Polygenic Mediation Analysis of Alzheimer's Disease Implicated Intermediate Amyloid Imaging Phenotypes

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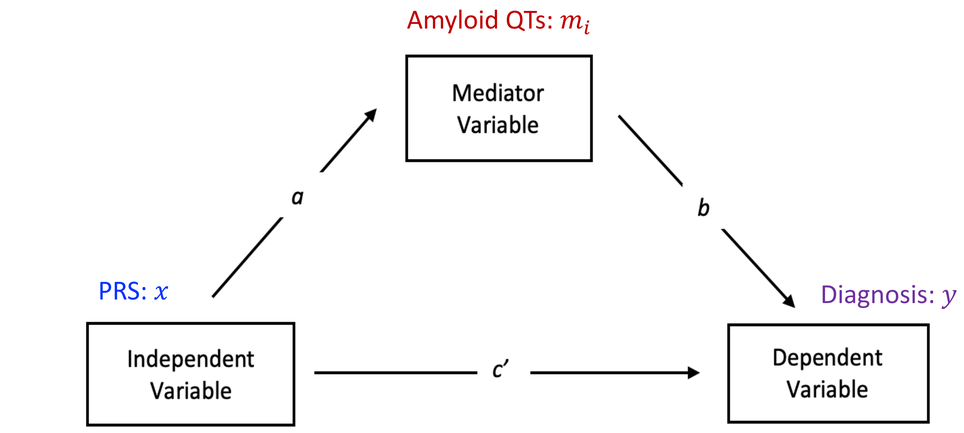
1. Introduction

Mediation models have been employed in the study of brain disorders to detect the underlying mechanisms between genetic variants and diagnostic outcomes implicitly mediated by intermediate imaging biomarkers. In this study, we propose a polygenic mediation analysis that comprises a polygenic risk score (PRS) to aggregate genetic effects of a set of candidate variants and then explore the implicit effect of imaging phenotypes between the PRS and disease status.

2. Materials And Methods

Diagnosis	HC	EMCI	LMCI	AD	P-value
Number	204	246	169	140	-
Gender (M/F)	100/104	128/118	90/79	76/64	7.72E-01
Age (mean±std)	75.70±6.46	71.33±7.32	73.78±8.72	75.10±8.01	4.20E-09
Education (mean±std)	16.32±2.72	16.04±2.63	16.18±2.87	15.64±2.69	1.39E-01
APOE ε4 present	27.59%	42.04%	49.11%	67.14%	8.13E-12



PCC	PRS+	PRS-	rs41289512	rs429358
PRS+	1	0.572	0.831	0.438
PRS-	0.572	1	0.018	0.073
rs41289512	0.831	0.018	1	0.484
rs429358	0.438	0.073	0.484	1

Group	Control	Case	# of subjects
1	HC	AD+EMCI+LMCI	759
2	HC	AD	344
3	HC	LMCI	373
4	HC	EMCI	450
5	HC	EMCI+LMCI	619

- Step 1: logistic regression
  $logit(\Pr(y=1)) = \beta_{11}x + \beta_{12}z + \epsilon_1$
- Step 2: linear regression
  $m_i = \beta_{21,i}x + \beta_{22,i}z + \epsilon_{2,i}$
- Step 3: logistic regression
  $logit(\Pr(y=1)) = \beta_{31,i}x + \beta_{32,i}m_i + \beta_{33,i}z + \epsilon_{3,i}$

$$\text{Prop\_mediation}(i) = \frac{\beta_{32,i}\cdot\beta_{21,i}}{\beta_{31,i}+(\beta_{32,i}\cdot\beta_{21,i})}$$

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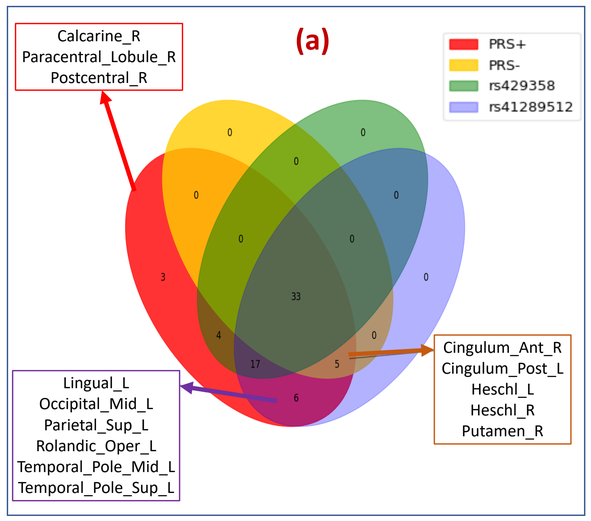
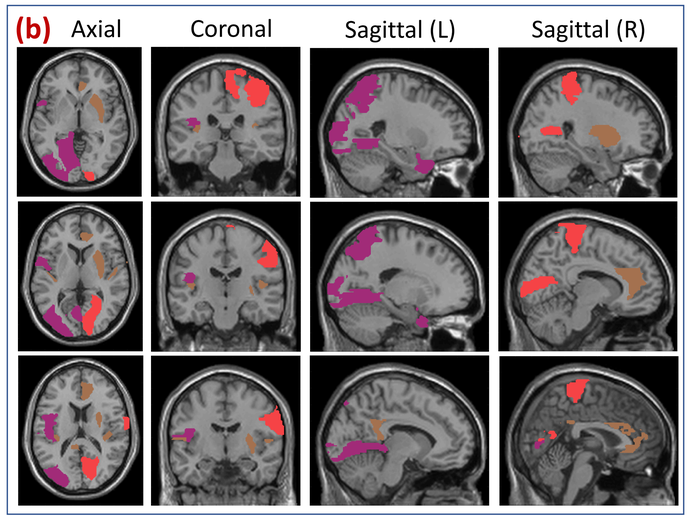
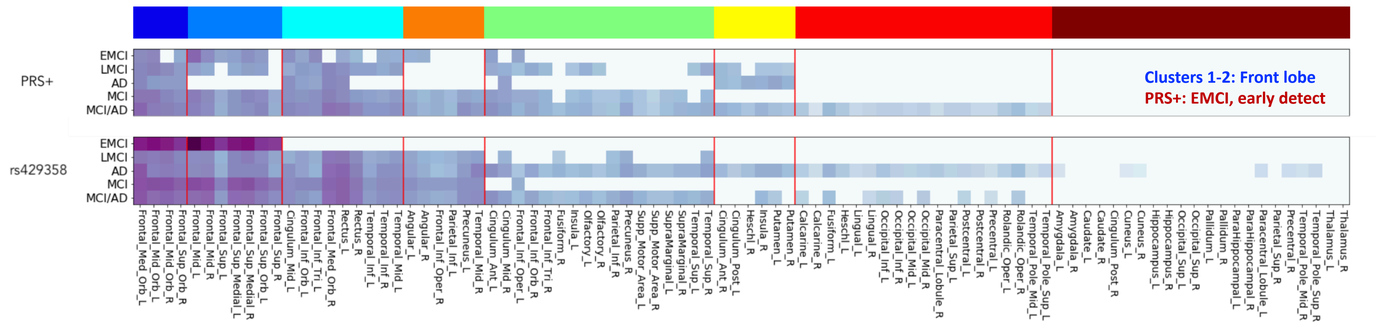
3. Results



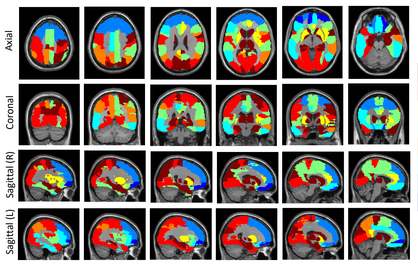
Mediators discovered over different PRSs for HC vs. MCI+AD



Brain mapping of regions discovered without rs429358



Cluster	Subcortical	Frontal	Cingulate	Parietal	Temporal	Occipital	Insula	Sensory-Motor Cortex
1	0	**4**	0	0	0	0	0	0
2	0	**7**	0	0	0	0	0	0
3	0	**5**	1	0	3	0	0	0
4	0	**5**	2	4	**5**	0	1	0
5	**2**	0	**2**	0	1	0	1	0
6	0	1	0	**4**	1	0	0	0
7	0	2	0	1	**6**	**6**	0	4
8	**10**	0	1	1	4	4	0	2



4. Conclusions

Polygenic mediation analysis is effective in identifying novel amyloid imaging mediators using PRS comprised from AD candidate SNPs that were not identified with well-known APOE SNP rs429358. Further evaluation of the PRS also demonstrated its power for early disease indicator discovery, which outperformed the APOE SNP alone, showing the promise of PRS on biomarker detection.