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UNIVERSITY OF AMSTERDAM

resolve biosciences

Cell type-specific vulnerability to traumatic brain injury

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VIB

KU LEUVEN

SAO Stichting Alzheimer Onderzoek
Onderzoek geeft hoop!

VIB tech watch

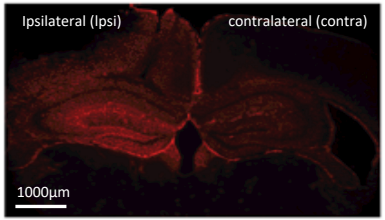
Introduction

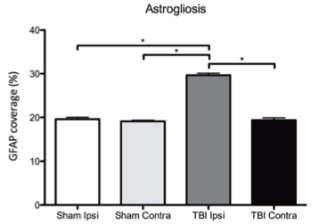
- In 50% of cases Traumatic Brain Injury (TBI) causes cognitive impairment = hippocampal dysfunction.

Controlled cortical impact model

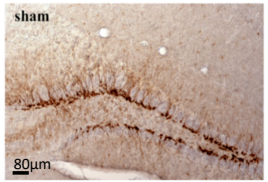
TBI results in

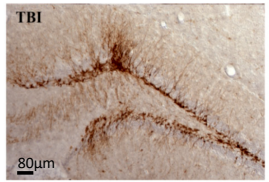
- Reactive astrogliosis in hippocampus, as confirmed by GFAP staining.

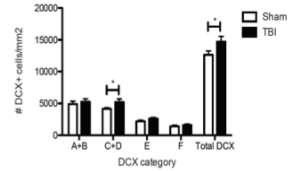




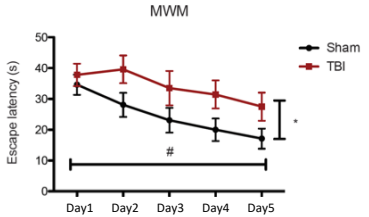
- Increase in the number of immature neurons in DG, as confirmed by DCX staining. DCX+ cells are classified as in Plümpe et al, BMC Neurosci 2006.







- Impaired spatial learning, as confirmed by Morris Water Maze behavioral test.



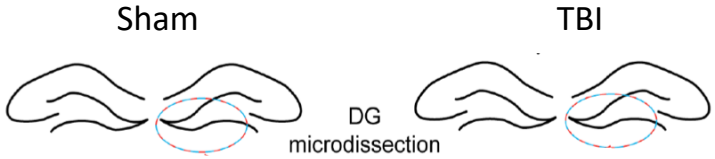
- Dysregulation and aberrant migration of newborn neurons [Neuberger et al, Stem Cell Rep 2017, Villasana et al, eNeuro 2015, Ibrahim et al Scientific Reports 2016].

Research questions

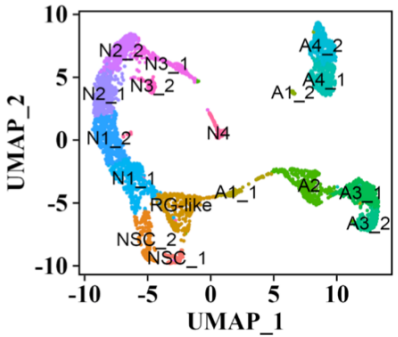
- How does TBI affect Neural Stem and Progenitor Cells (NSPCs) and their immature progeny?
- How does the cell type positioning alter?

Single cell whole transcriptome analysis

The workflow

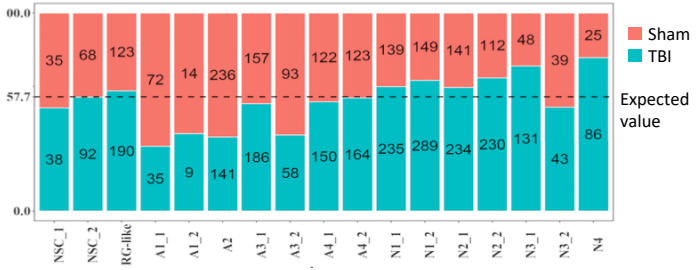


- FACS isolation of GFP+ stem and progenitor cells.
- Single cell RNA-seq by 10X v3 Chromium technology.
- Clustering ~8000 high quality single cells by Seurat algorithm [Butler et al Nat Biotechnol. 2018] reveals:

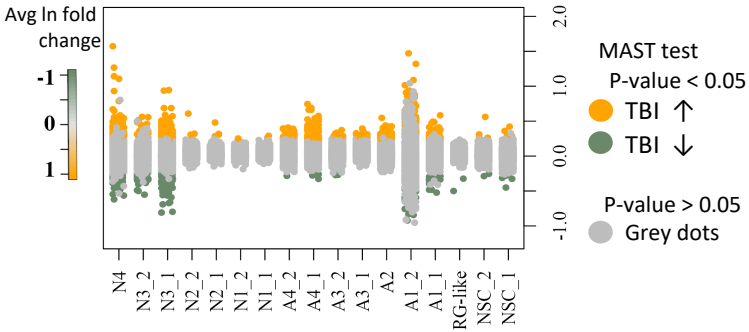


1. Astrocytic lineage [A…]
2. Neuronal lineage [N…]
3. NSC-like cells NSC1/2
4. RG-like cells

- The number of astrocytes drops after TBI, while the number of neurons increases.



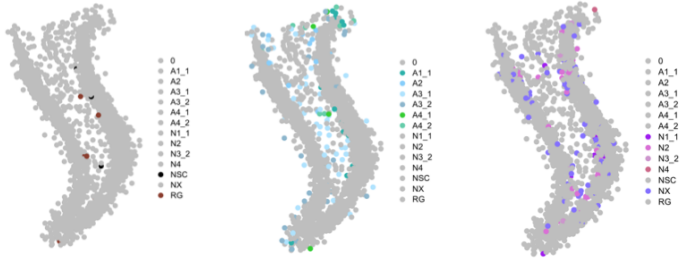
- Differential gene expression analysis reveal a number of up/down regulated genes in each of the subpopulations:



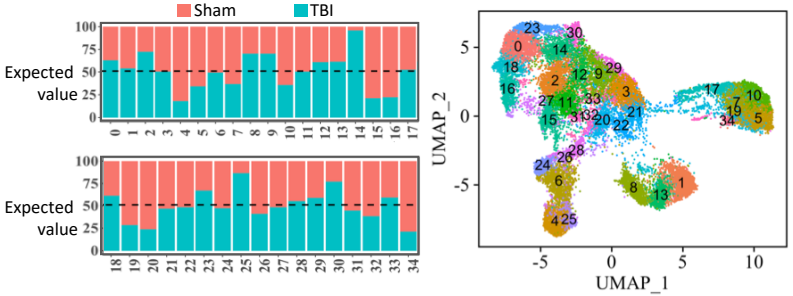
Resolve Biosciences: 100-plex in situ transcriptomics analysis*

* Poster: Quantitative spatial analysis of 67 genes to study the effect of amyloid pathology in Alzheimer's Disease (AD)

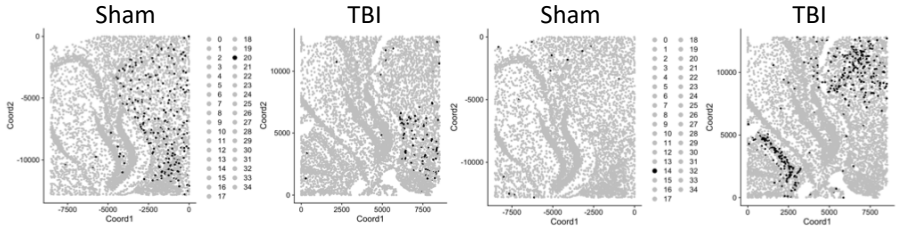
- 100 high level cell type, differentially expressed and up/down regulated genes are chosen for staining.
- 2 Sham and 2 TBI mice hippocampi (including DGs) are stained for chosen markers.
- Predicted NSPCs are found scattered in DG both in TBI and Sham conditions.



- Spatial data is clustered in **the whole hippocampus.**



- Differential positioning of cell types is observed between Sham and TBI mice hippocampi and surrounding tissue.



Conclusions

- Neurogenesis is activated after TBI, however the number of astrocytes drops, which may lead to dysfunction of newborn neurons.
- Resolve Biosciences staining validates the presence of NSPCs subtypes in DG and reveals differential positioning of cells between Sham and TBI mice hippocampi and surrounding tissue.

Future work

- Investigate the molecular signatures of astrogliosis and neurogenesis observed after TBI.
- Reveal the identity of spatially altered cell types.