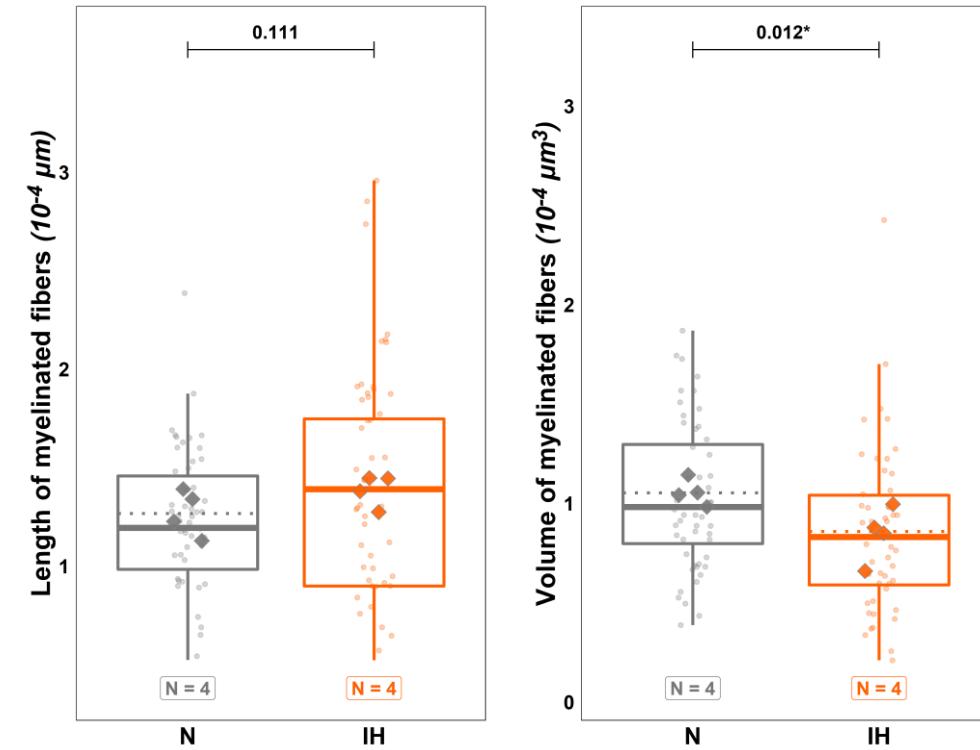
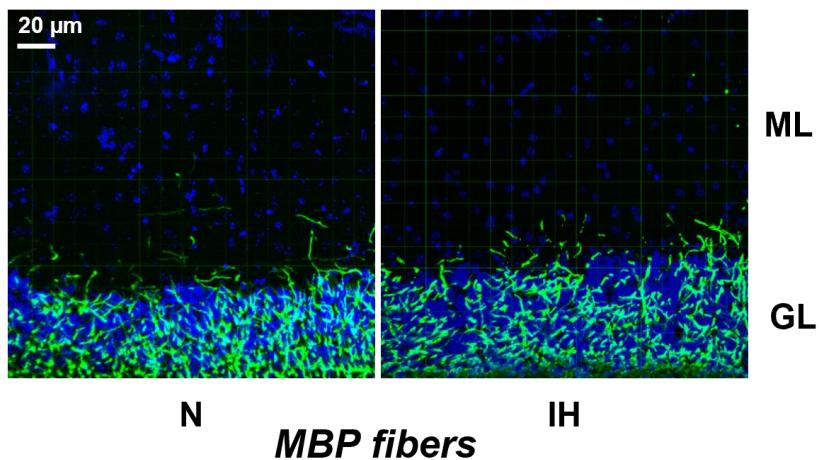
- sur-innervation des cellules de Purkinje
- sur-innervation des cellules en grain



→ L'HI AFFECTE LES AFFÉRENCES EXTRA-CÉRÉBELLÉUSES.

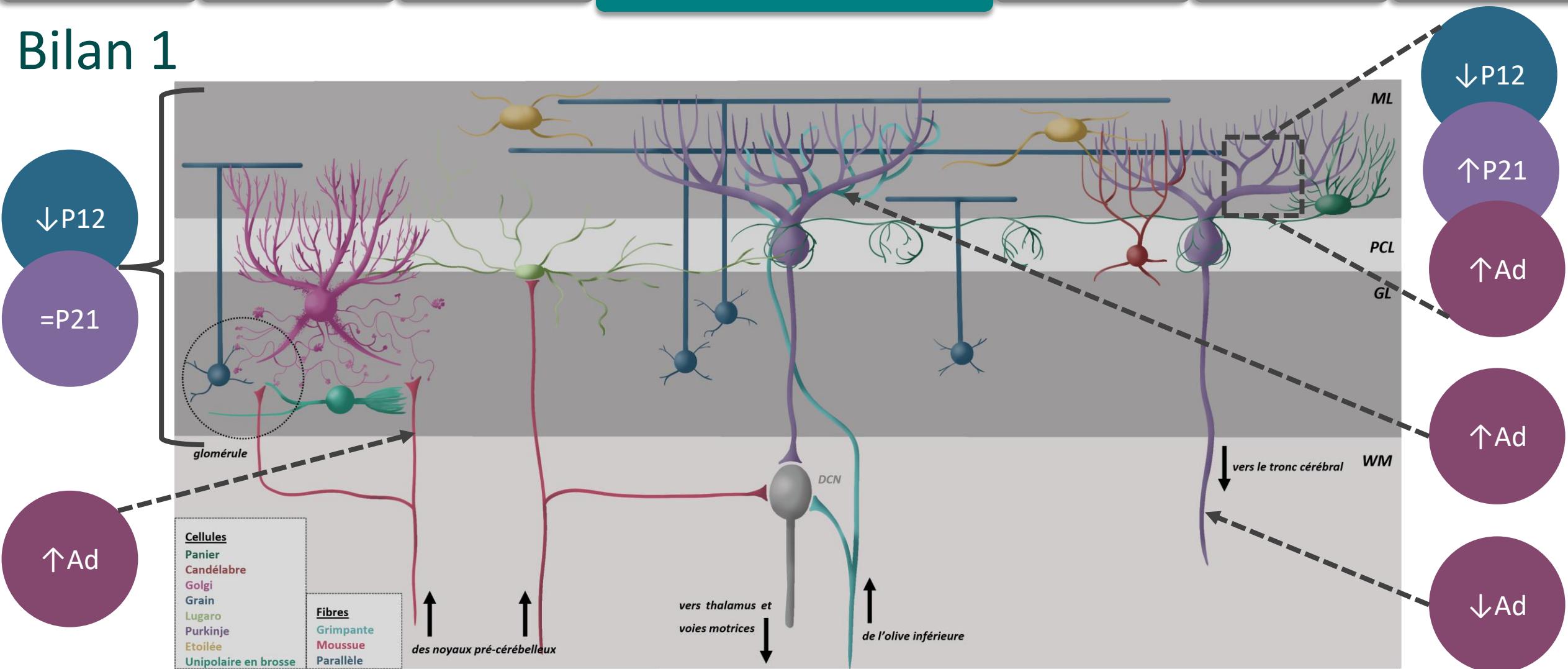
3 Afférences cérébelleuses

- Le volume (mais pas la longueur) des fibres myélinisées est réduit post HI
- GL → Ce deficit concerne surtout les axones des PC



→ L'HI IMPACTE LA MYÉLINISATION DES PCs.

Bilan 1



L'HI induit un retard de croissance qui est compensé dans le temps.

L'HI impacte le développement moteur et la force musculaire.

L'HI cause des troubles du développement et de l'apprentissage à long terme.

RESEARCH

Open Access



Intermittent hypoxia in a mouse model of apnea of prematurity leads to a retardation of cerebellar development and long-term functional deficits

S. Leroux¹, A. Rodriguez-Duboc^{1,2}, A. Arabo³, M. Basille-Dugay¹, D. Vaudry^{1,2,4}* and D. Burel^{1,2,4*}



ARTICLE 1

Abstract

Background: Apnea of prematurity (AOP) is caused by respiratory control immaturity and affects nearly 50% of premature newborns. This pathology induces perinatal intermittent hypoxia (IH), which leads to neurodevelopmental disorders. The impact on the brain has been well investigated. However, despite its functional importance and immaturity at birth, the involvement of the cerebellum remains poorly understood. Therefore, this study aims to identify the effects of IH on cerebellar development using a mouse model of AOP consisting of repeated 2-min cycles of hypoxia and reoxygenation over 6 h and for 10 days starting on postnatal day 2 (P2).

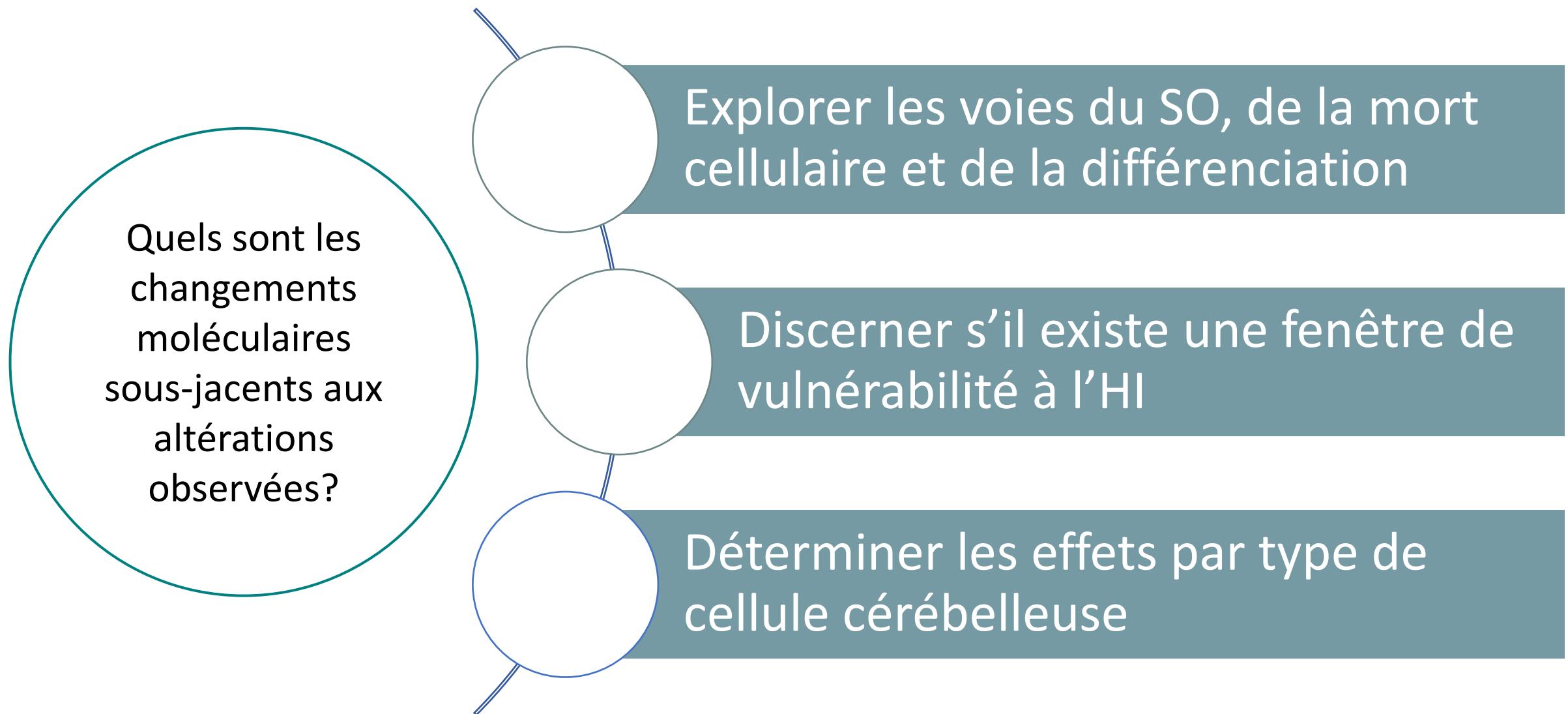
Results: At P12, IH-mice cerebella present higher oxidative stress associated with delayed maturation of the cerebellar cortex and decreased dendritic arborization of Purkinje cells. Moreover, mice present with growth retardation and motor disorders. In response to hypoxia, the developing cerebellum triggers compensatory mechanisms resulting in the unaltered organization of the cortical layers from P21 onwards. Nevertheless, some abnormalities remain in adult Purkinje cells, such as the dendritic densification, the increase in afferent innervation, and axon hypomyelination. Moreover, this compensation seems insufficient to allow locomotor recovery because adult mice still show motor impairment and significant disorders in spatial learning.

Conclusions: All these findings indicate that the cerebellum is a target of intermittent hypoxia through alterations of developmental mechanisms leading to long-term functional deficits. Thus, the cerebellum could contribute, like other brain structures, to explaining the pathophysiology of AOP.

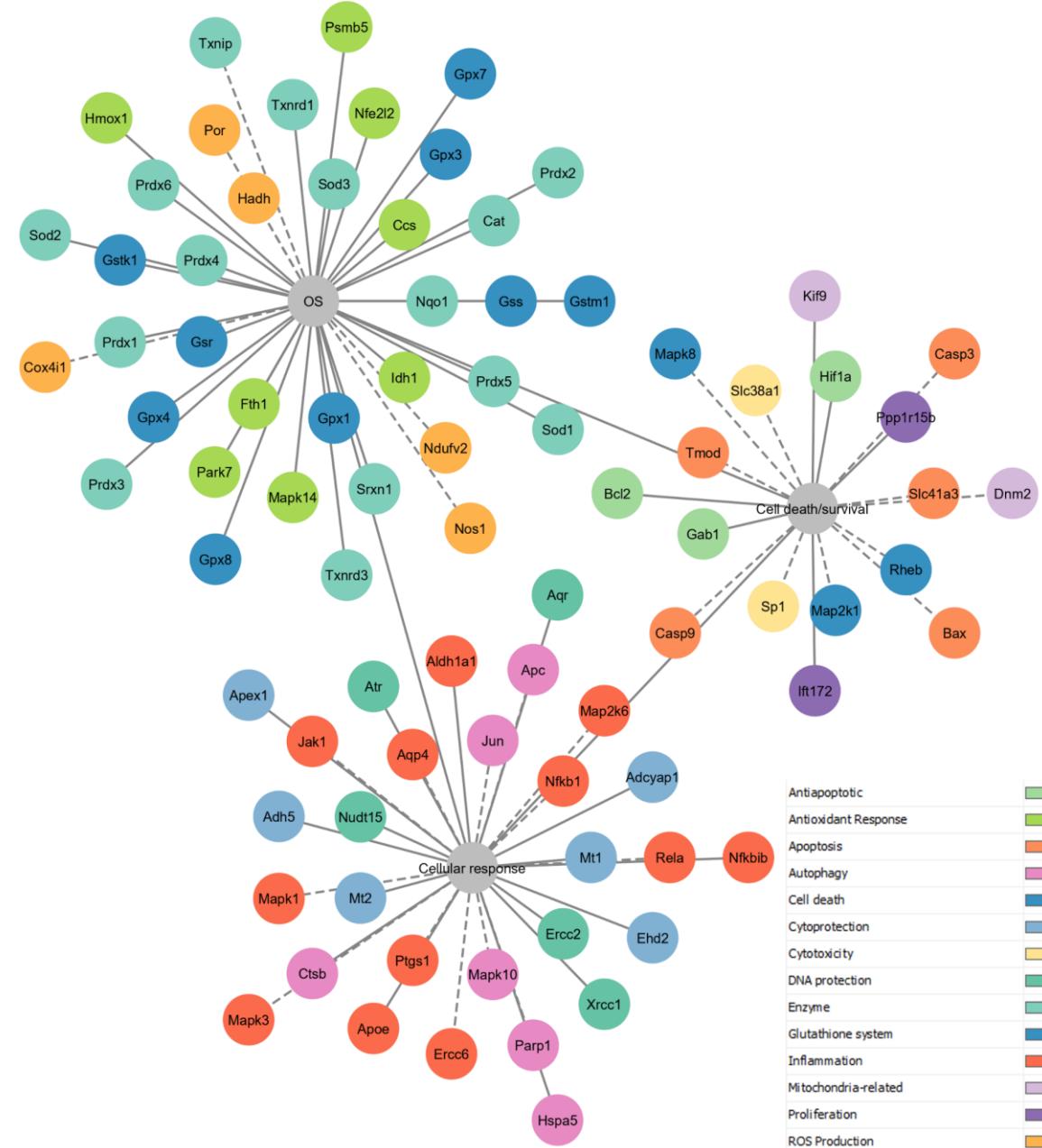
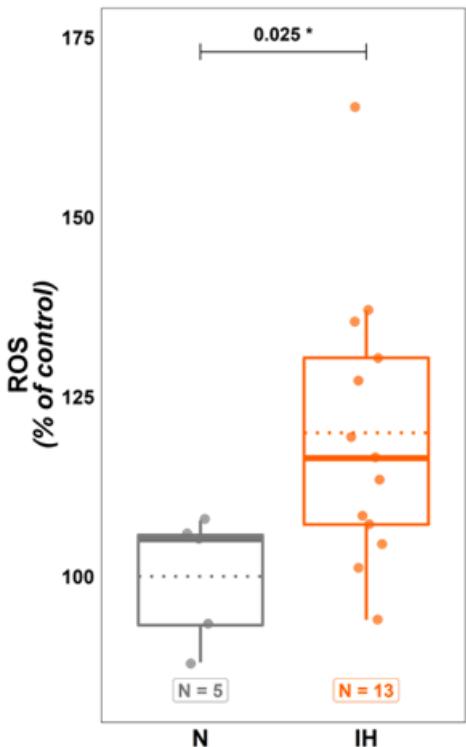
Keywords: Apnea of prematurity, Intermittent hypoxia, Cerebellum, Purkinje cells



QUELLES SONT LES ALTÉRATIONS MOLÉCULAIRES SOUS-JACENTES À CES RÉSULTATS?



1 Stress oxydatif: panel



Panel validé par Dr. Hélène Lacaille

2

Stress oxydatif: régulation

P4

- ↓ defense antioxydante
- GPX, SOD1

P8

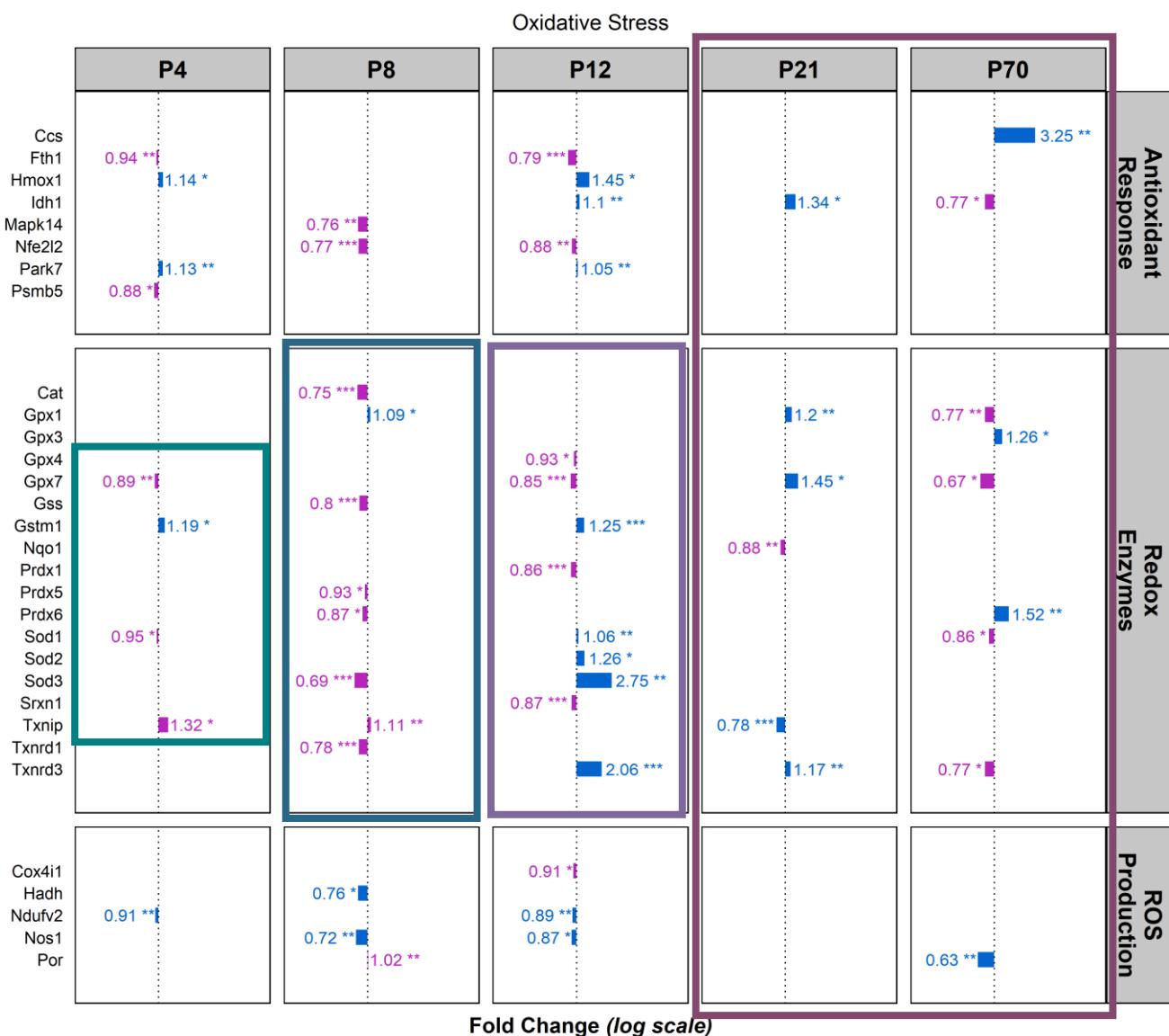
- vulnérabilité ↑
- SOD3, CAT

P12

- compensation partielle
- SOD, GPX, FTH1

P21-P70

- effets à long terme
- IDH1, CCS



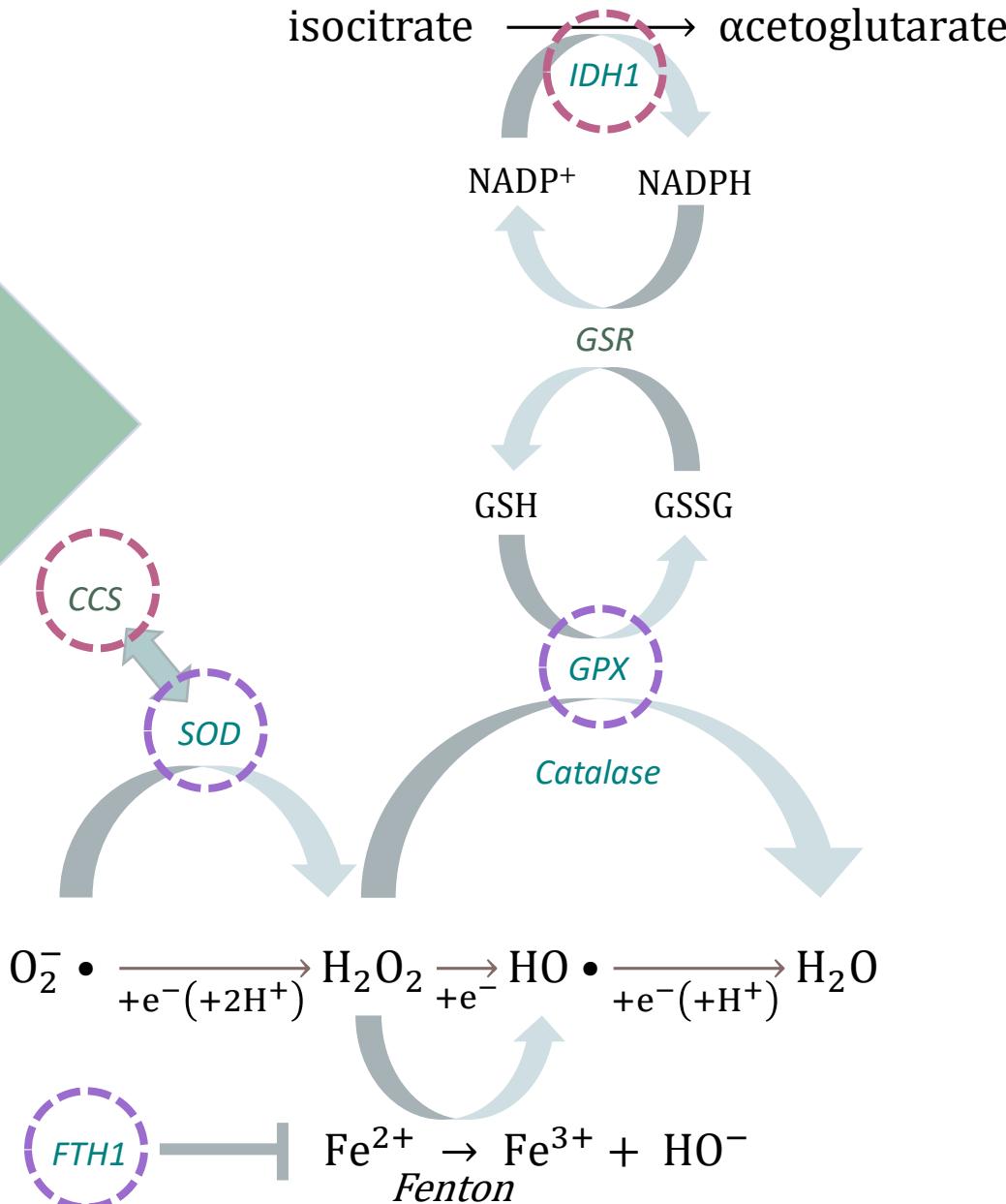
3 Stress oxydatif: régulation

- Compensation à court terme
- Acteurs immédiat de redox

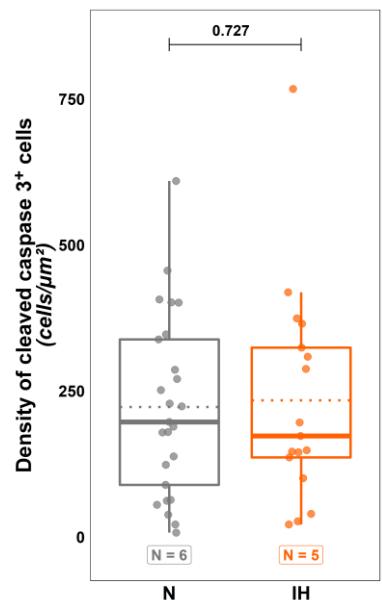
P21/70

- Compensation à long terme
- Réactions en amont

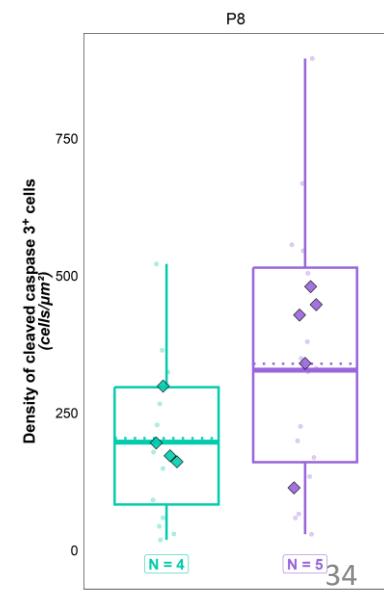
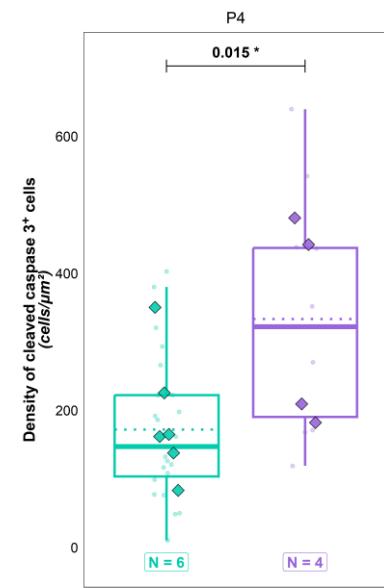
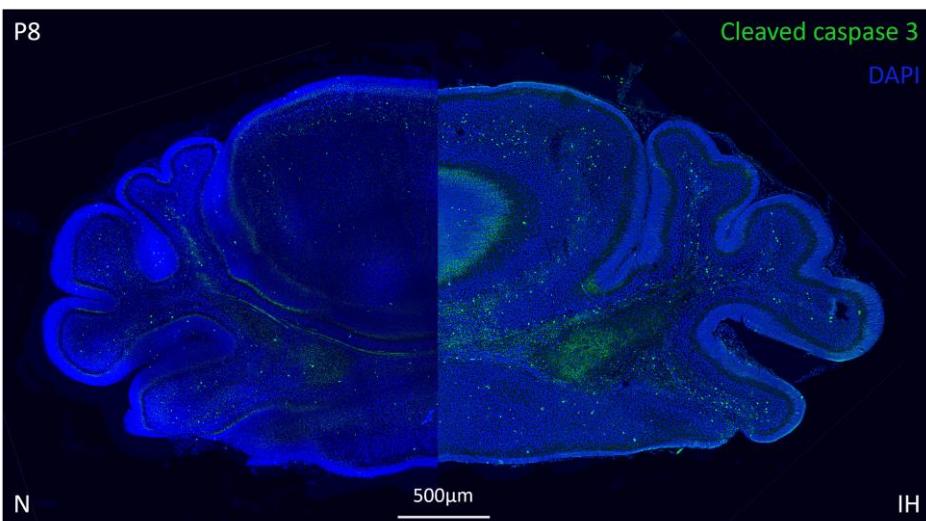
➡ ON DISCERNE UNE
ALTÉRATION DU SYSTÈME
ANTIOXYDANT AU COURS DU
TEMPS.



1 Mort cellulaire: caspase

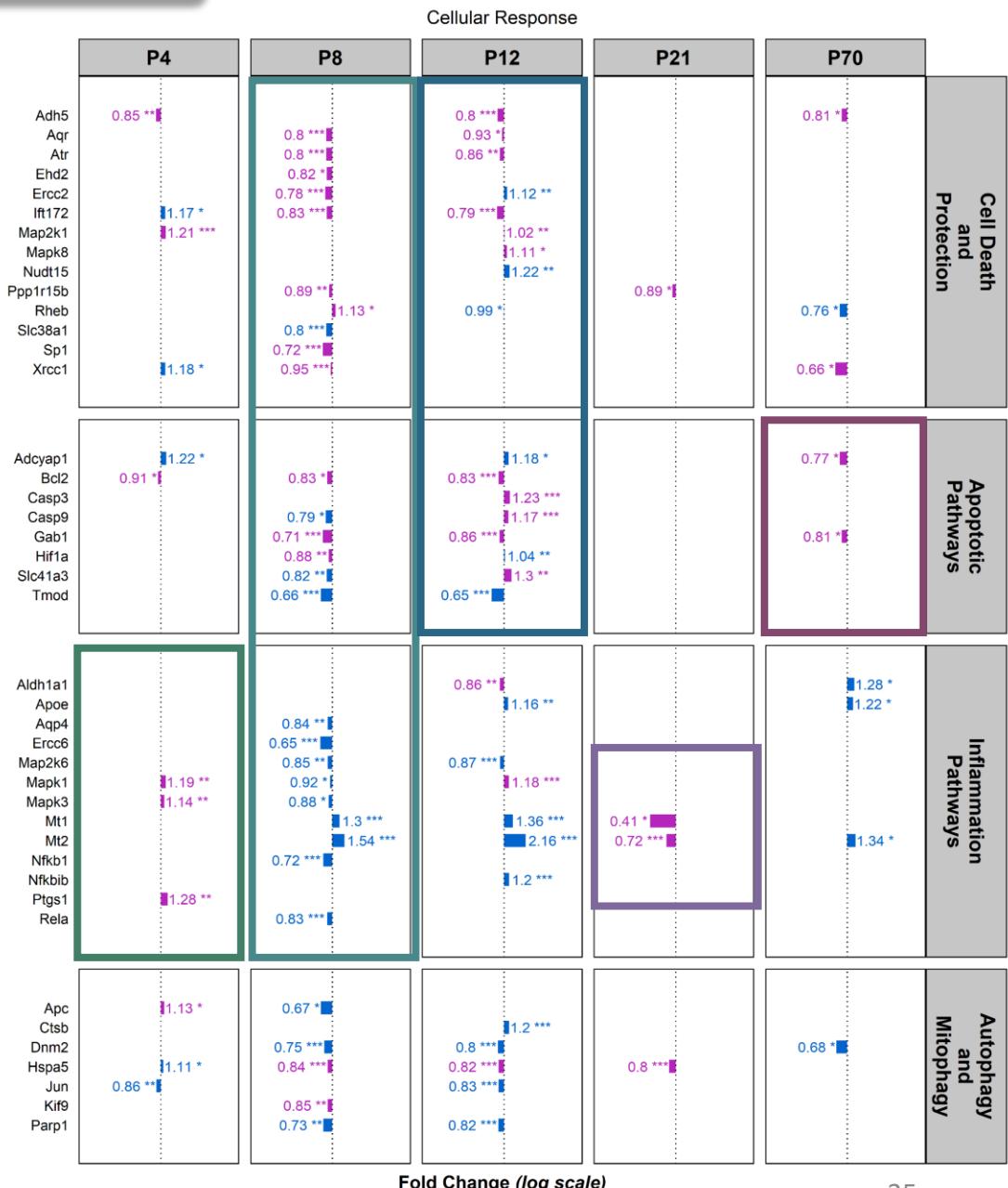
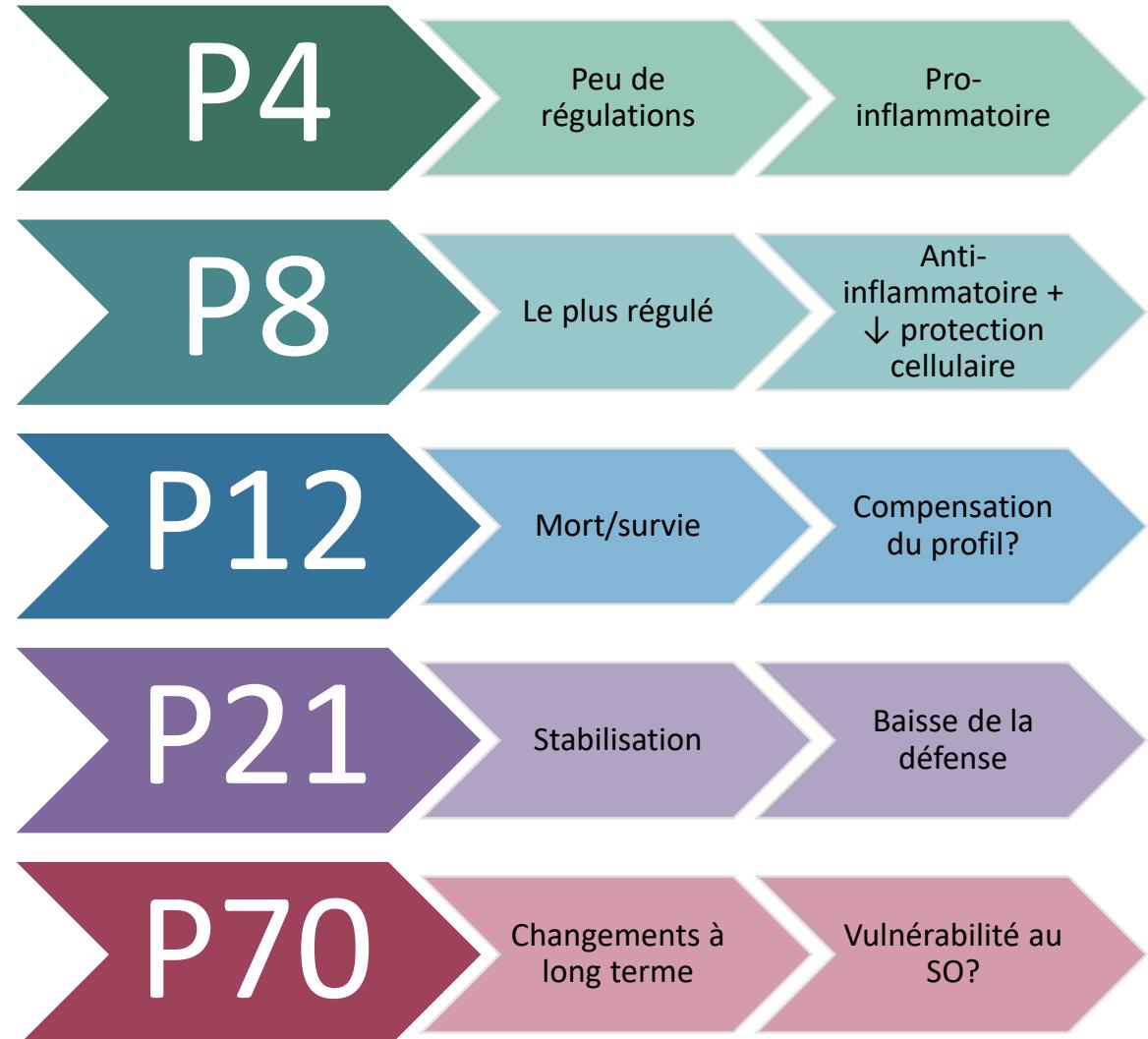


Au vu des résultats P12,
est-ce que la mort
cellulaire a lieu plus tôt?



2

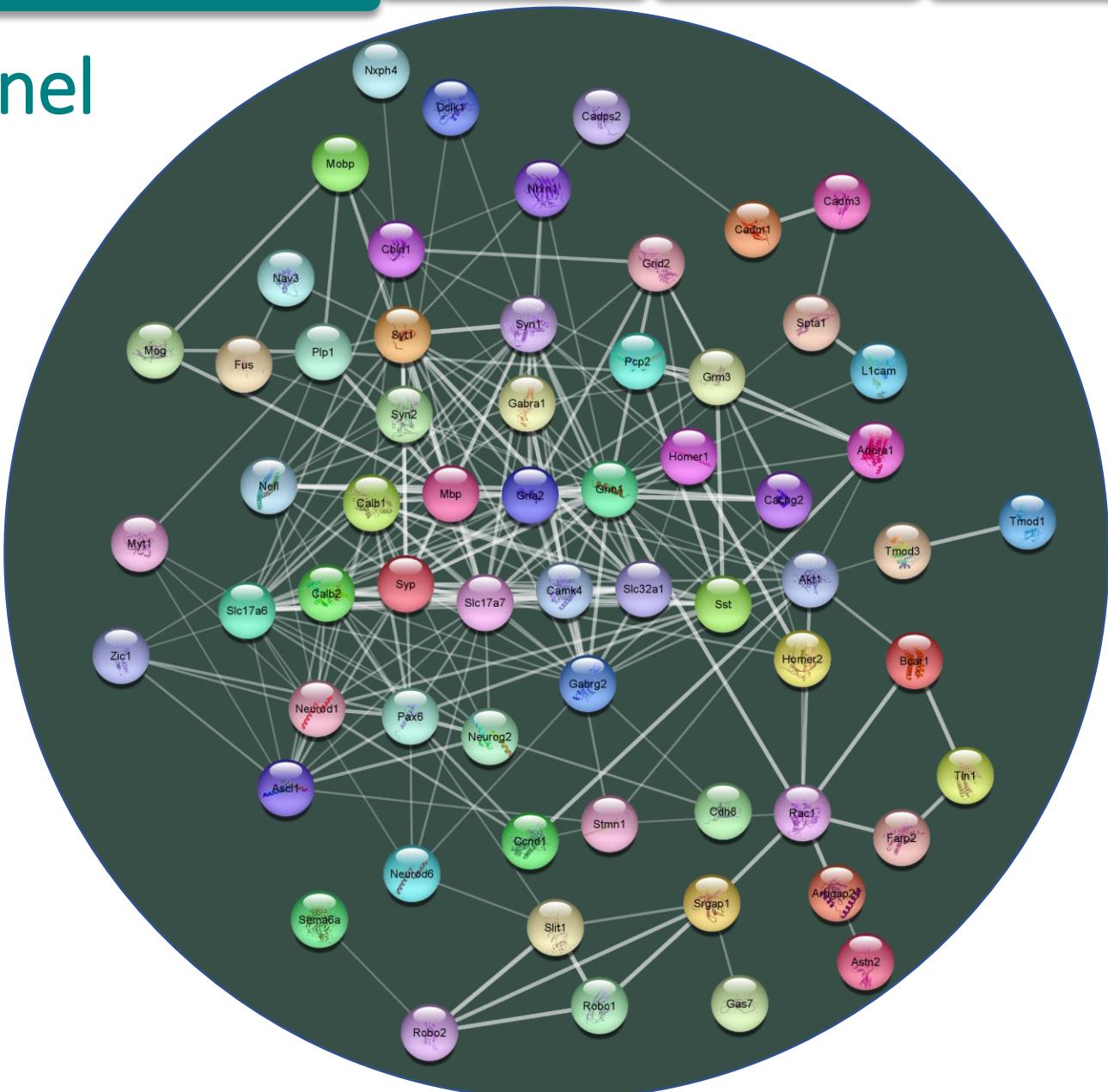
Mort cellulaire: autres voies



1

Neurodéveloppement: panel

- Recherche bioinformatique
 - 54 gènes choisis → Panel
 - Validation
 - Voies étudiées:
 - prolifération, différenciation, migration et communication
 - Microdissection laser des couches:
 - EGL, ML, PC, IGL, WM
 - Stades:
 - P4, P8, P12, P21 et P70



2

Neurodéveloppement: résultat

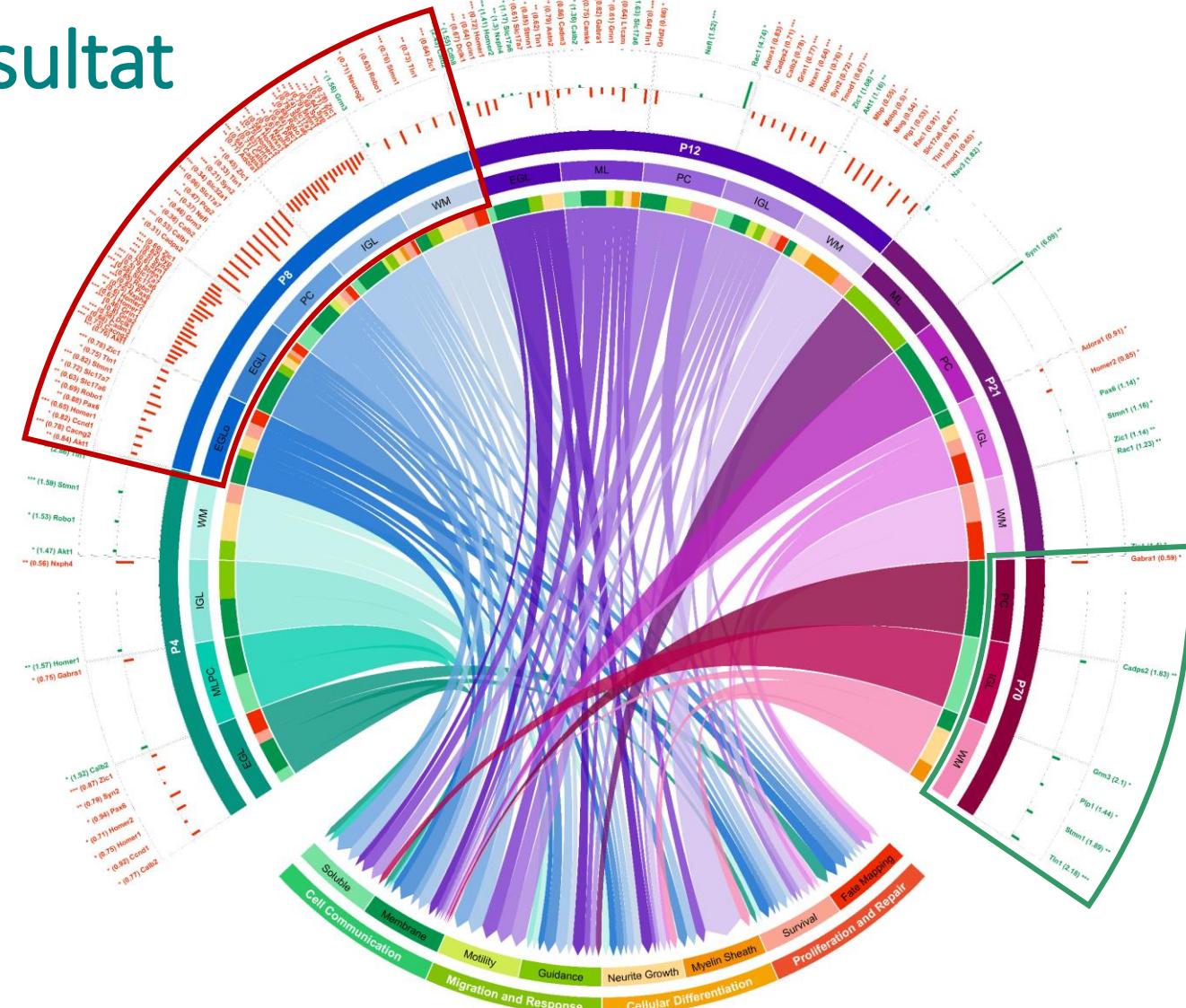
■ Interprétation

- Stade, couche, fold change
 - Voies et fonctions

Effets principaux

 - Fenêtre de vulnérabilité: P8
 - Régulation à long terme: P70

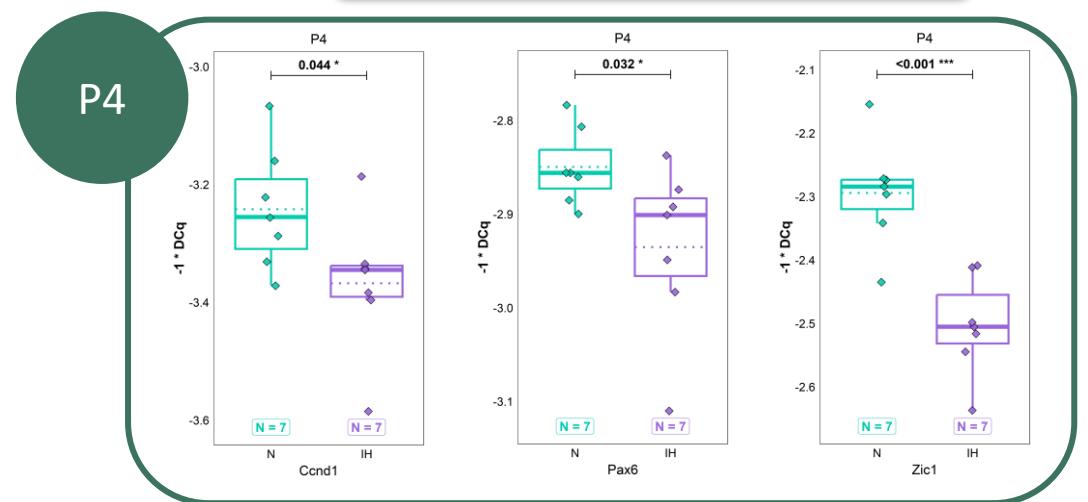
Représentation globale des effets moléculaires de l'HI



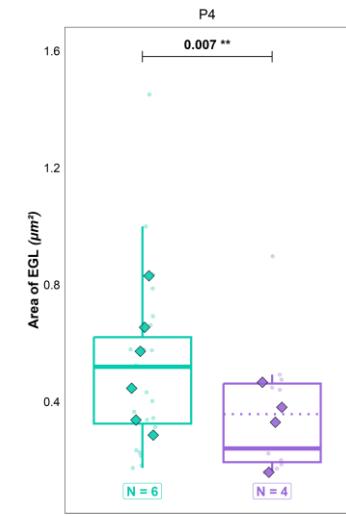
QUELS SONT LES EFFETS TRANSCRIPTOMIQUES PRÉCIS PAR COUCHE CÉRÉBELLÉUSE?

1 EGL

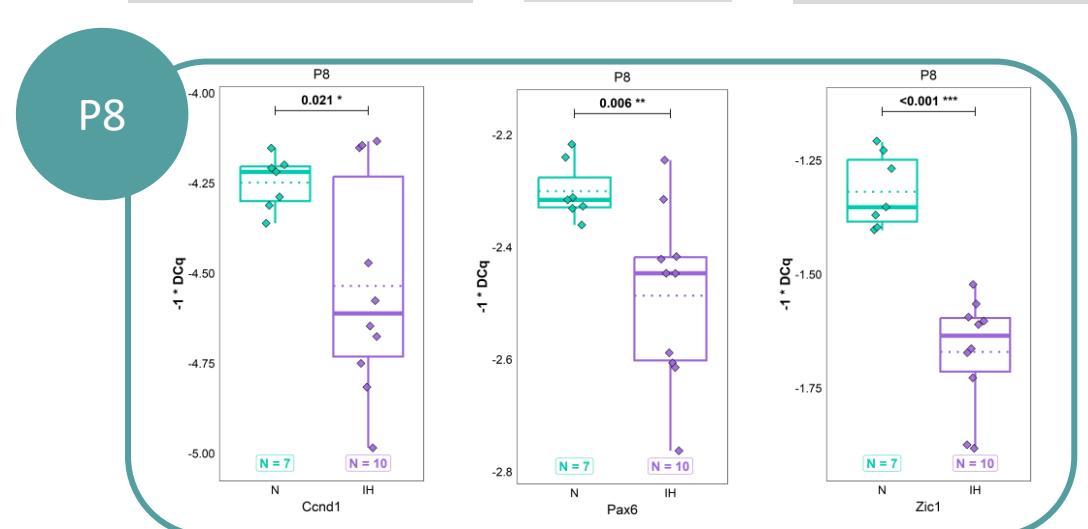
Couche granulaire externe



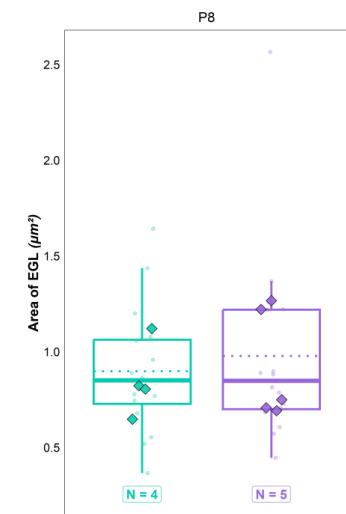
↓ EGL à P4



Prolifération



= EGL à P8



P4-P8

L'HI AFFECTE LA PROLIFÉRATION DES GCs.

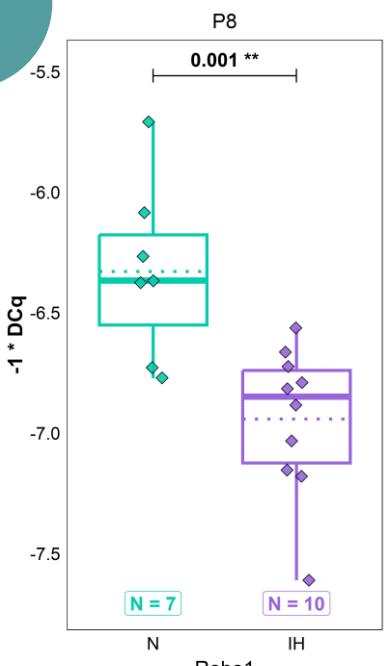
2 EGL

Couche
pré migratoire

Migration

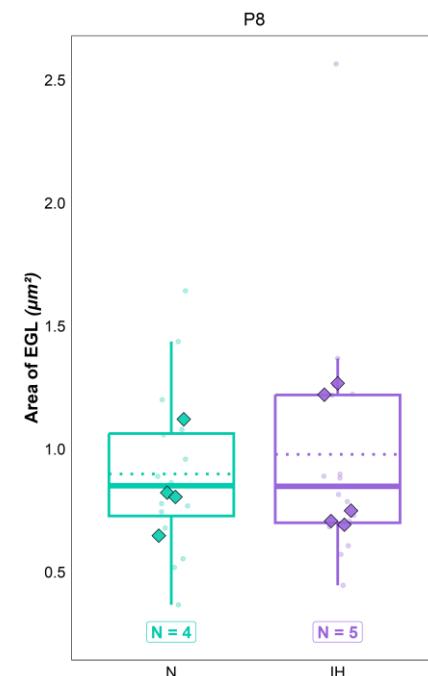
P8

P8



roundabout guidance receptor 1

L'HI CAUSE UN RETARD DE
MIGRATION QUI PEUT EXPLIQUER LE
RÉTABLISSEMENT HISTOLOGIQUE.



3 EGL

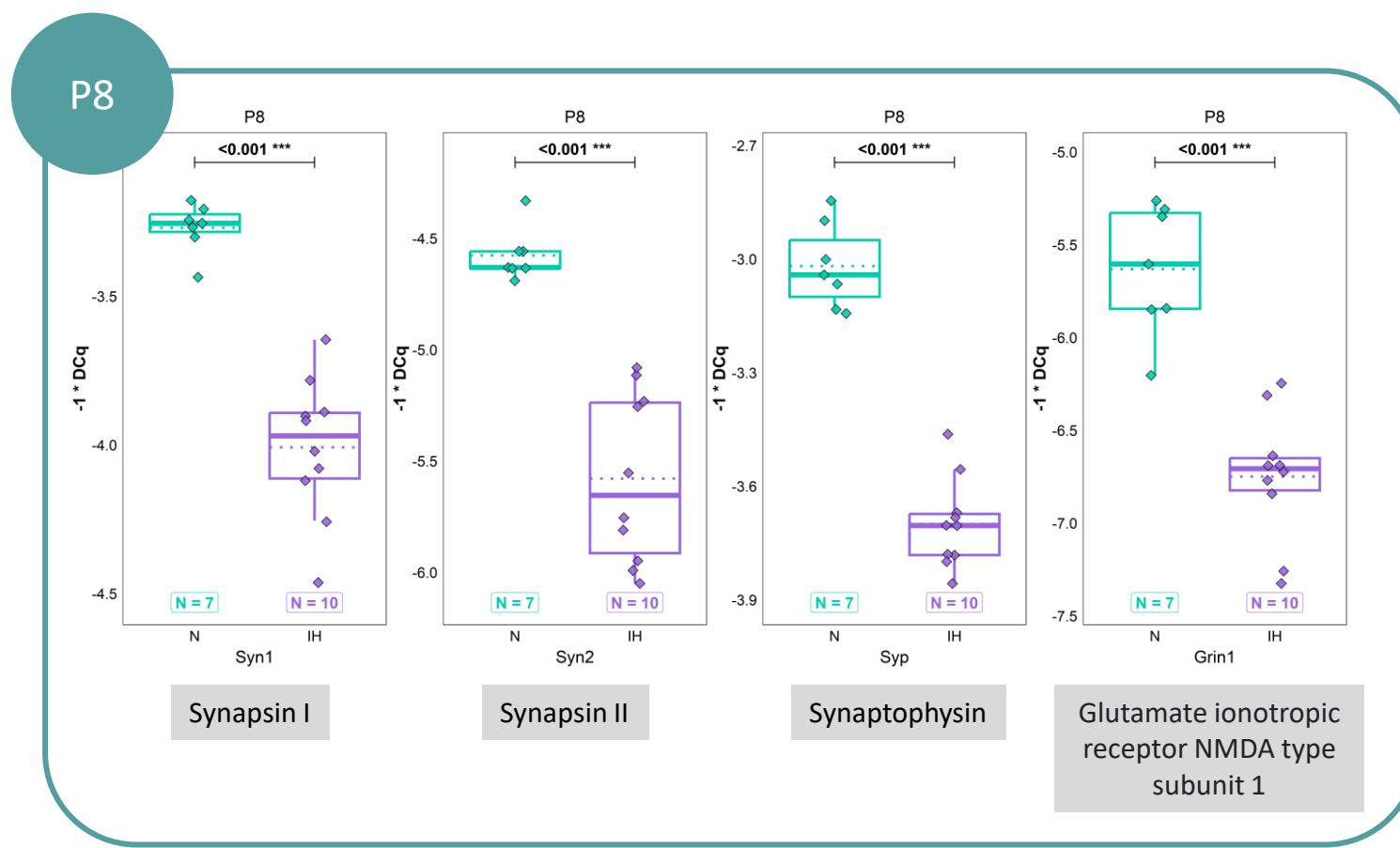
Couche
préémigratoire



Maturation



P8



→ L'HI AFFECTE LA MATURATION
DES GCs PRÉMIGRATOIRES DANS L'EGL.

1 ML

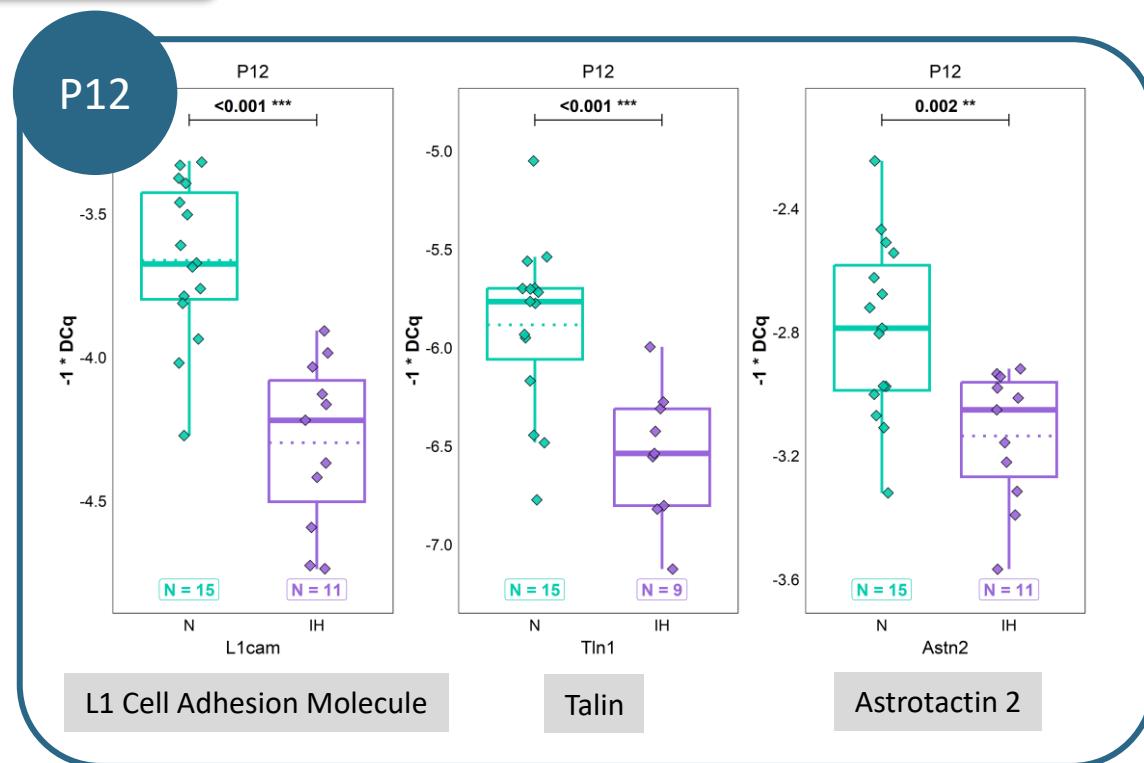
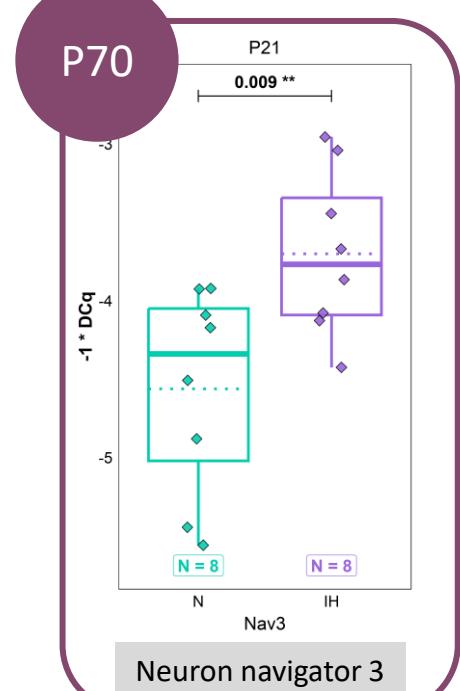
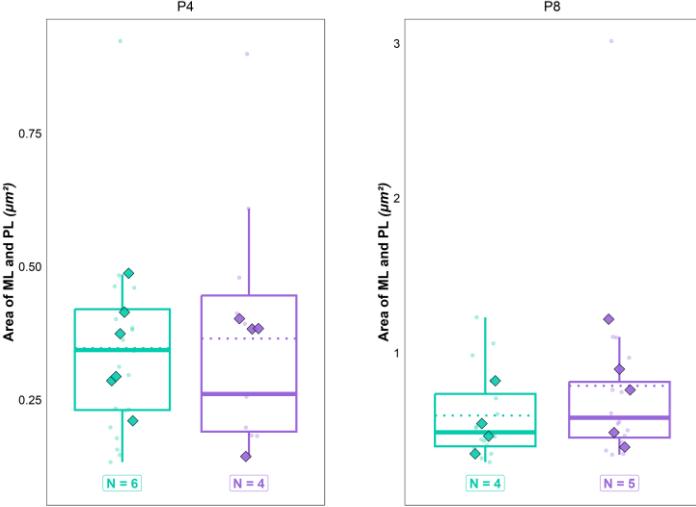
Couche moléculaire



Migration



P12-P21



→ **L'HI AFFECTE
LA MIGRATION À P12 MAIS
COMPENSATION À P21 PERMET
DE RATTRAPER LE RETARD.**

2 ML

Couche moléculaire

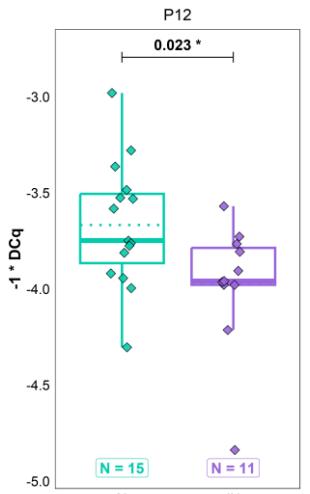


Connectivité

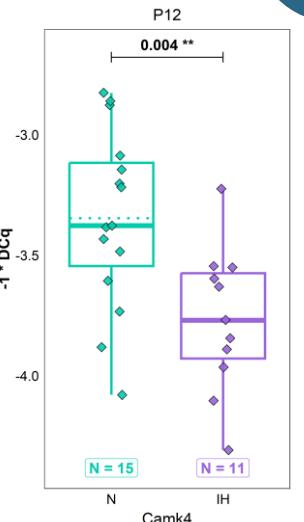


P12

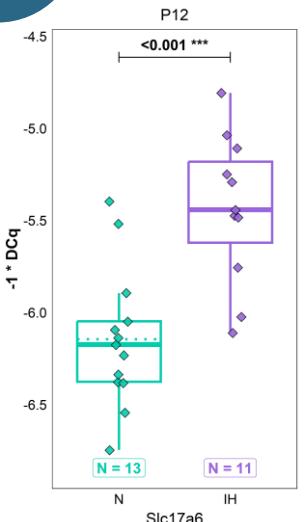
P12



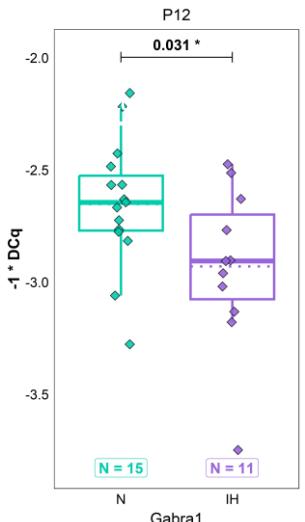
Glutamate ionotropic receptor NMDA type subunit 1



Calcium/calmodulin dependent protein kinase IV



Vesicular glutamate transporter 2



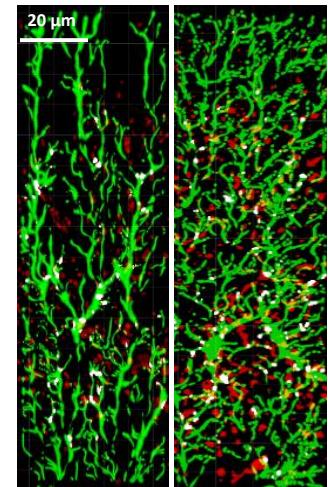
Gamma-aminobutyric acid type A receptor subunit alpha1

Foliation et mémoire

PF

CF

Interneurones GABAergiques



Vglut2
(fibres grimpantes)

→ L'HI AFFECTE LA CONNECTIVITÉ DES PC ET LE CIRCUIT CÉRÉBELLEUX.

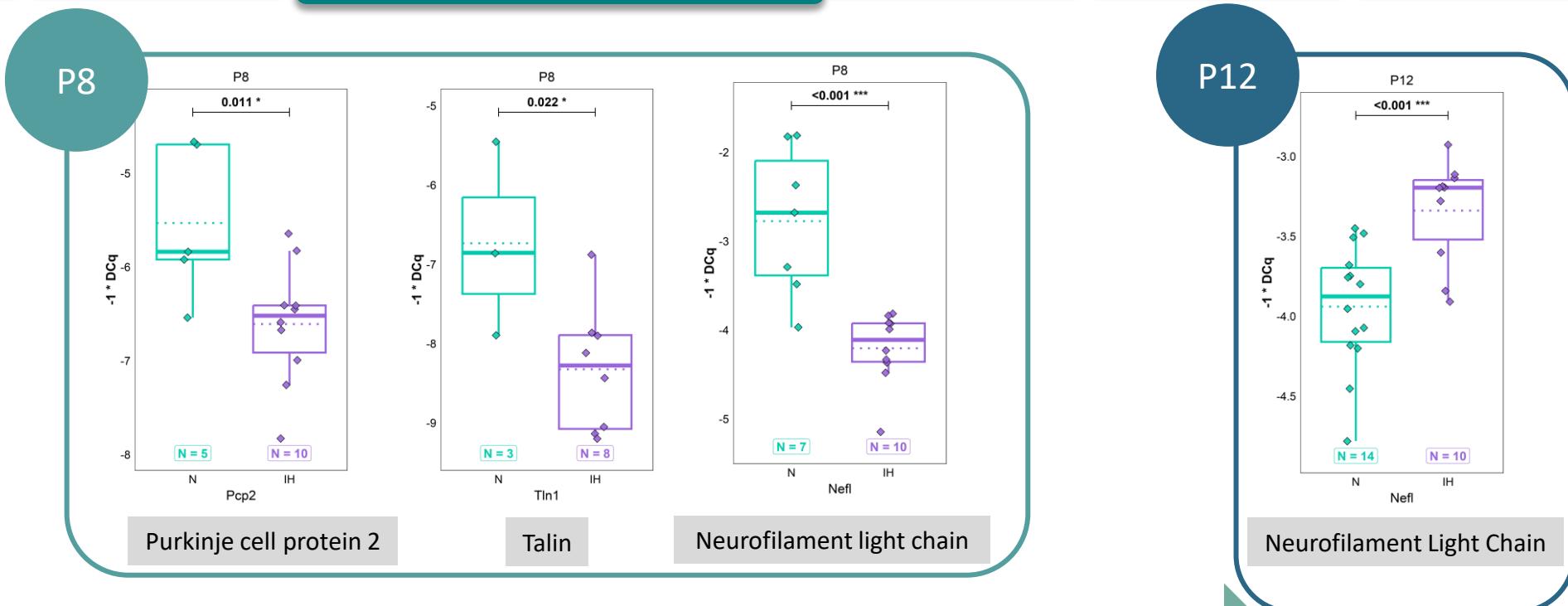
1 PC

Cellules de Purkinje

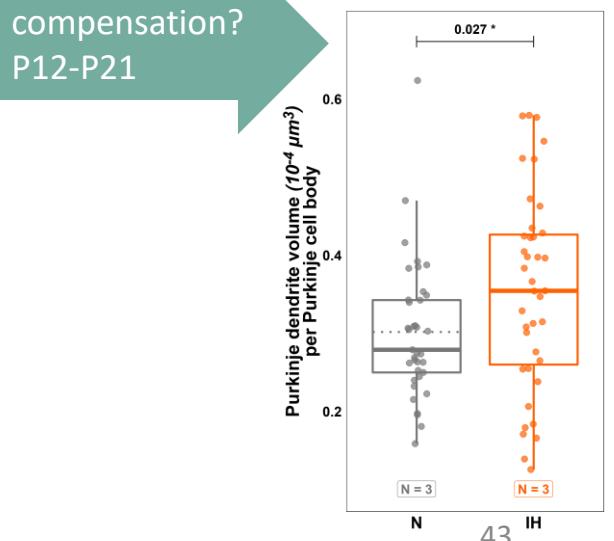
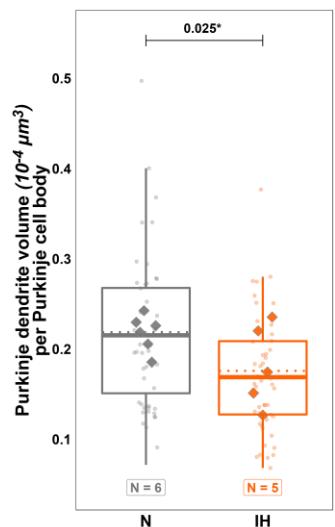


Morphologie

P8-P12



→ L'HI IMPACTE LA MORPHOLOGIE DES CELLULES DE PURKINJE.



2 PC

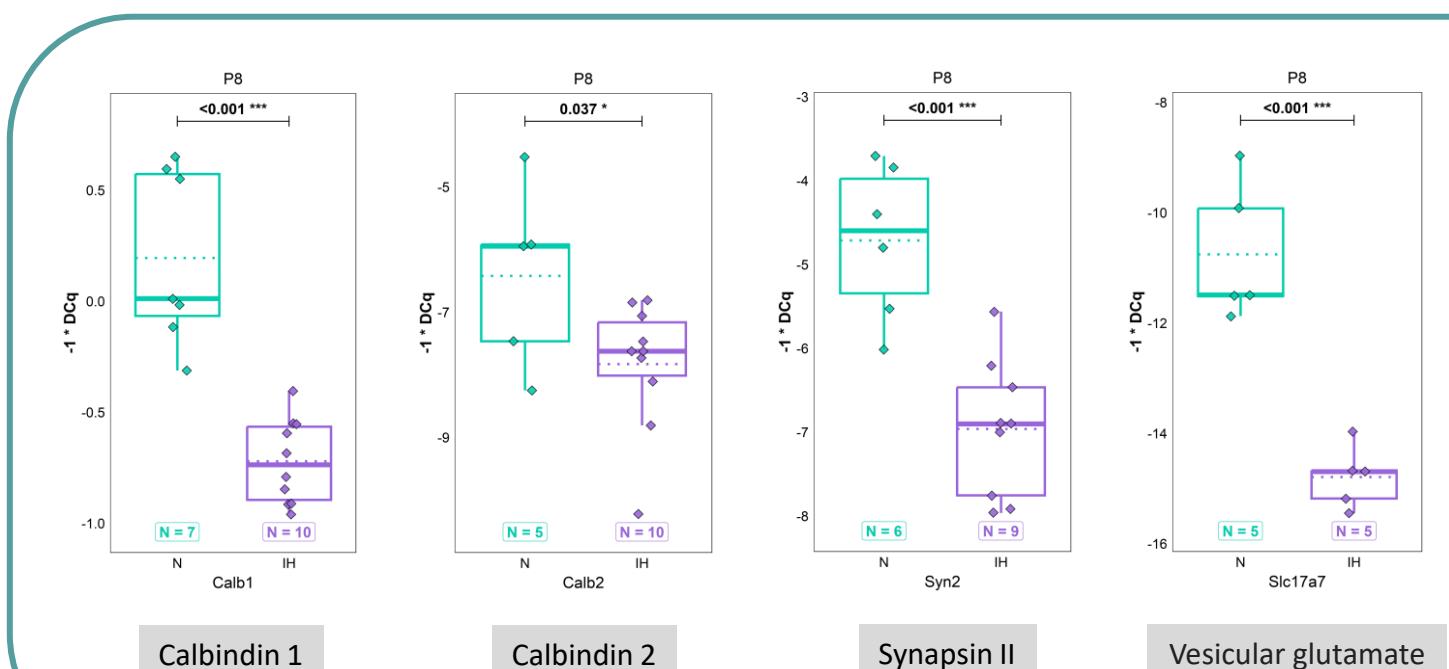
Cellules de Purkinje



Connectivité



P8



P8

→ L'HI IMPACTE LA
CONNECTIVITÉ ET LA SÉLECTION
DES SYNAPSES GC-PC.

3 PC

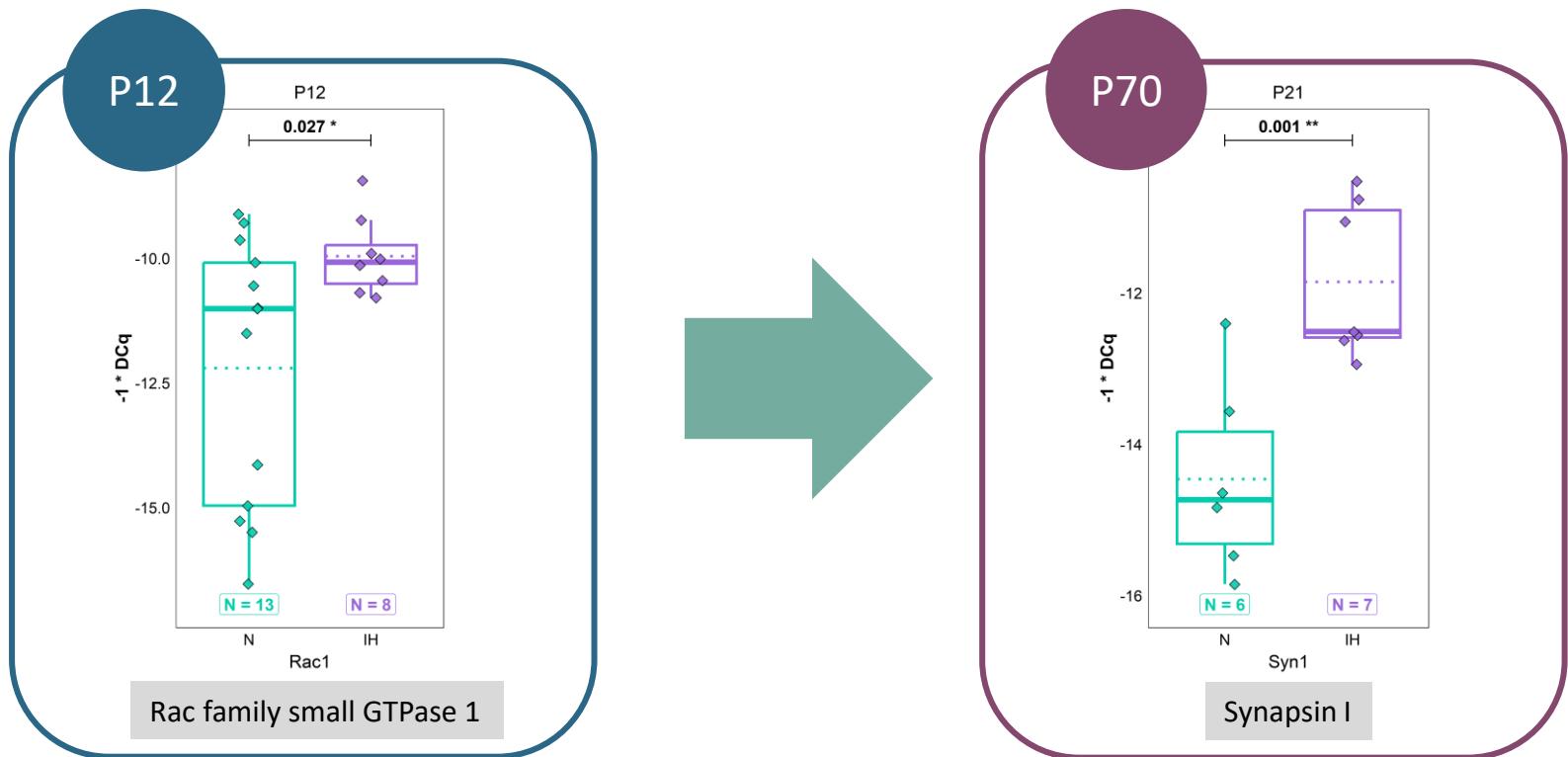
Cellules de Purkinje



Morphologie



P8-P12



(Mulherkar et al., 2014)

→ L'HI POURRAIT INDUIRE
UNE PLASTICITÉ COMPENSATOIRE
À LONG TERME.

1

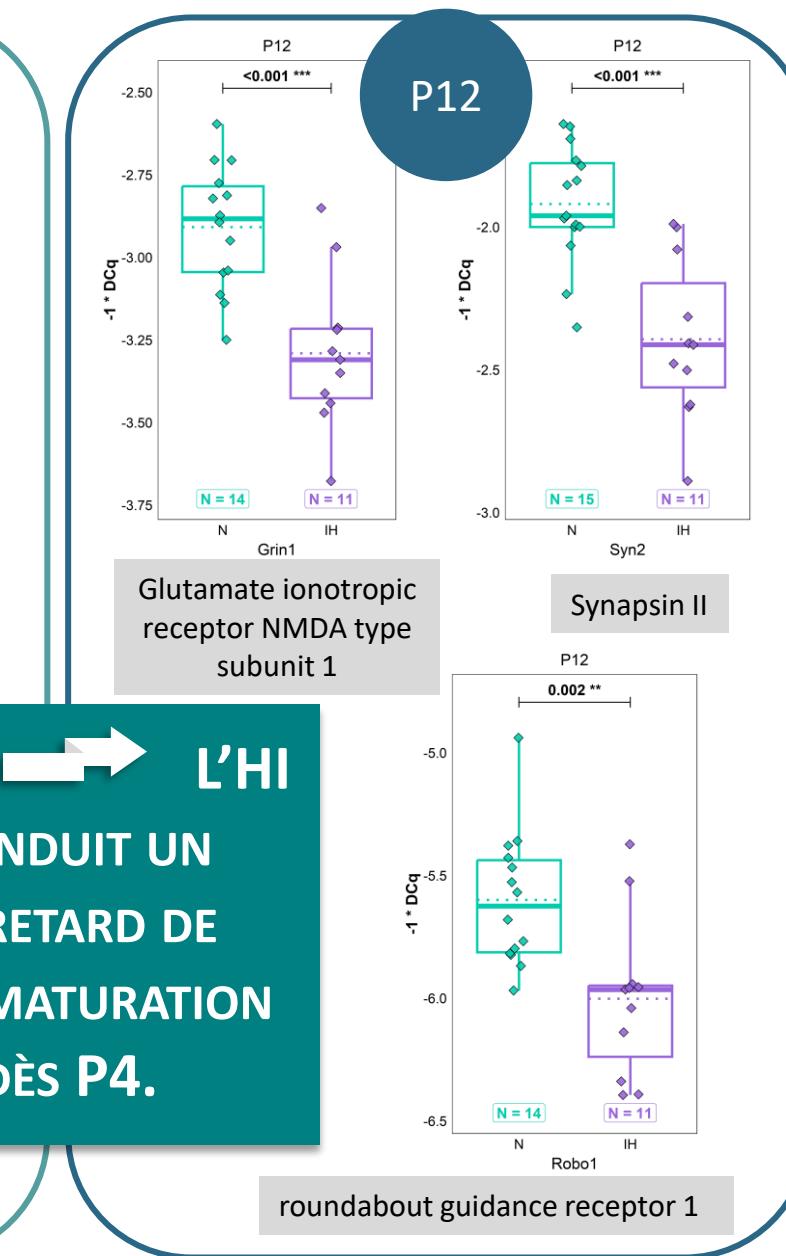
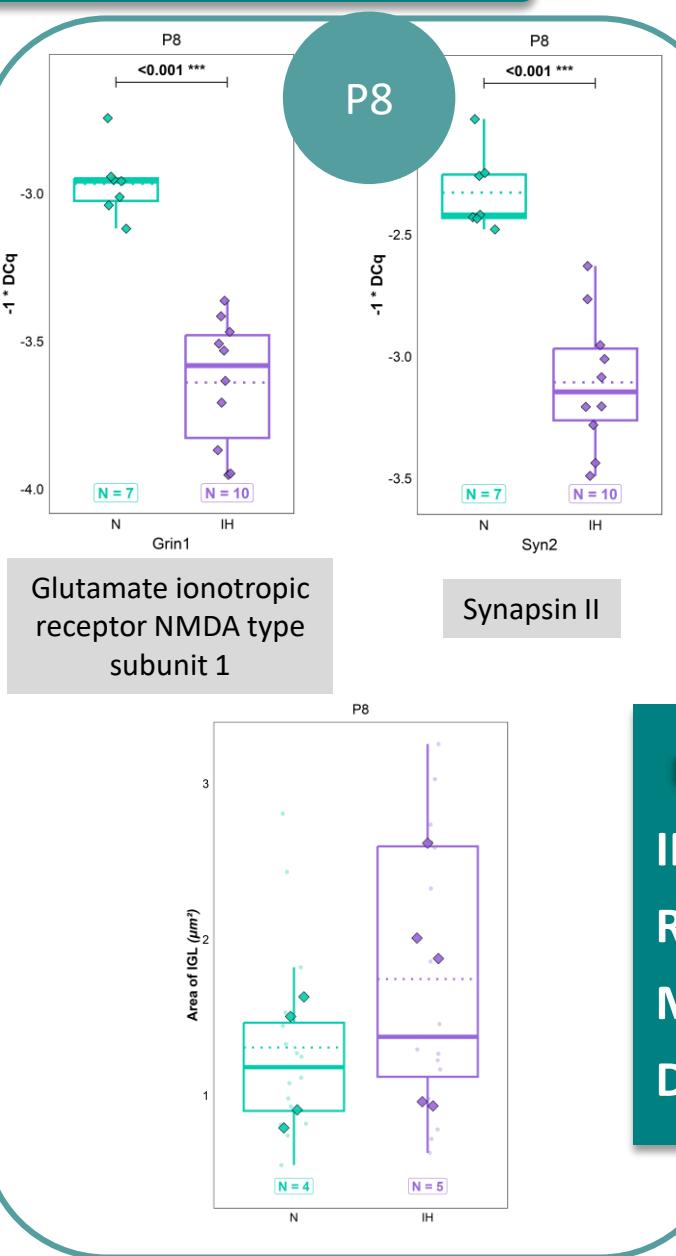
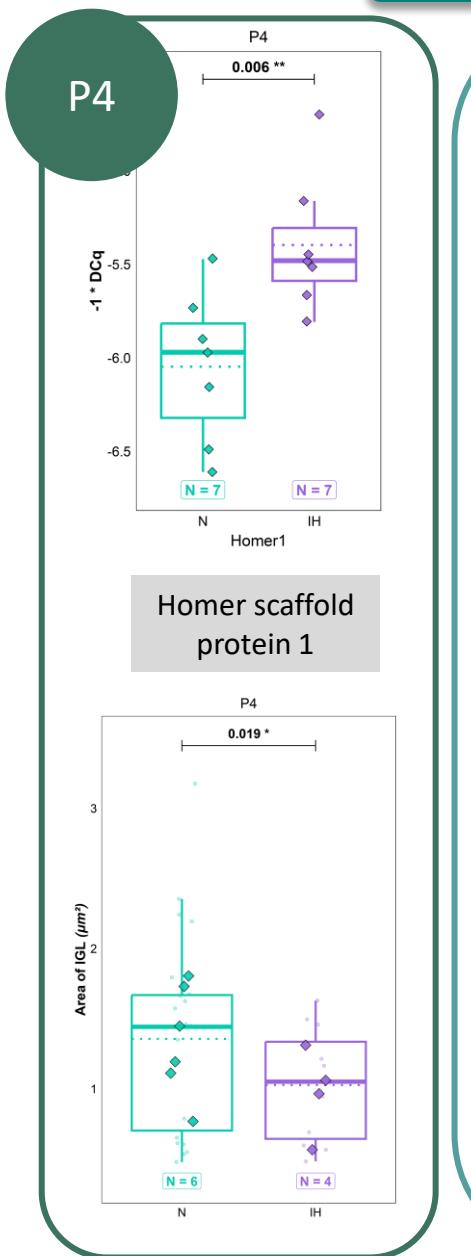
IGL

Couche
granulaire
interne



Maturation

P4-P12



**L'HI
INDUIT UN
RETARD DE
MATURATION
DÈS P4.**

2 IGL

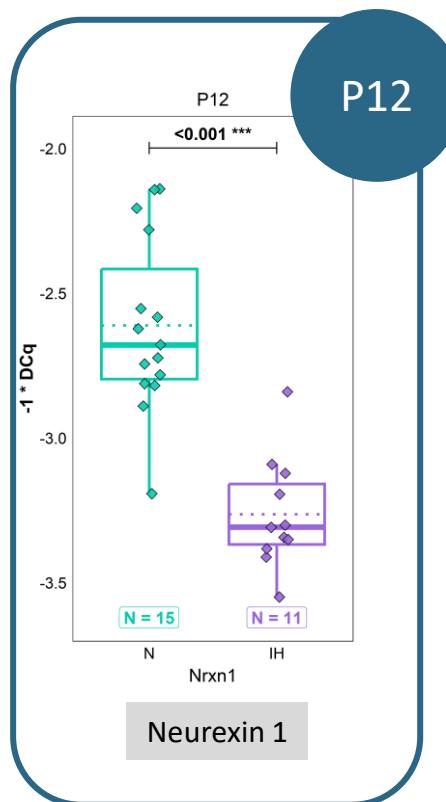
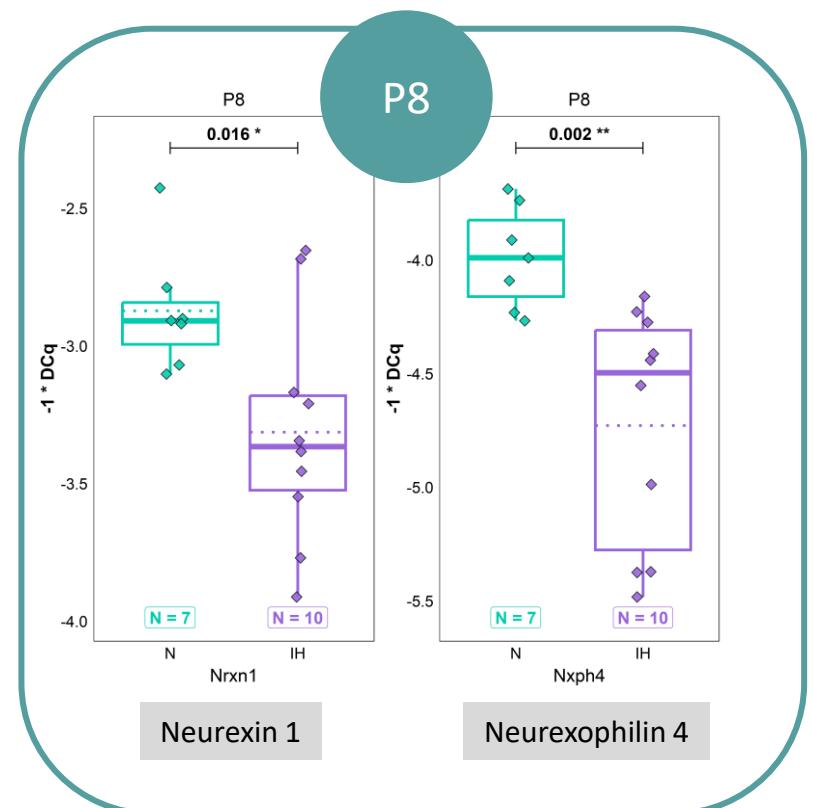
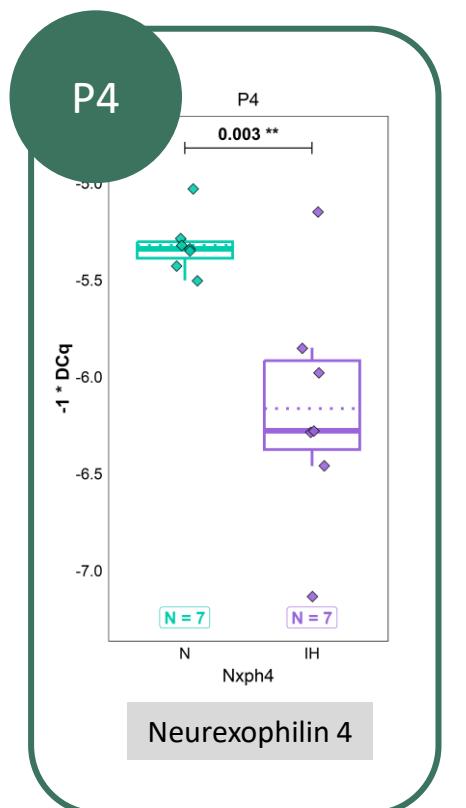
Couche granulaire interne



Neurotransmission
Golgi-GC



P4-P8



→ L'HI ALTÈRE L'AXE
NEUREXINE/NEUREXOPHILINE À PLUSIEURS
STADES, CE QUI PEUT EXPLIQUER LES
ALTÉRATIONS MOTRICES OBSERVÉES.

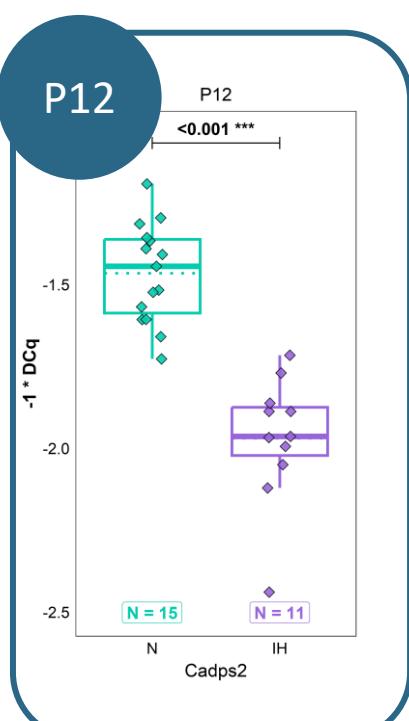
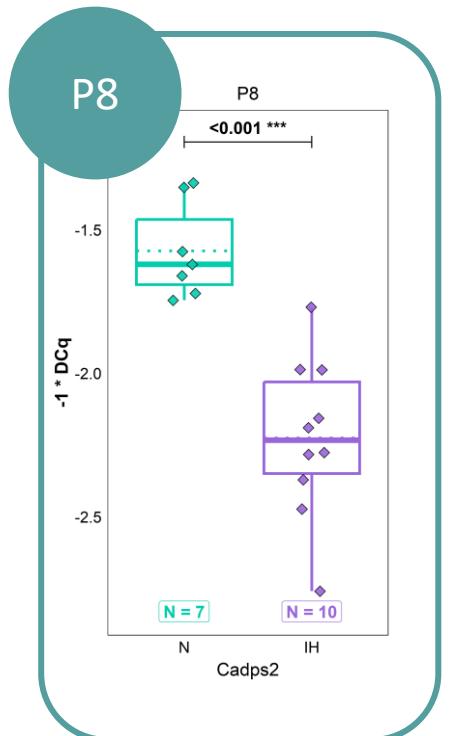
(Meng *et al.*, 2019)

3 IGL

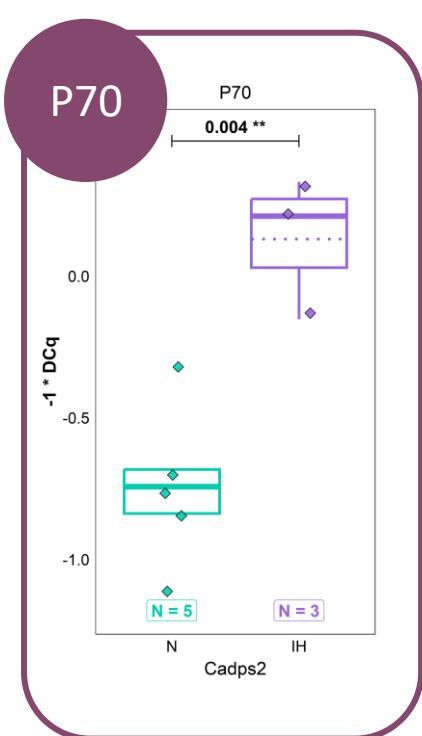
Couche granulaire interne

Maturation des GCs

P8-P70



Calcium dependent secretion activator 2



→ L'HI CAUSE UN DÉFICIT DE MATURATION À P8-P12 ET UNE SUREXPRESSION À L'ÂGE ADULTE QUI POURRAIT INDICER UNE DÉGÉNÉRESCENCE NEURONALE.

(Sadakata *et al.*, 2007)

(Smajić *et al.*, 2021; Lorenzo-Betancor *et al.*, 2022)

1 WM

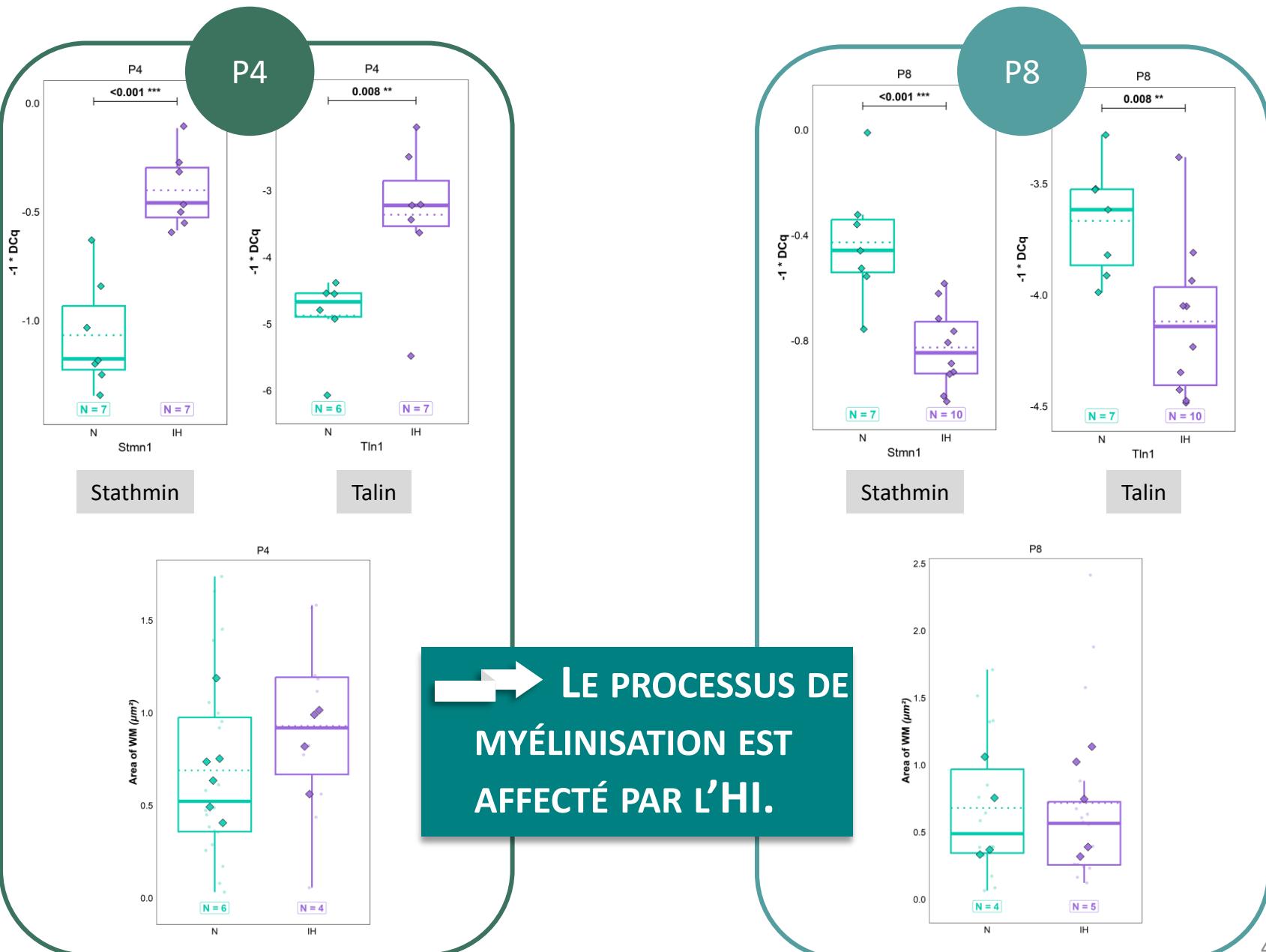
Substance blanche



Myélinisation



P4-P8



2 WM

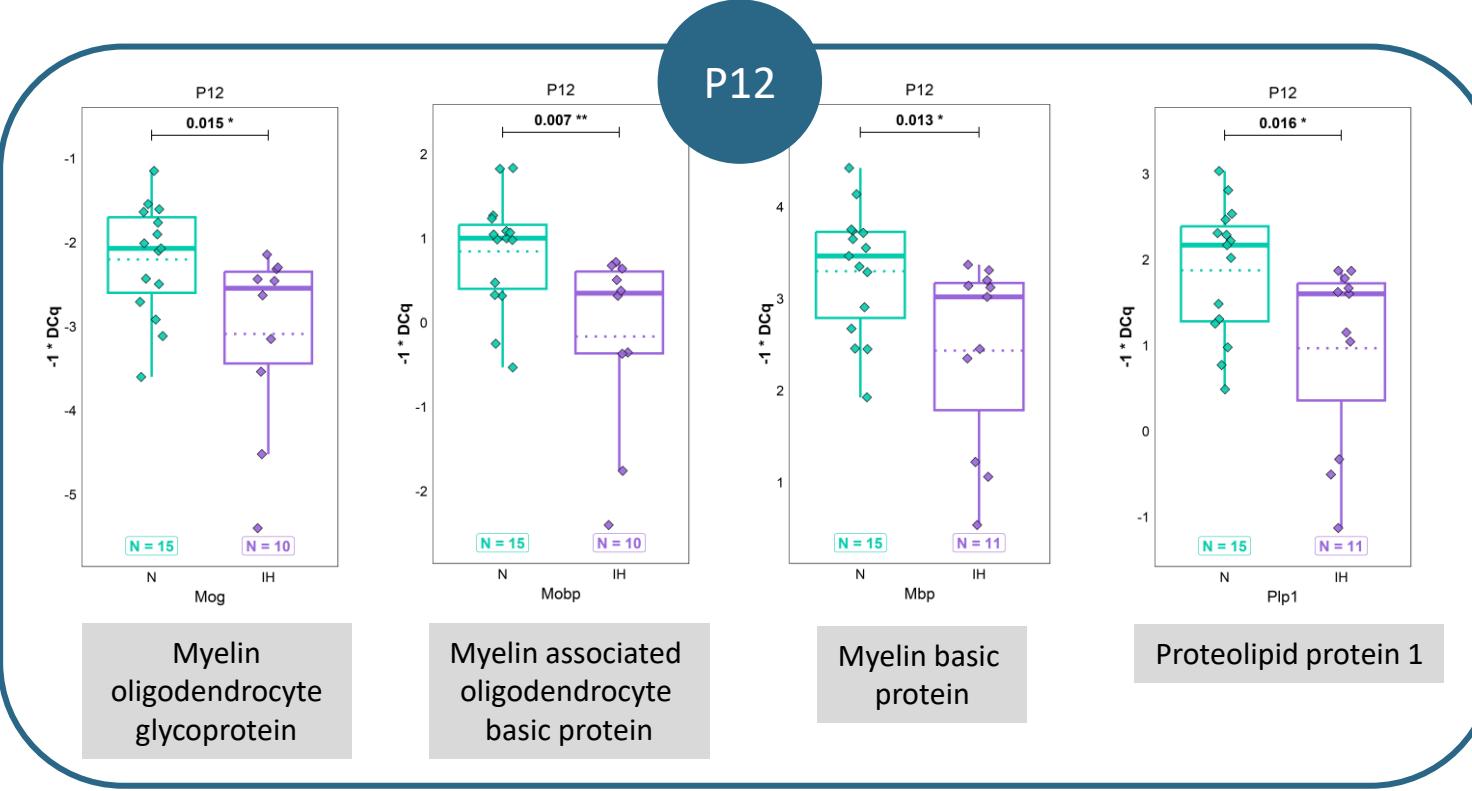
Substance blanche



Myélinisation



P12



→ LE PROCESSUS DE MYÉLINISATION EST AFFECTÉ PAR L'HI.

3 WM

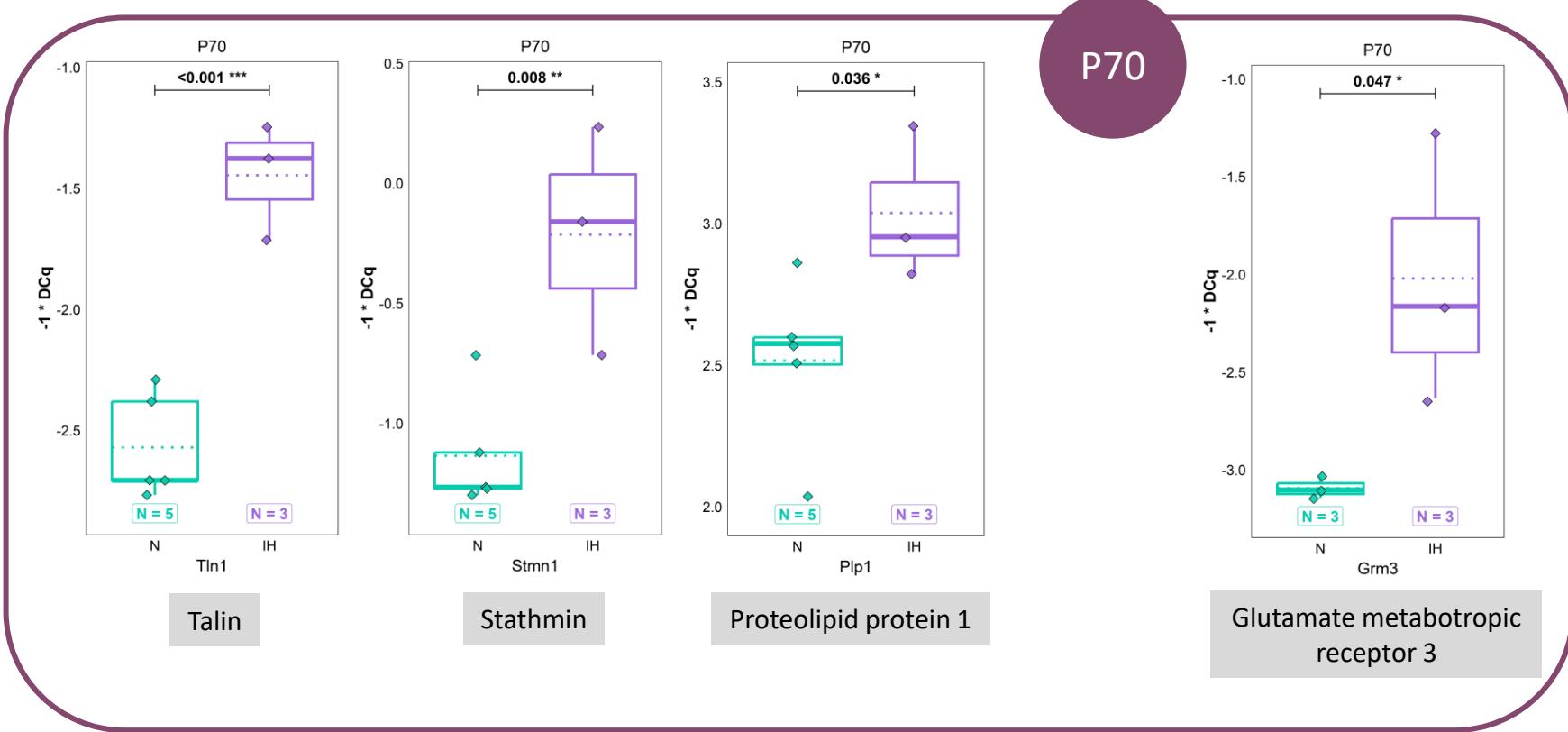
Substance blanche



Myélinisation



P70

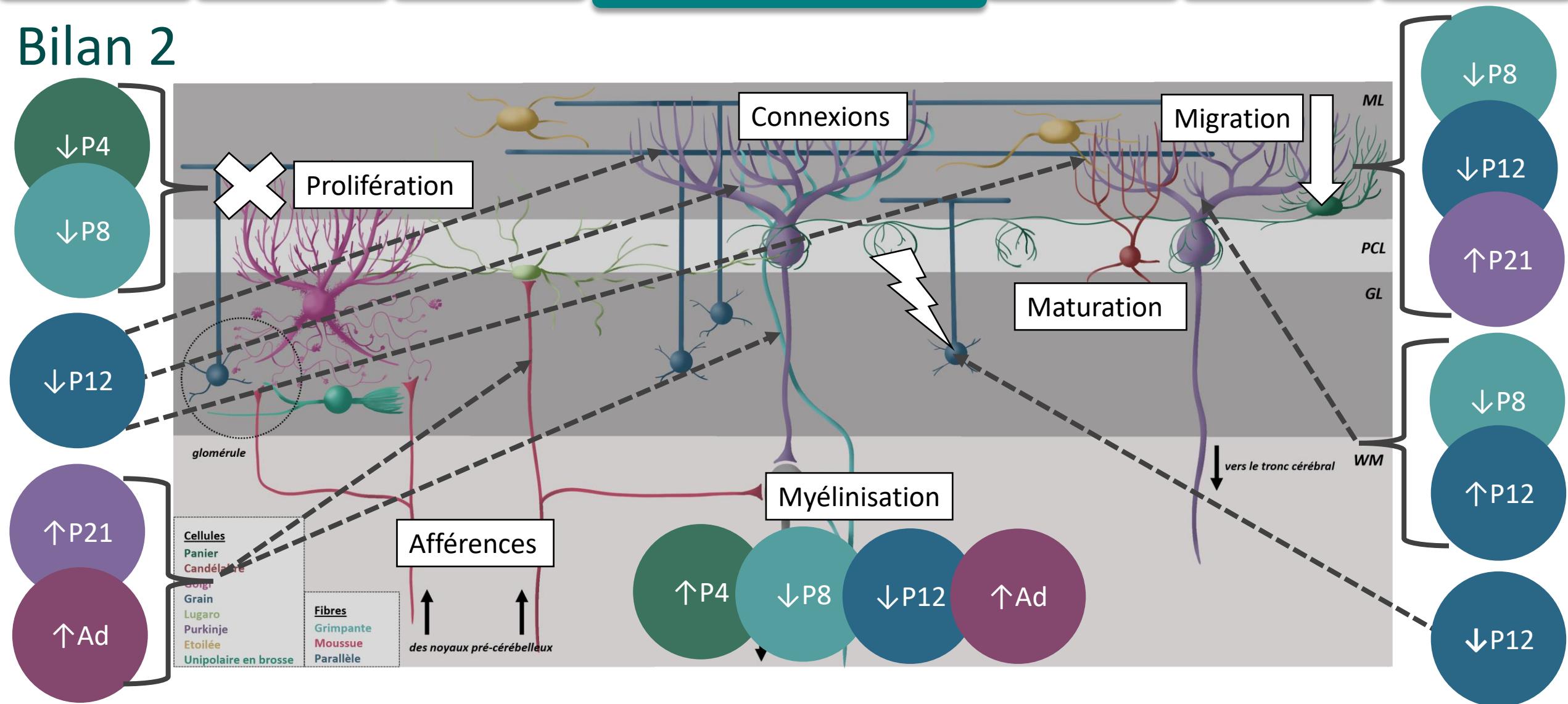


→ L'HI INDUIT UNE
SUREXPRESSION DE GÈNES
ASSOCIÉS À LA MYÉLINISATION
CHEZ L'ADULTE.

Microglie et
inflammation?

(Zinni *et al.*, 2021)

Bilan 2



➡ UNE HI PÉRINATALE CAUSE DES CHANGEMENTS TRANSCRIPTOMIQUES TOUT AU LONG DE LA VIE.

Rodriguez-Duboc *et al.*

RESEARCH

Apnea of Prematurity induces short and long-term development-related transcriptional changes in the murine cerebellum.

Agalie Rodriguez-Duboc¹, Magali Basille-Dugay², Aurélien Debonne^{1,3}, Marc-Aurèle Rivière⁴, David Vaudry^{1,3} and Daphné Burel^{1,3*}

Abstract

Apnea of prematurity (AOP) occurs in over 50% of preterm infants and induces a perinatal intermittent hypoxia (IH) which represents a leading cause of morbimortality worldwide. At birth, the human cerebellar cortex is still immature, making it vulnerable to perinatal events. Moreover, a correlation between cerebellar functions and the deficits observed in children having suffered from AOP has been demonstrated. Yet the cerebellar alterations underpinning this link remain poorly understood. Thus, to shed light the involvement of the cerebellum in perinatal hypoxia-related sequelae, we developed a mouse model of AOP. In previous works, we found that IH induces an oxidative stress in the developing cerebellum with an overexpression of genes involved in reactive oxygen species production and an underexpression of genes encoding antioxidant enzymes. These alterations suggest a failure of the defense system against oxidative stress and could be responsible for neuronal death in the cerebellum.

Based on these results, we performed a transcriptomic study of the genes involved in the processes that occur during cerebellar development. We analyzed the expression of these genes at various developmental stages and in different cell types, by real time PCR. This enabled us to pinpoint a timeframe of vulnerability at P8, which represents the age with the most downregulated genes in the cerebellum. Moreover, we identified several neuronal differentiation pathways that are impacted by our IH protocol such as proliferation, migration and differentiation. This indicates that IH can modify the phenotype of various cells, and then contribute to the histological and behavioral deficits already observed in this model.

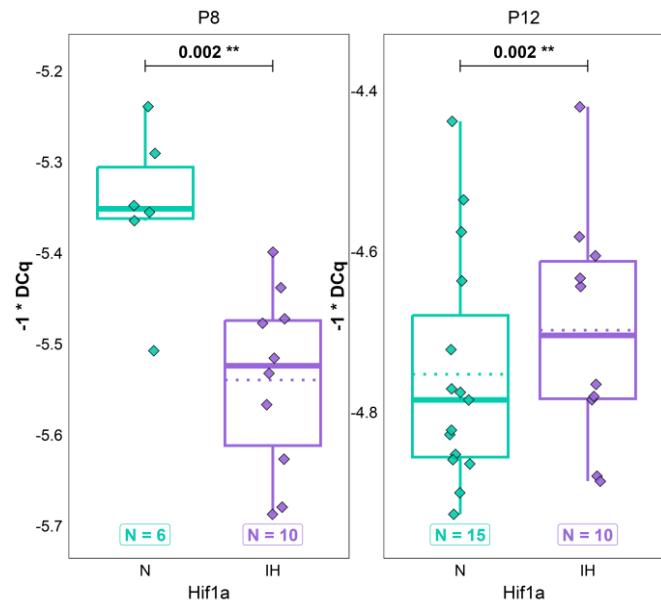
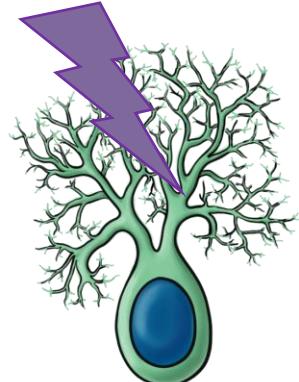
Overall, our data point out that the cerebellum is highly sensitive to IH, and provide elements to better understand the pathophysiology of AOP by deciphering the cellular and molecular causal mechanisms. In the long term, the present results could lead to the identification of novel therapeutic targets to improve the clinical management of this highly prevalent pathology.

Keywords: Cerebellum; Development; Intermittent hypoxia; Perinatal; Apnea of prematurity; Histology; Apoptosis; Oxidative Stress; Transcriptome; Differentiation

ARTICLE 2

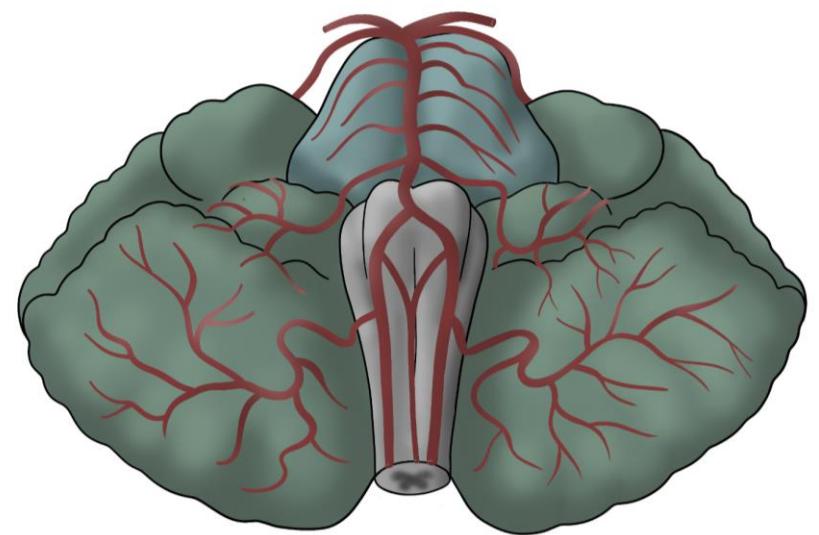
EN COURS DE SOUMISSION DANS MOLECULAR AND CELLULAR NEUROSCIENCE.

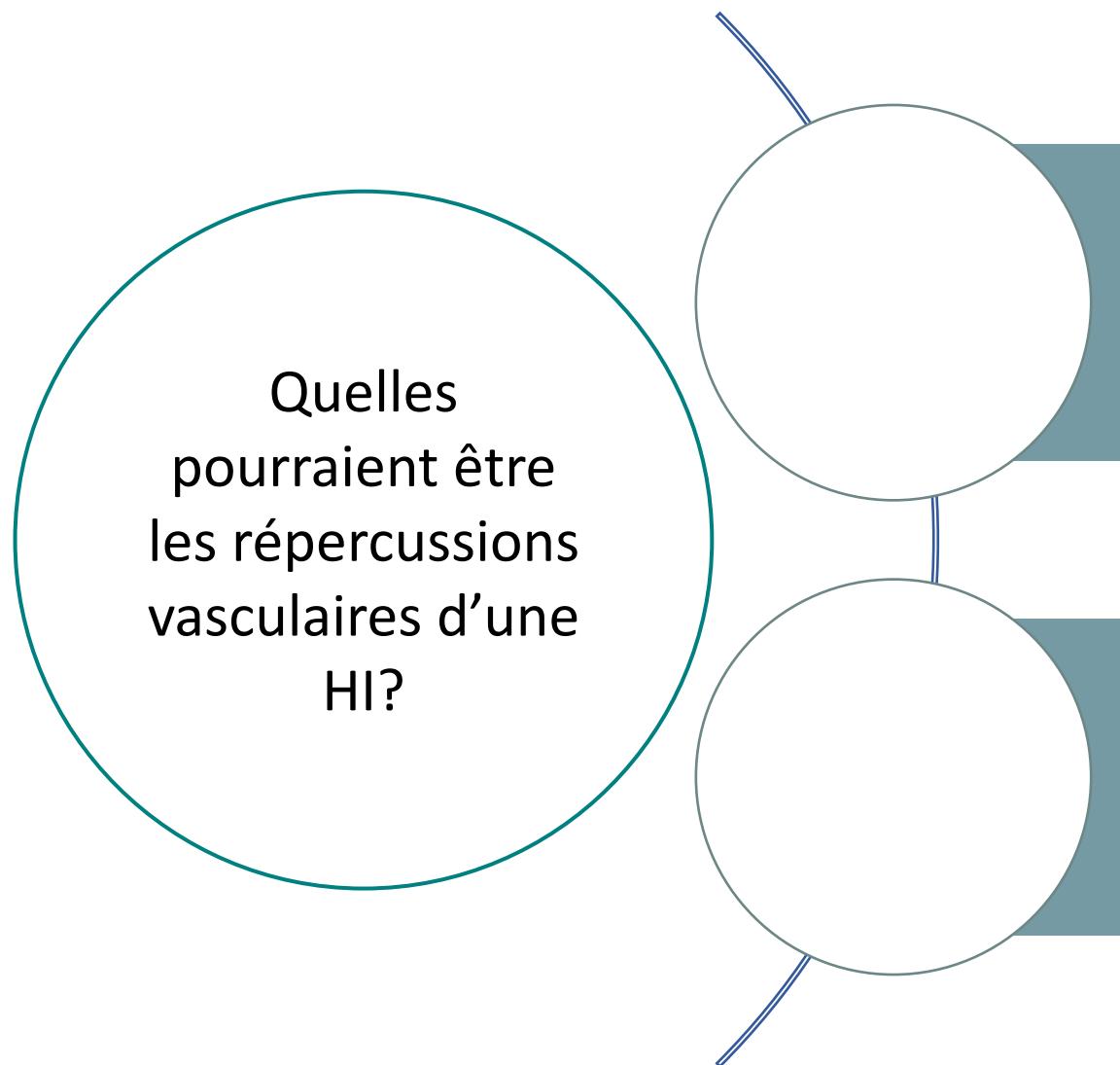
Hif1 α



Axe
angiopoietine tie

Vascularisation?



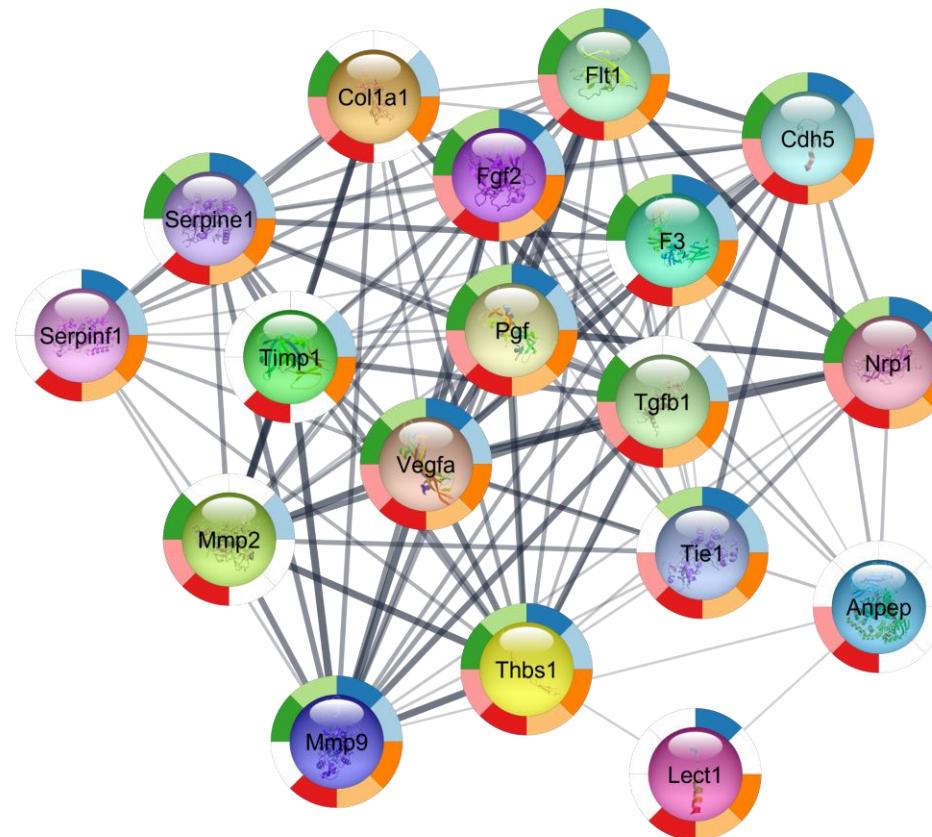


Etudier des gènes associés à la vascularisation dans le cervelet

Déterminer si l'HI induit un changement structurel des vaisseaux *in situ*

1 Vascularisation: panel

- Recherche bioinformatique
- 23 gènes choisis → Panel
- Voies étudiées:
 - angiogénèse, migration, matrice extracellulaire
- Stades:
 - P4, P8, P12, P21 et P70



STRING Enrichment ▾

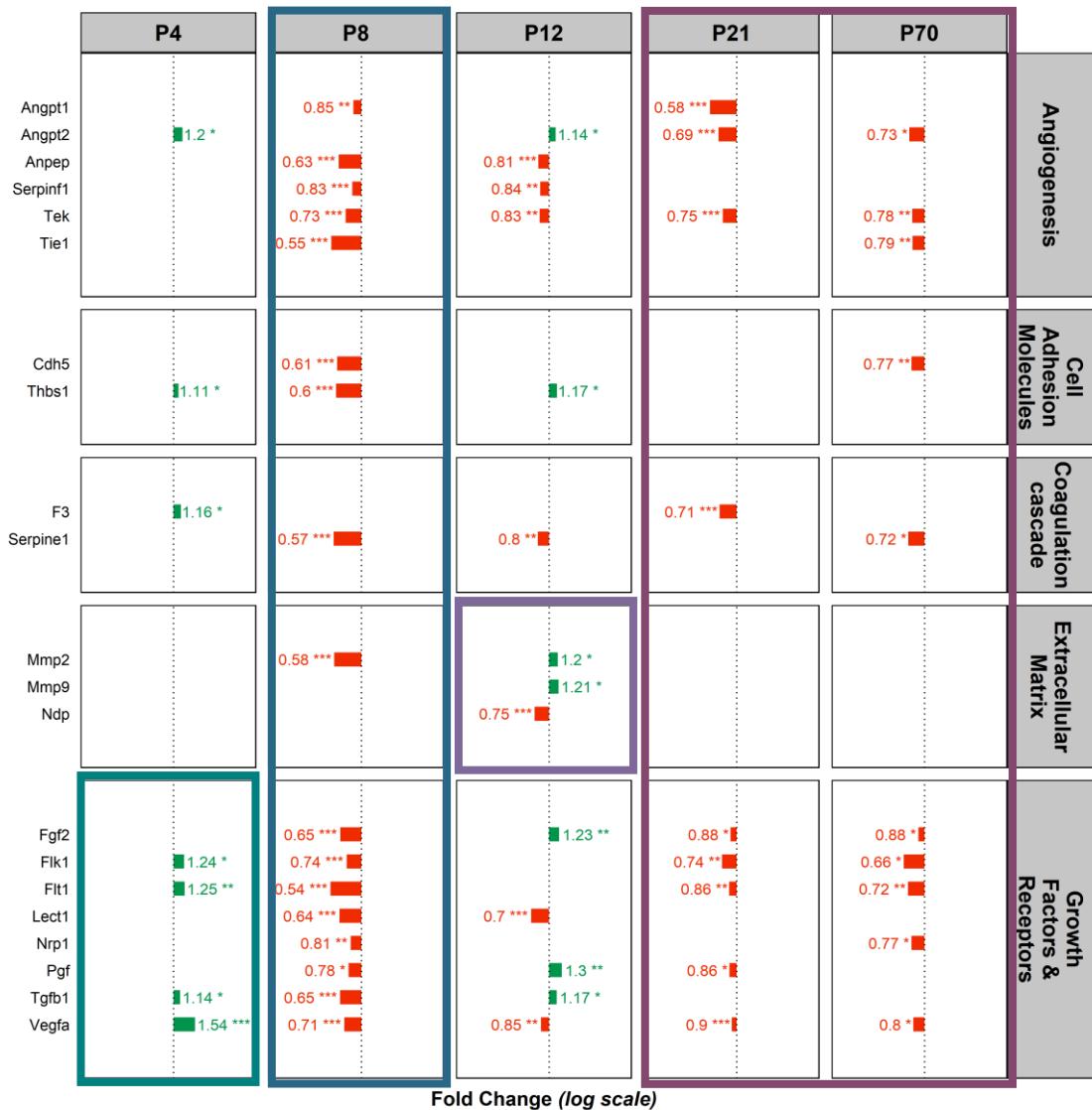
PPI Enrichment: 1.0E-16

category	chart color	term name	description	FDR value
GO Biological Process	#4682B4	GO:0030334	Regulation of cell migration	1,3E-16
GO Biological Process	#0045765	GO:0045765	Regulation of angiogenesis	1,3E-16
GO Biological Process	#46B4B4	GO:0045766	Positive regulation of angiogene...	9,01E-16
GO Biological Process	#46B4B4	GO:0030335	Positive regulation of cell migrat...	2,72E-14
GO Biological Process	#F08080	GO:0001568	Blood vessel development	7,52E-13
GO Biological Process	#E61A19	GO:0051239	Regulation of multicellular organ...	8,09E-13
GO Biological Process	#F0A61A	GO:0022603	Regulation of anatomical structu...	1,19E-12
GO Biological Process	#F0A61A	GO:2000026	Regulation of multicellular organ...	6,76E-12

2

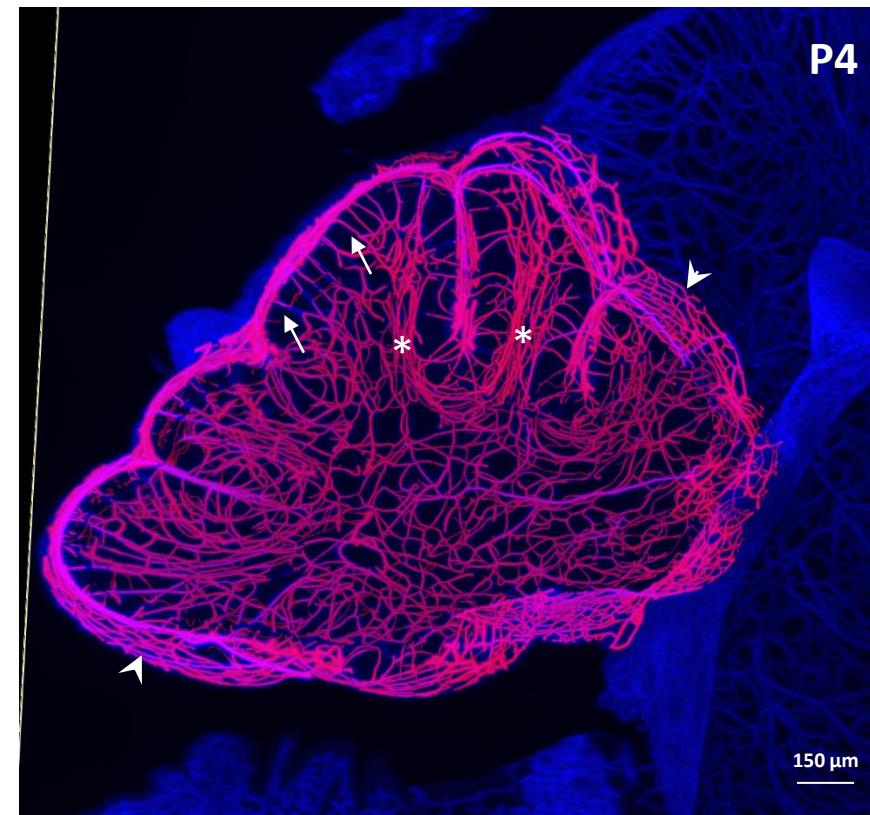
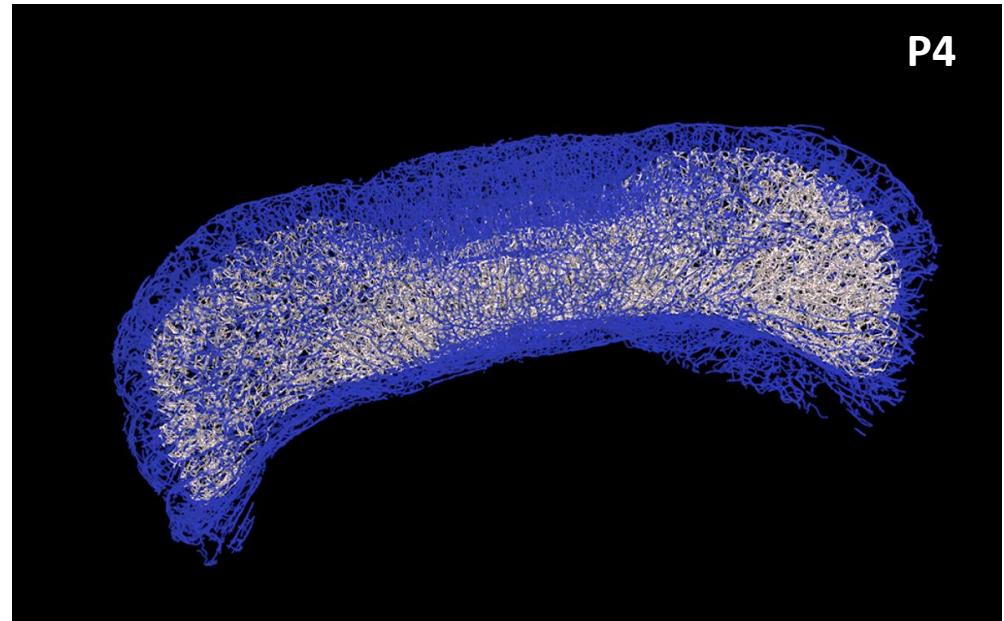
Vascularisation: transcriptomique

- ↑ facteurs de croissance
- vulnérabilité avec $\simeq 74\% \downarrow$
- compensation partielle ?
- effets à long terme



3 Vascularisation: imagerie

- Protocole de transparisation
- CD31/αSMA/podocalyxine
- Microscopie à feuille de lumière
- Modélisation du réseau

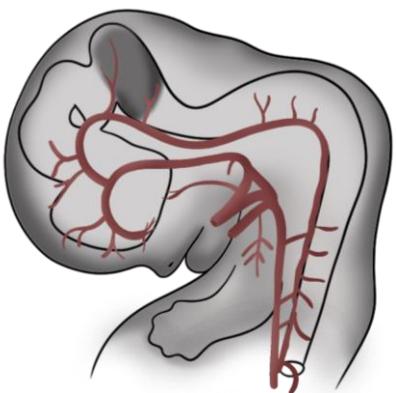


- Cervelets prélevés et transparisés
- Axe de recherche poursuivi par Camille Racine (M2 neurosciences)



EFFET DE L'HI SUR LA DENSITÉ, LE VOLUME, ET LA RAMIFICATION DU RÉSEAU VASCULAIRE?

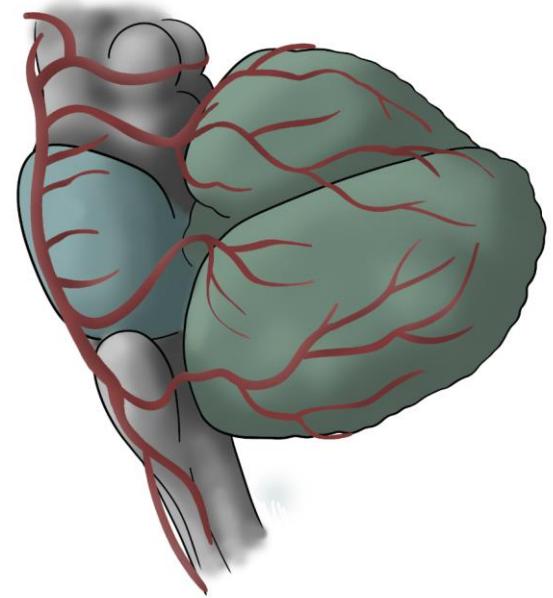
1 Perspectives



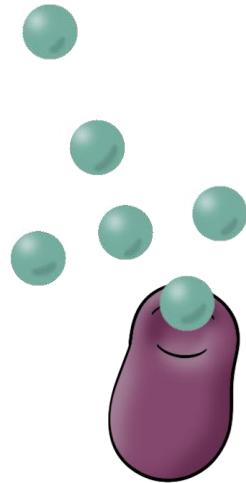
Travaux sur la vascularisation

Embranchements,
densité, taille...?

Effets de l'AdP sur
la vascularisation



2 Perspectives

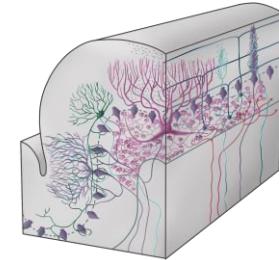
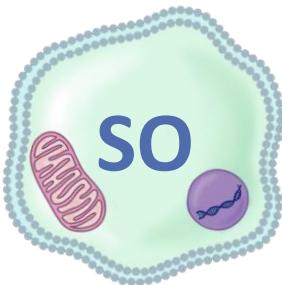
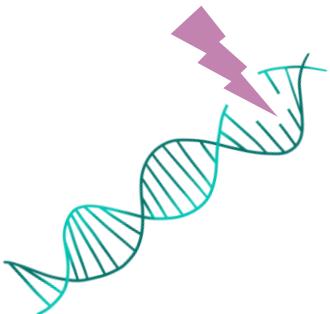
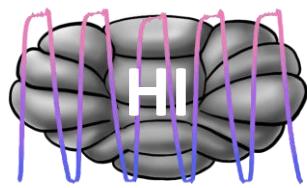


Etude
protéomique

Test de facteurs
neurotrophiques

Compensation
des effets?





Modèle murin
d'AdP

Effet de l'HI sur le
cervelet

Régulations
moléculaires

Stress oxydatif
cellulaire

Effets histologiques
et anatomiques

Altérations
comportementales

Perspectives
thérapeutiques

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