Subtype-specific biomarkers for AD from anatomical and functional connectomes via GNN

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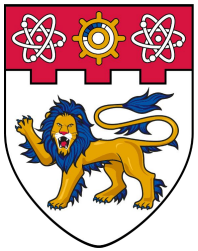

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Background

Heterogeneity in AD

- Instead of assuming that there are generalisable biomarkers, we could look for **potential biomarkers for sub-populations** instead

Multimodal data provides a more holistic view

- **GNN** helps to facilitate multimodal fusion
- Lack of sufficient multimodal datasets, but we investigate the use of anatomical connectomes (**AC**) derived from structural MRI along with functional connectomes (**FC**) from functional MRI

Existing studies

Majority of AD studies based on deep learning focus on **classification**

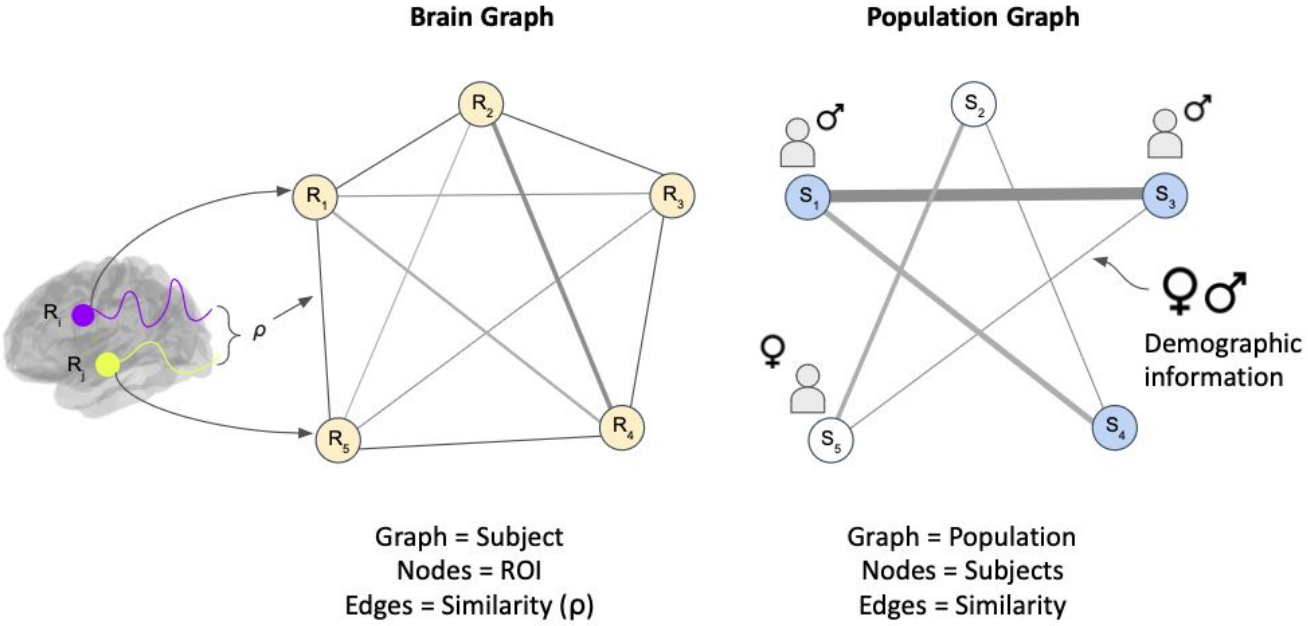
Few existing studies on subtyping based on fMRI, largely unsupervised

- Non-matrix factorisation was used on FC matrices to reveal 4 AD subtypes [1], each affecting different regions of the brain including the prefrontal cortex and also functional modules such as the default mode network.
- They do not account for **confounding factors** (e.g. age, gender) and they are unable to leverage on **label information**.

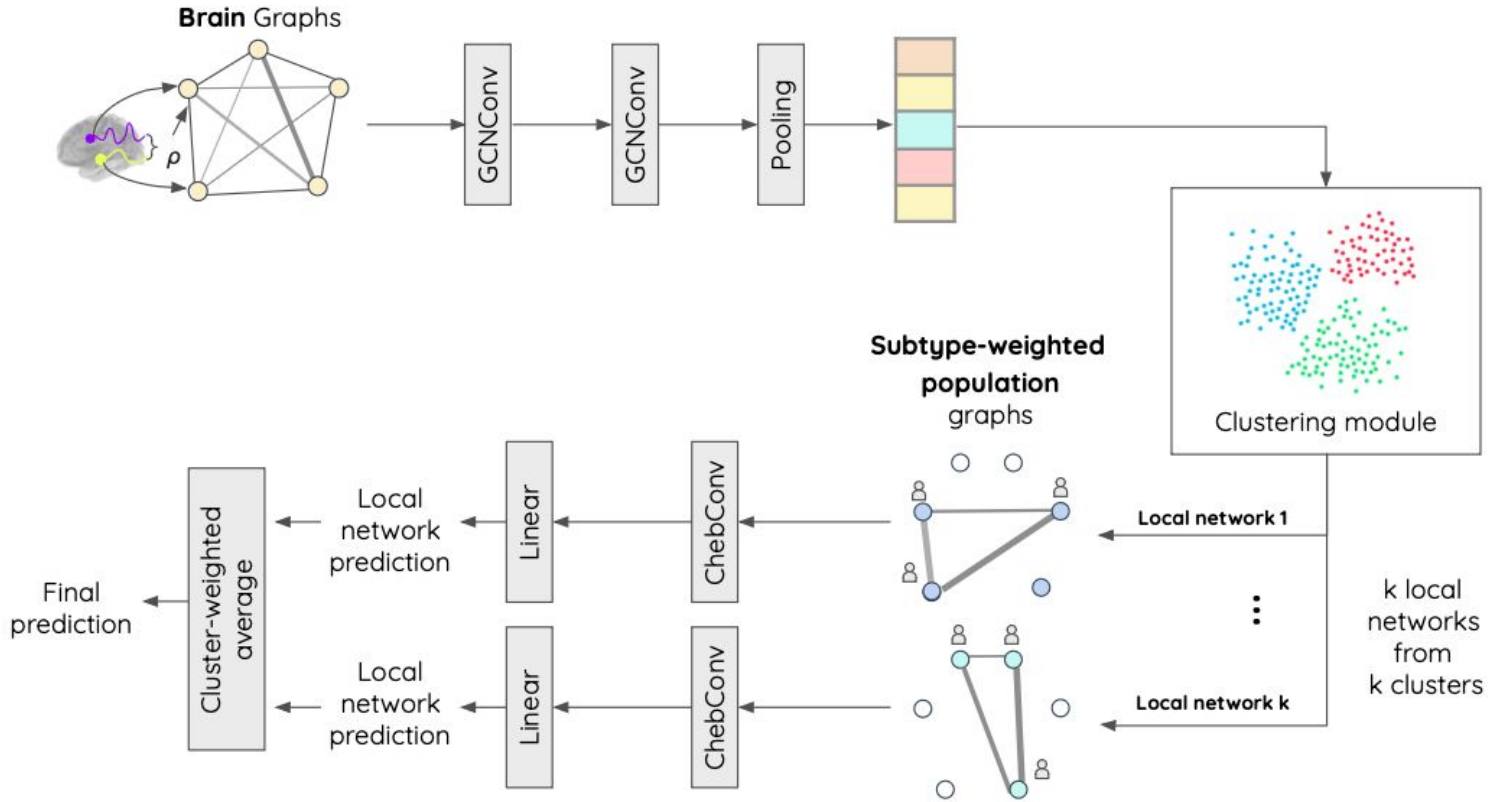
To address these issues, we propose **SplitGNN**, which performs classification and clustering simultaneously to arrive at **subtype-specific biomarkers**

[1] Pindong Chen, Hongxiang Yao, Betty M Tijms, Pan Wang, Dawei Wang, Chengyuan Song, Hongwei Yang, Zengqiang Zhang, Kun Zhao, Yida Qu, et al., "Four distinct subtypes of Alzheimer's disease based on resting- state connectivity biomarkers," Biological Psychiatry, vol. 93, no. 9, pp. 759–769, 2023.

SplitGNN


Brain Graph
Population Graph
R1
R2
R3
R4
R5
Ri
Rj
ρ
S1
S2
S3
S4
S5
Demographic information
Graph = Subject
Nodes = ROI
Edges = Similarity (ρ)
Graph = Population
Nodes = Subjects
Edges = Similarity

SplitGNN


Brain Graphs
ρ
GCNConv
GCNConv
Pooling
Clustering module
Subtype-weighted population graphs
Local network 1
Local network k
k local networks from k clusters
ChebConv
ChebConv
Linear
Linear
Local network prediction
Local network prediction
Cluster-weighted average
Final prediction

Datasets

ADNI-2

- Has both structural MRI and fMRI data
- Not many subjects: 49 normal controls (NC), 29 AD

ANMerge

- Only structural MRI
- More subjects: 117 NC, 133 mild cognitive impairment (MCI) and 126 AD

A total of 129 ROIs

- Desikan-Killiany atlas (68 ROIs ; excludes subcortical areas)
- 61 subcortical ROIs were added from Seitzman et al. [2] (updated Power atlas)

[2] Benjamin A Seitzman, Caterina Gratton, Scott Marek, Ryan V Raut, Nico UF Dosenbach, Bradley L Schlag- gar, Steven E Petersen, and Deanna J Greene, “A set of functionally-defined brain regions with improved representation of the subcortex and cerebellum,” Neuroimage, vol. 206, pp. 116290, 2020.

Experiment setup

sMRI brain graphs created via Morphometric INverse Divergence (MIND) [3]

- Edges built using 5 sMRI features (Cortical thickness, GM volume, Surface Area, Mean curvature, Sulcal Depth)
  - 1 / 1 + KL(a,b)
  - Cortical ROIs only
- Node features
  - Concatenation of the corresponding row for the ROI in the cortical similarity network, along with 5 features above
  - When fMRI data is available, the connection profile is concatenated with the sMRI features

[3] Isaac Sebenius, Jakob Seidlitz, Varun Warrier, Richard AI Bethlehem, Aaron Alexander-Bloch, Travis T Mallard, Rafael Romero Garcia, Edward T Bullmore, and Sarah E Morgan, “Robust estimation of cortical similarity networks from brain MRI,” Nature Neuroscience, pp. 1–11, 2023.

Classification performance

Ensemble of local networks in SplitGNN is essential for improved performance

- Simply combining BG and PG does not do better than using BG only

SplitGNN would benefit from the use of **larger datasets**; limited improvements in smaller dataset (e.g. ADNI)

Table 1. Accuracy and F1 measure on ANMerge dataset

Model	Accuracy	F1
LR	73.67 ± 2.5	76.36 ± 1.9
BG only	77.76 ± 2.3	79.75 ± 1.0
BG + PG only	75.71 ± 4.9	78.42 ± 4.6
SplitGNN	81.22 ± 3.9	81.76 ± 3.5

Table 2. Experiment results on ADNI dataset

Model	Accuracy	F1
LR	79.38 ± 2.9	68.97 ± 5.1
BG only	79.38 ± 5.2	62.23 ± 15.0
BG + PG only	83.13 ± 6.6	69.90 ± 15.6
SplitGNN	83.75 ± 7.5	70.56 ± 15.3

Salient features

3 subtypes of AD were identified, along with subtype-specific biomarkers:

- R isthmus cingulate cortex (cluster AD-1),
- R rostral middle frontal gyrus, L caudal anterior cingulate (cluster AD-2)
- L inferior parietal lobule (cluster AD-3).

Left cuneus was found to be a consistent class-wide biomarker

Conclusion

SplitGNN provides a technique to perform clustering and classification simultaneously, producing **subtype-specific biomarkers**

MIND can be used to generate anatomical connectomes for disorder prediction tasks, for future multimodal studies

Future work in this research direction could consider:

- Using larger datasets, on other disorders
- Deep learning-based clustering (e.g. Deep Embedded Clustering [4])

[4] J. Xie, R. Girshick, and A. Farhadi, 'Unsupervised deep embedding for clustering analysis', in International conference on machine learning, 2016, pp. 478–487.