ACT U19 Project 2

Cognitively Defined Subgroups of Alzheimer's Disease (AD) Dementia

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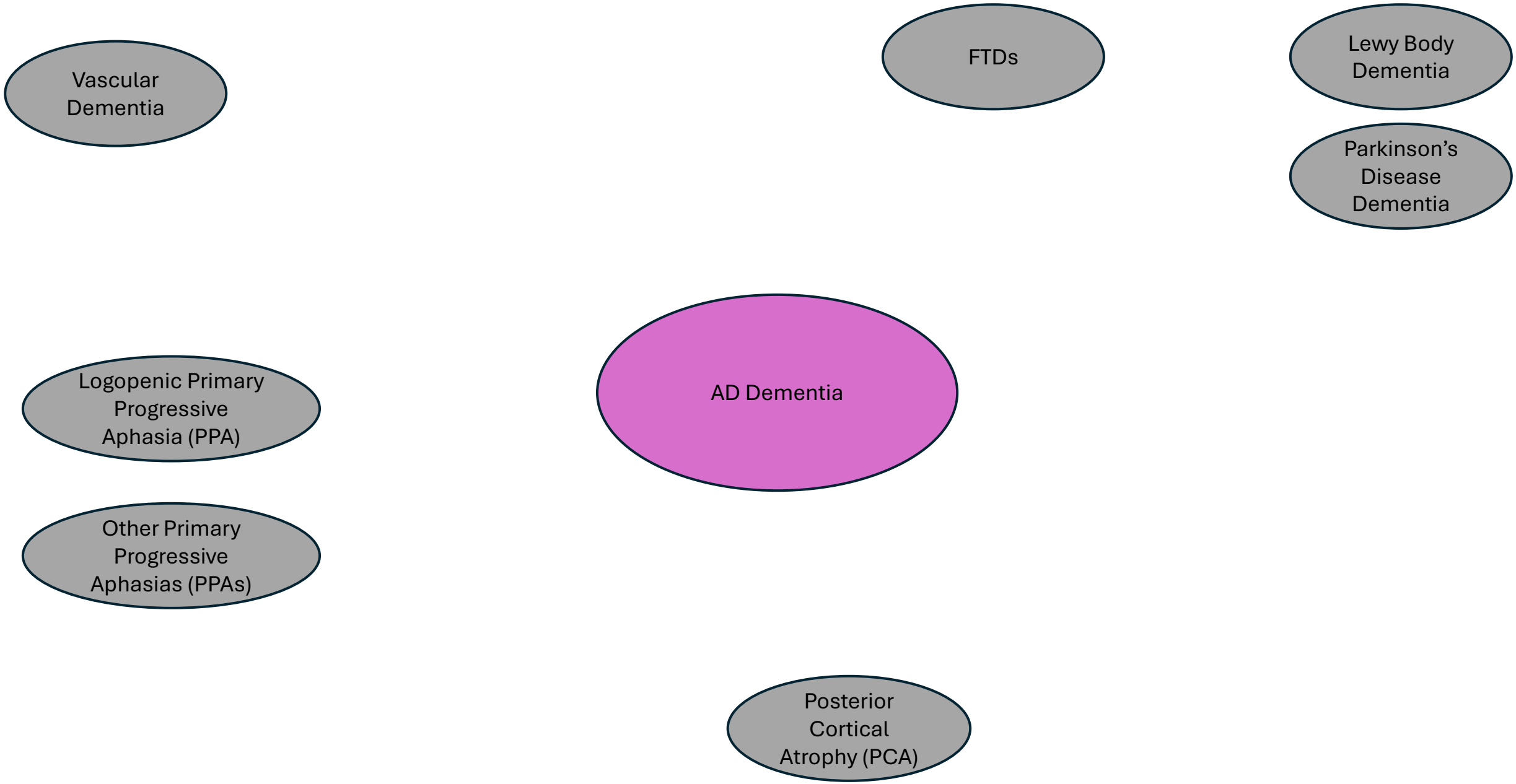
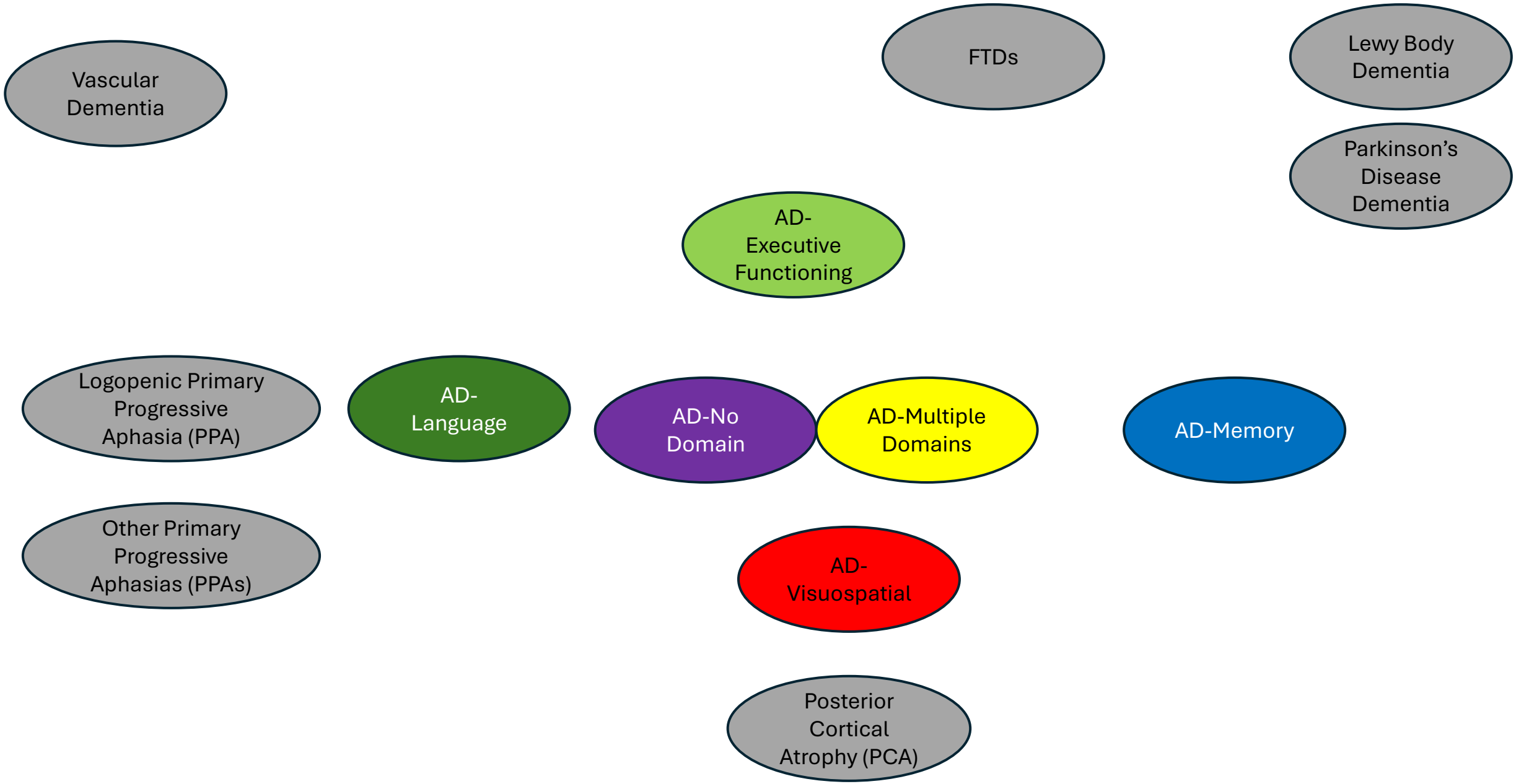
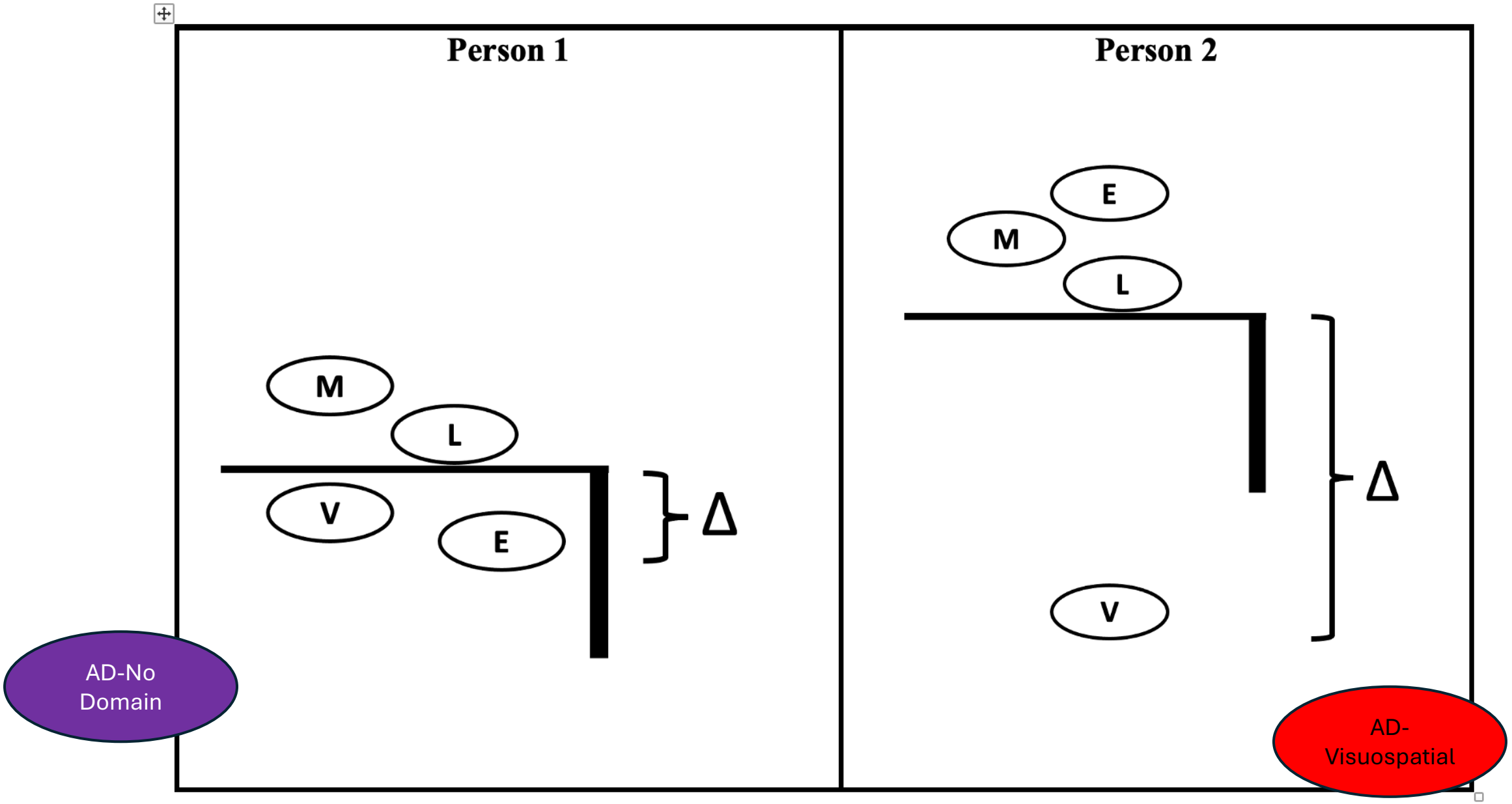
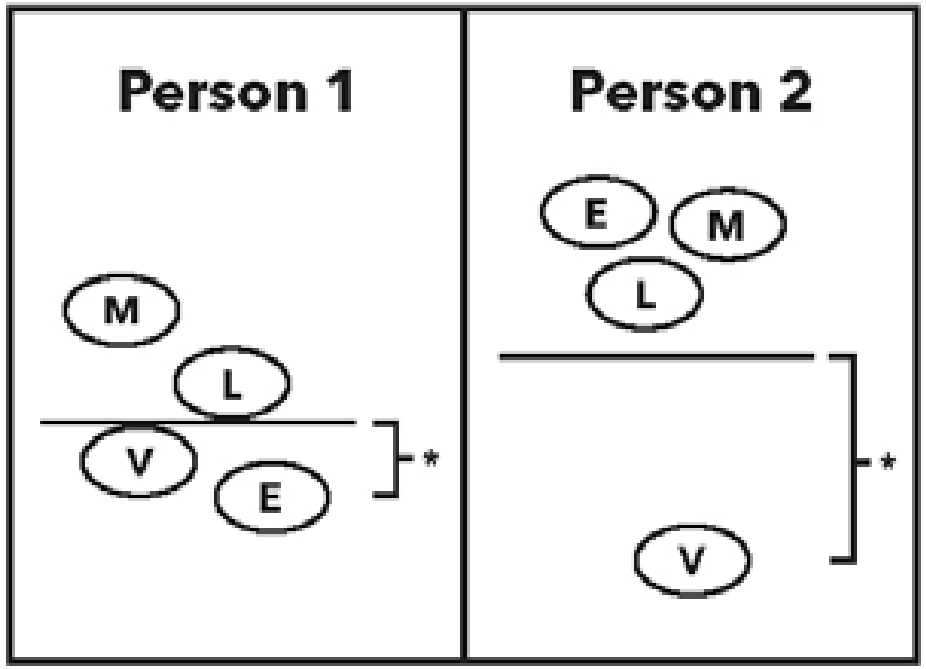

Vascular Dementia
FTDs
Lewy Body Dementia
Parkinson's Disease Dementia
Logopenic Primary Progressive Aphasia (PPA)
AD Dementia
Other Primary Progressive Aphasias (PPAs)
Posterior Cortical Atrophy (PCA)


Vascular Dementia
FTDs
Lewy Body Dementia
Parkinson's Disease Dementia
AD-Executive Functioning
Logopenic Primary Progressive Aphasia (PPA)
AD-Language
AD-No Domain
AD-Multiple Domains
AD-Memory
Other Primary Progressive Aphasias (PPAs)
AD-Visuospatial
Posterior Cortical Atrophy (PCA)

Supplementary Fig. 2 – Schematic of subgrouping approach



Cognitively defined AD subgroups



Memory (M), executive functioning (E), language (L), and visuospatial (V) scores are derived from ACT's dementia battery at the time of AD diagnosis.

- The figure depicts an example of such scores ranging from low (bottom) to high (top) for two AD participants.
- A person's average across domains is shown by the horizontal line.

Using differences from that average (shown by the brackets), each person is assigned to an AD subgroup.

- Person 1's scores are clustered closely together and thus assigned AD-No Domain.
- Person 2's V score is much lower than their other scores and thus assigned AD-Visuospatial.

Project 2 Aims

Differences across cognitively defined AD subgroups in:

- Aim 1: Neuroimaging measures
- Aim 2: Neuropathology outcomes
- Aim 3: Clinical, functional, living situation, caregiver network, and economic outcomes

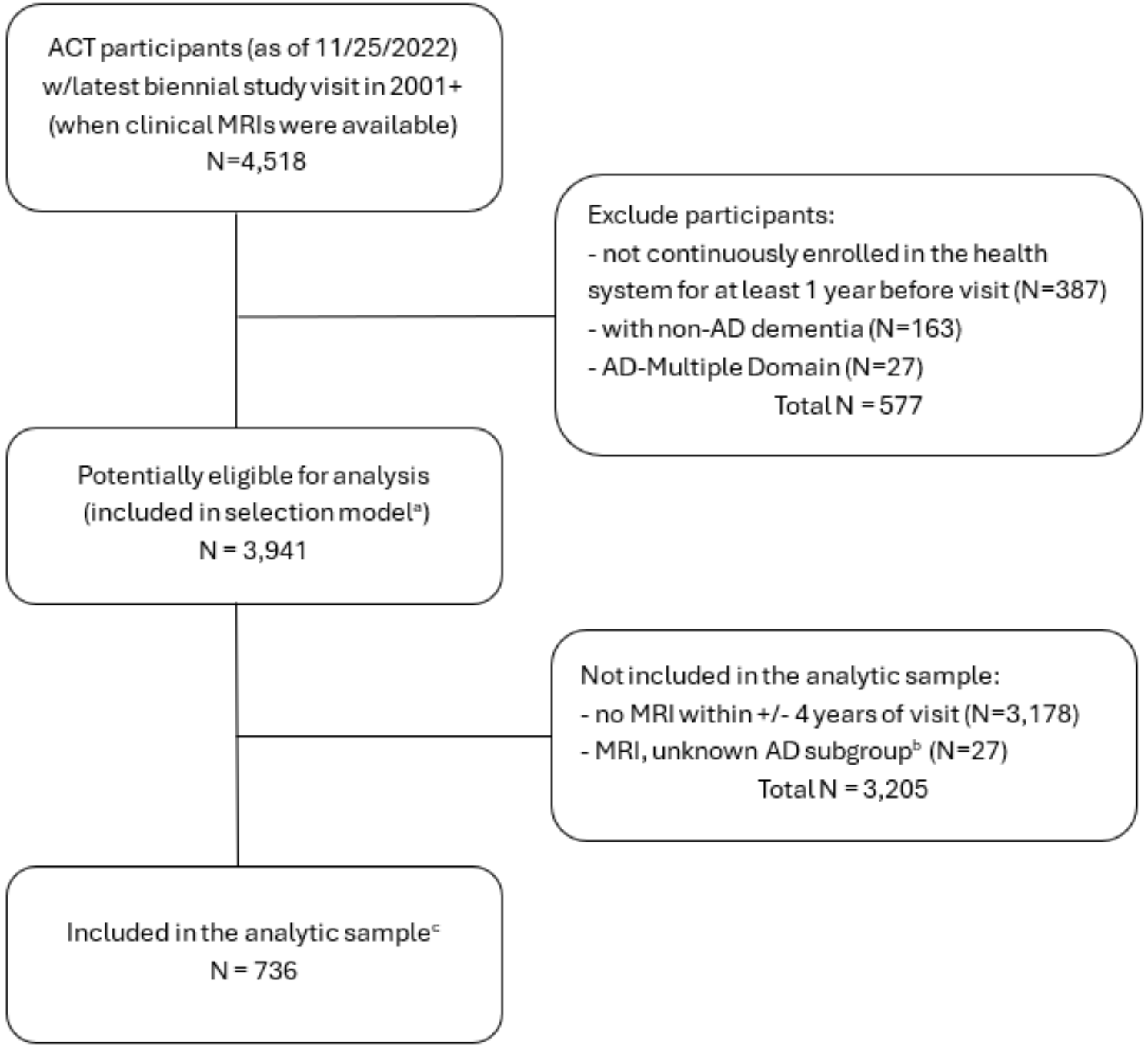
Aim 1: Neuroimaging

- Compare neuroimaging findings (NIH-defined common data elements) between:
  - 5 AD subgroups
  - No dementia

- Primary questions of interest are focused on differences in white matter hyperintensity distribution and hemorrhage.

- Differences between groups estimated using covariate adjusted ordinal, logistic, or Poisson regression models incorporating weights to account for selection into analytic sample

Figure 1. Flow diagram describing analytic study sample.



Aim 1: Neuroimaging

Table 1. Demographic characteristics* across cognitively defined subgroups

Characteristics	Total (n=736)	No dementia (Cognitively normal controls) (n=516)	AD dementia				
			AD- No Domains (n=110)	AD- Memory (n=35)	AD- Visuospatial (n=31)	AD- Language (n=26)	AD- Executive (n=18)
Women, n (%)	417 (57%)	283 (55%)	68 (62%)	23 (66%)	19 (61%)	14 (54%)	10 (56%)
Self-reported Non-Hispanic White, n (%)	650 (88%)	460 (89%)	97 (88%)	27 (77%)	27 (87%)	25 (96%)	14 (78%)
Years of education, mean (SD)	10.0 (5.5)	9.9 (5.5)	10.5 (6.0)	9.3 (5.2)	9.9 (5.8)	9.8 (5.4)	10.5 (4.0)
Age at visit, mean (SD)	82.5 (6.5)	81.7 (6.5)	84.4 (6.2)	82.9 (6.9)	85.2 (5.8)	84.2 (5.1)	83.6 (4.8)
Years between visit and MRI, mean (SD)	-0.5 (1.7)	-0.7 (1.7)	-0.0 (1.6)	-0.0 (1.8)	-0.2 (1.4)	-0.5 (1.4)	-0.0 (1.5)
Hypertension, n (%)	449 (61%)	312 (60%)	72 (65%)	19 (54%)	23 (74%)	13 (50%)	10 (56%)
Diabetes, n (%)	128 (17%)	84 (16%)	18 (16%)	6 (17%)	9 (29%)	5 (19%)	6 (33%)
Cerebrovascular disease, n (%)	381 (52%)	257 (50%)	61 (55%)	19 (54%)	17 (55%)	13 (50%)	14 (78%)
Atrial fibrillation, n (%)	176 (24%)	128 (25%)	22 (20%)	8 (23%)	7 (23%)	6 (23%)	5 (28%)
Myocardial infarction, n (%)	56 (8%)	42 (8%)	5 (5%)	2 (6%)	4 (13%)	1 (4%)	2 (11%)
Heart failure, n (%)	119 (16%)	83 (16%)	21 (19%)	5 (14%)	6 (19%)	1 (4%)	3 (17%)

* Data in this table is from the visit with an AD diagnosis or the most recent visit (cognitively normal controls).

Aim 1: Neuroimaging - Demographics

55-60% women

80-90% white non-Hispanic

Potentially relevant (not statistically-significant) differences in

-Cerebrovascular disease (executive 78% compared to 50-55% in other groups)

-Hypertension (visuospatial 74% compared to 50% in language)

-Diabetes (executive 33% compared to ~16% in others)

Aim 1: Neuroimaging

Table 2. Modeling results for white matter hyperintensities (WMH)

	AD- No Domains (n=110)	AD- Memory (n=35)	AD- Visuospatial (n=31)	AD- Language (n=26)	AD- Executive (n=18)	Joint p-value**
Estimates comparing each cognitively defined subgroup to a reference group of No dementia (n=516)						
Modified Scheltens Scale	1.53 (0.90, 2.61)	0.79 (0.35, 1.81)	1.68 (0.68, 4.20)	1.09 (0.55, 2.15)	2.52 (0.95, 6.65)	0.282
Frontal lobe	**2.12 (1.19, 3.79)**	1.21 (0.49, 2.98)	**2.77 (1.14, 6.72)**	1.68 (0.83, 3.39)	1.27 (0.44, 3.65)	0.091
Parietal lobe	1.36 (0.83, 2.22)	1.24 (0.57, 2.70)	1.36 (0.56, 3.29)	1.88 (0.84, 4.21)	2.63 (0.99, 6.99)	0.303
Occipital lobe	1.24 (0.69, 2.23)	0.51 (0.21, 1.25)	2.26 (0.90, 5.69)	**0.23 (0.07, 0.75)**	3.20 (0.98, 10.43)	**0.004**
Temporal lobe	1.12 (0.64, 1.96)	0.58 (0.24, 1.40)	1.45 (0.59, 3.55)	0.56 (0.22, 1.38)	2.02 (0.79, 5.18)	0.258
Frontal caps	1.32 (0.72, 2.42)	0.81 (0.32, 2.03)	0.68 (0.26, 1.80)	1.90 (0.75, 4.81)	1.19 (0.32, 4.39)	0.529
Occipital caps	1.17 (0.66, 2.10)	0.51 (0.19, 1.35)	1.06 (0.41, 2.73)	1.29 (0.48, 3.49)	2.58 (0.71, 9.35)	0.450
Periventricular bands	1.34 (0.76, 2.34)	0.91 (0.34, 2.42)	1.27 (0.41, 4.00)	1.01 (0.32, 3.16)	2.46 (0.60, 9.99)	0.774
ARWMC scale	**1.74 (1.02, 2.96)**	0.84 (0.33, 2.09)	1.95 (0.90, 4.25)	1.06 (0.49, 2.30)	**2.62 (1.02, 6.79)**	0.116
Frontal lobe	**2.02 (1.15, 3.52)**	0.93 (0.34, 2.57)	**2.58 (1.10, 6.06)**	1.41 (0.68, 2.94)	1.75 (0.47, 6.49)	0.114
Parieto-occipital sulcus	1.28 (0.77, 2.13)	1.28 (0.49, 3.35)	1.16 (0.54, 2.47)	1.32 (0.51, 3.37)	1.72 (0.51, 5.76)	0.879
Temporal lobe	0.99 (0.56, 1.73)	0.57 (0.23, 1.44)	1.31 (0.66, 2.59)	0.51 (0.20, 1.36)	2.37 (0.91, 6.18)	0.153
Basal ganglia	**2.28 (1.22, 4.24)**	1.30 (0.49, 3.43)	1.27 (0.64, 2.50)	1.91 (0.91, 3.97)	**3.55 (1.00, 12.69)**	0.058
Infratentorial/Cerebellum	1.66 (0.95, 2.93)	0.78 (0.37, 1.67)	2.35 (0.88, 6.25)	0.81 (0.32, 2.05)	**2.47 (1.02, 5.94)**	0.072
Estimates comparing each cognitively defined subgroup (column) to one of the other subgroups (row) as the reference						
Modified Scheltens Scale – Occipital lobe						
Ref: AD-No Domains	N/A	0.41 (0.16, 1.08)	1.82 (0.68, 4.86)	**0.18 (0.05, 0.65)**	2.58 (0.78, 8.54)	
Ref: AD-Memory	2.44 (0.93, 6.44)	N/A	**4.45 (1.36, 14.61)**	0.44 (0.11, 1.84)	**6.31 (1.57, 25.41)**	
Ref: AD-Visuospatial	0.55 (0.21, 1.47)	**0.22 (0.07, 0.74)**	N/A	**0.10 (0.02, 0.43)**	1.42 (0.33, 6.06)	**0.002**
Ref: AD-Language	**5.50 (1.53, 19.73)**	2.25 (0.54, 9.33)	**10.02 (2.31, 43.38)**	N/A	**14.20 (2.87, 70.20)**	
Ref: AD-Executive	0.39 (0.12, 1.28)	**0.16 (0.04, 0.64)**	0.71 (0.17, 3.02)	**0.07 (0.01, 0.35)**	N/A	
ARWMC scale – Temporal lobe						
Ref: AD-No Domains	N/A	0.58 (0.22, 1.50)	1.33 (0.67, 2.63)	0.52 (0.19, 1.44)	2.40 (0.94, 6.10)	
Ref: AD-Memory	1.73 (0.67, 4.46)	N/A	2.29 (0.82, 6.41)	0.90 (0.25, 3.20)	**4.15 (1.21, 14.20)**	
Ref: AD-Visuospatial	0.75 (0.38, 1.50)	0.44 (0.16, 1.22)	N/A	0.39 (0.14, 1.13)	1.81 (0.67, 4.90)	0.090
Ref: AD-Language	1.92 (0.69, 5.32)	1.11 (0.31, 3.95)	2.55 (0.89, 7.31)	N/A	**4.61 (1.28, 16.66)**	
Ref: AD-Executive	0.42 (0.16, 1.06)	**0.24 (0.07, 0.83)**	0.55 (0.20, 1.49)	**0.22 (0.06, 0.78)**	N/A	

Aim 1: Neuroimaging - WMH

Differences from No Dementia

-Higher frontal WMH in **AD NoDomain** (OR 2.2) and **AD Visuospatial** (OR 2.7)

-Higher composite ARWMC score in **AD NoDomain** (OR 1.7) and **AD Executive** (OR 2.6)

Between group differences

Higher occipital WMH in **AD Visuospatial** compared to AD Memory (OR 4.5) and AD Language (OR 10.0)

Higher occipital WMH in **AD Executive** compared to AD Memory (OR 6.3) and AD Language (OR 14.2)

Higher temporal WMH in **AD Executive** compared to AD Memory (OR 4.2) and AD Language (OR 4.6)

Aim 1: Neuroimaging

Table 3. Modeling results for hemorrhages and microbleeds

	AD- No Domains (n=42)	AD- Memory (n=18)	AD- Visuospatial (n=11)	AD- Language (n=16)	AD- Executive (n=6)	Joint p-value**
Estimates comparing each cognitively defined subgroup to a reference group of No dementia (n=302)						
Hematoma / Hemorrhage	1.41 (0.56, 3.52)	0.72 (0.22, 2.33)	**7.78 (1.70, 35.67)**	**4.82 (1.19, 19.47)**	0.83 (0.03, 19.77)	0.061
Any microbleeds	1.34 (0.54, 3.31)	0.32 (0.06, 1.66)	3.66 (0.77, 17.52)	3.42 (0.94, 12.44)	0.92 (0.04, 22.21)	0.165
Count of microbleeds	1.85 (0.49, 7.01)	0.37 (0.07, 1.83)	**5.28 (1.23, 22.71)**	**6.21 (1.25, 30.76)**	2.43 (0.20, 30.14)	**0.028**
Estimates comparing each cognitively defined subgroup (column) to one of the other subgroups (row) as the reference						
Hematoma / Hemorrhage						
Ref: AD-No Domains	N/A	0.51 (0.14, 1.82)	**5.54 (1.17, 26.13)**	3.43 (0.73, 16.01)	0.59 (0.02, 15.74)	
Ref: AD-Memory	1.96 (0.55, 7.03)	N/A	**10.88 (1.73, 68.36)**	**6.73 (1.08, 41.86)**	1.16 (0.04, 33.74)	
Ref: AD-Visuospatial	**0.18 (0.04, 0.85)**	**0.09 (0.01, 0.58)**	N/A	0.62 (0.10, 3.94)	0.11 (0.00, 3.72)	0.081
Ref: AD-Language	0.29 (0.06, 1.36)	**0.15 (0.02, 0.92)**	1.62 (0.25, 10.31)	N/A	0.17 (0.01, 5.10)	
Ref: AD-Executive	1.69 (0.06, 45.09)	0.86 (0.03, 25.05)	9.38 (0.27, 327.08)	5.80 (0.20, 171.46)	N/A	
Count of microbleeds						
Ref: AD-No Domains	N/A	0.20 (0.04, 1.12)	2.84 (0.57, 14.22)	3.35 (0.52, 21.46)	1.31 (0.09, 19.36)	
Ref: AD-Memory	5.05 (0.89, 28.57)	N/A	**14.36 (2.03, 101.52)**	**16.91 (2.20, 129.89)**	6.61 (0.43, 101.37)	
Ref: AD-Visuospatial	0.35 (0.07, 1.76)	**0.07 (0.01, 0.49)**	N/A	1.18 (0.18, 7.84)	0.46 (0.03, 7.01)	**0.050**
Ref: AD-Language	0.30 (0.05, 1.91)	**0.06 (0.01, 0.45)**	0.85 (0.13, 5.65)	N/A	0.39 (0.02, 7.17)	
Ref: AD-Executive	0.76 (0.05, 11.30)	0.15 (0.01, 2.32)	2.17 (0.14, 33.09)	2.56 (0.14, 46.93)	N/A	

Aim 1: Neuroimaging - Hemorrhage

Differences from No Dementia

-Higher odds of hematoma or hemorrhage in **AD Visuospatial** (OR 7.8) and **AD Language** (OR 4.8)

-Higher count of microbleeds in **AD Visuospatial** (mean 5.3) and **AD Language** (mean 6.2)

Between group differences

-Higher odds of hematoma or hemorrhage in **AD Visuospatial** relative to AD NoDomains (OR 5.4)

-Higher odds of hematoma or hemorrhage in **AD Visuospatial** (OR 10.9) and **AD Language** (OR 6.7) relative to AD Memory

-Higher count of microbleeds in **AD Visuospatial** (mean 41.3) and **AD Language** (mean 16.9) relative to AD Memory

Aim 1: Neuroimaging - Discussion

Finding: Higher occipital WMH in **AD-visuospatial**

-relative to AD-memory and AD-language

-potential comorbid or synergistic vascular component

-other literature: increased occipital WMH in posterior cortical atrophy.

Finding: Increased occipital and temporal WMH in **AD-Executive**

-relative to AD-memory and AD-language

-nonsignificant increase in most areas

- other literature: increased WMH in dysexecutive AD

Aim 1: Neuroimaging - Discussion

Finding: Lower WMH in **AD-memory** and **AD-Language**

-these areas had distinct patterns of increased atrophy

-potentially reflects relative dominance of neurodegeneration as mechanism of impairment.

-adds to other findings establishing AD-memory as a distinct group.

- other literature: most interesting comparison uses groupings with a larger memory subgroup and less strict threshold for separating that group. This study showed slight increase in WMH in AD-memory.

-combination of results may indicate a stricter threshold more accurately identifies a unique subgroup of patients with dominant memory impairment.

Aim 1: Neuroimaging - Discussion

Finding: Higher odds of hemorrhage and microbleed count in **AD-visuospatial** and **AD-language**

-may reflect increased comorbid CAA or hypertension

-other literature: mixed results. In our path, CAA prevalence not increased. Some studies show less % of logopenic PPA and PCA patients with microbleeds. One study similarly showed increased microbleed count in logopenic PPA and PCA

Aim 2: Neuropathology

- Compare each neuropathology outcome between:
  - 5 AD subgroups
  - Non-AD dementia
  - No dementia

- Primary questions of interest are focused on differences within the 5 AD subgroups specifically

- Differences between groups estimated using covariate adjusted ordinal logistic regression models incorporating weights to account for selection into analytic sample

Figure 1. Flow diagram describing analytic study sample.

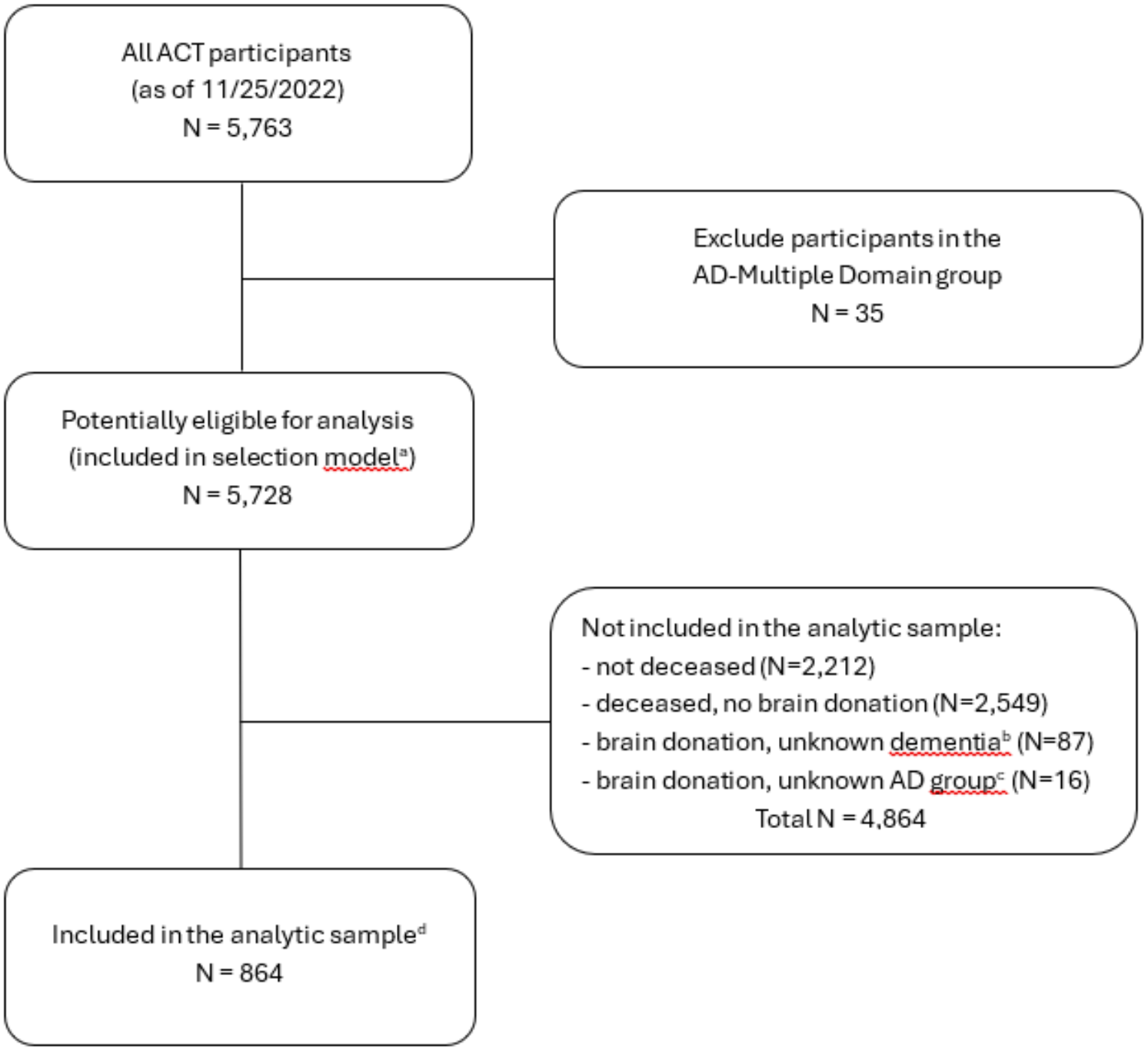


Table 1. Participant characteristics, overall and stratified by dementia and AD cognitive subgroup status.

Characteristics	Total (n=864)	No dementia[a] (n=432)	Non-AD dementia[b] (n=74)	AD dementia[c]				
				AD- No Domains (n=196)	AD- Visuospatial (n=55)	AD- Memory (n=50)	AD- Language (n=30)	AD- Executive (n=27)
Women	494 (57%)	234 (54%)	36 (49%)	124 (63%)	30 (55%)	33 (66%)	19 (63%)	18 (67%)
Race/Ethnicity								
American Indian or Alaska native	1 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	18 (2%)	5 (1%)	0 (0%)	6 (3%)	2 (4%)	3 (6%)	1 (3%)	1 (4%)
Black or African American	10 (1%)	5 (1%)	0 (0%)	3 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (4%)
Hispanic or Latino	2 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)
White	809 (94%)	409 (95%)	73 (99%)	181 (92%)	53 (96%)	43 (86%)	28 (93%)	22 (81%)
Another category / More than one	23 (3%)	13 (3%)	1 (1%)	5 (3%)	0 (0%)	2 (4%)	1 (3%)	1 (4%)
Unknown or not reported	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Years of biennial visit follow-up	9.9 (5.9)	10.2 (6.1)	9.0 (5.8)	10.0 (5.8)	9.4 (5.8)	9.5 (5.4)	9.3 (5.2)	8.5 (4.1)
Age at biennial visit	86.1 (6.6)	86.2 (7.1)	84.3 (5.8)	86.3 (6.1)	86.3 (5.8)	86.9 (6.1)	86.6 (6.3)	86.3 (5.9)
Years from visit to death	2.7 (2.8)	1.0 (0.6)	3.4 (2.6)	4.8 (3.3)	4.6 (3.6)	4.4 (2.7)	4.1 (2.3)	4.3 (2.7)
Years of education	14.8 (3.0)	15.1 (3.0)	15.0 (3.5)	14.2 (2.8)	15.1 (3.2)	14.7 (3.1)	15.2 (2.5)	13.3 (3.2)
≥1 *APOE* ε4 allele	240 (29%)	100 (24%)	30 (41%)	65 (35%)	13 (25%)	21 (43%)	7 (25%)	4 (16%)
APOE genotype not available	41 (5%)	22 (5%)	1 (1%)	10 (5%)	3 (5%)	1 (2%)	2 (7%)	2 (7%)
Coronary artery disease	266 (31%)	152 (35%)	22 (30%)	47 (24%)	18 (33%)	12 (24%)	9 (30%)	6 (22%)
Cerebrovascular disease	251 (29%)	128 (30%)	35 (47%)	42 (21%)	19 (35%)	10 (20%)	11 (37%)	6 (22%)
# of ADLs with difficulty	1.5 (1.8)	1.6 (1.8)	2.5 (2.1)	1.2 (1.6)	1.7 (1.8)	0.7 (1.3)	1.0 (1.6)	1.8 (1.8)
ADL data not available	70 (8%)	24 (6%)	12 (16%)	15 (8%)	3 (5%)	7 (14%)	4 (13%)	5 (19%)
Timed 10-foot walking task								
Able to perform	601 (70%)	305 (71%)	37 (50%)	146 (74%)	39 (71%)	37 (74%)	21 (70%)	16 (59%)
Unable to perform	45 (5%)	26 (6%)	4 (5%)	8 (4%)	4 (7%)	1 (2%)	0 (0%)	2 (7%)
Not assessed / not available	70 (8%)	24 (6%)	12 (16%)	15 (8%)	3 (5%)	7 (14%)	4 (13%)	5 (19%)

Data provided in this table are from the biennial study visit at which participants were diagnosed with dementia (of any type), or from the most recent biennial study visit for those without dementia (cognitively normal controls). Values shown in this table are either n (%) or mean (standard deviation) depending on the characteristic. AD=Alzheimer's disease determined per NINCDS-ADRDA criteria.

Table 3. Comparing the odds of greater levels of pathology for the AD and non-AD dementia groups relative to the no dementia group.

Neuropathology outcomes	Non-AD dementia OR (95% CI)	AD dementia					
		AD- No Domains OR (95% CI)	AD- Visuospatial OR (95% CI)	AD- Memory OR (95% CI)	AD- Language OR (95% CI)	AD- Executive OR (95% CI)	Omni-p (5-df)[a]
AD Neuropathology							
Thal phase	**2.04 (1.15, 3.64)**	**2.87 (1.72, 4.77)**	1.24 (0.68, 2.25)	**3.91 (1.85, 8.29)**	**2.66 (1.24, 5.69)**	2.37 (0.97, 5.83)	<0.001*
Braak stage	**2.69 (1.68, 4.31)**	**4.14 (2.64, 6.48)**	**2.46 (1.32, 4.58)**	**6.82 (3.59, 12.96)**	**5.81 (2.66, 12.70)**	**5.87 (2.45, 14.07)**	<0.001*
CERAD score	**2.45 (1.38, 4.36)**	**3.48 (2.16, 5.59)**	1.80 (0.96, 3.39)	**3.90 (2.03, 7.50)**	**4.35 (2.02, 9.36)**	**2.65 (1.20, 5.87)**	<0.001*
ADNC score	**2.76 (1.60, 4.78)**	**4.30 (2.63, 7.04)**	**2.69 (1.37, 5.30)**	**7.43 (3.56, 15.49)**	**4.96 (2.20, 11.15)**	**4.90 (1.94, 12.43)**	<0.001*
Cerebral amyloid angiopathy	1.07 (0.62, 1.86)	1.17 (0.73, 1.87)	0.64 (0.35, 1.20)	1.58 (0.87, 2.88)	1.02 (0.45, 2.34)	1.90 (0.82, 4.42)	0.135
Non-AD, non-vascular							
LATE	0.82 (0.46, 1.46)	**1.76 (1.09, 2.83)**	1.10 (0.60, 2.00)	**3.01 (1.55, 5.82)**	**3.94 (1.64, 9.48)**	1.36 (0.60, 3.08)	0.002*
Hippocampal sclerosis	1.72 (0.67, 4.40)	**2.52 (1.23, 5.13)**	1.54 (0.60, 3.98)	**6.84 (2.96, 15.78)**	**5.19 (1.73, 15.58)**	2.68 (0.91, 7.95)	<0.001*
Lewy body disease	1.74 (0.94, 3.22)	1.45 (0.80, 2.62)	**2.41 (1.18, 4.93)**	**2.20 (1.04, 4.68)**	2.44 (0.93, 6.38)	**2.70 (1.02, 7.16)**	0.065
Vascular							
Gross infarcts	**3.85 (2.22, 6.66)**	**2.51 (1.51, 4.18)**	**2.54 (1.32, 4.90)**	1.45 (0.73, 2.86)	**4.78 (2.23, 10.23)**	**2.76 (1.16, 6.54)**	<0.001*
Any microinfarcts	**2.34 (1.29, 4.24)**	**1.64 (1.01, 2.66)**	1.50 (0.83, 2.72)	0.93 (0.47, 1.82)	**2.24 (1.02, 4.90)**	**3.10 (1.38, 6.96)**	0.033*
Cerebral microinfarcts	**2.14 (1.21, 3.79)**	1.36 (0.81, 2.30)	1.44 (0.77, 2.70)	0.98 (0.47, 2.04)	2.15 (0.94, 4.96)	1.92 (0.85, 4.30)	0.368
Deep microinfarcts	**2.68 (1.39, 5.17)**	**1.97 (1.13, 3.44)**	1.65 (0.80, 3.40)	1.03 (0.47, 2.28)	2.29 (0.93, 5.64)	**3.05 (1.19, 7.80)**	0.065
Atherosclerosis	1.77 (0.94, 3.32)	1.20 (0.72, 2.00)	1.02 (0.55, 1.91)	1.32 (0.63, 2.73)	2.09 (0.65, 6.67)	0.80 (0.30, 2.14)	0.764
Arteriolosclerosis	**3.09 (1.58, 6.05)**	1.45 (0.83, 2.53)	1.73 (0.83, 3.59)	1.40 (0.67, 2.94)	1.77 (0.76, 4.15)	2.26 (0.73, 7.06)	0.561

Odds ratios (OR) and 95% confidence intervals (CI) are estimated from ordinal logistic regression models – a separate model for each neuropathology outcome – adjusted for sex/gender, age at death, years of education, and years from visit to death, and which incorporated inverse-probability weighting to account for selection into the analytic sample. ORs>1 correspond to higher levels of the neuropathology outcome in the specified group relative to the no dementia group; ORs with CIs that exclude 1 have been bolded.

[a] P-value corresponds to a 5-degree of freedom omnibus test of any differences between the 5 AD dementia subgroups and the non-dementia group for the specified neuropathology outcome; p<0.05 have been denoted with *.

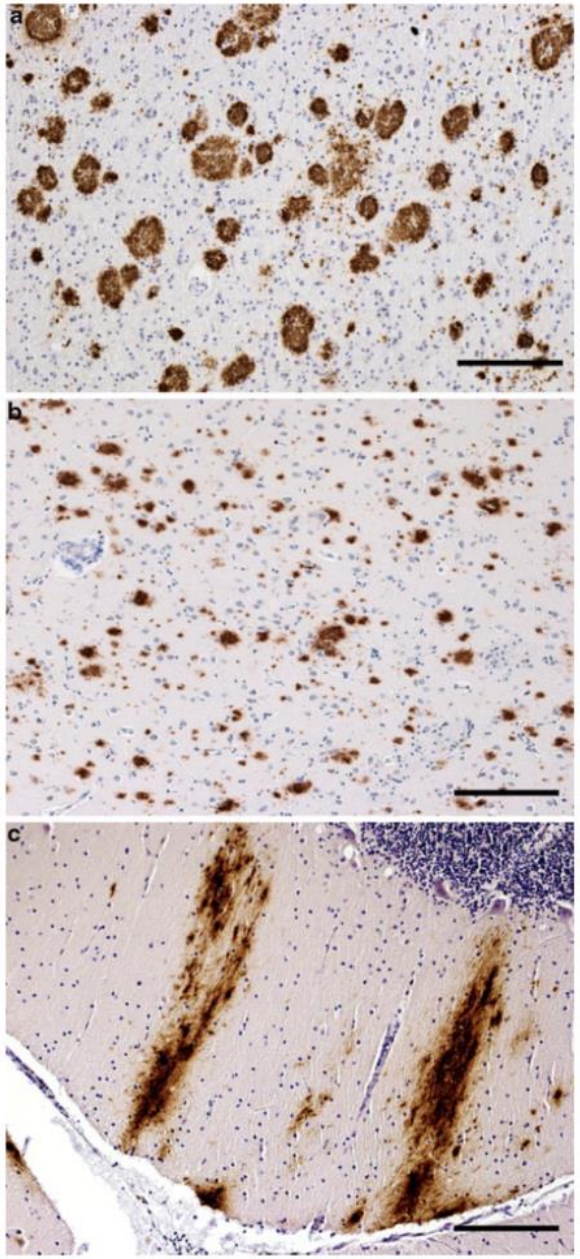
Table 4. Comparing the odds of greater levels of pathology between the AD-cognitive subgroups.

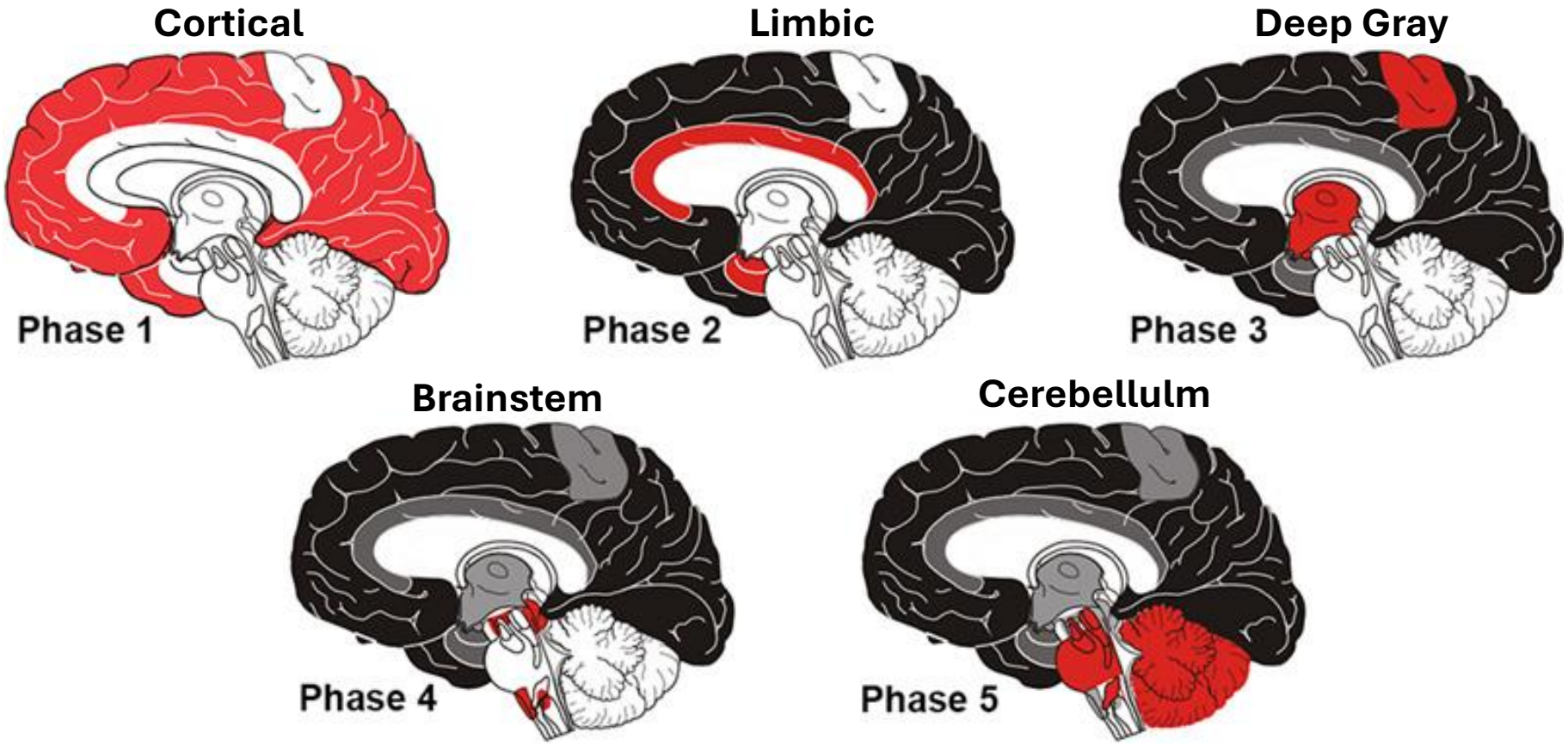
	AD dementia					
Neuropathology outcomes	**AD- No Domains OR (95% CI)**	**AD- Visuospatial OR (95% CI)**	**AD- Memory OR (95% CI)**	**AD- Language OR (95% CI)**	**AD- Executive OR (95% CI)**	**Omni-p (4-df)[a]**
AD Neuropathology						
Thal phase	**2.32 (1.34, 4.01)**	1 (reference)	**3.17 (1.46, 6.87)**	2.15 (0.98, 4.75)	1.92 (0.77. 4.80)	0.021*
Braak stage	1.69 (0.93, 3.06)	1 (reference)	**2.78 (1.32, 5.84)**	2.37 (0.99, 5.65)	2.39 (0.93, 6.19)	0.063
CERAD score	**1.93 (1.08, 3.45)**	1 (reference)	**2.17 (1.03, 4.55)**	**2.41 (1.05, 5.54)**	1.47 (0.62, 3.50)	0.142
ADNC score	1.60 (0.87, 2.95)	1 (reference)	**2.76 (1.24, 6.14)**	1.84 (0.77, 4.40)	1.82 (0.67, 4.97)	0.168
Cerebral amyloid angiopathy	**1.81 (1.01, 3.23)**	1 (reference)	**2.45 (1.21, 4.96)**	1.59 (0.64, 3.91)	**2.95 (1.18, 7.36)**	0.087
Non-AD, non-vascular						
LATE	1.60 (0.91, 2.84)	1 (reference)	**2.75 (1.34, 5.63)**	**3.60 (1.41, 9.16)**	1.24 (0.53, 2.94)	0.018*
Hippocampal sclerosis	1.63 (0.70, 3.82)	1 (reference)	**4.43 (1.62, 12.14)**	**3.36 (1.03, 10.92)**	1.74 (0.53, 5.68)	0.022*
Lewy body disease	0.60 (0.32, 1.13)	1 (reference)	0.91 (0.41, 2.06)	1.01 (0.36, 2.83)	1.12 (0.41, 3.08)	0.335
Vascular						
Gross infarcts	1.74 (0.94, 3.21)	1.76 (0.81, 3.78)	1 (reference)	**3.30 (1.45, 7.49)**	1.90 (0.76, 4.76)	0.082
Any microinfarcts	1.77 (0.94, 3.35)	1.62 (0.77, 3.40)	1 (reference)	**2.42 (1.00, 5.82)**	**3.35 (1.37, 8.19)**	0.087
Cerebral microinfarcts	1.38 (0.69, 2.78)	1.46 (0.66, 3.25)	1 (reference)	2.19 (0.84, 5.69)	1.95 (0.77, 4.90)	0.481
Deep microinfarcts	1.91 (0.93, 3.94)	1.60 (0.67, 3.83)	1 (reference)	2.22 (0.82, 6.01)	**2.96 (1.07, 8.15)**	0.249
Atherosclerosis	0.91 (0.46, 1.82)	0.78 (0.35, 1.75)	1 (reference)	1.59 (0.45, 5.64)	0.61 (0.20, 1.83)	0.712
Arteriolosclerosis	1.03 (0.54, 1.97)	1.23 (0.53, 2.86)	1 (reference)	1.26 (0.51, 3.14)	1.61 (0.50, 5.23)	0.898

Odds ratios (OR) and 95% confidence intervals (CI) are estimated from the same models used to produce Table 3 results. For ease of presentation, the AD-subgroup that tended to have the lowest levels for the given domain of neuropathology outcomes (AD Neuropathology; Non-AD, non-vascular; Vascular) was chosen as the reference category. ORs>1 correspond to higher levels of the neuropathology outcome in the specified AD-cognitive subgroup relative to the specified reference group; ORs with CIs that exclude 1 have been bolded.

[a] P-value corresponds to a 4-degree of freedom omnibus test of any differences between the 5 AD dementia subgroups for the specified neuropathology outcome; $p<0.05$ have been denoted with *.

Thal phase = Amyloid Distribution

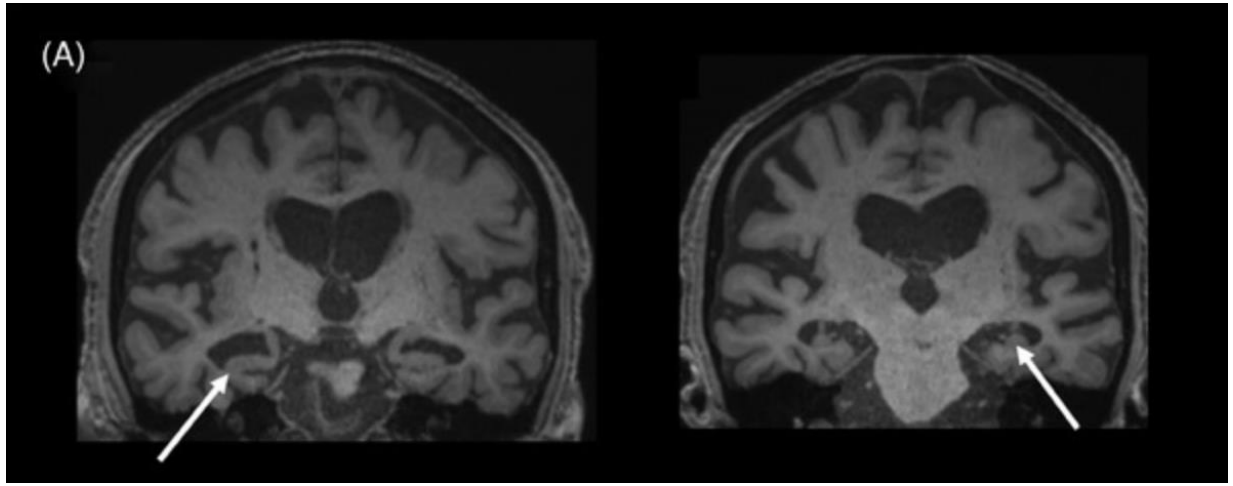




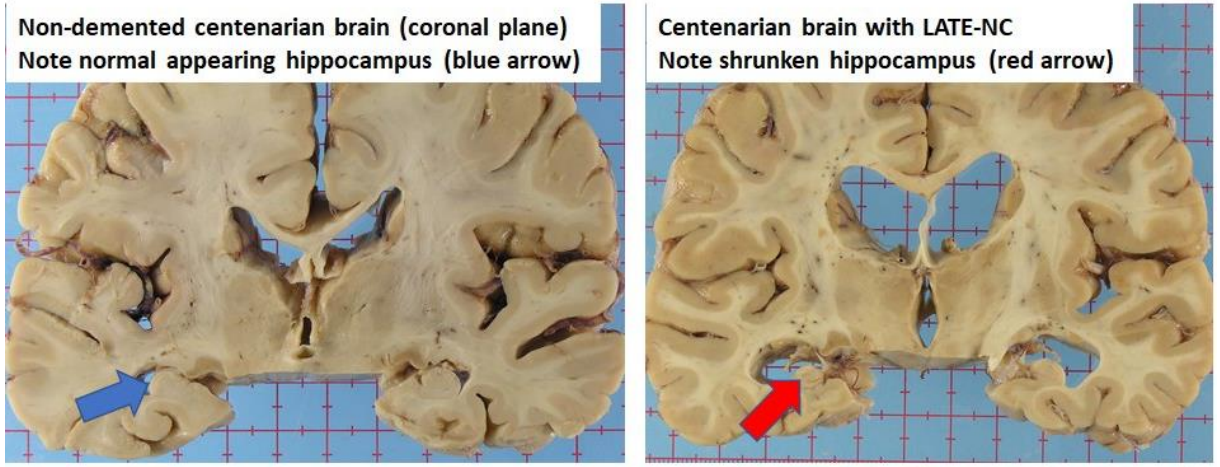
- Higher Thal phase = increased association with dementia
- Unclear why increased Thal was associated specifically with the AD memory group

Limbic-Predominant Age-Related TDP-43 Encephalopathy Neuropathologic Change (LATE-NC)

Associated with marked hippocampal atrophy and more rapid rates of atrophy

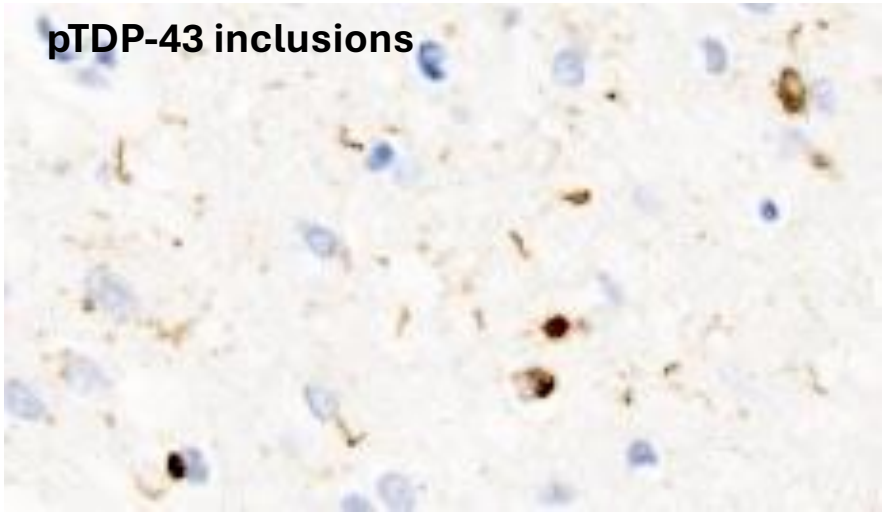


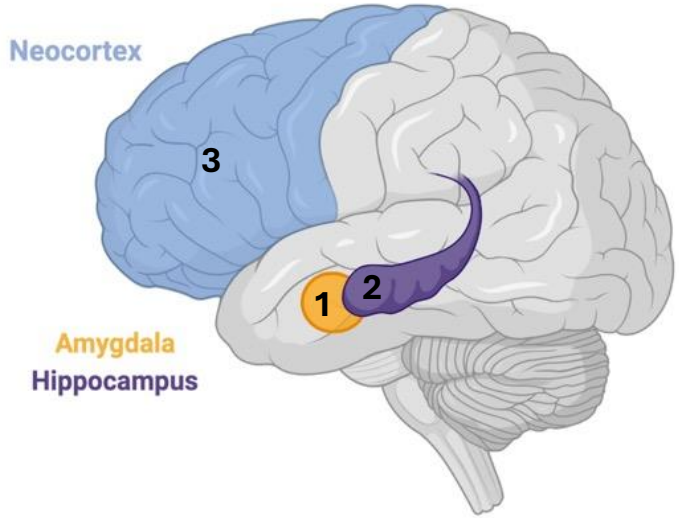
Wolk et al. Alzheimer Dement (2025)

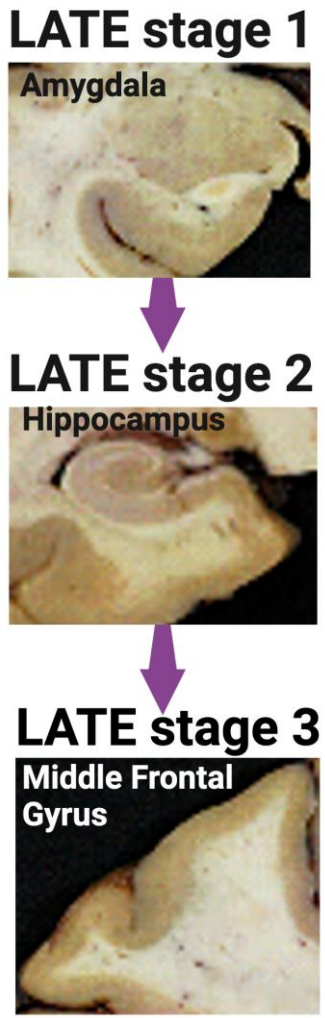


Peter Nelson, University of Kentucky

pTDP-43 aggregates identified predominantly in limbic structures (amygdala, hippocampus)

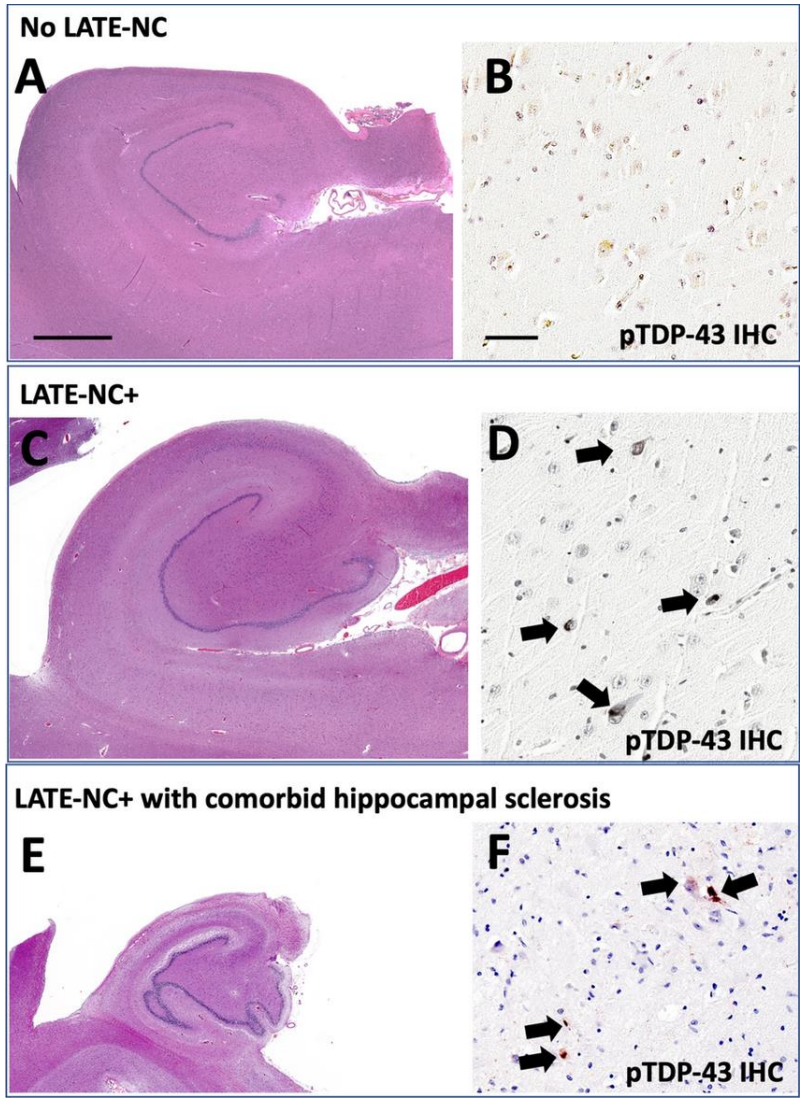




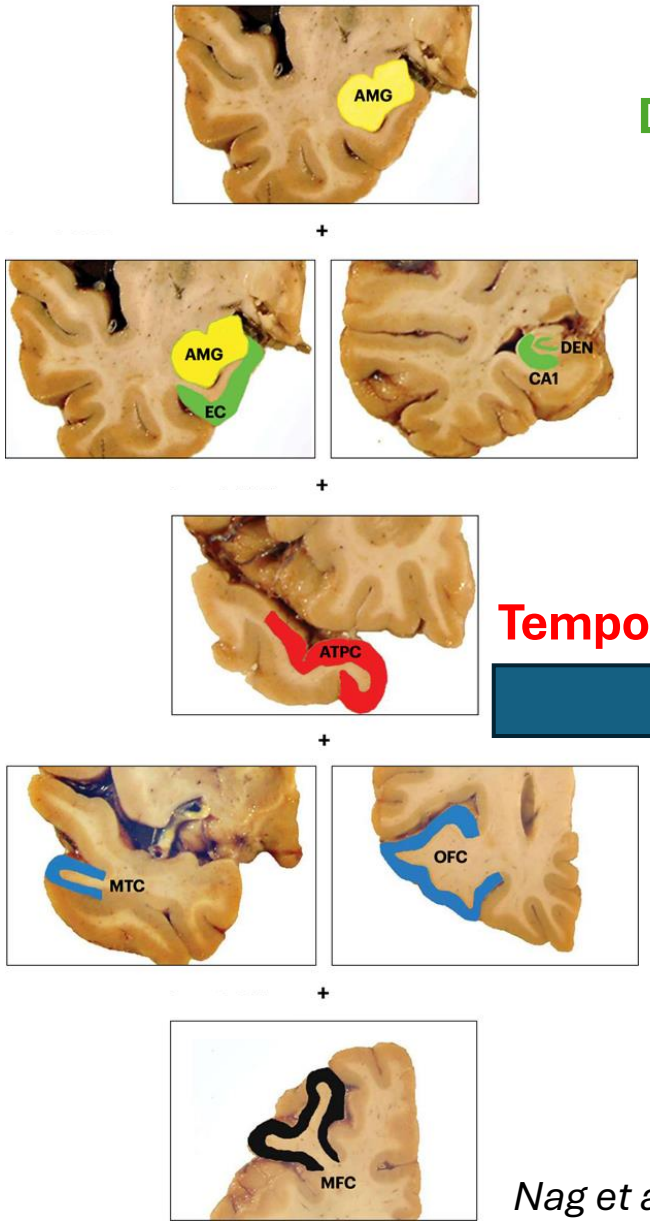


TDP-43 and HS pathology in AD memory and language groups

Hippocampal sclerosis associated with severe LATE-NC



Dugan et al. Acta Neuropathol. Commun. (2021)



Destruction of Limbic structures → **Memory Dysfunction**

Other brain regions become involved as LATE-NC progresses

Temporal pole pathology → **Language Dysfunction?**

- Currently no biomarkers for TDP-43
- Does careful neuropsych testing help identify this common co-pathology?

Nag et al. Acta Neuropathol. Commun. (2018)

Aim 3: Lived experience

- Qualitative research with clinical free text data
- Using Natural Language Processing to extend this method to a larger dataset
- Created three sub-corpora:
  1) Caregiving
  2) Living situation
  3) Patient-initiated communications (secure messages)

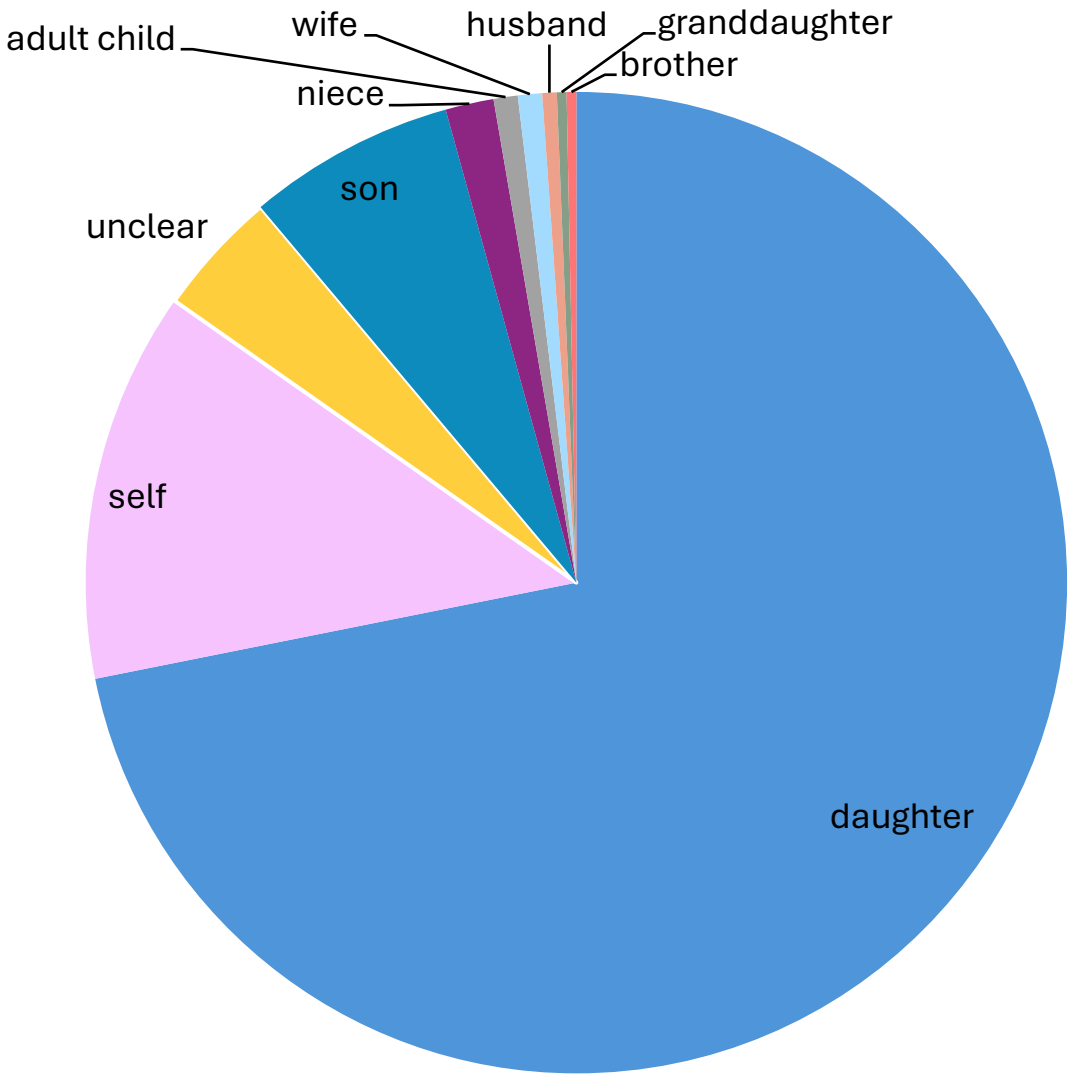
Patient-initiated communications

- Secure messages are now the primary way patients and caregivers communicate with providers outside of appointments[1]
- Messages sent through these portals can offer insight into relational and logistical realities of caregiving
- Timeliness of messages as a record of what the healthcare system knew, when
- Patient needs and concerns in their own voice/the voices of caregivers

1. Han, H. R., Gleason, K. T., Sun, C. A., Miller, H. N., Kang, S. J., Chow, S., ... & Bauer, T. (2019). Using patient portals to improve patient outcomes: systematic review. JMIR human factors, 6(4), e15038

Patient-initiated communications

- We qualitatively coded 950 messages
  - 65% sent from patient/caregiver
  - 35% from medical personnel
- Of those sent from the patient side, only about 14% were sent by the patient themselves, the rest were sent by caregivers, overwhelmingly daughters



Number of Messages, by Author (n=629)

all terms relative to the patient

Message themes

Theme	Details	Illustrative Quotes
Health care system navigation	requesting referrals or documentation, communicating the view of another clinician, seeking explanations of costs and insurance coverage, etc	Right now my dad is receiving [benefit], would this be covered? There is some question if it is supplied from [insurer] or an outside vendor. If you are able to find someone that could answer this question it would be helpful. I spent a couple of hours this morning trying to get this question answered but did not have any final answer from the departments that I called. *** I really want to avoid going through urgent care and managed to get an apt today with the intervention radiologist who put the last stomach tube in. I'm told by customer service that I need your recommendation for this visit to be covered, even though it saves her energy and health as well as saves [insurer] money for us to go directly. *** I never take the metro and would like to update my Access Van certification. Can you do that without having me come in to see you?
Medication concerns or requests	discussing or debating the effects of medications, arranging for the correct dosage, requesting new medications or proposing to discontinue medications	Dr.__, this is [participant's] son. My sisters and I are now wondering if there is merit in changing her morning dose of seroquel from half a tablet to a full tablet. The details that brought this about are in the paragraphs that follow. We understand the increased fall risk from increased dosage, but as she always has someone with her when she walks, we are willing to take that on if you think the increased dosage would help. Or if you have any other ideas? *** There is a possibility she took an extra dose, She called me that she had accidently taken some extra pills. Realizing her mistake, she called me but couldn't tell me what pills she had taken or how many. When I checked out the medication box, I seem to recall that it appeared some warfarin was missing from a door that should have had some in there. *** My brother is concerned that all of this is due to the anti-depressants. However, my sister and I feel that she has greatly improved on the anti-depressants.
Transitions in care	adjusting or attempting to adjust caregiving arrangements and responsibilities, including changing housing arrangements, implementing new care strategies, and reporting caregiver burnout	The [facility] can't really monitor her for 3 meals a day unless they put her in the memory unit, which nobody wants to do at this point! (Also, they have no room in the memory unit.) *** He prefers to be alone, still does not want to be in any kind of home whatsoever, and I respect his decision. However, I am experiencing some care-giver burnout with his care, and it was suggested that I ask you about possible Hospice, for respite care for myself, even though he's not considered "terminal." Not sure how that all works. When I've called any home health agencies, they've told me that his insurance will not cover home nursing care. *** I am wondering if her coverage provides for nursing assistants to come to the house and check on her during the day to make sure she is eating and taking her correct medication?

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