ABNORMAL MYELINATION DURING BRAIN DEVELOPMENT IN FRAGILE X MICE

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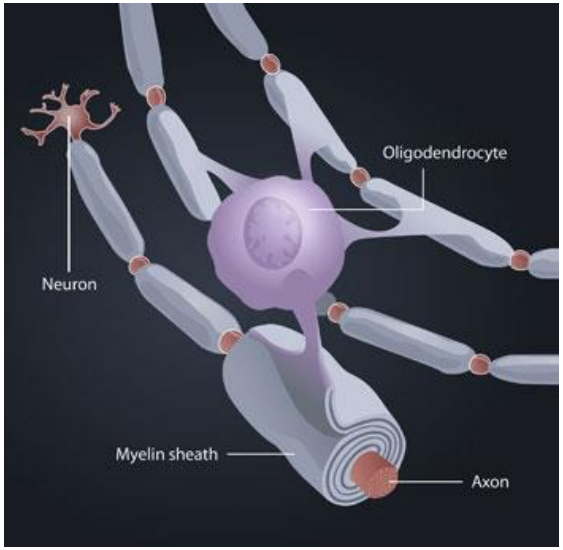
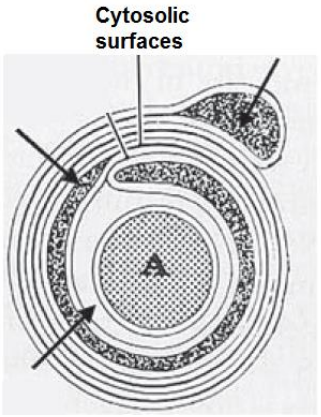
The basics of myelination

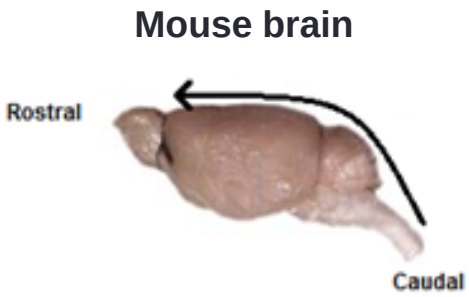
CNS myelination

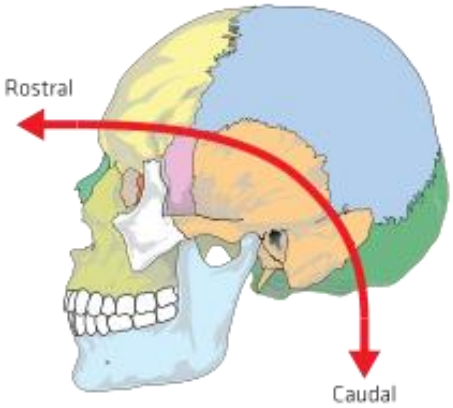
- Conducted by oligodendrocytes
- Mainly postnatal, caudal -> rostral direction
- Axonal electrical conductance (timing and speed)
- **Neuronal development**



- 2 major myelin proteins: MBP, CNPase
  - Myelin basic protein (MBP): structural
  - CNPase: debatable but important role





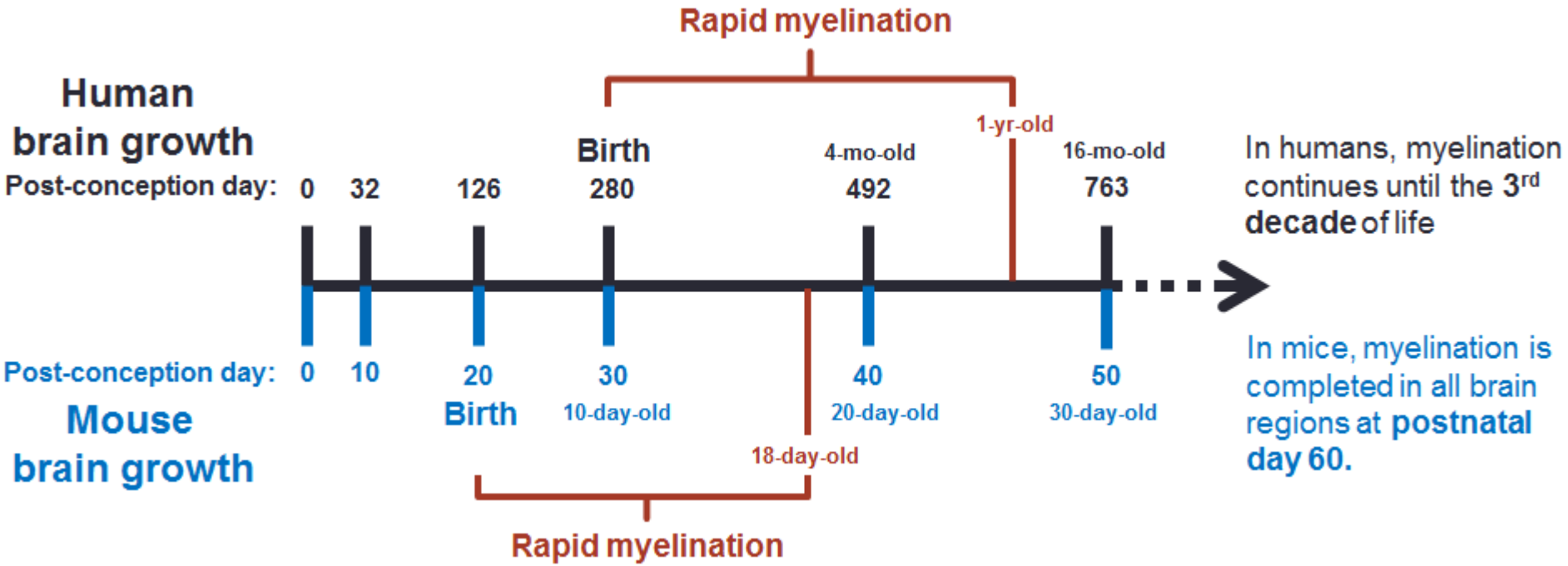


Mouse model of FXS

Fmr1 KO, C57/BL6

- Well characterized model of FXS
- **Cellular** / **molecular** mechanism of myelination

Comparison of **human** vs. **mouse** brain development:

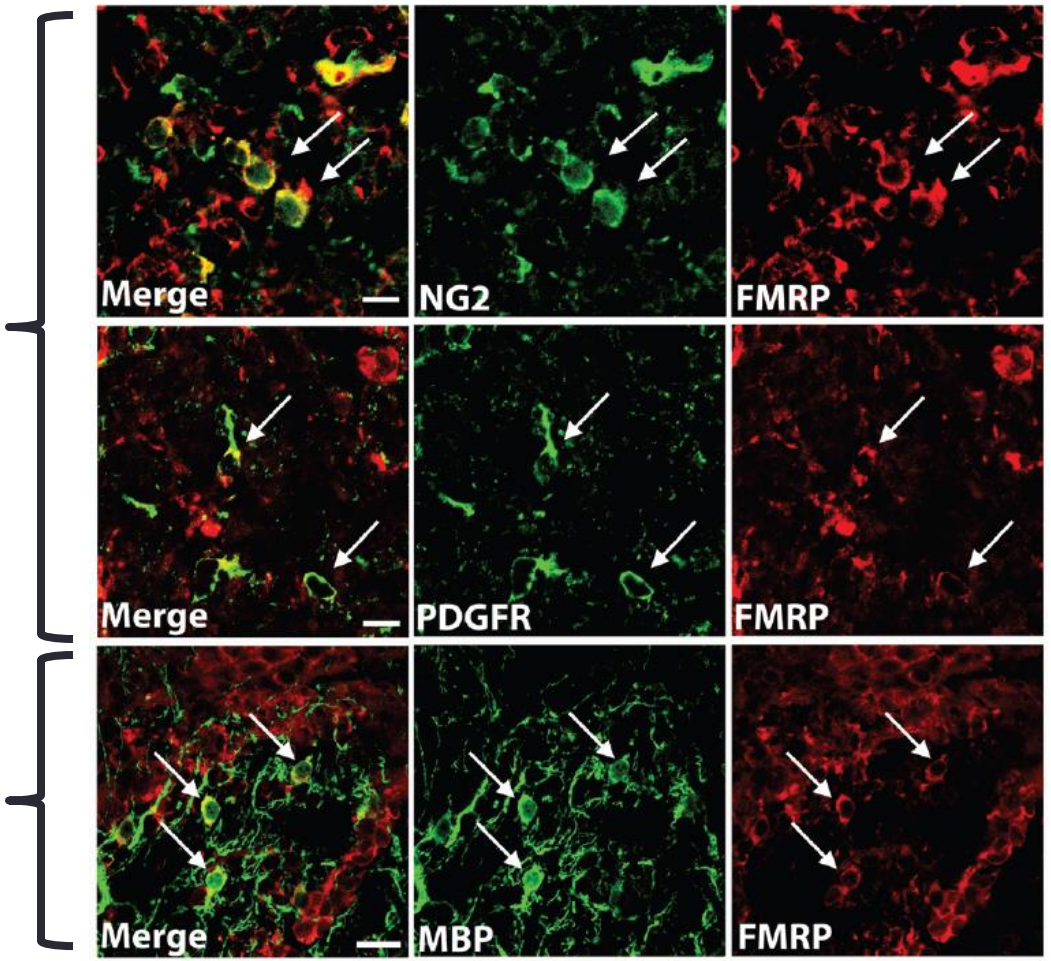


Why study myelination in FXS?

- **Oligodendrocyte precursor cells** (OPCs) and **mature oligodendrocytes** express FMRP

Co-localization of OPC markers **NG2** (neuro/glial antigen 2) and **PDGFR** (platelet-derived growth factor receptor) with **FMRP**

Co-localization of mature oligodendrocyte marker **MBP** (myelin basic protein) with **FMRP**



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Why study myelination in FXS?

- White matter abnormalities in affected patients
  - MRI/DTI imaging → **fractional anisotropy (FA)** values, indicator of **white matter integrity**
  - Reduced WM FA in **autism** (Barnea-Goraly et al., 2010)
  - Reduced WM FA in **FXS** (Barnea-Goraly et al., 2003)
  - WM integrity **correlates with intelligence** (Penke et al., 2012)

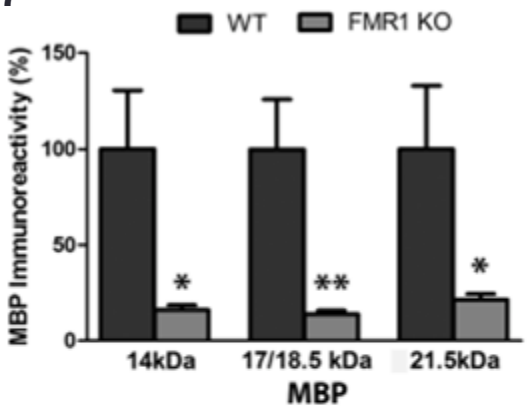
White matter matters!!!

- We study white matter abnormalities in FXS at a cellular and molecular level
  - Quantify the expression of myelin and oligodendrocyte proteins in the fragile X mouse brain vs. the normal wild type brain at multiple time points and in multiple regions

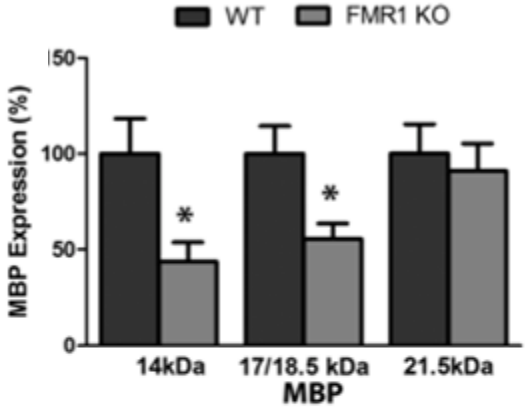
Delayed myelination in FXS mice

- Delayed myelination in Fmr1 KO mice cerebellum:

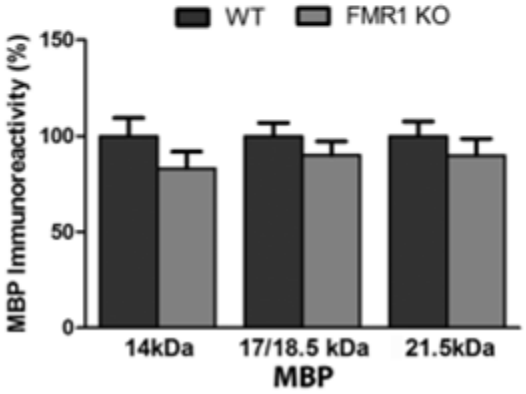
Postnatal day 7



Postnatal day 15



Postnatal day 30



Delayed expression of MBP in fragile X mouse catches up to WT levels at **Postnatal day 30**

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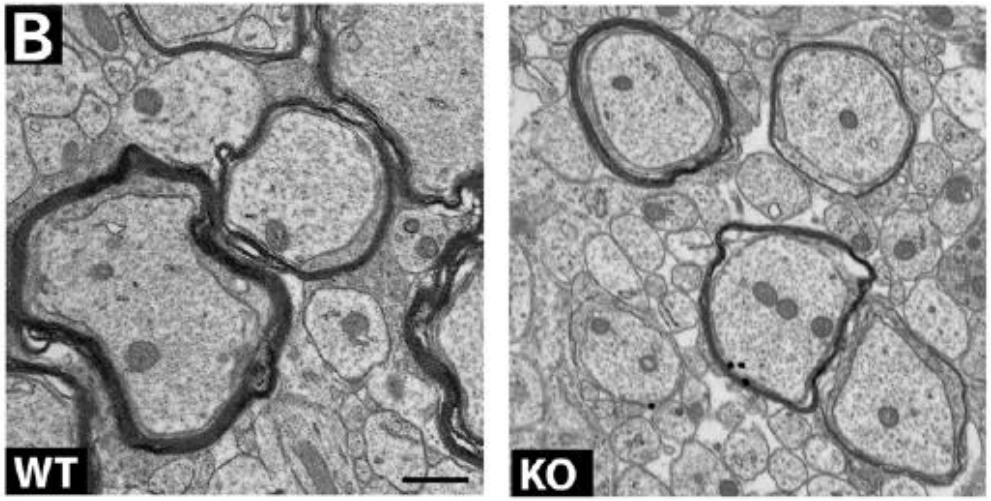
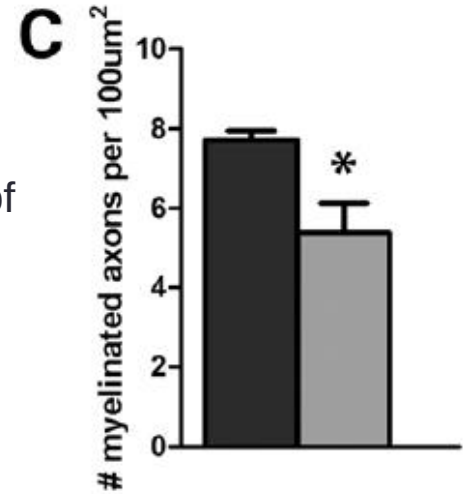
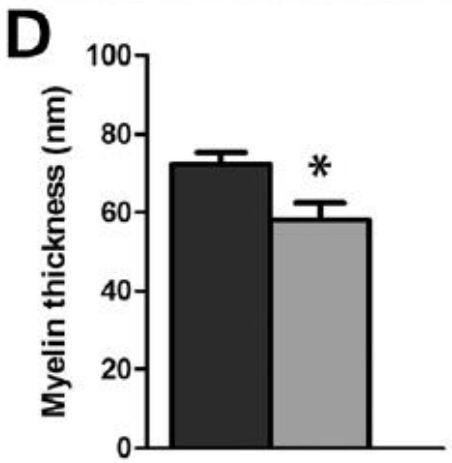
Reduced myelination in developing FXS mice

Postnatal day 7 cerebellum



Reduced number of myelinated axons





Reduced thickness

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Delayed myelination in across the developing fragile X brain

- Our recent work suggest that the delayed myelination is not restricted to the cerebellum and occurs globally in the developing fragile X brain.

- More rostrally located regions show delayed myelination at later developmental time points while caudal regions show this delay at relatively earlier time points
  - Suggests the defect occurs in early myelination stages
  - Consistent with the rostrocaudal direction of myelination

Stress alters myelination

- Stress leads to elevation of corticosteriod levels

- Stress and corticosteroid treatment **increase the generation and differentiation of oligodendrocytes** in normal adult rats (Chetty et al., 2014)

- Therefore, early developmental stress would increase corticosteriod levels which could then **promote myelination**

Stress response is dysregulated in FXS

- **Greater corticosteroid response** to stress in **human** autism (Spratt et al., 2012) and in FXS patients (Wisbeck et al., 2000) and in **fragile X mice** (Markham et al., 2006).

- Could stress response dysregulation be a factor in delayed myelination in fragile X mice?
  - Our evidence suggests that early developmental stress **differentially alters myelination** in fragile X compared with wild type mice.
  - More rostrally located brain regions are affected more by stress than caudal regions at the same developmental time point.

Main conclusions

1. Myelination is delayed in the developing fragile X brain

2. Stress alters myelination differently in the fragile X brain than in the normal wild type brain.

Implication: abnormal myelination could impair neuronal development and function

- Proper neuronal development relies on the correct timing and speed of neuronal firing.
  - The presence/absence as well as the thickness of myelin sheath both affect axonal conductance and therefore neuronal firing

- Myelination defect occurs during a sensitive developmental period
  - **Lasting neuronal impairments!**

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