Research Meeting

UK Biobank Working Task, Polygenic Risk Scores, Low Rank Mixup Augmentations, and Imputation of FC

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Outline

UK Biobank

Working Task

Working Task Scan

- We have finished pre-processing the UKB working task scan
- Hariri faces/shapes "emotion" task [Hariri et al. 2002, Barch et al. 2013][1]
  - 34,898 subjects with first working task scan
  - 2,550 subjects with second working task scan
  - 40,627 subjects with first resting state scan
  - 2,867 subjects with second resting state scan
- These are the subjects for which our SPM12 pipeline succeeded and we have MNI-space volumes/timeseries
  - Resting state scan: 20227-2/3
  - Working task scan: 20249-2/3

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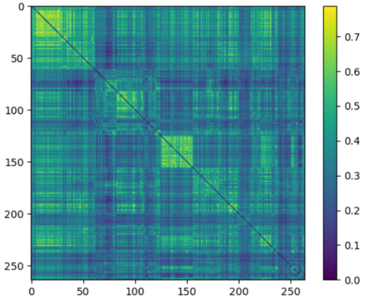
[1] UK Biobank Brain Imaging Documentation Version 1.9 September 2022

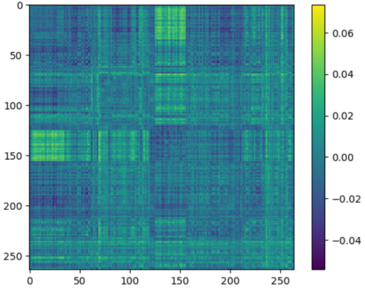
Rest and Working Mean FC First Scan

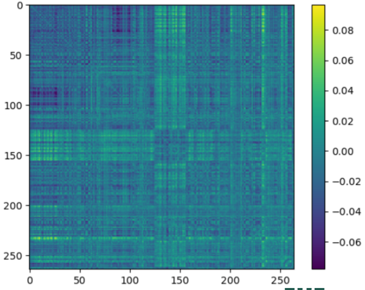
- Average resting state and working task FC for first scan
- Left: resting state
- Right: working task



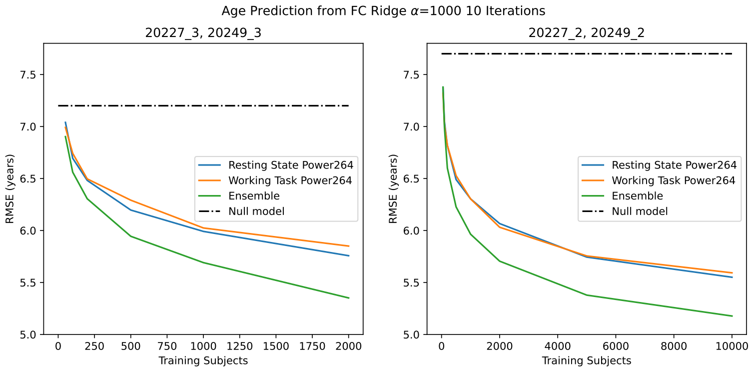
Difference Between First and Second Scan

- Difference in mean FC between longitudinal scans
- Left: resting state
- Right: working task
- Both tasks show difference between first and second longitudinal scans, with somewhat similar patterns



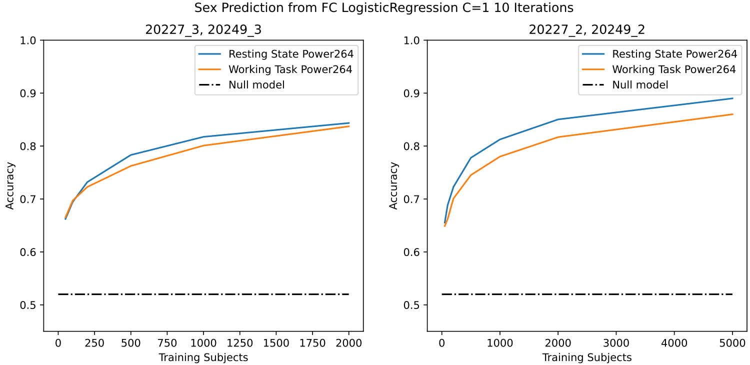


Working Task Age Prediction



- Second scan (left) and first scan (right)
- Ensemble of resting and work significantly better
- May possibly be able to make ensemble with ICA55 FC and PC

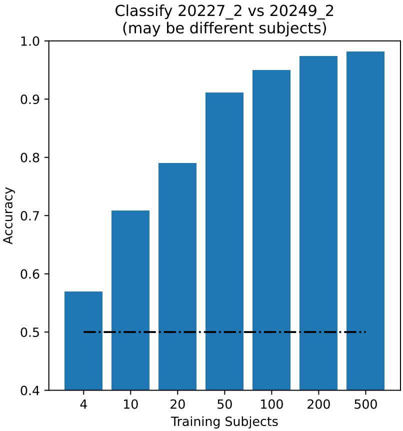
Working Task Sex Prediction



- Working task slightly worse that resting state
- Less clear ensemble would improve classification
  - More to say on this in later section

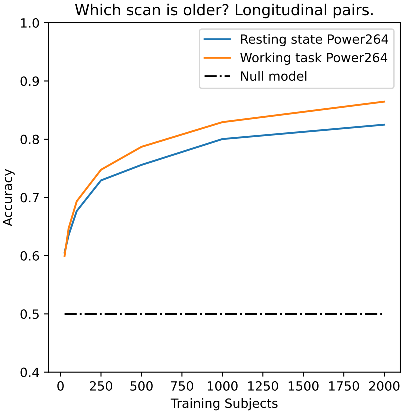
Distinguishing Resting State and Working Task

- We see that the easiest thing to do with fMRI (FC) is to distinguish between different scanner tasks



Longitudinal fMRI First vs Second Scan

- As we found for the resting state, it is possible in most case to pick which of the working task scans of a pair is older
- Input is difference of FCs



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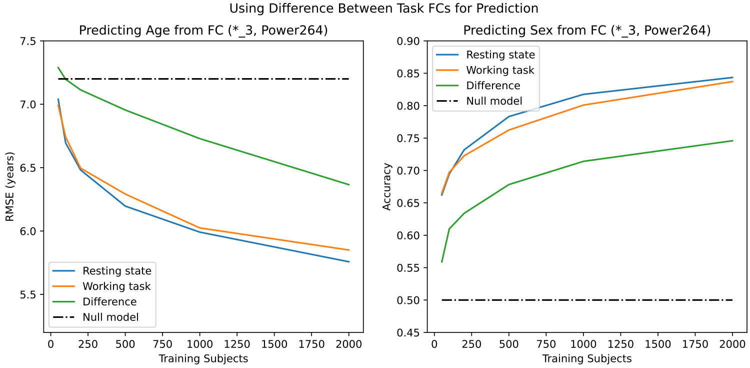
Predicting Age and Sex from Difference of Scanner Task FCs

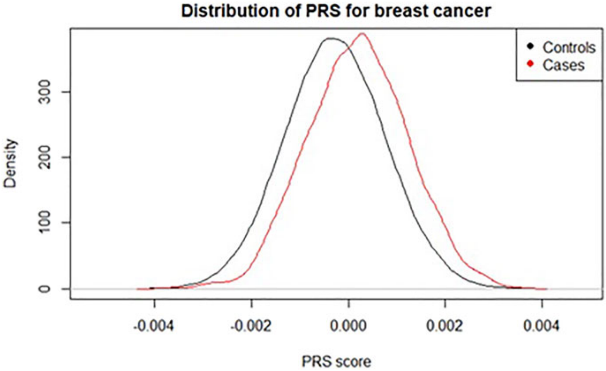
- Both age and sex can be moderately well predicted from the difference of scanner task FCs (age $\alpha = 1000$, sex $C = 1$)
- Not as well as from either of the original FCs
- May be possible to use in ensemble



Polygenic Risk Scores (PRS)

Tutorials for Calculation of PRSs

- Many tutorials exist for conducting genome wide association studies and calculating PRSs (see figure below)[2]
- The UKB provides pre-calculated scores



[2] Collister et al. (2022) 10.3389/fgene.2022.818574

Almost 90 Risk Scores

- UKB includes polygenic risk scores for almost 90 fields (26201-26290)
  - 28 diseases
  - 25 quantitative traits
  - "outperform a broad set of 81 published PRSs"[3]
- e.g., genetics principal component [ancestry] (26201), Alzheimer's (26206), height, obesity, schizophrenia risk
- Includes standard and enhanced risk scores, not overlapping subjects

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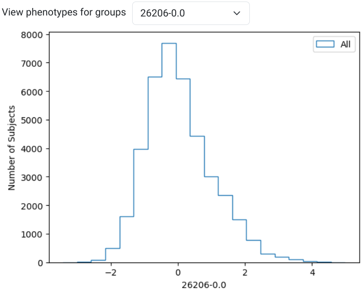
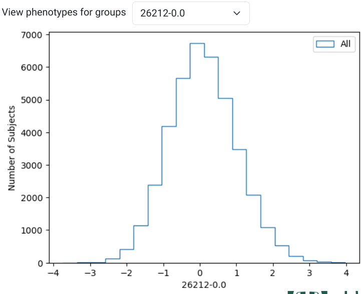
[3] Thompson et al. (2022) 10.1101/2022.06.16.22276246

Example of PRSs

- We correlate these per-subject scalar PRS scores with each functional connectivity feature (34,716 for each subject)
- Correcting for multiple comparisons (Bonferroni)
- Here we see PRS histograms for AD (26206) and atrial fibrillation (26212)





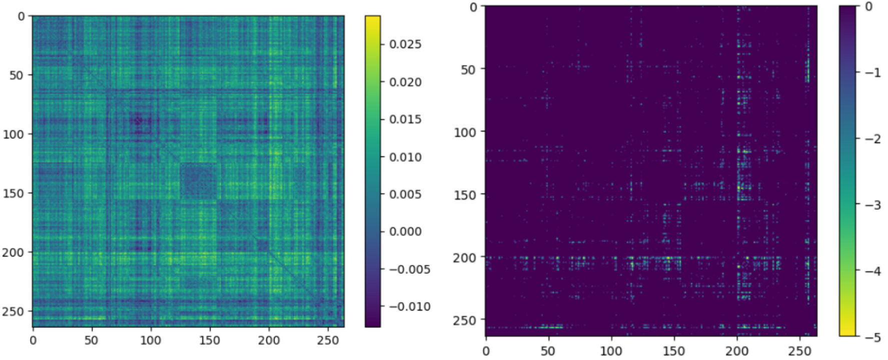
Most Significant FC-PRSs

General Health Trend

Interestingly, many of the most highly FC-correlated features are indicative of general health or physical build

- Atrial fibrillation (26212), BMI (26216/26217), bone mineral density (26234), height (26240/26241), HDL cholesterol (26242), hypertension (26244), ischemic stroke (26248), osteoporosis (26258/26259), type II diabetes (26285)
- Less significant: cardiovascular disease (26223), coronary artery disease (26227)
- Others: principal genetic component (26201), Parkinson's disease (26260), schizophrenia (26275/26276)

Atrial Fibrillation (26212)



- Left: FC correlations with PRS
- Right: Log of p-value of correlations (clipped at -5)

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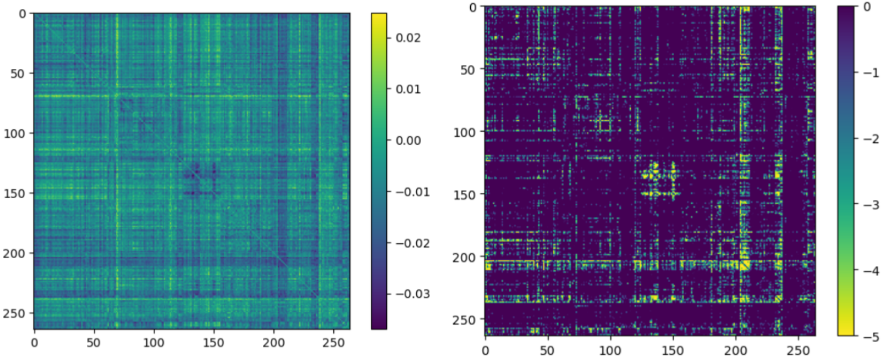
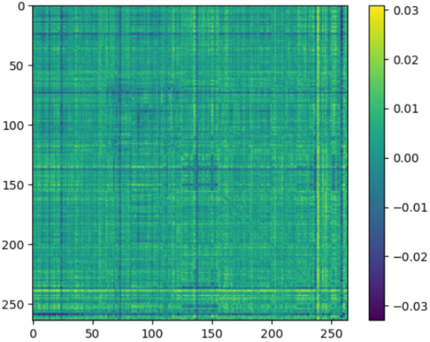
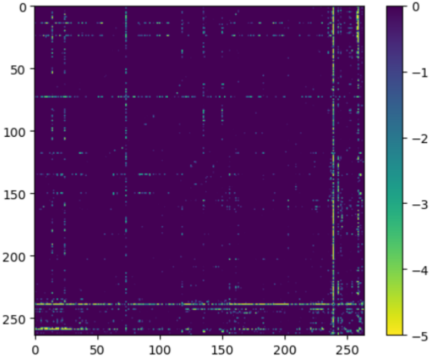
BMI (26216/26217)

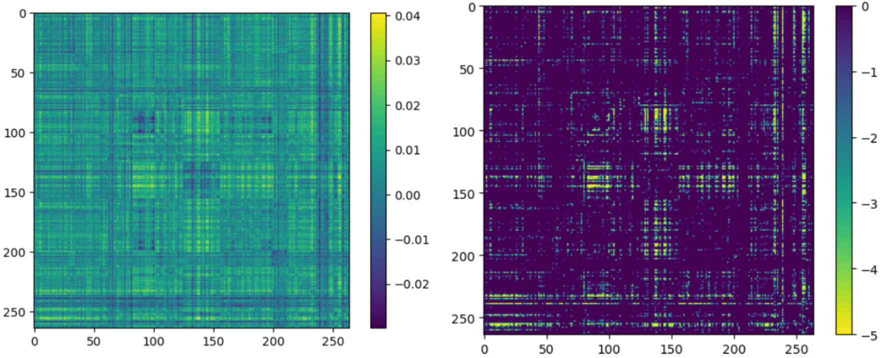


Bone Mineral Density (26234)



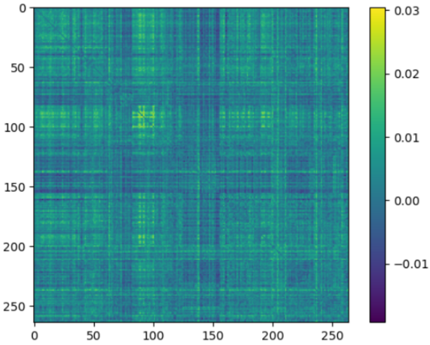


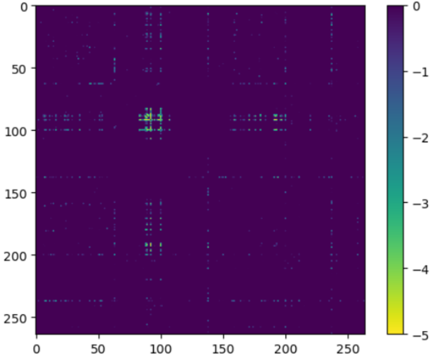
Height (26240)



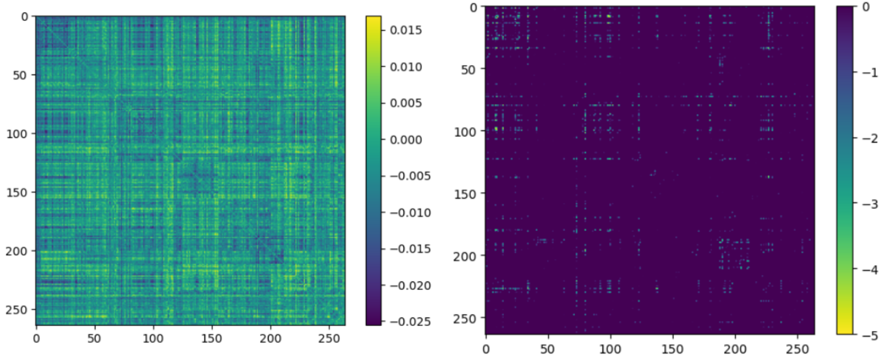
- Valid separately for males and females

HDL Cholesterol (26242)

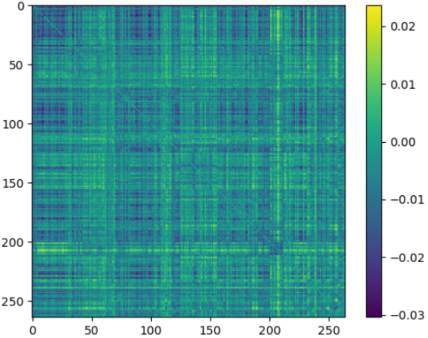


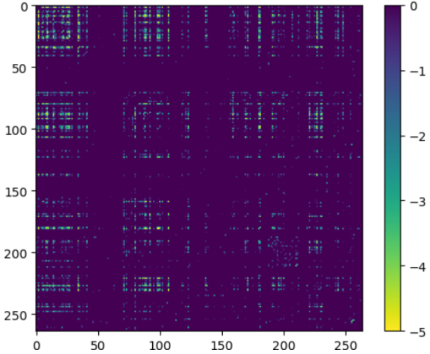


Hypertension (26244)



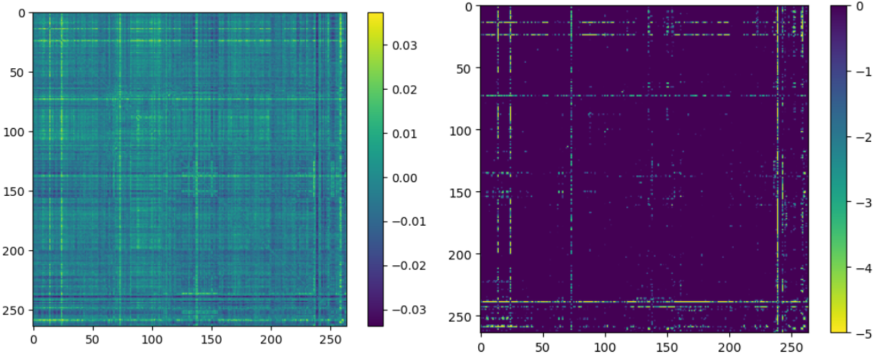
Ischemic Stroke (26248)





- Similar to hypertension above

Osteoporosis (26258)



- It seems there are about 5 ROIs that are consistently associated with osteoporosis (and BMD)
- Either increased or decreased connectivity

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BMD and Osteoporosis Associated FCs

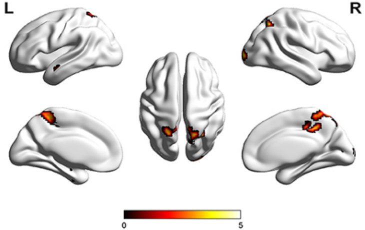
Power264 ROI	AAL Name	MNI Coords	Network
15	Postcentral_L	(-38,-27,69)	Somatomotor
25	"undefined"	(-38,-15,69)	Somatomotor
74	Angular_L	(-39,-75,44)	DMN
240	Temporal_Inf_L	(-56,-45,-24)	Uncertain
260	Fusiform_L	(-31,-10,-36)	Uncertain

- There aren't many studies associating osteoporosis with FC
- Here is one on Diabetic Osteoporosis examined using Regional Homogeneity (ReHo)[4]

[4] Liu et al. (2022) 10.3389/fnagi.2022.851929

Significant Regions of ReHo Group Differences from that Study

- Their reported significant differences



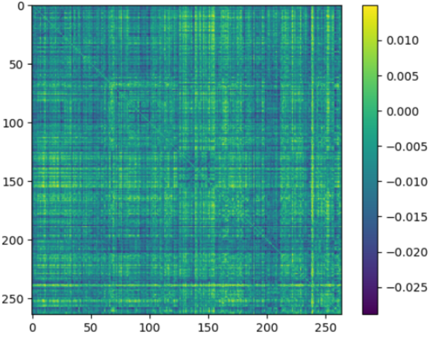
Brain region	MNI coordinates			T value	Cluster Size
	X	Y	Z		
Temporal_Mid_L (aal)	−48	−6	−21	4.4099	56
Occipital_Sup_R (aal)	24	−99	3	4.3332	62
Parietal_Sup_R (aal)	18	−60	63	3.4653	113
Angular_R (aal)	27	−60	48	4.3883	60
Precuneus_L (aal)	−15	−39	54	3.7383	118

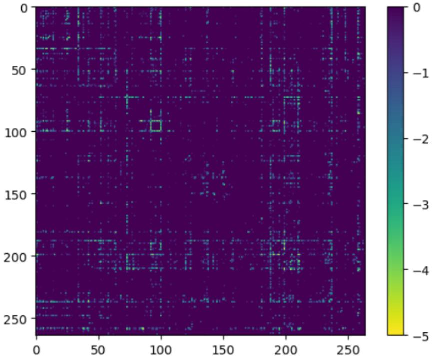
L, left; R, right; AAL, Anatomical Automatic Labeling; MNI, Montreal Neurological Institute; cluster_size > 50.

Most FC-Associated Regions On Edge of MNI Space

- All but one of the 5 regions we found are at the very edge of gray matter in MNI space
  - All except ROI-260
  - Likely registration effects or differences in gray matter thickness contribute
- Even discounting 4 edge regions there are still many FCs that reach significance threshold
- Web viewer for MNI space coordinates: `https://bioimagesuiteweb.github.io/webapp/mni2tal.html`

Type II Diabetes (26285)

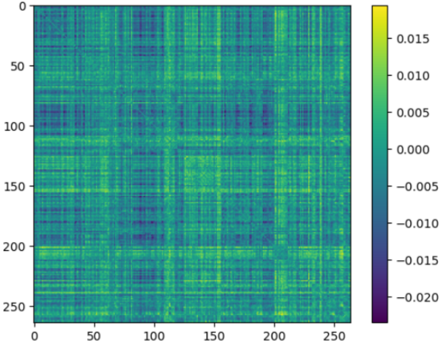


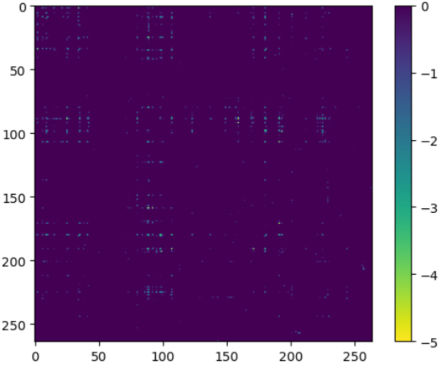


- Compare e.g. bottom right "box" around ROIs 200-250 with BMI plots (+SUB network)

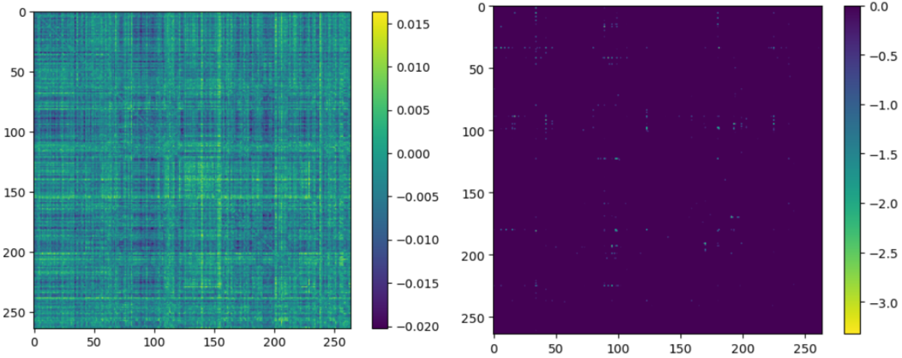
Cardiovascular Disease (26223)

- Now start the less significant general health correlates





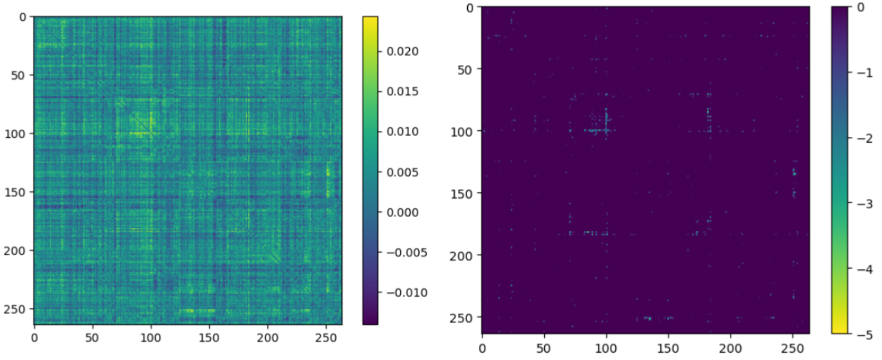
Coronary Artery Disease (26227)



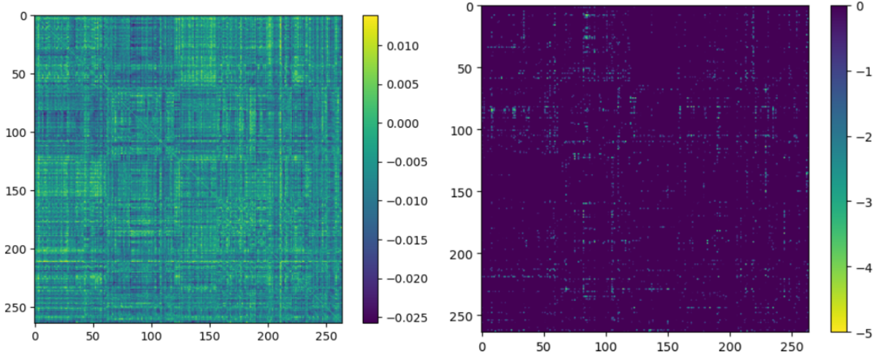
- Significant regions similar to the last plot

Parkinson's Disease (26260)

- Last two significant PRS fields don't fit under the umbrella of general health or physique



Schizophrenia (26275)



- SZ is one of the easiest traits to predict, but its correlation with FC is weaker than some of the other PRS field correlations

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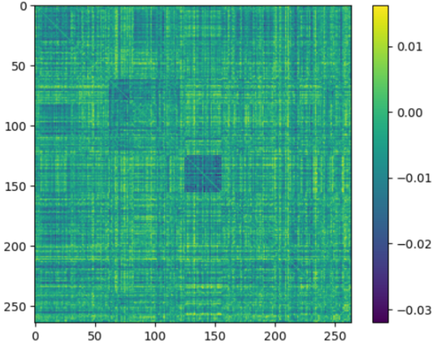
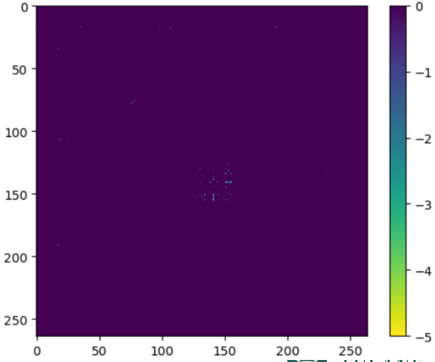
Alzheimer's PRS Score (26206)

- We did find significant association between some resting state VIS-VIS FCs and Alzheimer's PRS
- Not as large overall correlation as most significant PRS fields





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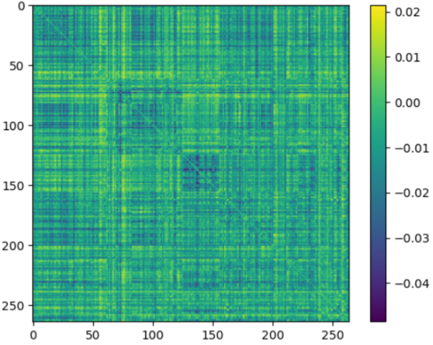
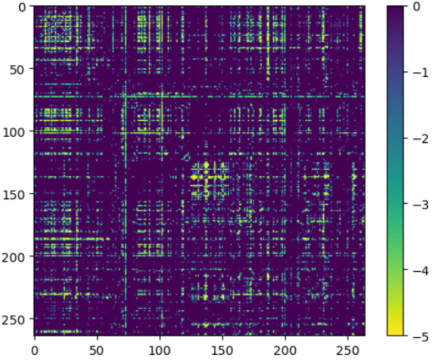
Principal Genetic Component [Ancestry] (26201)

- Most significant of all
- Not surprising, given strength of race signal in FC[5][6]
- However, UKB is approximately 98% Caucasian



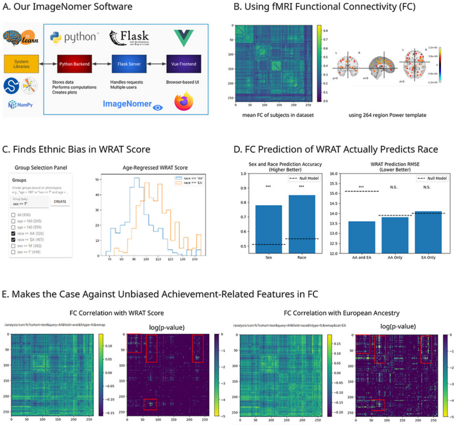


[5] Orlichenko et al. (2023) 10.1016/j.ynirp.2023.100191

[6] Li et al. (2023) 10.1126/sciadv.abj1812

ImageNomer + Race Confound

- ImageNomer paper describing race signal in FC has been published
- Working on a new, quicker version of the interface
  - Required because of large subject number in UKB
  - Many graphs in this section created on the new version



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Collaboration on AD Correlated with Blood Transfusion

- A medical student at Tulane was inspired by a recent study on Intracerebral Hemorrhage and Blood Transfusion related to amyloid[7]
- Wanted to take a look at correlation between blood transfusion and AD in the "All of Us" and UKB datasets
- She stated the All of Us dataset included 815 patients with blood transfusion but only 18 with AD + blood transfusion
- Likewise, the overlap is low in the UKB (68 subject intersection)

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[7] Zhao et al. (2023) 10.1001/jama.2023.14445

AD Seems to be Independent of Blood Transfusion

- Assuming independence of the clinical variables, we expect 69.3 subjects to have both AD and Transfusion codes
- Appears to be no correlation
- However, UKB has ICD10, ICD9, OPCS4, and OPCS3 codes for many subjects, so additional correlates may be easy to explore
- Especially with FC or using novel methods

	Alzheimer's	
Transfusion	No	Yes
No	488,600	2,976
Yes	10,767	68

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Low Rank Mixup Augmentations for Contrastive Learning

Motivation for Augmentations

- fMRI and functional connectivity (FC) allow for unmatched analysis of human cognition in vivo
- Contrastive learning has achieved state of the art results in computer vision and medical imaging

Problem

Most contrastive learning frameworks require large numbers of subjects or data augmentations

- Most fMRI studies recruit fewer than 100 subjects

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Low Rank FC Augmentations

Solution

We create an augmentation strategy for FC based on mixup of the rank-1 approximation of FC (first component)

- Based on the fact that the first component is not effective for phenotype prediction

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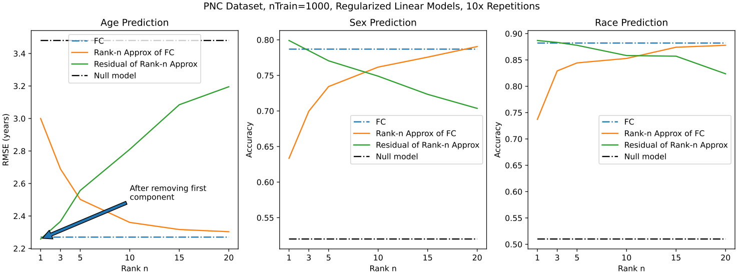
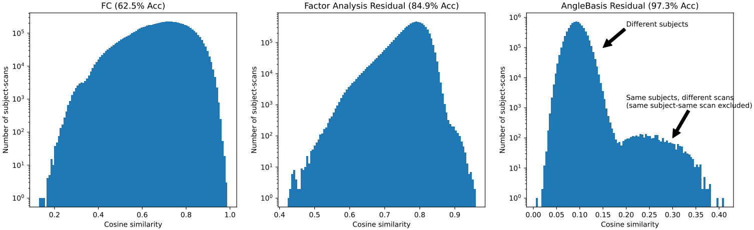
First Component is Not Effective for Prediction (But Residual Is)

- First component can be used for weak prediction
- Removing the first component (rank 1 approximation of FC) yields a residual with equal or slightly better predictive accuracy
- L-BGFS convergence is also (much) faster with residual

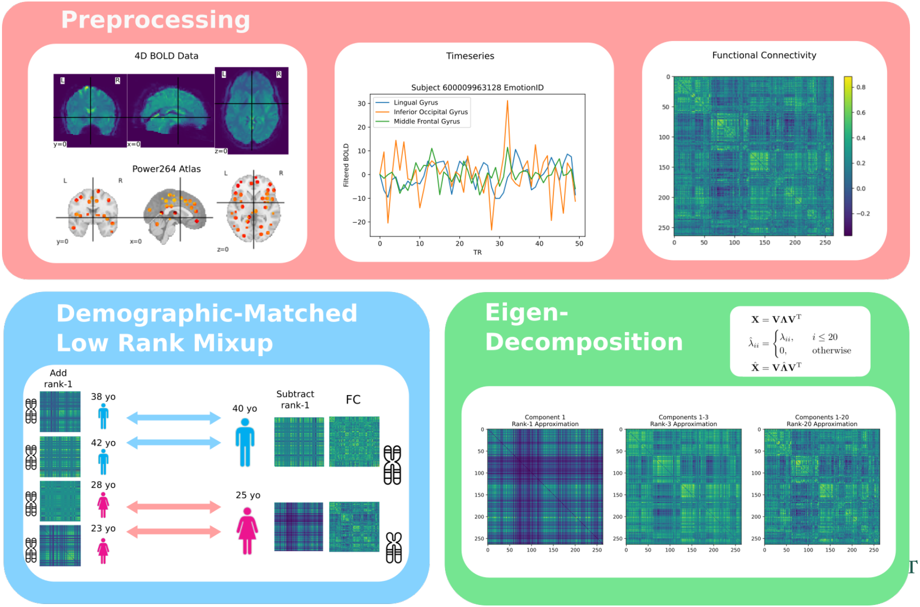


Residual Also Greatly Increases Fingerprinting Accuracy

- In the PNC dataset, residual can identify different scan of same subject from 1000+ peers with nearly 100% accuracy
- Compared to around 60% accuracy for FC
- Figure is for AngleBasis, similar finding for residual based on low-rank decomposition



Overview of Framework



Construction of Rank-n Approximation to FC

- Construct low rank approximation to FC $\mathbf{X}$ using the eigendecomposition
- Only keep the top N eigenvalues; set the rest to zero
- $\mathbf{\Lambda}$ and $\mathbf{V}$ are sorted by eigenvalue magnitude
- Note that FC is a PSD (probably PD) matrix

$$
\begin{aligned}
\mathbf{X} &= \mathbf{V}\mathbf{\Lambda}\mathbf{V}^{\mathsf{T}} \\
\hat{\lambda}_{ii} &= \begin{cases} \lambda_{ii}, & i \leq N \\ 0, & \text{otherwise} \end{cases} \\
\mathbf{X}^{(N)} &= \mathbf{V}\hat{\mathbf{\Lambda}}\mathbf{V}^{\mathsf{T}}
\end{aligned} \tag{1}
$$

Construction of Positive Samples for Contrastive Learning

- Subjects are augmented by subtracting first component of subject and adding first component of donor
- Donors drawn from a categorical distribution based on phenotype similarity
- $\mathrm{I}[\cdot]$ is an indicator function for (approximate) phenotype equivalence

$$m_{y,i}(j) = \mathrm{I}[y_i == y_j]$$

$$\mathbf{p}_{y,i} = \mathrm{Softmax}(\mathbf{m}_{y,i}), \qquad \mathbf{p}_i = \mathrm{Softmax}(\prod_{y}^{N_y} \mathbf{p}_{y,i}) \tag{2}$$

$$\tilde{\mathbf{X}}_i = \mathbf{X}_i - \mathbf{X}_i^{(1)} + \mathbf{X}_j^{(1)}, \qquad j \sim \mathrm{Categorical}(\mathbf{p}_i)$$

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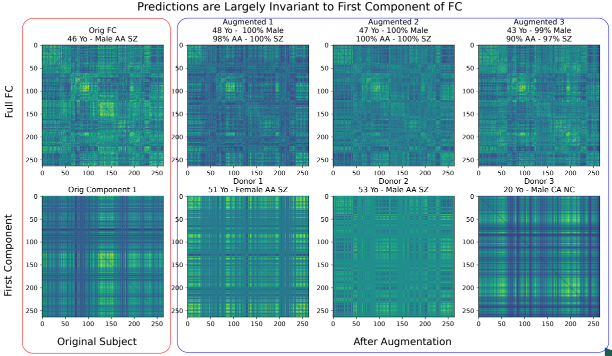
Examples of Positive Samples

- Positive samples are labeled “Augmented 1”, “Augmented 2”, and “Augmented 3”
- Negative samples are original FCs of other subjects



Training

- Network is trained by minimizing 3 losses
  - InfoNCE for contrastive learning
  - BinaryCrossEntropy for binary variable prediction
  - RMSE for continuous variable prediction

$$
\begin{aligned}
\mathcal{L}_{NCE} &= -\frac{1}{NM}\sum_{n,i}^{N,M} \log \frac{e^{\mathbf{q}_i^\top \mathbf{k}_i^+/\tau}}{e^{\mathbf{q}_i^\top \mathbf{k}_i^+/\tau} + \sum_{j=1}^{K} e^{\mathbf{q}_i^\top \mathbf{k}_{i,j}^-/\tau}} \\
\mathcal{L}_{CE} &= -\frac{1}{N}\sum_{i}^{N} (y_{i,0}\log(p_{i,0}) + y_{i,1}\log(p_{i,1})) \\
\mathcal{L}_{RMSE} &= \left(\frac{1}{N}\sum_{i}^{N}(y_i - \hat{y}_i)^2\right)^{1/2}
\end{aligned}
\tag{3}
$$

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Moderately Improved Prediction Results

- Prediction results are improved 2-10% over MLP and GCN models not using augmentations
- Using PNC and BSNIP datasets

Dataset	Phenotype	Metric	MLP	GCN	CL+LRAug	p-value
BSNIP	Age	RMSE (yr)	11.82 ± 0.62	11.07 ± 0.67	$\mathbf{10.25} \pm \mathbf{0.64}$	<0.001
BSNIP	Sex	Accuracy	68.1 ± 4.6	66.4 ± 6.1	$\mathbf{71.7} \pm \mathbf{5.1}$	0.003
BSNIP	Race	Accuracy	76.0 ± 3.8	72.4 ± 6.1	$\mathbf{77.7} \pm \mathbf{4.4}$	0.026
BSNIP	SZ	Accuracy	75.2 ± 3.6	71.2 ± 6.7	$\mathbf{76.9} \pm \mathbf{4.4}$	0.017
PNC	Age	RMSE (yr)	2.62 ± 0.14	2.44 ± 0.12	$\mathbf{2.18} \pm \mathbf{0.07}$	<0.001
PNC	Sex	Accuracy	77.9 ± 2.0	73.7 ± 9.8	$\mathbf{79.7} \pm \mathbf{2.2}$	<0.001
PNC	Race	Accuracy	87.7 ± 1.6	86.6 ± 3.8	$\mathbf{89.8} \pm \mathbf{1.9}$	<0.001

- Work will be presented at a NeurIPS 2023 Workshop
  - Medical Imaging Meets NeurIPS

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Other Uses of Low-Rank Residual: Voting

- Assume N independent voters having $p = 0.8$ accuracy
- Then the accuracy of their overall decision is given below

# of Voters	1	2	3	4	5
Overall Accuracy	0.8	0.8	0.896	0.896	0.94208

$$
\begin{aligned}
p_{tot} &= \sum_{i=0}^{\lceil N/2 \rceil} \binom{N}{i} p^{N-i}(1-p)^i, \qquad N \text{ odd} \\
p_{tot} &= \sum_{i=0}^{N/2-1} \binom{N}{i} p^{N-i}(1-p)^i, \qquad N \text{ even} \\
&\quad + \frac{1}{2}\binom{N}{N/2} p^{N/2}(1-p)^{N/2}
\end{aligned} \tag{4}
$$

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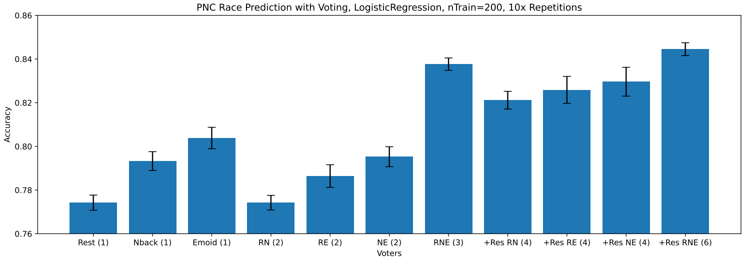
Validation on PNC Race

- To validate with "ground truth," we can use the PNC dataset
- Three scanner tasks: rest, nback, and emoid
- Neither these tasks nor their residuals are truly independent from each other
- We still see accuracy increases at odd voter number boundaries



UKB Voting for Binary Classification

- We have two scanner tasks in the UKB, which would be insufficient for an ensemble to increase accuracy in binary classification
- Using low rank residual, we can increase the number of voters to 4
- Although none of the 4 data sources are truly independent
- Previous slide showed that including residual in voting improves performance, though not as much as a separate task
- Can also accomplish through, e.g., FC and PC

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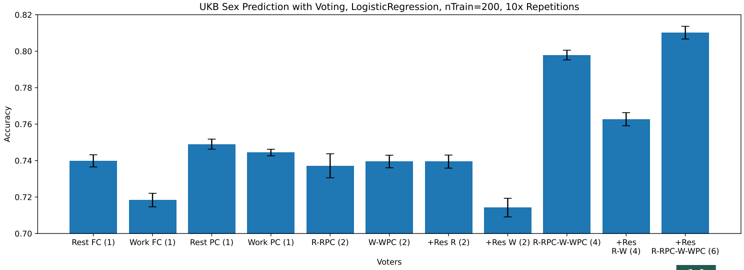
UKB Voting Increases Sex Prediction Accuracy

- As before, combining any two modalities does not increase prediction accuracy
    - Combining three or more does
- PC greater benefit in voting than residual
- Residual still has some benefit when added to FC-PC ensemble



Imputation of FC Within and Between Datasets

Motivation: Missing Data

Problem of Missing Data

Oftentimes in large datasets we have one or more scanner tasks that are missing

- In PNC, not all subjects with fMRI have rest, nback, and emoid scans
- PNC has 9000+ subjects with SNP data but only slightly more than 1500 with fMRI data

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Motivation: Small Datasets

Problem of Small Datasets

Most new fMRI studies recruit fewer than 100 subjects

- Two studies with data on OpenNeuro, Fibromyalgia[a] and VicariousPunishment[b], enrolled only female subjects
- VicariousPunishment enrolled only young college-age subjects

[a] ds004144 Balducci et al. (2022)
[b] ds004775 Weber et al. (2023)

- Can we attempt to extrapolate any of these results to males or older subjects/children?

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Naive Method: Train a Deep Model (PNC)

- We have a ground truth of rest, nback, and emoid scans for 1300+ subjects
- Train an MLP to reconstruct nback scan FC from rest scan FC
- Null model is basically Gaussian noise
- Clearly, a more well thought-out procedure must be used

Null Model RMSE	Train RMSE	Test RMSE
0.28	0.09-0.07	0.25-0.23

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Future Work

Idea

Generate a distribution of candidates and cull unsuitable ones

- Also use contrastive learning to move between SNPs and FC

Thank you!

- Any question?