



Distinct spatial metabolic patterns with limbic predominance differentiate LATE from Alzheimer's disease



Dahyun Yi, PhD¹, Min Soo Byun^{2,3}, Hyejin Ahn⁴, Gijung Jung³, Jun Sung Kim³, Yoon Suk Oh³, Woo Jin Cha³, Yura Choi³, Jun-Young Lee^{2,5}, Koung Mi Kang³, Chul-Ho Sohn³, Yun-Sang Lee³, Yu Kyeong Kim⁵, Bo Kyung Sohn⁶, and Dong Young Lee^{1,2,3,4,†} for the KBASE Research Group

¹Institute of Human Behavioral Medicine, Medical Research Center, Seoul National University, Seoul, Korea, Republic of (South), ²Seoul National University College of Medicine, Seoul, Korea, Republic of (South), ³Seoul National University Hospital, Seoul, Korea, Republic of (South), ⁴Interdisciplinary Program of Cognitive Science, Seoul National University College of Humanities, Seoul, Korea, Republic of (South), ⁵Department of Neuropsychiatry, SMG-SNU Boramae Medical Center, Seoul, Korea, Republic of (South), ⁶Department of Psychiatry, Sanggye Paik Hospital, College of Medicine, Inje University, Seoul, Korea, Republic of (South)

Background

Limbic-predominant age-related TDP-43 encephalopathy (LATE) frequently co-occurs with Alzheimer's disease (AD), yet in vivo markers that distinguish LATE-related neurodegeneration from amyloid-driven AD remain limited. Although neuropathology suggests preferential limbic involvement in LATE, it is unclear whether distinct spatial metabolic patterns beyond classification metrics are detectable in vivo, particularly in mixed pathology. We examined whether LATE is associated with an independent, limbic-predominant cerebral glucose metabolism (CM) signature that differentiates from AD.

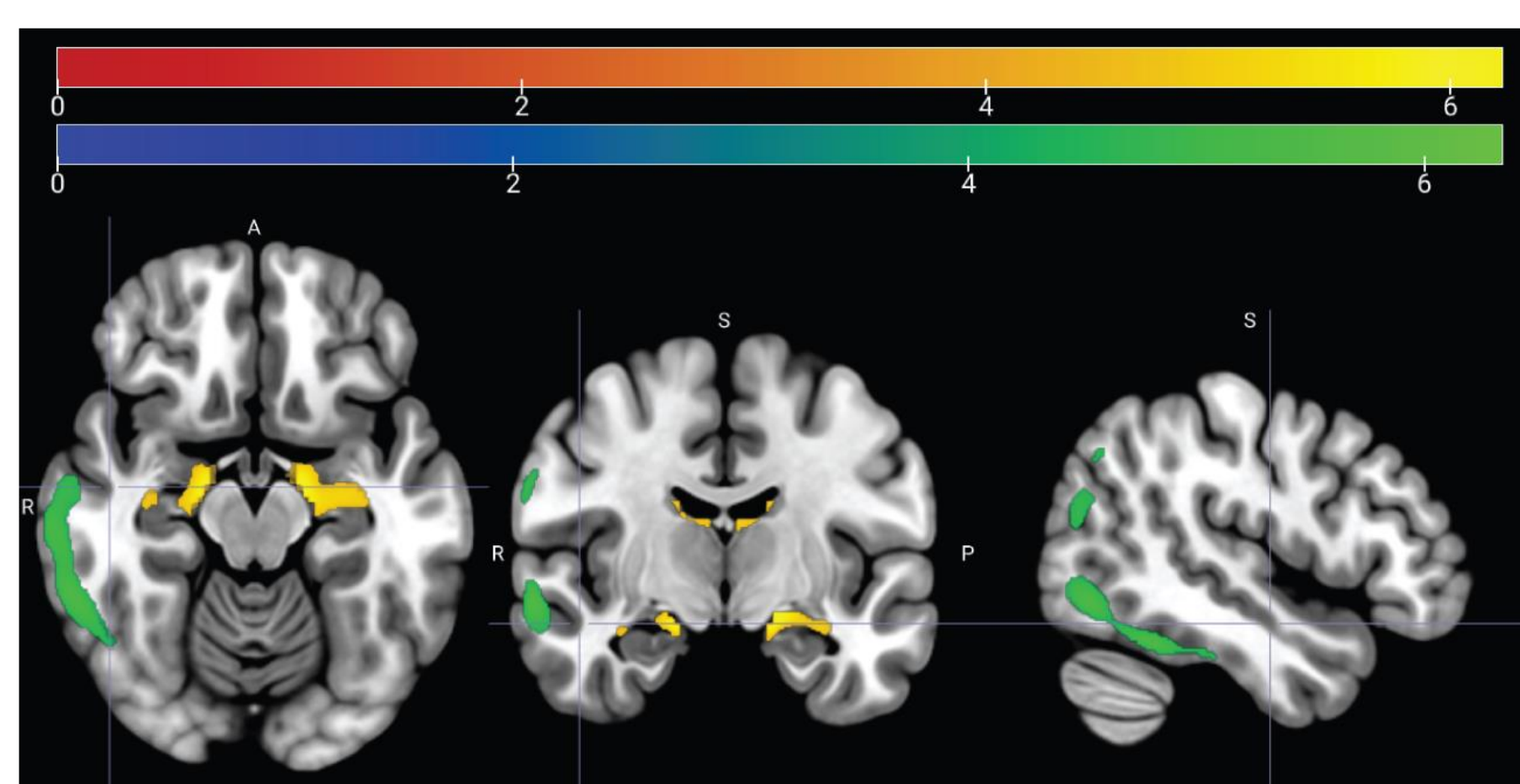
Methods

- We analyzed FDG-PET and amyloid-PET data from 520 participants (cognitively normal [CN], MCI, and AD dementia) in the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE).
- Among individuals with an amnesic presentation, LATE positivity was defined by severe hippocampal atrophy and/or an abnormal inferior temporal-to-medial temporal (IT/MT) CM ratio in the absence of amyloid positivity.
- The IT/MT cutoff was derived from an age-adjusted normative distribution using young and old CN participants as the reference.
- Participants were classified into four groups: CN, LATE-only, AD-only (amyloid-positive without LATE features), and mixed LATE & AD.
- Voxel-wise FDG-PET analyses were performed in SPM12 to characterize group differences in spatial CM patterns. FDG SUVRs were extracted from the regions identified voxel-wise, and group differences were evaluated using ANCOVA controlling for age and sex.



Results

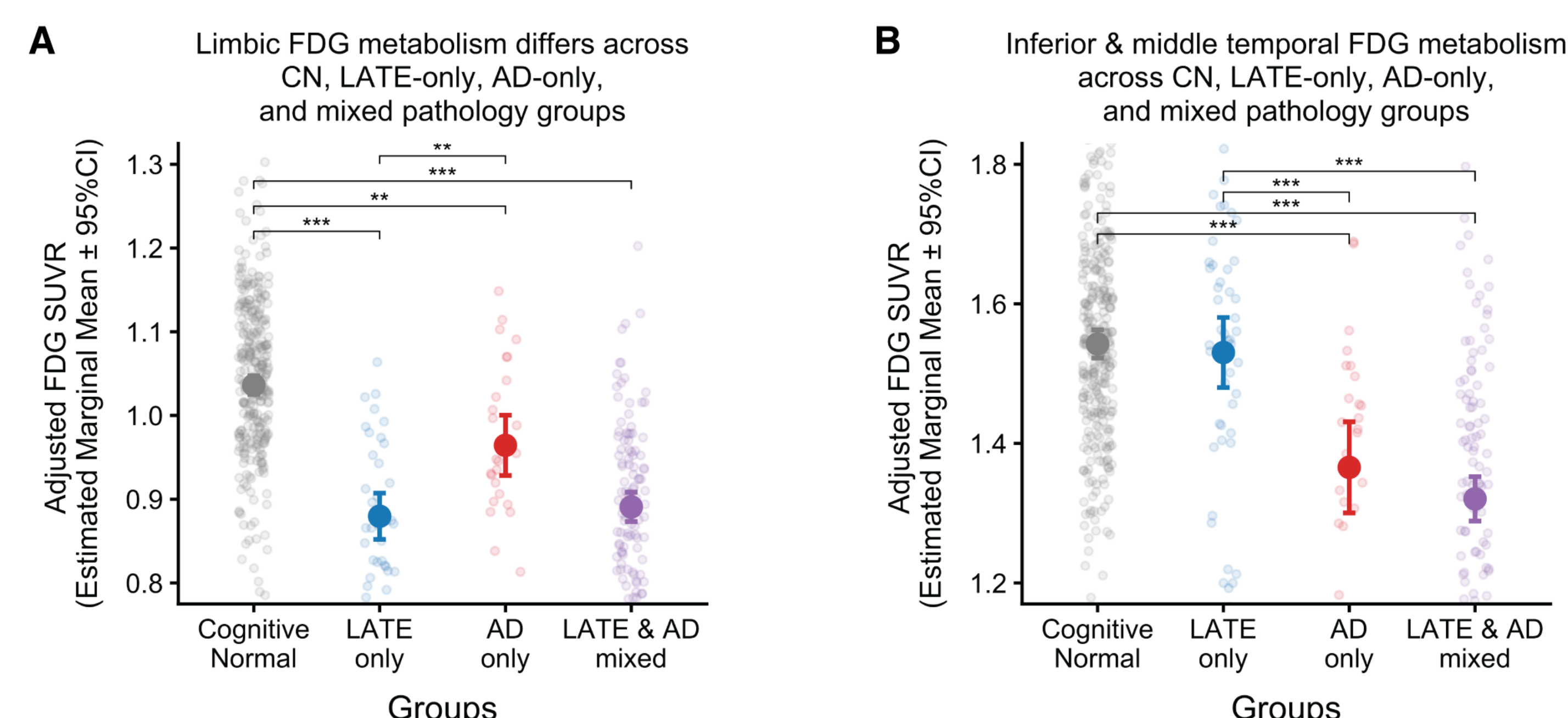
Figure 1. Voxelwise FDG-PET contrasts between LATE-only and AD-only.



Note. Statistical parametric maps show regions of lower FDG metabolism in LATE-only compared with AD-only (yellow), localizing primarily to medial temporal and medial frontal regions, and regions of higher FDG metabolism in LATE-only relative to AD-only (green), involving inferior and middle temporal cortex. Maps are displayed on the MNI152 template and thresholded at FWE-corrected $p < 0.05$.

Voxel-wise analyses comparing LATE-only and AD-only revealed distinct metabolic patterns. Lower CM in LATE-only was found in medial frontal/cingulate cortex as well as medial temporal and limbic regions, including the amygdala, hippocampus, para-hippocampal gyrus, whereas higher CM in LATE-only was observed in inferior and middle temporal neocortex extending into posterior association areas (Figure 1).

Figure 2. ROI-based FDG metabolism across diagnostic and pathological groups.



Note. Points represent estimated marginal means of FDG standardized uptake value ratios (SUVRs) extracted from regions identified in voxelwise analyses (Figure 1), with error bars denoting 95% confidence intervals. Group differences were assessed using ANCOVA controlling for age and sex. Compared with cognitively normal individuals, the LATE-only group showed pronounced limbic hypometabolism, exceeding that observed in AD-only, while the mixed pathology group demonstrated a metabolic profile similar to LATE-only. In contrast, FDG metabolism in temporal regions identified as relatively preserved in LATE-only did not exceed cognitively normal levels, indicating relative preservation.

Statistical significance is indicated as $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***)

ROI analyses showed that, in limbic regions, LATE-only showed significantly lower adjusted CM than AD-only and cognitively normal individuals, with mixed LATE & AD resembling LATE-only (Figure 2A). In temporal regions, CM in LATE-only did not differ from cognitively normal, while AD-only and mixed groups showed significantly lower CM (Figure 2B), indicating relative temporal preservation in LATE-only.

Conclusion

- LATE is characterized by disproportionate limbic metabolic vulnerability with relative preservation of lateral temporal metabolism, defining a spatial neurodegenerative signature that is distinct from amyloid-driven AD and shapes regional metabolic patterns in mixed pathology.

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