Oligodendrocyte maturation and myelination deficits in Parkinson's disease

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1 Background

Parkinson's disease (PD) research has long been very neurocentric, with preferential degeneration of dopamine (DA) neurons in the substantia nigra being a hallmark of pathology.

Recent transcriptomic studies have found early associations between oligodendrocytes (OLs) and genetic risk for PD (Fig. 1).

DA neurons are known to have increased energy demands, thus alterations in the myelin that physiologically lowers the energetic requirements for signal transmission, may be detrimental for their high energetic burden and oxidative stress levels.

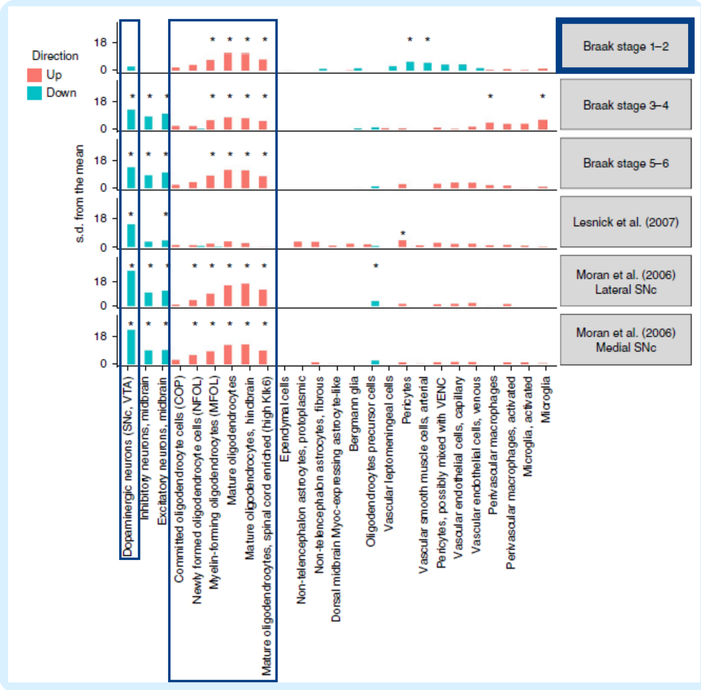

Figure 1: Enrichment of Parkinson's disease differentially expressed genes in cell types from the substantia nigra (Bryois et al., Nature Genetics, 2020)

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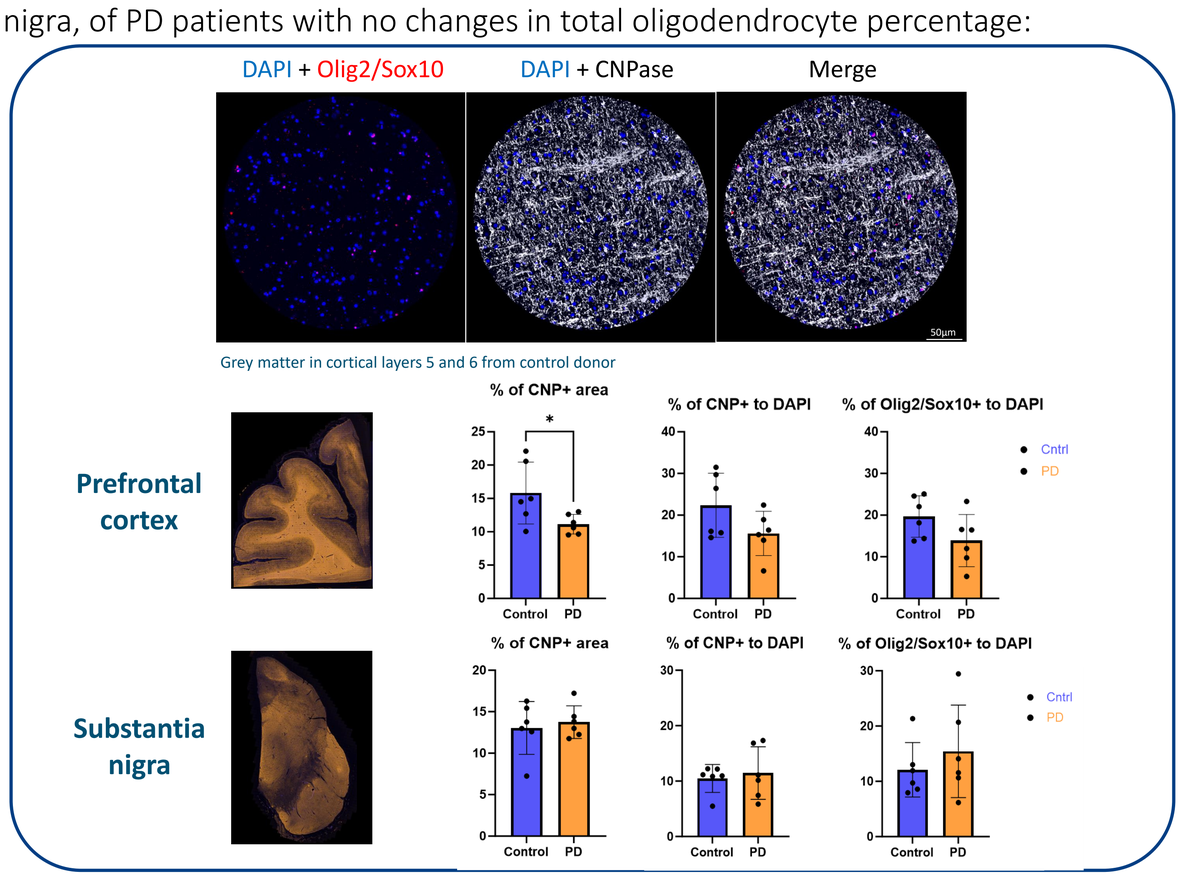
Causal role for oligodendrocytes in PD etiology?

Potential therapeutic target?

2 Loss of myelin coverage in PD brain

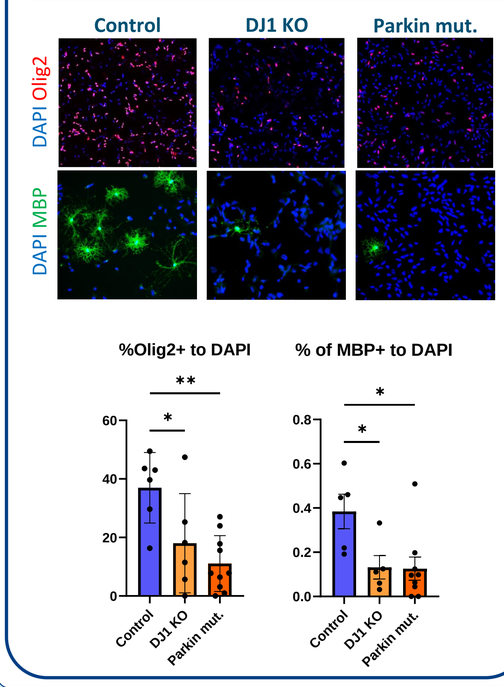
Total myelin covered area is reduced in the prefrontal cortex, but not the substantia nigra, of PD patients with no changes in total oligodendrocyte percentage:



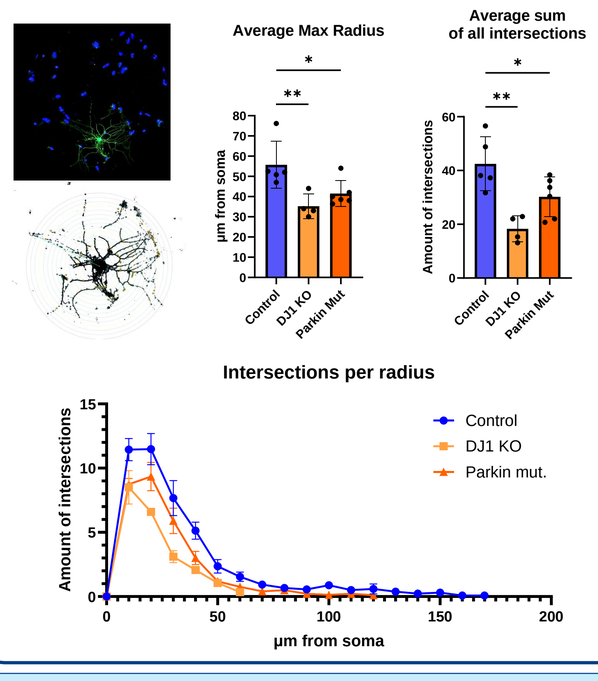
3 Differentiation and maturation deficits

Through iPSC modelling, we were able to observe a lower amount of oligodendroglial lineage cells and mature OLs in our familial PD cell-lines. These also exhibited signs of lower maturity:

Reduced OL amount



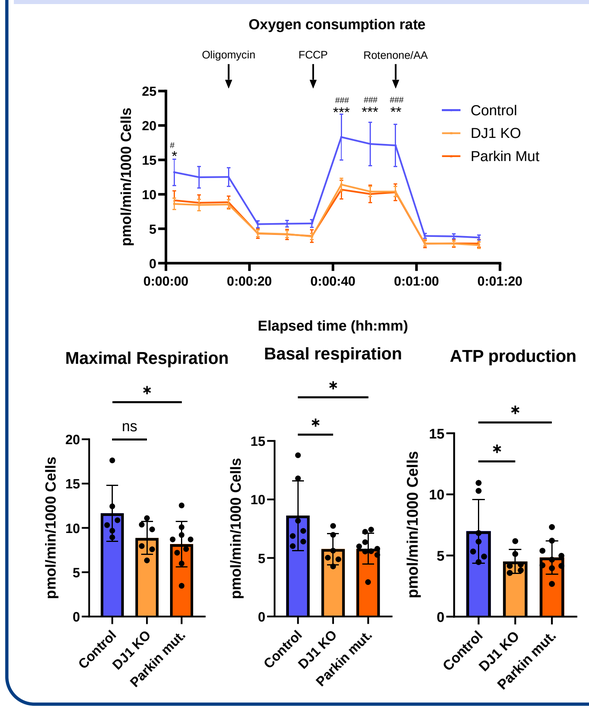
Reduced size and complexity



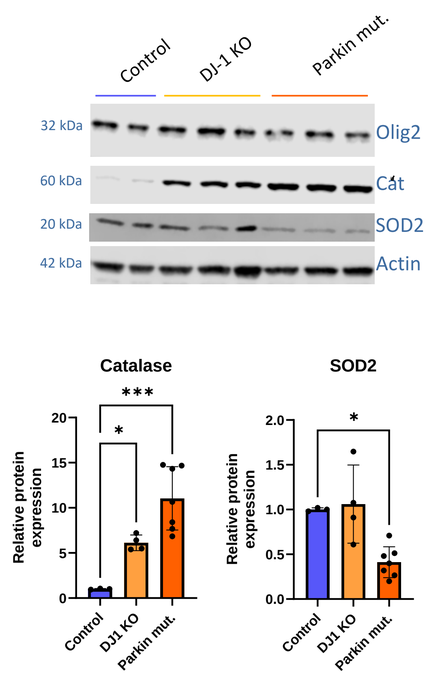
4 Signs of oxidative stress

Upon further investigation, our familial PD OLs showed deficits in mitochondrial function, as well as evidence of elevated oxidative stress:

Reduced oxygen consumption

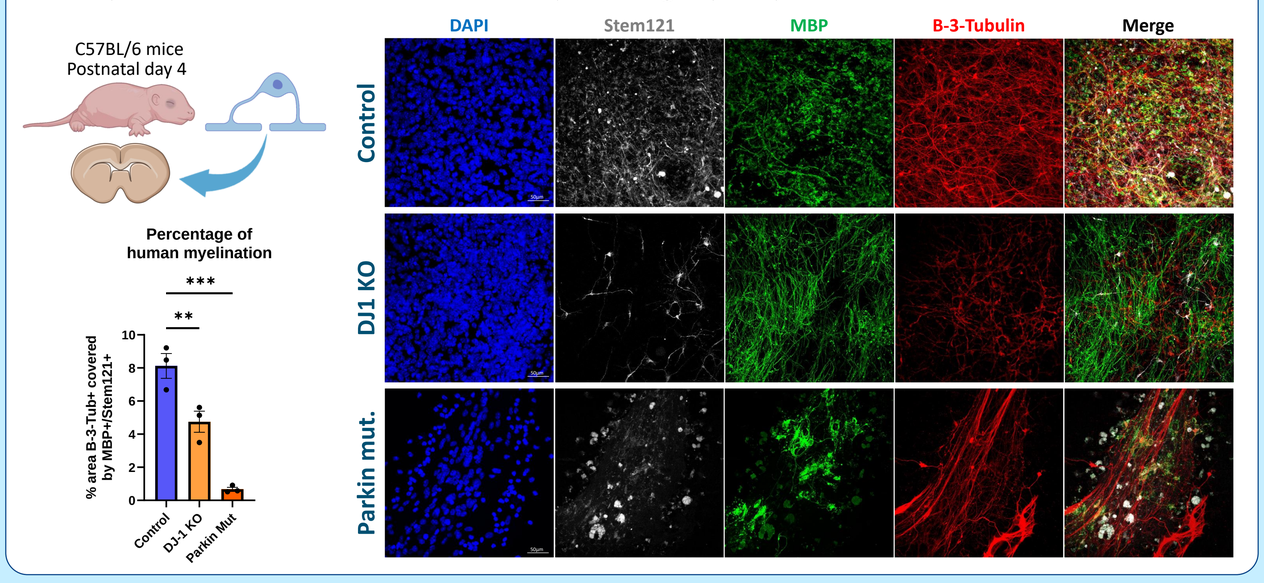


Protein expression changes



5 Deficit in myelination

We then implanted our iPSC-derived oligodendrocytes onto *ex vivo* mouse cerebellum slices and kept them in culture to assess their myelinating capacity:



6 Conclusions

PD oligodendrocytes exhibit a possible functional change in the prefrontal cortex, shifting away from their canonical myelination, as well as a potential involvement in the non-motor symptoms of PD.

Mutant oligodendrocytes show inhibited differentiation and signs of oxidative stress, which have been previously shown to hinder their maturation.

These maturation defects lead to a loss in their myelinating capacity, causing a possible loss of their protective properties and enhanced neuron vulnerability

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All illustration were generated in Bioart.niaid.nih.gov

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