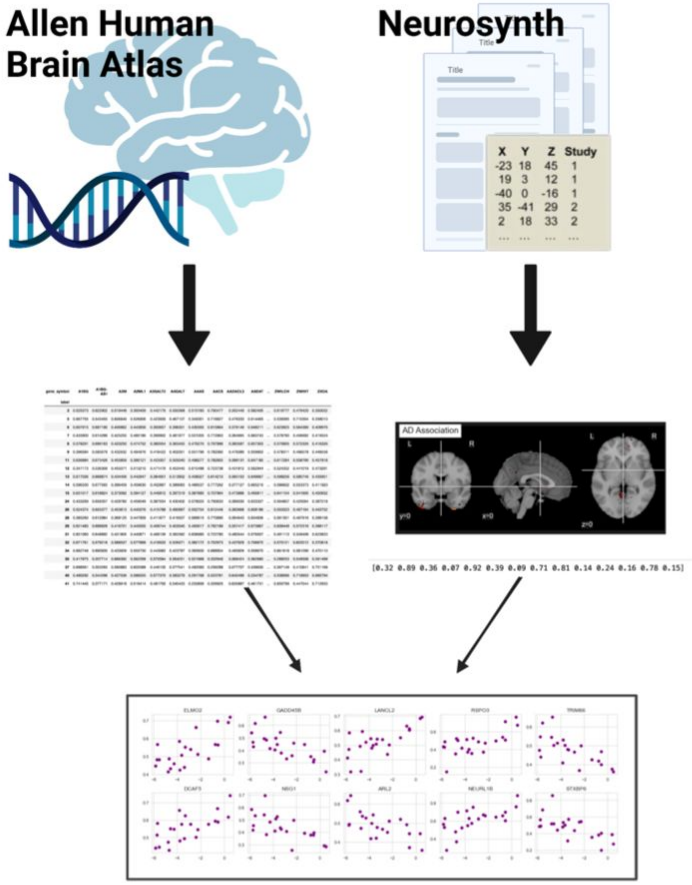
Gene Expression Analysis of Alzheimer's Disease

With Neurosynth, AHBA, and Neuromaps

- Previous Project (COGS 138)
  - Neurosynth
  - AHBA
- Neuromaps
  - Datasets, Transformations, Comparisons/Stats
- Conclusion
  - Next steps

Previous Project

- Allen Human Brain Atlas (AHBA) microarray data
  - → gene expression matrix
    - 6 donors brain-wide gene expression data
    - Accessed via abagen
- Neurosynth term-based meta-analysis of fMRI articles
  - → AD-association array
    - 267 studies, 8375 activations
- Alzheimer's Disease Gene Analysis - 3 ways
  - **1** Over- and under-expressed genes in five highest AD areas
  - **2** AD association - expression correlation
  - **3** GBA ('guilt by association' - genes most correlated with four literature known AD genes: APOE, APP, PSEN1, PSEN2)



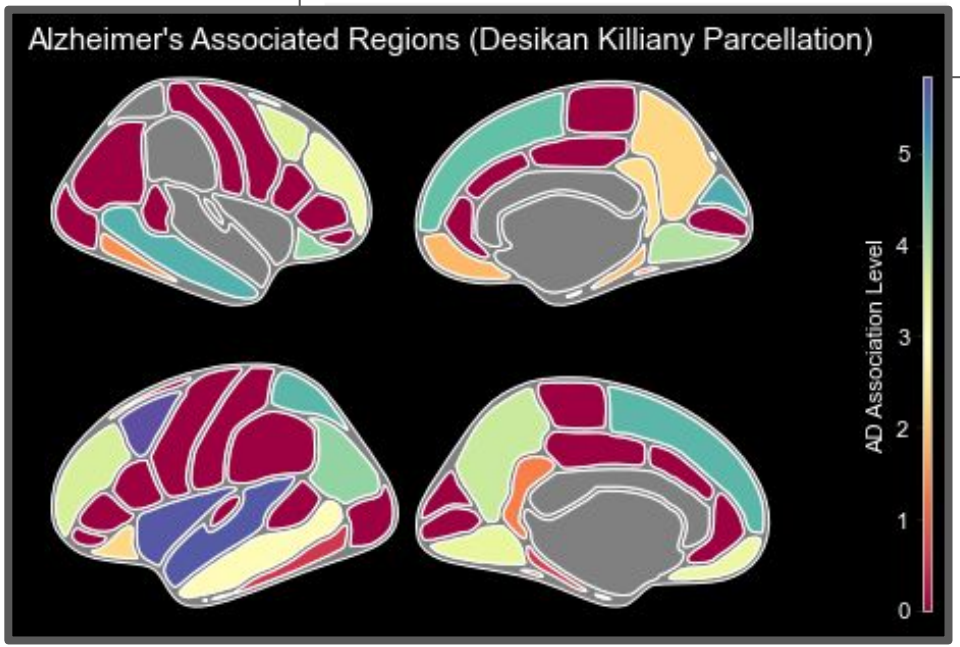
Alzheimer's Disease

- Pathologically characterized by the presence of **amyloid plaques** between neurons and **tau tangles** within neurons, but whether these are causative* or consequential is unknown
- Sporadic (late onset) vs Familial (early onset) AD
  - Sporadic: 95% of cases
    - APOE (e4) risk factor
  - Familial: 5% of cases
    - APP, PSEN1, PSEN2
- Reimagining Alzheimer's Disease - An Age-Based Hypothesis
  - Diverges from amyloid cascade hypothesis* and proposes new steps of progression
    - (initiating injury → microglial activation and inflammatory response → altered brain cell physiology → major synaptic dysfunction and neuronal loss → AD)

Previous Project

- 5 most AD associated brain regions
  - Entorhinal Cortex
  - Hippocampus
  - Inferior Temporal Cortex
  - Parahippocampal
  - Fusiform Gyrus

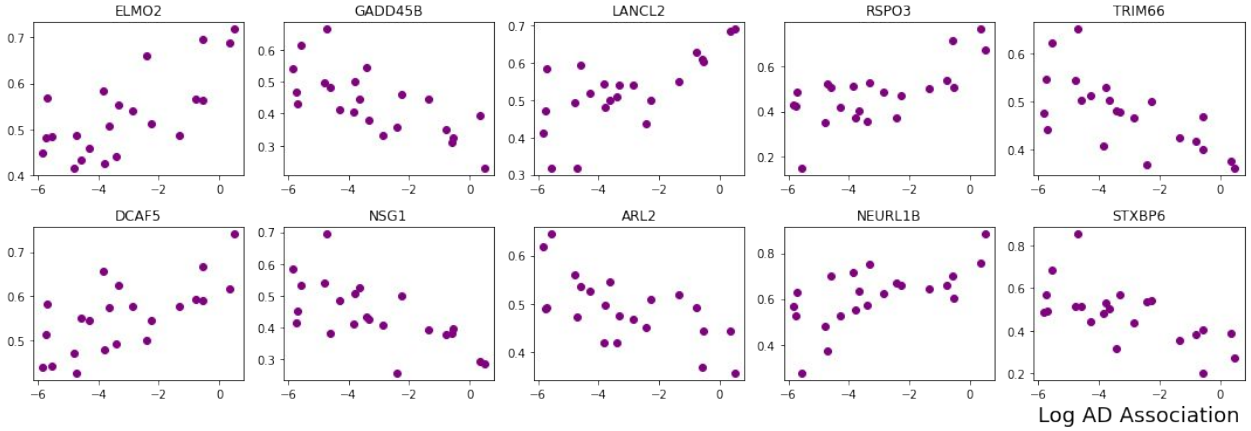
id	label	hemisphere	structure
1	bankssts	L	cortex
2	caudalanteriorcingulate	L	cortex
3	caudalmiddlefrontal	L	cortex
4	cuneus	L	cortex

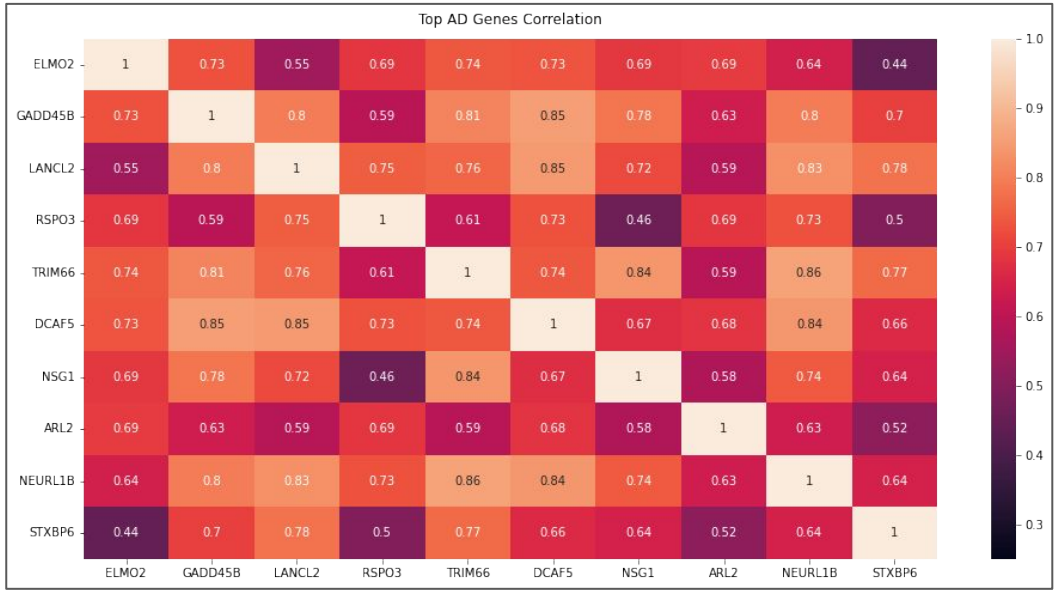


Over-expressed genes in top Neurosynth AD regions (entorhinal, hippocampus, inferior temporal, parahippocampal, fusiform)	CTNND2, FAM171B, DIO2, PEA15, GUK1, C14orf132, TYRO3, PHF24, NR2F2, PYDC1, HIST1H2BK, KRT14, NSMF, RAB27B, FBXO41, FABP7, C1orf50, BMS1P14, CACNG3, FOXG1, CHST9, XYLT1, GPT2, GPR34, ASCL2, SOWAHA, KCNG1, C2orf80, LSM3, MMD, NEURL1B, STX1A, C3orf14, DEAF1, PCK2, ADGRV1, RILPL2, IL1B, PID1, IL33, UG0898H09, C1orf21, SELENBP1, KCNIP3, PPP4R4, ST6GALNAC6, RTL6, DDN, PARVB, RIIAD1, DLG2, SRRD, EIF3H, LYRM9, SNX7, TAGLN3, TMEM200A, OLFM1, BDKRB2, PALMD, EMX2OS, MYO16, ERFE, GPC5, UROS, C2CD4C, PTRHD1, METTL6, SBF1, KRT17, LINC00937, EHBP1L1, LINC02217, CPLX3, GMFB, SOBP, CNTN5, HDGFL3, CLDN10, WIZ, ALKAL2, ALDH2, HIRA, GMFG, POLE4, CCDC148, GABRA5, SLC1A2, ST20, VPS29, SHC3, PDYN, SCG3, ADIRF, EXOC3L2, C2orf69, HPCAL4, MGST1, WNT7B, PRPH2, VSIG4, NPTX1, HCG23, PPM1M, HSPB11, MPHOSPH6, EMX2, CPE, NPY, LHX2, ARL16, FAM149A, SLC25A18, MYRIP, CCND2, NUPR2, OGG1, GDA, TTC9B, EAF2, TKFC, LRRC56, VTI1B, SLC26A4-AS1, VIM, EPOP, KLK7, BEGAIN, YPEL1, ETNPPL, ADGRG1, CEP170B, BORCS7, PCOLCE2, SLC16A2, TSTD1, PALM, CGREF1, NEURL1, GTF2H5, GTF3C6, KCNMB4, NKAIN3, LOC100507516, CFD, CEP83, ENC1, RXRA, CA11, EMID1, ERICH6-AS1, UQCR11, HSPB3, ERC2, ADD3, PTPRZ1, PDE2A, IFT22, RGS4, ACP1, RPL12, NISCH, CELF3, SMAD2, TMSB10, DLL3, OXCT1, FAM107A, ARNT2, HOPX, RAB3B, STX17-AS1, ELFN2, CENPW, SEMA4A, B4GALT2, GGCT, PACSIN1, CBX6, ARHGAP6, PRKCD, KIF21B, RAPGEF4
Under-expressed genes in top Neurosynth AD regions (entorhinal, hippocampus, inferior temporal, parahippocampal, fusiform)	CHN2, OR6C76, C18orf25, ZBTB21, PPP4R3A, STC2, OGDHL, FLT4, RILP, ZBTB1, ACHE, CPNE9, EIF5A2, ZMAT4, TCHH, ALG3, LTB, DACH1, HAPLN4, CUL5, LANCL3, TRAM2, SMPX, VASH2, FBXO32, ELMOD2, FER1L4, TRIM52, ARMC8, SCN1A, ODF2, LAG3, DENND1B, ZDHHC5, EPB41, SYT2, RICTOR, ELMO3, PARD6B, LYST, VAMP1, CREBRF, CORO6, ZNF136, ATP4A, KBTBD3, TGM1, ASB13, FZD6, ALS2CL, LRCH1, SLC25A32, SPTSSB, LINC00515, MAP2K3, MPP1, TP53TG3D, RFX7, CDH7, EXTL2, TDRD1, SV2C, CNST, KANSL1, RARB, TNNT2, LGI3, FGF9, HLTF, XKR6, TBC1D19, HS3ST5, DPP7, UBN2, TUBD1, SIAE, AVPI1, EPN3, PIM3, SERTAD4, NRG1, SLC38A2, OSBPL5, INSM2, TPBG, GPAT3, LOC727896, ADAM22, INTS9, P2RX6, CHRNA2, PAIP1, GPCPD1, AMDHD1, ONECUT2, HR, KNG1, MYO15A, INTS4P1, GNG13, ARHGEF17, SHD, IFNLR1

Top 10 AD Correlated Genes

GENE X GENE





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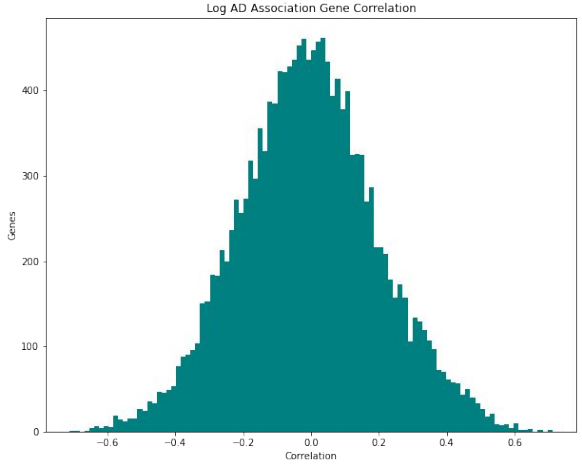
AD X GENE

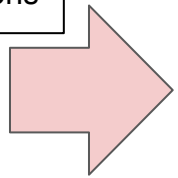


Genes known to be involved in Alzheimer's Disease:

- APOE
- APP
- PSEN1
- PSEN2

> "Potential disease genes can be identified using a guilt-by-association (GBA) approach that highlights genes that are co-expressed with multiple disease genes." [Van Dam 2018]

top gene to AD gene correlations



APOE

gene_symbol	
EDNRB	0.986767
MT2A	0.965316
ADGRA3	0.963022
MT1B	0.961312
LST1	0.960423
AQP4	0.960042
MT1L	0.959132
ARHGEF40	0.959022
KCNN3	0.955905
ACSBG1	0.955781

APP

gene_symbol	
SLC38A7	0.897132
UBALD2	0.889848
CCDC157	0.884438
TAPT1-AS1	0.883525
PRR14L	0.882558
ARID1A	0.880863
MSL1	0.880702
LINC01881	0.879183
PRPF40A	0.878882
ZNF14	0.877206

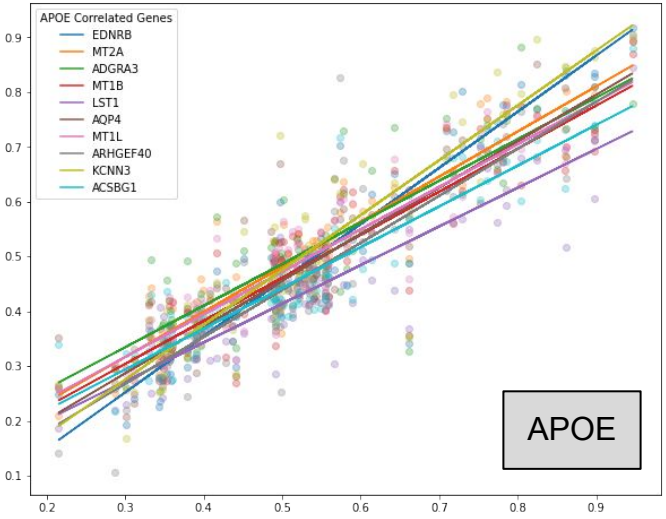
PSEN1

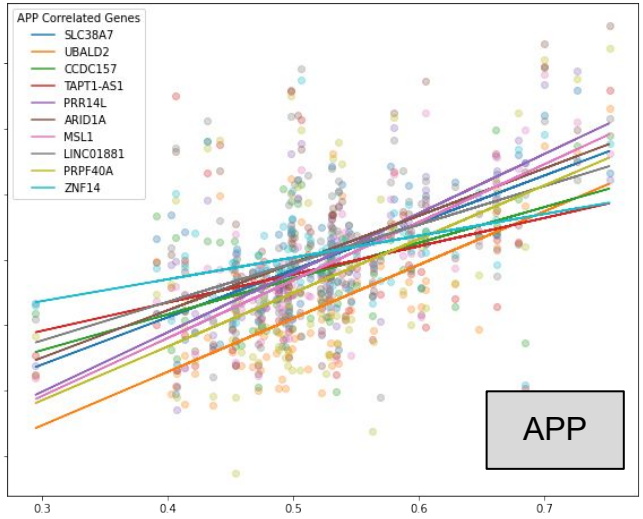
gene_symbol	
THBS2	0.965358
FRMD4B	0.963605
ZFYVE16	0.956477
C10orf90	0.955541
SLAIN1	0.953328
CLDN11	0.949402
LAMP2	0.949338
SHROOM4	0.947610
GALNT15	0.945550
KLK6	0.943128

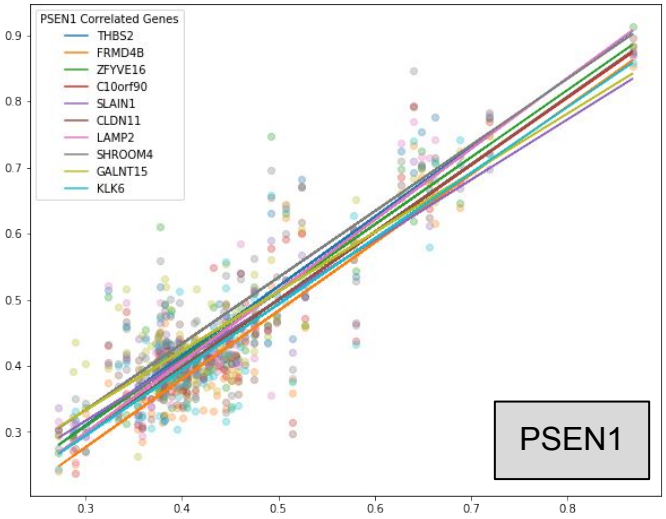
PSEN2

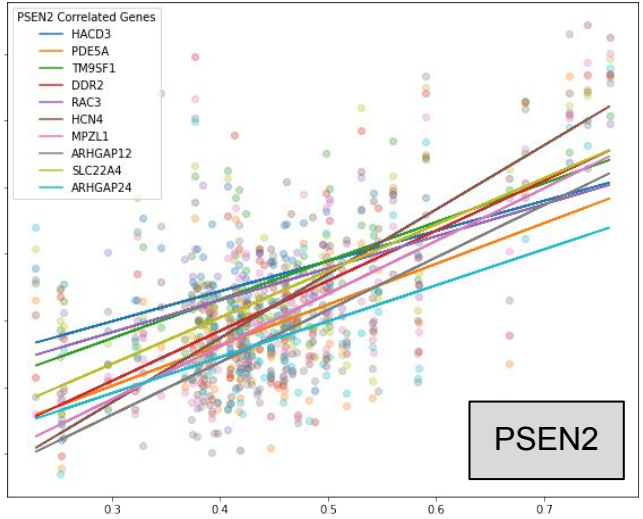
gene_symbol	
HACD3	0.905230
PDE5A	0.904320
TM9SF1	0.894978
DDR2	0.892764
RAC3	0.890650
HCN4	0.882533
MPZL1	0.881878
ARHGAP12	0.881367
SLC22A4	0.879597
ARHGAP24	0.878208

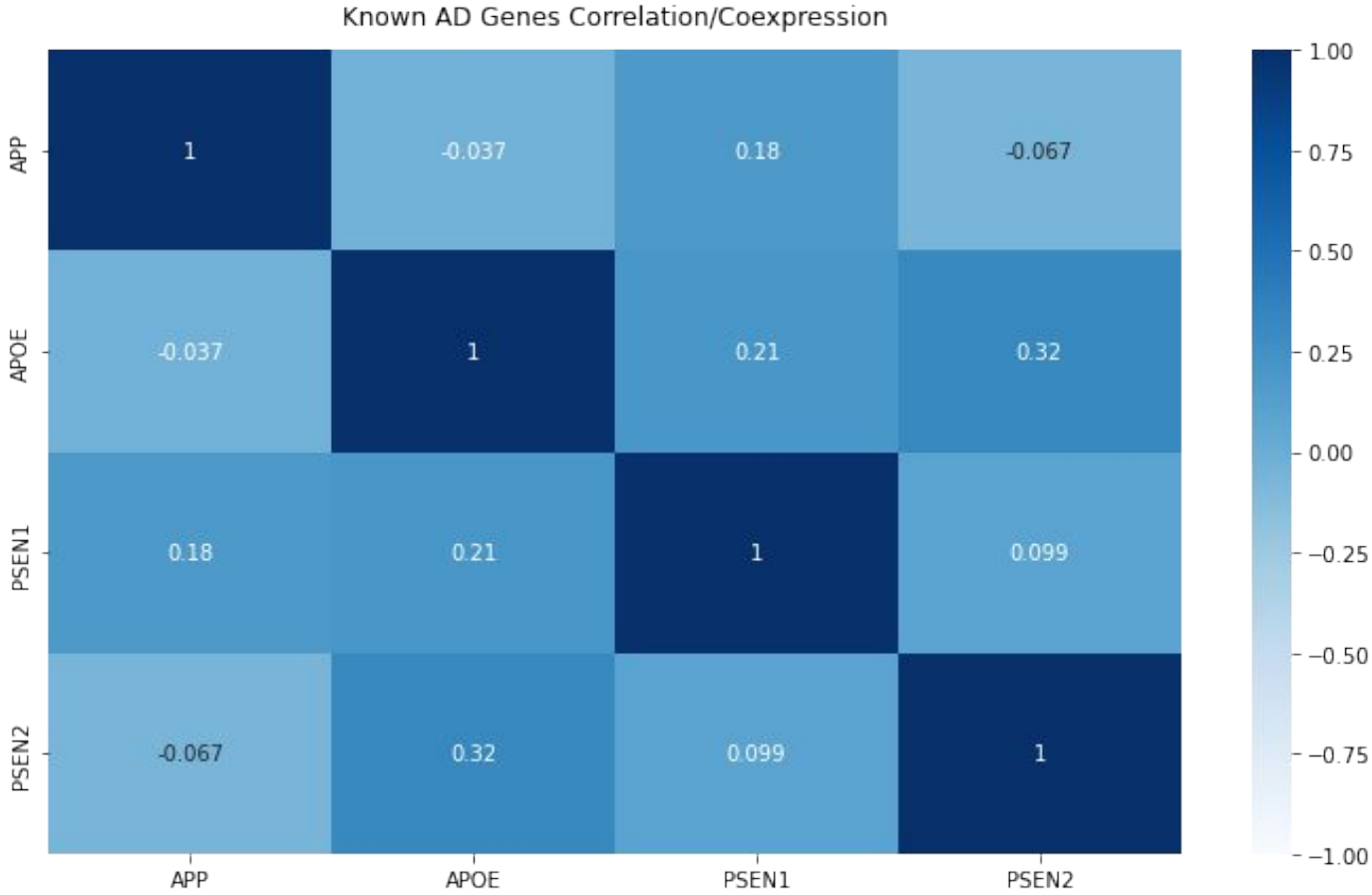
top gene to AD gene correlations










Known AD Genes Correlation/Coexpression
APP
APOE
PSEN1
PSEN2
1
-0.037
0.18
-0.067
-0.037
1
0.21
0.32
0.18
0.21
1
0.099
-0.067
0.32
0.099
1
APP
APOE
PSEN1
PSEN2
1.00
0.75
0.50
0.25
0.00
−0.25
−0.50
−0.75
−1.00

Neuromaps Overview

- Standardized workflow for contextualizing brain maps with broader literature

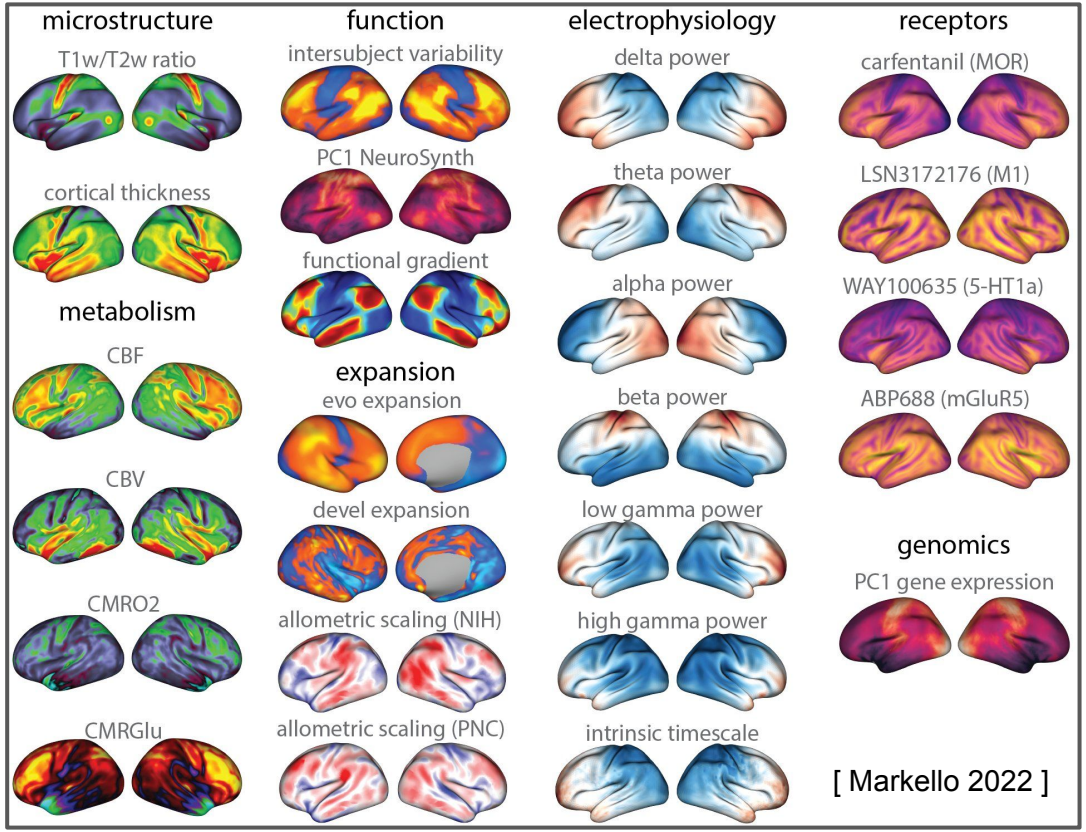
- **Access to a wide repository of brain maps taken from the published literature**
  - available_annotations(), available_tags()
- **High-quality transformations between four standard coordinate systems**
  - MNI152, fsaverage, fsLR, CIVET
- **Uniform interfaces for statistical comparisons between brain maps**
  - Method for estimating map-to-map similarity that accounts for spatial autocorrelation

Neuromaps

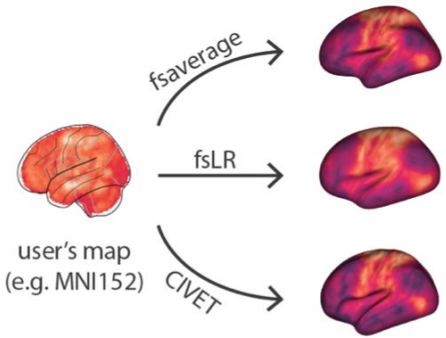
Datasets

- Currently has 72 brain annotations from recent literature and allows users to upload their own annotations to dataset
- Annotations are uploaded in their original coordinate system and organized under tags:

  [ASL, MEG, MRI, PET, fMRI, functional, genetics, meta-analysis, receptors, structural]



Neuromaps



Transformations

- Registration fusion framework
  - for mapping volumetric to surface
- Multimodal surface matching (MSM) framework
  - for mapping surface to surface
- MNI152 → civet, fsaverage,fsLR, MNI152
- civet → fsLR, fsaverage, civet
- fsLR → civet, fsaverage, fsLR
- fsaverage → civet, fsLR, fsaverage

Parcellations

- Performing analysis on voxel or vertex level data is computationally intensive

```
from neuromaps.parcellate import Parcellater
parc = Parcellater(atlas['image'], 'mni152')
AD_parc = parc.fit_transform(AD_association, 'mni152')
```

Neuromaps

Statistics

1. Transform brain annotations of interest to same space and density/resolution
2. Compare images or arrays

Permutation Testing 

- Spatial null models can be used to assess the significance of these correlations
- Accounts for spatial autocorrelation which can dramatically inflate p-values and drive false results in gene analyses

Naive Models

parametric - scipy pearsonr

```
# input must be array-like, same length
r, p = stats.pearsonr(img_civet1,img_civet2)
print(f'Correlation: {r}, P-value: {p}')
```

```
Correlation: 0.5343663262765331, P-value: 0.0
```

non-parametric - neuromaps stats method

Calculates two-tailed p-value for hypothesis of whether samples a and b are related using permutation tests.

```
# input must be array-like, same length
r, p = neuromaps.stats.permtest_metric(img_civet1, img_civet2)
```

```
r, p
```

```
(0.5343663096427917, 0.000999000999000999)
```

Spatial permutation models

neuromaps compare_images with null model

```
rotated = nulls.alexander_bloch(civet1, atlas='civet', density='41k',
                                n_perm=100, seed=1234)

r, p = neuromaps.stats.compare_images(civet1,civet2, nulls=rotated)
print(f'Correlation: {r}, P-value: {p}')
```

```
Correlation: 0.3770379047549592, P-value: 0.009900990099009901
```

vs. neuromaps compare_images without providing a null model

```
r1 = neuromaps.stats.compare_images(civet1,civet2)
print(f'Correlation: {r1}')
```

```
Correlation: 0.3770379047549592
```

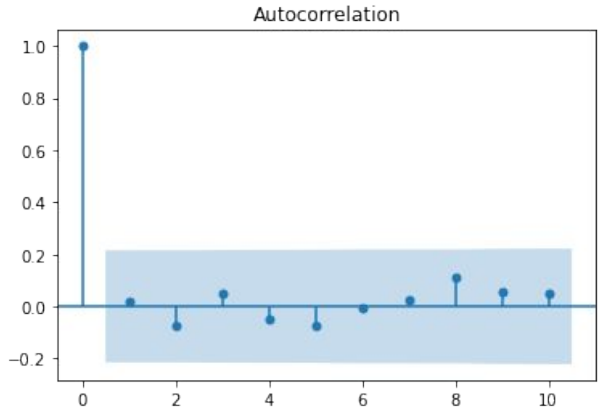
Spatial Autocorrelation

"In spatially-embedded systems—like the brain—**neighboring data points are not statistically independent**, violating the assumptions of many common inferential frameworks. As an example, consider computing a correlation between two brain maps. When using a standard parametric null (i.e., the Student's t-distribution), the spatial autocorrelation of the maps **violates the inherent requirement that the model errors are independent and identically distributed** (i.i.d.)."

Inflated p-values

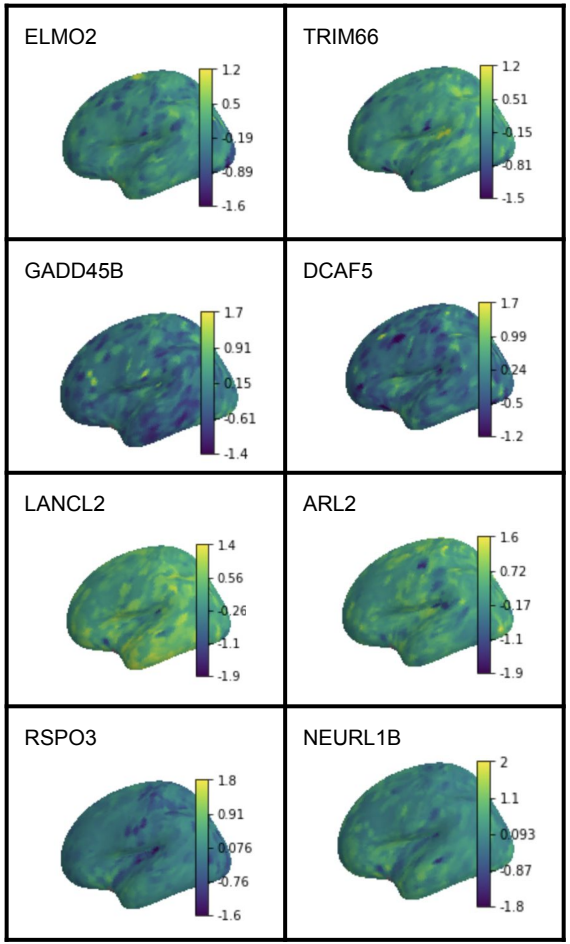
Options:

- Always compare brain maps with spatial nulls
  - If using MNI152 data, transform to surface first
- Check for autocorrelation first, if low use naive non parametric `neuromaps.stats.permtest_metric()`



AD Association Map Autocorrelation: Low

NEUROMAPS MEG OSCILLATION MAPS

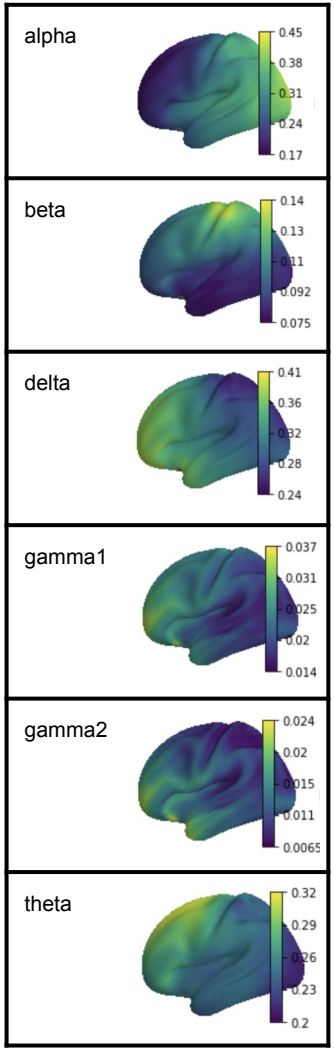


MEG maps to AD Genes

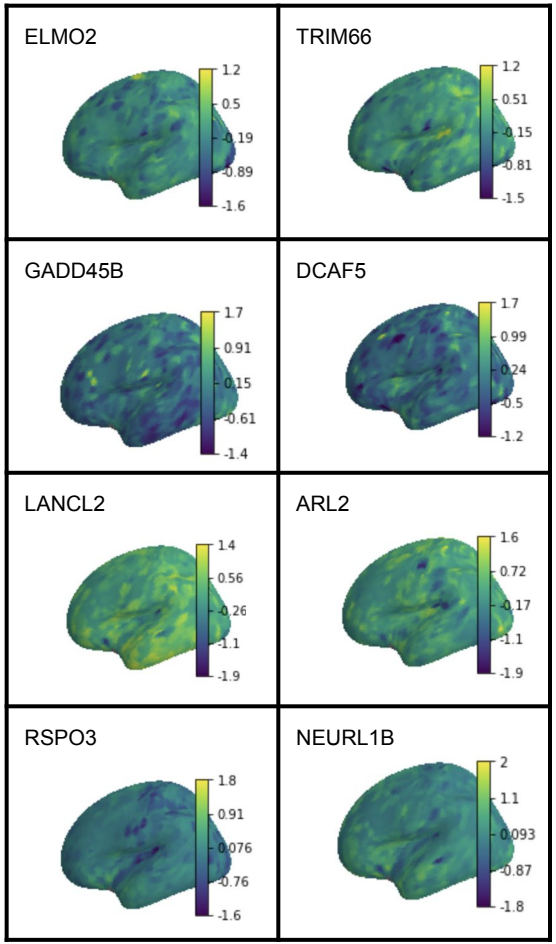
- Correlation results were generally low
  - RSPO3 & alpha: r = -0.217
  - NEURL1B & alpha: r = -0.225
  - NEURL1B & beta: r = -0.275
  - GADD45B & delta: r = -0.302
  - RSPO3 & delta: r = 0.312
  - NEURL1B & delta: r = 0.359
  - GADD45B & gamma2: r = -0.295
  - RSPO3 & gamma2: r = 0.292
  - NEURL1B & gamma2: r = 0.321

MEG maps cross correlation

- alpha & delta: r = -0.838
- alpha & gamma1: r = -0.880
- alpha & theta: r = -0.886
- delta & gamma2: r = 0.843

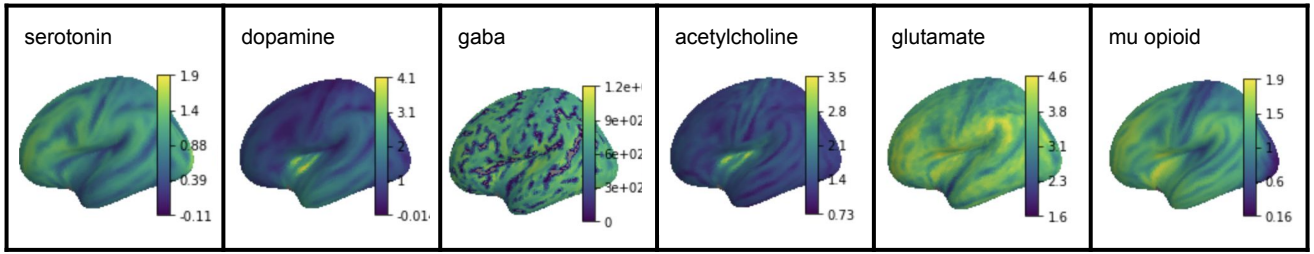


NEUROMAPS RECEPTOR MAPS / AD GENES CORRELATION

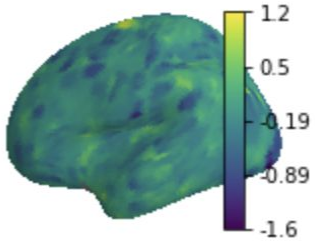


Moderate correlation (r > 0.3) & statistically significant (p < 0.05)

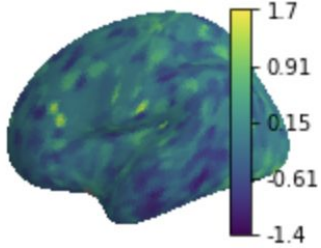
```
receptor maps || genes

serotonin: ELMO2, GADD45B, LANCL2, TRIM66, NEURL1B
dopamine: STXBP6, GADD45B, LANCL2, RSPO3, NEURL1B
gaba: GADD45B, LANCL2, RSPO3, TRIM66, NEURL1B, STXBP6
norepinephrine: NONE
acetylcholine: GADD45B, LANCL2, RSPO3, TRIM66, NEURL1B, STXBP6
glutamate: GABB45B, LANCL2, RSPO3, TRIM66, NEURL1B
mu opioid: STXBP6
```



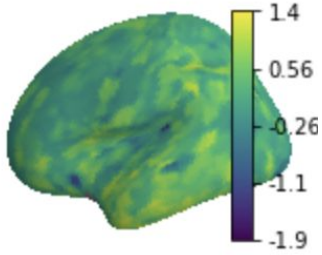
ELMO2



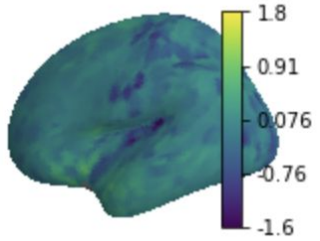
GADD45B



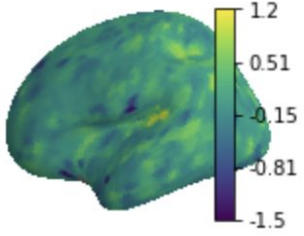
LANCL2



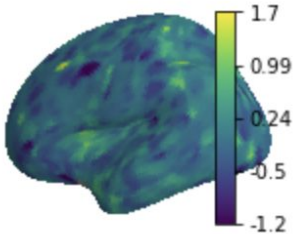
RSPO3



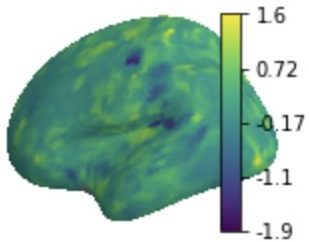
TRIM66



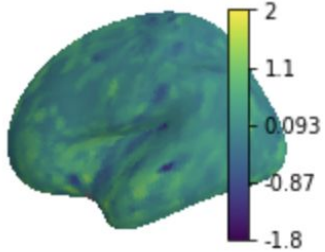
DCAF5



ARL2



NEURL1B



Next Steps

- Alzheimer’s Disease Neuroimaging Initiative (ADNI)
- Allen Institute: Aging, Dementia, TBI Dataset
- Volumetric // Parcellated Spatial Null Models
    - correlation is altered when transforming mni152 → fsaverage but available neuromaps methods were too computationally intensive
- Continue pairwise correlations of different Neuromaps annotations and Neurosynth terms related to AD (episodic /working memory, mild cognitive impairment, atrophy, age, etc.)

Links & References

- Markello, RD, Hansen, JY, Liu, ZQ, Bazinet, V, Shafiei, G, Suarez, LE, Blostein, N, Seidlitz, J, Baillet, S, Satterthwaite, TD & Chakravarty, M. (2022). Neuromaps: structural and functional interpretation of brain maps. Biorxiv. doi:10.1101/bioRxiv.475081
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- R.D. Markello, B. Misic (2021). Comparing spatial null models for brain map. Neuroimage, 236, p. 118052, 10.1016/j.neuroimage.2021.118052
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- Neurosynth: https://neurosynth.org
- Access Allen Human Brain Atlas Gene Expression Data w/ abagen: https://abagen.readthedocs.io
- Check for autocorrelation in Python: https://scicoding.com/4-ways-of-calculating-autocorrelation-in-python/
- Neuromaps Setup & User Guide: https://netneurolab.github.io/neuromaps/index.html
- Information and recommendations for spatial nulls: https://markello-spatialnulls.netlify.app/index.html
- Project repo: https://github.com/voytekresearch/BIRD