

# Characterizing neuroanatomical, cognitive, and genetic risk heterogeneity signatures in Alzheimer's disease using machine learning

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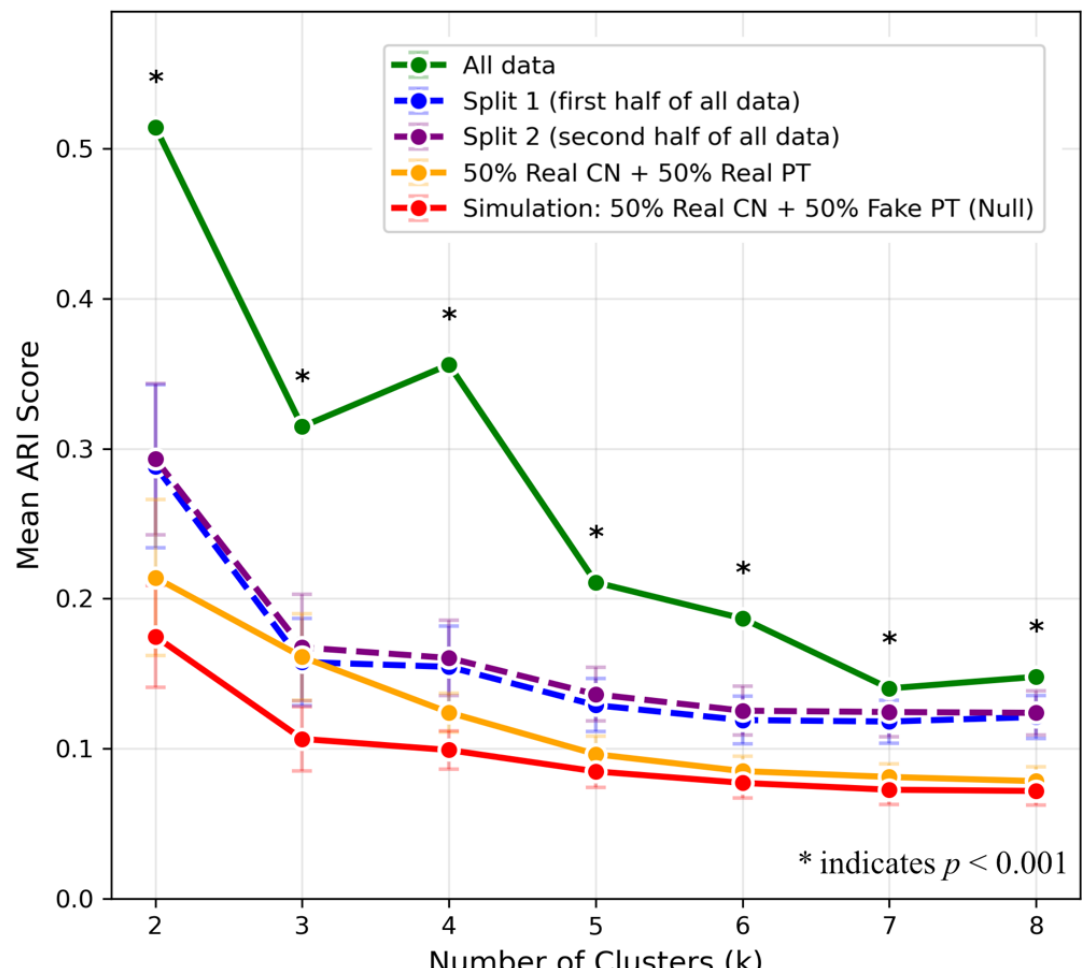
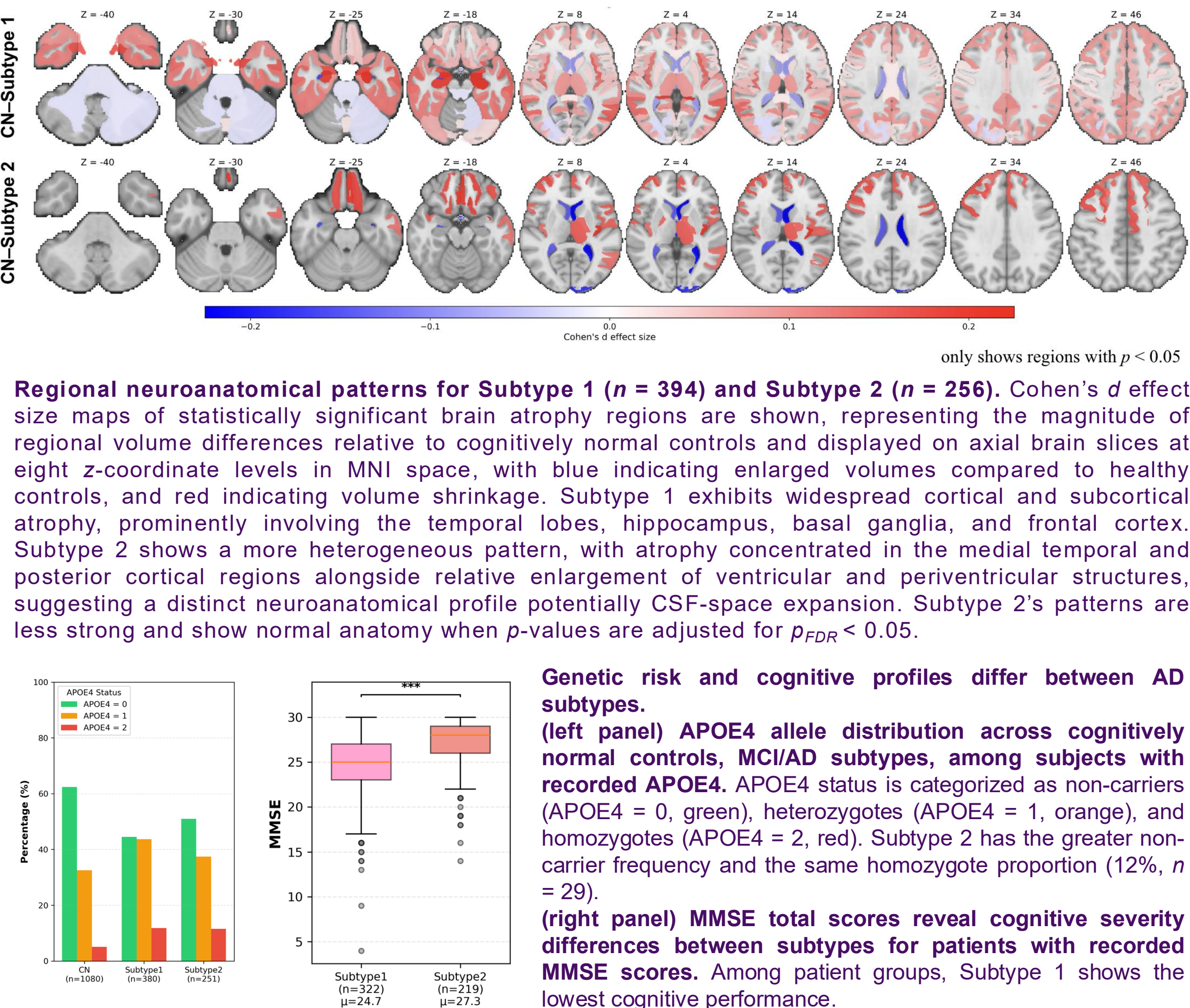
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## Two subtypes of MCI/AD revealed with distinct neuroanatomical, genetic, and cognitive profiles

| BACKGROUND                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | RESULTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | RESULTS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | CONCLUSIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| <p><b>Why This Matters</b></p> <p>Alzheimer's disease (AD) is characterized by substantial clinical and biological heterogeneity, which complicates disease prediction, treatment response, and contributes to accelerated functional decline and diminished quality of life.</p> <p><b>Research Question:</b> To identify neuroanatomical heterogeneity patterns and mapping their relationships with cognition and genetics.</p> <p><b>Methods</b></p> <ul style="list-style-type: none"><li>We analyzed structural MRI data from 1091 Knight ADRC and 668 ADNI participants, including 1108 cognitively normal controls and 650 patients at various stages of early mild cognitive impairment (EMCI, <math>n = 173</math>), late MCI (LMCI, <math>n = 152</math>), and AD dementia (<math>n = 319</math>).</li><li>Semi-supervised machine learning with ten-fold cross-validated 50 repetitions was performed using 145 regional brain volumes. Subtypes were compared on brain volume patterns, APOE4 genotype status, and Mini-Mental State Examination (MMSE) scores.</li></ul> | <p><b>Mean Adjusted Rand Index (ARI) scores with standard deviations from 5 reproducible clustering experiments</b></p>  <p><b>Mean Adjusted Rand Index scores from 50 repeats of 10-fold cross-validation clustering for <math>k = 2</math> to <math>k = 8</math> across multiple reproducible experiments.</b> Error bars represent standard deviation. The two-cluster solution (<math>k = 2</math>) achieved the highest clustering stability (mean ARI = 0.51, green line) across all experimental conditions, full data, half-split validation, and balanced case-control ratios, significantly outperforming the null hypothesis of random clustering, confirming robust and reproducible patient stratification. ARI scores systematically decrease with increasing cluster numbers, suggesting that a two-subtype model provides the most reliable clustering. Different colored lines represent distinct datasets or experimental conditions: green (all samples), dashed (splits 1 and 2), orange (half CNs and half PTs), red (null hypothesis). ARI values range from -1 (random labeling) to 1 (perfect agreement).</p> | <p><b>Regional neuroanatomical patterns for Subtype 1 (<math>n = 394</math>) and Subtype 2 (<math>n = 256</math>).</b> Cohen's <math>d</math> effect size maps of statistically significant brain atrophy regions are shown, representing the magnitude of regional volume differences relative to cognitively normal controls and displayed on axial brain slices at eight z-coordinate levels in MNI space, with blue indicating enlarged volumes compared to healthy controls, and red indicating volume shrinkage. Subtype 1 exhibits widespread cortical and subcortical atrophy, prominently involving the temporal lobes, hippocampus, basal ganglia, and frontal cortex. Subtype 2 shows a more heterogeneous pattern, with atrophy concentrated in the medial temporal and posterior cortical regions alongside relative enlargement of ventricular and periventricular structures, suggesting a distinct neuroanatomical profile potentially CSF-space expansion. Subtype 2's patterns are less strong and show normal anatomy when <math>p</math>-values are adjusted for <math>p_{FDR} &lt; 0.05</math>.</p>  <p><b>Genetic risk and cognitive profiles differ between AD subtypes.</b> (left panel) APOE4 allele distribution across cognitively normal controls, MCI/AD subtypes, among subjects with recorded APOE4. APOE4 status is categorized as non-carriers (APOE4 = 0, green), heterozygotes (APOE4 = 1, orange), and homozygotes (APOE4 = 2, red). Subtype 2 has the greater non-carrier frequency and the same homozygote proportion (12%, <math>n = 29</math>). (right panel) MMSE total scores reveal cognitive severity differences between subtypes for patients with recorded MMSE scores. Among patient groups, Subtype 1 shows the lowest cognitive performance.</p> | <p>Two reproducible MCI/AD subtypes with distinct neuroanatomical, genetic, and cognitive profiles.</p> <ul style="list-style-type: none"><li>Subtype 1 exhibits classical AD pathology with widespread limbic, temporal, and frontal atrophy, elevated APOE4 burden, and severe cognitive impairment.</li><li>Subtype 2 demonstrates remarkable brain volume resilience, lower APOE4 frequency, milder cognition decline, yet higher PRS. These findings reveal heterogeneous pathological mechanisms underlying AD and highlight the need for multimodal biomarker characterization to elucidate distinct disease pathways.</li></ul> |
| <p><b>CONTACT</b></p> <p>For any questions regarding this poster, please contact Nam Hoang Le at <a href="mailto:le.h@wustl.edu">le.h@wustl.edu</a>.</p> <p>Funding agency: The authors thank National Institutes of Health (NIH) K01AG083230 for their support in this research.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p> <b>ALZHEIMER'S ASSOCIATION</b>   </p>                                                                                                                                                                                                                                                                                                                                                                                                                     |