Microglial Fate in Neurodegeneration

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Introduction

Background:

- Microglia are brain-resident immune cells that aid in injury repair and regulate brain health.
- These cells are highly involved in neurodegenerative diseases such as Alzheimer's disease (AD).
- Previously, in an acute neurodegeneration mouse model induced by facial nerve axotomy (FNX), our lab observed that microglial cells that proliferated in response to brain tissue damage and neuronal death appeared to migrate to other parts of the brain after recovery (Tay et al., 2017).
- It is unknown whether this process of proliferation and migration is the same in chronic neurodegeneration.

Main Goal:

- Verify if microglia are redistributed and permanently retained in the brain after FNX

Hypothesis:

- The proliferation and retention of microglial cells occurring in AD contribute to the disease's progression.
- However, microglial migration and relocation occur during clinical recovery after FNX, an acute model for neurodegeneration.

Methodology

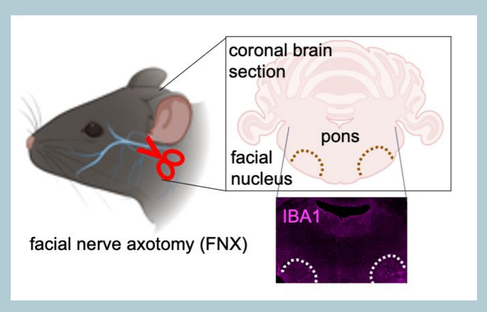
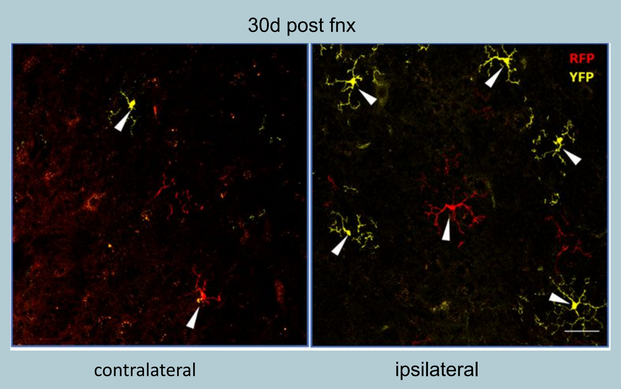


Figure 1. A facial nerve axotomy was performed on mice. This procedure simulated neurodegeneration, allowing us to track the response of microglia.



IBA-1 and Confetti Counting:

Figure 2. A microscopy software, Zen, was used to manually count the microglial cells. IBA-1 counting entailed counting all microglial cells in the pons and facial nucleus regions. However, confetti counting marked only a few randomized microglial cells in the same regions with different colors, allowing us to track the migration of those cells over time.

Results

30 days post FNX

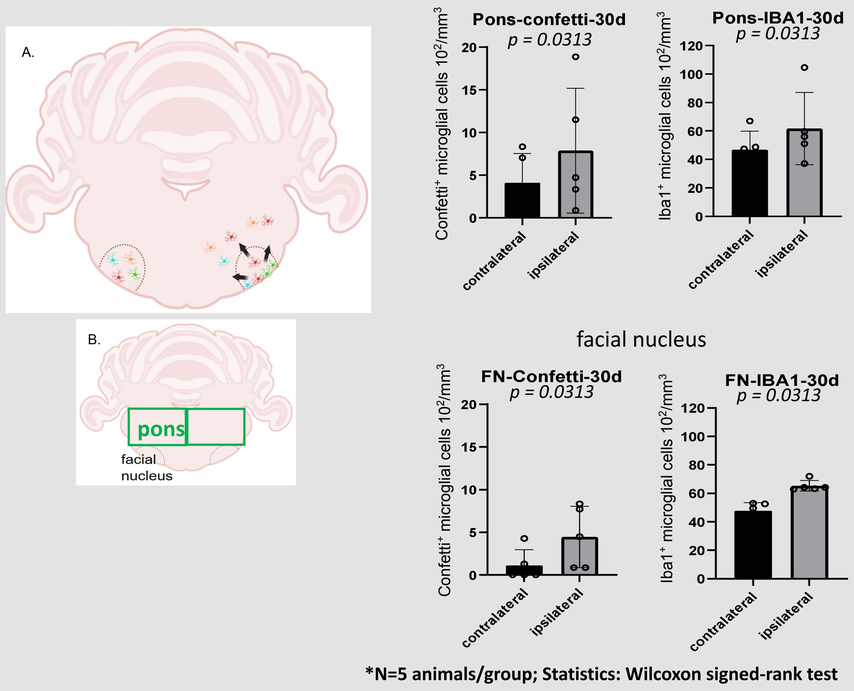


Figure 3. Microglia migrate out of the facial nucleus into the pons at the onset of recovery. (A): Using confetti counting, we are able to see the movement of microglia out of the facial nucleus. (B): This figure indicates the area encompassed by the pons region and the facial nucleus.

90 days post FNX

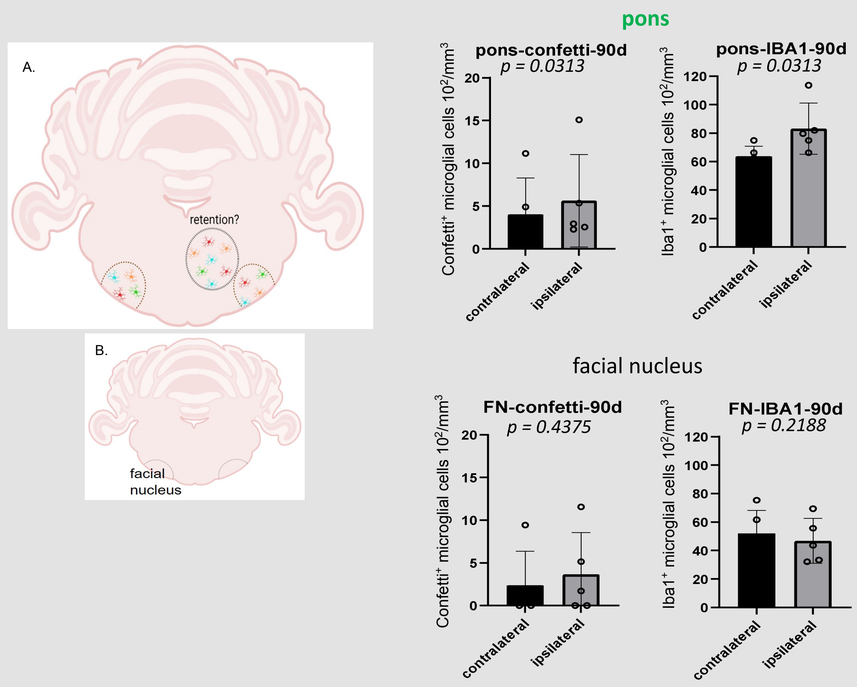


Figure 4. Microglia are retained within the brain parenchyma after clinical recovery. (A): The microglia that migrated to the pons are observed to be retained there 90 days after injury. (B): This figure indicates the area encompassed by the facial nucleus.

Confetti Distribution

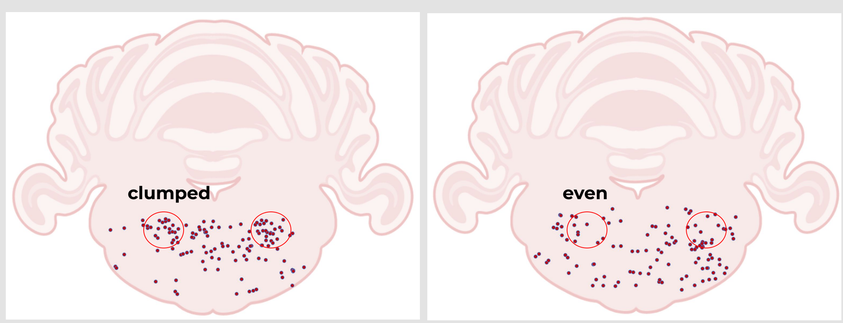


Figure 5. Trajectory of the microglia based on confetti counting. From 30 days to 90 days post FNX, we observe a change in the concentration of microglia in the pons. For 30 days, there is a greater concentration of microglia in the pons. However, for 90 days, we see a more even distribution of microglia

Results Cont.

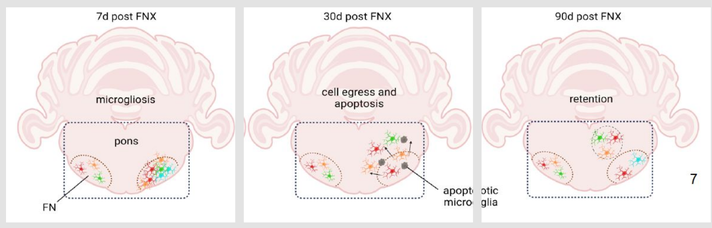


Figure 6. Microglial distribution 7 days, 30 days, and 90 days post FNX. Microglial cells first concentrate near the injury site during recovery, but slowly migrate out to the pons.

Conclusion

Discussion:

- Through IBA-1 and Confetti counting, we can conclude that microglia migrate out of the facial nucleus and are retained in the pons after recovery from injury.
- During migration, microglial cells disperse so that there is a more even distribution of cells instead of a clumped distribution.

Significance:

- Our study provides more insight into the role of microglia in the progression of neurodegeneration.

Future Directions:

- We will use transcriptomics to understand microglial signatures that have retained within the pons.

References

1. Tay, T. L.; Mai, D.; Dautzenberg, J.; Fernández-Klett, F.; Lin, G.; Sagar; Datta, M.; Drougard, A.; Stempfl, T.; Ardura-Fabregat, A.; Staszewski, O.; Margineanu, A.; Sporbert, A.; Steinmetz, L. M.; Pospisilik, J. A.; Jung, S.; Priller, J.; Grün, D.; Ronneberger, O.; Prinz, M. A New Fate Mapping System Reveals Context-Dependent Random or Clonal Expansion of Microglia. *Nature Neuroscience* **2017**, *20* (6), 793–803. DOI:10.1038/nn.4547.

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