



Molecular biology of the mini-puberty, LH-RH and cognition

Vincent Prevot

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France*

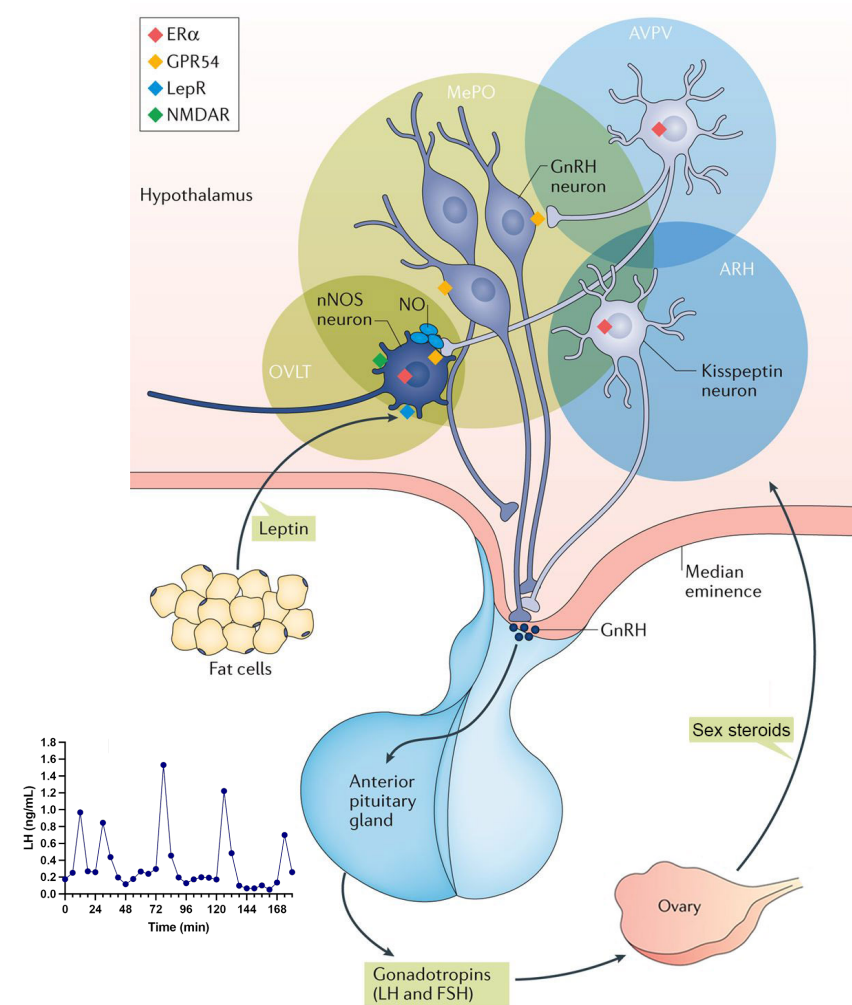


The 5th International Andrology Symposium
Cryptorchidism: Molecular Biology meets
Endocrinology and Surgery
26/27 September 2025



HYPOTHALAMIC – PITUITARY – GONADAL AXIS

GnRH neurons are the **master regulators** of the HPG-axis

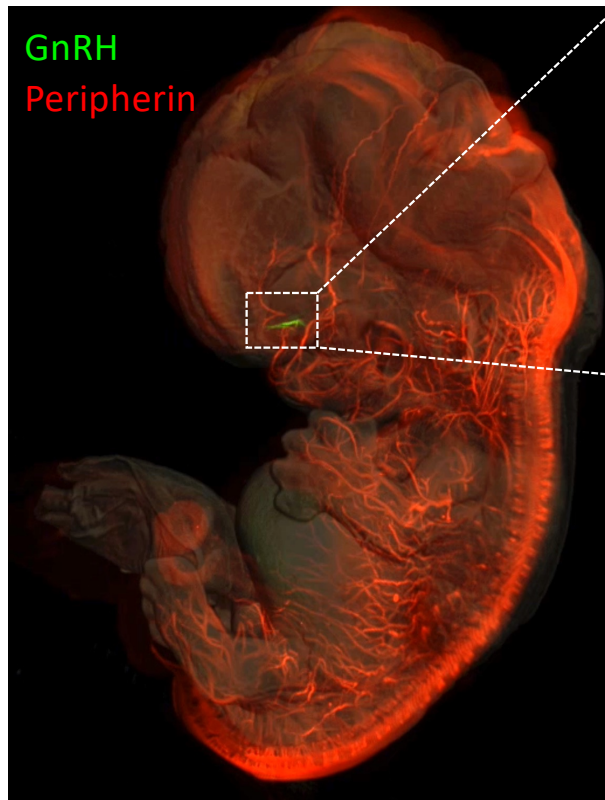


Chachlaki, Garthwaite & Prevot (2017) *Nat Rev Endocrinol* PMID: 28621341

HYPOTHALAMIC – PITUITARY – GONADAL AXIS

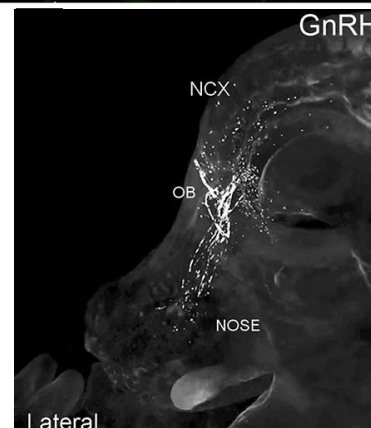
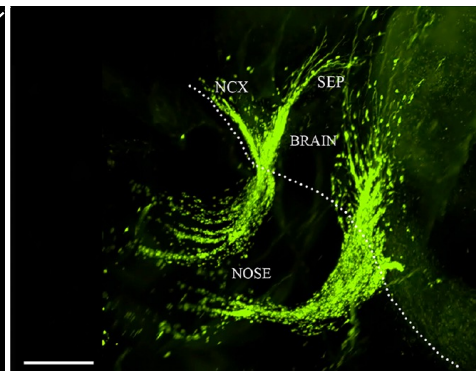
GnRH neurons are the **master regulators** of the HPG-axis

- Originate from outside the brain

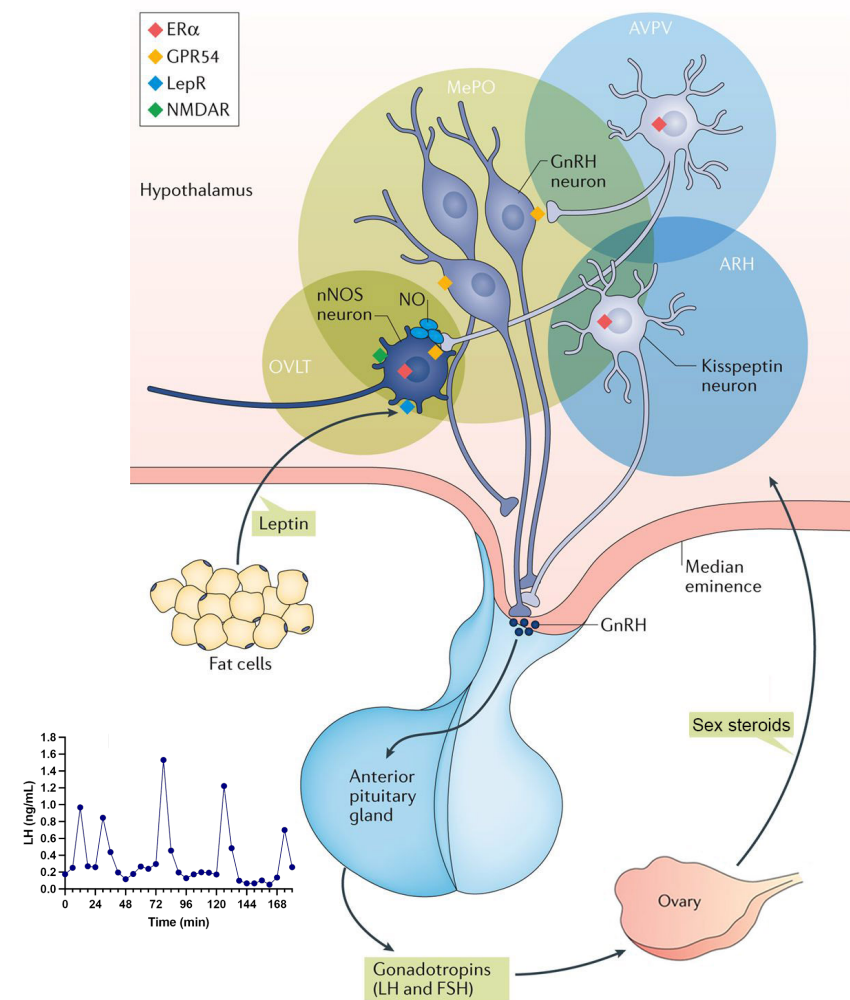


Human Fetus, CS19, 7 weeks of gestation

Casoni et al *Development*, 2016 143(21):3969-3981



Mouse embryo, E16.5

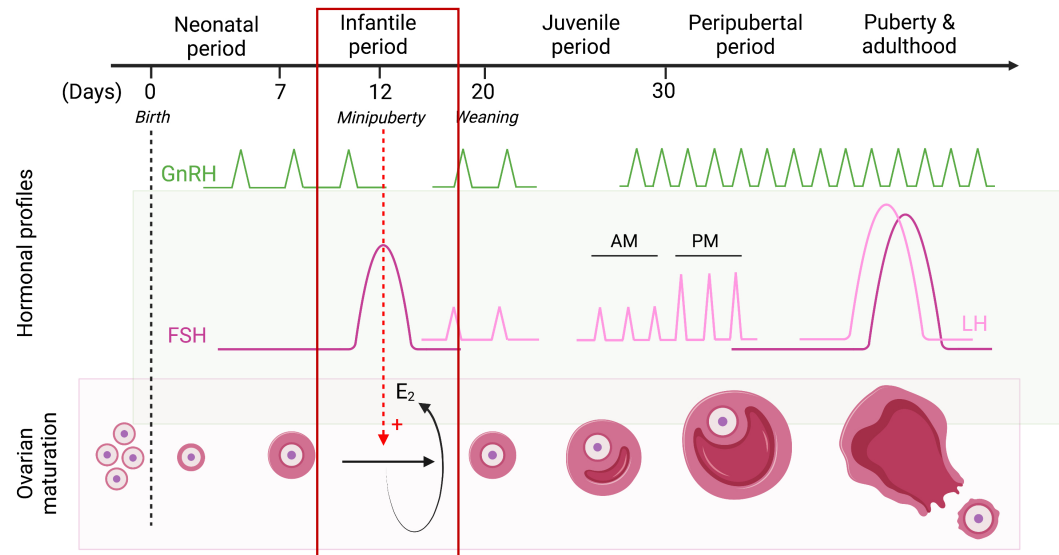


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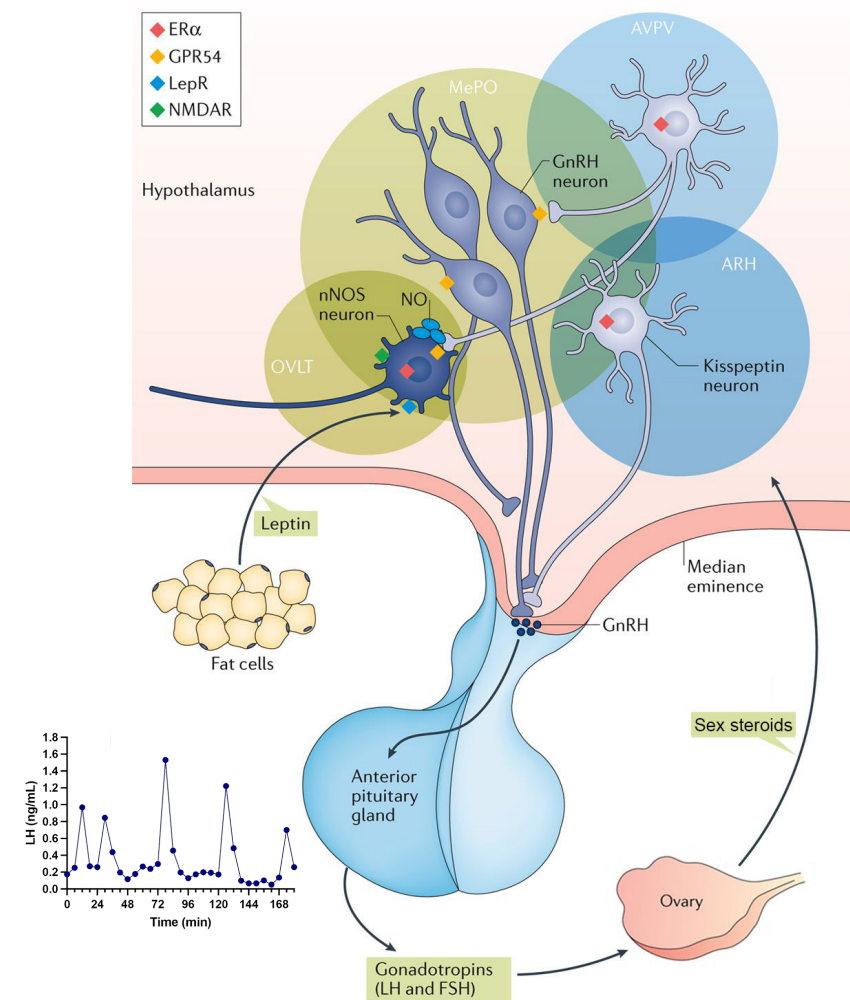
HYPOTHALAMIC – PITUITARY – GONADAL AXIS

GnRH neurons are the **master regulators** of the HPG-axis

- Postnatal maturation of the GnRH neuronal network



Prevot (2015) Knobil and Neill's Physiology of Reproduction

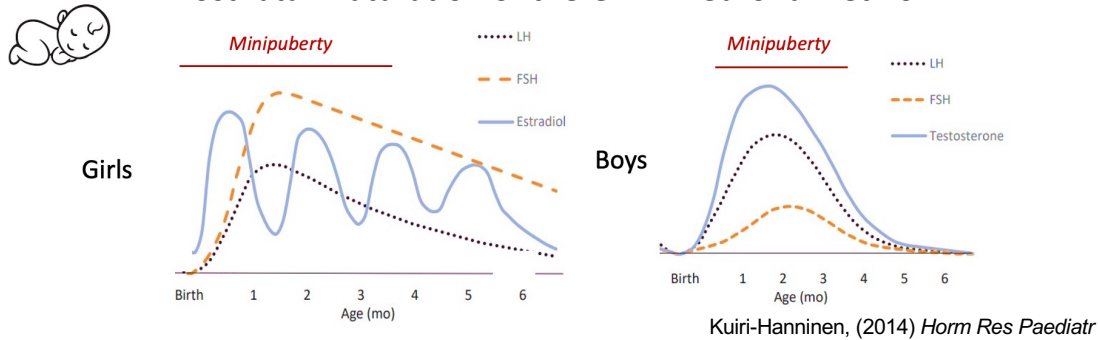


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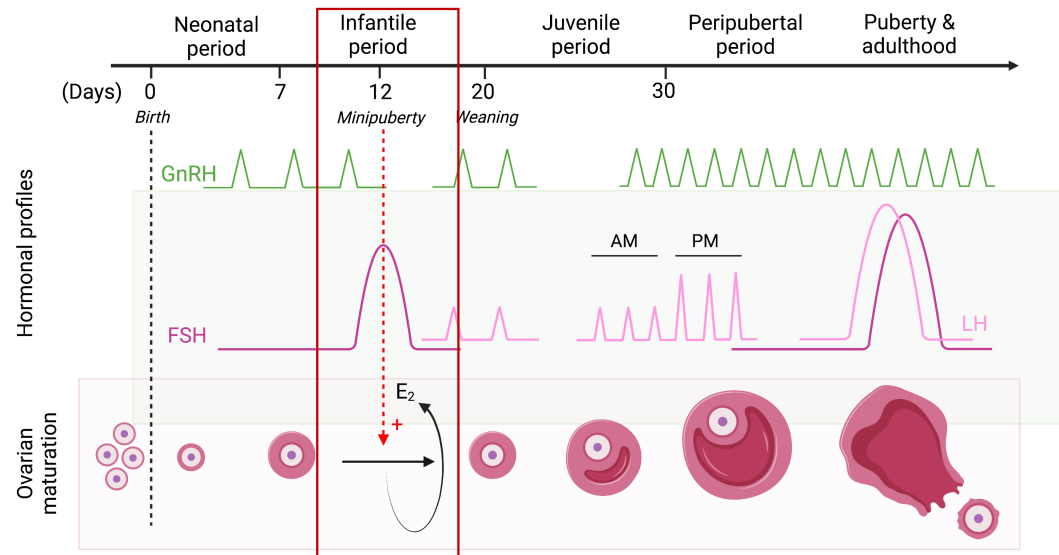
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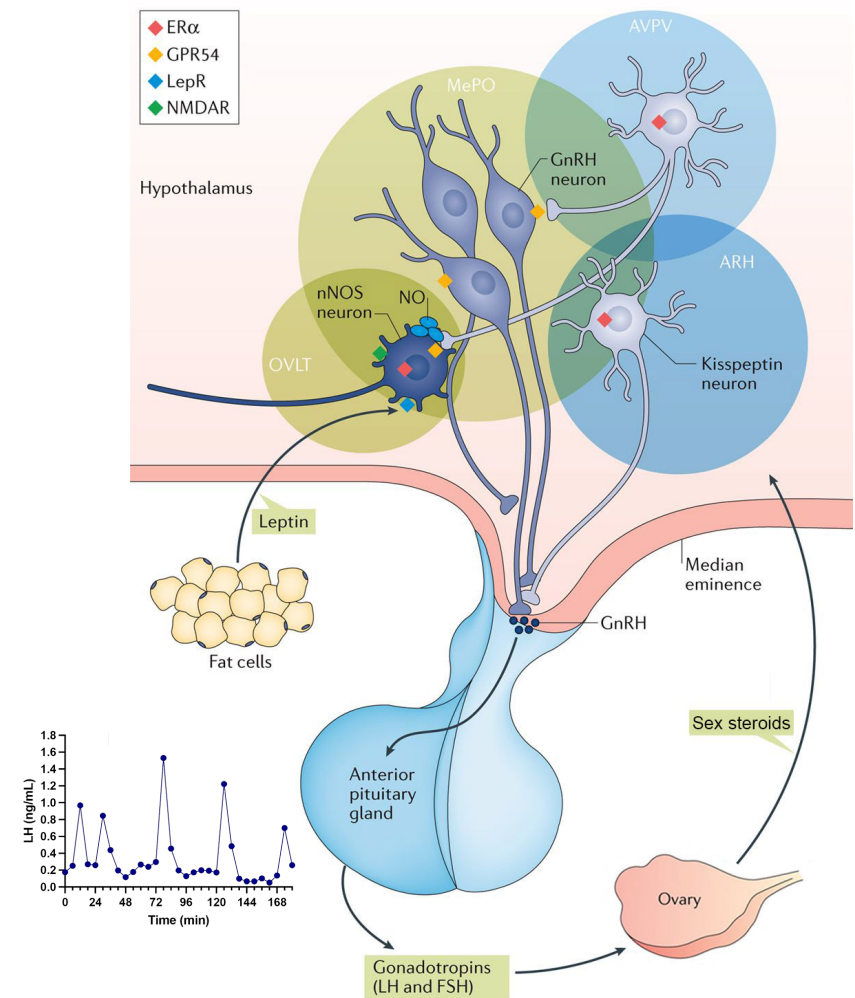
- Postnatal maturation of the GnRH neuronal network



Kuiri-Hanninen, (2014) *Horm Res Paediatr*



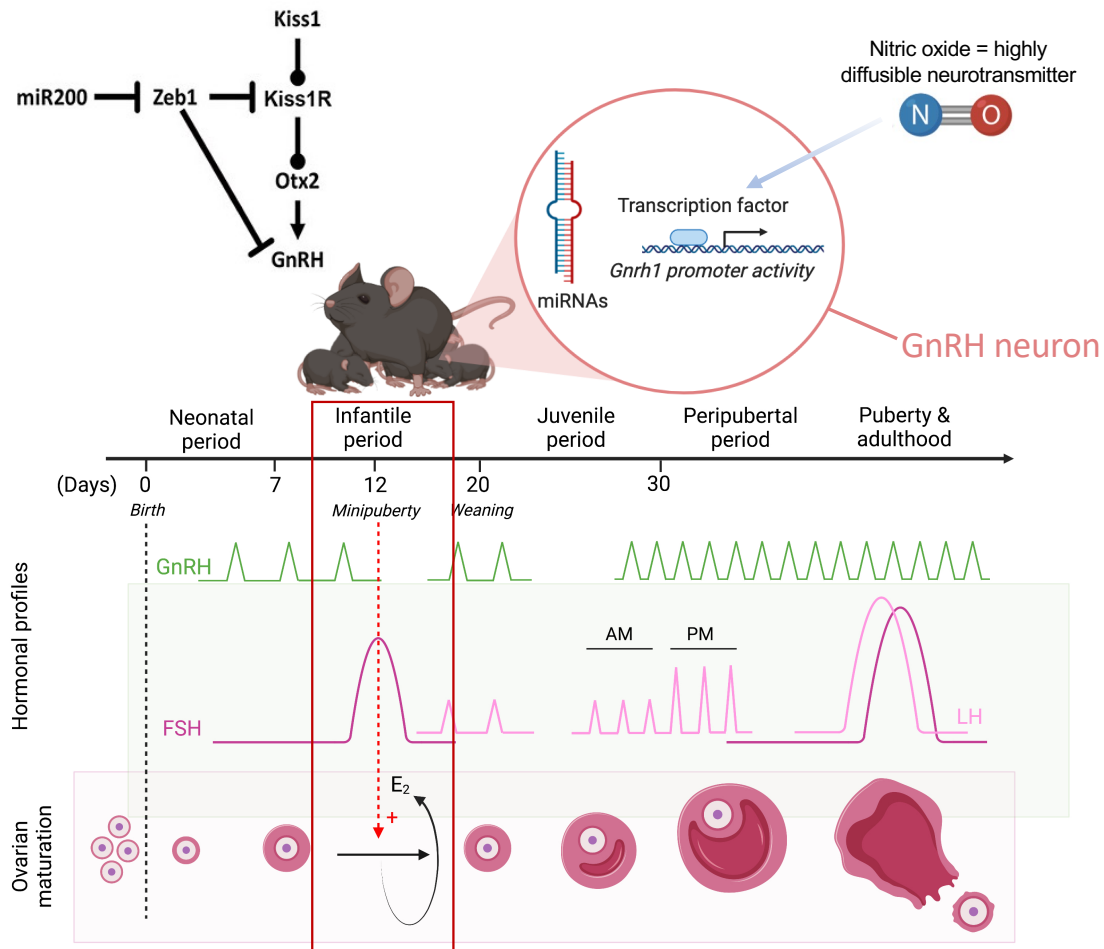
Prevot (2015) *Knobil and Neill's Physiology of Reproduction*



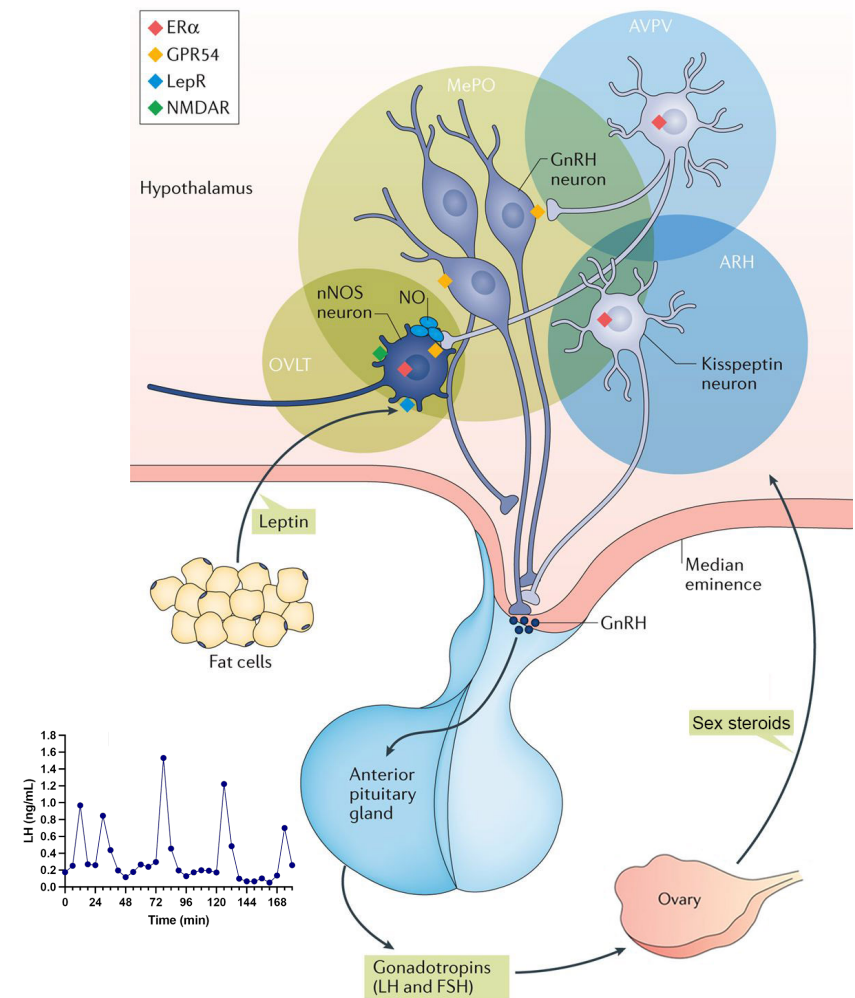
Chachlaki, Garthwaite & Prevot (2017) *Nat Rev Endocrinol* PMID: 28621341

HYPOTHALAMIC – PITUITARY – GONADAL AXIS

Messina et al. (2016) Nat Neurosci PMID: 27135215

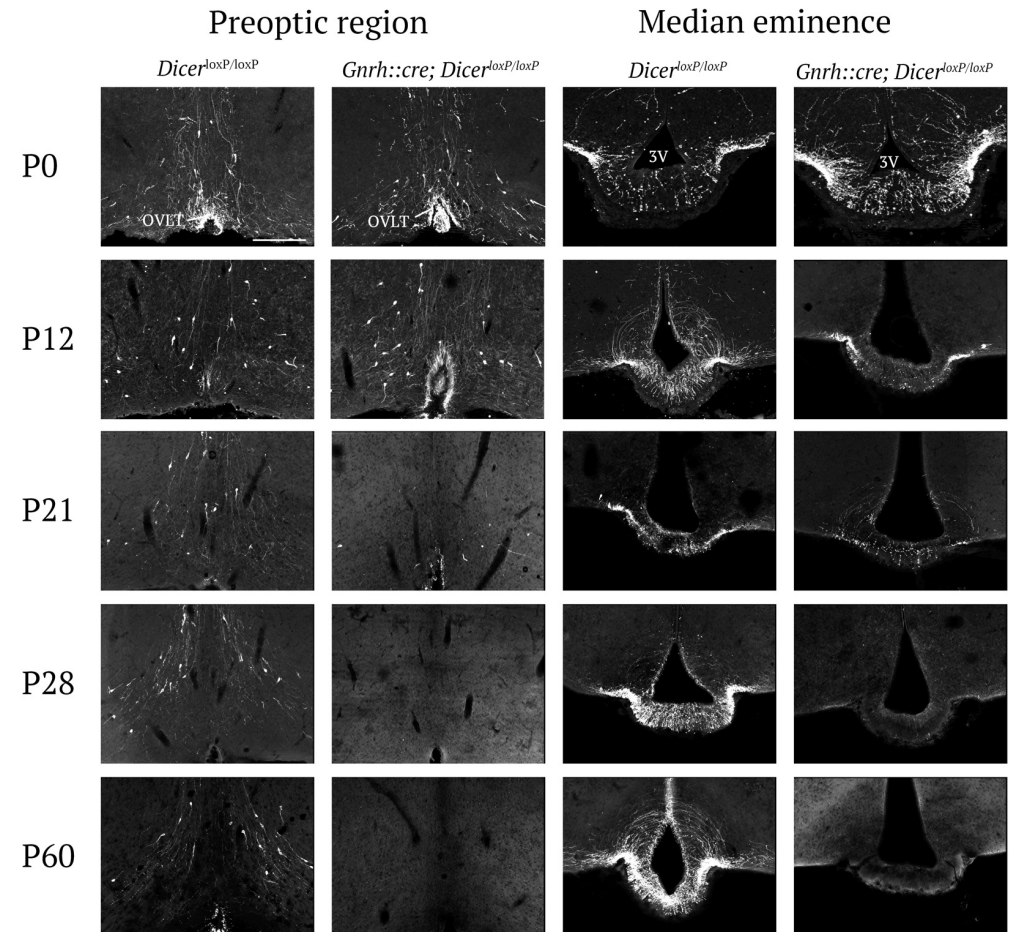
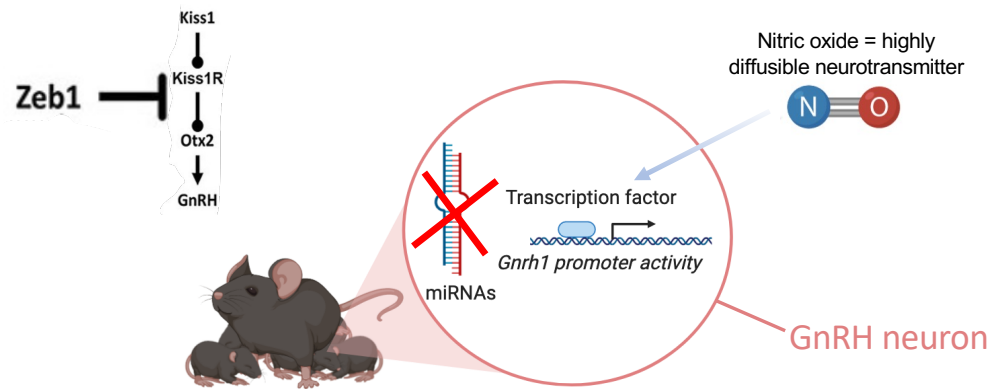


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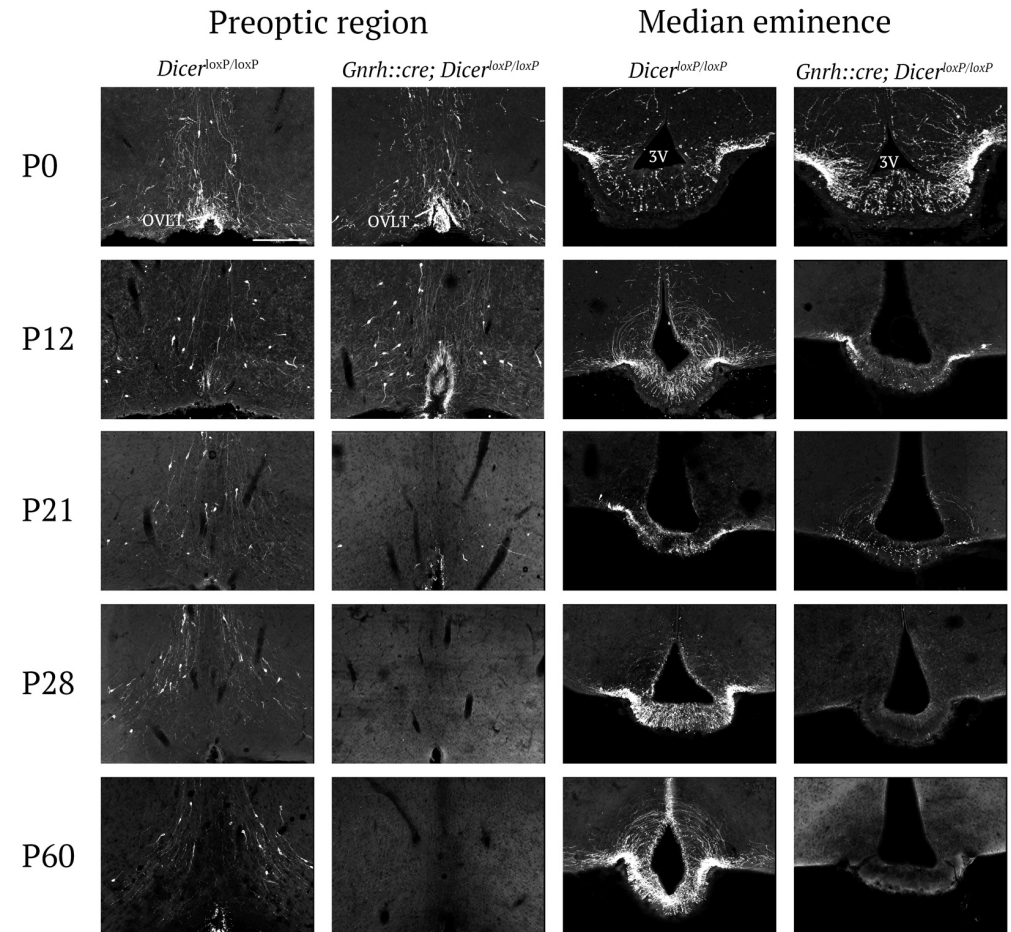
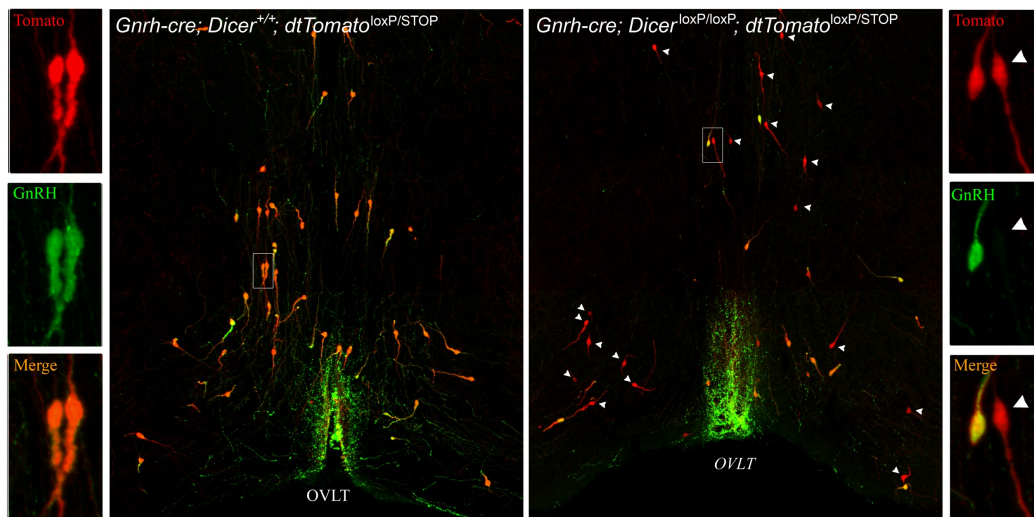
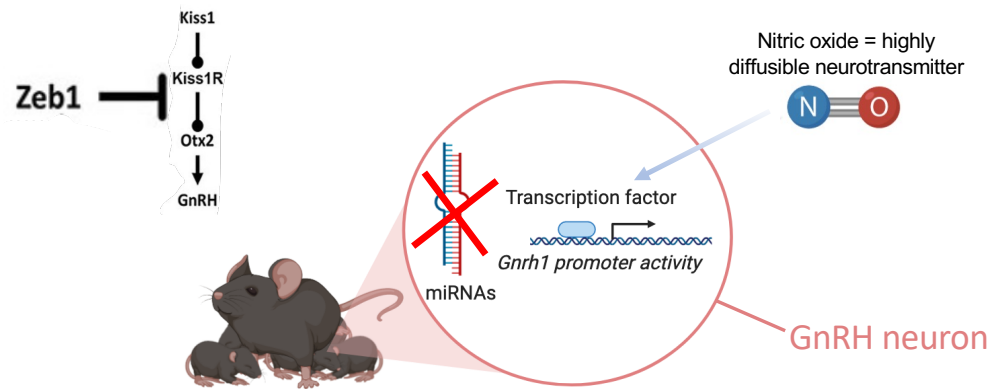


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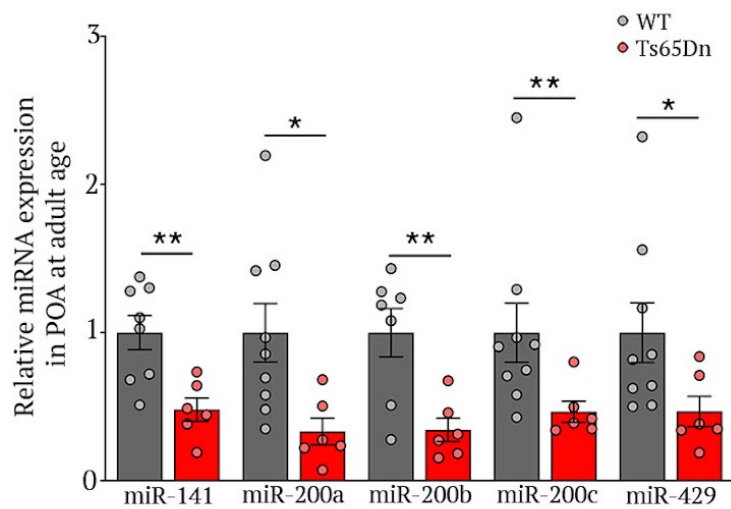
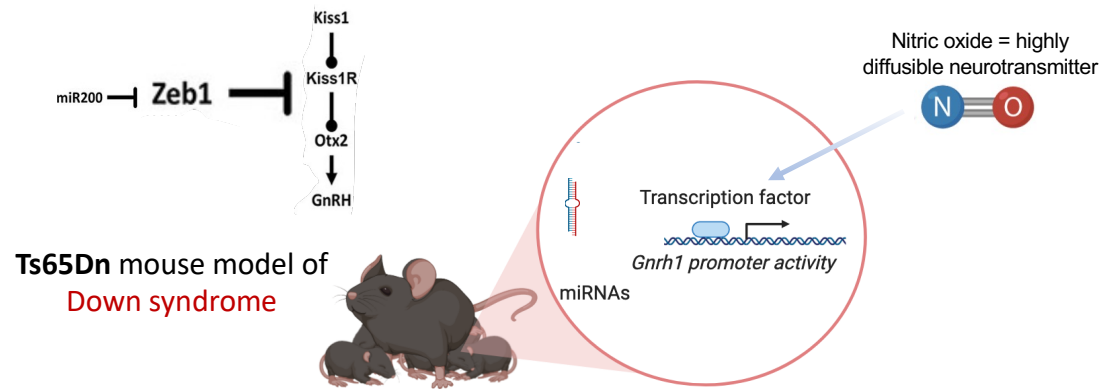
A key role for miRNA **at minipuberty** for life-long GnRH production



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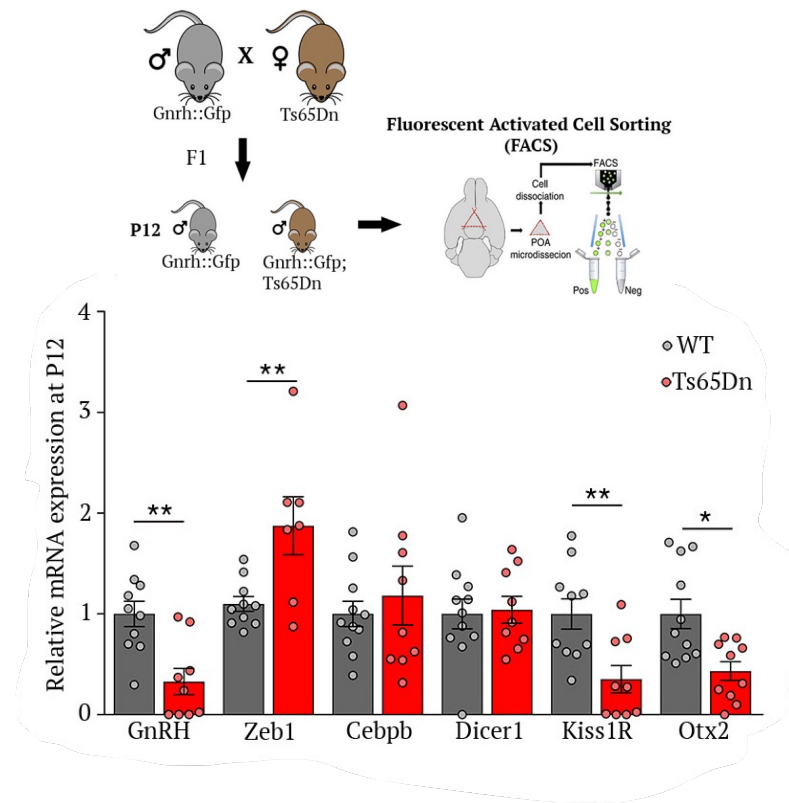
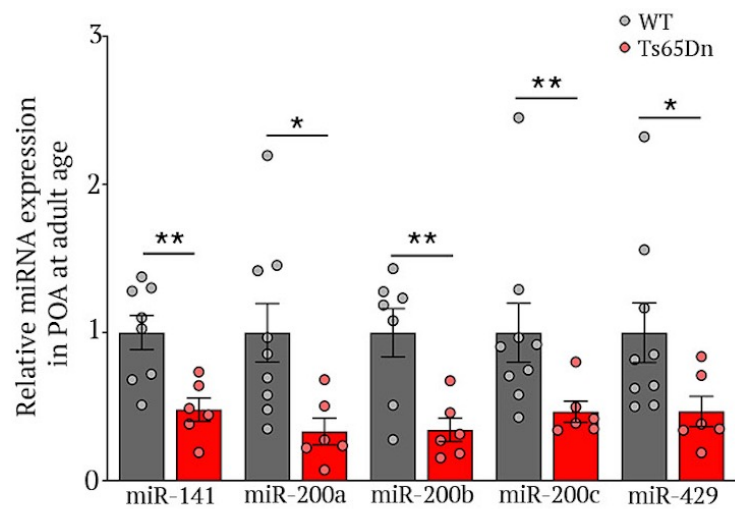
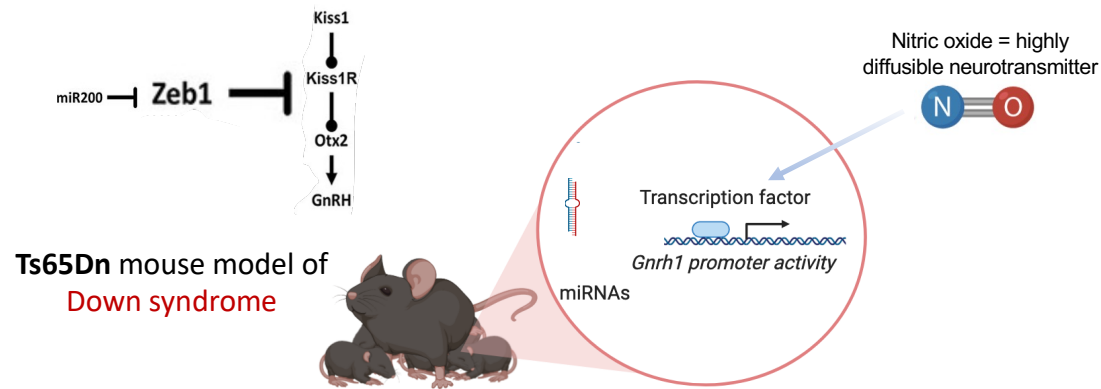


Chromosomal-generated miRNA imbalance **at minipuberty** alters GnRH production with age

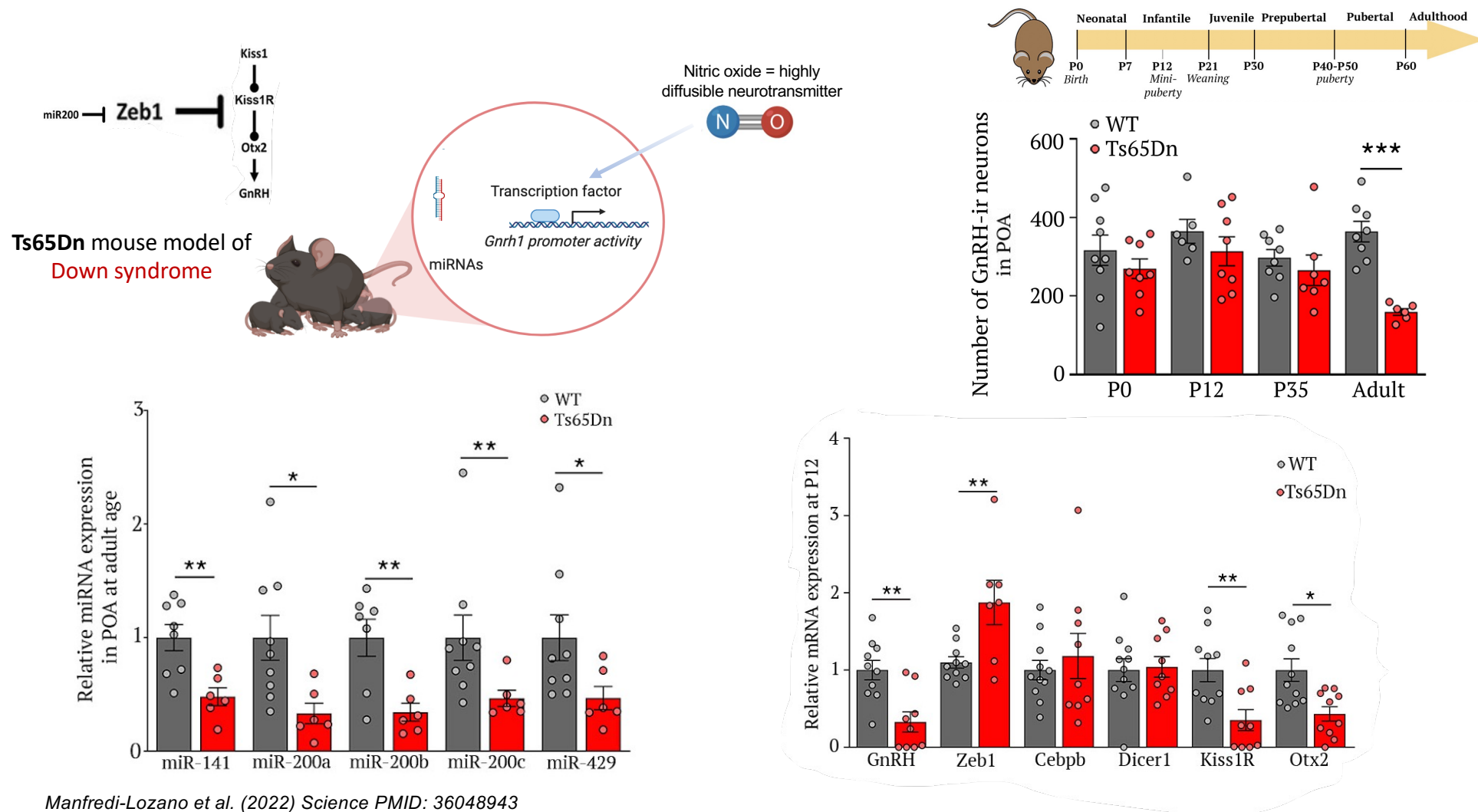


Manfredi-Lozano et al. (2022) Science PMID: 36048943

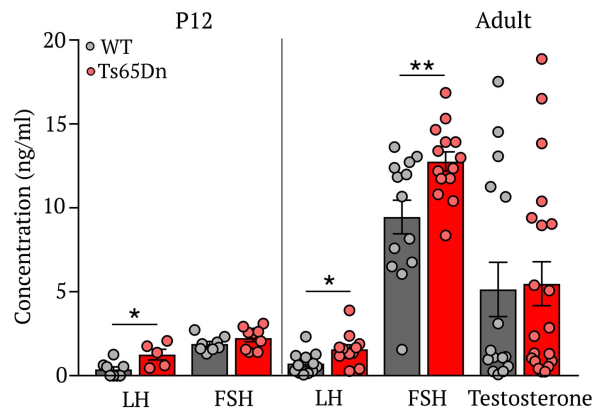
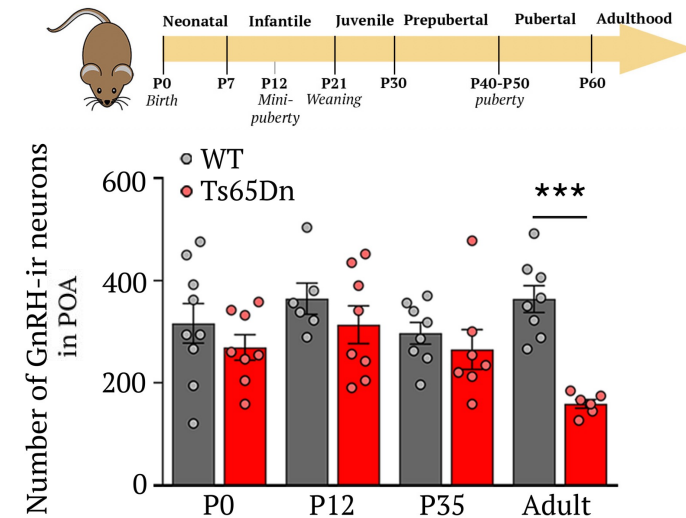
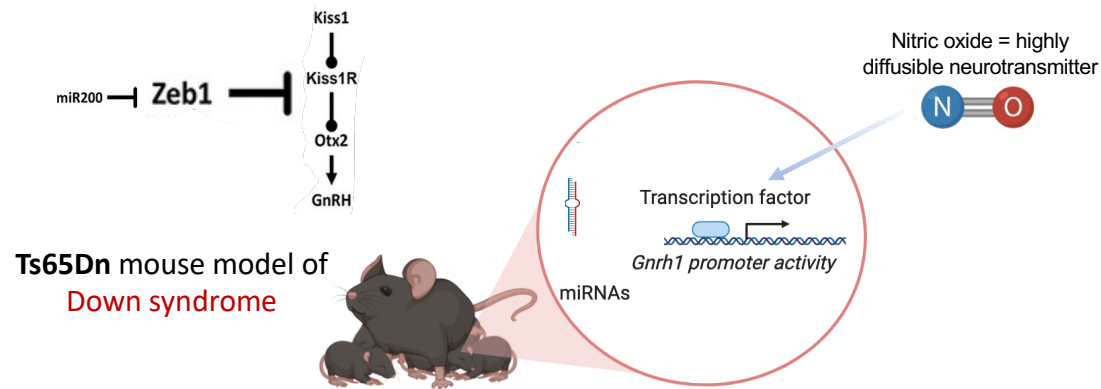
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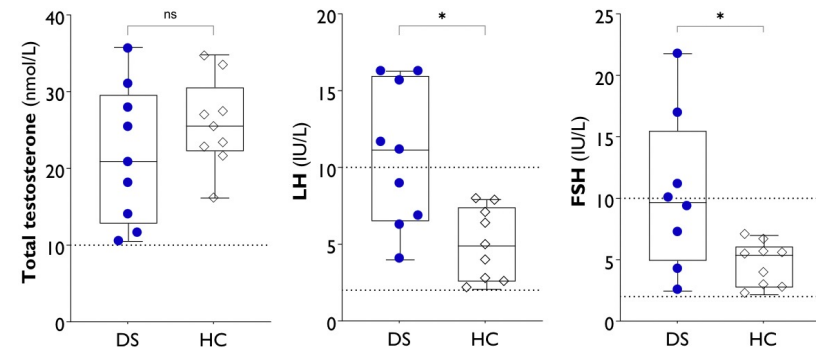
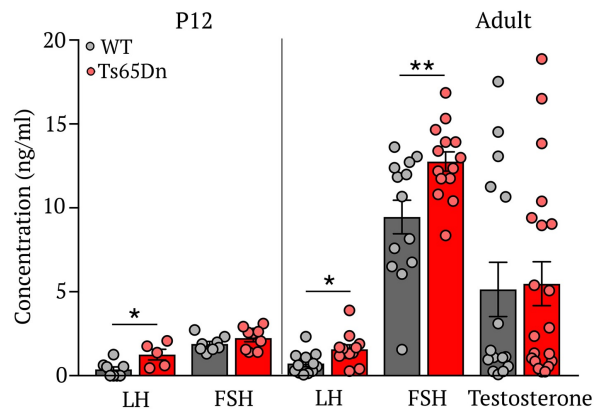
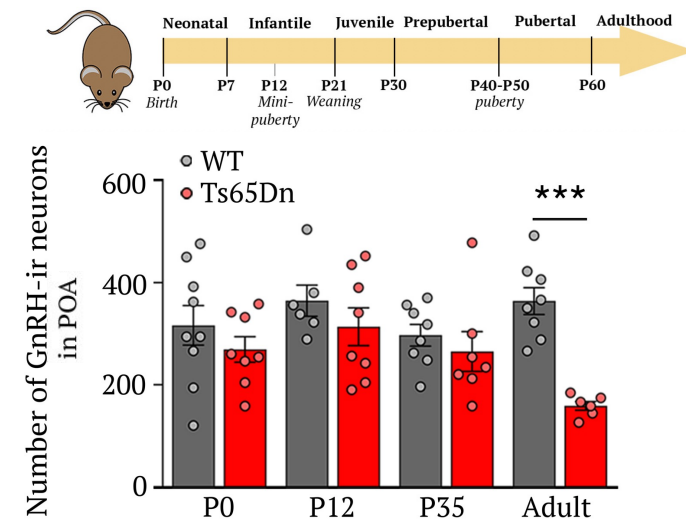
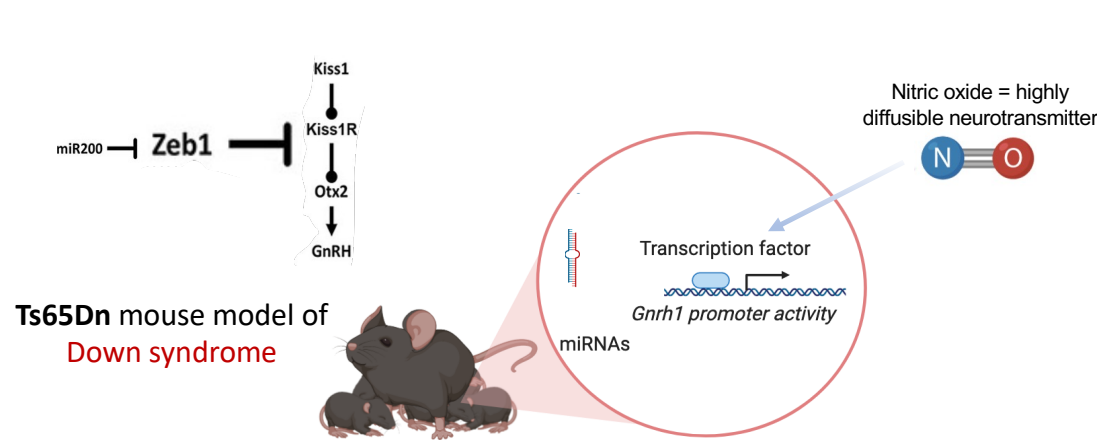
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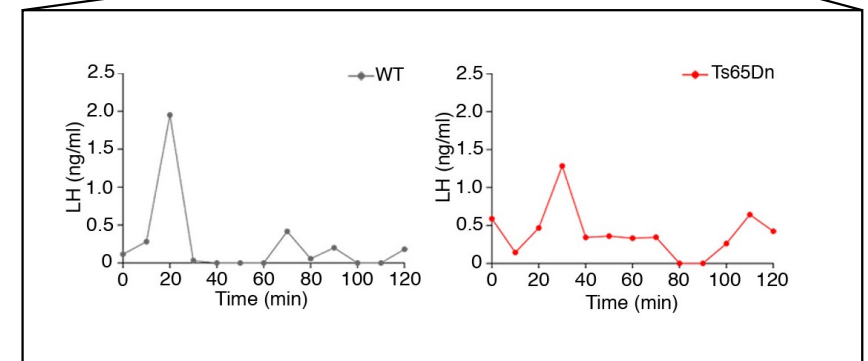
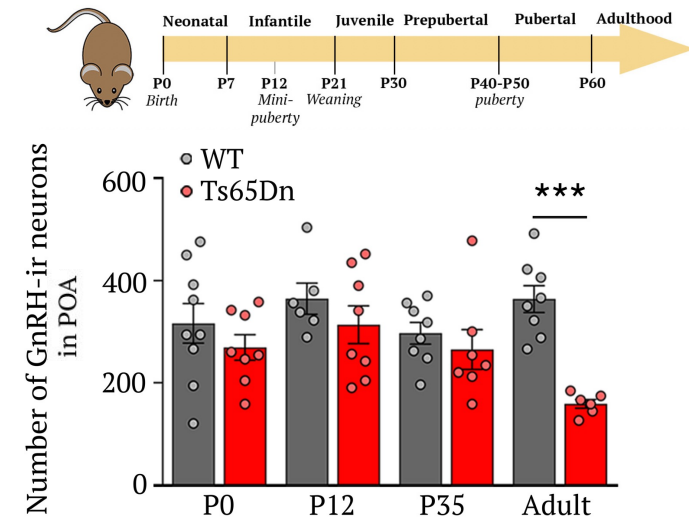
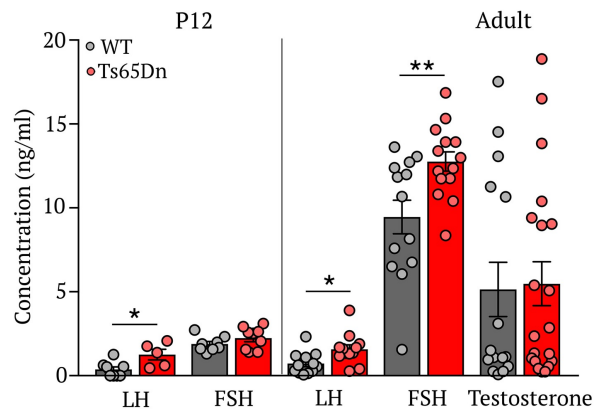
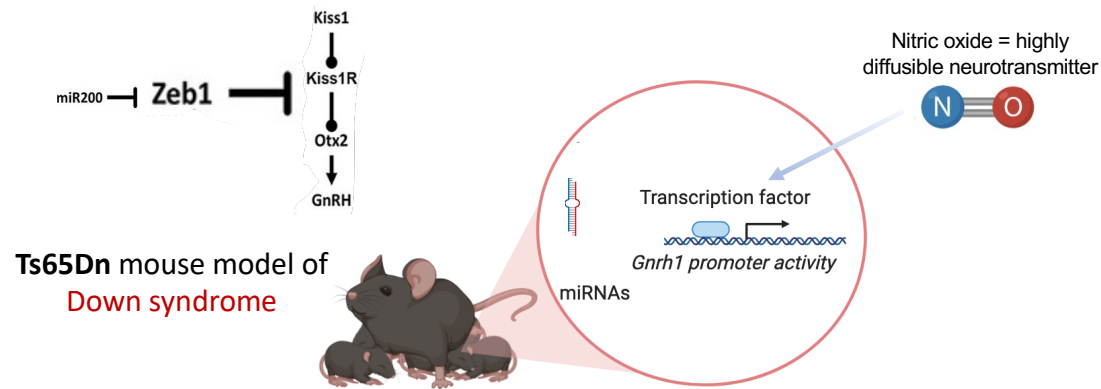
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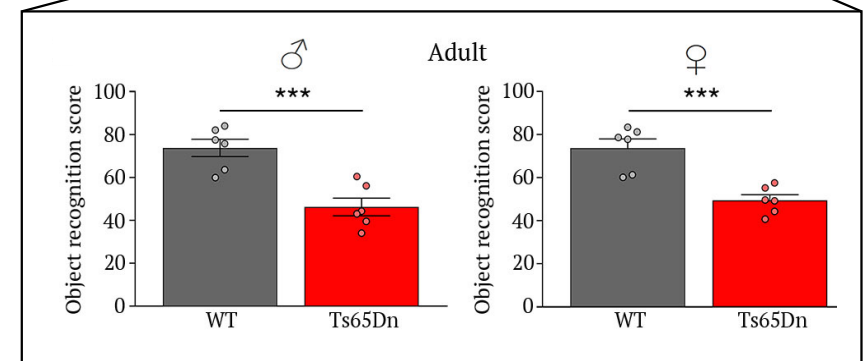
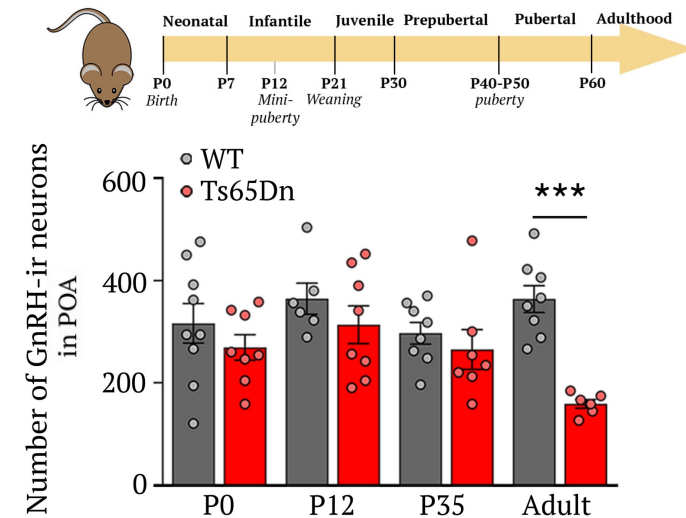
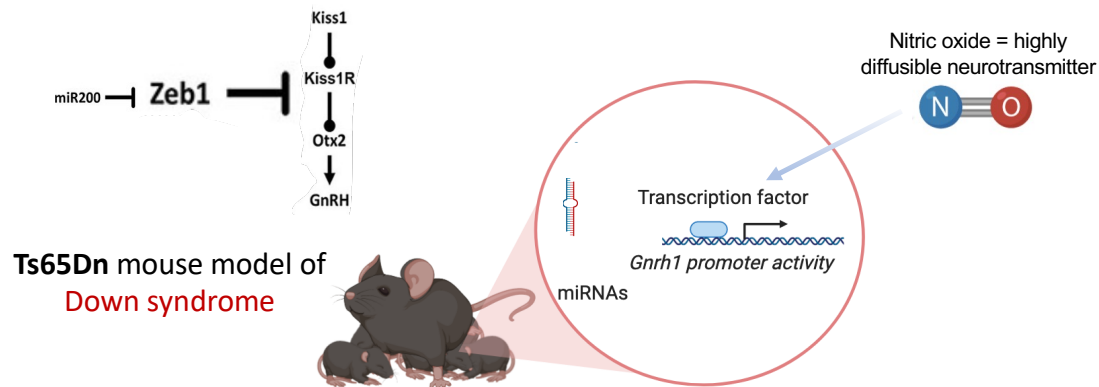
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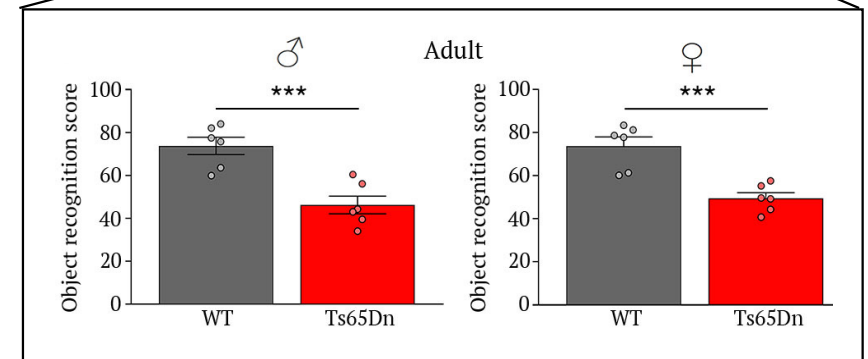
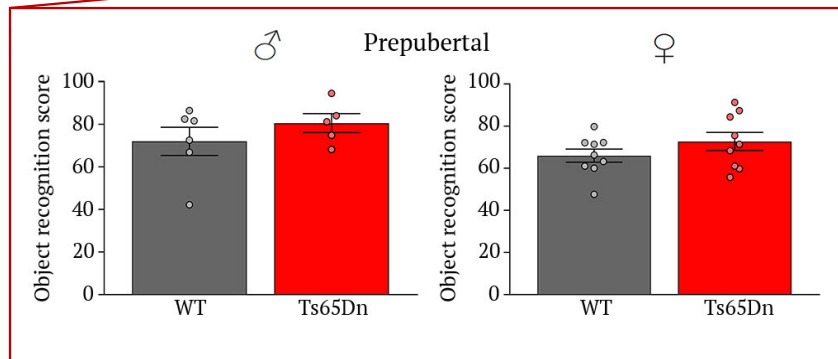
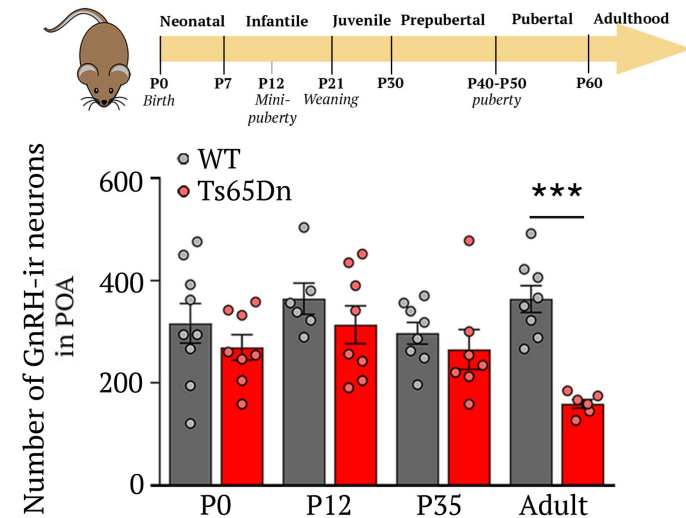
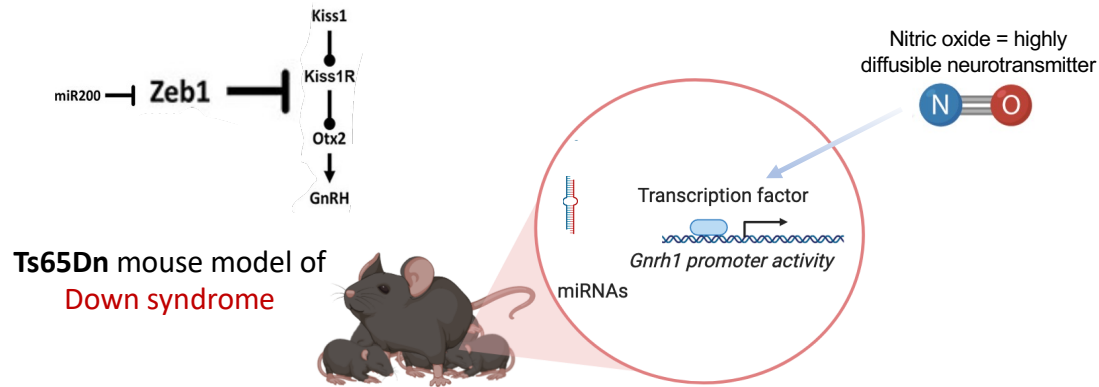
Chromosomal-generated miRNA imbalance at minipuberty **alters GnRH pulsatile release**



Ts65Dn mice exhibit age-related cognitive decline alongside GnRH alteration

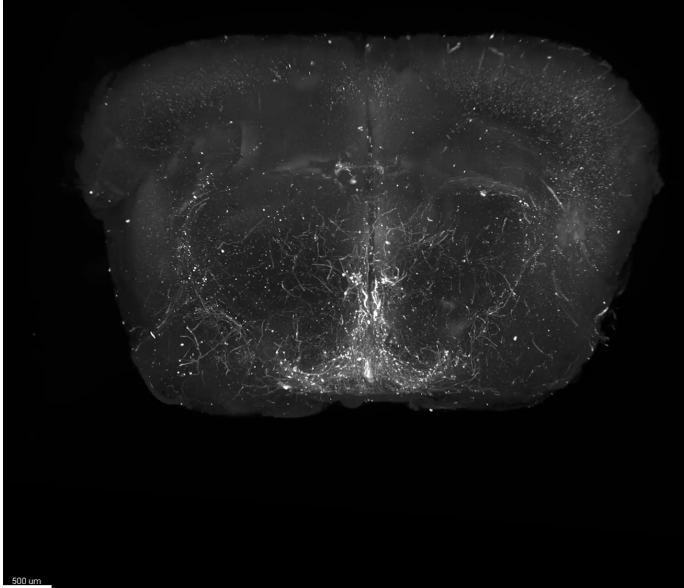


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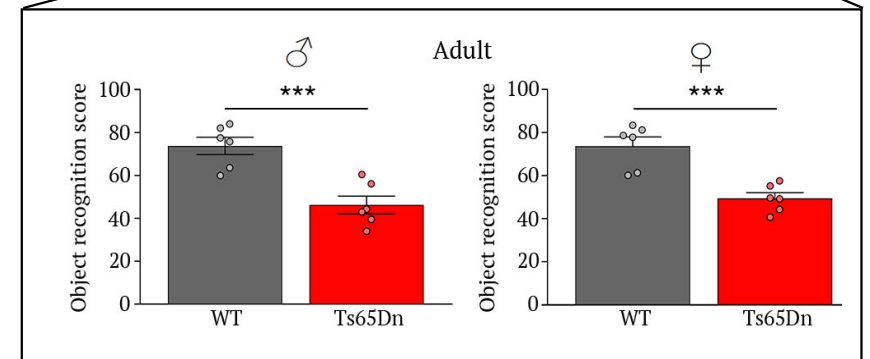
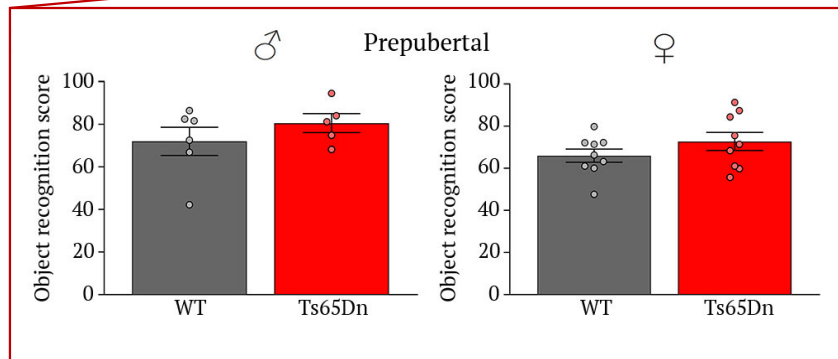
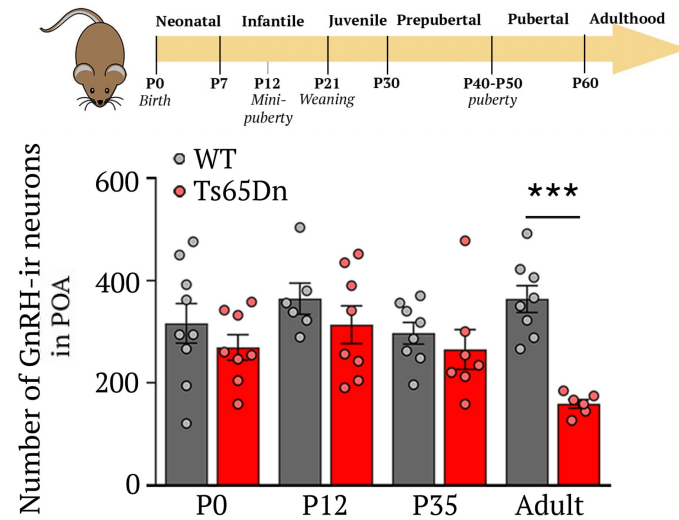


Is there a possibility of a **causal link**?

GnRH neuronal projections

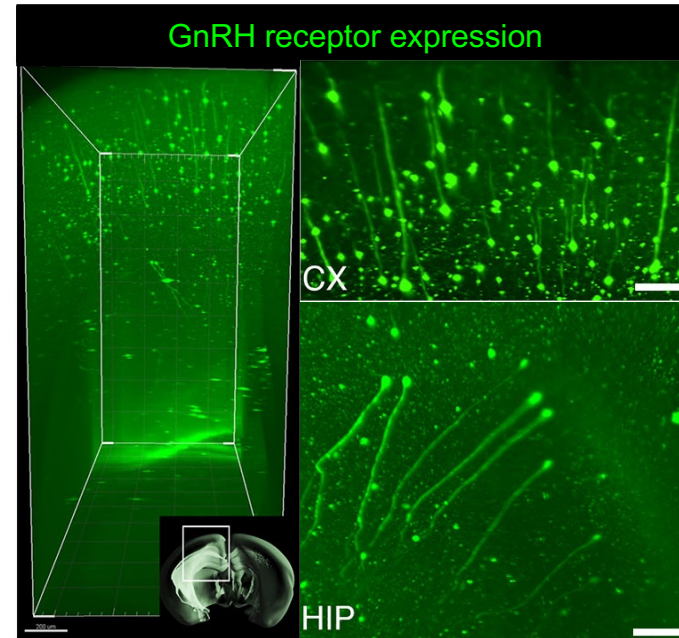
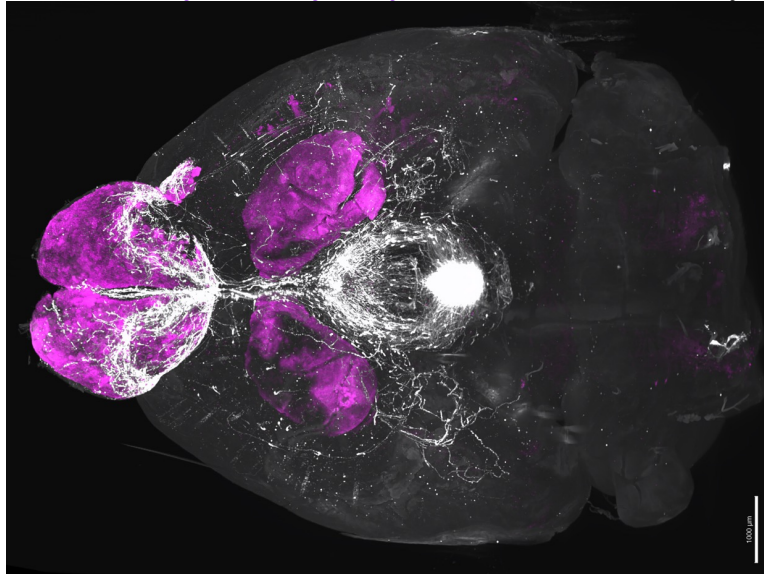


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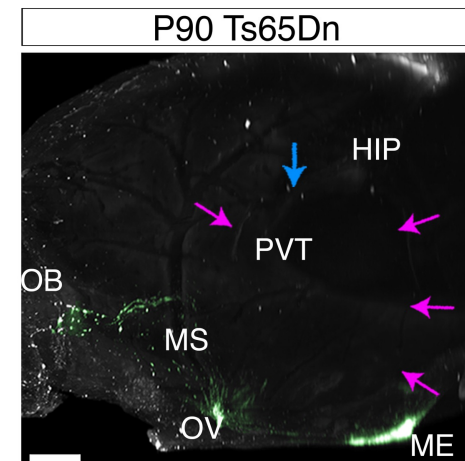
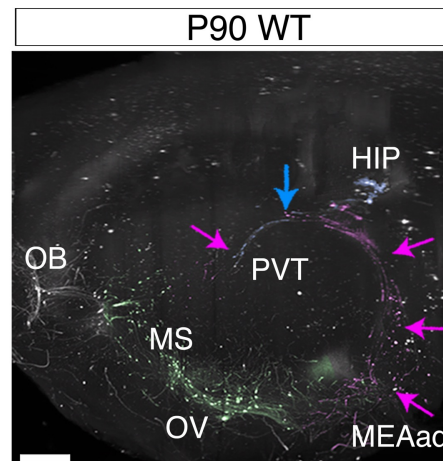
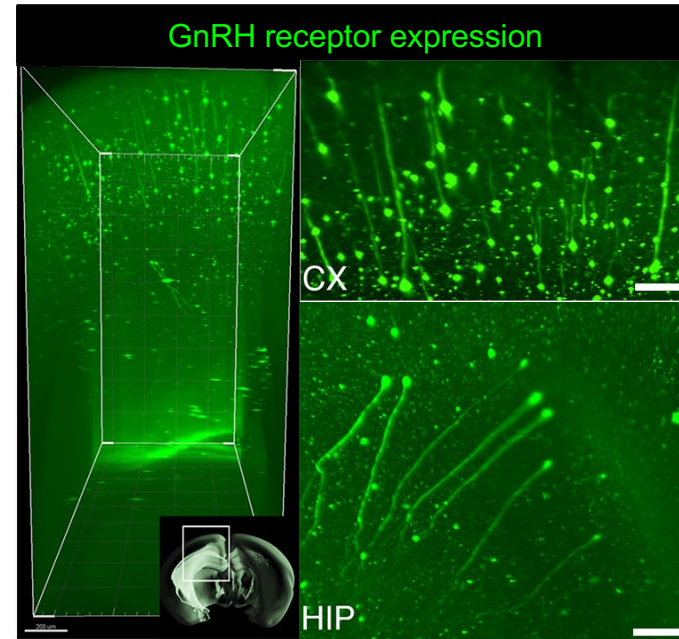
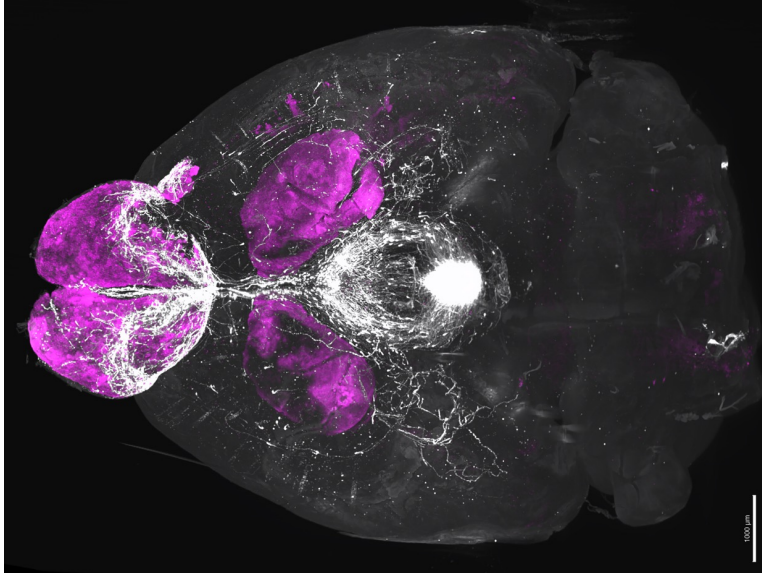
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GnRH and **tyrosine hydroxylase** immununoreactivity



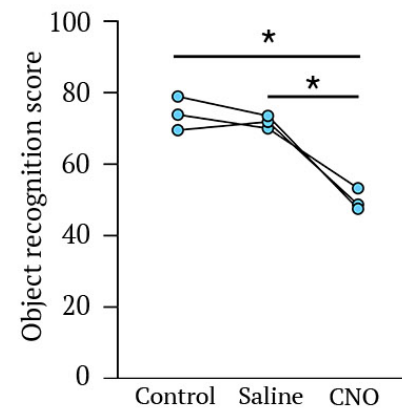
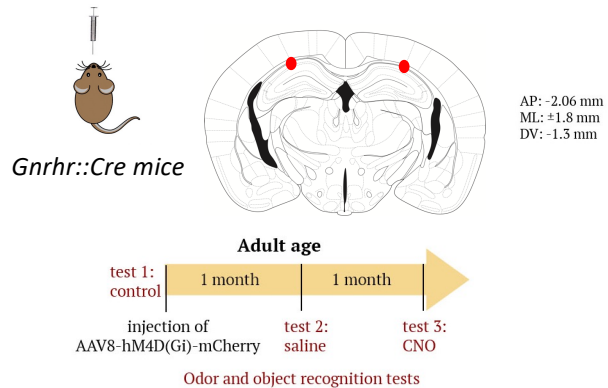
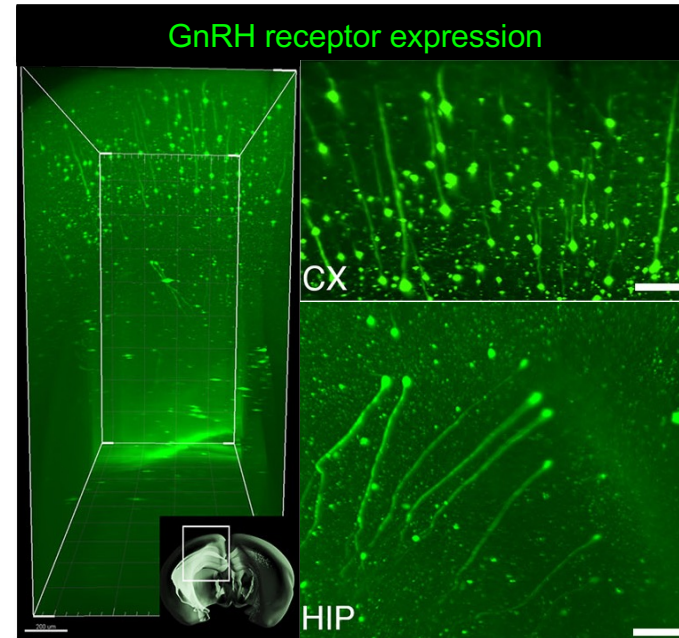
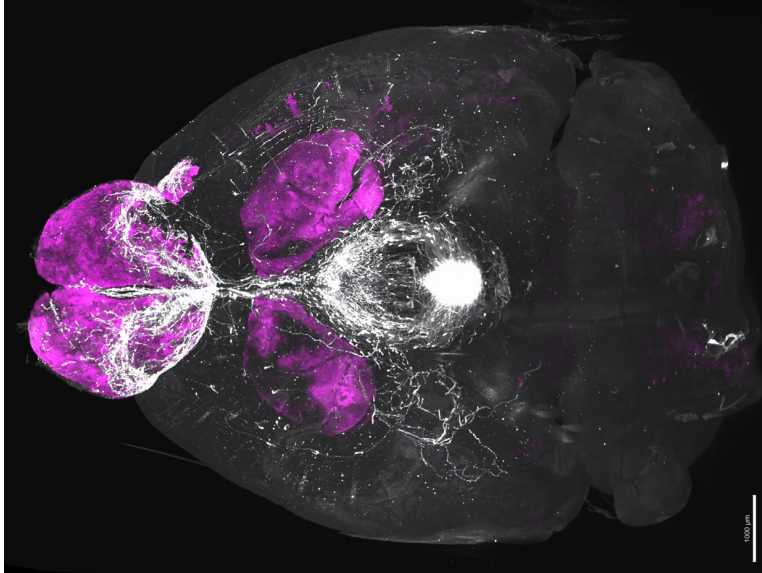
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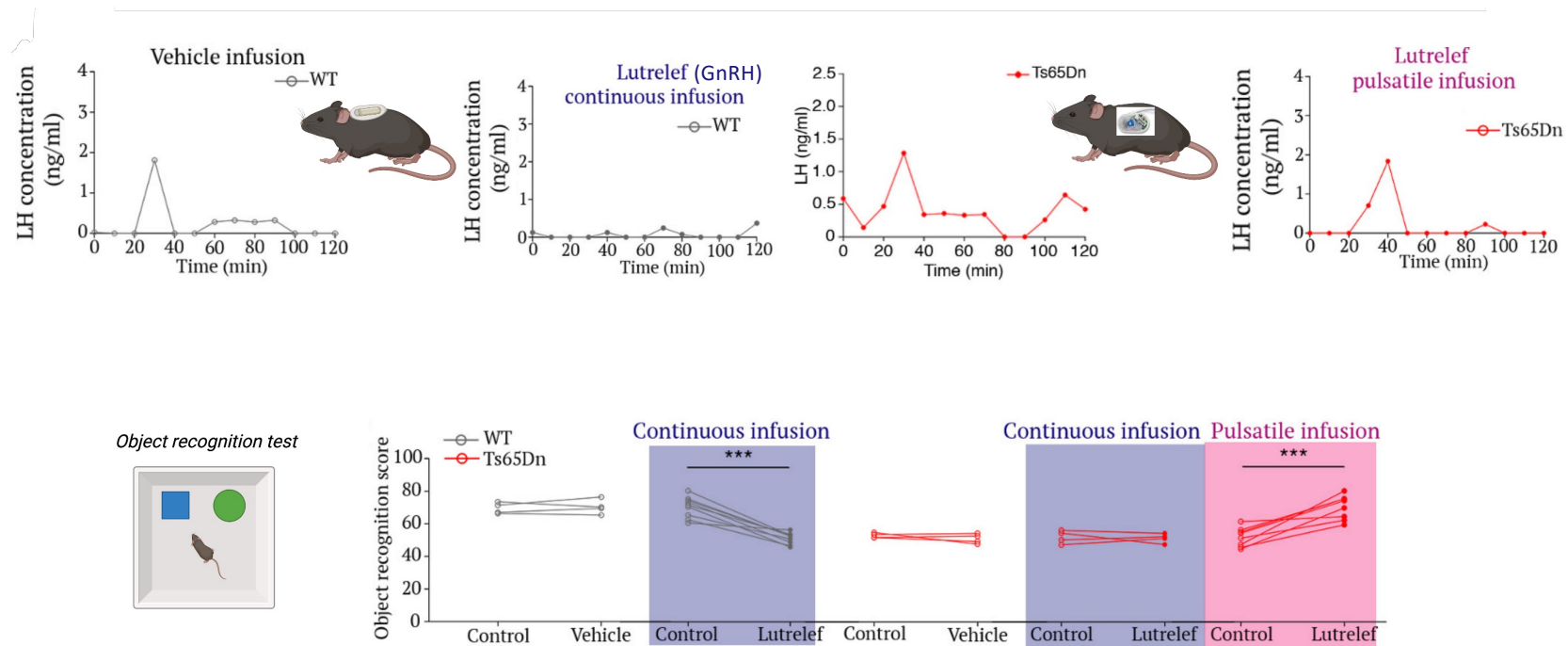


Is there a possibility of a **causal link**?

GnRH and **tyrosine hydroxylase** immununoreactivity



Restoring physiological patterns of **pulsatile GnRH release** improves cognition in Ts65Dn mice



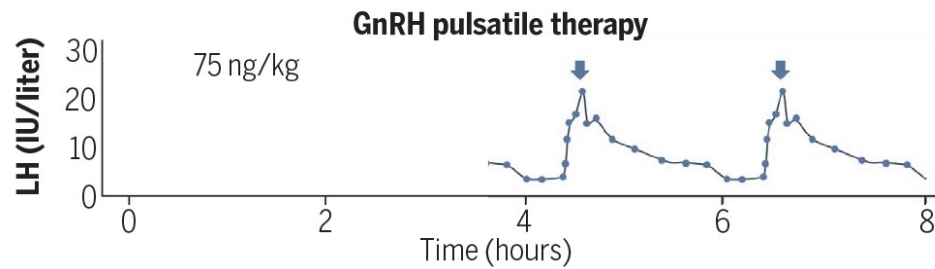
Pulsatile GnRH therapy improves cognitive functions deficits in DS men



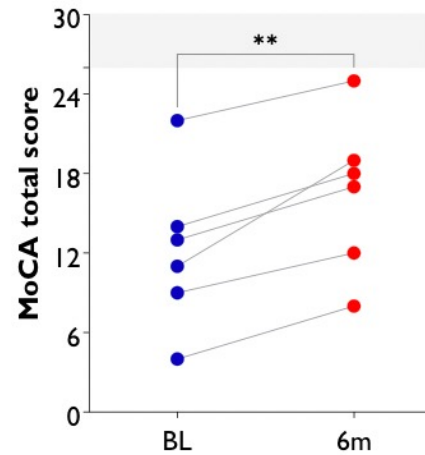
GnRH (Lutrelef)

Safe and well tolerated treatment

1 pulse (75ng/kg of GnRH)/ 2h



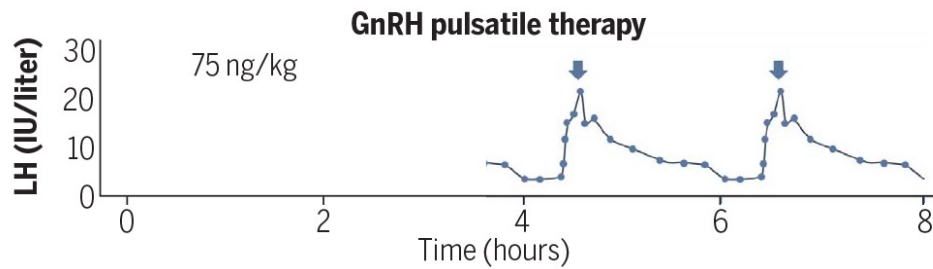
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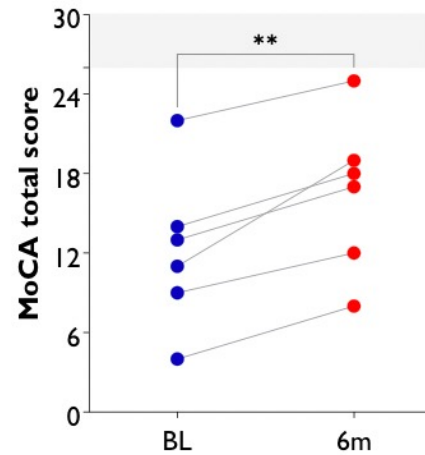
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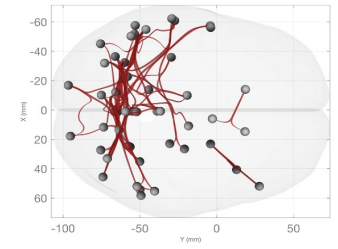
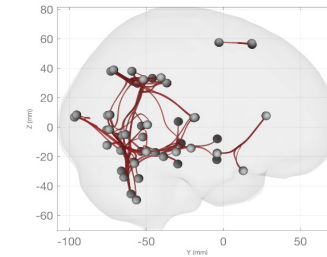
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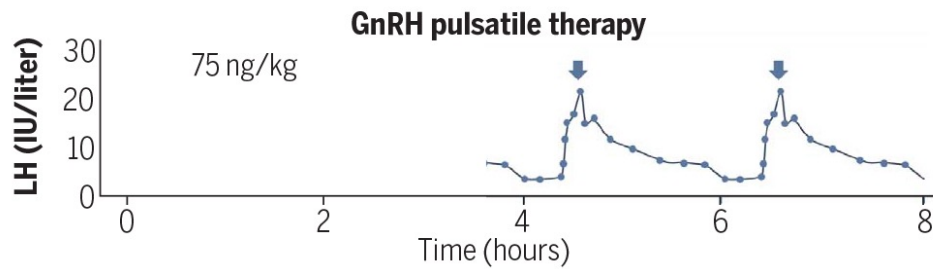
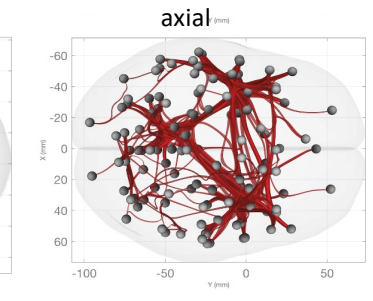
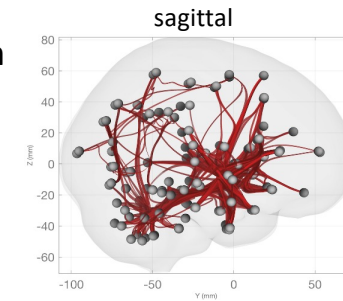
1 pulse (75ng/kg of GnRH)/ 2h



BL



6m



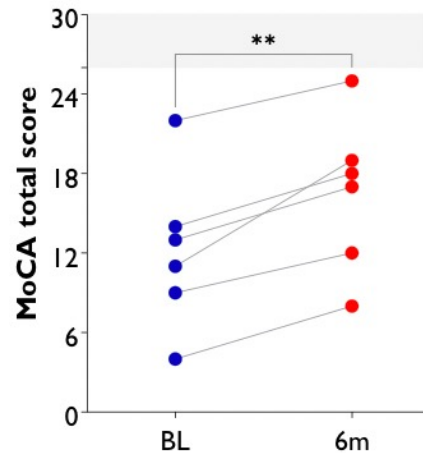
Pulsatile GnRH therapy improves cognitive functions deficits in DS men



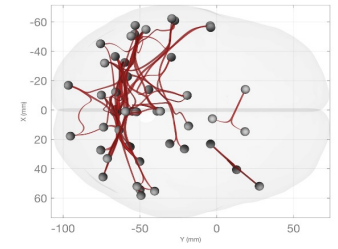
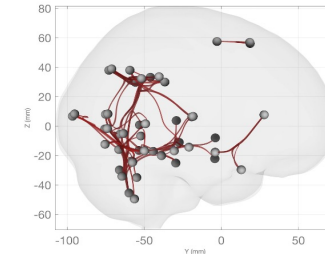
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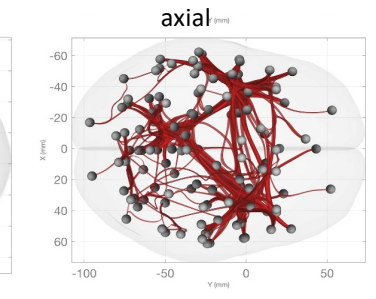
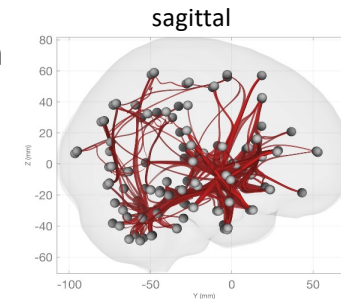
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BL



6m



RESEARCH

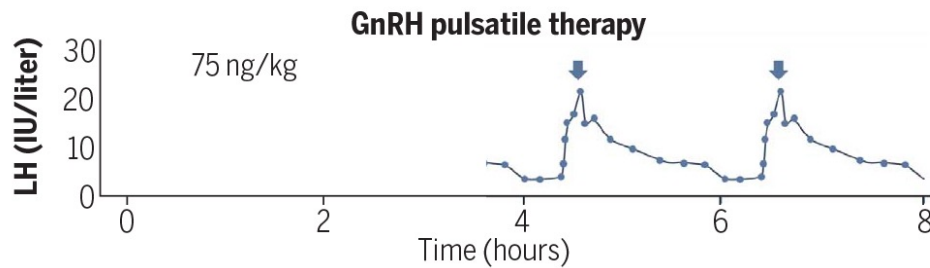
RESEARCH ARTICLE

NEURODEVELOPMENT

GnRH replacement rescues cognition in Down syndrome

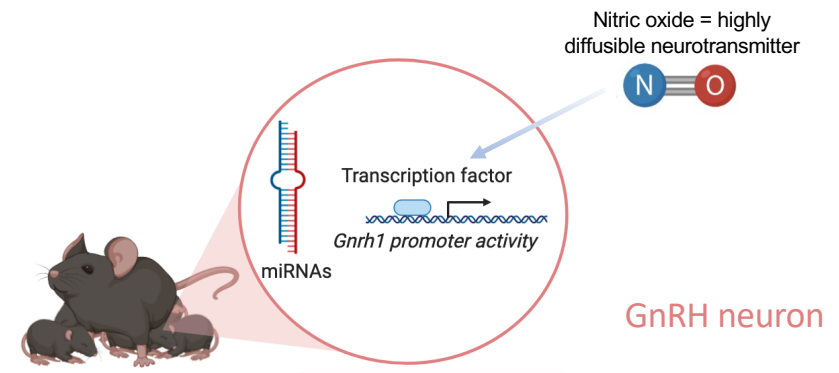
Maria Manfredi-Lozano^{1,2,†}, Valerie Leysen^{1,2,†}, Michela Adamo^{3,4,†}, Isabel Paiva⁵, Renaud Rovera⁶, Jean-Michel Pignat⁷, Fatima Ezzahra Timzoura^{1,2}, Michael Candlish^{8,†}, Sabiha Eddarkaoui¹, Samuel A. Malone^{1,2}, Mauro S. B. Silva^{1,2,§}, Sara Trova^{1,2,¶}, Monica Imbernon^{1,2}, Laurine Decoster^{1,2}, Ludovica Cotellessa^{1,2}, Manuel Tena-Sempere⁹, Marc Claret^{10,11}, Ariane Paoloni-Giacobino¹², Damien Plassard¹³, Emmanuelle Paccou³, Nathalie Vionnet³, James Acierno³, Aleksandra Maleska Maceski¹⁴, Antoine Lutti¹⁵, Frank Pfrieger¹⁶, S. Rasika^{1,2}, Federico Santoni⁴, Ulrich Boehm⁸, Philippe Ciofi¹⁷, Luc Buée¹, Nasser Haddjeri⁶, Anne-Laurence Boutillier⁵, Jens Kuhle¹⁴, Andrea Messina^{3,4}, Bogdan Draganski^{15,18}, Paolo Giacobini^{1,2,‡}, Nelly Pitteloud^{3,4,*}, Vincent Prevot^{1,2,*}

Manfredi-Lozano et al., *Science* **377**, eabq4515 (2022) 2 September 2022



What could be the consequence of **exacerbated minipuberty**?

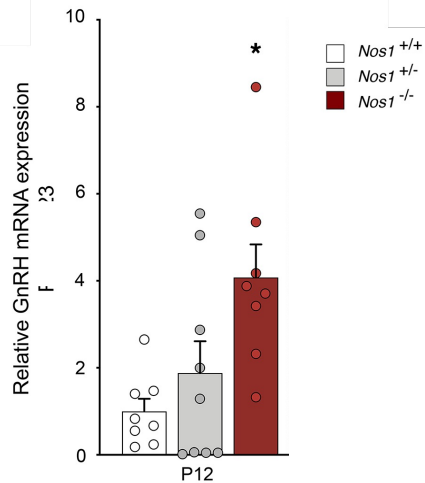
The *Gnrh* promoter repressor Cebpb is activated nitric oxide (NO)



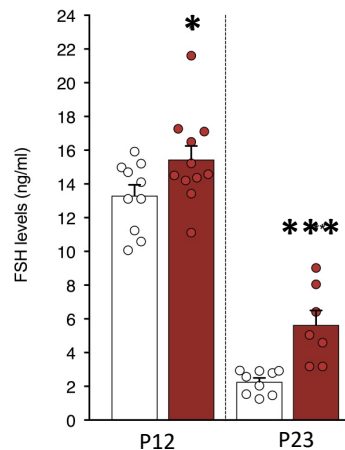
Nitric oxide (NO) is produced by the enzyme coded by *Nos1* gene



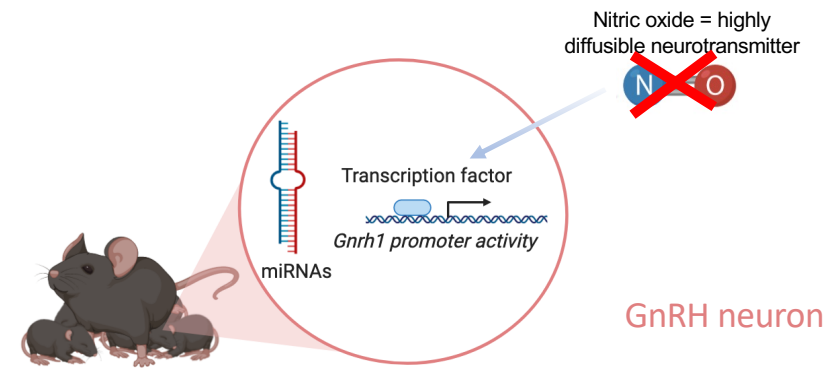
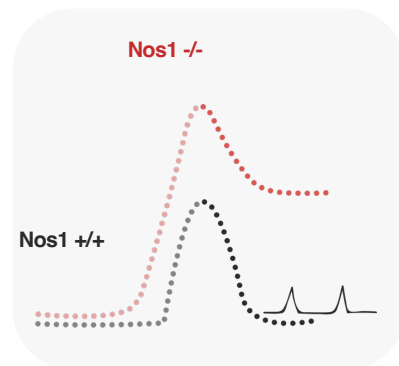
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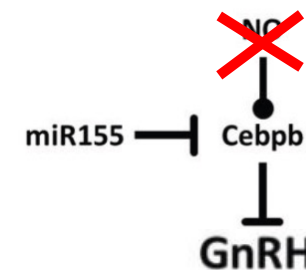
Minipubertal *Gnrh* mRNA levels are increased



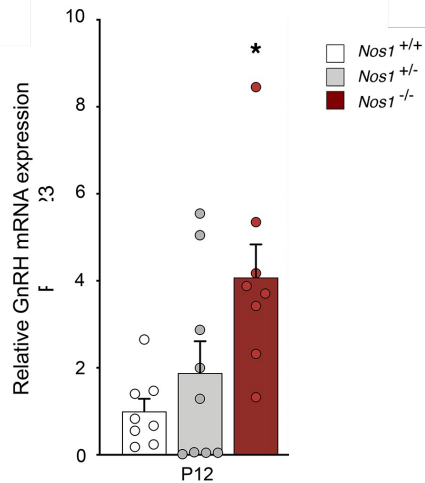
Minipuberty is exacerbated



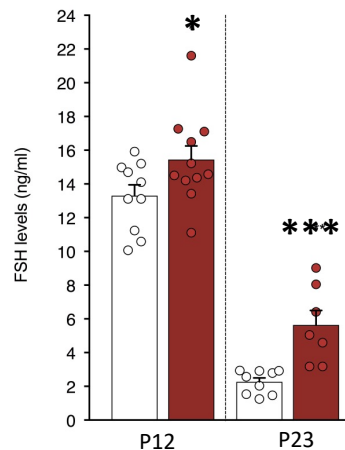
Nitric oxide (NO) is produced by the enzyme coded by ~~*Nos1*~~ gene



What could be the consequence of exacerbated minipuberty?



Minipubertal *Gnrh* mRNA levels are increased



Minipuberty is exacerbated

Reminiscent of the phenotype of babies born prematurely...

Increased Activity of the Hypothalamic-Pituitary-Testicular Axis in Infancy Results in Increased Androgen Action in Premature Boys

Tanja Kuiri-Hänninen, Raija Seuri, Erja Tyrväinen, Ursula Turpeinen, Esa Hämäläinen, Ulf-Håkan Stenman, Leo Dunkel,* and Ulla Sankilampi*

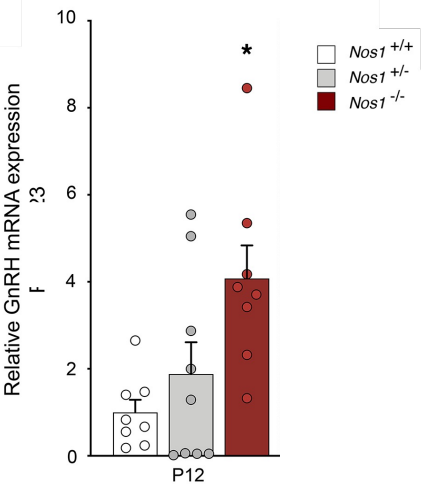
J Clin Endocrinol Metab, January 2011, 96(1):98–105

Postnatal Developmental Changes in the Pituitary-Ovarian Axis in Preterm and Term Infant Girls

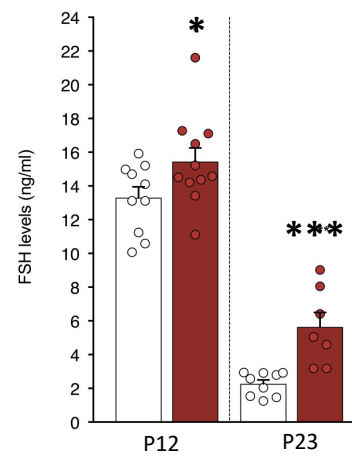
Tanja Kuiri-Hänninen,* Sanna Kallio,* Raija Seuri, Erja Tyrväinen, Annikki Liakka, Juha Tapanainen, Ulla Sankilampi,** and Leo Dunkel**

J Clin Endocrinol Metab, November 2011, 96(11):3432–3439

What could be the consequence of exacerbated minipuberty?



Minipubertal *Gnrh* mRNA levels are increased

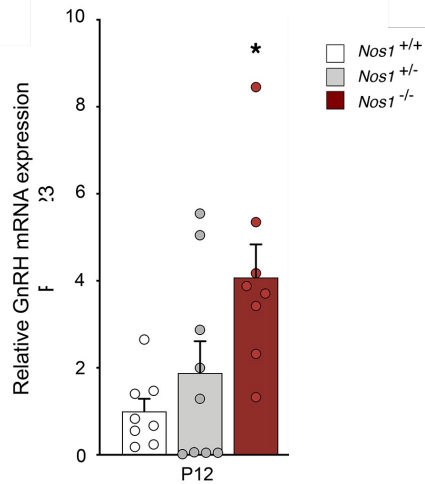


Minipuberty is exacerbated

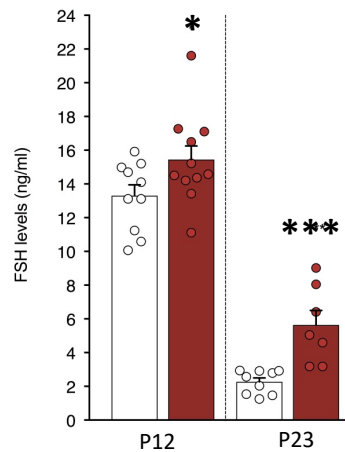
Table 1. Genotype and clinical phenotype of six probands with ultra-rare heterozygous *NOS1* mutations. Nucleotide and protein changes are based on reference cDNA sequence NM_000620.4. MAF, minor-allele frequency in gnomAD exome controls; CHH, congenital hypogonadotropic hypogonadism; nCHH, normosmic CHH; KS, CHH with anosmia (Kallmann syndrome); M, male; F, female. Bold, associated phenotypes present in *Nos1*-deficient mice.

Patient	Sex	<i>NOS1</i> mutations	rs number	MAF (%)	Diagnosis	Inheritance	Associated phenotypes
A II-1	M	c.691G>A [p.Ala ²³¹ Thr]	—	Absent	nCHH	Sporadic	—
B II-1	M	c.779G>A [p.Arg ²⁶⁰ Gln]	rs547371716	0.0019	KS	Familial	Supernumerary tooth
C II-1	M	c.3320C>T [p.Thr ¹¹⁰⁷ Met]	rs201943901	0.0064	KS	Familial	Bilateral cryptorchidism Micropenis Crowded teeth
D II-1	F	c.3370G>A [p.Glu ¹¹²⁴ Lys]	rs372660293	0.0055	KS	Familial	Scoliosis Osteoporosis
E II-1	M	c.3370G>A [p.Glu ¹¹²⁴ Lys]	rs372660293	0.0055	nCHH	Sporadic	Bilateral hearing loss Obesity
F II-1	F	c.3669A>G [p.Ile ¹²²³ Met]	—	Absent	nCHH	Sporadic	Intellectual disability Left hearing loss

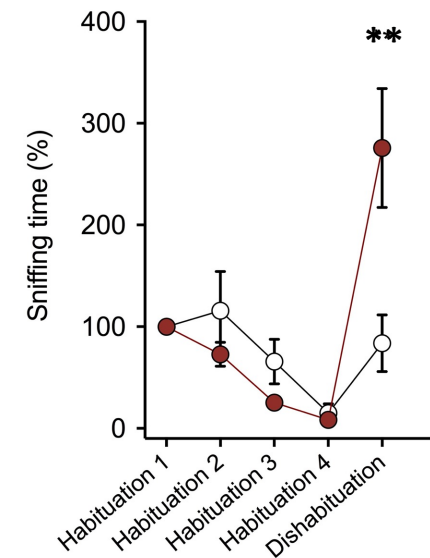
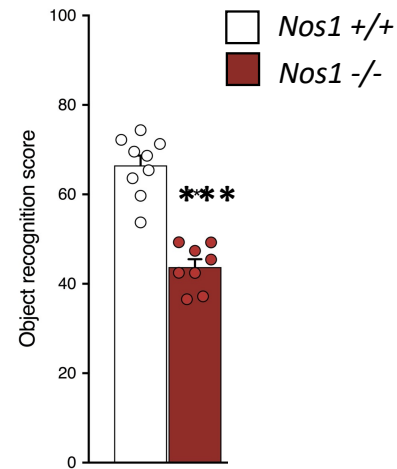
What could be the consequence of exacerbated minipuberty?



Minipubertal *Gnrh* mRNA levels are increased



Minipuberty is exacerbated

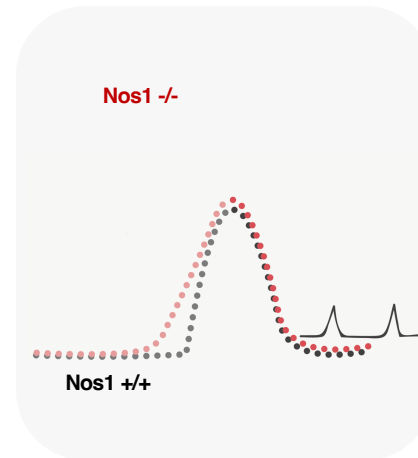
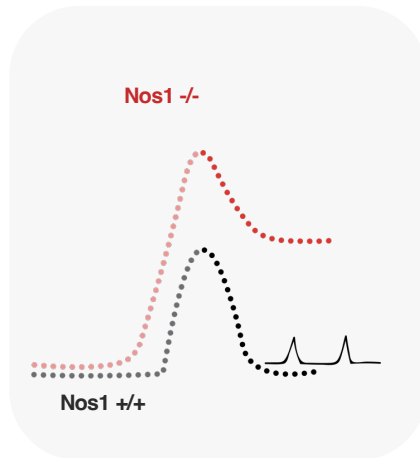


Adult *Nos1* KO show impaired cognition

Can we rescue the phenotype?

NO deficiency

altered minipuberty



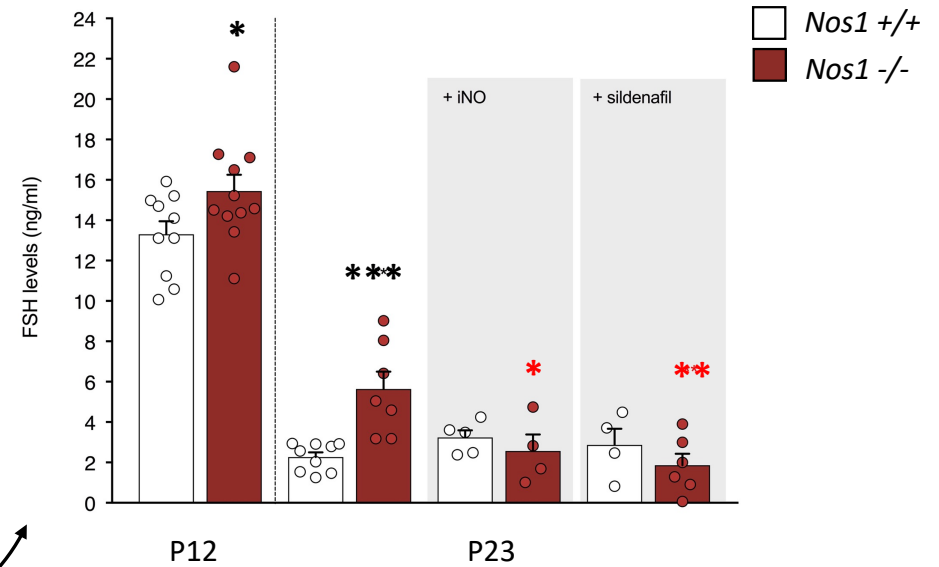
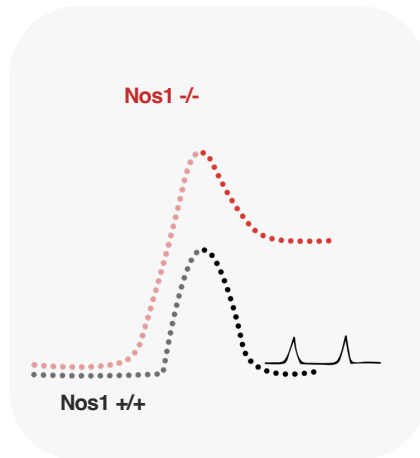
inhaled NO

sildenafil (PDE5 inhibitor)

Can we rescue the phenotype?

NO deficiency + NO replenishment therapy

rescued minipuberty



inhaled NO

sildenafil (PDE5 inhibitor)

Can we rescue the phenotype?

NO deficiency + NO replenishment therapy

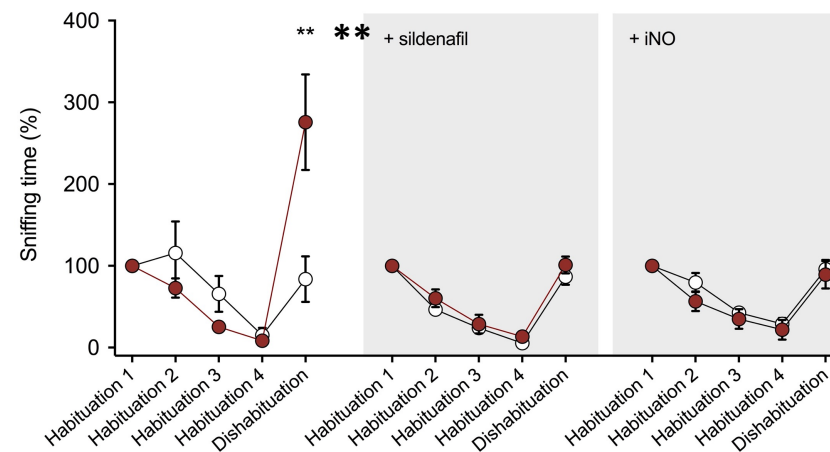
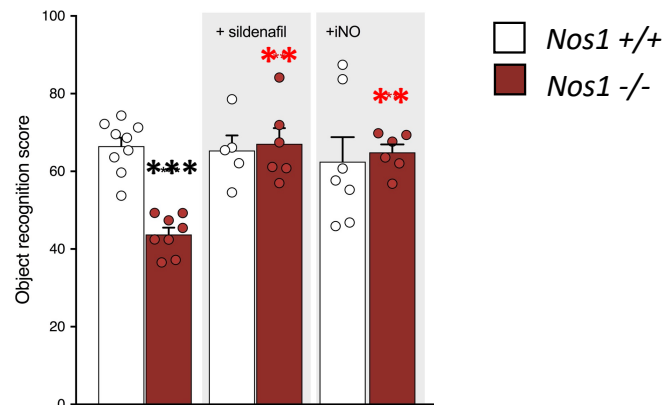
rescued mental comorbidities

HYPOGONADOTROPIC HYPOGONADISM

NOS1 mutations cause hypogonadotropic hypogonadism with sensory and cognitive deficits that can be reversed in infantile mice

Konstantina Chachlaki^{1,2,3,4,5,†}, Andrea Messina^{3,4,†}, Virginia Delli^{1,2,‡}, Valerie Leysen^{1,2,‡}, Csilla Mauranyi⁶, Chieko Huber⁷, Gaëtan Ternier^{1,2}, Katalin Skrapits⁶, Georgios Papadakis^{3,4}, Sonal Shruti^{1,2,§}, Maria Kapanidou⁸, Xu Cheng^{3,4,¶}, James Acierno^{3,4}, Jesse Rademaker^{3,4}, Sowmyalakshmi Rasika^{1,2}, Richard Quinton⁹, Marek Niedziela¹⁰, Dagmar L'Allemand¹¹, Duarte Pignatelli¹², Mirjam Dirlewander¹³, Mariarosaria Lang-Muritano¹⁴, Patrick Kempf¹⁵, Sophie Catteau-Jonard^{1,2,16}, Nicolas J. Niederländer^{3,4}, Philippe Ciofi¹⁷, Manuel Tena-Sempere^{18,19,20}, John Garthwaite²¹, Laurent Storme^{2,22}, Paul Avan²³, Erik Hrabovszky⁶, Alan Carleton⁷, Federico Santoni^{3,4}, Paolo Giacobini^{1,2}, Nelly Pitteloud^{3,4,*}, Vincent Prevot^{1,2,*}

Chachlaki et al., *Sci. Transl. Med.* **14**, eabh2369 (2022) 5 October 2022



No 847941

Horizon2020
European Union Funding
for Research & Innovation

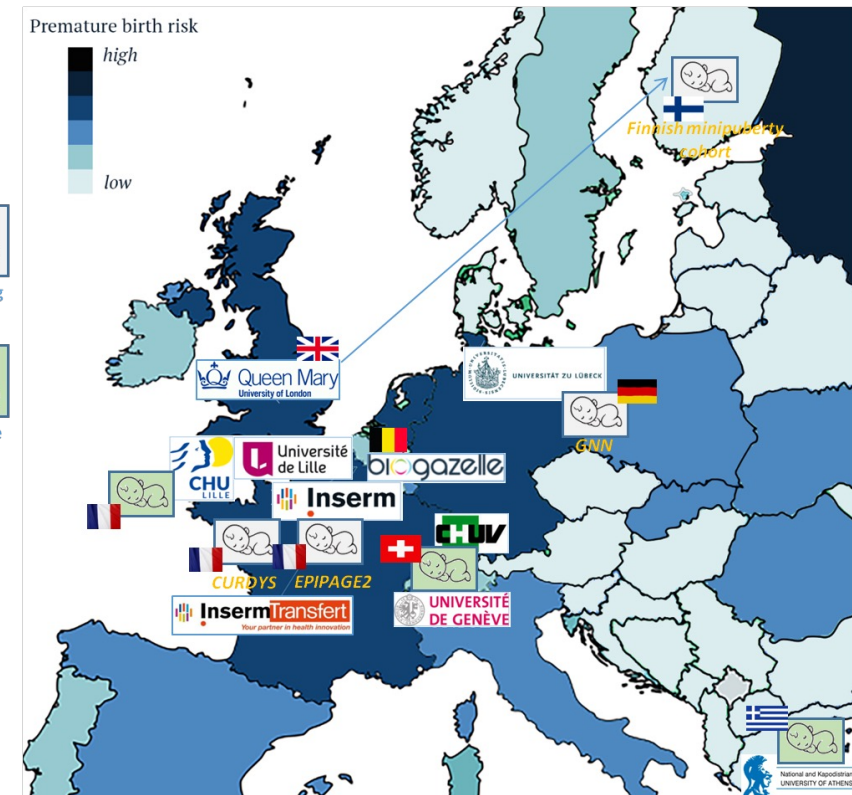
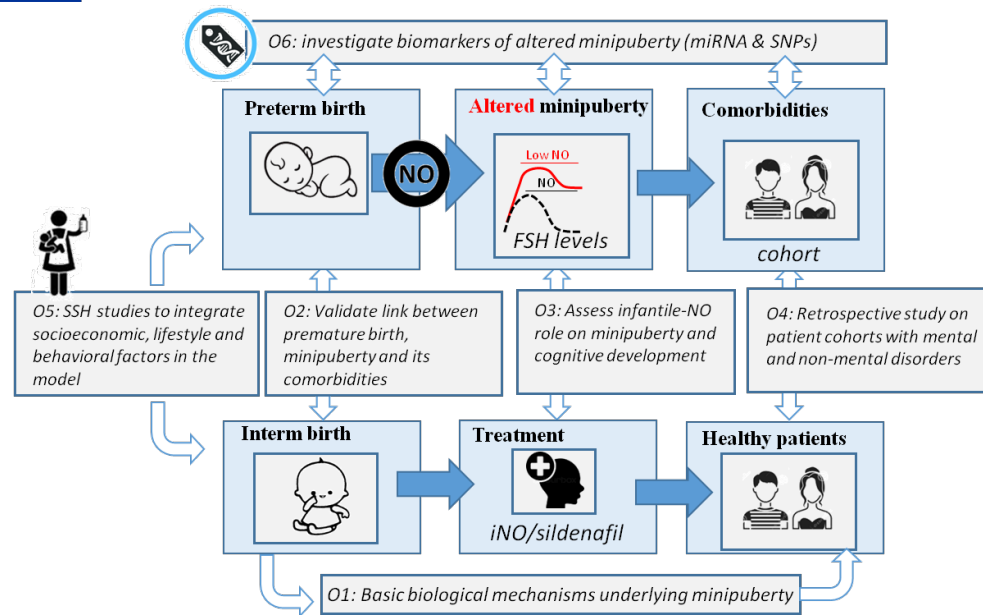
Could NO replenishment therapy improve mental and non-mental comorbidities in **premature babies**?



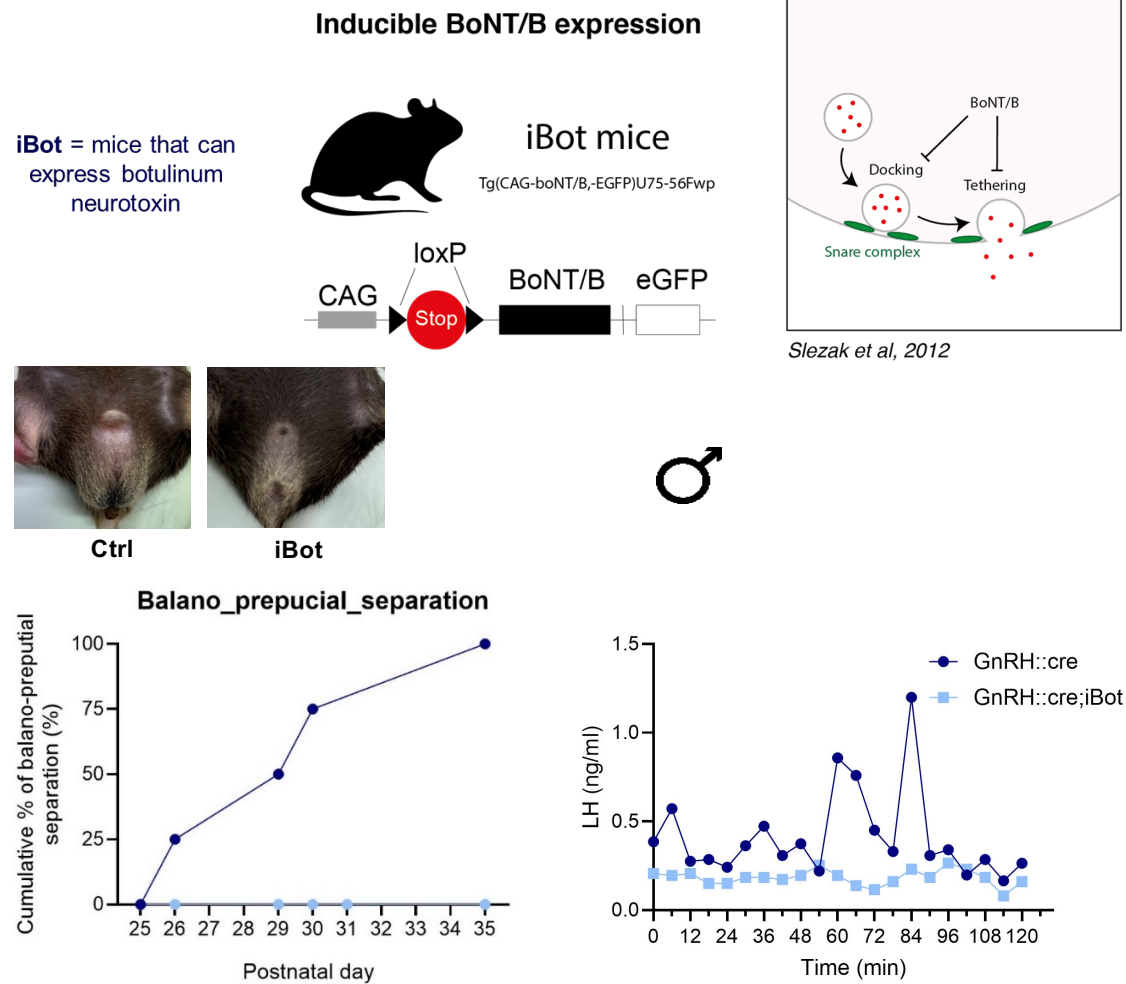
No 847941



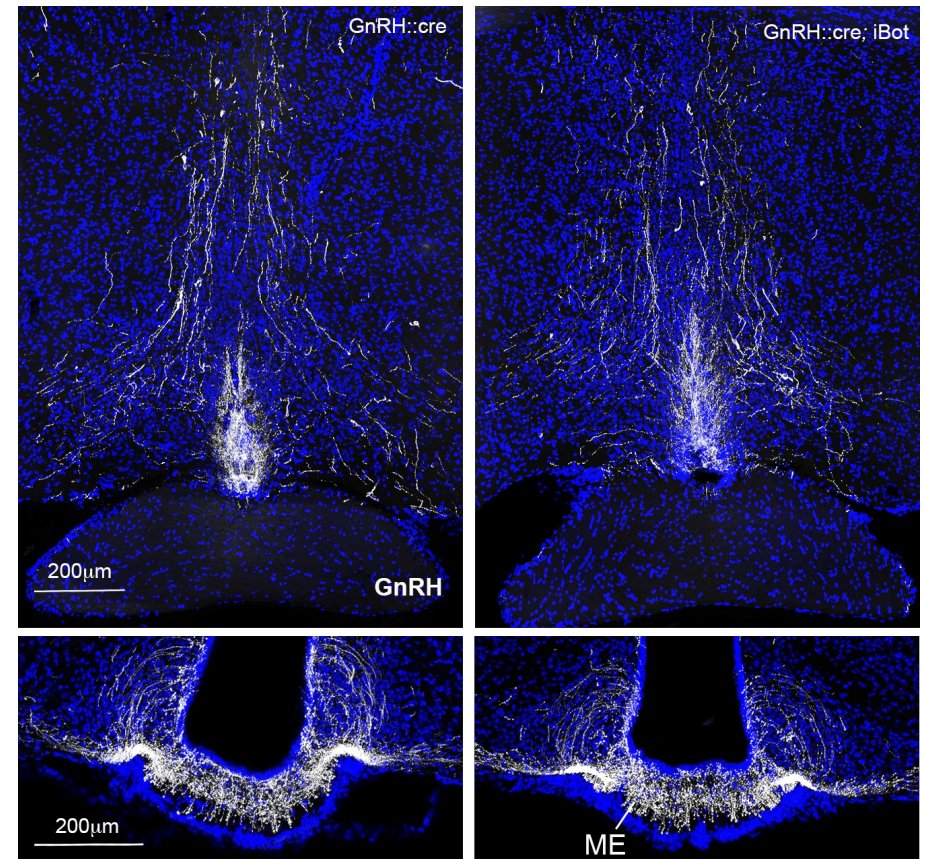
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Impairing the exocytotic activity of GnRH neurons results in **hypogonadotropic hypogonadism**



Sicardi, Vanacker, Duquenne et al., unpublished



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Valerie Leysen
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Konstantina Chachlaki
Samuel Malone
Mauro Silva
Andrea Messina



Konstantina Chachlaki



Horizon2020
European Union Funding
for Research & Innovation

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BM-1105 GnRH deficiency



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Prof. Waljit Dhillon



Prof. Nelly Pitteloud

