Hydrocephalus/SANS Subgroup Updates
ABDR - Monday, June 30, 2025

INTRODUCTION

- Idiopathic normal pressure hydrocephalus (NPH)
- CSF buildup in the ventricles
- Three main symptoms:
  - Gait dysfunction
  - Urinary incontinence
  - Cognitive Impairment
- Difficult to diagnose: *Only 50-75% of patients have all three symptoms simultaneously*[1]

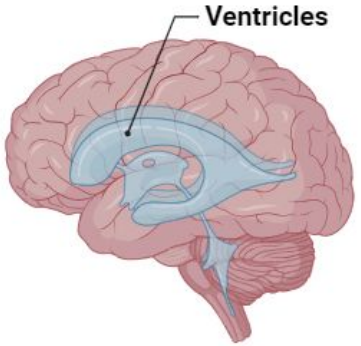


Figure 1. Ventricles in the brain

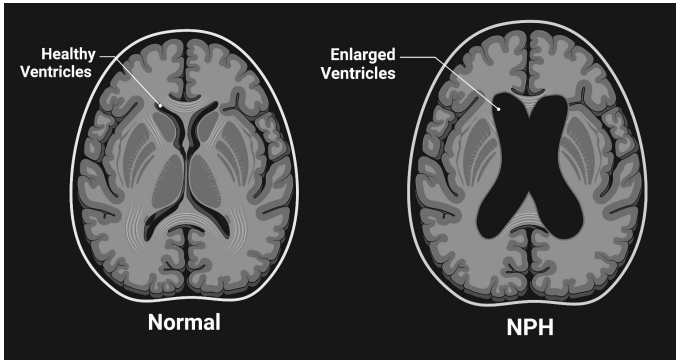


Figure 2. Drawing of MRI showing enlarged ventricles in NPH

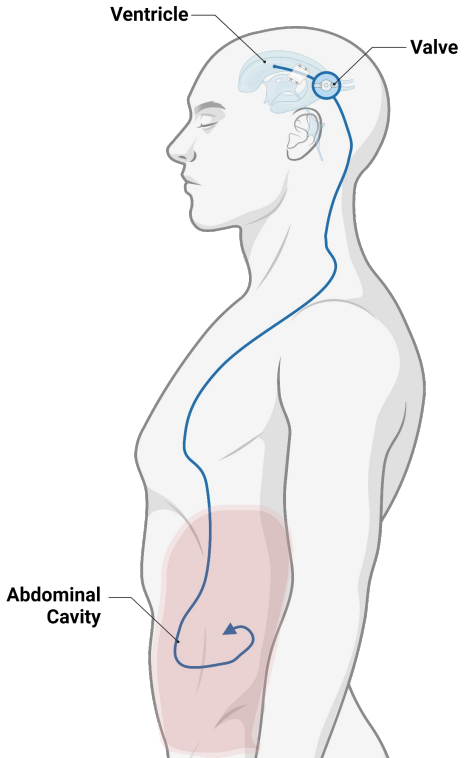
1. Cleveland Clinic, 2022

INTRODUCTION

- Estimated cause of 6% of all dementia cases[1]
  - Genetic factors suspected, but not well established
  - Current management starts with CSF tap and then insertion of a shunt
- 80% of NPH cases thought to be misdiagnosed[1]

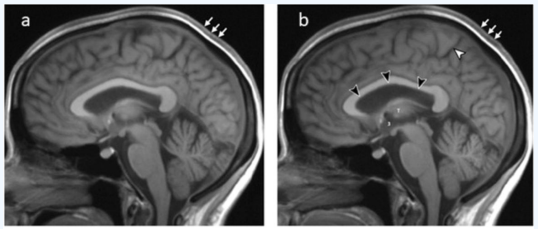
Given that NPH can drastically reduce quality and quantity of life, effective diagnosis is crucial. It is crucial to understand the underlying genomics and mechanisms of NPH to help patients on Earth.

Figure 3. Ventriculoperitoneal shunt



1. Kiefer & Unterberg, 2012; 2. Wu et al., 2019

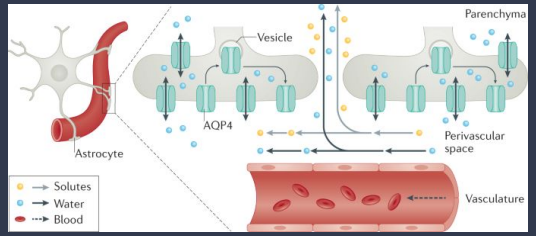
Hydrocephalus/SANS in Space



In the same astronaut, **(a)** preflight baseline image and **(b)** matching postflight day 1 image show expansion of the lateral ventricle (black arrowheads), narrowing of the cingulate sulcus (white arrowhead), and thickening of the intermediate signal scalp soft tissues (arrows).

- 70% of astronauts experience SANS
- 11-25% sustained increase in ventricular volume even 6mo+
- Increase in free water in deep white matter hyperintensities
- Narrowing of subarachnoid space accompanies ventriculomegaly
    - *Closely resembles parameters of diagnosis for NPH*

Molecular



Aquaporins

SVZ/Progenitor Defects

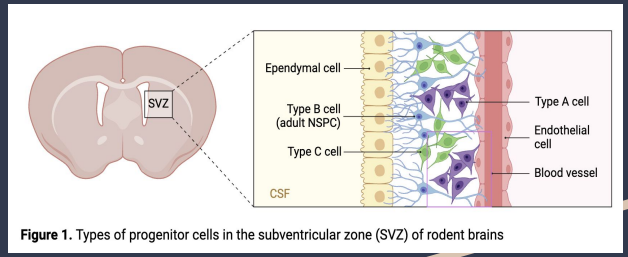
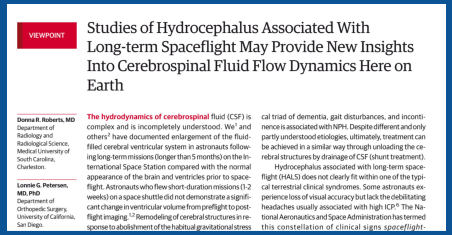


Figure 1. Types of progenitor cells in the subventricular zone (SVZ) of rodent brains

There are few studies specifically investigating molecular changes to the choroid plexus/SVZ in microgravity

Imaging



VIEWPOINT

Studies of Hydrocephalus Associated With Long-term Spaceflight May Provide New Insights Into Cerebrospinal Fluid Flow Dynamics Here on Earth

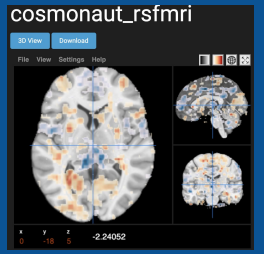
Donna R. Roberts, MD
Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston.

Lonnie G. Petersen, MD, PhD
Department of Orthopedic Surgery, University of California, San Diego.

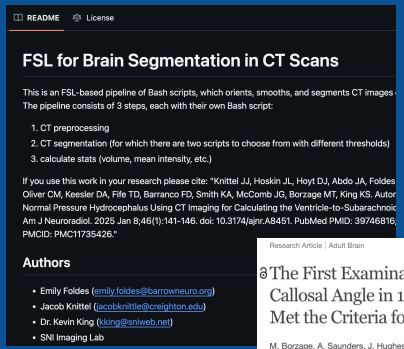
The hydrodynamics of cerebrospinal fluid (CSF) is complex and is incompletely understood. We[1] and others[2] have documented enlargement of the fluid-filled cerebral ventricular system in astronauts following long-term missions (longer than 5 months) on the International Space Station compared with the normal appearance of the brain and ventricles prior to spaceflight. Astronauts who flew short-duration missions (1-2 weeks) on a space shuttle did not demonstrate a significant change in ventricular volume from preflight to postflight imaging.[1,2] Remodeling of cerebral structures in response to abolishment of the habitual gravitational stress

cal triad of dementia, gait disturbances, and incontinence is associated with NPH. Despite different and only partly understood etiologies, ultimately, treatment can be achieved in a similar way through unloading the cerebral structures by drainage of CSF (shunt treatment).

Hydrocephalus associated with long-term spaceflight (HALS) does not clearly fit within one of the typical terrestrial clinical syndromes. Some astronauts experience loss of visual accuracy but lack the debilitating headaches usually associated with high ICP.[6] The National Aeronautics and Space Administration has termed this constellation of clinical signs *spaceflight-*



"HRP has scoped the LSAH/LSDA teams to a limited amount of unfunded data requests per year, typically smaller requests. Those that we can work often take longer because we work them as time permits (HRP requests are prioritized)."



README License

FSL for Brain Segmentation in CT Scans

This is an FSL-based pipeline of Bash scripts, which orients, smooths, and segments CT images
The pipeline consists of 3 steps, each with their own Bash script:

1. CT preprocessing
2. CT segmentation (for which there are two scripts to choose from with different thresholds)
3. calculate stats (volume, mean intensity, etc.)

If you use this work in your research please cite: "Knittel JJ, Hoskin JL, Hoyt DJ, Abdo JA, Foldes Oliver CM, Keesler DA, Fife TD, Barranco FD, Smith KA, McComb JG, Borzage MT, King KS. Autor Normal Pressure Hydrocephalus Using CT Imaging for Calculating the Ventricle-to-Subarachnoic Am J Neuroradiol. 2025 Jan 8;46(1):141-146. doi: 10.3174/ajnr.A8451. PubMed PMID: 39746816, PMCID: PMC11735426."

Authors

- Emily Foldes (emily.foldes@barrowneuro.org)
- Jacob Knittel (jacobknittle@creighton.edu)
- Dr. Kevin King (kking@sniweb.net)
- SNI Imaging Lab

Shift to adapting FSL to MRI, running on existing data, looking for more sources potentially analog environments

Research Article | Adult Brain

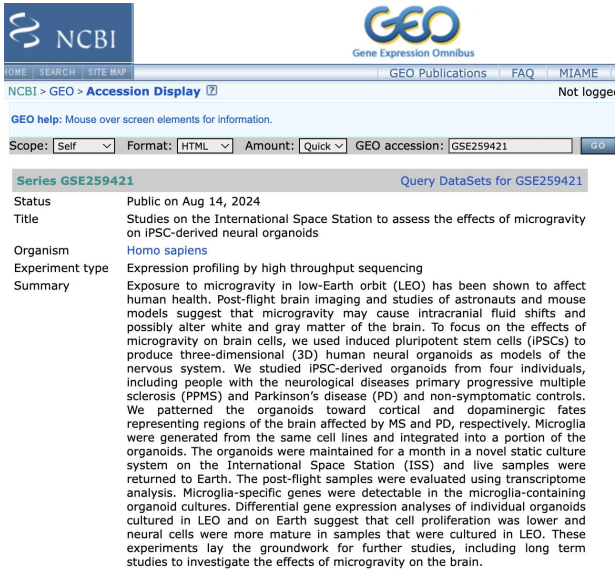
The First Examination of Diagnostic Performance of Automated Measurement of the Callosal Angle in 1856 Elderly Patients and Volunteers Indicates That 12.4% of Exams Met the Criteria for Possible Normal Pressure Hydrocephalus

M. Borzage, A. Saunders, J. Hughes, J.G. McComb, S. Blüml and K.S. King

American Journal of Neuroradiology November 2021, 42 (11) 1942-1948; DOI: https://doi.org/10.3174/ajnr.A7294

Investigating Molecular Changes Using **GSE259421**

- **Used organoids because iPSCs more accurately reflect cells of the SVZ (neural progenitor hypothesis also exists as a potential cause)**
- **Consists of both dopaminergic and cortical organoids, with 4 unique subjects/cell lines & Bulk RNA-Seq**
- **38 days post-microgravity exposure**



Marotta D, Ijaz L, Barbar L, Nijsure M et al. Effects of microgravity on human iPSC-derived neural organoids on the International Space Station. *Stem Cells Transl Med* 2024 Dec 16;13(12):1186-1197. PMID: 39441987

Outline...Still Tentative

Based off literature search (n=79*)

Created list of candidate NPH genes

Removing genes with low counts (n<5), metadata, etc.

Curating expression matrix

Normalization for DESEQ2 (C/O)

Normalization for LASSO (Cortical)

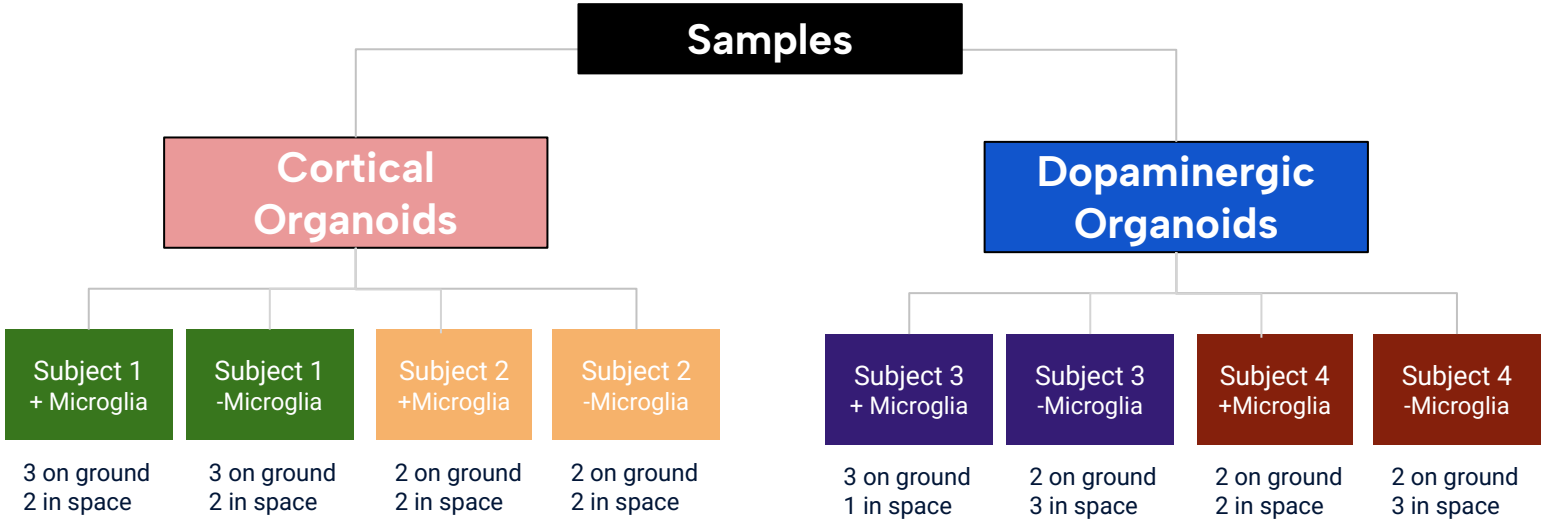
Train model (Cortical)

Normalize DOPA & run on DOPA

Generate confusion matrix & ROC curve

Test on other datasets?? Refine which candidate genes repeatedly show up

Organoid Changes Using GSE259421

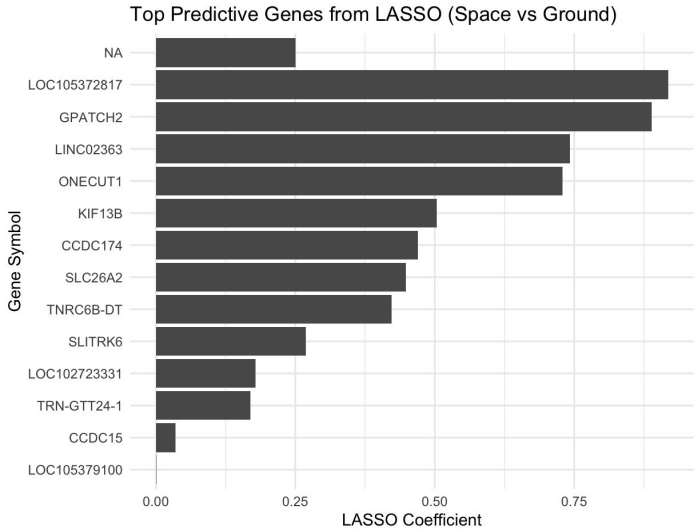


36 samples total, 18 in cortical and 18 in dopaminergic

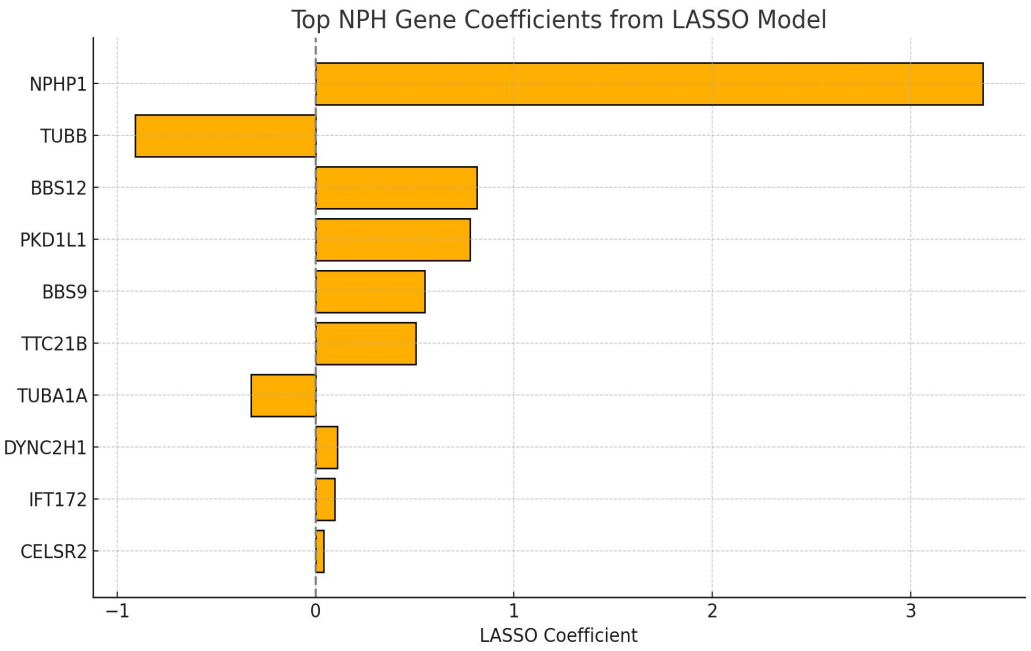
Organoid Changes Using GSE259421 - LASSO on All Grouped

Gene	Cilium	Cilia	Ciliopathy	Ventriculomegaly
KIF13B	5	5	1	0
ONECUT1	4	4	2	0
SLC26A2	2	2	0	0
CCDC15	1	1	0	0
LOC105372817	0	0	0	0
GPATCH2	0	0	0	0
LINC02363	0	0	0	0
CCDC174	0	0	0	1
TNRC6B-DT	0	0	0	0
SLITRK6	0	0	0	0
LOC102723331	0	0	0	0
TRN-GTT24-1	0	0	0	0
LOC105379100	0	0	0	0

Created using Entrez in R.



Organoid Changes Using GSE259421- NPH genes



	Actual	
Predicted	0	1
0	10	0
1	0	8

	GeneSymbol	EntrezID	Coefficient
1	CELSR2	1952	0.04027613
2	IFT172	26160	0.09673852
3	NPHP1	4867	3.36277826
4	TTC21B	79809	0.50564430
5	BBS12	166379	0.81361343
6	TUBB	203068	-0.90900859
7	BBS9	27241	0.54908463
8	PKD1L1	168507	0.77907904
9	DYNC2H1	79659	0.10892893
10	TUBA1A	7846	-0.32543898

Organoid Changes Using GSE259421- NPH genes

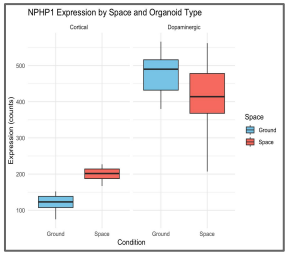
Prediction accuracy drops to ~66.7% :')

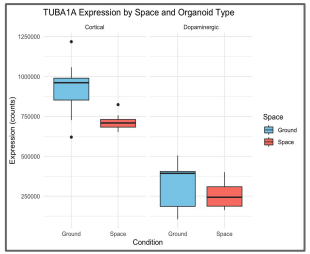
- Dopaminergic organoids have drastically different expression than cortical organoids

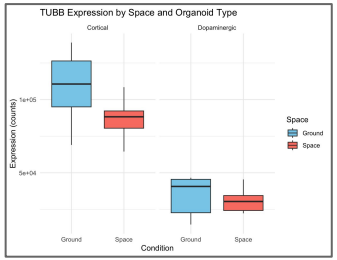
	Actual	
Predicted	0	1
0	7	5
1	2	4

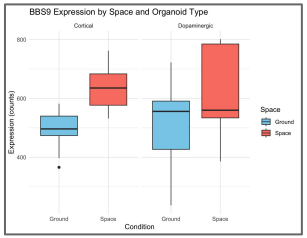
Organoid Changes Using GSE259421- NPH genes

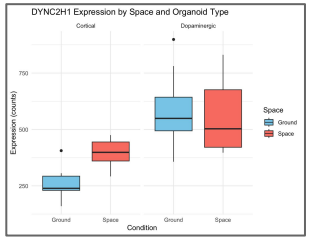
6 genes only sig. different in cortical organoids

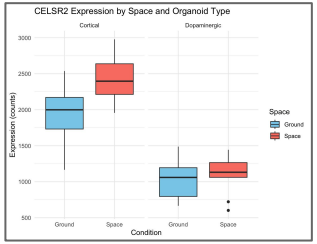






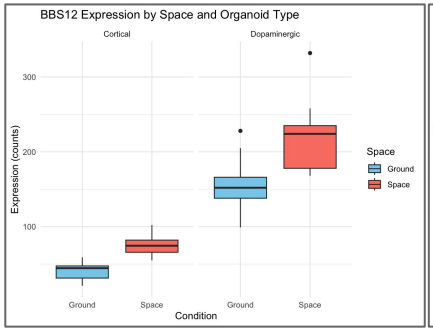


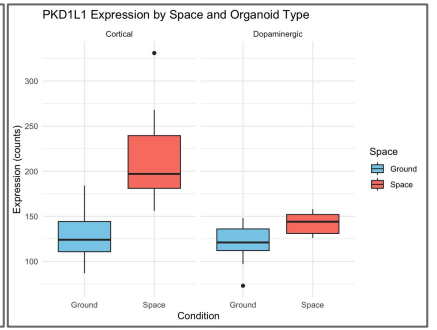


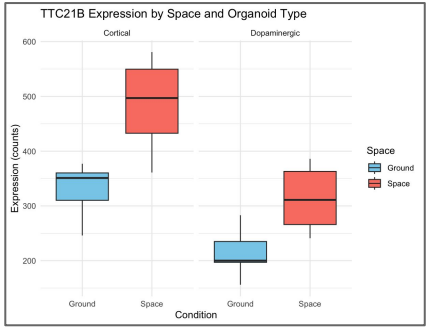


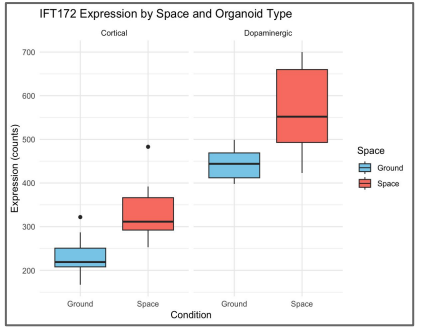
***p<0.05, Wilcoxon rank sum test**

4 genes sig. different in both organoids

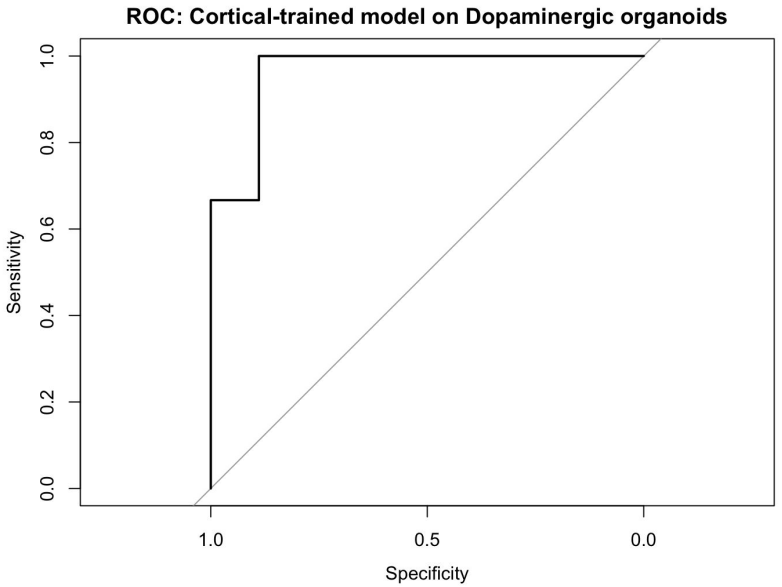








Organoid Changes Using GSE259421- NPH genes

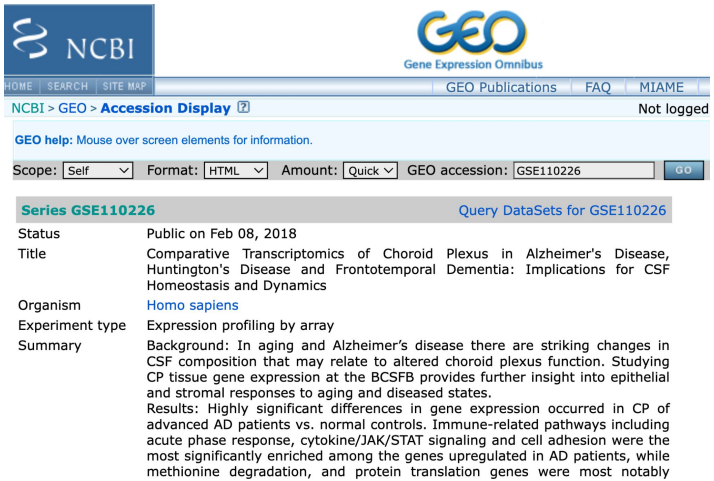


AUC: 0.962962962962963"

- **IFT172, BBS12, TTC21b** are all involved with building & maintaining cilia. **PKD1L1** is found in cilia & plays a role in *sensing fluid flow*

Maybe microgravity impacts cilia-mediated fluid flow sensing and cilia structure across neuron types(?)

Applying findings to On-Earth Data, Future Steps


NCBI

Gene Expression Omnibus

HOME | SEARCH | SITE MAP | GEO Publications | FAQ | MIAME

NCBI > GEO > **Accession Display** Not logged

GEO help: Mouse over screen elements for information.

Scope: Self Format: HTML Amount: Quick GEO accession: GSE110226 GO

Series GSE110226 Query DataSets for GSE110226

Status	Public on Feb 08, 2018
Title	Comparative Transcriptomics of Choroid Plexus in Alzheimer's Disease, Huntington's Disease and Frontotemporal Dementia: Implications for CSF Homeostasis and Dynamics
Organism	Homo sapiens
Experiment type	Expression profiling by array
Summary	Background: In aging and Alzheimer's disease there are striking changes in CSF composition that may relate to altered choroid plexus function. Studying CP tissue gene expression at the BCSFB provides further insight into epithelial and stromal responses to aging and diseased states. Results: Highly significant differences in gene expression occurred in CP of advanced AD patients vs. normal controls. Immune-related pathways including acute phase response, cytokine/JAK/STAT signaling and cell adhesion were the most significantly enriched among the genes upregulated in AD patients, while methionine degradation, and protein translation genes were most notably

- https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE110226

BBS2, GNA12, EVC2 all significantly differentially expressed genes also part of the NPH list. GNA12 was a very strong predictor from the large-scale GWAS, suggesting that what we're seeing here might be overlap in aging/NPH diagnosis overlapping with Alzheimer's.

I'll be running the model we trained on this dataset shortly, still working on aligning probes

Also next steps: applying this to OSD-32 after converting to mouse orthologs (microarray data from mice brains)

High ICP Exosome Patients (Ground Study - OSD363)

CSF

Genes	P-Value	FoldChange	Log2(FoldChange)
STAT5B	0.006064498	106.982234	6.741227425
TGM2	0.010723998	58.04288723	5.85904738
CD86	0.017767216	0.035699093	-4.807968769
S100A9	0.036088464	91.52837469	6.516147157
RIPK2	0.04805839	0.111435553	-3.165718504

Plasma

Genes	P-Value	FoldChange	Log2(FoldChange)
CXCR3	0.00768178	0.05214204	-4.2614092
TLR3	0.0159636	0.19328631	-2.3711887
LEFTY2	0.02011616	2.6443669	1.40292236
TNFSF4	0.03453125	6.00897553	2.58711905
CD70	0.03805422	0.11625619	-3.1046206
EREG	0.03805422	51.925596	5.69837397
CD80	0.03822381	0.16800093	-2.5734589