

Cognitive Phenotypes and Their Clinical Correlates in Individuals with Late Onset Unexplained Epilepsy

P4-0804

Rani A. Sarkis^{1,2}, Alessandro Guazzo^{1,2}, Emily L Johnson³, Leah J Blank⁴, Tyler E Gaston⁵, Mouhsin M Shafi^{6,2} , Rodrigo Zepeda⁷, Kyle R Pellerin^{1,2}, Alexis Hankerson^{1,2}, Rebecca E Amariglio^{1,2}, Gad A Marshall^{1,2} ,M Brandon Westover^{6,2}, Alice D Lam^{1,2}

¹Department of Neurology, Mass General Brigham, Massachusetts, USA. ²Harvard Medical School, Boston, Massachusetts, USA. ³Department of Neurology, Johns Hopkins Medicine, Baltimore, Maryland, USA. ⁴Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ⁵Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama, USA. ⁶Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA. ⁷Department of Neurology, University of Texas Southwestern, Dallas, Texas, USA.

Background

Late-onset unexplained epilepsy (LoUE), defined as epilepsy onset after age 55 without an identifiable cause, has been identified as a risk factor for accelerated cognitive decline and has been linked with Alzheimer’s disease and related dementias (ADRD). Cognitive impairment is frequently observed in LoUE, yet its nature and heterogeneity remain poorly characterized

Methods

Participants were recruited from the **ELUCID Study** (Epilepsy of Late-onset Unknown etiology as a risk factor for Cognitive Impairment and Dementia), a multicenter, prospective longitudinal observational study of LoUE, focused on understanding mechanisms and predicting outcomes of dementia in LoUE, and from the **Brigham and Women’s LoUE study**.

Inclusion criteria: new onset seizures age ≥55, onset within last 3 years, absence of cortical lesions on MRI, absence of provoking factors, and absence of diagnosis of dementia.

Participants underwent a neuropsychological battery assessing Executive Function (EF), Processing Speed (PS), Language(L), Memory(M), and Global Cognition (G).

Raw neuropsychological scores were standardized using reference values from the Harvard Aging Brain Study. Gaussian Mixture Modeling (GMM) was applied to derive data-driven cognitive phenotypes.

To identify clinical factors associated with cognitive function, we conducted univariate regression analyses examining relationships between cognition and ~50 clinical variables spanning demographics, epilepsy characteristics, medical comorbidities, and adjusting for age, sex, and education.

Funding

The ELUCID study is funded by NIH / NIA R01 NS130119 BWH-LoUE was funded by the American Epilepsy Society Junior Investigator Grant and NIH K23NS119798 (RAS)

Results

Within the LoUE cohort of 191 participants (41% female, average age 69 ± 7 years), 6 cognitive phenotypes were identified (Figure 1).

Epilepsy relevant factors associated with worse cognition included (Figure 2): Longer duration (PS,L), Left hemispheric epilepsy lateralization (L). Presence of epileptiform abnormalities on clinical EEG (L), Higher lifetime frequency of Focal seizures with impaired awareness (L, G), and use of ≥ 2 antiseizure medications (M, G).

Vascular and lifestyle factors associated with worse cognition included: Smoking history (PS,M,G) and cumulative smoking pack-years (L, G), history of diabetes (EF), elevated serum creatinine (G). We did not find significant associations of BMI, hypertension, hypercholesterolemia, obstructive sleep apnea, alcohol use disorder, or healthy lifestyle score.

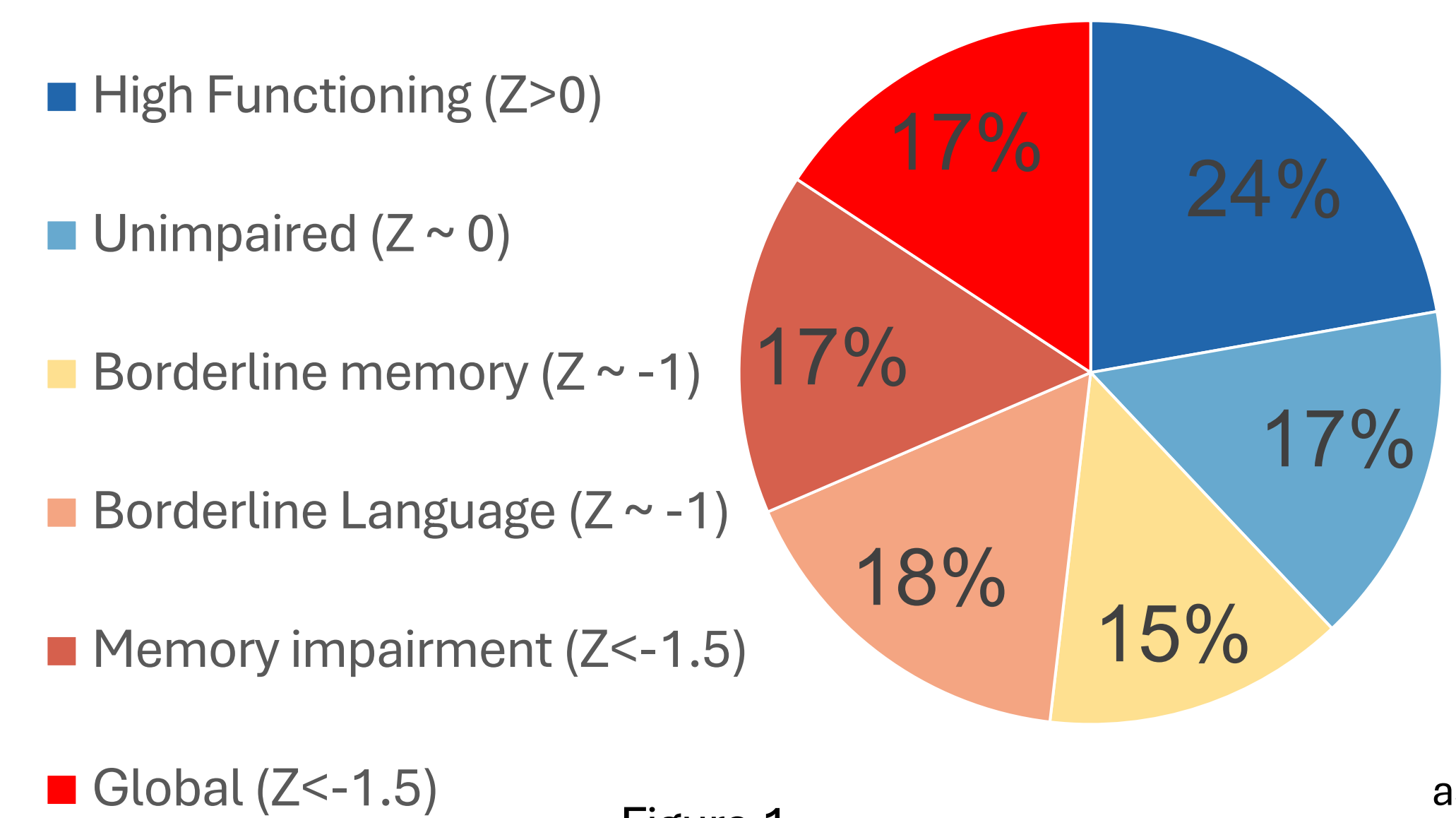


Figure 1.
Pie chart showing
Cognitive phenotypes in LoUE

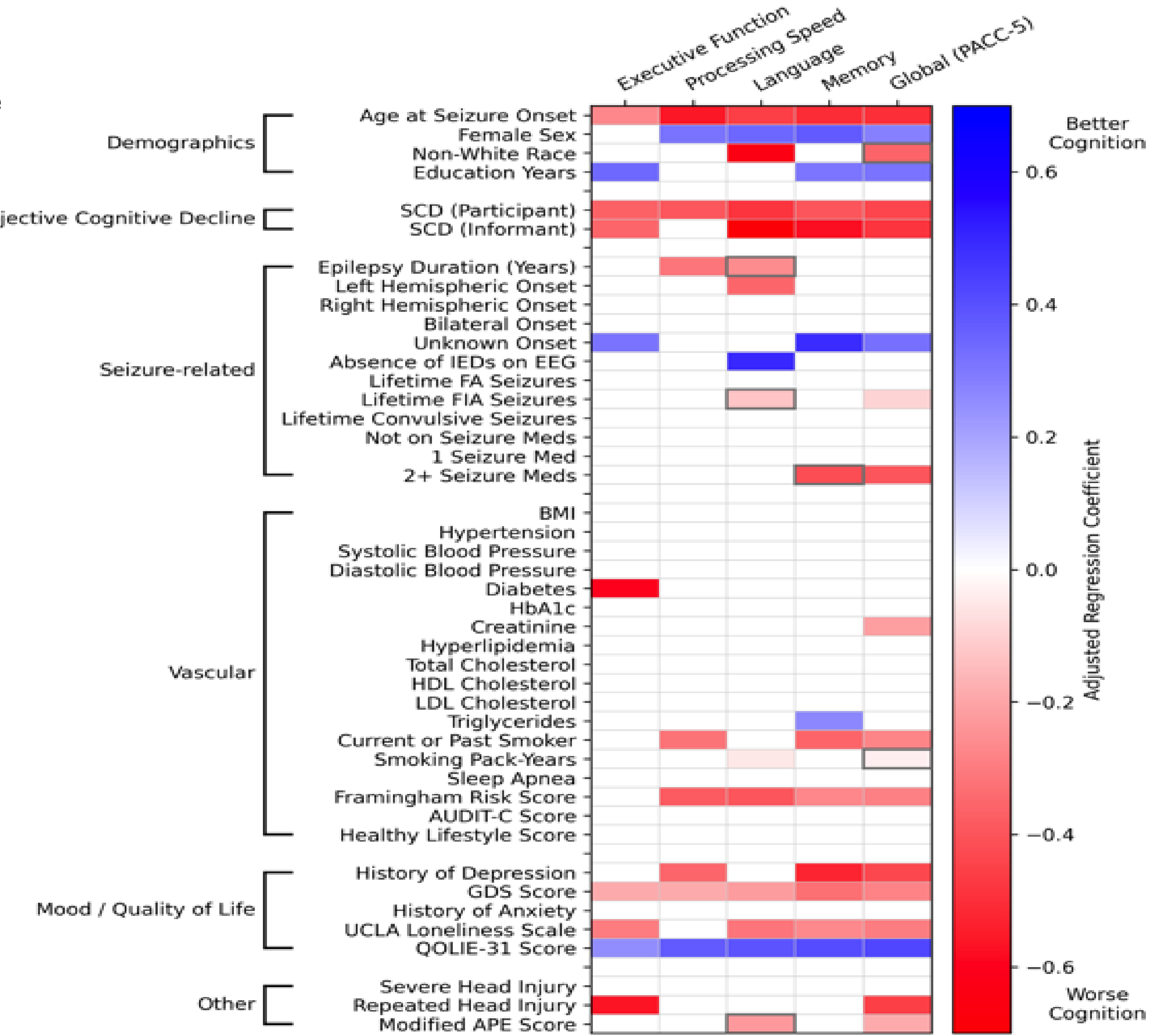


Figure 2. Covariate-adjusted regression results across cognitive outcomes. Each cell displays the covariate-adjusted regression coefficient for a given predictor-outcome pair, adjusted for age, sex, education. Only coefficients surviving FDR correction ($\alpha = 0.10$) are shown; non-significant associations are displayed in white. Cells with p-values between 0.10 and 0.12 are displayed as trends toward significance and are outlined in grey. Positive coefficients, indicating association with better cognitive performance, are shown in increasing shades of blue; negative coefficients, indicating association with worse cognitive performance, are shown in increasing shades of red. Rows represent clinical predictors grouped by category; columns represent the five domain-level cognitive z-scores.

Conclusions

- In this prospective study of individuals with LoUE, within a few years of disease onset we identify cognitive impairments in 59%.
- Observed associations with clinical features suggest that these factors may both contextualize cognitive risk in this population and, where modifiable, represent actionable targets.