# Studying the Microglial Transcriptome in response to Early Life Stress and Aging

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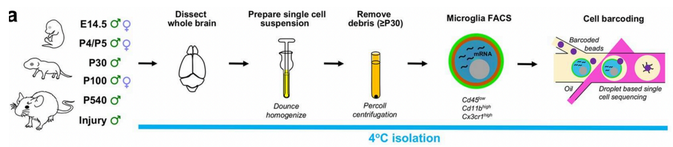
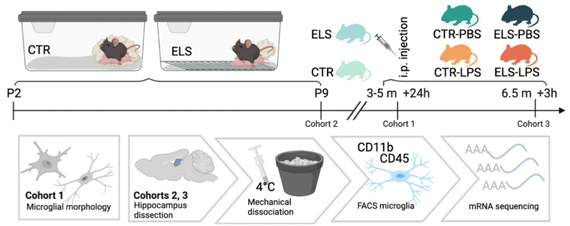
## INTRODUCTION

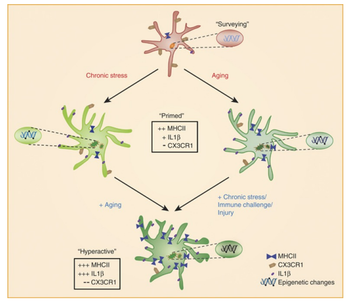
- Microglia are the immune cells of the brain, responsible for maintaining homeostasis within the central nervous system
- Early-life experiences, such as childhood abuse, neglect, or trauma, have been implicated in shaping microglial phenotype and function
- **Can we use microglial genetic markers to uncover whether early life stress (ELS) ages the brain?**




Aging triggers a shift toward a more immunogenic profile including an increase in inflammatory microglia[1].

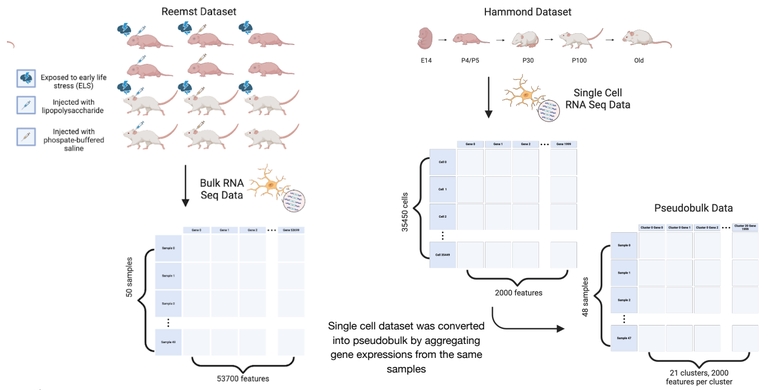



Early Life Stress (ELS) specifically has been connected with impacting microglial function[2]. This was determined by exposing a group of young mice to stress via environmental conditions such as limited bedding. These mice, along with a control group, were injected either with lipopolysaccharide (LPS) or phosphate-buffered saline (PBS) to see if LPS would cause unique perturbations in the brain of mice exposed to ELS.

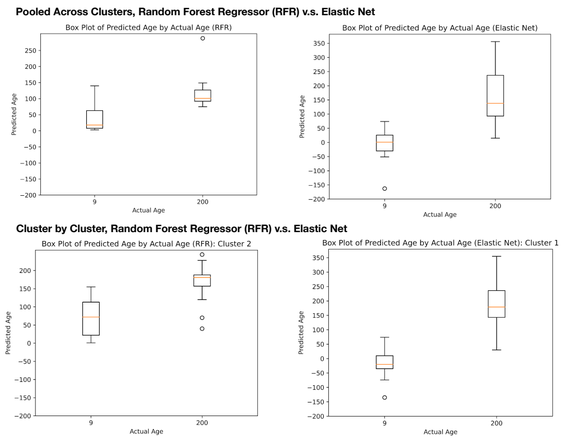



Individuals exposed to lifetime stress exhibit epigenetic changes resembling those seen in aging-associated diseases[3].

## DATASET

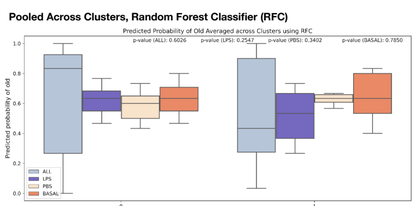



## RESULTS




**The Elastic Net model does better at predicting the true age of mice** compared to the the Random Forest Regressor model. Certain clusters tend to perform better than the version where genes expressions are pooled across all clusters


**Genes indicative of age are generally upregulated in older mice and downregulated in younger mice** when the pseudobulk data is filtered to only include the top 10 important genes from the Elastic Net model

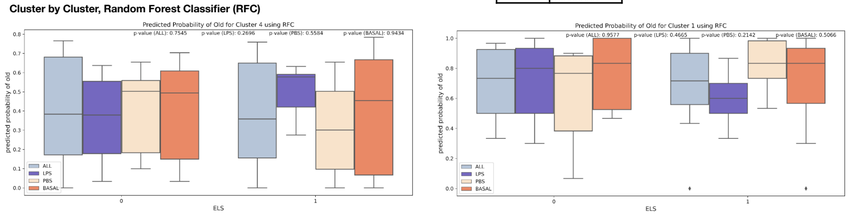



| Feature | Importance |
|---|---|
| Csmd3 | 0.066667 |
| Apoc1 | 0.066667 |
| Tacc3 | 0.066667 |
| Ncapd2 | 0.061166 |
| Ccnb2 | 0.033333 |
| Kif20b | 0.033333 |
| Zfp654 | 0.033333 |
| Spc25 | 0.033333 |
| Cenpa | 0.033333 |
| Fabp5 | 0.033333 |

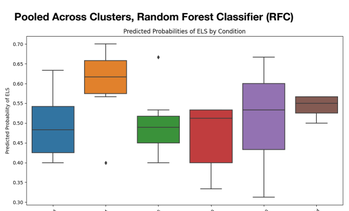
RFC feature importance of top 10 important genes

: Biomarker for Alzheimer's Disease

: Biomarker for Cancer




**Stressed mice are predicted to be older than non-stressed mice** particularly among the PBS condition. On a cluster by cluster level, this was observed in 10 out of 21 clusters, with the strongest associations among the PBS condition




| Feature | Importance |
|---|---|
| Rcn2 | 0.018067 |
| Pdp1 | 0.017936 |
| Rbm28 | 0.017857 |
| Opn3 | 0.016012 |
| Mapre3 | 0.015687 |
| Fbxo9 | 0.015554 |
| Mllt6 | 0.014690 |
| Gm26916 | 0.014043 |
| Ttbk2 | 0.013675 |
| Ip6k2 | 0.013527 |

RFC feature importance of top 10 important genes

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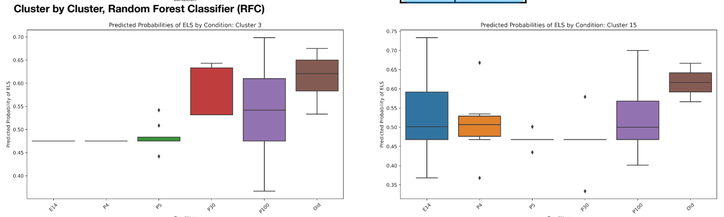
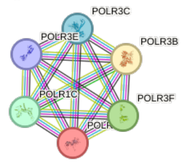


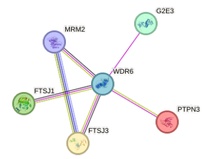

**Older age groups are associated with the ELS condition**, with the exception of P4 mice, when pooled across clusters. On a cluster by cluster level, this outcome of the oldest age group having the highest probability of ELS was observed in 6 out of 21 clusters

## CONCLUSION

Findings from this study can help inform the development of more effective therapeutic interventions and personalized treatment strategies aimed at mitigating the detrimental effects of trauma on brain health and mental well-being.

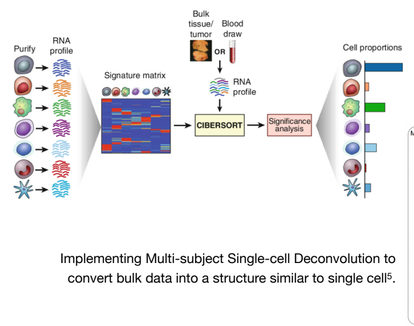



POLR3H has been implicated with being a novel cause of primary ovarian insufficiency, an indicator of female infertility

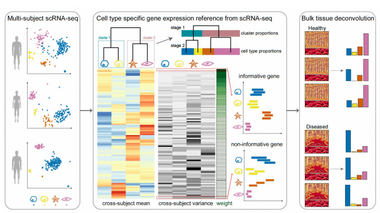



WDR6 is a prognostic biomarker that correlates with immune infiltration in lung cancer and plays a role in the regulation of feeding behavior and longevity in the brain

## FUTURE DIRECTIONS




Performing CIBERSORT, a computational method used to characterize cell type proportions in bulk tissue gene expression profiles (GEPs)[4].




Implementing Multi-subject Single-cell Deconvolution to convert bulk data into a structure similar to single cell[5].

## REFERENCES & ACKNOWLEDGEMENTS

1. Hammond, T. *et al*. *Immunity*, 50(1), 253–271 (2019).
2. Reemst, K. *et al. Transl Psychiatry* 12, 507 (2022).
3. Biltz, R.G. *et al*. *Nat Immunol* 23, 1527–1535 (2022).
4. Chen, B., *et al*. *Methods in molecular biology*, 1711, 243–259 (2018).
5. Wang X. *et al. Nat Commun* 10, 380 (2019).

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