Phenotypic variability in late-onset amnestic mild cognitive impairment

Deepti Putcha[1], Caitlin Loxton[2], Yuta Katsumi[2], and Bradford C., Dickerson[2]

[1] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[2] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Key Take Aways: (**1**) Aβ-positive late-onset Amnestic MCI is not a uniform phenotypic entity; 6 neuropsychologically distinct phenotypes were identified in ADNI that have a characteristic cognitive profile and rate of decline. (**2**) The Amnestic-predominant phenotype showed a greater rate of clinical decline and cortical atrophy in the medial temporal lobes compared to the Non-Amnestic phenotypes (Dysexecutive, Language, Visuospatial). (**3**) Cognitive phenotyping at the MCI stage could offer a foundation for more precise patient stratification in clinical trials, person-specific prognostic counseling, and personalized disease management.

BACKGROUND

•Late-onset AD (LOAD) is traditionally conceptualized as a clinically homogeneous **amnestic** syndrome, yet accumulating evidence suggests substantial heterogeneity in its cognitive and neurobiological features[1,2,3].

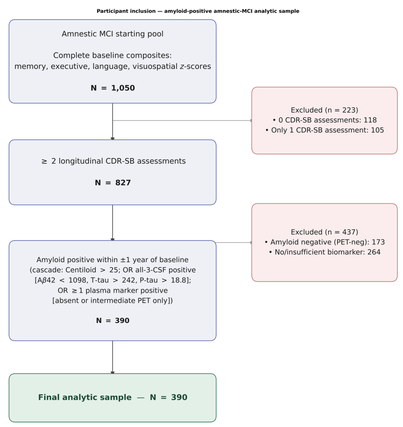
•We do not yet understand:
- If this phenotypic heterogeneity is present at the earlier stage of amyloid-positive late-onset amnestic mild cognitive impairment (LOAD-aMCI)
- If the heterogeneity in LOAD-aMCI is consistent with what has been observed in early-onset AD (EOAD-aMCI)[4,5].
- The downstream implications of phenotypic heterogeneity, including different rates of decline and regional differences in brain structure.

•The goals of the current study are:
1. Characterize phenotypic heterogeneity in the ADNI biomarker-confirmed late-onset aMCI sample using rule-based cognitive subtyping.
2. Determine how these phenotypes differ on (a) Baseline demographic and clinical characteristics, (b) Longitudinal trajectory of clinical decline, and (c) baseline structural atrophy patterns.

•Characterizing phenotypic heterogeneity within Aβ-positive LOAD-aMCI has direct implications for clinical trial design, prognosis, and personalized care. Pooling phenotypically distinct patients may dilute treatment effects and obscure differential progression rates

METHODS

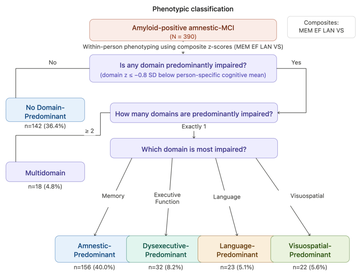
- We studied **390 Aβ-positive MCI** with symptom onset after the age of 65 (LOAD-aMCI) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Data was pooled across ADNI-1, ADNI-Go, ADNI-2, and ADNI-3.
- All had complete baseline neuropsychological assessment and longitudinal ratings on the Clinical Dementia Rating scale (CDR). A subset (N=306) had longitudinal Montreal Cognitive Assessment (MoCA) scores. Most (N= 387) had baseline cortical thickness MRI data.
- **Person-centered rule-based cognitive phenotyping** was applied, consistent with prior phenotypic subtyping approaches[1,2,5]. See flowchart in Results.
- **Clinical trajectory modeling:**
  - Linear mixed models (LMM) with random intercepts and random slopes were used to estimate longitudinal CDR-SB trajectories. Models included phenotype × time interactions and controlled for baseline CDR-SB.
  - The same LMM approach was used to estimate longitudinal MoCA trajectories.

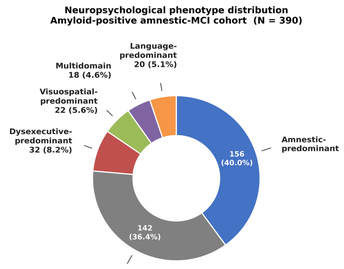


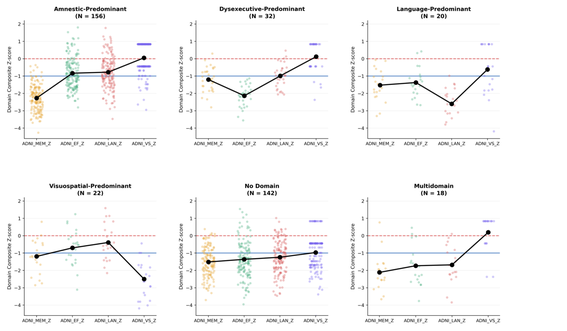
- **Structural MRI:** Vertex-wise GLM were computed across the cortical surface using FreeSurfer to identify regions of significant atrophy, covaried for age and sex. Cluster-based correction for multiple comparisons was applied ($p < .05$, two-tailed). Mean cortical thickness was extracted from anatomically defined ROIs. One-way ANOVAs tested group differences across the neuropsychological phenotypes, with post-hoc pairwise comparisons (Tukey HSD) and a false discovery rate correction ($q < .05$).

RESULTS

6 Distinct Cognitive Phenotypes



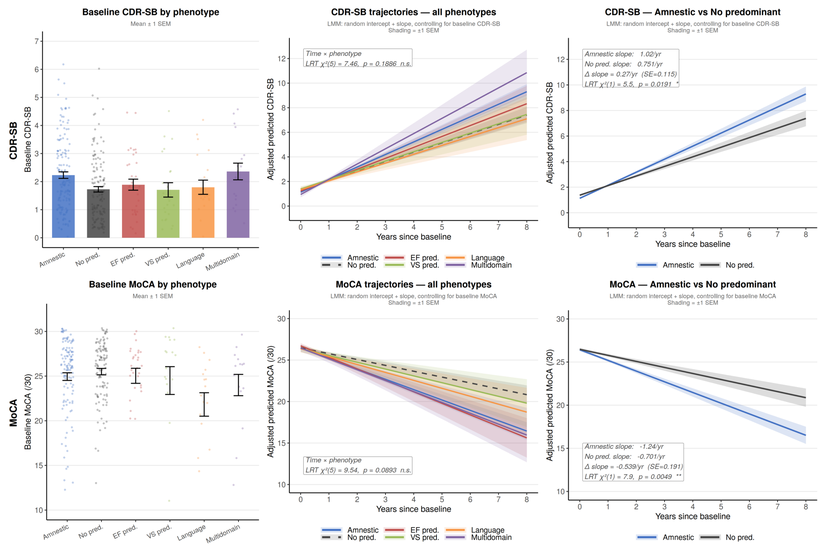




	Amnestic-predominant	Dysexecutive-predominant	Language-predominant	Visuospatial-predominant	Multidomain	No Domain	Total	p value
n	156	32	20	22	18	142	390	
Age, years	72.3 (6.6)	**76.1 (6.3)**	73.5 (5.0)	**72.1 (7.4)**	75.4 (8.7)	74.3 (7.0)	73.5 (6.9)	**0.020**[a]
Female sex	60 (38.5%)	13 (40.6%)	16 (80.0%)	**6 (27.3%)**	**6 (33.3%)**	**68 (47.9%)**	169 (43.3%)	**0.005**[b]
Education, years	16.2 (2.6)	16.9 (2.5)	15.1 (2.5)	16.3 (2.6)	15.3 (3.1)	15.6 (3.0)	15.9 (2.8)	0.053[a]
CDR Global	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.5 (0.5–0.5)	0.269[c]
CDR-SB	2.0 (1.0–3.0)	2.0 (1.0–2.6)	1.5 (1.4–2.6)	**1.2 (0.6-2.5)**	**2.2 (1.5-3.0)**	1.5 (1.0–2.5)	1.5 (1.0–3.0)	**0.016**[c]
MoCA	24.9 (4.8)	25.0 (4.6)	21.8 (5.4)	24.5 (6.6)	24.0 (4.6)	25.5 (3.8)	24.9 (4.6)	0.072[a]
APOE ε4 homozygotes	35 (22.4%)	4 (12.5%)	2 (10.0%)	4 (18.2%)	1 (5.6%)	19 (13.4%)	65 (16.7%)	0.185[b]

[a]One-way ANOVA [b]Chi-square [c]Kruskal-Wallis Bold = most extreme group mean/proportion when $p < 0.05$

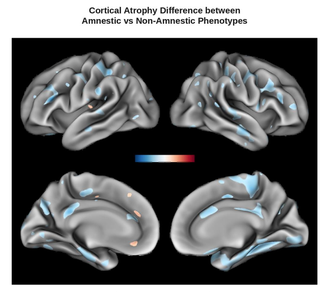
Phenotypes differ on longitudinal trajectories of clinical decline (CDR-SB and MoCA)

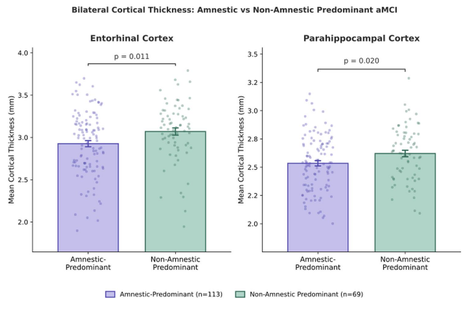


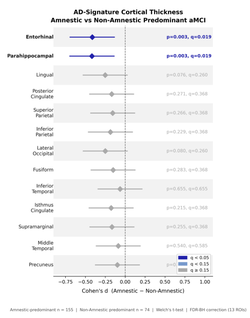
Baseline pure Amnestic or Multidomain phenotypes decline more quickly over time functionally (CDR-SB) and cognitively (MoCA) compared to Non-Amnestic or No-predominant phenotypes

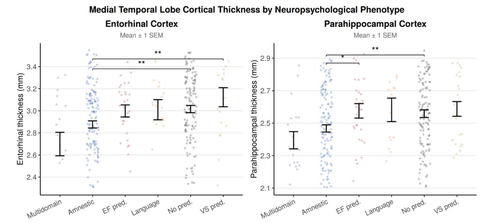
RESULTS

Phenotypes differ on extent of MTL atrophy









The Amnestic-predominant and Multidomain phenotypes have greater medial temporal lobe (MTL) cortical atrophy compared to the Non-Amnestic presentations

CONCLUSIONS

•Six distinct Aβ-positive late-onset aMCI cognitive phenotypes were identified with cognitive rule-based phenotyping.

•**Longitudinal CDR-SB and MoCA trajectories diverge between phenotypes**, such that pure Amnestic and Multidomain baseline phenotypes decline fastest, while the group with no predominant domain of impairment declines slowest.

•**Structural neuroimaging supports the validity of phenotypic classification**, with greater MTL atrophy in Amnestic vs Non-Amnestic Predominant phenotypes (Dysexecutive, Language, Visuospatial).

•These findings support a **phenotype-informed framework for studying and caring for amyloid-positive MCI,** in which the neuropsychological profile, rate of clinical and cognitive decline, and cortical atrophy pattern each provide complementary information about disease expression.

•Future work should examine whether phenotype at the MCI stage predicts downstream conversion to distinct Alzheimer's dementia subtypes (e.g., PCA, lvPPA, Dysexecutive Syndromes). Outcomes should extend beyond the memory-centric CDR-SB and MoCA screening tools.

REFERENCES & ACKNOWLEDGMENTS

1. Crane, P. K., Groot, C., Ossenkoppele, R., Mukherjee, S., Choi, S. E., Lee, M., Scollard, P., Gibbons, L. E., Sanders, R. E., Trittschuh, E., Saykin, A. J., Mez, J., Nakano, C., Donald, C. M., Sohi, H., Alzheimer's Disease Neuroimaging, I., & Risacher, S. (2024). Cognitively defined Alzheimer's dementia subgroups have distinct atrophy patterns. *Alzheimers Dement, 20*, 1739-1752.
2. Crane, P. K., Trittschuh, E., Mukherjee, S., Saykin, A. J., Sanders, R. E., Larson, E. B., McCurry, S. M., McCormick, W., Bowen, J. D., Grabowski, T., Moore, M., Bauman, J., Gross, A. L., Keene, C. D., Bird, T. D., Gibbons, L. E., Mez, J., Executive Prominent Alzheimer's Disease, G., & Risk Factors, I. (2017). Incidence of cognitively defined late-onset Alzheimer's dementia subgroups from a prospective cohort study. *Alzheimers Dement, 13*, 1307-1316.
3. Qiu, Y., Jacobs, D. M., Messer, K., Salmon, D. P., & Feldman, H. H. (2019). Cognitive heterogeneity in probable Alzheimer disease: Clinical and neuropathologic features. *Neurology, 93*, e778-e790.
4. Mendez, M. F. (2019). Early-onset Alzheimer Disease and Its Variants. *Continuum (Minneap Minn), 25*, 34-51.
5. Putcha, D., Katsumi, Y., Touroutoglou, A., Eloyan, A., Taurone, A., Thangarajah, M., Aisen, P., Dage, J. L., Foroud, T., Jack, C. R., Jr., Kramer, J. H., Nudelman, K. N. H., Raman, R., Vemuri, P., Atri, A., Day, G. S., Duara, R., Graff-Radford, N. R., Grant, I. M., Honig, L. S., Johnson, E. C. B., Jones, D. T., Masdeu, J. C., Mendez, M. F., Musiek, E., Onyike, C. U., Riddle, M., Rogalski, E., Salloway, S., Sha, S., Turner, R. S., Wingo, T. S., Wolk, D. A., Womack, K., Carrillo, M. C., Rabinovici, G. D., Dickerson, B. C., Apostolova, L. G., Hammers, D. B., & Consortium, L. (2025). Heterogeneous clinical phenotypes of sporadic early-onset Alzheimer's disease: a neuropsychological data-driven approach. *Alzheimers Res Ther, 17*, 38.

We gratefully acknowledge the participants who make this work possible.
This work was supported by the following grants: NIH K23 AG065450, R21AG051987, R01DC014296, P01AG005134, and P30AG062421. For questions, please contact dputcha@mgh.harvard.edu.