Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference

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The heterogeneity of neurodegenerative diseases is a key confound to disease understanding and treatment development, as study cohorts typically include multiple phenotypes on distinct disease trajectories. Here we introduce a machine-learning technique—Subtype and Stage Inference (SuStaIn)—able to uncover data-driven disease phenotypes with distinct temporal progression patterns, from widely available cross-sectional patient studies. Results from imaging studies in two neurodegenerative diseases reveal subgroups and their distinct trajectories of regional neurodegeneration. In genetic frontotemporal dementia, SuStaIn identifies genotypes from imaging alone, validating its ability to identify subtypes; further the technique reveals within-genotype heterogeneity. In Alzheimer's disease, SuStaIn uncovers three subtypes, uniquely characterising their temporal complexity. SuStaIn provides fine-grained patient stratification, which substantially enhances the ability to predict conversion between diagnostic categories over standard models that ignore subtype ($p = 7.18 \times 10^{-4}$) or temporal stage ($p = 3.96 \times 10^{-5}$). SuStaIn offers new promise for enabling disease subtype discovery and precision medicine.

Author contributions

A.L.Y., D.C.A., J.D.R. and J.M.S. conceived and designed the experiments and wrote the manuscript. A.L.Y. implemented the programming code and analysed the data. N.P.O. and R.V.M. provided feedback on the experiment design. R.V.M. made the brain images in Figs. 1–4, 6 and Supplementary Figures 13–14. M.B. derived the asymmetry measure for GENFI participants. K.Y. advised on sub-scores of the ADAS related to praxic, spatial and memory domains. Members of the ADNI and GENFI consortia recruited patients and collected and pre-processed data. All authors contributed to reviewing and editing of the report.

Additional information

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