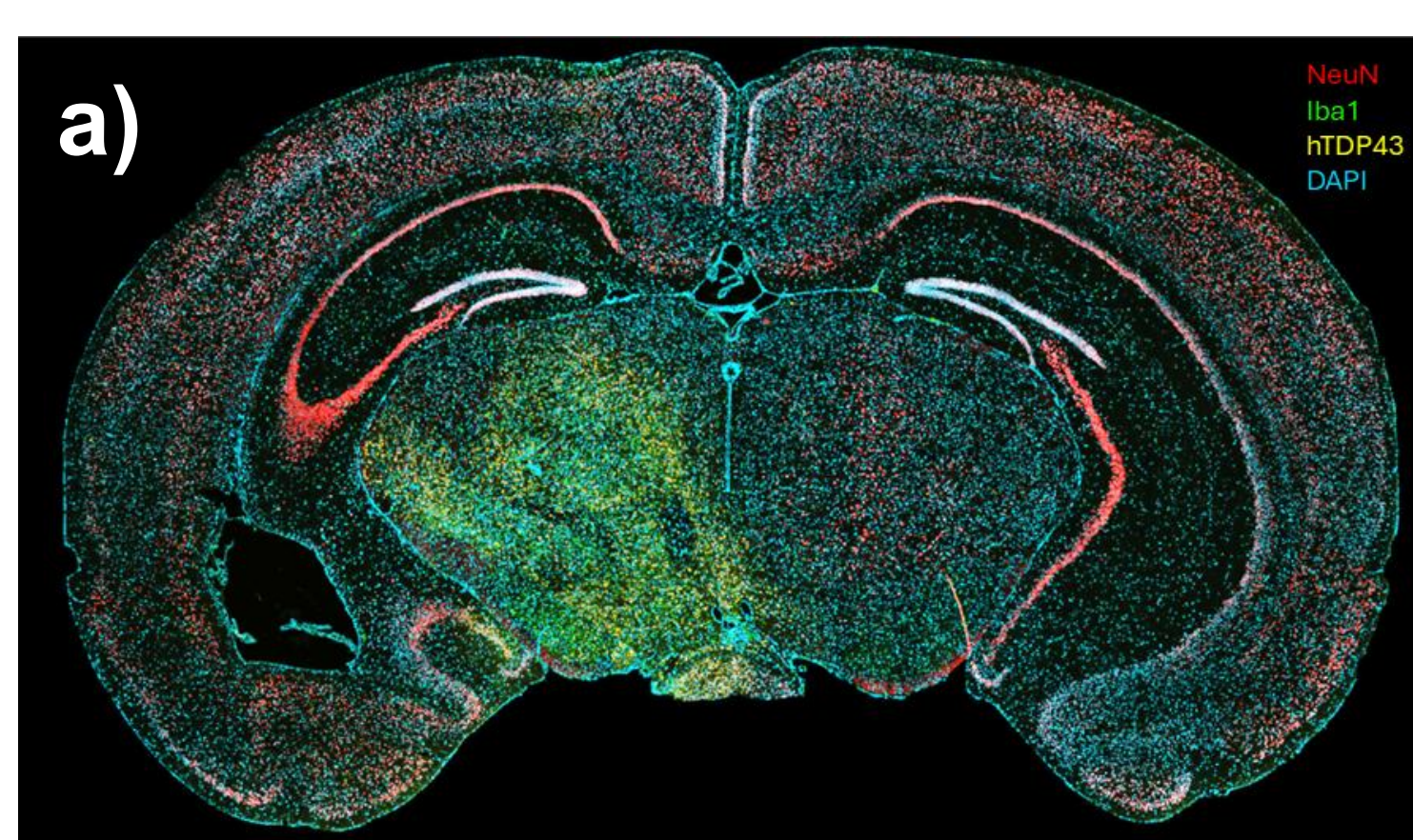




Introduction

- Microglia are thought to play a key role in many neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [1,2]
- Interactions between microglia and neuronal soma, termed **somatic purinergic junctions**, are hypothesized to be a key site for sensing neuronal health [3,4]
 - Their role in neurodegenerative diseases is currently unknown

Methods



- Quantitatively assess interactions between microglia and neuronal soma in a TDP-43 mouse model (unilateral injection of AAV-hTDP43 or AAV-null into the SN of WT mice).
- IF sections stained for DAPI, Iba1, NeuN, hTDP43, and pTDP43.
- Fully automated method for microglia detection, morphological classification, and microglia-neuron interactions characterization.

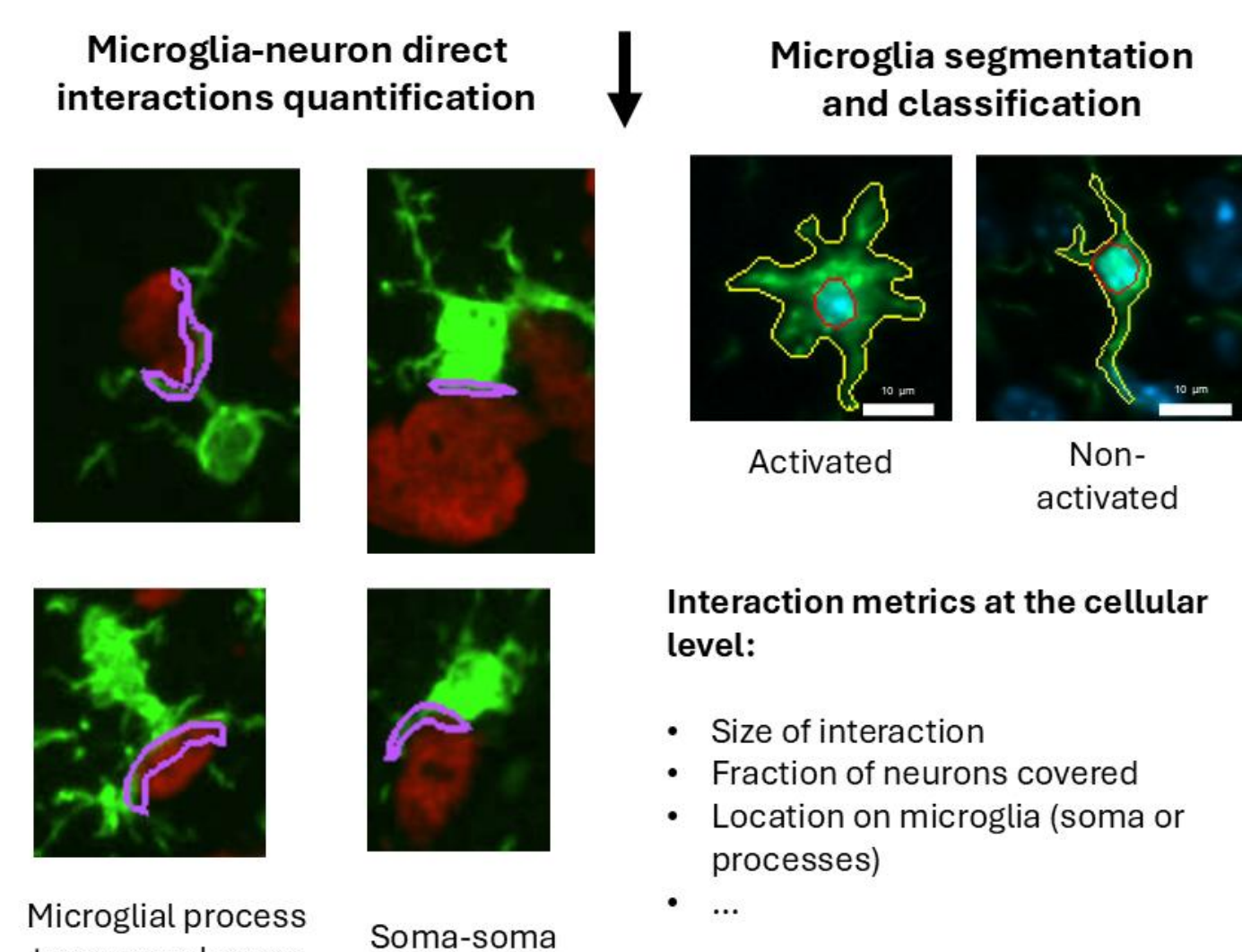
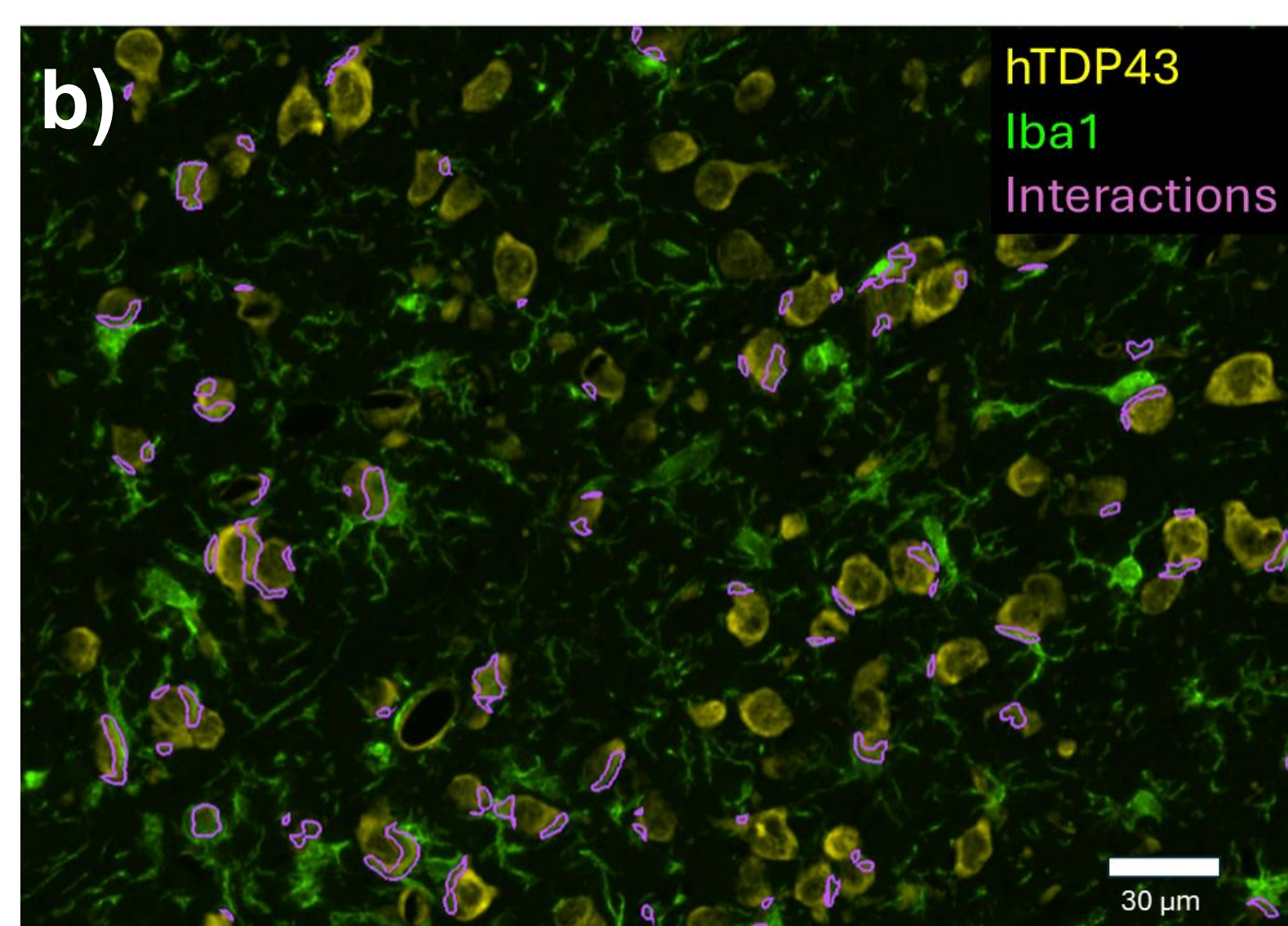


Fig. 1 a) Overview of automated platform for microglia and microglia-neuron interaction characterization; **b)** Sample multiplex IF image with identified microglia-neuron interactions



Results

MICROGLIOSIS QUANTIFICATION

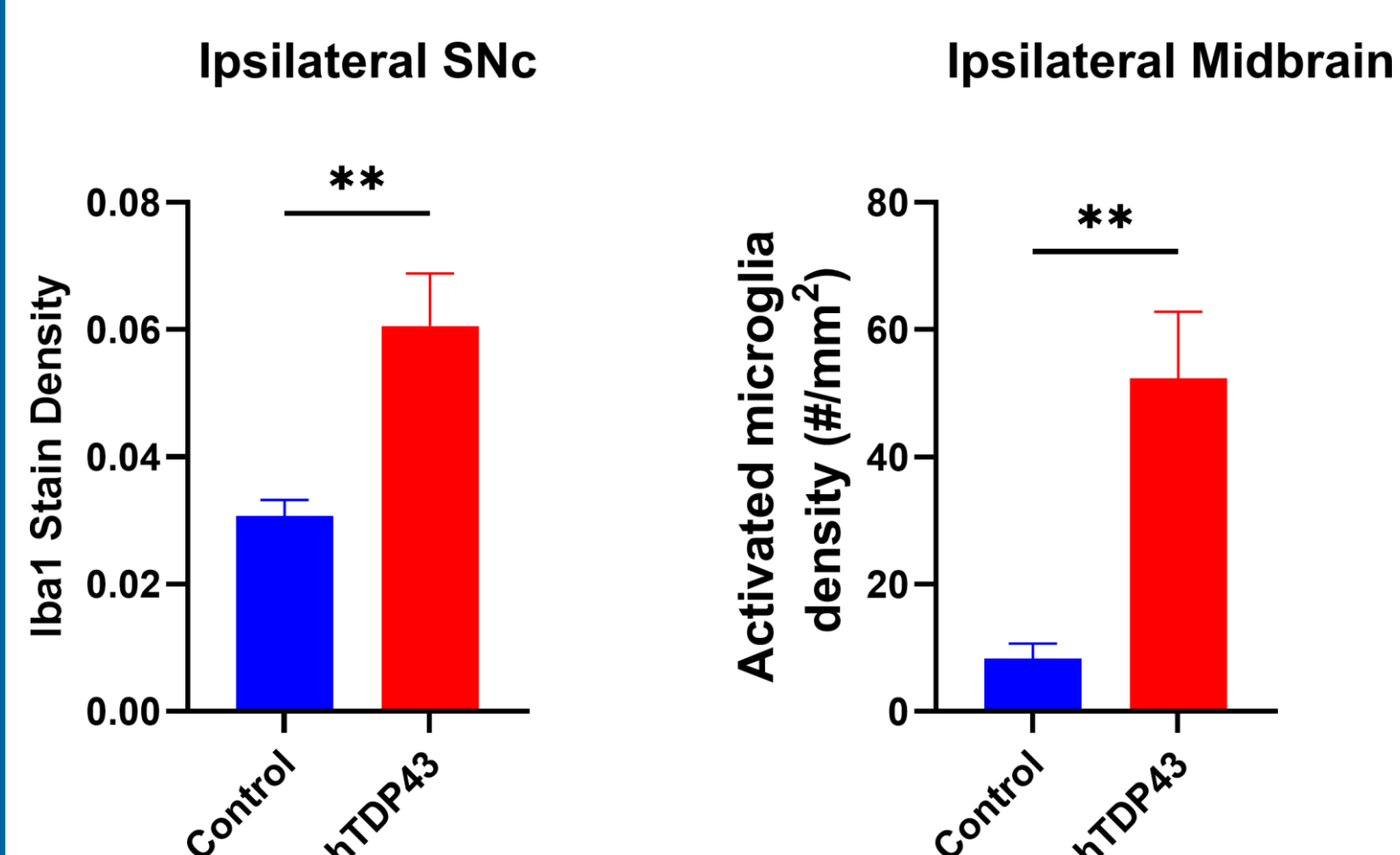


Fig 2. AAV-hTDP43 causes severe microgliosis.

Quantification of microgliosis with Iba-1 stain density and density of activated microglia show a large increase in the disease group. (N=8 animals per group)

INCREASE IN MICROGLIA-NEURON INTERACTIONS

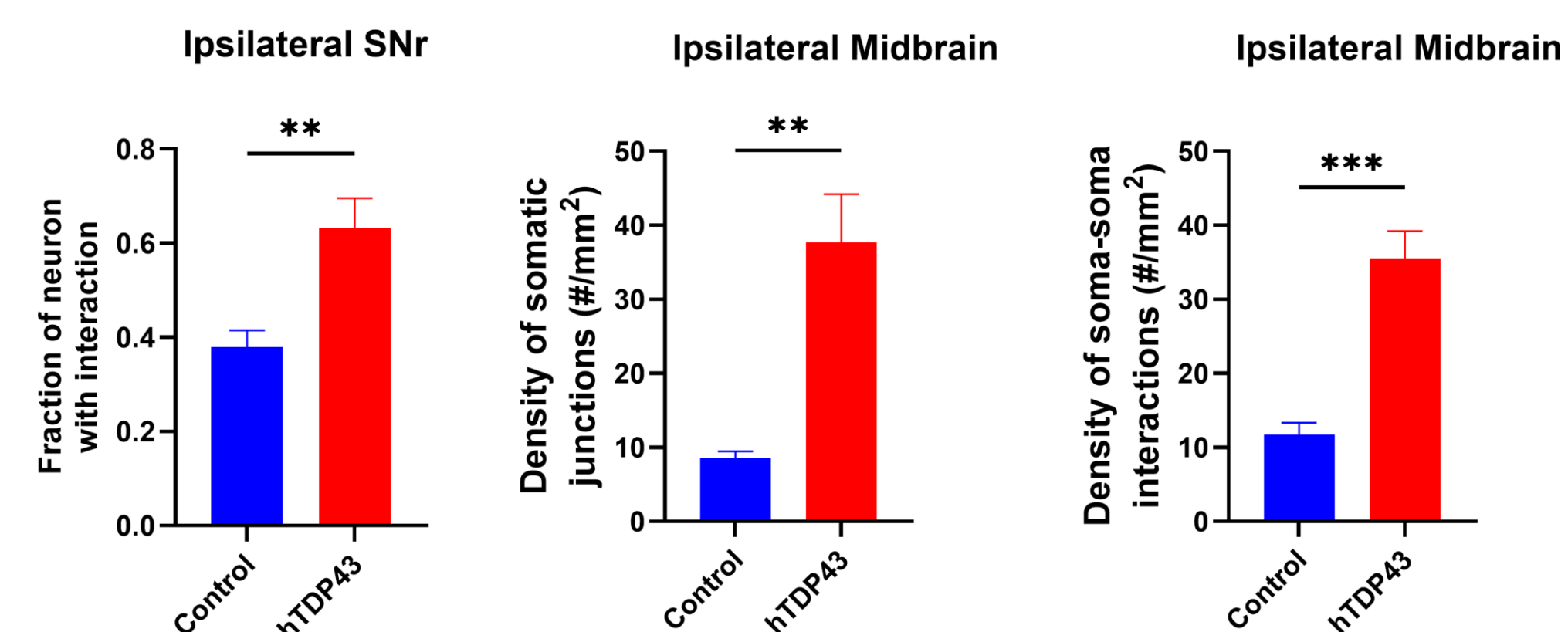


Fig 3. Increase in number of microglia-neuron interactions. The fraction of neuron with microglial interaction increases in the disease model.

CHANGE IN THE TYPE OF INTERACTIONS

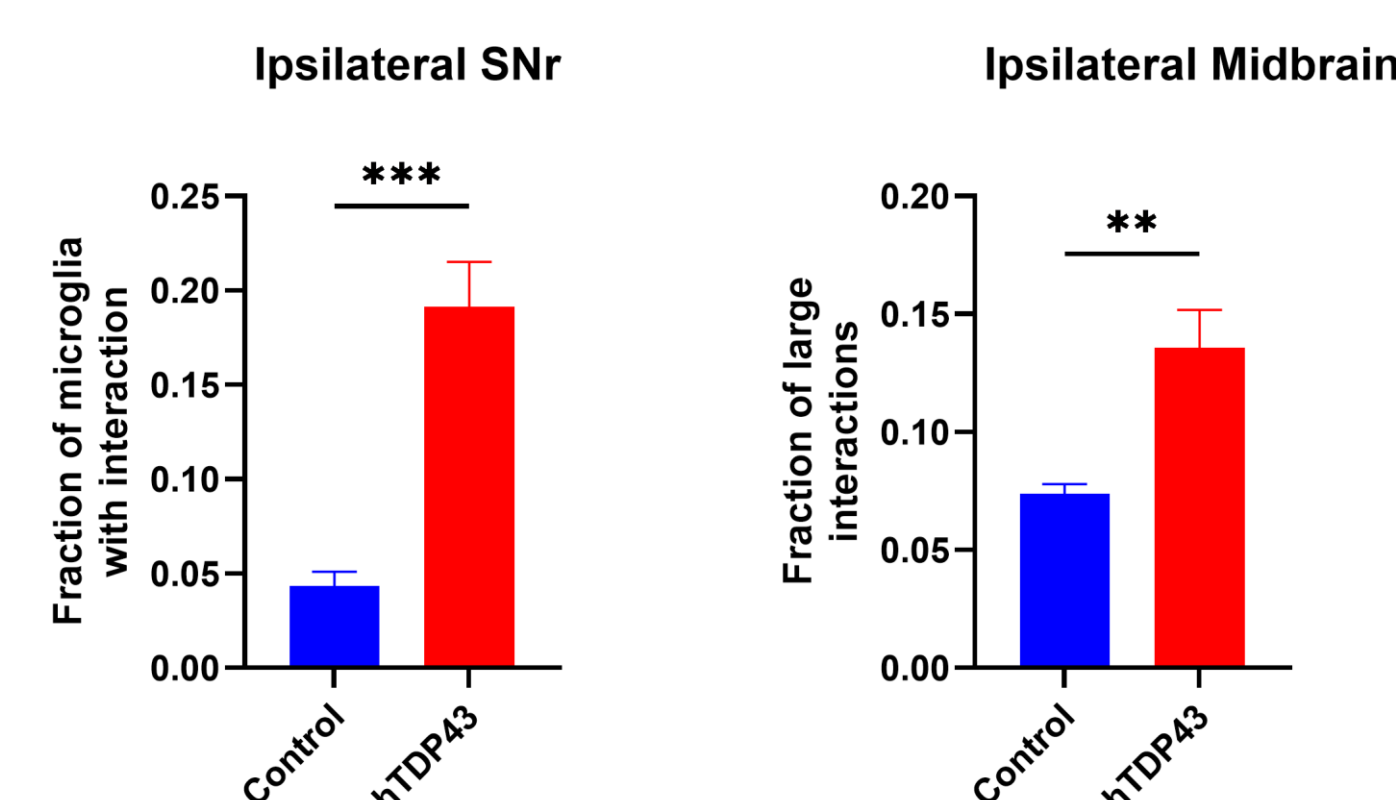


Fig 4. Change in the nature of the microglia-neuron interactions. The fraction of microglia with interaction and fraction of large interaction (area covered or perimeter covered >0.5) increases in the disease model.

INTERACTIONS CORRELATE WITH SINGLE CELL PATHOLOGICAL BURDEN

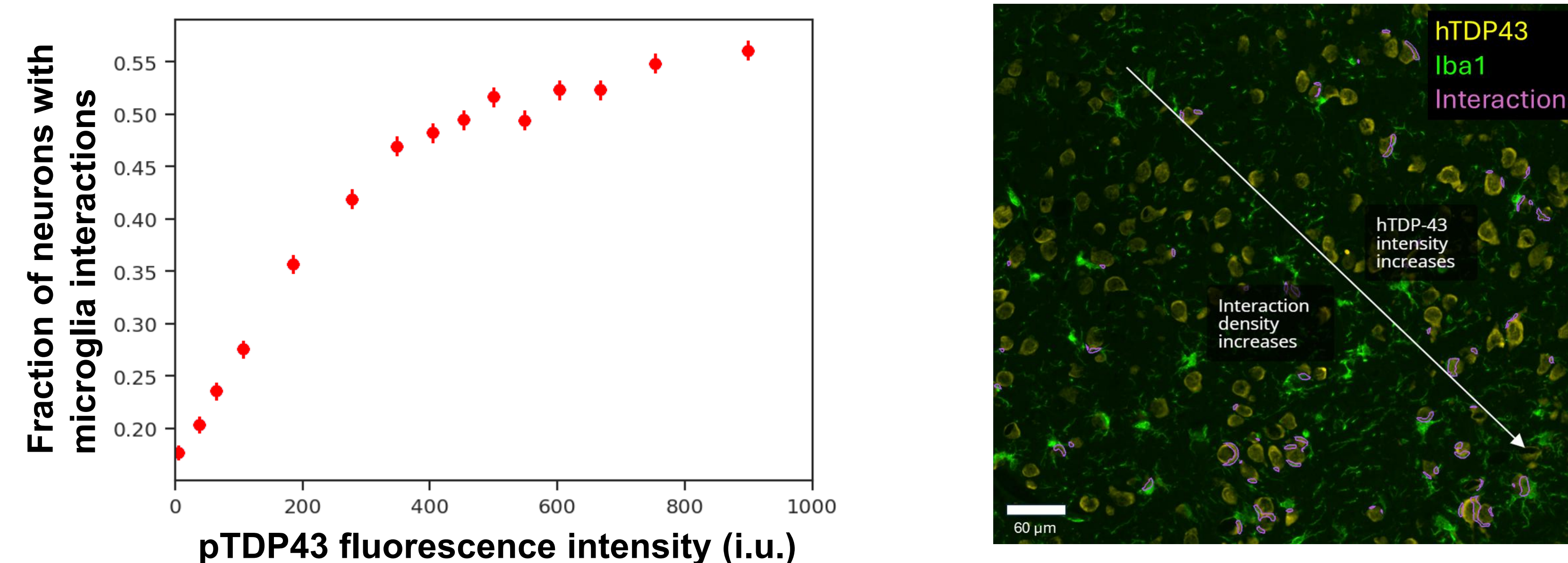


Fig 5. Cells with higher pTDP-43 burden are more likely to undergo interactions. Fraction of neurons with interactions as a function of pTDP43 intensity. Each point is a bin of 3,000 cells averaged in x and y (n=46,371 cells across N=8 animals).

Conclusions

- The quantity and the type of microglia-neuron interaction are affected in this disease model. Cells with higher pathological burden have more interactions.
- This approach may provide sensitive measure for the preclinical assessment of putative therapeutic agents.

References

- [1] Hickman *et al.*, *Nat. Neurosci.* (2018)
- [2] Salter *et al.*, *Nat. Med.* (2017)
- [3] Cserép *et al.*, *Science* (2020)
- [4] Cserép *et al.*, *Neuron* (2021)