GROUP TOPIC 1: single cell sequencing data from human prefrontal cortex, major depressive disorder versus healthy controls

https://www.nature.com/articles/s41593-020-0621-y
https://www.nature.com/articles/s41467-023-38530-5

https://github.com/EugOT/CN-pr-MDD-snRNA-seq/blob/main/notebooks/load_snRNA-seq-MDD-for-concatenated.ipynb

Project notes
Further research questions

1. How does neuroinflammation affect the function of PV interneurons in patients with MDD, and can ketamine counteract these effects?
Chronic stress and neuroinflammation have been shown to impact the functionality of PV interneurons, disrupting inhibitory control in the prefrontal cortex, which is critical in MDD pathology. Exploring how inflammatory markers such as IL-6 and TNF-α alter PV interneuron function and whether ketamine's known anti-inflammatory properties can restore their activity could provide valuable insights. This research might support the hypothesis that targeting inflammation could enhance ketamine's therapeutic efficacy, ultimately leading to more individualized treatment strategies. (Beurel et al., 2020).

2. What are the long-term effects of ketamine on PV interneuron plasticity and connectivity in the prefrontal cortex?
Ketamine's rapid antidepressant effects are well-documented, but its long-term impact on PV interneurons, particularly regarding their plasticity and network connectivity, remains underexplored. Investigating whether repeated ketamine administration induces lasting structural and functional changes in PV interneurons could shed light on its potential for sustained therapeutic benefits or risks, such as cognitive side effects. Insights from longitudinal studies could inform treatment protocols to maximize benefits while minimizing adverse effects. (Abdallah et al., 2018).

References
Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron, 107(2), 234–256. https://doi.org/10.1016/j.neuron.2020.06.002
Abdallah, C. G., Sanacora, G., Duman, R. S., & Krystal, J. H. (2018). The neurobiology of depression, ketamine and rapid-acting antidepressants: Is it glutamate inhibition or activation? Pharmacology & Therapeutics, 190, 148–158. https://doi.org/10.1016/j.pharmthera.2018.05.010 - ID701 Missing eduPersonEntitlement (ePE)

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Project name: ***Depression Group***

Project members

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Time table

Tbd

Project goals / no-goals

Hypothesis based on paper collections

Data sets - codeing

Demonstrations- Presentation

Further questions

Communication

https://github.com/ridzie/CN-pr-MDD-snRNA-seq

Signal App

Documentation

References / Data sets

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Project notes
Suggestions for project topics

Cell type specific transcriptomic differences in depression show similar patterns between males and females but implicate distinct cell types and genes

- Although our study included **data from over 160,000 nuclei**, the number of subjects was small relative to the large number of genes tested for associations with MDD. The **relatively small number of subjects** included in this study limits our statistical power to detect cell type specific disease-relevant genes and pathways.
- Further, our results may not be generalizable to all populations and this work will need to be extended with larger sample sizes from **diverse populations**.
- We did not identify a separate sub-population of disease associated microglia as observed in some neurological disorders. This may partly be due to the **lack of cytoplasmic transcripts in snRNA-seq** limiting the information about microglial states.
- We cannot draw conclusions about the proximity of microglia to PV interneurons or the presence of PNNs,as snRNA-seq involves dissociation of the tissue with loss of spatial and structural information. Neither can we conclude that protein expression is changed for our DEGs. Future studies using **spatial transcriptomic techniques coupled with immunohistochemistry** may better answer these questions.

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Project notes
Suggestions for project topics

Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte precursor cells and excitatory neurons

Table 2. Open Research Questions
1. Does dysregulation of the immune system contribute to MDD pathology?
What are the important immune system components that contribute to MDD?
Do these act independently or in synergy to promote MDD?
Is central or peripheral immune system dysregulation mediating the effects?
What are the CNS systems that are altered by the immune system dysregulation that promote MDD?
Are there different immune system alterations that promote MDD in different individuals, or are specific changes common to many MDD patients?
2. What causes immune system dysregulation linked to MDD?
To what extent do genetic influences determine these immune system characteristics?
Does stress (and is it acute or chronic) contribute to immune dysregulation linked to MDD?
How does the environment modulate the immune system dysregulation linked to MDD?
Do repeated episodes of depression cause long-lasting changes in immune characteristics?
Does the microbiome contribute to immune system dysregulation in MDD?
3. Can treating immune system dysregulation facilitate recovery from MDD and/or promote resilience to MDD onset?
What are the immune system targets that are effective interventions for MDD?
Can controlling the stress response normalize immune system characteristics?
Is controlling peripheral immune system characteristics sufficient to counteract MDD or does the central immune system need to be targeted?
Do non-invasive interventions (therapy, nutrition, exercise) normalize immune system alterations associated with MDD?
Are microbiome interventions that alter the immune system effective in MDD?