Molecular assessment of the developmental "Gaba switch" in the cerebral cortex of the Fus$^{\Delta NLS/+}$ mouse model of ALS

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Introduction

Like other neurodegenerative diseases (NDD), ALS is a typical late-onset disease. But with reported paediatric and juvenile cases, and the neurodevelopmental roles of several ALS-related genes, some genetic cases of ALS might have a neurodevelopmental origin (Fig. 1).
This is particularly true for FUS, whose mutations are responsible for juvenile cases in humans, perinatal lethality of Fus$^{\Delta NLS/\Delta NLS}$ homozygous mice [1], and brain developmental defects of Fus$^{\Delta NLS/+}$ heterozygous mice. In addition, adult Fus$^{\Delta NLS/+}$ mice present with cortical hyperexcitability and impaired cortical GABAergic synapses [2], reminiscent of an alteration in the developmental "GABA switch" (Fig. 2). This project aims to investigate if molecular alterations already arise at early stages in Fus$^{\Delta NLS/+}$, focusing on the "GABA switch" as a candidate mechanism.

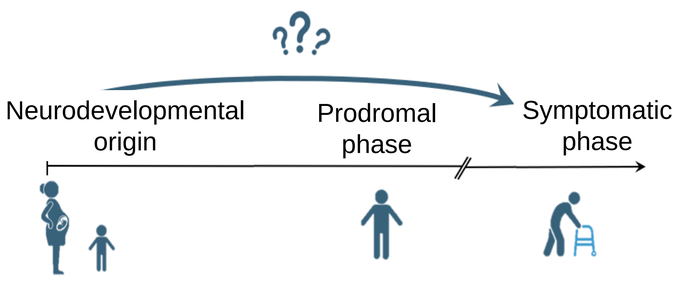


Figure 1. Scheme of the hypothesis of a neurodevelopmental origin of ALS.

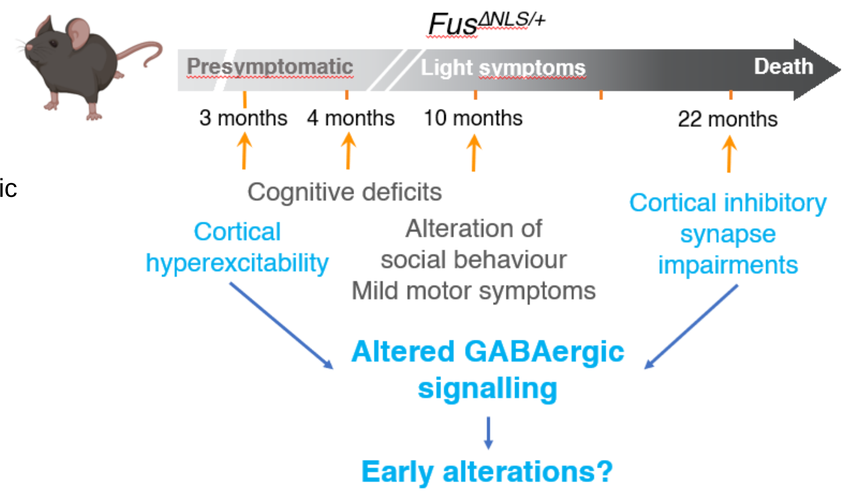


Figure 2. Fus$^{\Delta NLS/+}$ ALS mouse model

The GABA switch

During development, GABA's action shifts from depolarizing in immature neurons to hyperpolarizing in mature ones. This results from a postnatal decrease in intracellular chloride, mediated by two transporters: NKCC1 (importer, high in immature neurons) and KCC2 (exporter, increasing after birth). The timing of this shift is critical, as delays are linked to neurodevelopmental impairments [3] (Fig. 3).

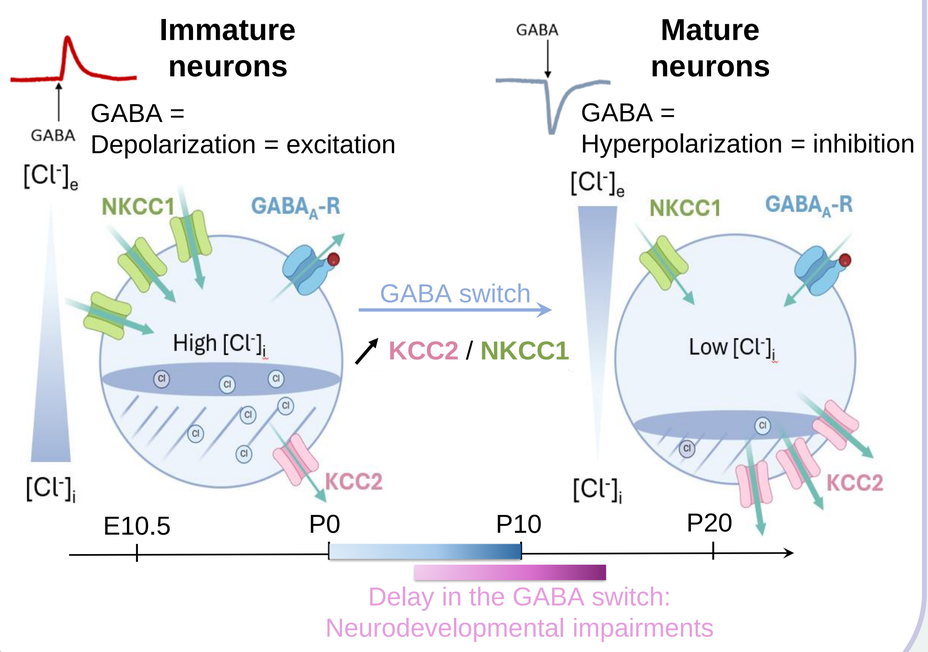
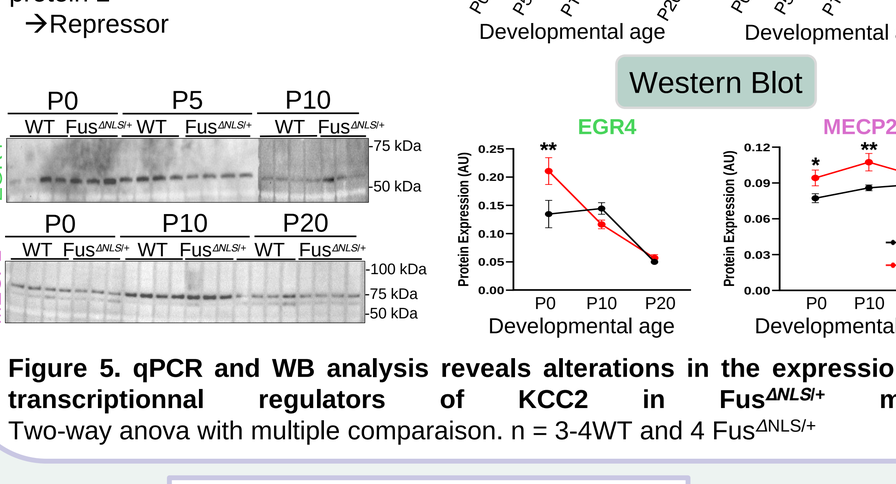


Figure 3. Schematic representation of the « GABA switch »

Materials & Methods



1. NKCC1 and KCC2 expression is altered in the postnatal cortex of Fus$^{\Delta NLS/+}$ mice

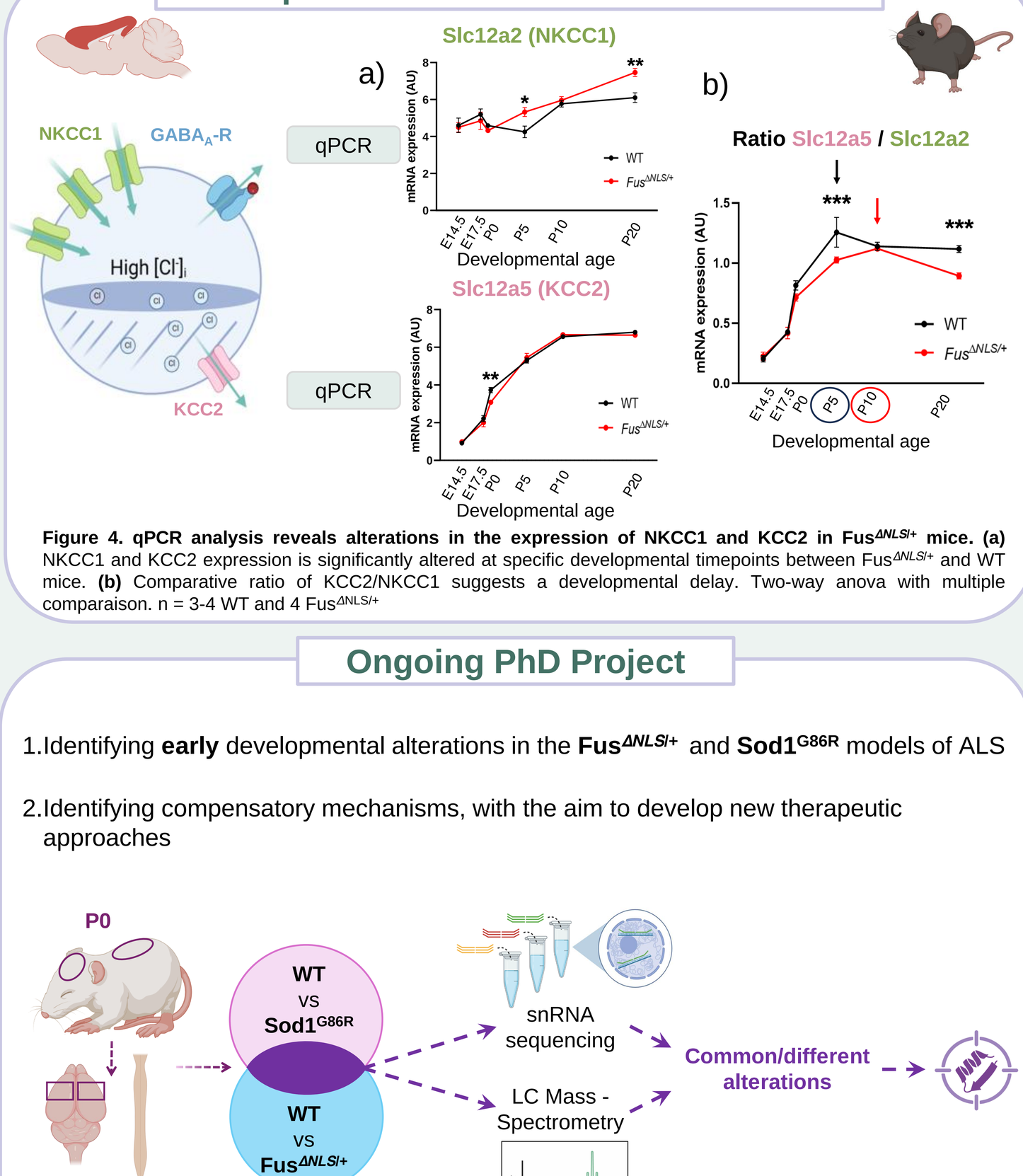


Figure 4. qPCR analysis reveals alterations in the expression of NKCC1 and KCC2 in Fus$^{\Delta NLS/+}$ mice. (a) NKCC1 and KCC2 expression is significantly altered at specific developmental timepoints between Fus$^{\Delta NLS/+}$ and WT mice. **(b)** Comparative ratio of KCC2/NKCC1 suggests a developmental delay. Two-way anova with multiple comparaison. n = 3-4 WT and 4 Fus$^{\Delta NLS/+}$

2. Alterations of transcriptional regulators of KCC2

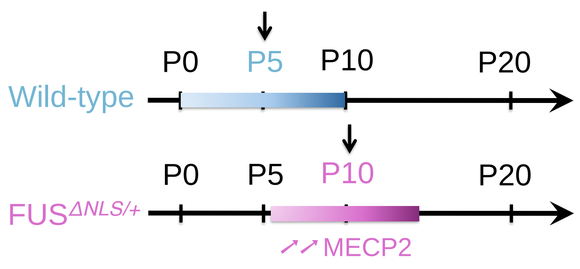
Figure 5. qPCR and WB analysis reveals alterations in the expression of transcriptionnal regulators of KCC2 in Fus$^{\Delta NLS/+}$ mice. Two-way anova with multiple comparaison. n = 3-4WT and 4 Fus$^{\Delta NLS/+}$

Ongoing PhD Project

1.Identifying **early** developmental alterations in the **Fus$^{\Delta NLS/+}$** and **Sod1^{G86R}** models of ALS

2.Identifying compensatory mechanisms, with the aim to develop new therapeutic approaches

Conclusion



The Fus$^{\Delta NLS/+}$ ALS mice model presents early molecular alterations

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Acknowledgements & References

[1] Scekic-Zahirovic et al., EMBO 2016
[2] Scekic-Zahirovic et al., Nat Commun 2021
[3] Schulte et al., Neuroscience & Biobehavioral Reviews 2018