Cognitively-defined AD Dementia Subgroups

ACT Study Project 2

Outline

- Why subgroups?
- Why cognitively defined subgroups?
- How do we define subgroups with cognitive tests?
- Our favorite stories for five subgroups, including new data from ACT P2
- What's next?

Why subgroups?

- A lot of heterogeneity in Alzheimer's-type dementia
- Maybe "Alzheimer's type dementia" is not one thing
- Maybe it would be useful to subgroup into different flavors, where the natural history is similar within a subgroup but differs across subgroups
- Implications for treatment trials (and ultimately treatments) if distinct biological underpinnings have implications for therapeutics
  - Matching up an appropriate drug to the subset of people who may benefit from it
- This in a nutshell is a particular strategy for "personalized medicine"
- This strategy has proven to be useful in many other settings, e.g. breast cancer

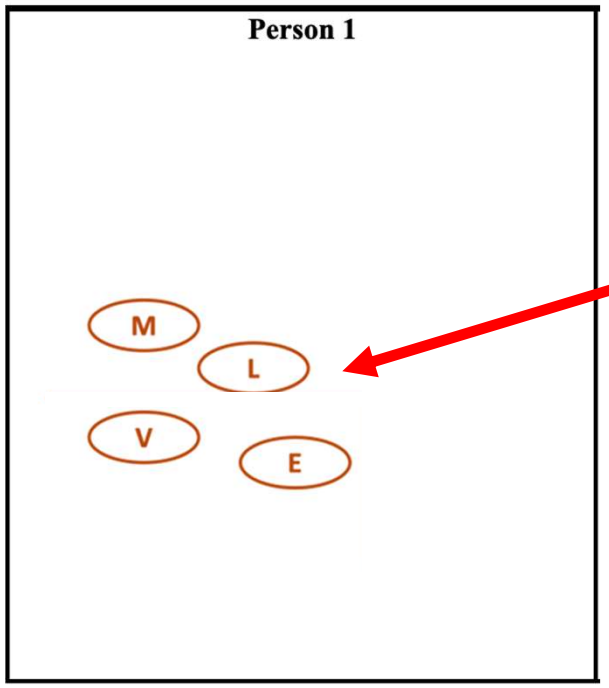
Why cognitively defined subgroups?

- AD dementia has a specific definition, requiring memory impairment, plus other domains, but there is a lot of heterogeneity in other domains
- As we'll talk about, there are other conditions characterized by AD pathology where memory is spared but profound influence on language (primary progressive aphasia, PPA) and visuospatial (posterior cortical atrophy, PCA)
  - The question of why the same pathological findings impact brains of some people in a PPA way with prominent language impacts while they impact brains with other people in an AD dementia way with prominent memory impacts has fueled research careers of giants in the field

Why cognitively defined subgroups?

- AD dementia has a specific definition, requiring memory impairment, plus other domains, but there is a lot of heterogeneity in other domains
- As we'll talk about, there are other conditions characterized by AD pathology where memory is spared but profound influence on language (primary progressive aphasia, PPA) and visuospatial (posterior cortical atrophy, PCA)
  - The question of why the same pathological findings impact brains of some people in a PPA way with prominent language impacts while they impact brains with other people in an AD dementia way with prominent memory impacts has fueled research careers of giants in the field
- A lot of inspiration from Dickerson and Wolk's paper on "dysexecutive" and "amnesic" AD dementia (2011)
  - Everyone had memory impairment, but could index relative impairment of memory and executive functioning
- Practical considerations: cognition is easy to collect, plentiful from research settings, and already considered in the process of differential diagnosis for neurocognitive syndromes

How do we define subgroups with cognitive tests?



Four cognitive scores

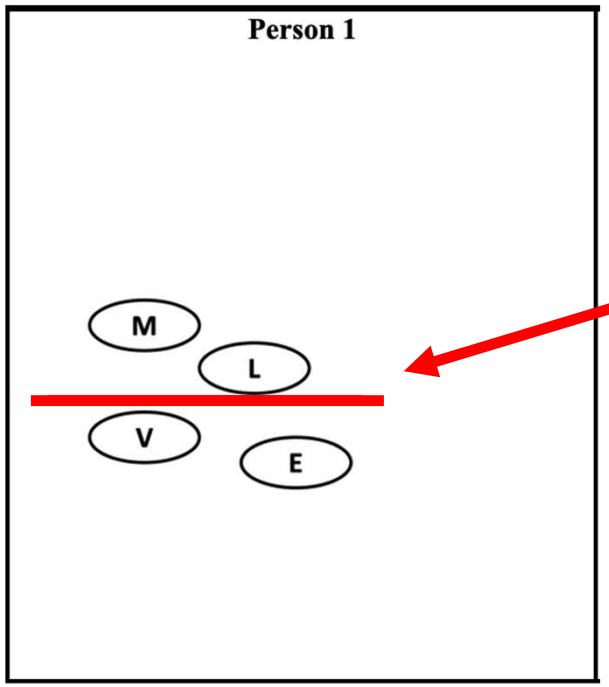
M = Memory

L = Language

V = Visuospatial

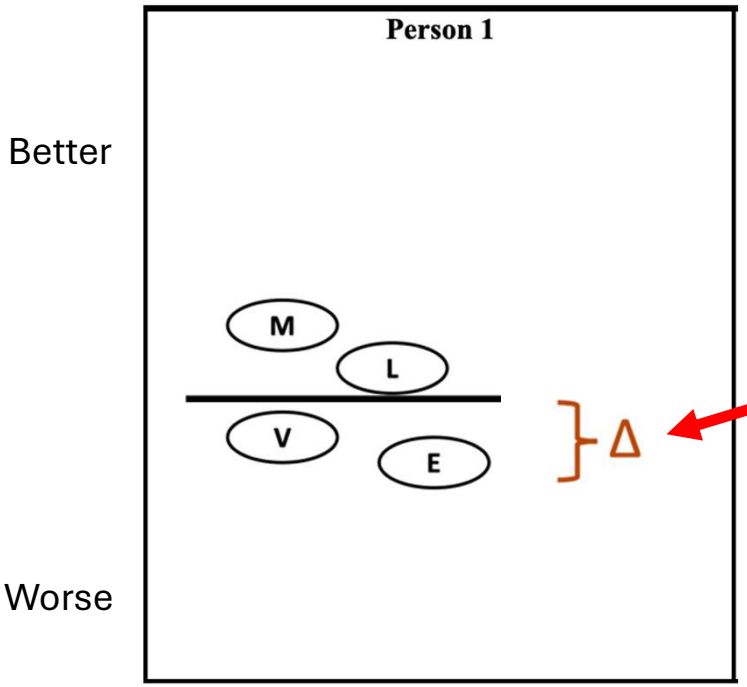
E = Executive functioning

Better



Worse

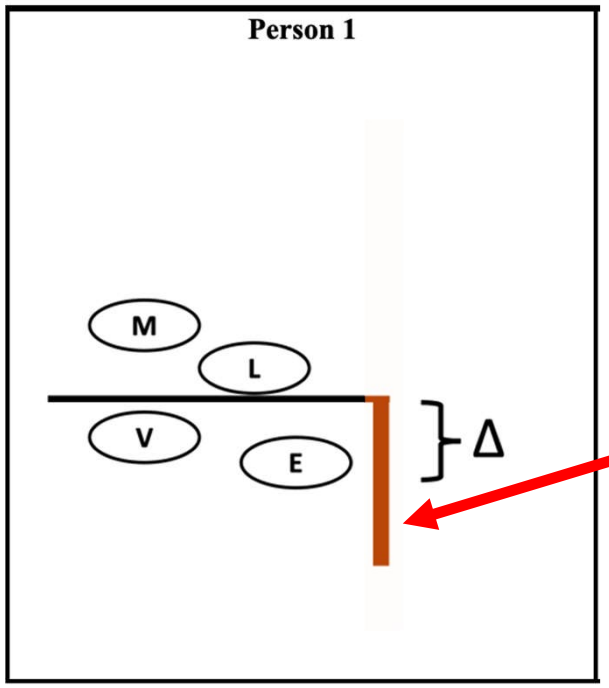
Average across those 4 domain scores



Difference of each domain from that average

This one is the executive functioning difference

Better

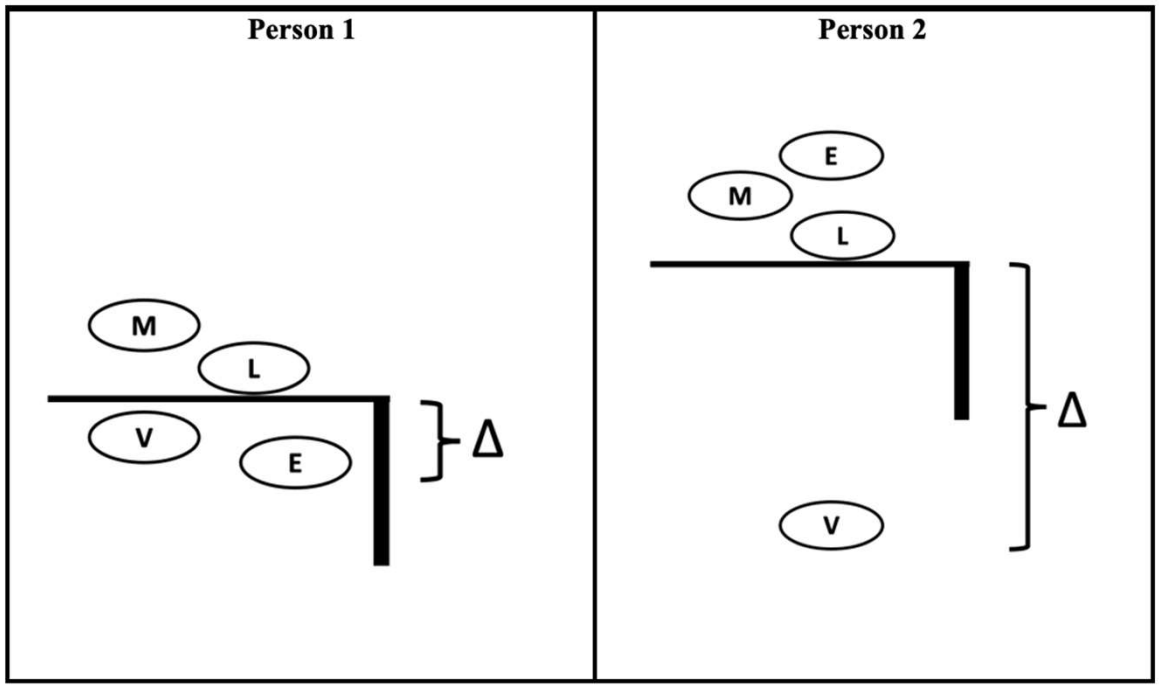


Worse

Comparison of each difference with a critical value
This one: no big difference.

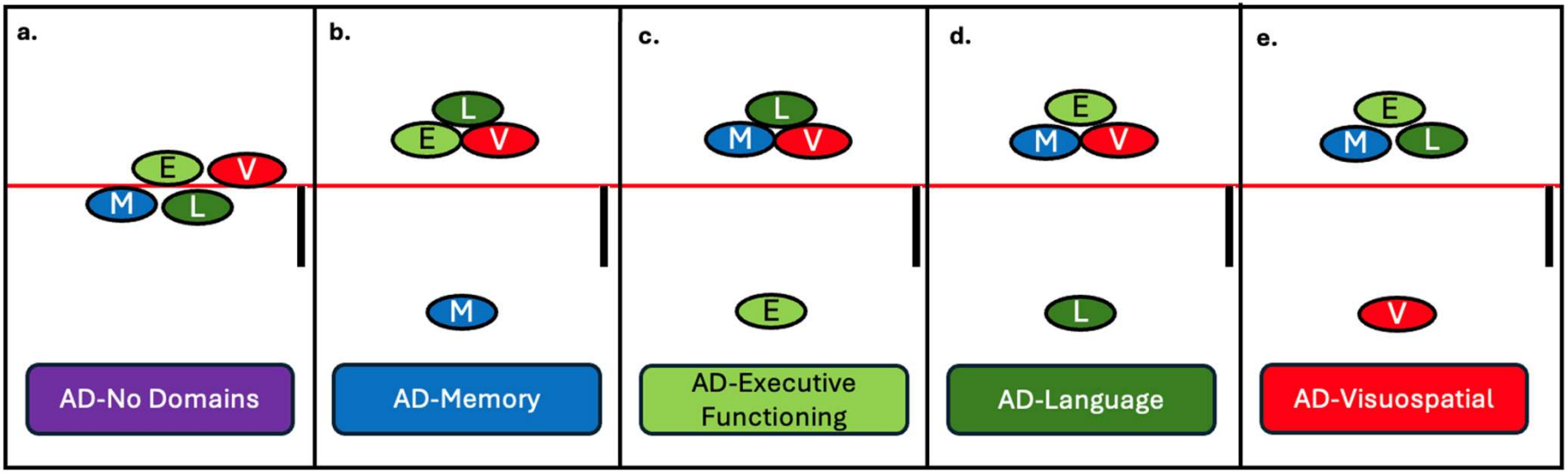
Better

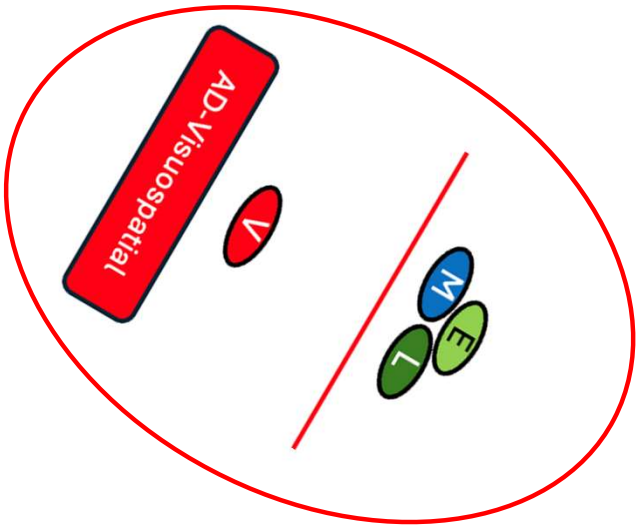
Worse

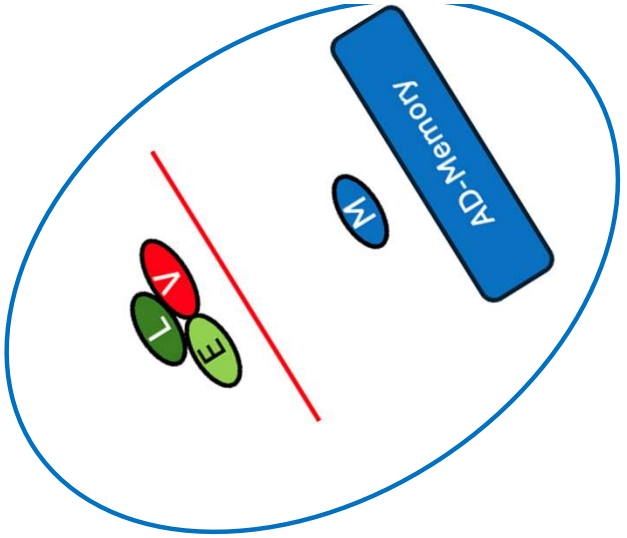


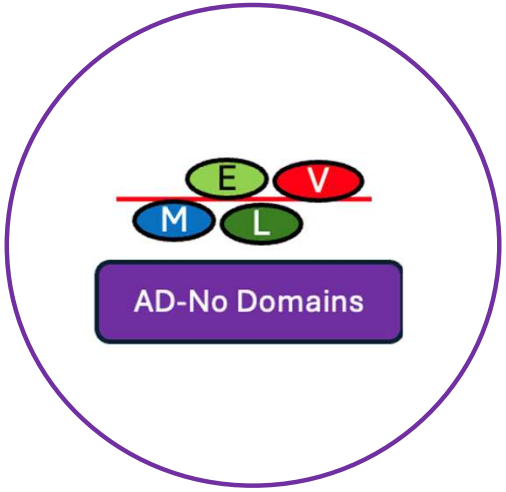
AD-No Domains

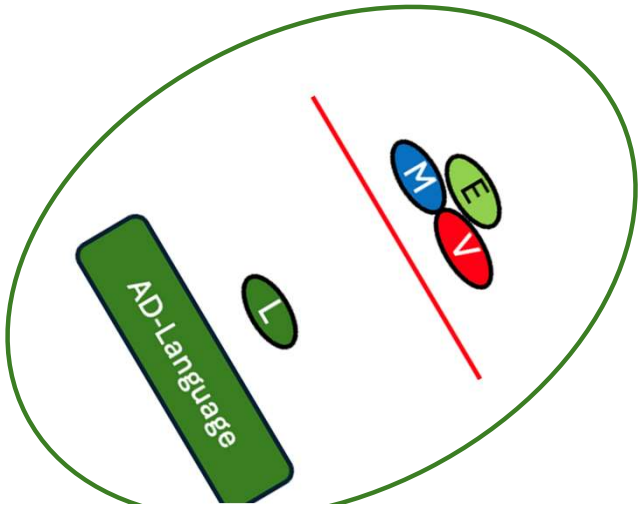
AD-Visuospatial

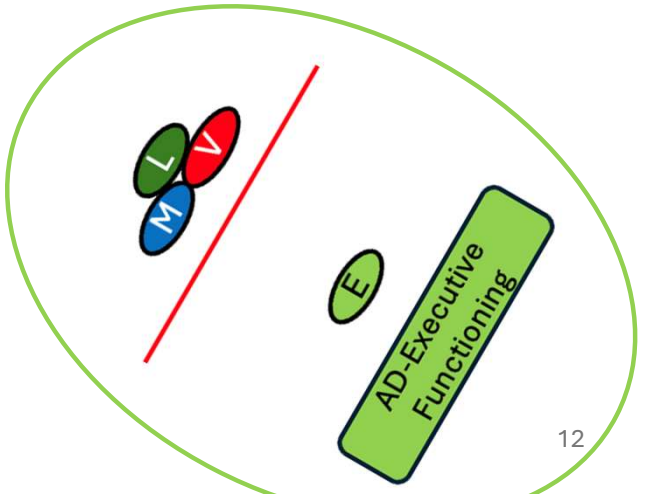

a.
E
V
M
L
AD-No Domains
b.
L
E
V
M
AD-Memory
c.
L
M
V
E
AD-Executive Functioning
d.
E
M
V
L
AD-Language
e.
E
M
L
V
AD-Visuospatial


AD-Visuospatial
V
M
E
L


AD-Memory
M
V
L
E

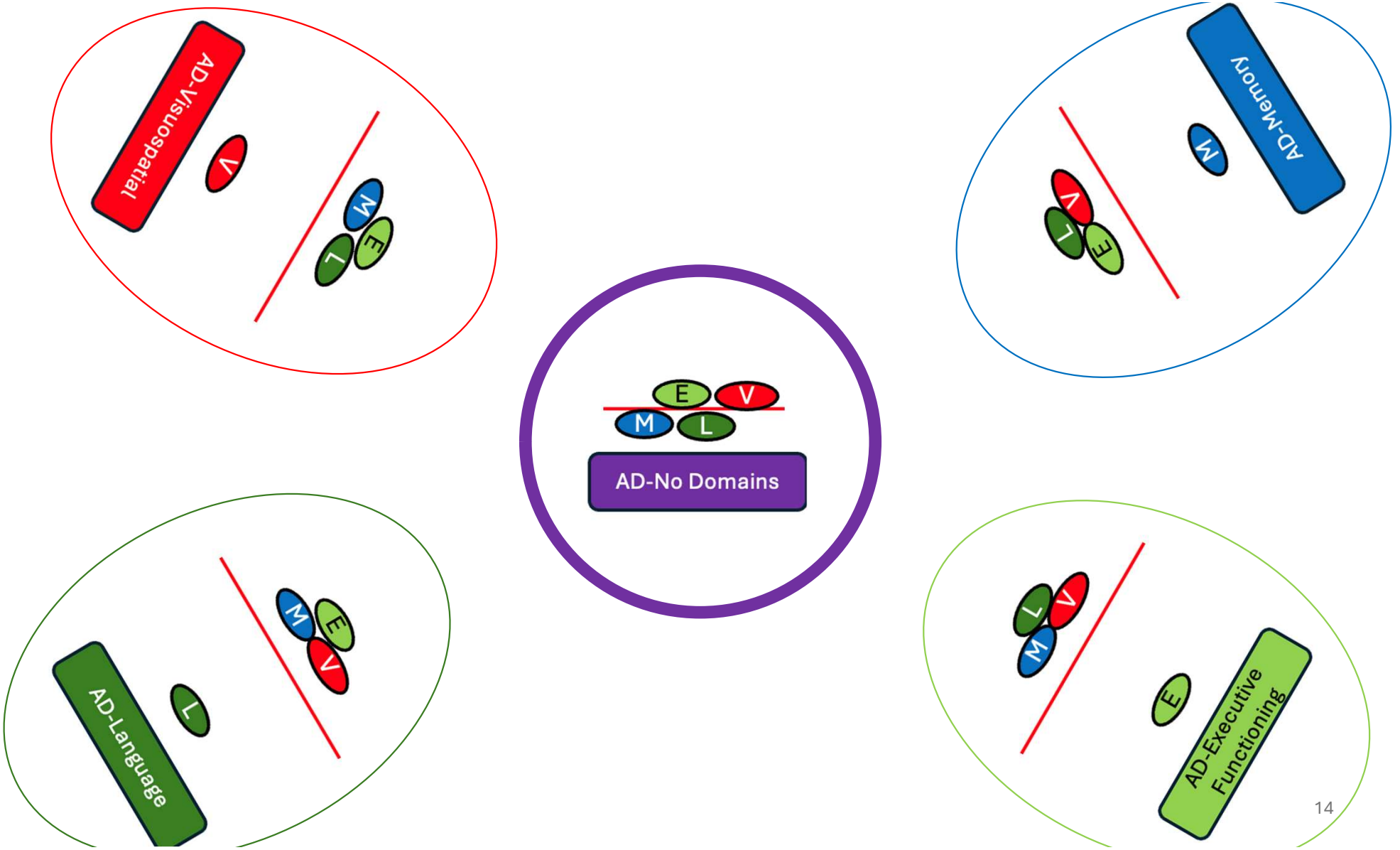

E
V
M
L
AD-No Domains


AD-Language
L
M
E
V

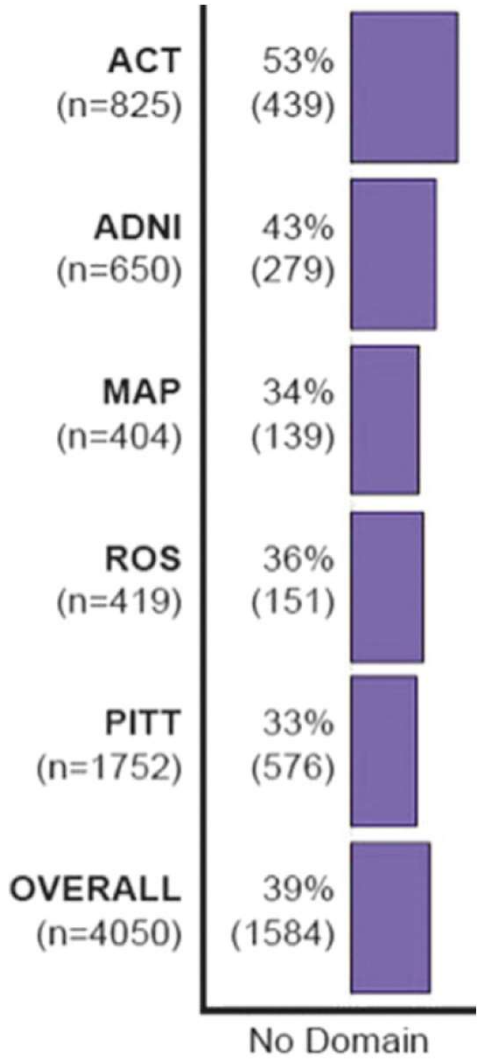

L
V
M
E
AD-Executive Functioning

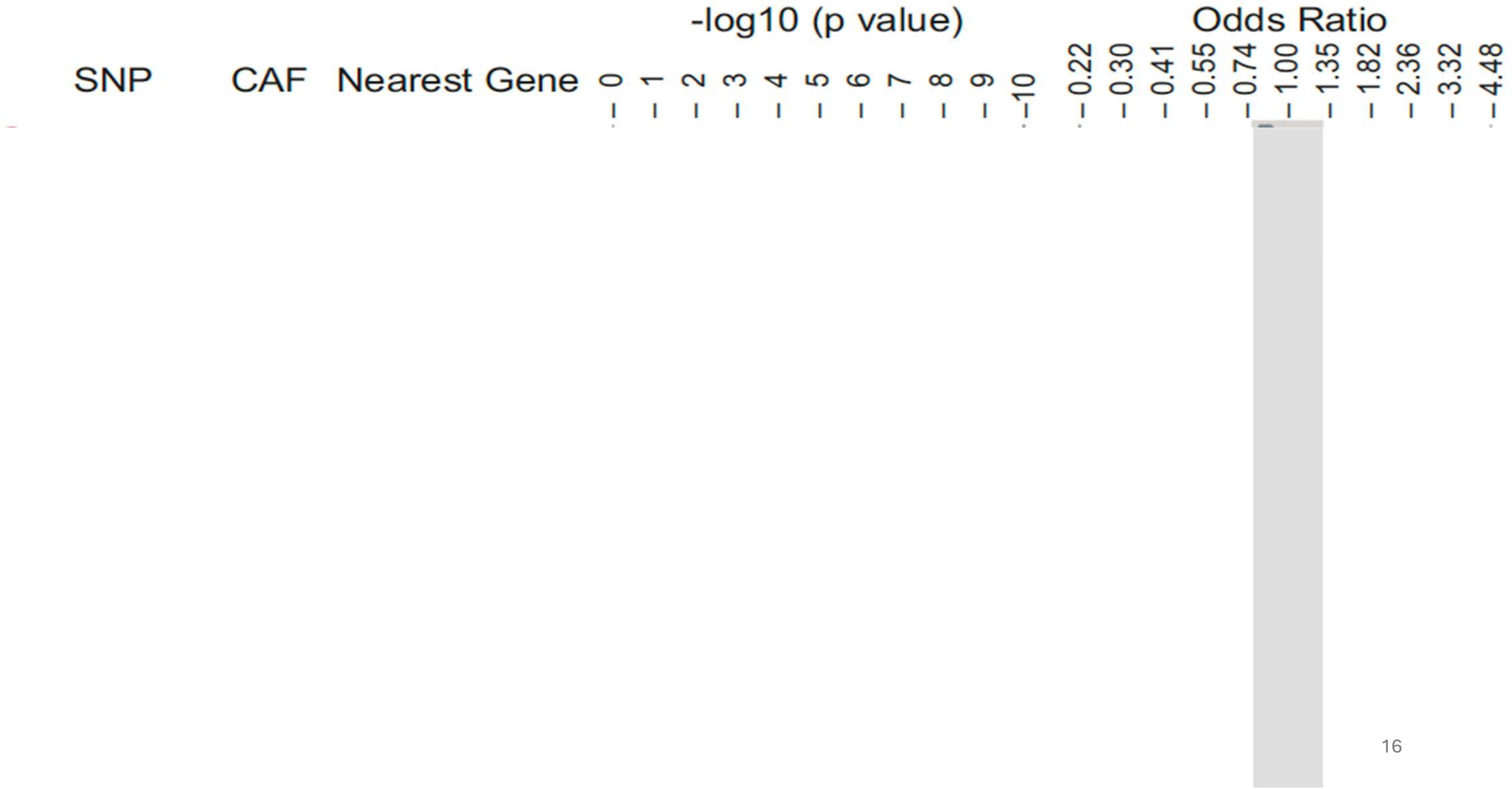
Outline

- Why subgroups?
- Why cognitively defined subgroups?
- How do we define subgroups with cognitive tests?
- **Our favorite stories for five subgroups, including new data from ACT P2**
- What's next?

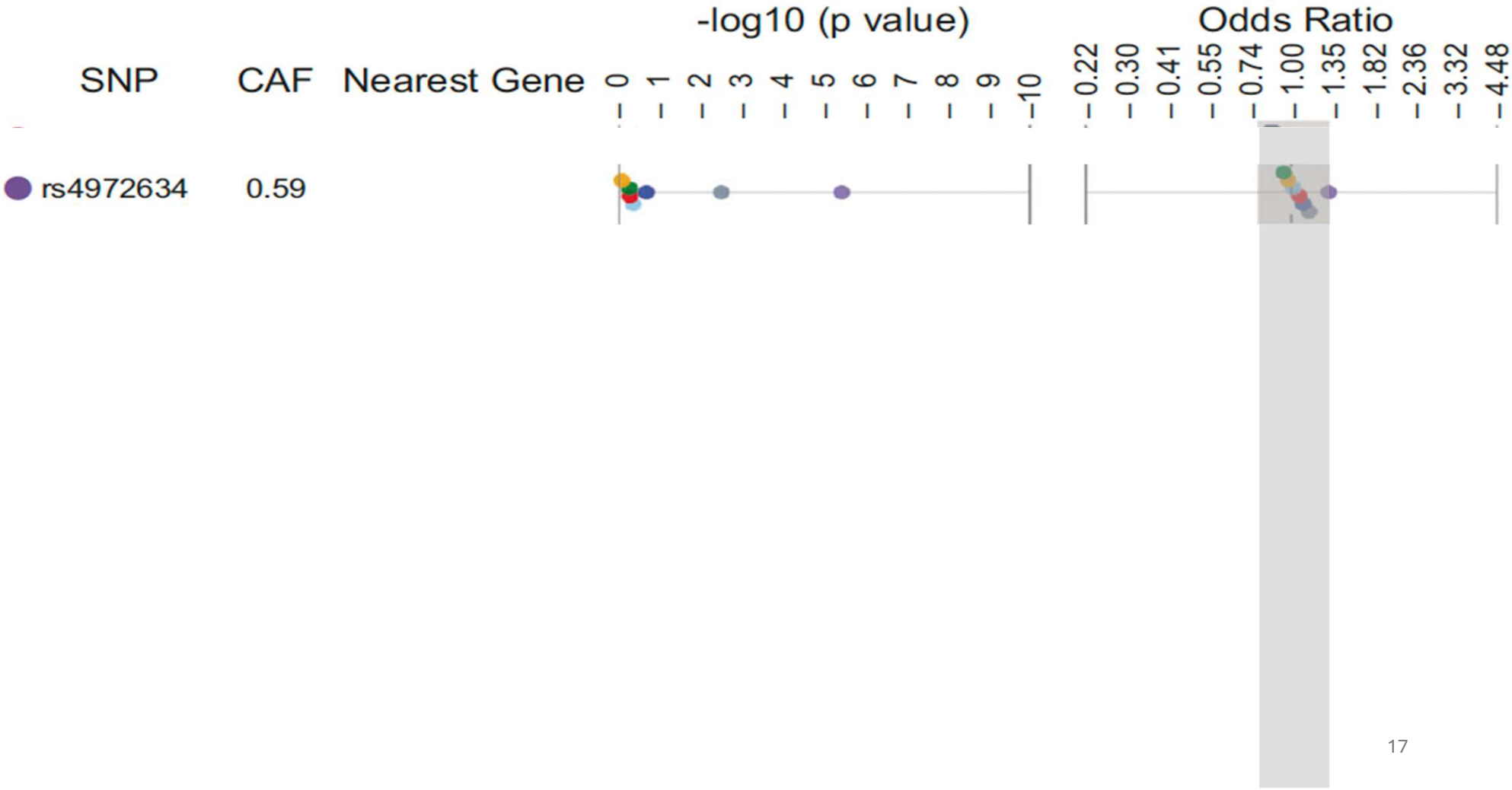

AD-Visuospatial
V
M
E
L
AD-Memory
M
V
L
E
E
V
M
L
AD-No Domains
AD-Language
L
M
E
V
L
V
M
E
AD-Executive Functioning

Mukherjee S, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. Mol Psychiatry. 2020;25(11):2942-51.

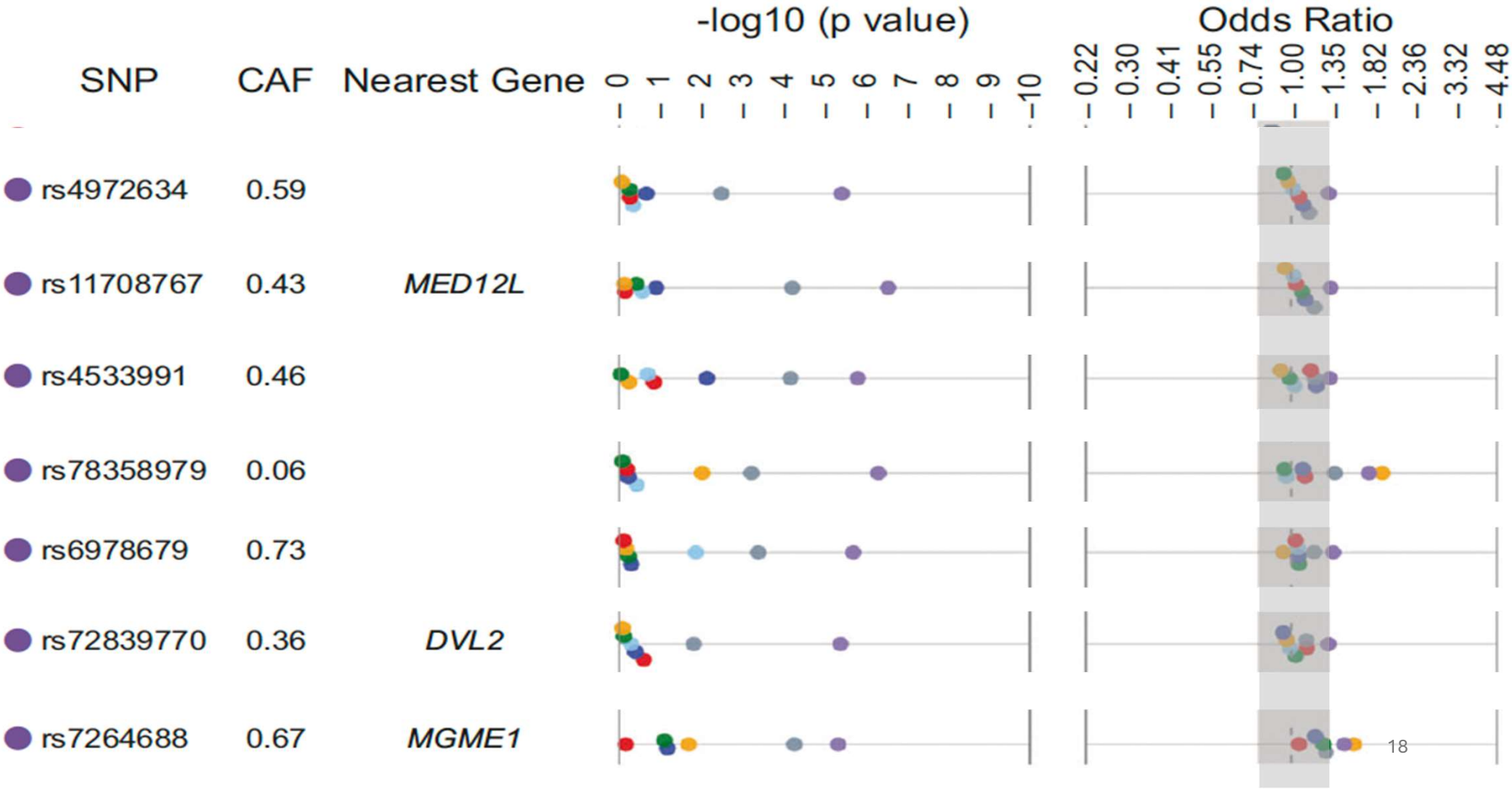


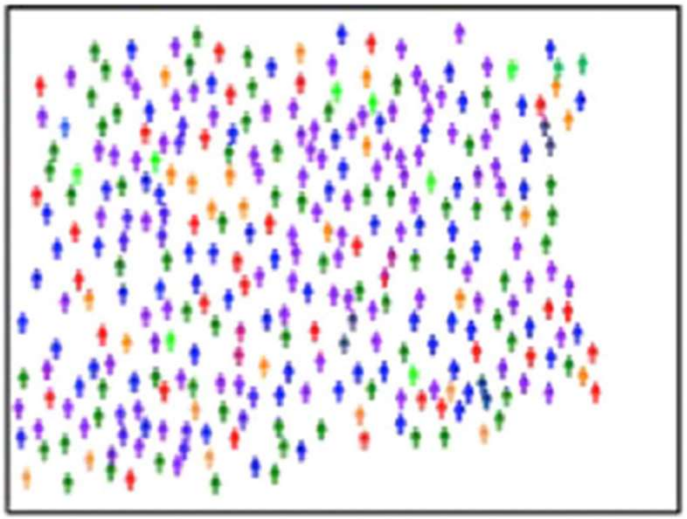

-log10 (p value)
Odds Ratio
SNP
CAF
Nearest Gene
0
1
2
3
4
5
6
7
8
9
10
0.22
0.30
0.41
0.55
0.74
1.00
1.35
1.82
2.36
3.32
4.48

Genome wide – 7 SNPs with odds ratios >1.3



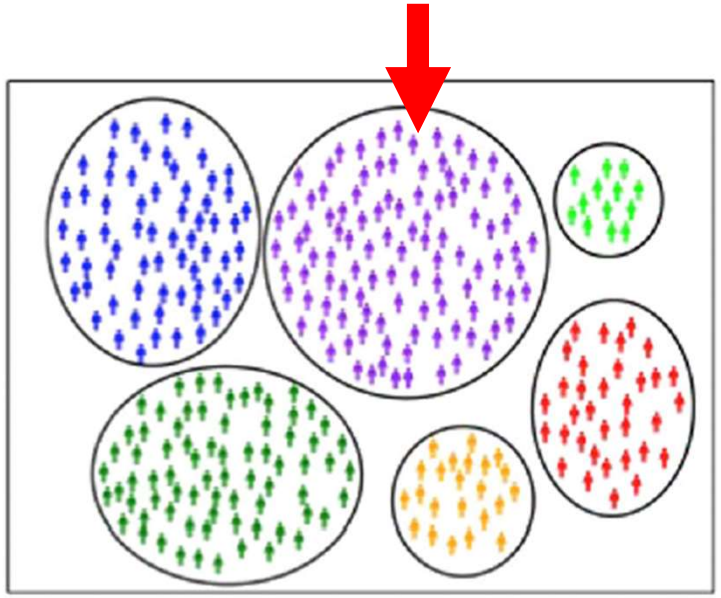
Genome wide – 7 SNPs with odds ratios >1.3





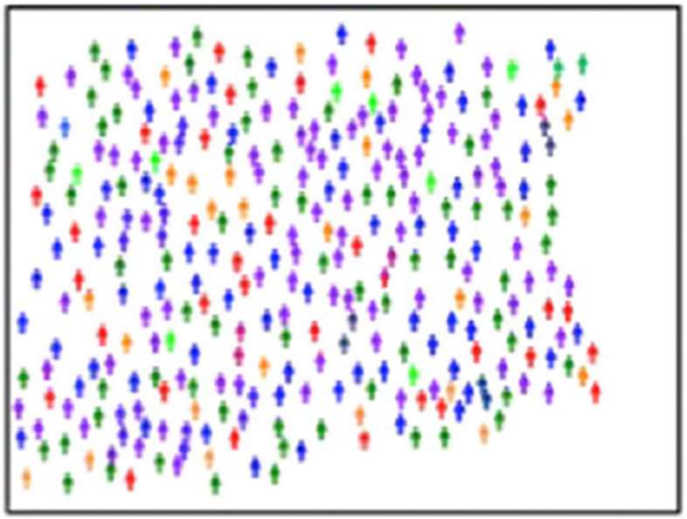
Much larger n
Heterogeneous mix of groups

Zero SNPs with OR > 1.3

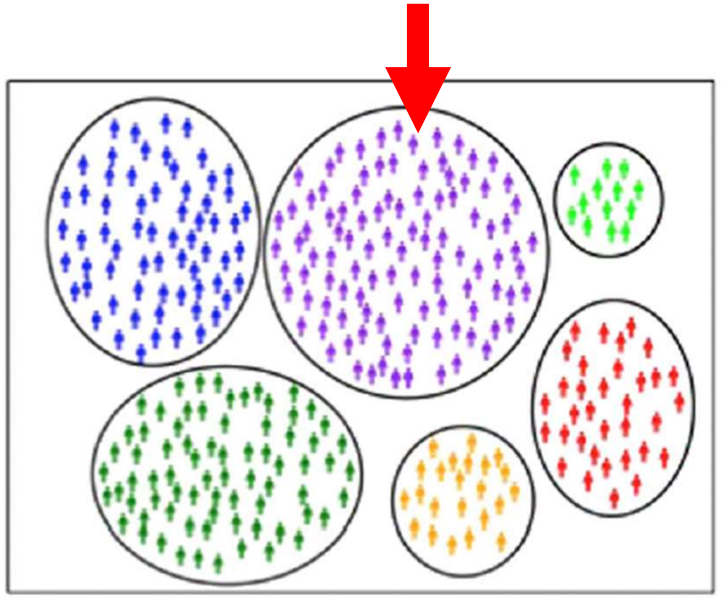


Much smaller n for the purple group alone
Homogenous group

7 SNPs with OR>1.3



Much larger n
Heterogeneous mix of groups
Zero SNPs with OR > 1.3

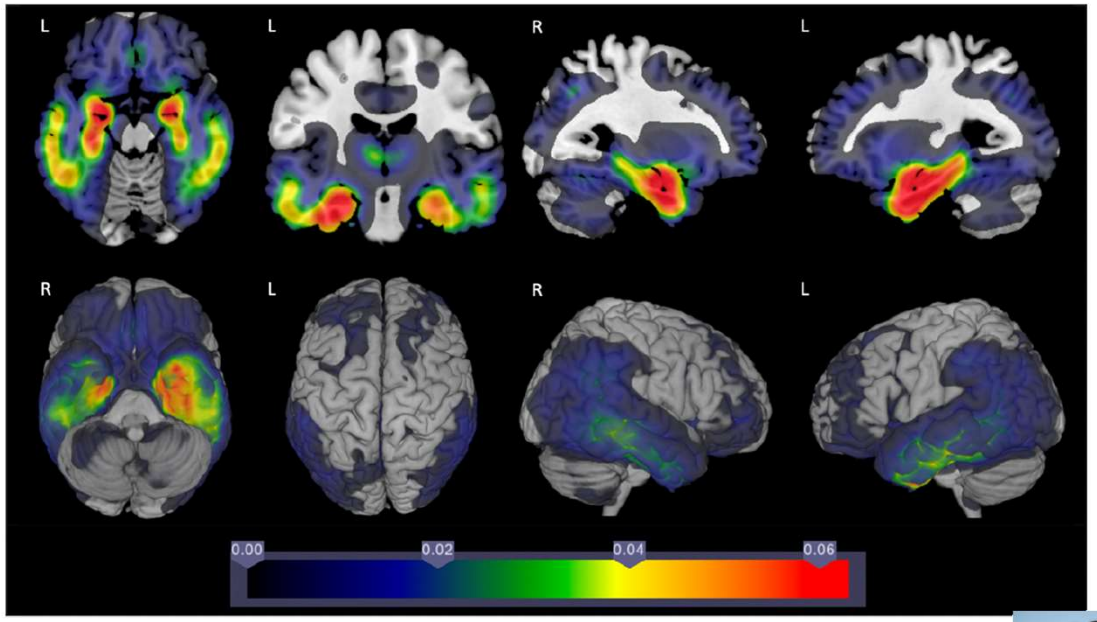


Much smaller n for the purple group alone
Homogenous group
7 SNPs with OR>1.3

Phenotype definition matters!

Imaging: Voxel comparisons to cognitively normal

AD-No Domains compared with Cognitively Normal



Crane PK, Groot C, Ossenkoppele R, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.

Findings for AD (all AD, not subgroups) compared to NC

Most consistent
- Medial Temporal Lobe structures
  - Hippocampus
  - Amygdala
  - Entorhinal cortex
  - Parahippocampal gyrus

Also frequently identified
- Temporal neocortex
- Parietal neocortex
- Insula
- Precuneus
- Anterior cingulate cortex
- Posterior cingulate cortex
- Frontal cortex
- Thalamus
- Caudate nucleus

From Busatto GF, Diniz BS, Zanetti MV. Voxel-based morphometry in Alzheimer's disease. *Expert Rev Neurother*. 2008 Nov;8(11):1691-702.

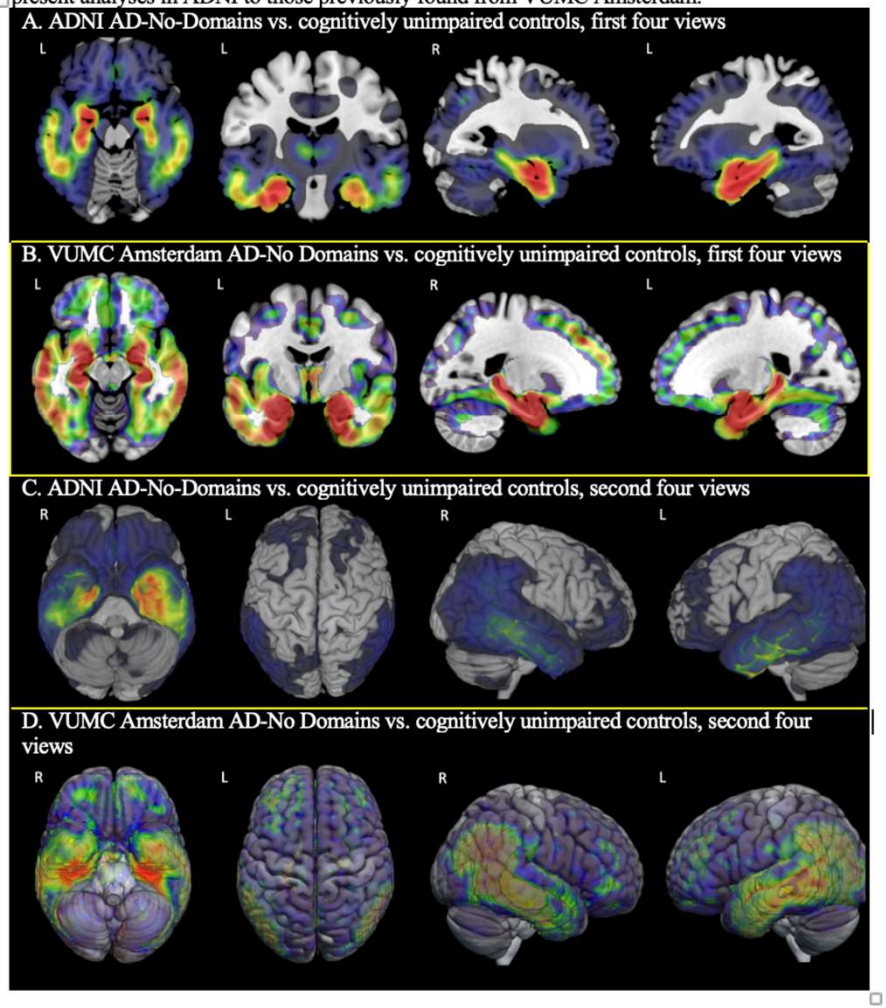
Replication: ADNI and VUMC Amsterdam

AD-No Domains compared with Cognitively Normal

Crane PK, Groot C, Ossenkoppele R, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.

Supplementary Fig. 21. VBM findings for AD-No Domains compared to cognitively normal elderly controls for ADNI and VUMC-Amsterdam late-onset AD.

We previously published similar analyses using data from a non-overlapping participant panel from the VUMC Amsterdam research cohort [3]. We have re-processed those data, limiting to older adults to facilitate direct comparison. In the Figures below we show comparisons from the present analyses in ADNI to those previously found from VUMC Amsterdam.



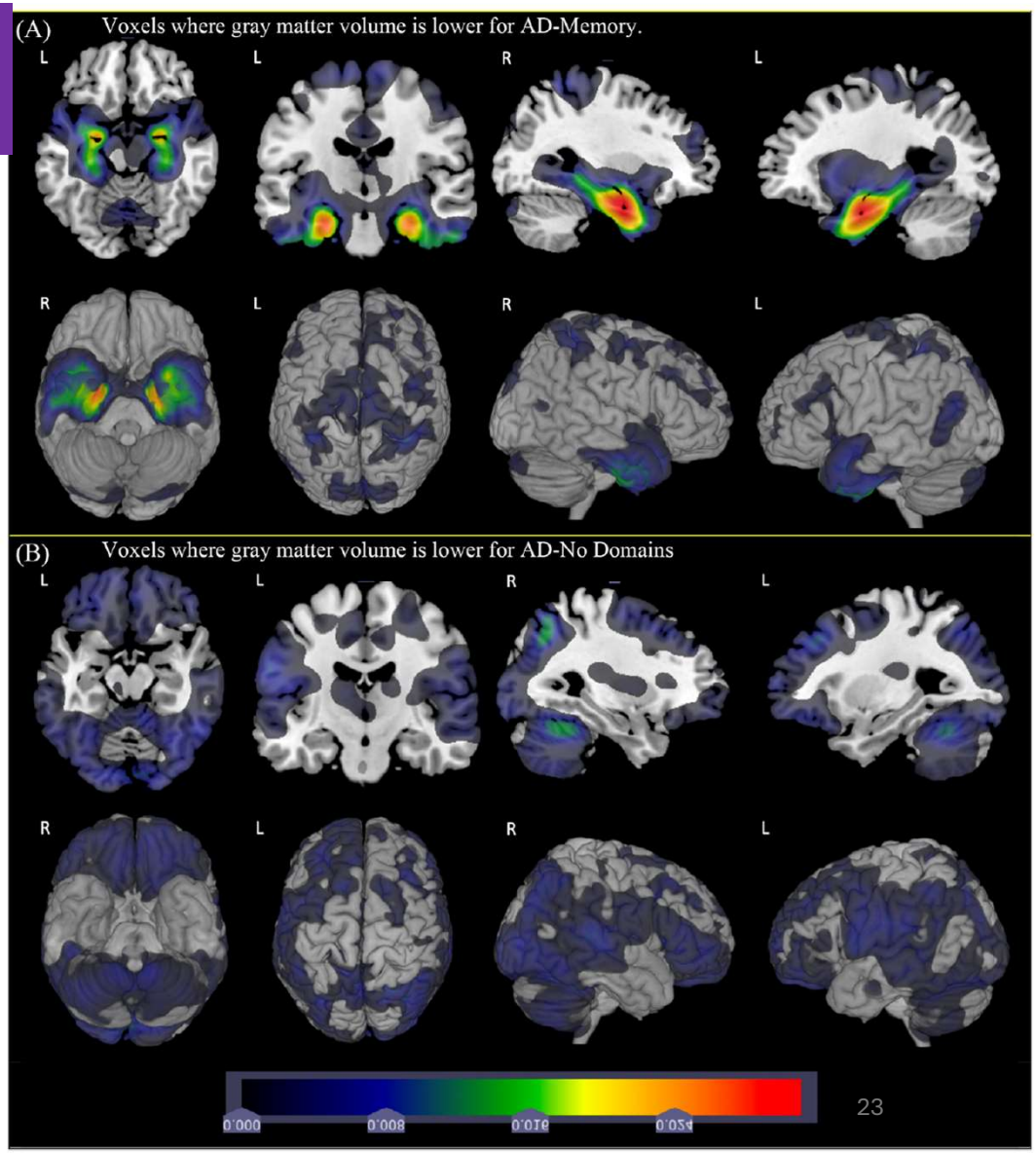
Imaging Comparison of AD-No Domains with AD-Memory

Regions where **AD-Memory**

Has more atrophy than **AD-No Domains**

Regions where **AD-No Domains**

Has more atrophy than **AD-Memory**



Findings from ACT standard neuropathology

Neuropathology	AD- No Domain OR (95% CI)
AD	
ADNC score	
Thal phase	
Braak stage	
CERAD score	
CAA	
Non-AD, non-vascular	
LATE	
Hippocampal sclerosis	
Lewy body disease	
Vascular	
Gross infarcts	
Any microinfarcts	
Cerebral microinfarcts	
Deep microinfarcts	
Atherosclerosis	
Arteriolosclerosis	

Findings from ACT standard neuropathology

Neuropathology	AD- No Domain OR (95% CI)
AD	
ADNC score	**3.58 (2.21, 5.79)**
Thal phase	**2.23 (1.35, 3.68)**
Braak stage	**4.20 (2.69, 6.55)**
CERAD score	**2.81 (1.76, 4.50)**
CAA	1.03 (0.64, 1.65)
Non-AD, non-vascular	
LATE	**1.73 (1.07, 2.77)**
Hippocampal sclerosis	**2.42 (1.19, 4.90)**
Lewy body disease	1.40 (0.77, 2.52)
Vascular	
Gross infarcts	**2.25 (1.36, 3.71)**
Any microinfarcts	1.64 (1.02, 2.62)
Cerebral microinfarcts	1.38 (0.83, 2.29)
Deep microinfarcts	1.98 (1.15, 3.40)
Atherosclerosis	1.20 (0.73, 1.98)
Arteriolosclerosis	1.33 (0.78, 2.27)

Findings from ACT standard neuropathology

Neuropathology	AD- No Domain OR (95% CI)
AD	
ADNC score	**3.58 (2.21, 5.79)**
Thal phase	**2.23 (1.35, 3.68)**
Braak stage	**4.20 (2.69, 6.55)**
CERAD score	**2.81 (1.76, 4.50)**
CAA	1.03 (0.64, 1.65)
Non-AD, non-vascular	
LATE	**1.73 (1.07, 2.77)**
Hippocampal sclerosis	**2.42 (1.19, 4.90)**
Lewy body disease	1.40 (0.77, 2.52)
Vascular	
Gross infarcts	**2.25 (1.36, 3.71)**
Any microinfarcts	1.64 (1.02, 2.62)
Cerebral microinfarcts	1.38 (0.83, 2.29)
Deep microinfarcts	1.98 (1.15, 3.40)
Atherosclerosis	1.20 (0.73, 1.98)
Arteriolosclerosis	1.33 (0.78, 2.27)

Findings from ACT standard neuropathology

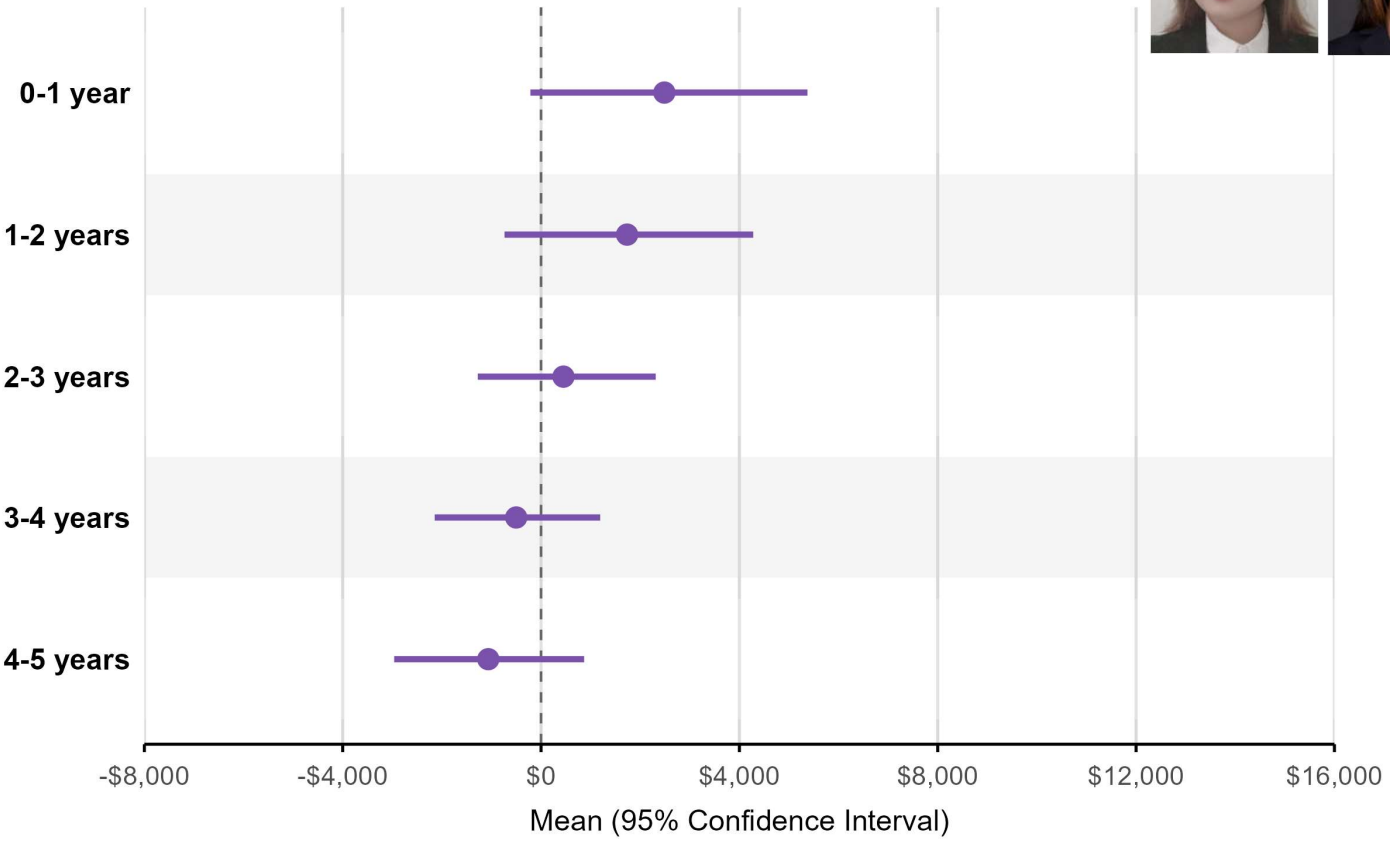
Neuropathology	AD- No Domain OR (95% CI)
AD	
ADNC score	**3.58 (2.21, 5.79)**
Thal phase	**2.23 (1.35, 3.68)**
Braak stage	**4.20 (2.69, 6.55)**
CERAD score	**2.81 (1.76, 4.50)**
CAA	1.03 (0.64, 1.65)
Non-AD, non-vascular	
LATE	**1.73 (1.07, 2.77)**
Hippocampal sclerosis	**2.42 (1.19, 4.90)**
Lewy body disease	1.40 (0.77, 2.52)
Vascular	
Gross infarcts	**2.25 (1.36, 3.71)**
Any microinfarcts	1.64 (1.02, 2.62)
Cerebral microinfarcts	1.38 (0.83, 2.29)
Deep microinfarcts	1.98 (1.15, 3.40)
Atherosclerosis	1.20 (0.73, 1.98)
Arteriolosclerosis	1.33 (0.78, 2.27)

Findings from ACT standard neuropathology

Neuropathology	AD- No Domain OR (95% CI)
AD	
ADNC score	**3.58 (2.21, 5.79)**
Thal phase	**2.23 (1.35, 3.68)**
Braak stage	**4.20 (2.69, 6.55)**
CERAD score	**2.81 (1.76, 4.50)**
CAA	1.03 (0.64, 1.65)
Non-AD, non-vascular	
LATE	**1.73 (1.07, 2.77)**
Hippocampal sclerosis	**2.42 (1.19, 4.90)**
Lewy body disease	1.40 (0.77, 2.52)
Vascular	
Gross infarcts	**2.25 (1.36, 3.71)**
Any microinfarcts	1.64 (1.02, 2.62)
Cerebral microinfarcts	1.38 (0.83, 2.29)
Deep microinfarcts	1.98 (1.15, 3.40)
Atherosclerosis	1.20 (0.73, 1.98)
Arteriolosclerosis	1.33 (0.78, 2.27)

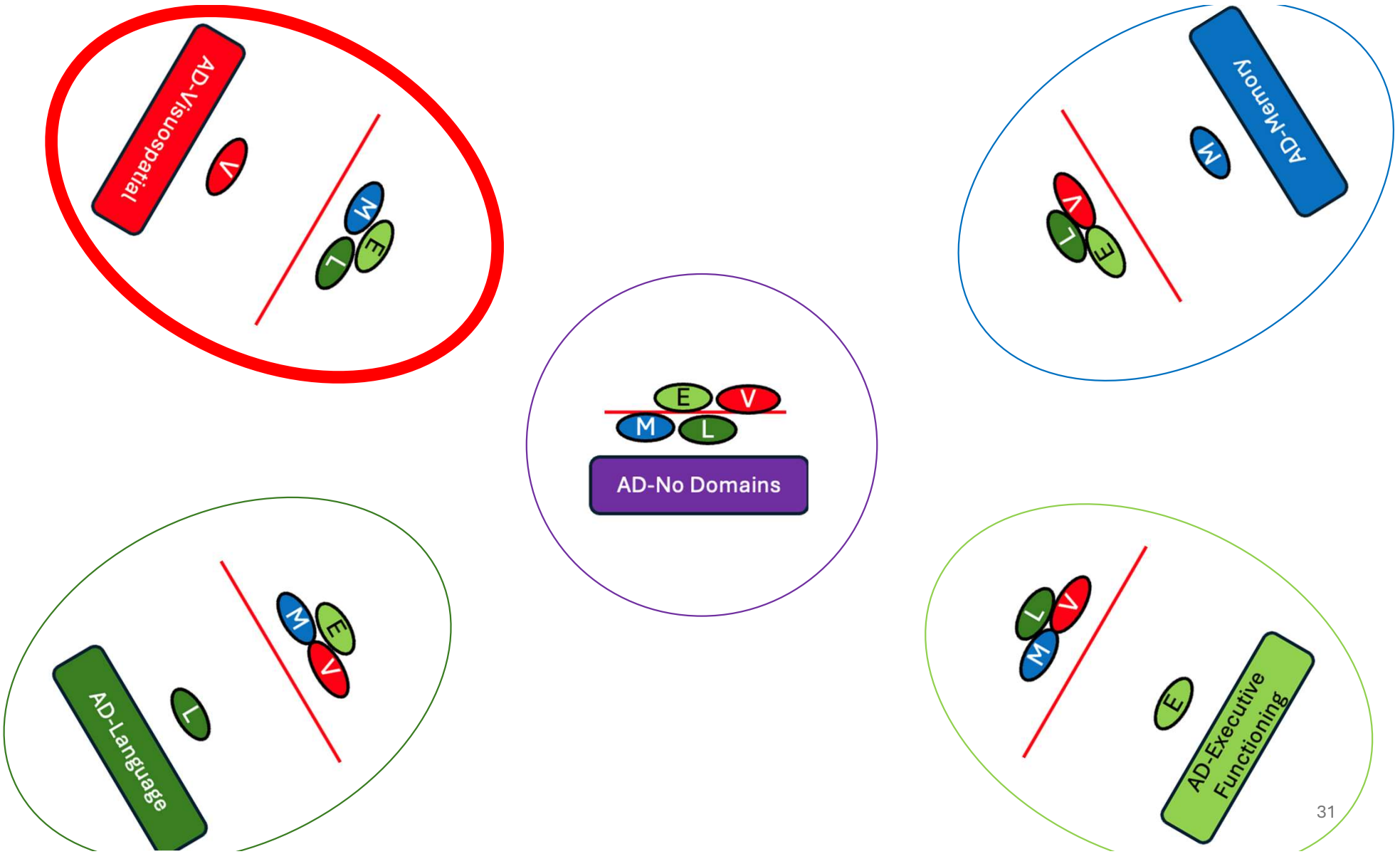
LOTS of neuropath findings

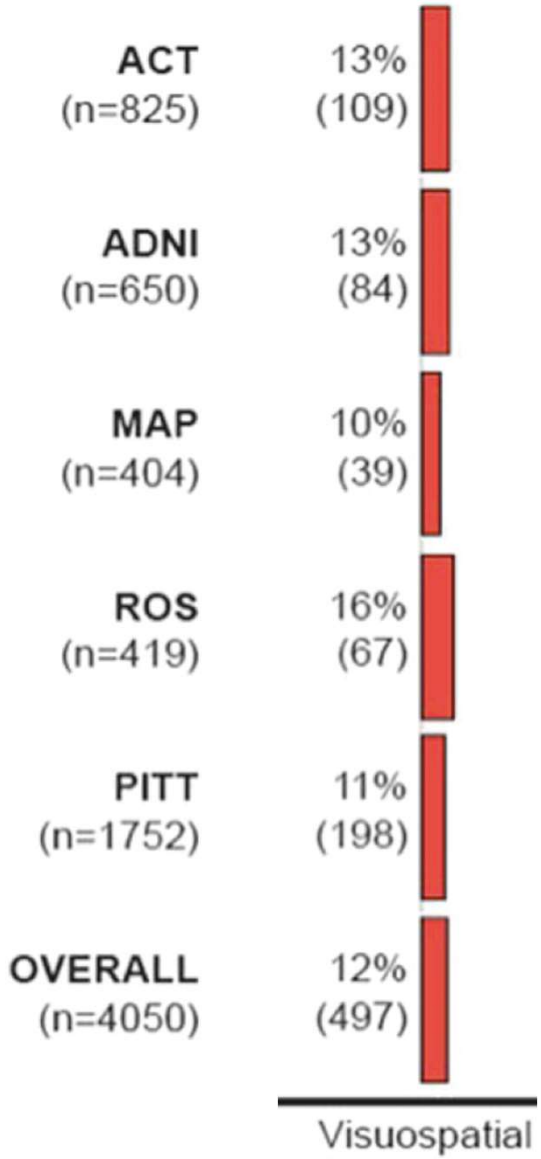
Costs – Adjusted for survival



Conclusions – AD-No Domains

- Genetics: multiple SNPs with strong effect sizes
- Imaging
  - Pattern of findings similar to that for AD-Dementia
  - Pattern of findings replicates for ADNI and VU Amsterdam
  - Distinct differences from AD-Memory – marked signal in hippocampus compared to controls, but less than AD Memory, and scattered areas of cortex with more atrophy in AD-No Domains
- Neuropathology (ACT Project 2)
  - More AD neuropathology than controls, more LATE and HS, more gross infarcts and deep microinfarcts
- Costs (ACT Project 2): Higher costs early; lower costs later

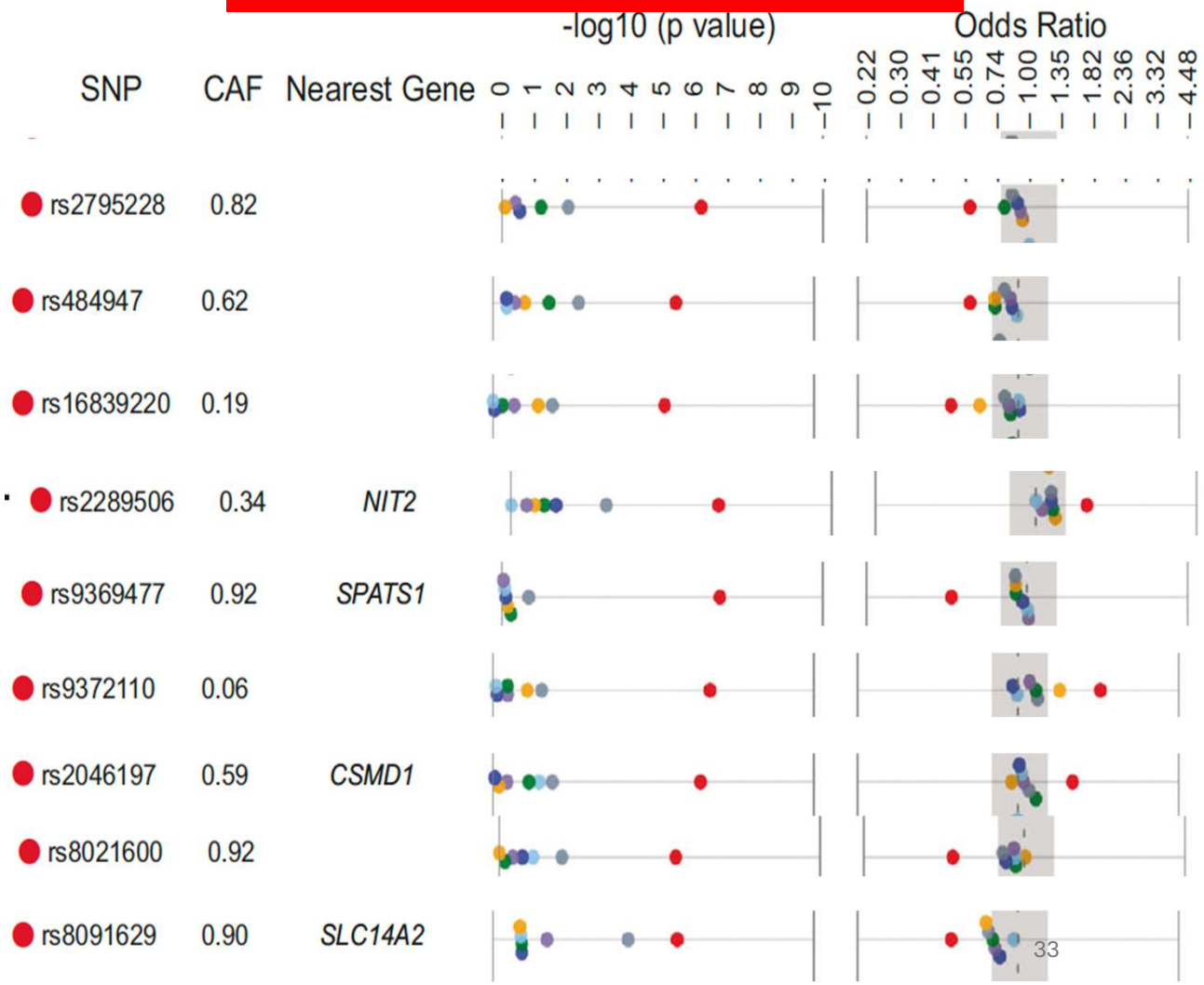

AD-Visuospatial
V
M
E
L
AD-Memory
M
V
L
E
E
V
M
L
AD-No Domains
AD-Language
L
M
E
V
L
V
M
E
AD-Executive Functioning



Mukherjee S, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. Mol Psychiatry. 2020;25(11):2942-51.

Genetics

Genome wide – 9 SNPs with odds ratios >1.3

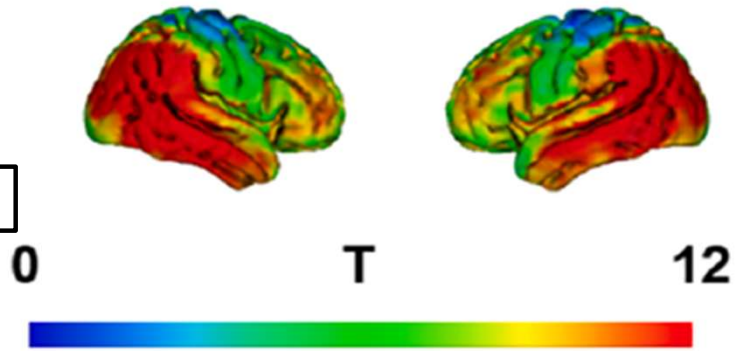


Imaging – comparison with PCA

AD-Visuospatial

vs.

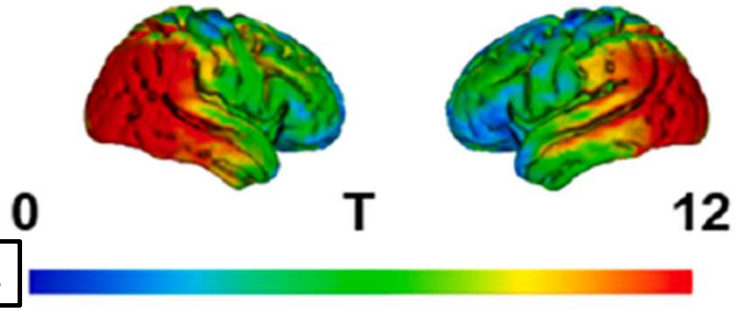
Cognitively Normal

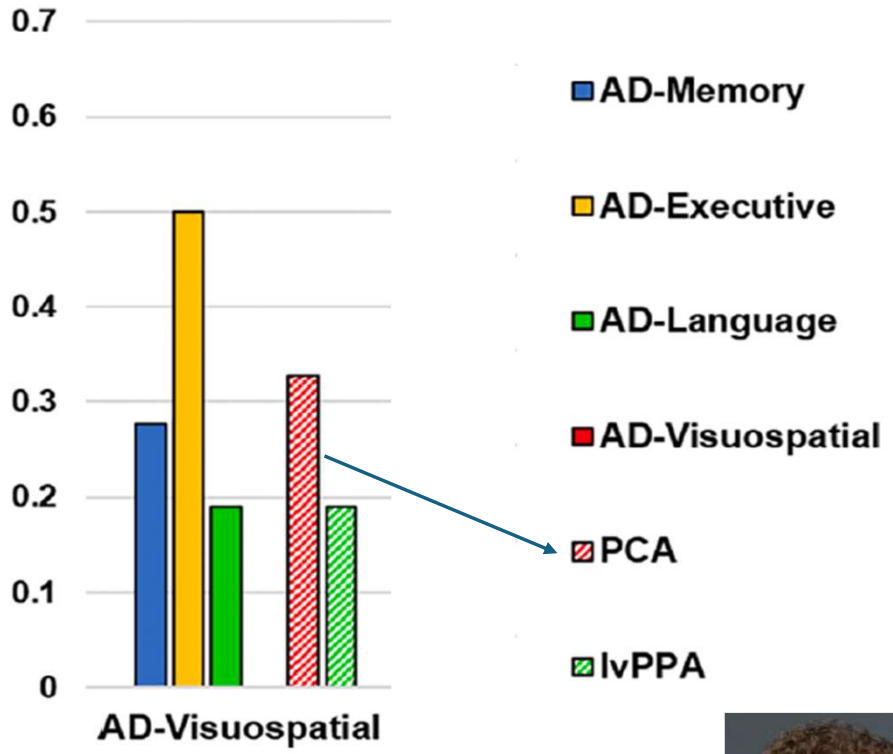


PCA

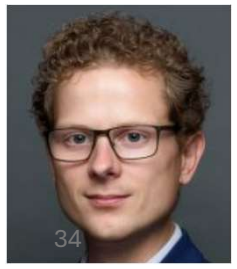
vs.

Cognitively Normal





Groot C, et al. Differential patterns of gray matter volumes and associated gene expression profiles in cognitively-defined Alzheimer's disease subgroups. Neuroimage Clin. 2021;30:102660.



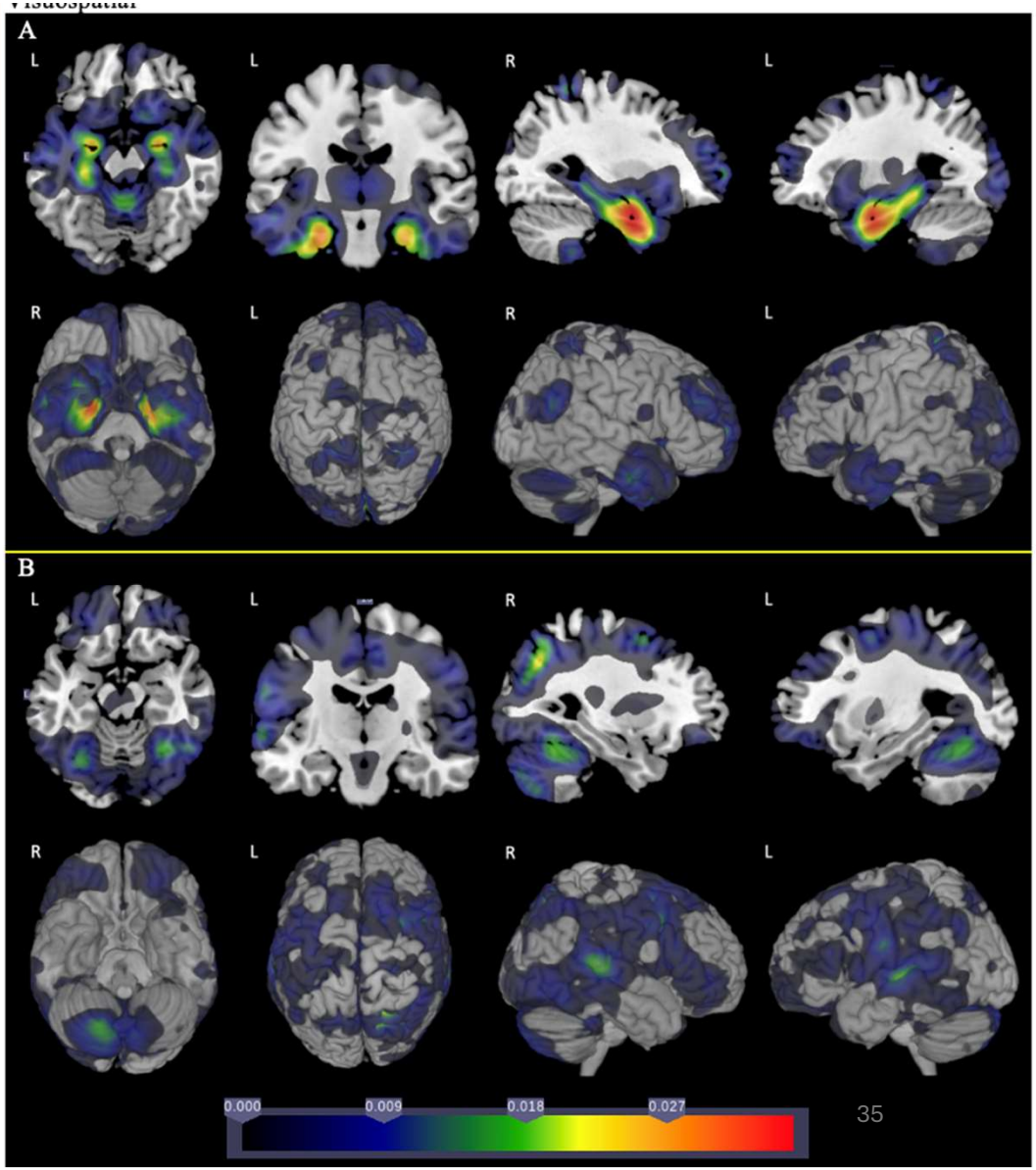
Imaging Comparison of AD Visuospatial with AD-Memory

Regions where **AD-Memory**

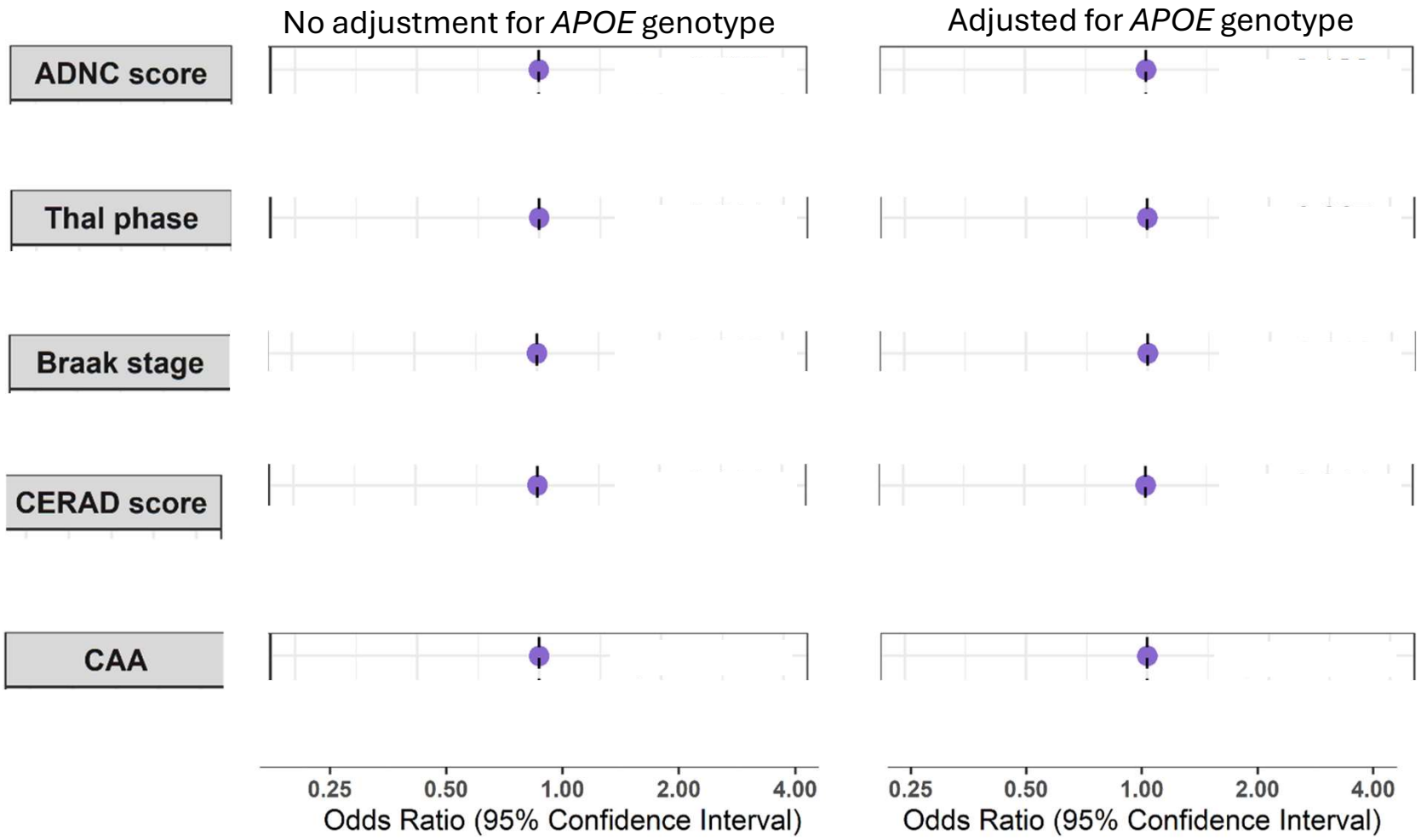
Has more atrophy than **AD-Visuospatial**

Regions where **AD-Visuospatial**

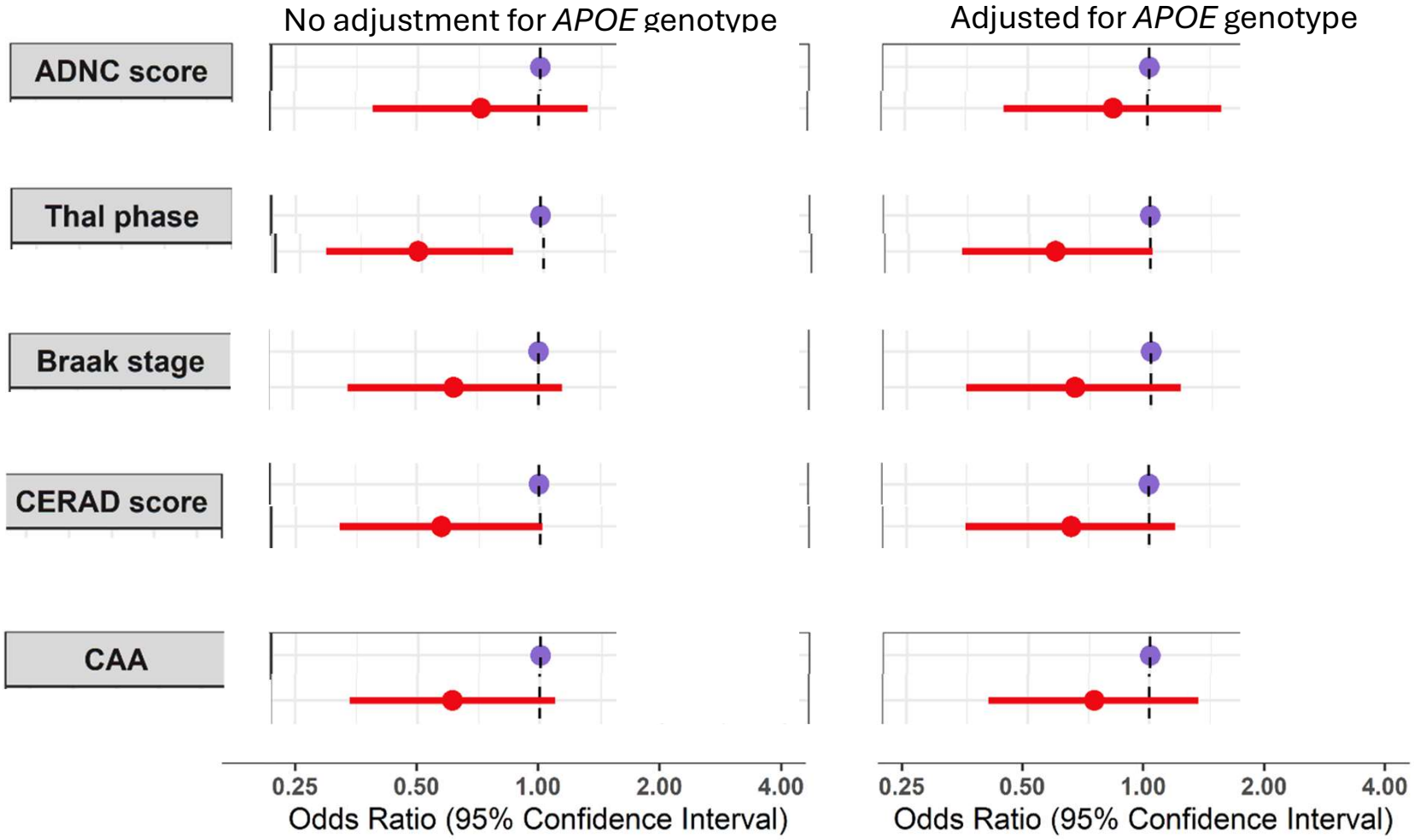
Has more atrophy than **AD-Memory**



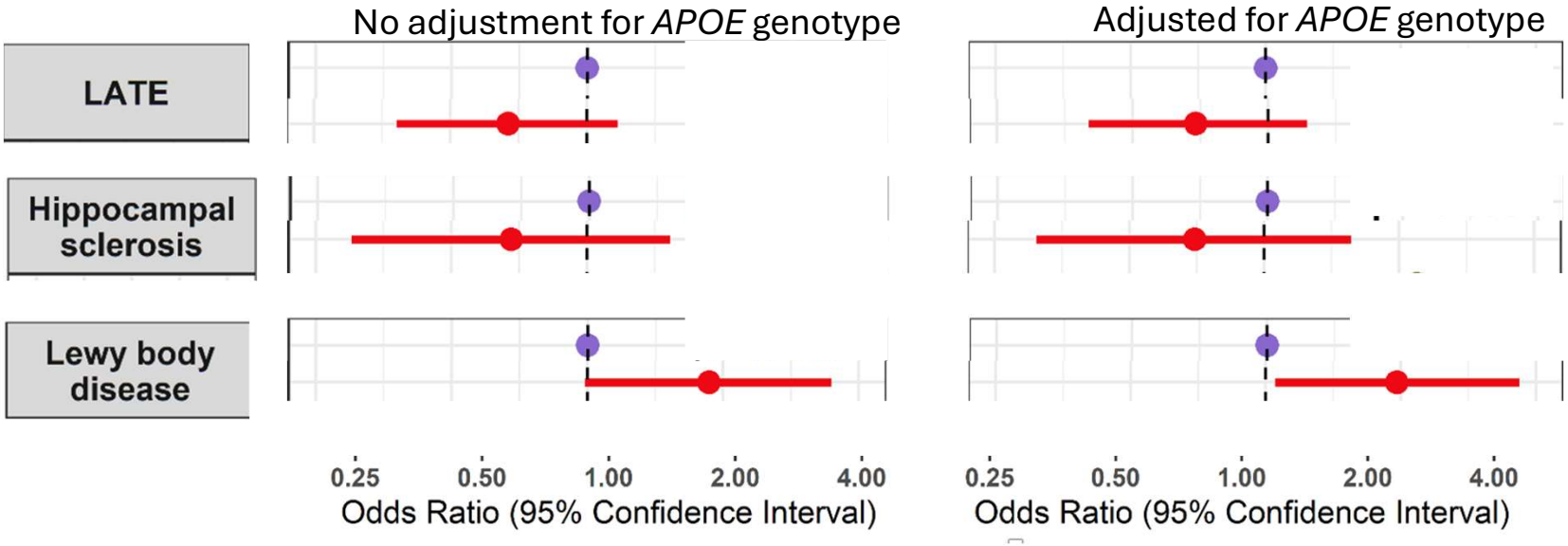
AD-No Domains is reference



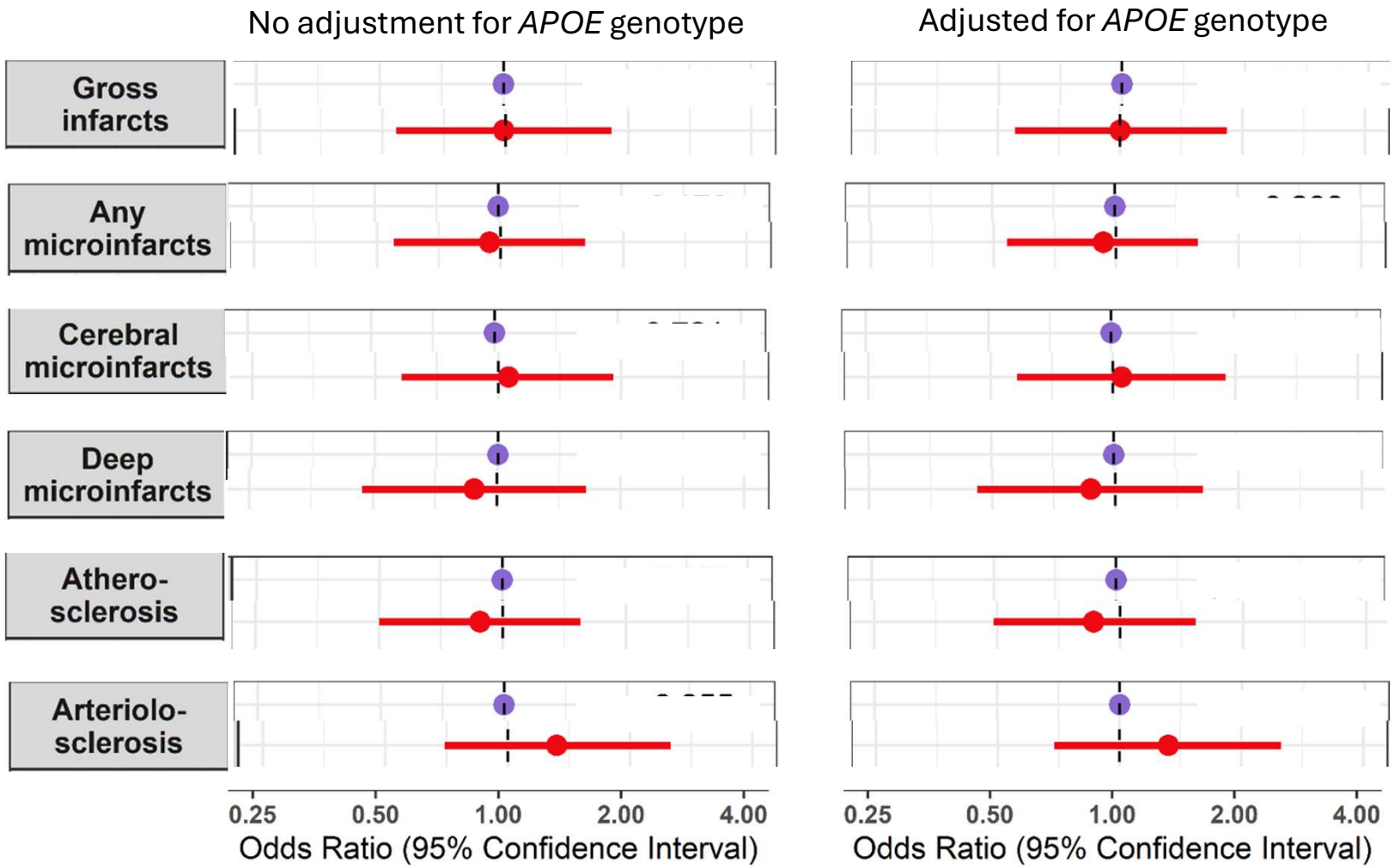
AD Neuropath in ACT: AD-VS lower than AD-ND



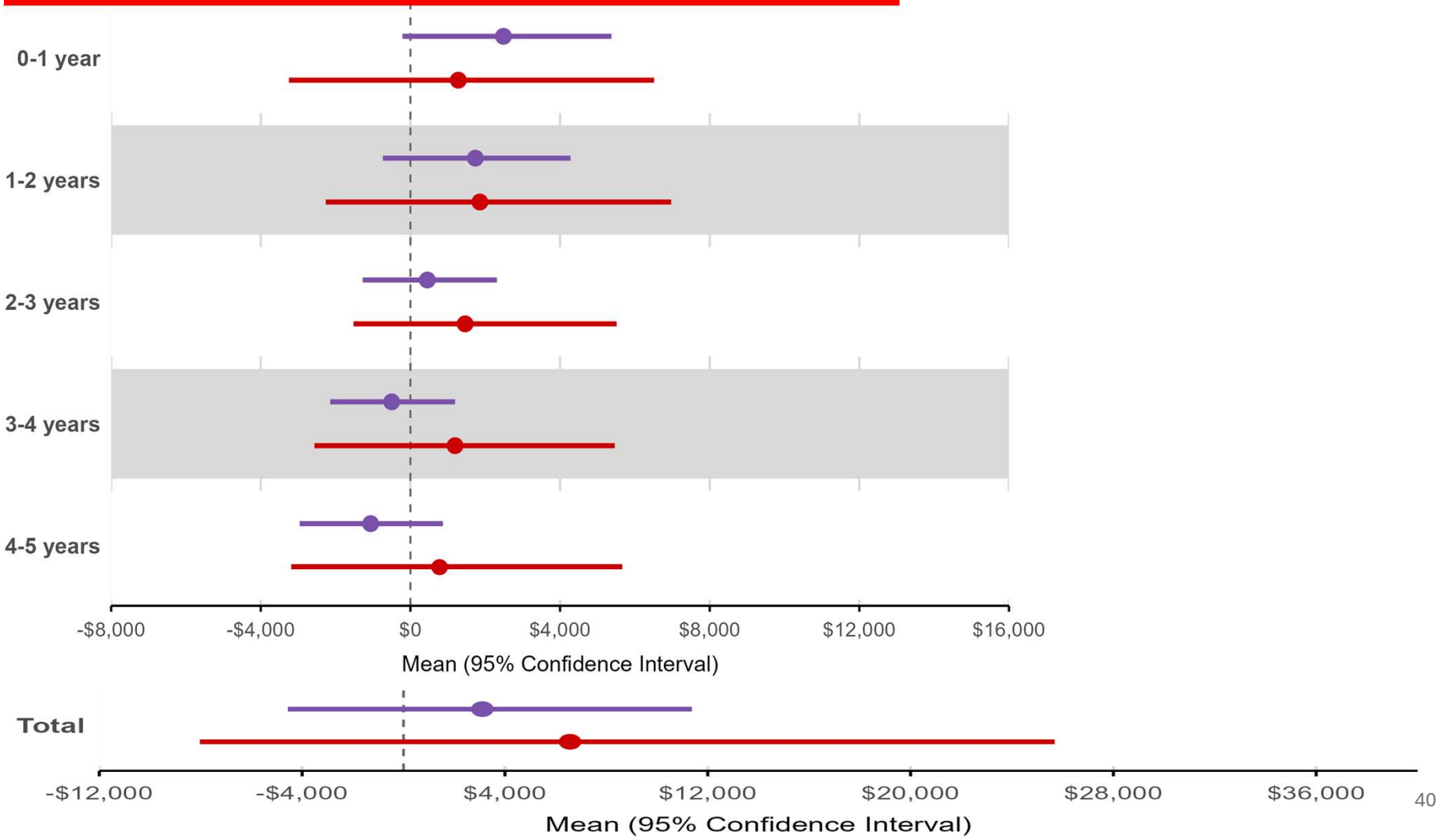
Other Neuropath in ACT: AD-VS less LATE, more LB



Vascular NP in ACT: AD-VS similar to AD-ND

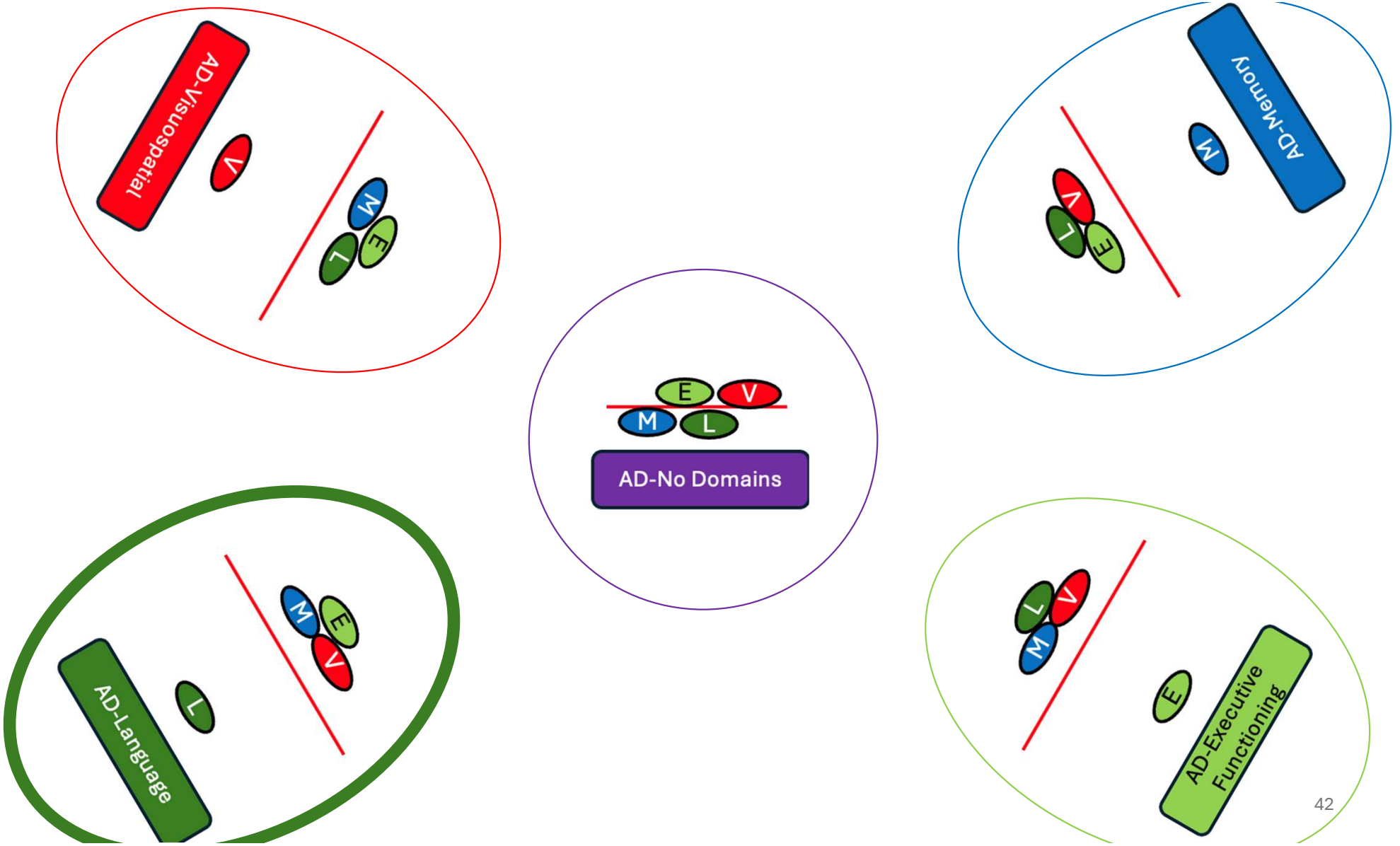


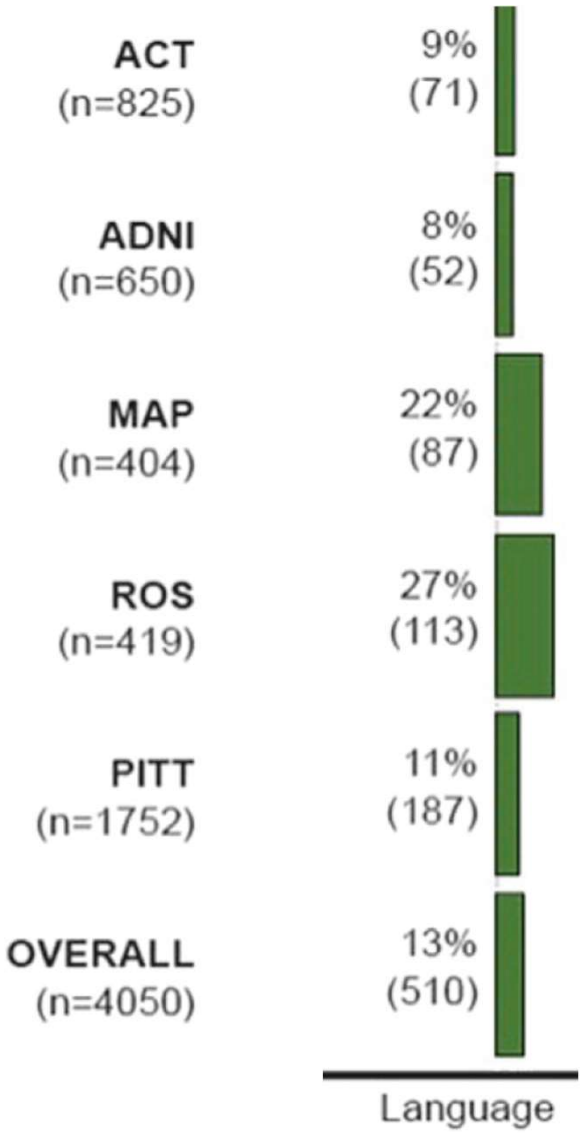
Costs – Adjusted for survival



Conclusions – AD-Visuospatial

- Genetics: multiple SNPs
- Imaging
  - Overlap with PCA, an atypical AD characterized by visuospatial complaints
- Neuropathology
  - Less AD neuropathology than AD-ND, similar vascular and LATE and HS, more Lewy bodies
- Costs: Somewhat higher costs than AD-No Domains

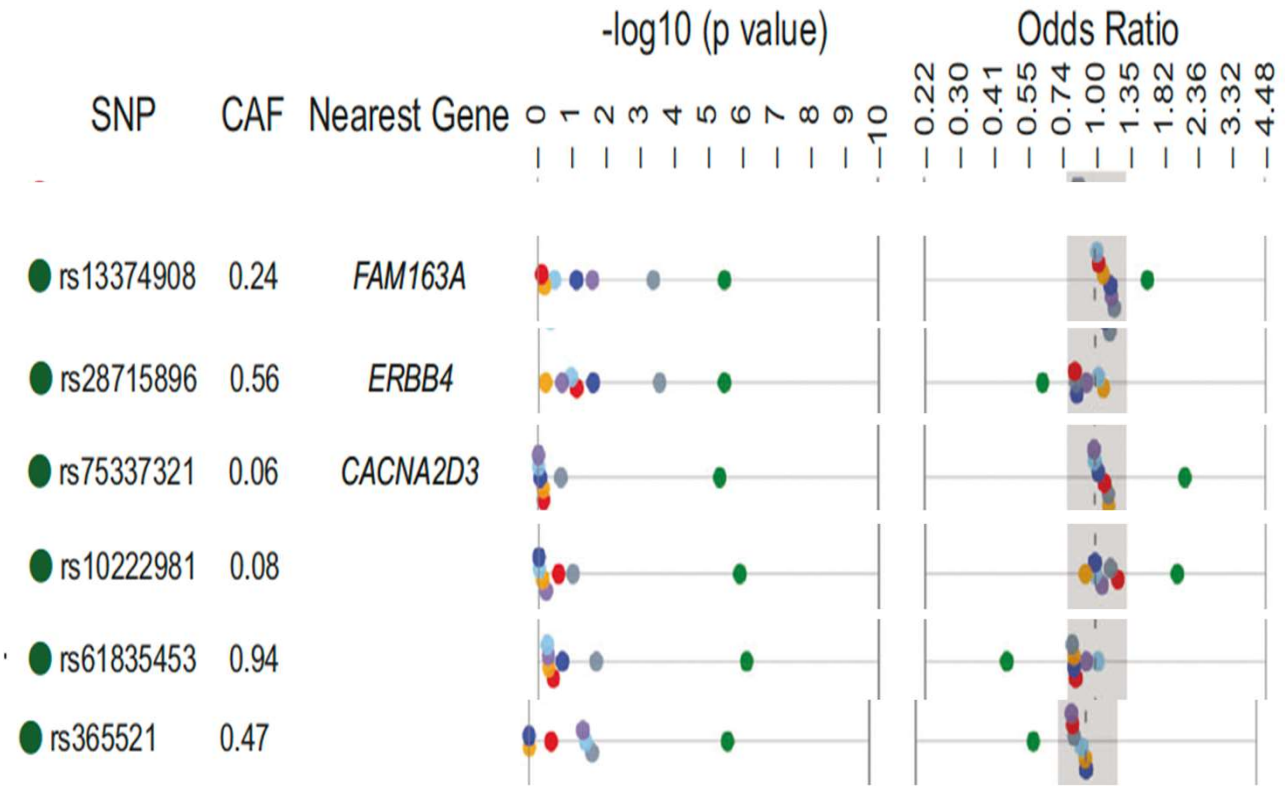

AD-Visuospatial
V
M
E
L
AD-Memory
M
V
L
E
E
V
M
L
AD-No Domains
AD-Language
L
M
E
V
L
V
M
E
AD-Executive Functioning



Mukherjee S, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. Mol Psychiatry. 2020;25(11):2942-51.

Genetics

Genome wide – 6 SNPs with odds ratios >1.3



Imaging – comparison with PPA

AD-Language

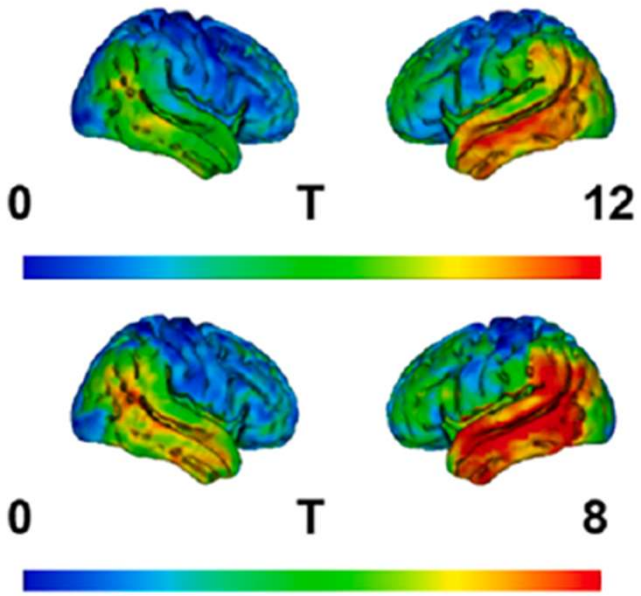
vs

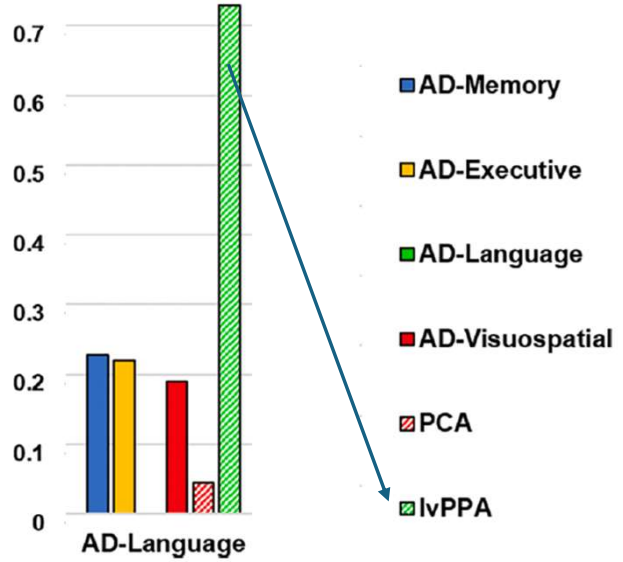
Cognitively Normal

PPA

vs

Cognitively Normal



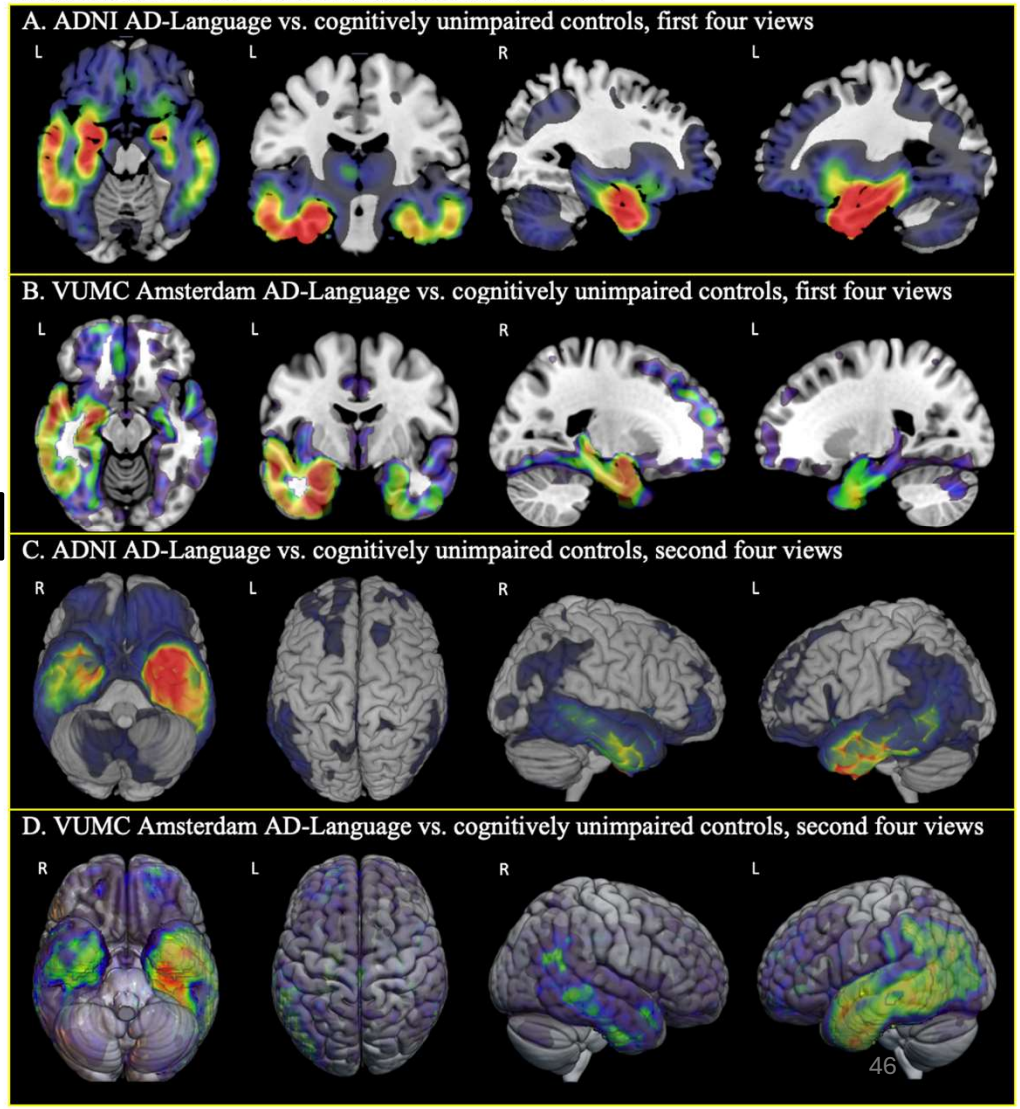


Groot C, et al. Differential patterns of gray matter volumes and associated gene expression profiles in cognitively-defined Alzheimer's disease subgroups. Neuroimage Clin. 2021;30:102660.

Imaging: comparisons with controls

AD-Language More atrophy than Cognitively Normal

Supplementary Fig. 23. VBM findings for AD-Language compared to cognitively normal elderly controls for ADNI and VUMC-Amsterdam late-onset AD



Crane PK, Groot C, Ossenkoppele R, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.

Laterality: findings from ADNI

TABLE 2 Asymmetry results fo

	AD-Language
Global cortex	−2.51
Frontal	
Frontal lobe	−1.13
Regional measures	
Medial orbitofrontal	−0.46
Middle frontal	−0.71
Pars opercularis	−0.58
Pars orbitalis	−0.22
Pars triangularis	−0.52
Precentral	−0.68
Rostral middle frontal	−0.52
Parietal	
Parietal lobe	−1.19
Regional measures	
Isthmus of cingulate	−0.51
Precuneus	−0.68
Supramarginal	−0.65
Temporal	
Temporal lobe	−2.35
Medial temporal lobe	−1.67
Lateral temporal lobe	−2.05
Regional measures	
Banks super temp sulcus	−0.88
Entorhinal cortex	−0.95
Fusiform	−1.29
Middle temporal	−1.59
Parahippocampal	−1.54
Superior temporal	−1.31
Temporal pole	−0.47
Occipital	
Occipital lobe	−0.71
Regional measures	
Cuneus	−0.22
Lateral occipital	−0.50
Lingual	−0.61
Pericalcarine	−0.24
Insula	−0.96
Sensorimotor	−0.80
Cerebellum	
Cerebellar white matter	−2.54
Cerebellar gray mater	−0.10
Deep structures	−0.18
Accumbens	−0.99
Amygdala	−0.73
Caudate	−1.53
Hippocampus	−0.77
Pallidum	−0.77
Putamen	−0.62
Thalamus	

Multiple asymmetrical regions

Crane PK, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.

Laterality findings overlap with an approach starting from tau PET scans

nature medicine

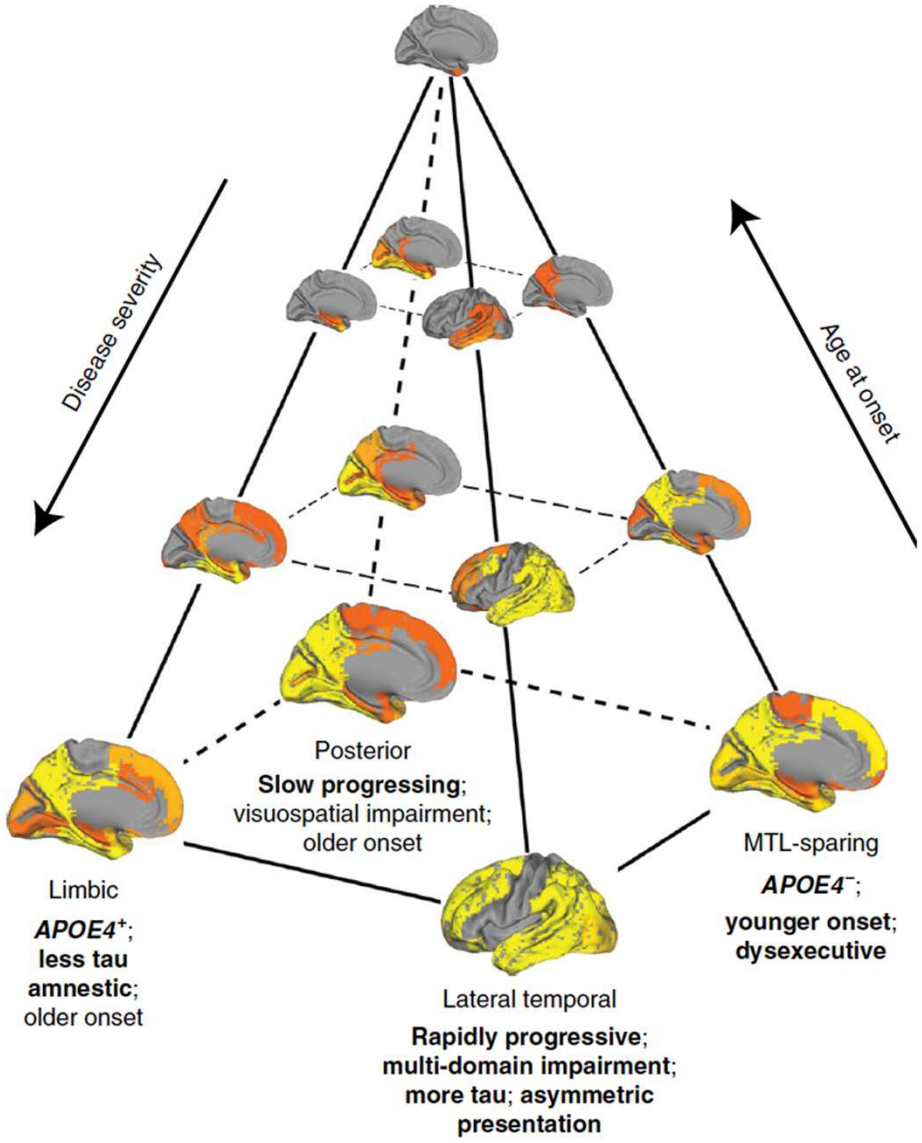
ARTICLES

https://doi.org/10.1038/s41591-021-01309-6

Check for updates

Four distinct trajectories of tau deposition identified in Alzheimer's disease

Jacob W. Vogel[1]✉, Alexandra L. Young[2], Neil P. Oxtoby[3,4], Ruben Smith[5,6], Rik Ossenkoppele[5,7], Olof T. Strandberg[5], Renaud La Joie[8], Leon M. Aksman[3,9], Michel J. Grothe[10,11], Yasser Iturria-Medina[1], the Alzheimer's Disease Neuroimaging Initiative*, Michael J. Pontecorvo[12], Michael D. Devous[12], Gil D. Rabinovici[8,13], Daniel C. Alexander[3,4], Chul Hyoung Lyoo[14], Alan C. Evans[1] and Oskar Hansson[5,15]✉



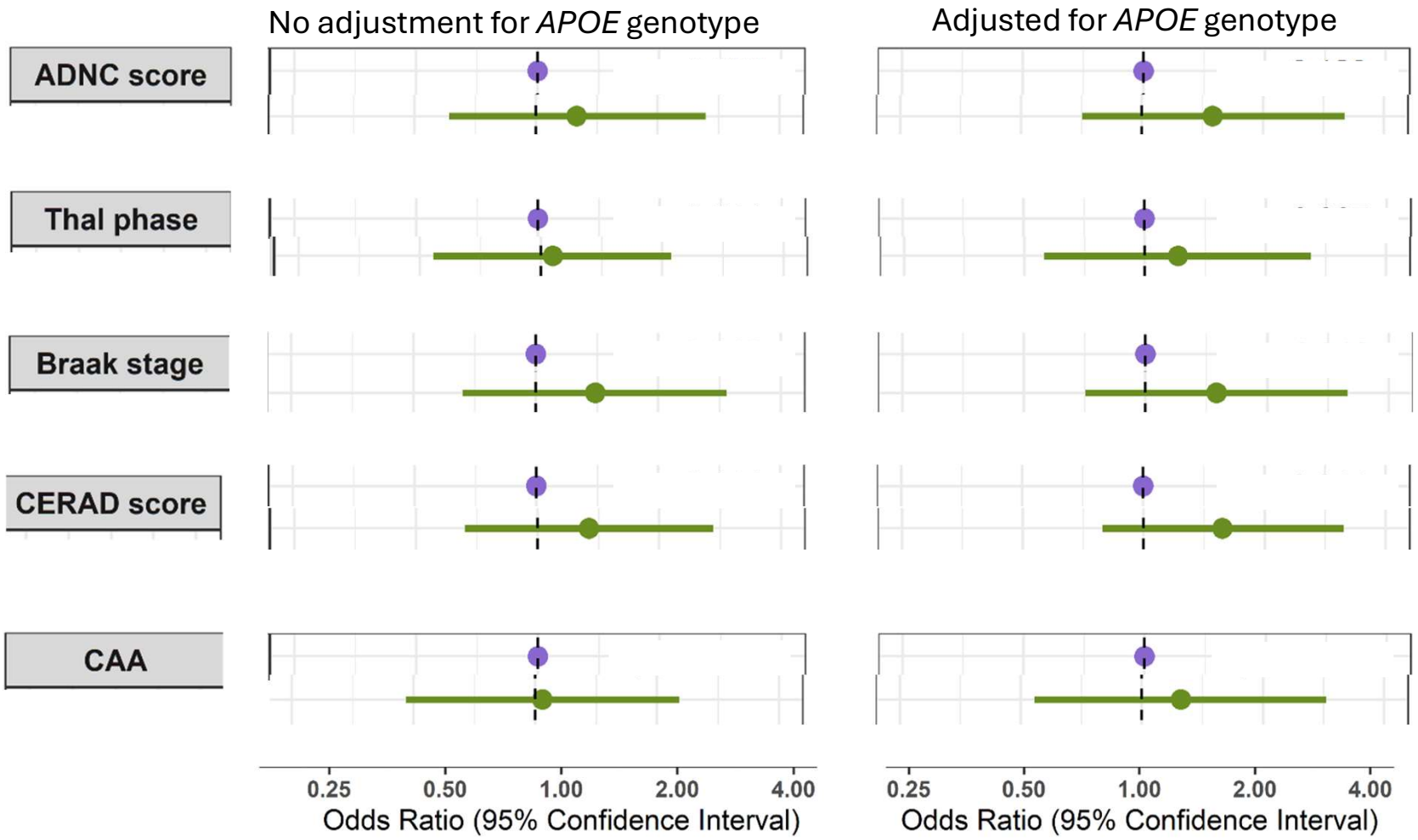
Posterior
Visuospatial

Limbic (hippocampus)
More *APOE* ε4
Amnestic ("Memory")

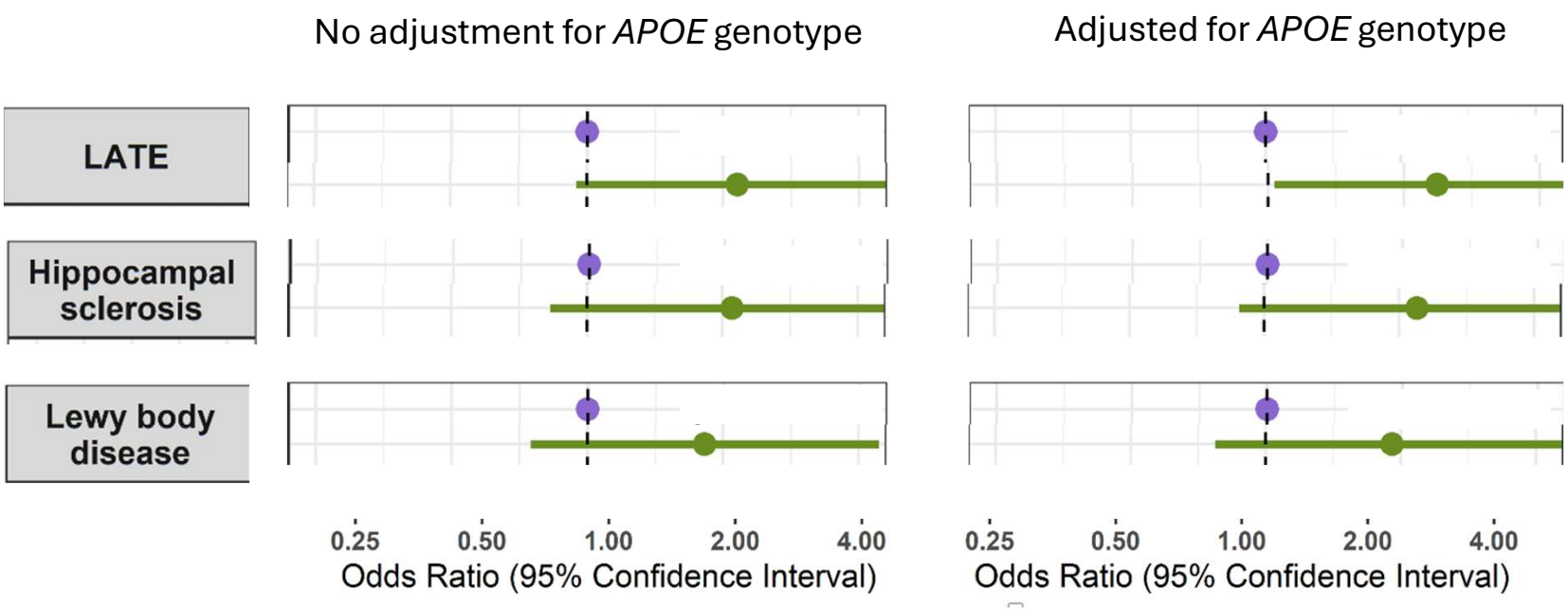
Sparing MTL
Dysexecutive

Lateral temporal
Asymmetric

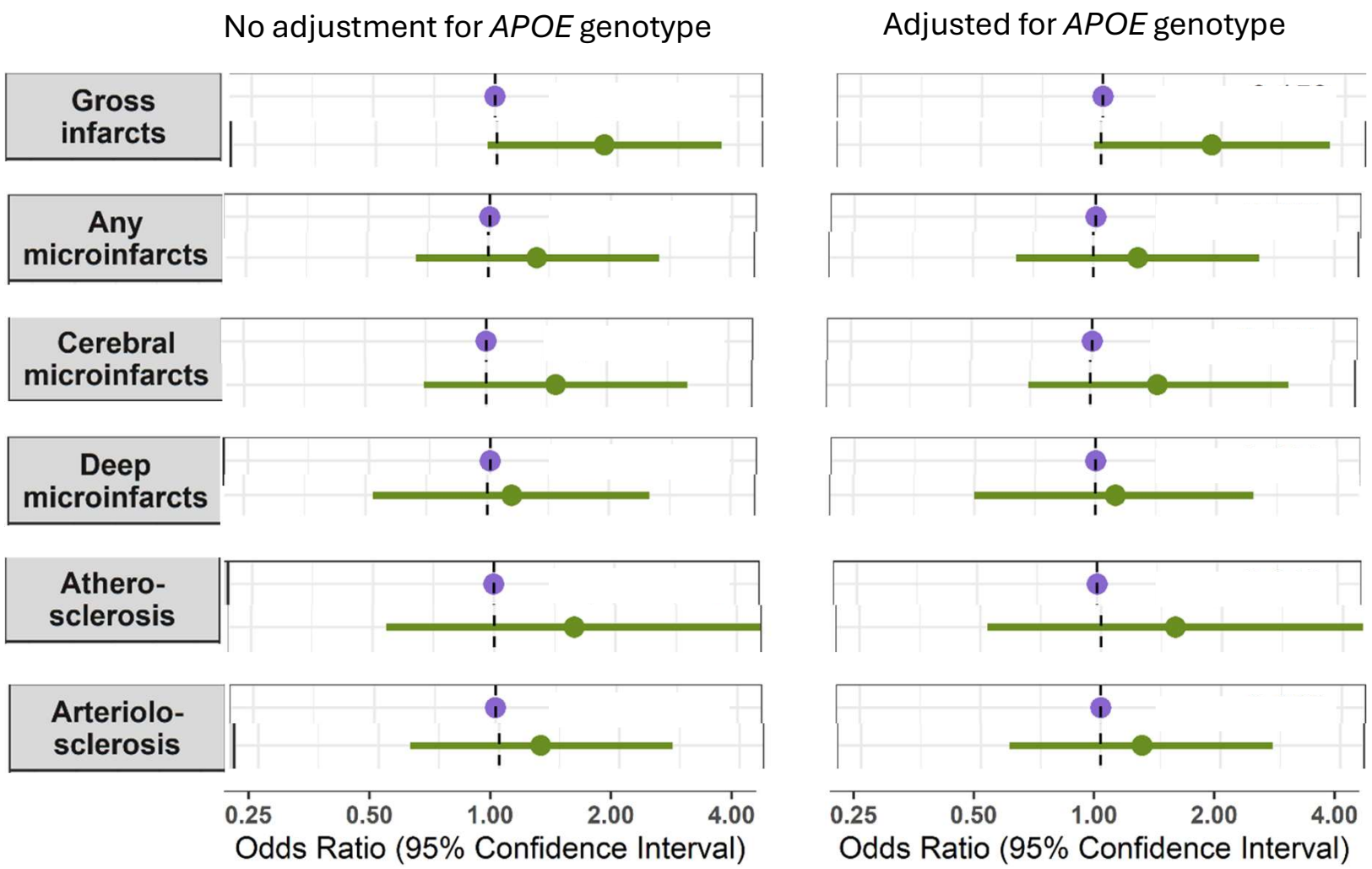
AD Neuropath: AD-Language similar to AD-ND



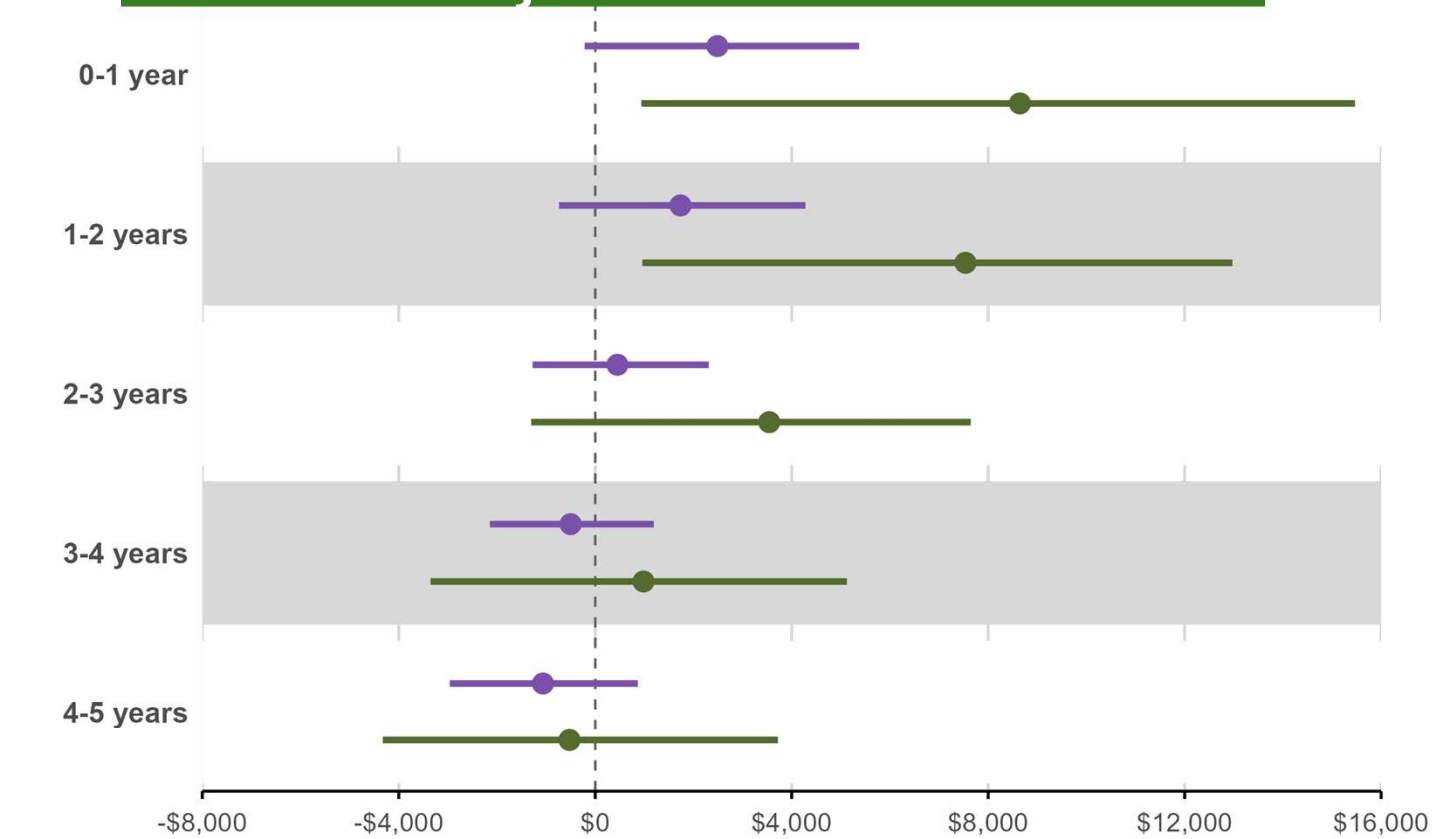
Other Neuropath: AD-Language > LATE, HS, LB than AD-ND

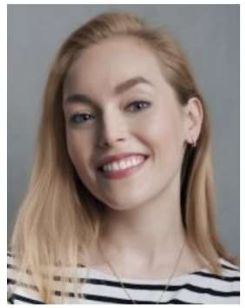


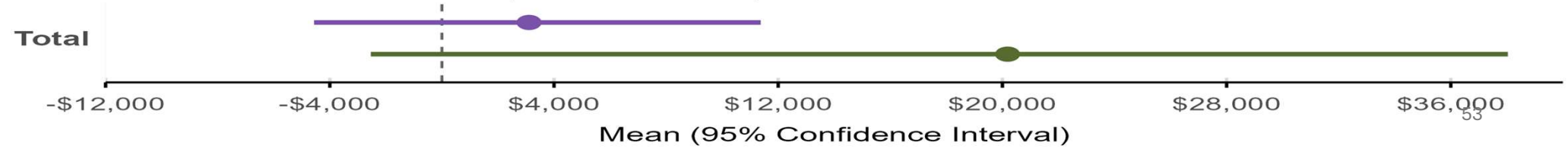
Vascular NP in ACT: AD-Lang slight > than AD-ND



Costs – Adjusted for survival

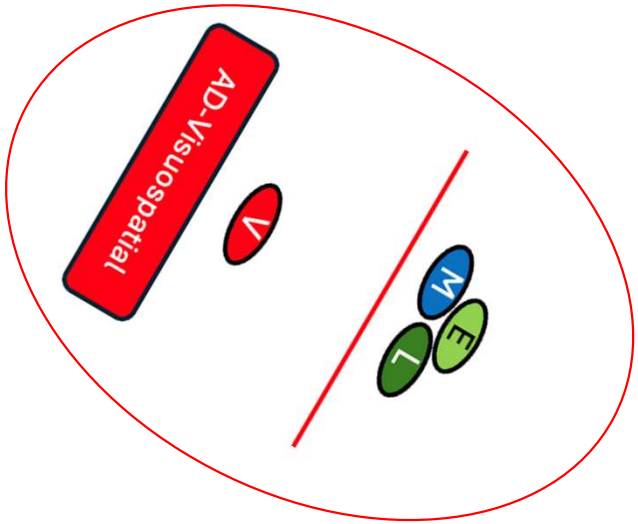


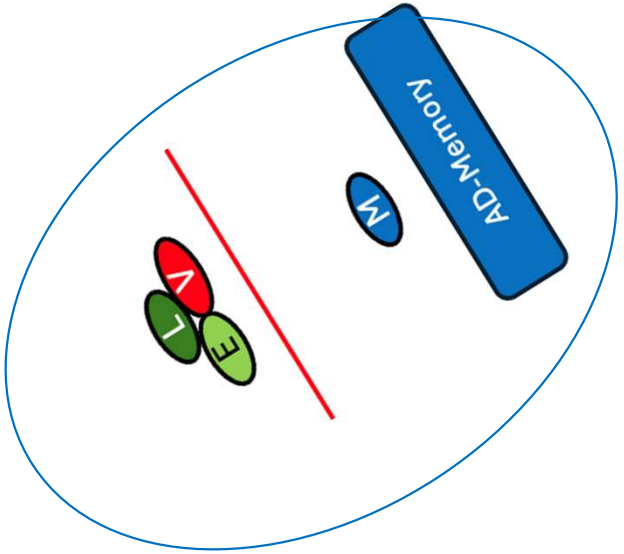


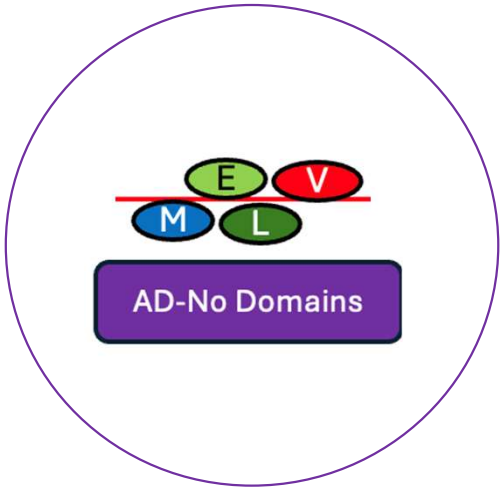


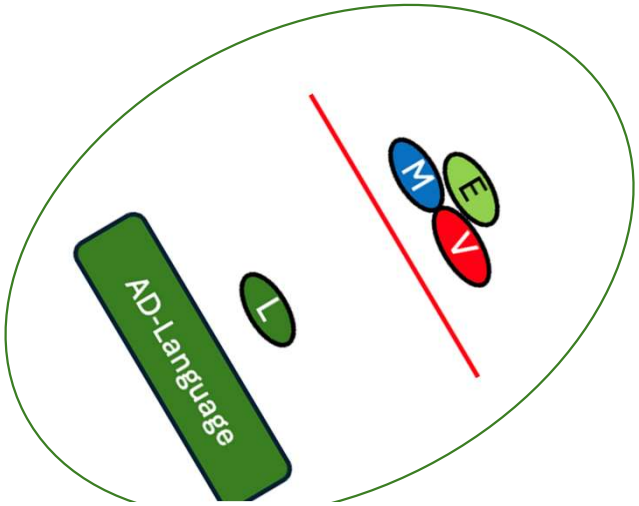
Conclusions – AD-Language

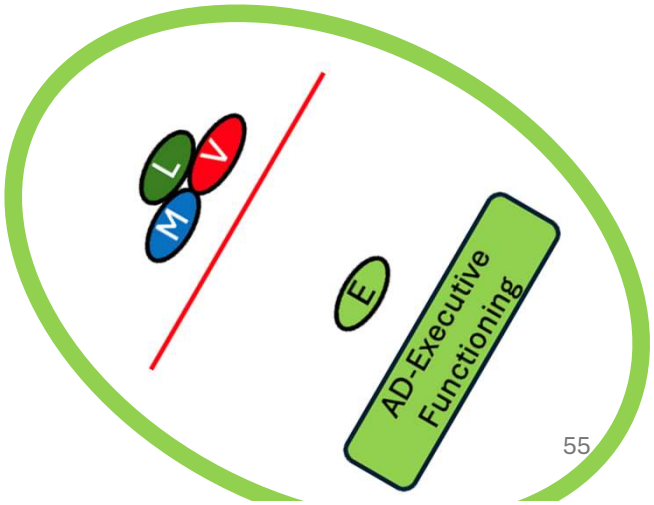
- Genetics: multiple SNPs
- Imaging
  - Strong Overlap with PPA, an atypical AD characterized by language complaints
  - Distinct differences from AD-Memory; Laterality differences; overlap with Vogel et al.
- Neuropathology
  - Similar AD neuropathology as AD-ND; more LATE, HS, and Lewy bodies; slightly more vascular pathology
- Cognition: Large declines across all domains except Language
- Costs: Highest cost of any subgroup. Difference from AD-No Domains most impressive early on (higher costs earlier)


AD-Visuospatial
V
M
E
L

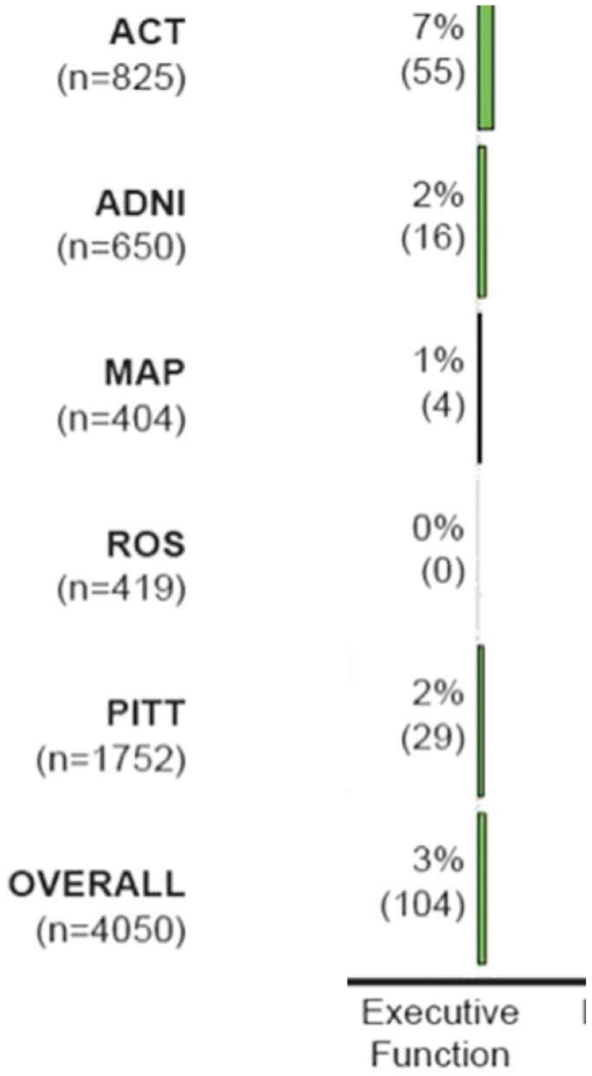

AD-Memory
M
V
L
E


E
V
M
L
AD-No Domains


AD-Language
L
M
E
V


L
V
M
E
AD-Executive Functioning

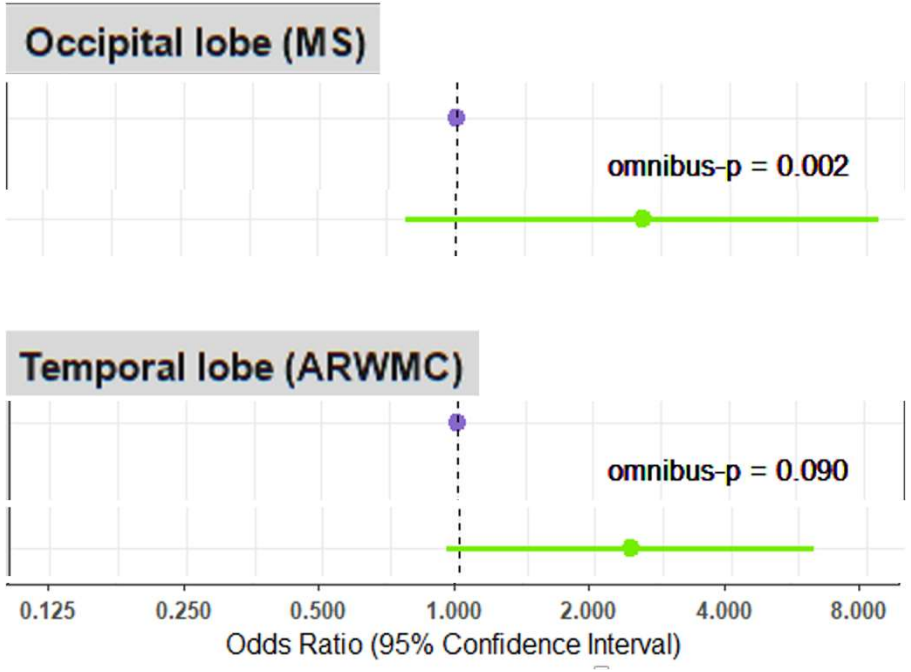
Subgroup 4: AD-Executive Functioning



Mukherjee S, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. Mol Psychiatry. 2020;25(11):2942-51.

WMH from ACT CDEs: AD-Exec > AD-No Domains

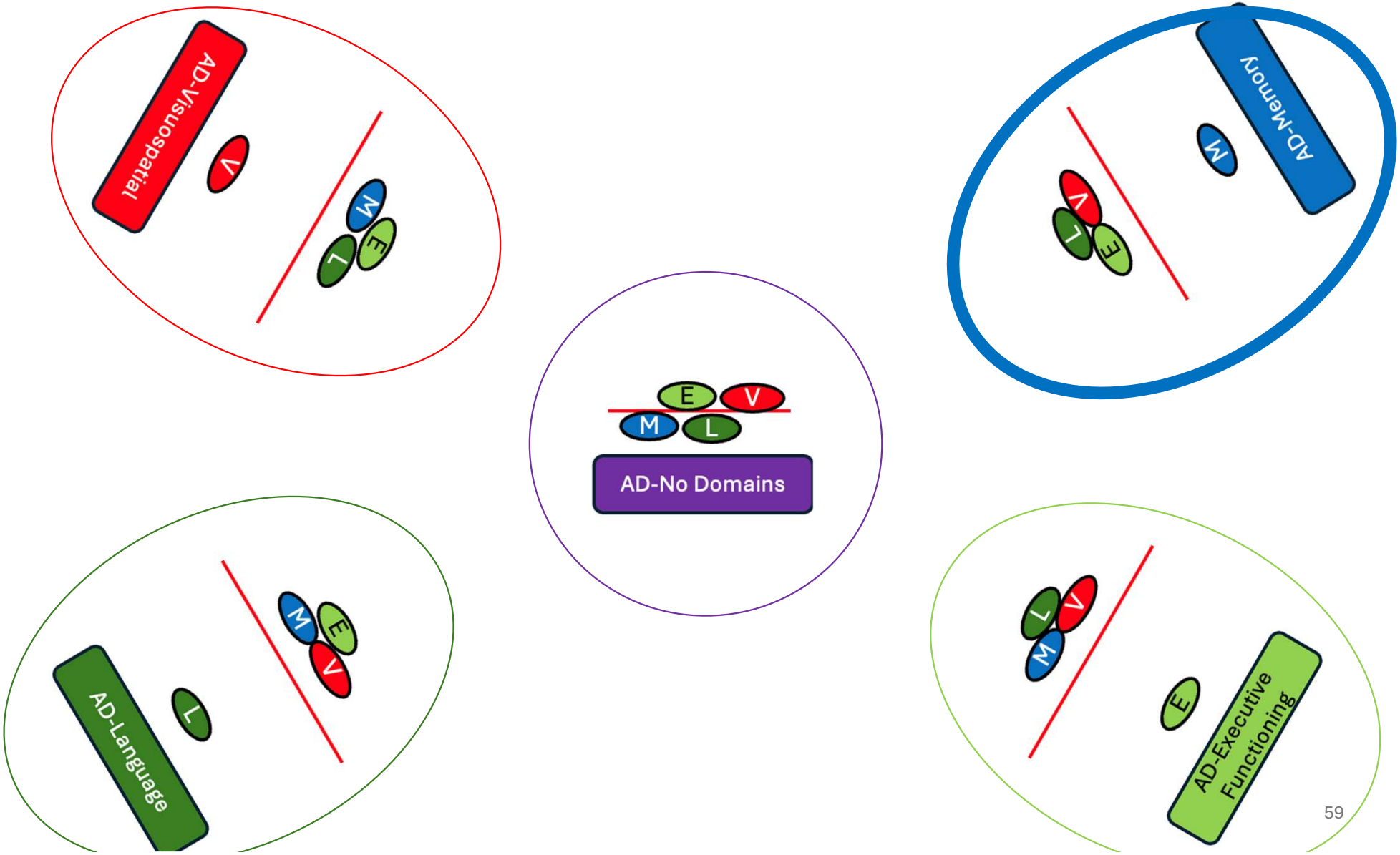
White matter hyperintensity scales	AD-Executive OR (95% CI)
Modified Scheltens	2.52 (0.95, 6.65)
Frontal lobe	1.27 (0.44, 3.65)
Parietal lobe	2.63 (0.99, 6.99)
Occipital lobe	3.20 (0.98, 10.43)
Temporal lobe	2.02 (0.79, 5.18)
Frontal caps	1.19 (0.32, 4.39)
Occipital caps	2.58 (0.71, 9.35)
Periventricular bands	2.46 (0.60, 9.99)
ARWMC	2.62 (1.02, 6.79)
Frontal lobe	1.75 (0.47, 6.49)
Parieto-occipital lobes	1.72 (0.51, 5.76)
Temporal lobe	2.37 (0.91, 6.18)
Basal ganglia	**3.55 (1.00, 12.69)**
Infratentorial / Cerebellum	**2.47 (1.02, 5.94)**
Fazekas	2.30 (0.80, 6.63)
Periventricular	2.41 (0.73, 8.01)
Deep white matter	2.21 (0.72, 6.74)

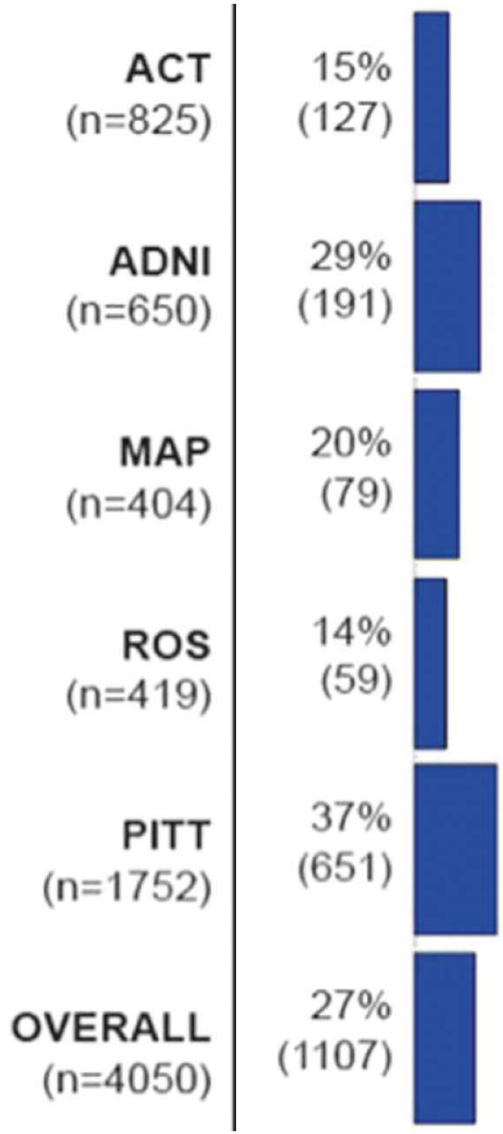


> WMH in occipital and temporal lobes than AD-ND

Conclusions – AD-Executive Functioning

- Imaging
  - Higher levels of WMH in occipital and temporal lobes (big confidence intervals)
- Need more data!


AD-Visuospatial
V
M
E
L
AD-Memory
M
V
L
E
E
V
M
L
AD-No Domains
AD-Language
L
M
E
V
L
V
M
E
AD-Executive Functioning



Mukherjee S, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. Mol Psychiatry. 2020;25(11):2942-51.

Genetics – *APOE* genotype

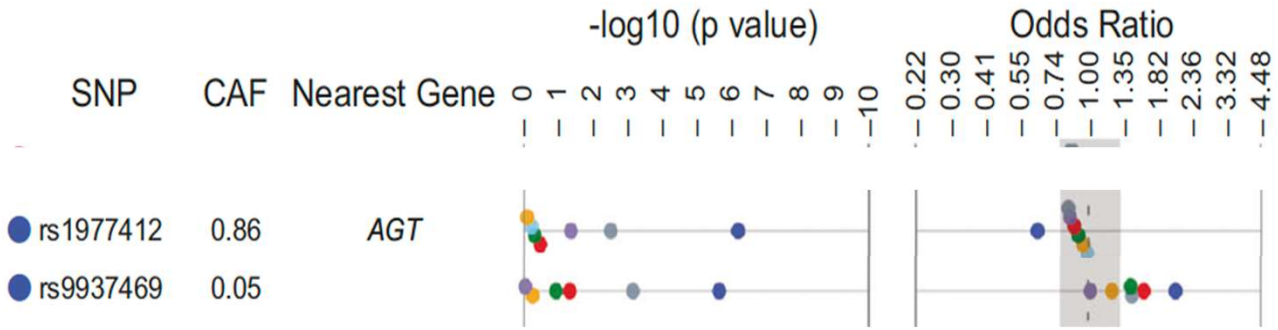
	All other groups		AD-Memory	
	Total n	*APOE* ε4 n (%)	Total n	*APOE* ε4 n (%)
ACT	600	192 (32%)	111	51 (46%)
ADNI	460	288 (63%)	190	139 (73%)
ROS	311	99 (32%)	75	33 (44%)
MAP	339	117 (35%)	54	26 (48%)
PITT	974	506 (52%)	587	411 (70%)
Overall	2686	1201 (45%)	1015	660 (65%)

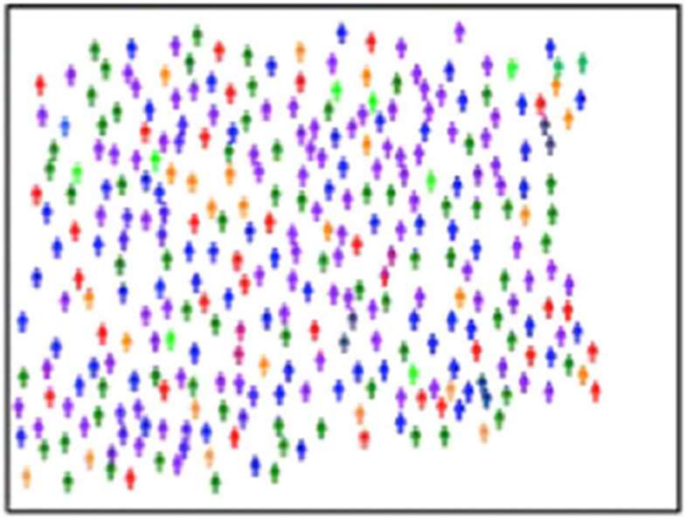
Mukherjee S, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. Mol Psychiatry. 2020;25(11):2942-51.

$p = 1.5 \times 10^{-27}$

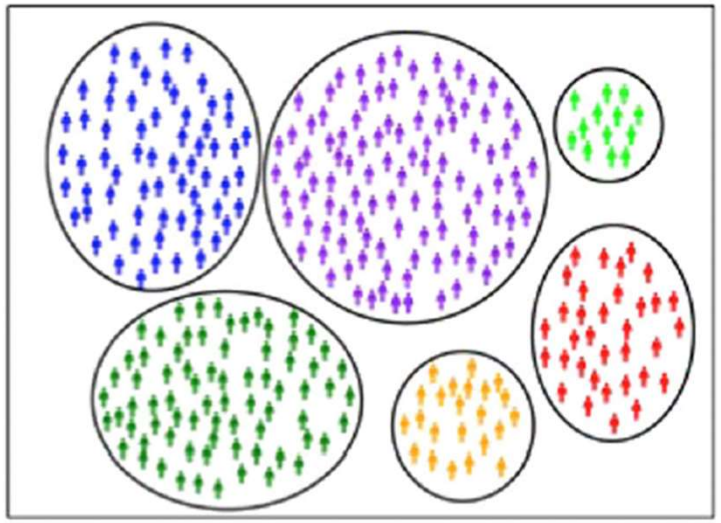
Genetics

Genome wide – 2 SNPs with odds ratios >1.3

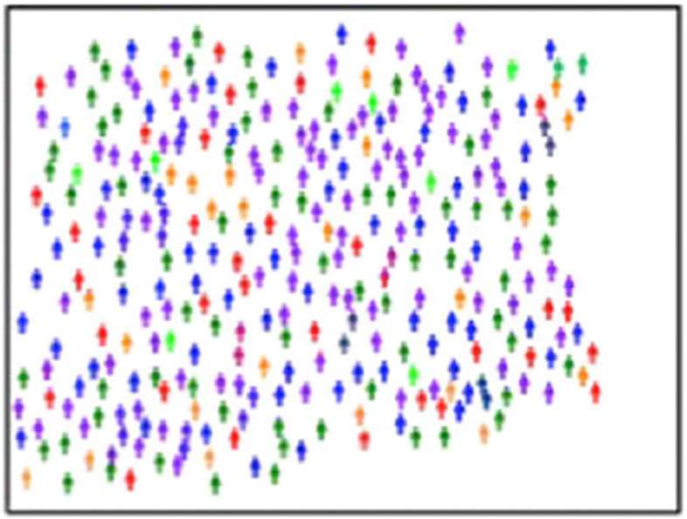




Much larger n
Heterogeneous mix of groups
Zero SNPs with OR > 1.3

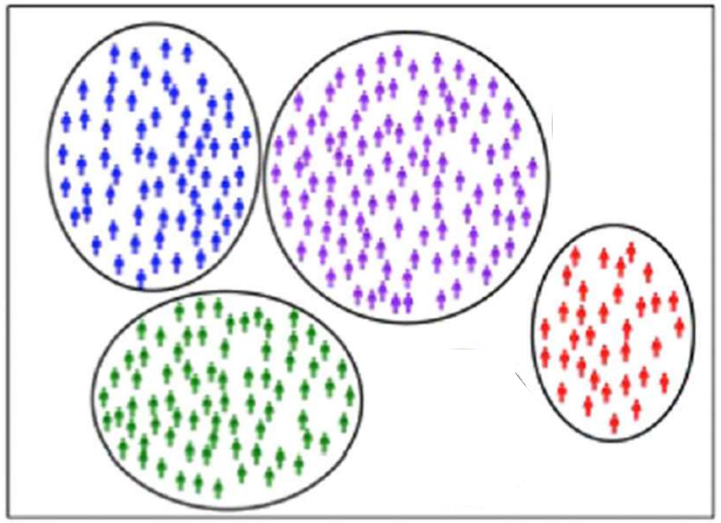


Much smaller but homogenous groups
MANY SNPs with OR>1.3



Much larger n
Heterogeneous mix of groups

Zero SNPs with OR > 1.3

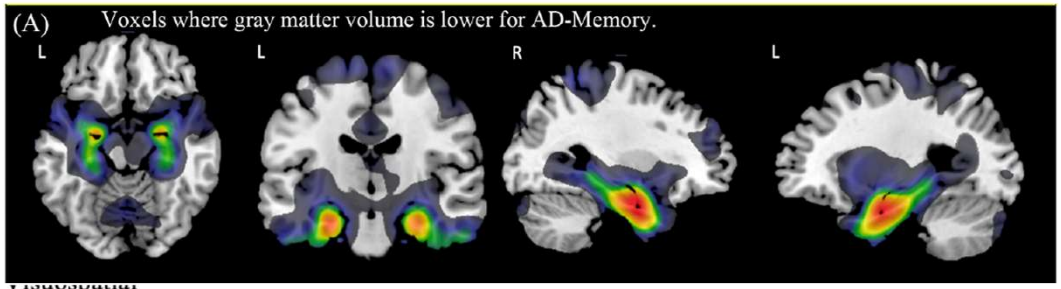


Much smaller but homogenous groups

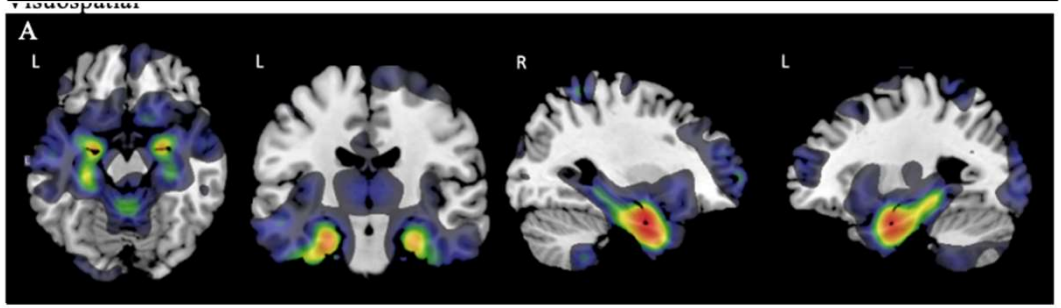
MANY SNPs with OR>1.3

Imaging comparisons with other subgroups

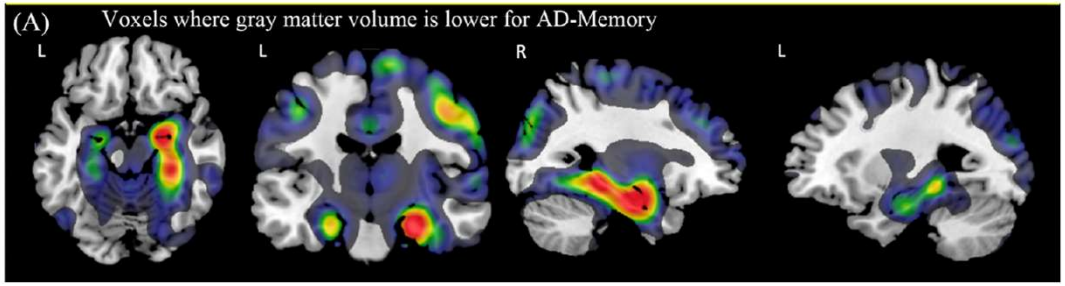
AD-Memory More atrophy than AD-No Domains



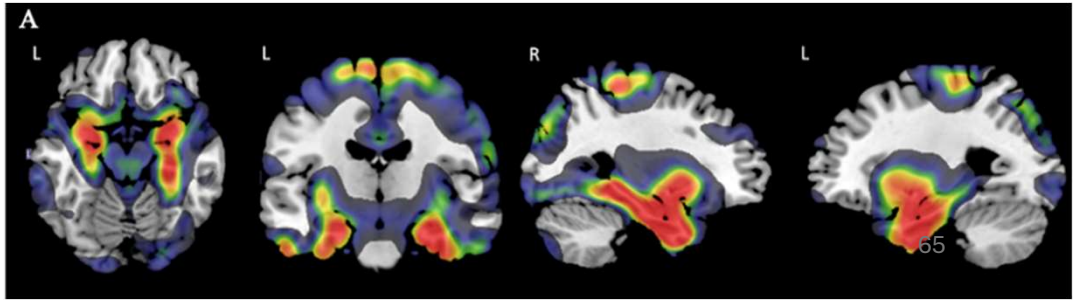
AD-Memory More atrophy than AD-Visuospatial



AD-Memory More atrophy than AD-Language



AD-Memory More atrophy than AD-Executive



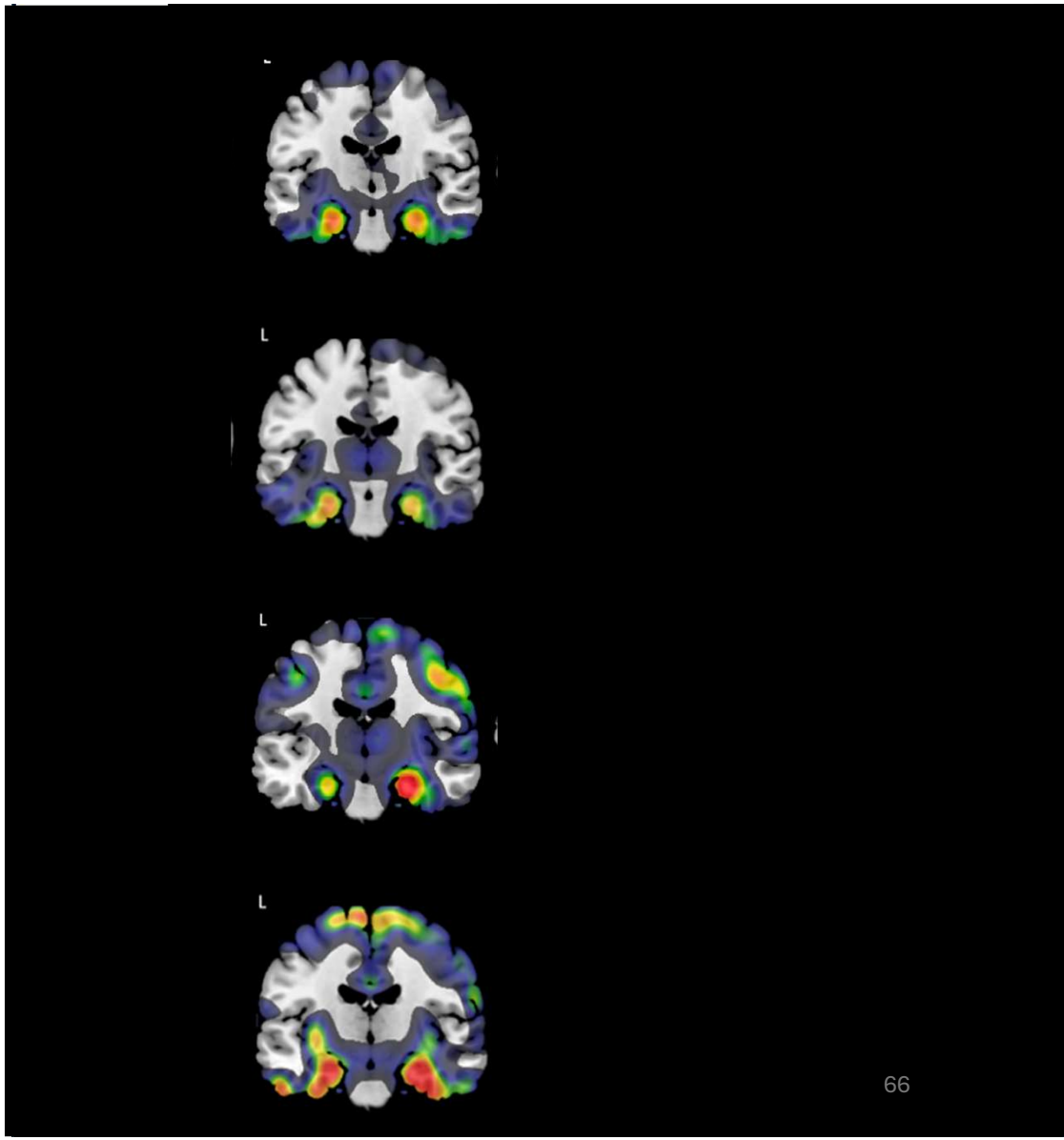
Imaging comparisons with other subgroups

AD-Memory More atrophy than AD-No Domains

AD-Memory More atrophy than AD-Visuospatial

AD-Memory More atrophy than AD-Language

AD-Memory More atrophy than AD-Executive



Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

Melissa E Murray, Neill R Graff-Radford, Owen A Ross, Ronald C Petersen, Ranjan Duara, Dennis W Dickson

Lancet Neurol 2011; 10: 785–96

Methods AD cases with a Braak neurofibrillary tangle stage of more than IV were identified from a brain bank database. By use of thioflavin-S fluorescence microscopy, we assessed the density and the distribution of neurofibrillary tangles in three cortical regions and two hippocampal sectors. These data were used to construct an algorithm to classify AD cases into typical, hippocampal sparing, or limbic predominant. Classified cases were then compared for clinical, demographic, pathological, and genetic characteristics. An independent cohort of AD cases was assessed to validate findings from the initial cohort.

Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study

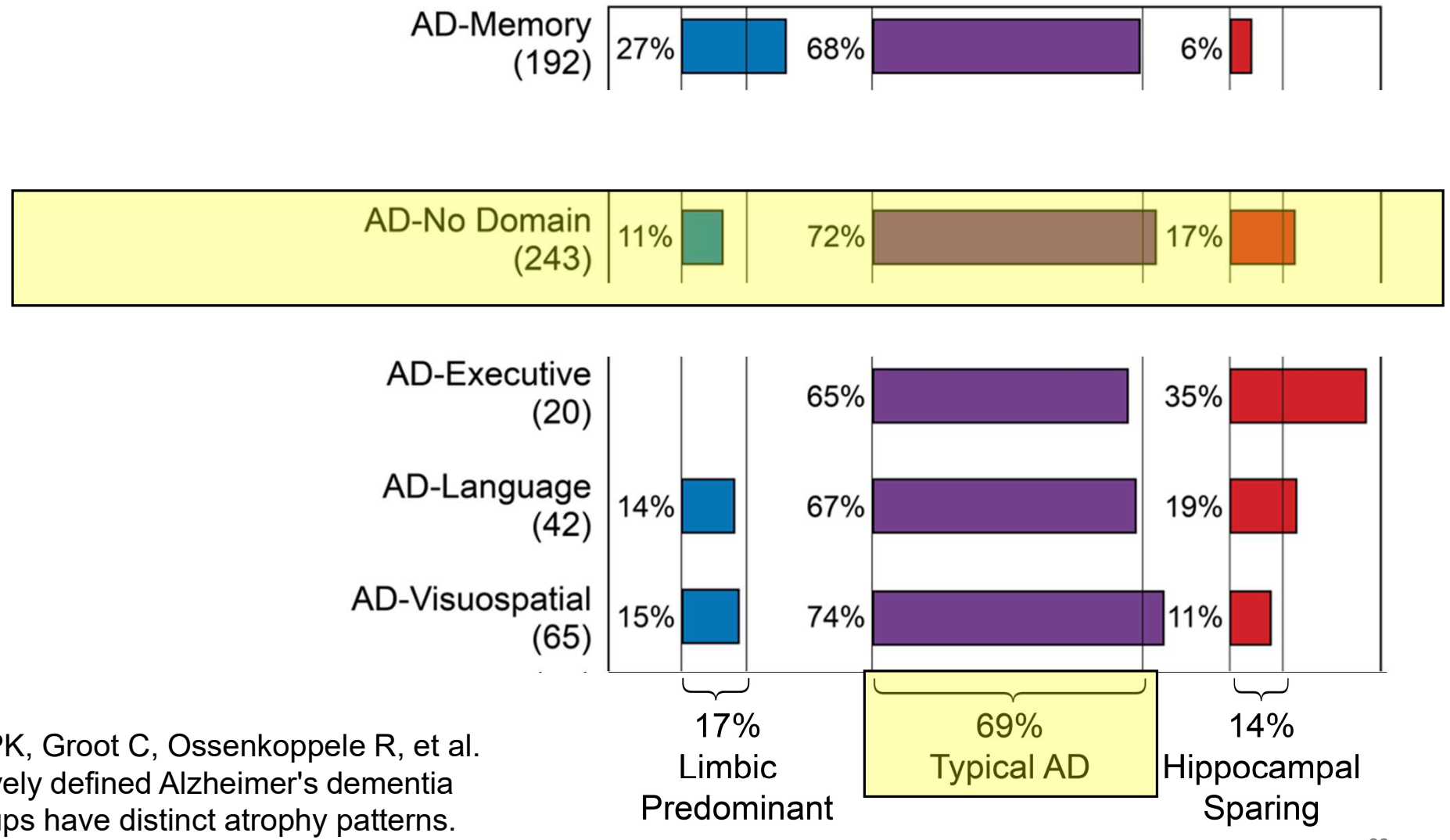
Melissa E Murray, Neill R Graff-Radford, Owen A Ross, Ronald C Petersen, Ranjan Duara, Dennis W Dickson

Lancet Neurol 2011; 10: 785–96

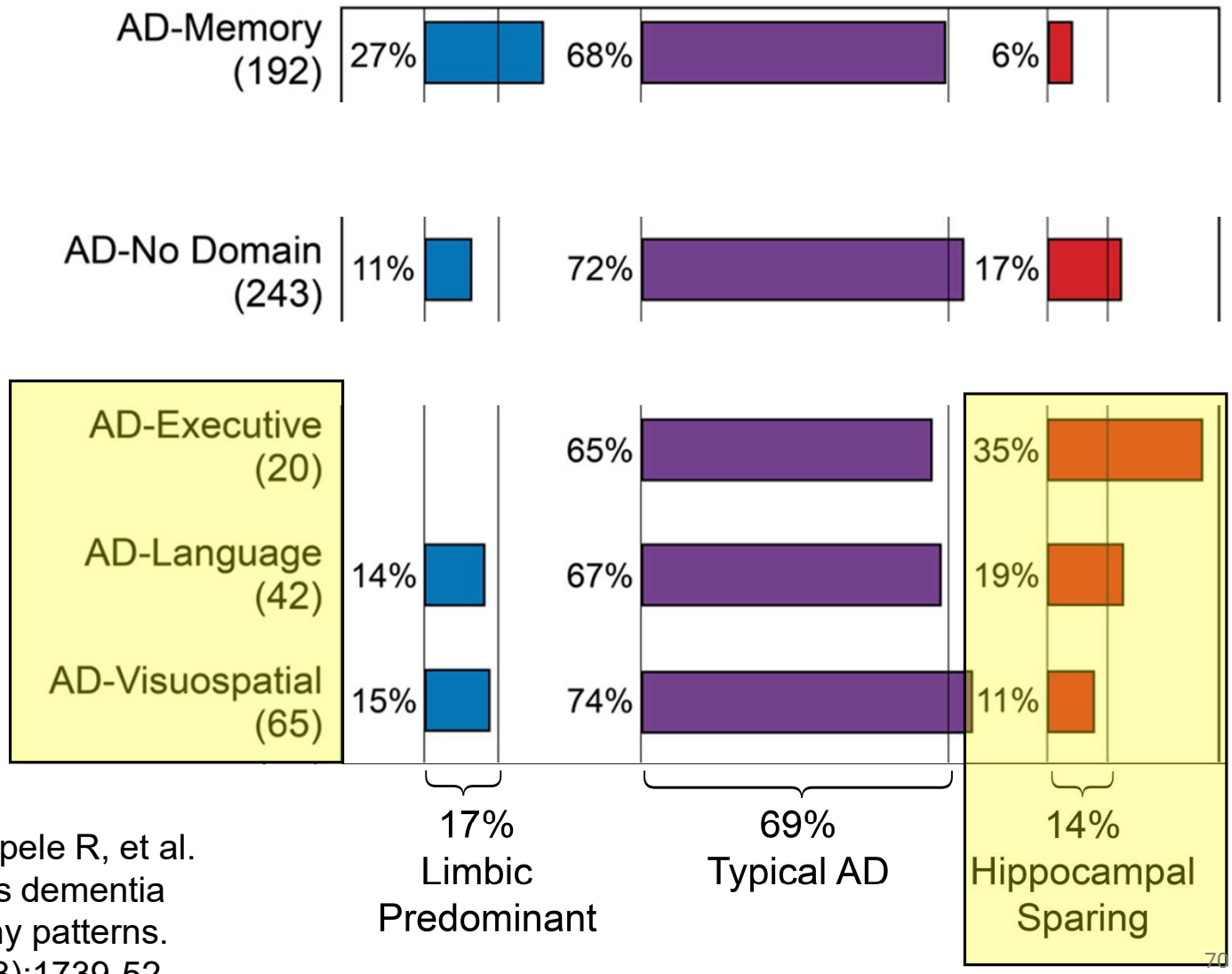
Methods AD cases with a Braak neurofibrillary tangle stage of more than IV were identified from a brain bank database. By use of thioflavin-S fluorescence microscopy, we assessed the density and the distribution of neurofibrillary tangles in three cortical regions and two hippocampal sectors. These data were used to construct an algorithm to classify AD cases into typical, hippocampal sparing, or limbic predominant. Classified cases were then compared for clinical, demographic, pathological, and genetic characteristics. An independent cohort of AD cases was assessed to validate findings from the initial cohort.

Risacher SL, et al. Alzheimer disease brain atrophy subtypes are associated with cognition and rate of decline. Neurology. 2017;89(21):2176-86.

"MRI-based AD subtypes (hippocampal sparing, limbic predominant, typical AD) were defined according to an algorithm analogous to one recently proposed for tau neuropathology."

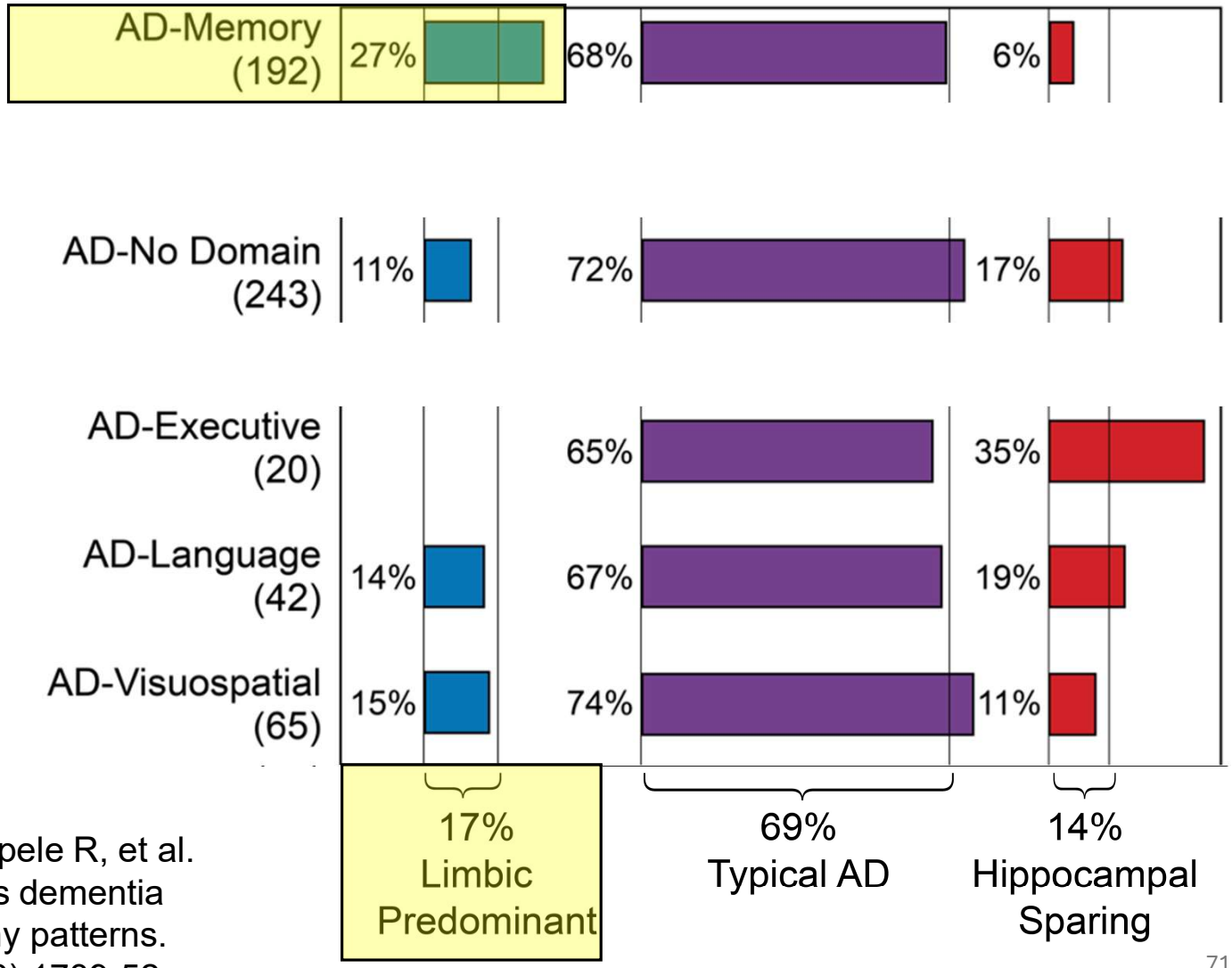


Crane PK, Groot C, Ossenkoppele R, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.



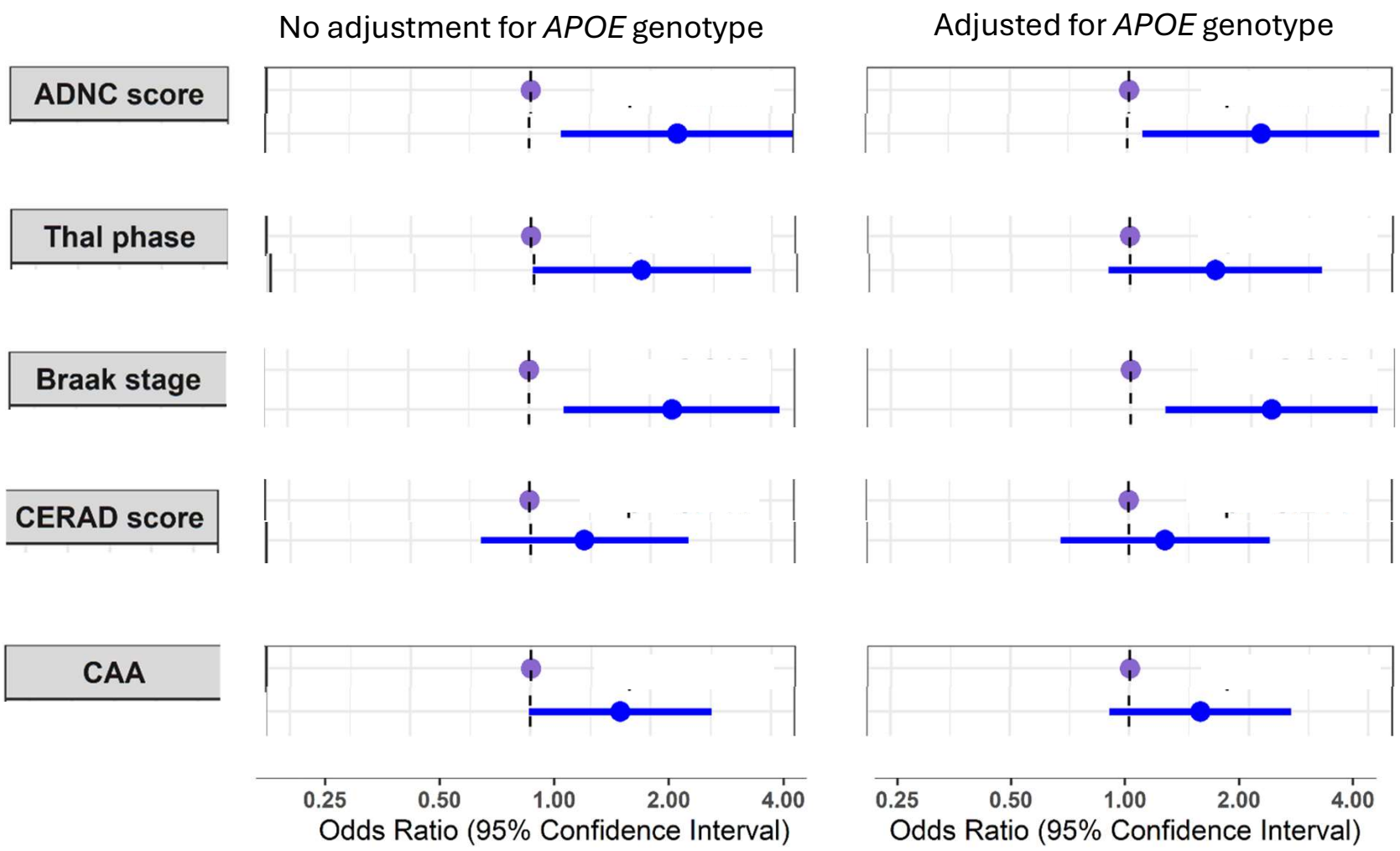
Crane PK, Groot C, Ossenkoppele R, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.

$p = 6.94 \times 10^{-6}$

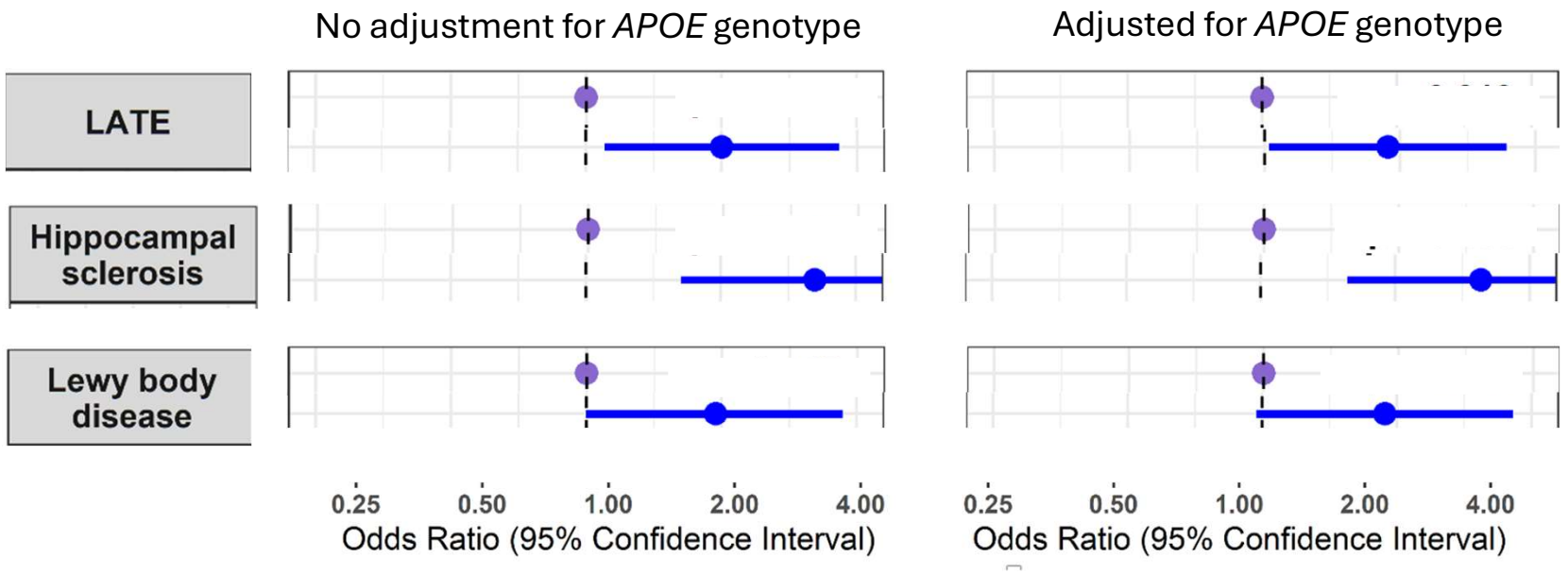


Crane PK, Groot C, Ossenkoppele R, et al. Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. Alzheimers Dement. 2024;20(3):1739-52.

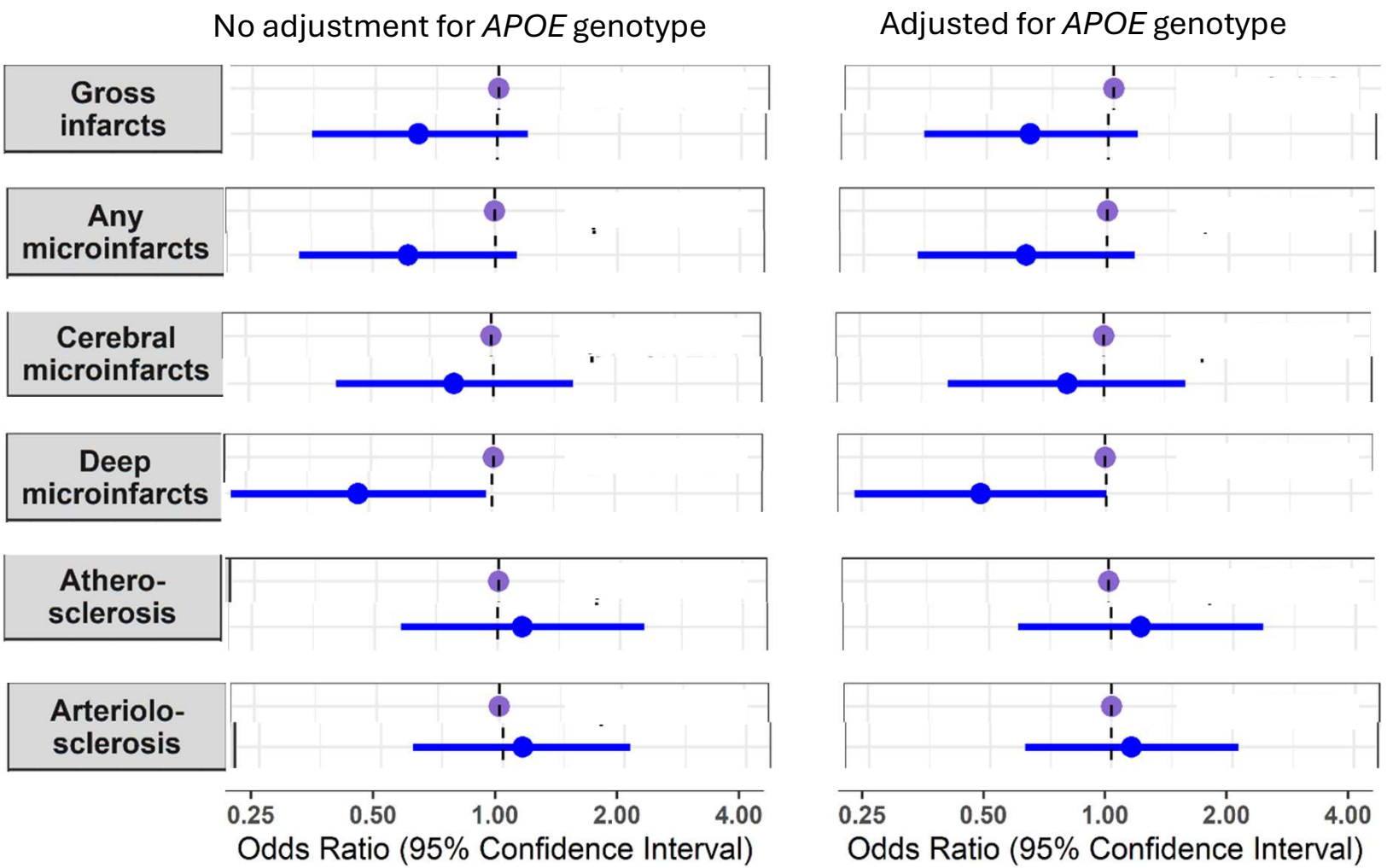
AD Neuropath in ACT: AD-Memory higher than AD-ND



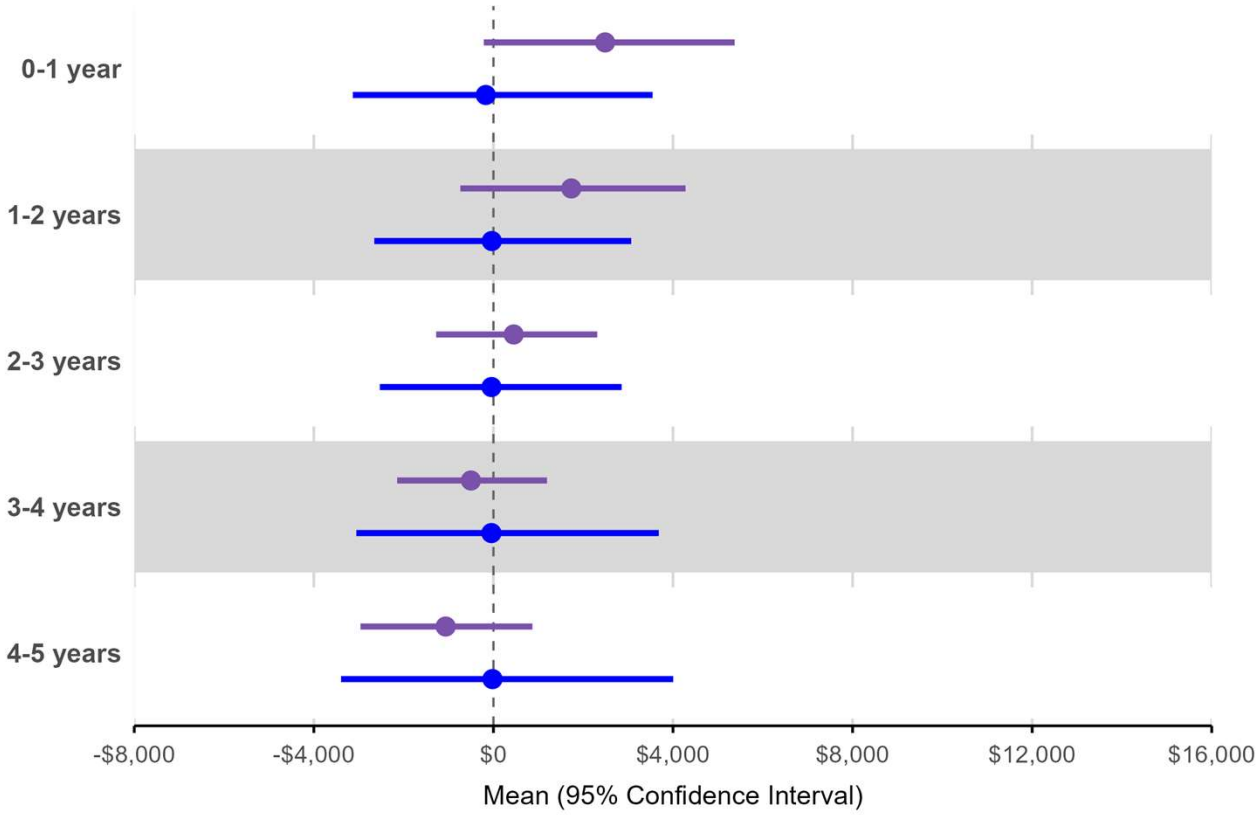
Other Neuropath in ACT: AD-Mem more LATE, HS, LB

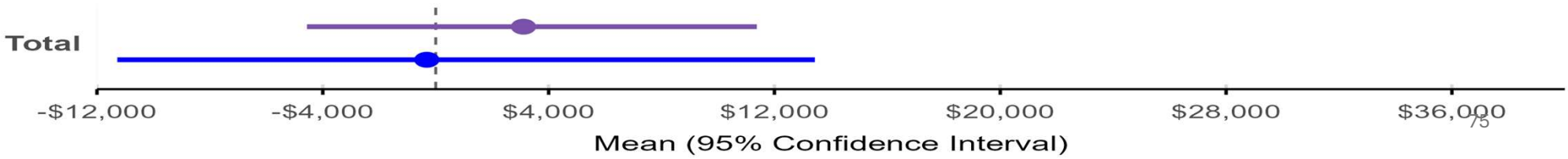


Vascular NP in ACT: AD-Mem less than AD-ND



Costs – Adjusted for survival





Conclusions – AD-Memory

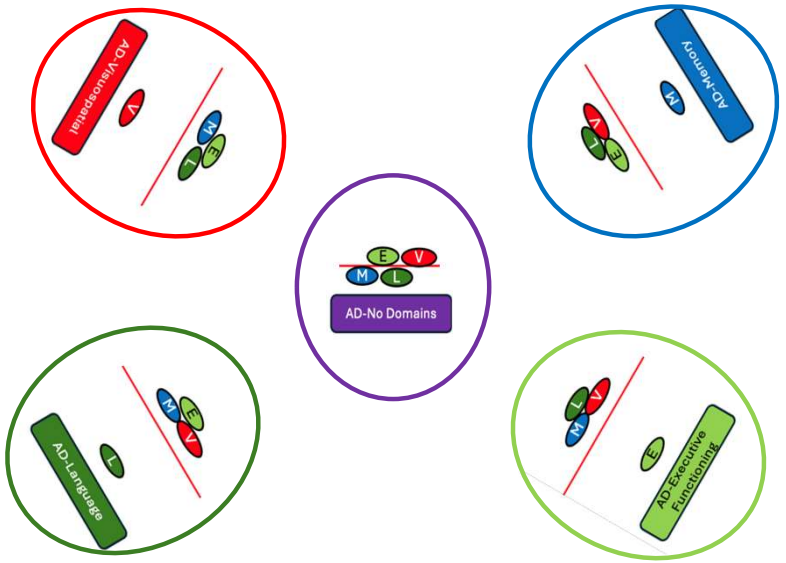
- Genetics: Strong *APOE* differences – multiply replicated, plus two genome-wide SNPs
- Imaging
  - Differences with all of the other subgroups – more intensive involvement of the medial temporal region and hippocampi
  - Overlap with imaging subgrouping scheme modeled on Murray et al.'s neuropathology-based approach – AD-Memory has significant overlap with the Limbic Predominant group
- Neuropathology
  - Higher AD neuropathology as AD-ND; more LATE, HS, and Lewy bodies; less vascular pathology
- Costs not that different from controls

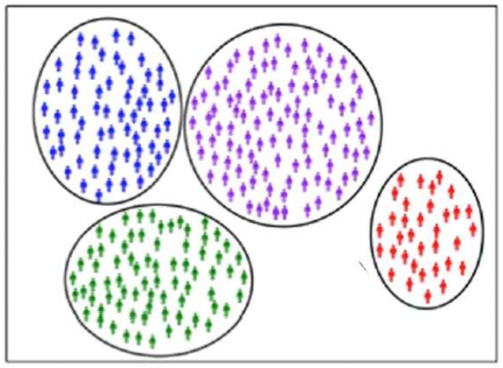
Outline

- Why subgroups?
- Why cognitively defined subgroups?
- How do we define subgroups with cognitive tests?
- Our favorite stories for five subgroups, including new data from ACT P2
- **What's next?**

Next steps: Genetics

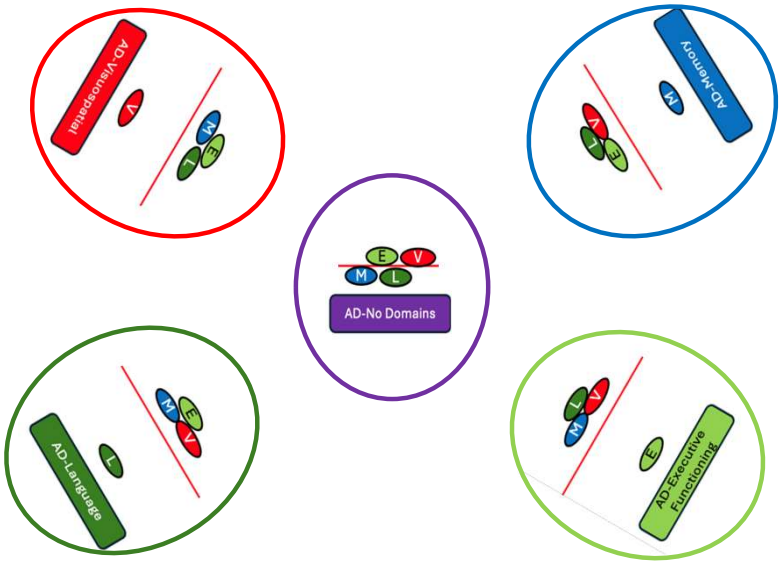
- Data particularly compelling on need for additional genetic analyses with larger n
  - Even with strong signals need larger n for genome-wide significance
  - Enables following up on other choices for thresholds (AD-Executive)
  - Post-GWAS analyses may be particularly valuable with more precise phenotypes.

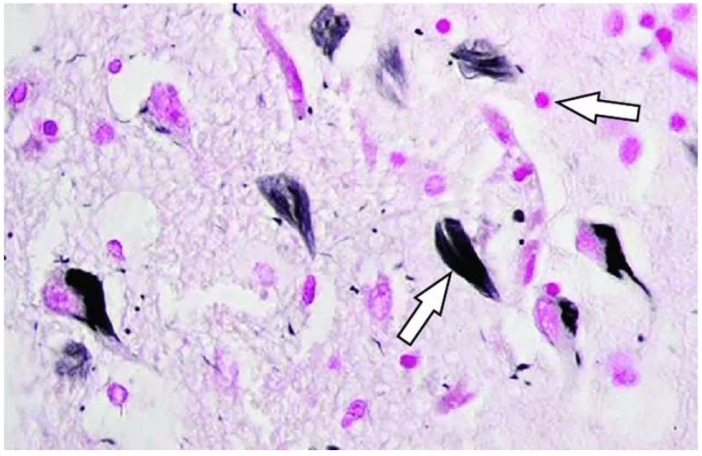




Next steps: Neuropathology

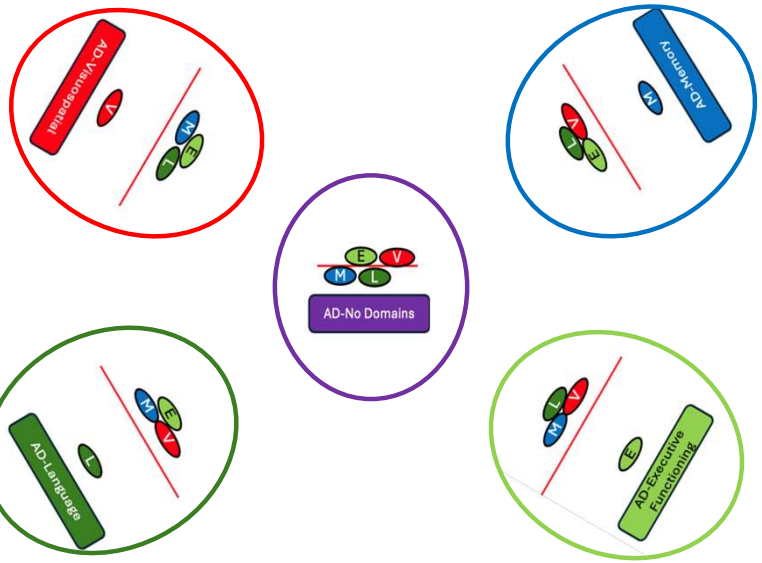
- Repeating standard neuropathology analyses in ROS/MAP data is low hanging fruit
- Both the Murray et al. and Vogel et al. papers suggest challenges to the Braak and Braak single trajectory model of tau pathology
- Quantitative neuropathology analyses in ACT coming soon to Project 2 near you!

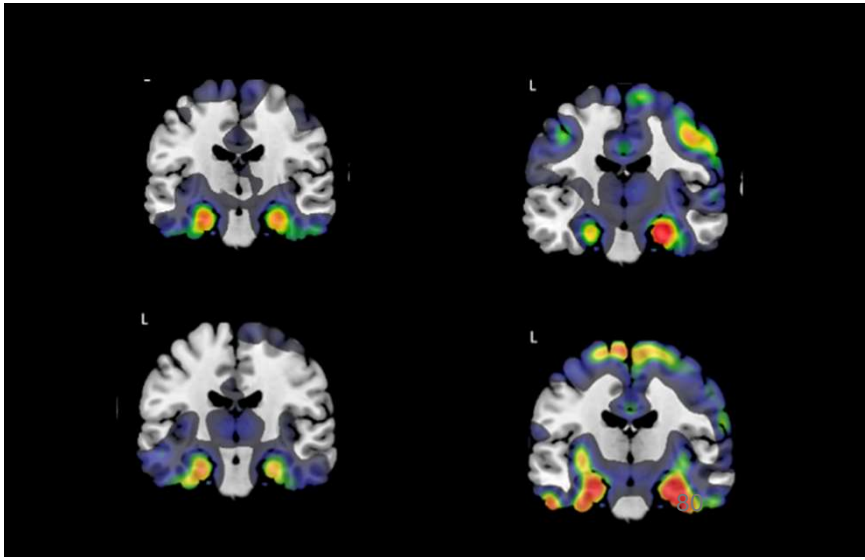




Next steps: Neuroimaging

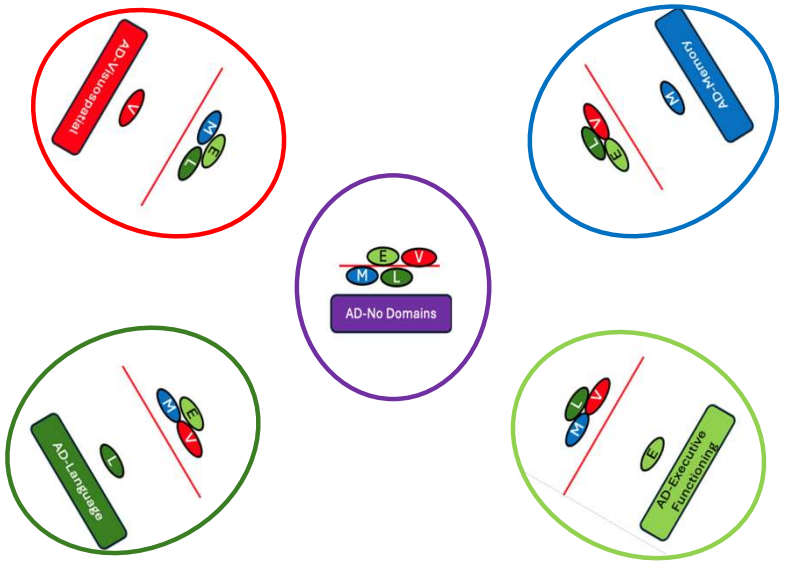
- Strong and replicated cross-sectional data from ADNI and VU-Amsterdam
- Two ongoing projects with longitudinal imaging data – one on cortical thickness and one on surface area
- ACT quantitative neuroimaging data? We hope to take a look in ACT Project 2.





Next steps: Lived experience with AD dementia

- Pretty impressive differences in costs
- Much left to learn
  - Behavioral and neuropsychiatric symptom differences?
  - Communication differences?
  - Caregiving differences?
  - Overlap with PPA?
  - Overlap with PCA?



Thank you!

- To the entire Project 2 team!
- And for this opportunity to present some of our work here today.