MRC Cognition and Brain Sciences Unit

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Multidimensional cognitive deficits in the aphasic and amnestic variants of Alzheimer's disease

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Introduction

- Debate continues over whether **Alzheimer's disease (AD) phenotypes** are distinct clinical entities or part of a graded multidimensional space[1-3]
- In this **two-part investigation**, we asked:
  1. Is multidimensional impairment only present in advanced cases and how does it compare to typical, amnestic AD (tAD)?
  2. Do memory deficits appear in a clinic-level assessment or require in depth research-level investigation?
  3. Is verbal episodic memory performance explained by language impairment?
  4. Do individuals with typical and atypical AD decline categorically or multidimensionally over time?
- For imaging, we assessed the associations between principal component analysis derived scores and grey matter volumes in key memory and language brain regions

Materials and Methods

1) **Retrospective study**: Research participants (N = 413) with a clinical diagnosis of tAD, logopenic variant of primary progressive aphasia (lvPPA)[4,5] and posterior cortical atrophy (PCA)[6] completed the Addenbrooke's Cognitive Examination – Revised (ACE-R)
2) **Deep phenotyping prospective study:** Twelve healthy controls and individuals with a clinical diagnosis of tAD (N = 9) and lvPPA (N = 18) completed a large battery of neuropsychological assessments and MRI[7]

	Control	tAD	lvPPA	lvPPA+	P*	BF_{10}
N	12	9	10	8	-	-
Age (years)	71.08 (8.89)	74.56 (6.48)	72.870 (8.98)	68.63 (5.64)	ns	0.31
Gender (male/female)	5/7	6/3	5/5	7/1	ns	0.54
Handedness (right/left)	10/2	8/1	9/1	8/0	ns	0.20
Symptom duration (years)	-	5.11 (2.32)	3.00 (1.05)	4.00 (1.85)	ns	1.66
Education (mean age)	21.5 (6.47)	17.44 (2.46)	16.70 (3.06)	17.38 (2.39)	ns	1.91

Statistical Analysis

1) Retrospective study:

Overall severity
- Each diagnostic group stratified into ranges based on ACE-R total scores as a proxy for overall severity
- Tabulation of the proportion of patients within normal and below cut-off ranges for each ACE-R domain **Figure 1**

ACE-R
- Bayesian ANOVA on total ACE-R and sub-domain scores **Figure 2**

2) Deep phenotyping study

ACE-R
- Bayesian ANOVA on total ACE-R and sub-domain scores **Figure 2**

PCA
- Principal component analysis on detailed neuropsychology followed by Bayesian ANOVA with principal component (PC) scores **Figure 3**

Memory
- Phase (e.g., immediate recall, delayed recall) x group Bayesian ANOVA for RAVLT (i.e., verbal) and ROFC (i.e., non-verbal) **Figure 4**

Longitudinal
- Visualization of the individual PC trajectories **Figure 5**

Imaging
- Bayesian linear regression with PC scores and grey matter volumes in regions of interest **Figure 6**

Behavioral Results

Figure 1: Proportions of patients who were within normal range or below published healthy control cut-off scores for each ACE-R domain stratified by overall performance

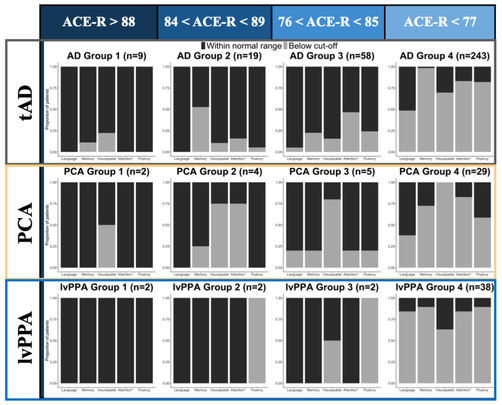


Figure 2: Scatterplots of ACE-R language, memory, and visuospatial domain scores over the (A) retrospective and (B) deep phenotyping studies

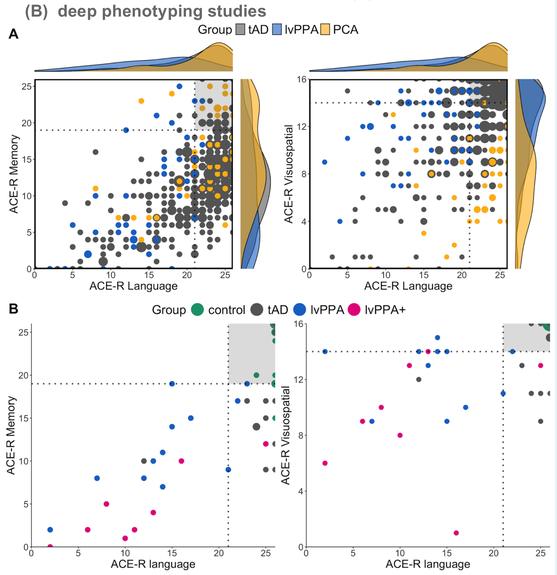


Figure 3: Principal component scores across groups

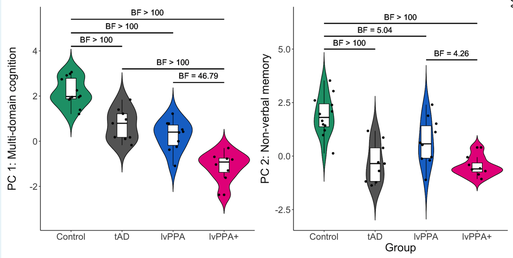


Figure 4: (A) Rey Auditory Verbal Learning Test (RAVLT) and (B) Rey Osterrieth Complex Figure (ROCF) scores across groups

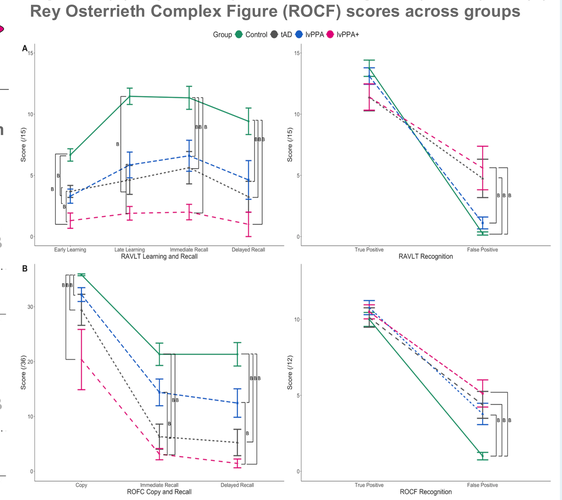
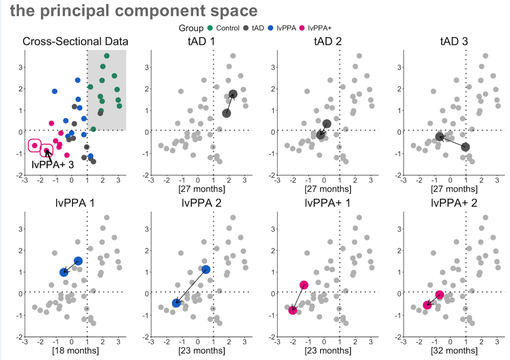


Figure 5: Phenotypic variation in longitudinal patients within the principal component space

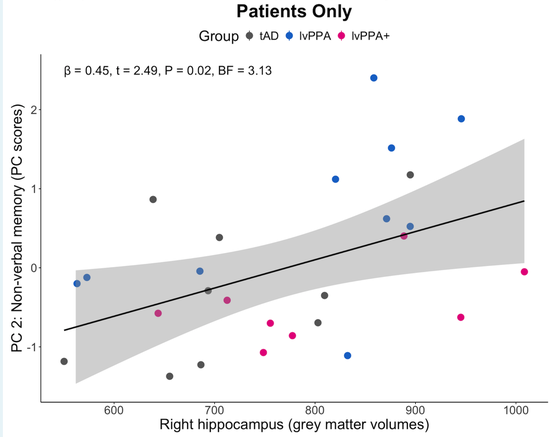


Summary of behavioral results:

1. Patient severity: Even some mild patients showed multi-domain cognitive impairments
2. Testing granularity: Multi-domain can be captured in clinic-level assessment
3. Assessment nature: Patients with lvPPA were impaired on both ROCF and RAVLT
4. Longitudinal design: Individuals showed a multidimensional pattern of decline

Imaging Results

Figure 6: Associations between Principal Component 2 scores and grey matter volume in the right hippocampus



Conclusion

The graded distinctions amongst typical and atypical AD phenotypes support a transdiagnostic, multidimensional neurocognitive geometry proposal for those sharing the same underlying disease process

References & Preprint ↓

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