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UC San Diego School of Medicine
Shiley-Marcos Alzheimer's Disease Research Center

Exploring Novel Functional Data Analysis and Machine Learning for Eye-Tracking in AD

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Oct 15th, 2024

Background and Significance

Alzheimer's disease (AD) is a significant public health concern and highly financially burdensome disease in the United States

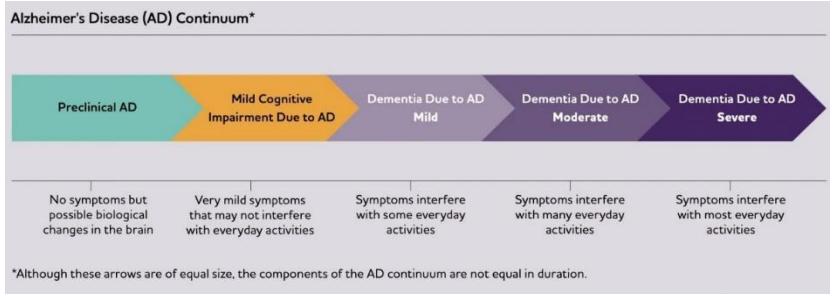

Figure: Alzheimer's Disease Continuum (Alzheimer's Association Report (2023))

- AD begins its pathological changes decades prior to the clinical onset of dementia (Golde, Schneider, and Koo (2011), Sperling et al. (2011))
  - Importance of early detection for managing disease progression
  - Interventions might be most effective at early stages
- Urgent need for low-cost method for detecting and staging AD from preclinical to symptomatic stages
  - Identify pathways for early interventions to slow the progression of the disease
  - Effective intervention and preparation for long-term care

Currently Available Biomarkers for AD

- Cerebrospinal fluid (CSF), plasma, imaging, genetics
  - e.g. amyloid beta (Aβ), tau, plasma ptau181, etc.
- Biomarkers crucial for AD detection often fail to correlate with cognitive functioning levels in preclinical AD
  - Diagnostic vs. prognostic
- Lacks prognostic clarity on the timeline of cognitive and clinical decline
- Expensive and/or invasive
- Need: Inexpensive and effective markers for early-stage AD

Novel Neurocognitive Binding Tasks for Early-Stage AD

- In AD, early synaptic dysfunction disrupts neural networks
- Particularly affecting tasks that require conjunctive binding – the integration of various sensory inputs into a coherent representation
- Eye-tracking (ET) in binding tasks emerging as economical and noninvasive tools
- Eye gaze and pupillary response measurements have been shown to be highly predictive of AD progression (Nakashima et al. (2010), Polden, Wilcockson, and Crawford (2020), Wolf and Ueda (2021), Hannonen et al. (2022), Seligman and Giovannetti (2015), Crawford et al. (2005), Kaufman et al. (2012), Chougule et al. (2019), Tokushige et al. (2023))

Visual Short Term Memory Binding Tasks at UCSD

- Visual Sensory Binding (VSB) and Visual Short-Term Memory Binding (VSTMB) at UCSD (NIH R01AG064002, PI: Diane Jacobs)
  - VSTMB: participants are presented study stimuli and recall stimuli
  - Answer whether items in the recall display are the same or different from those presented at study display
  - Two conditions: shape-only and shape-color
  - Each with 32 trials

Visual Short Term Memory Binding Tasks at UCSD

- High-frequency eye tracking by Tobii Pro Fusion eye tracker
- Multiple ET modalities time series
  - Pupil sizes
  - Eye gaze (coordinates of the targets and eye gaze)

SCREEN BASED

Tobii Pro Fusion

Screen-based eye tracker, capturing gaze data at speeds up to 250 Hz. This powerful research system supports from fixation to saccade-based research outside of the lab.

Figure: https://www.tobii.com/products/eye-trackers

Visual Short Term Memory Binding Tasks at UCSD

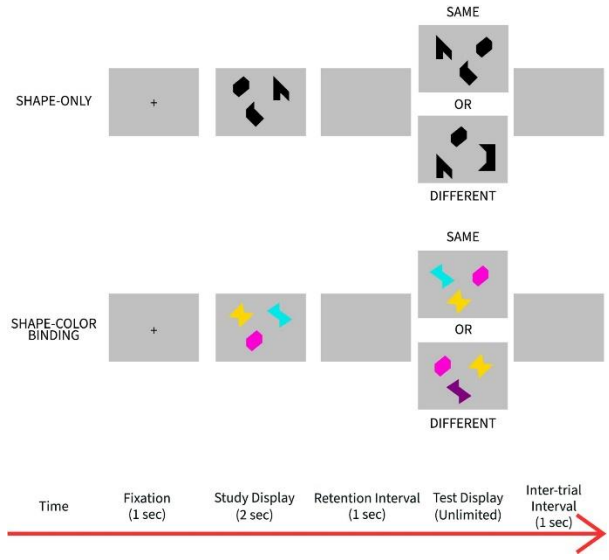

Figure: Timeline of VSTMB tasks

Overall Goal of Statistical Analysis

- Current analyses of ET data often rely on simplified, single-dimensional summary metrics
  - e.g. mean fixation duration and saccade amplitude
- Leveraging the multi-modal ET and behavioral markers and functional data analysis approaches
- e.g. multi-level functional principal component analysis (MFPCA)

Overall Goal of Statistical Analysis

- Evaluate ET as distinctive markers for differentiating groups:
  - Cognitively unimpaired vs. mild cognitive impairment (MCI)
  - Cognitively unimpaired biomarker (pTau) negative (CN-), cognitively unimpaired biomarker positive (CN+), and MCI
- Understand variability in ET markers and behavioral data using interpretable features
- Track longitudinal changes in ET and behavioral markers
- Advance understanding of the disease
  - Modes of cognitive decline
  - Rate of cognitive decline

Patterns of the Performances in Tasks by Group

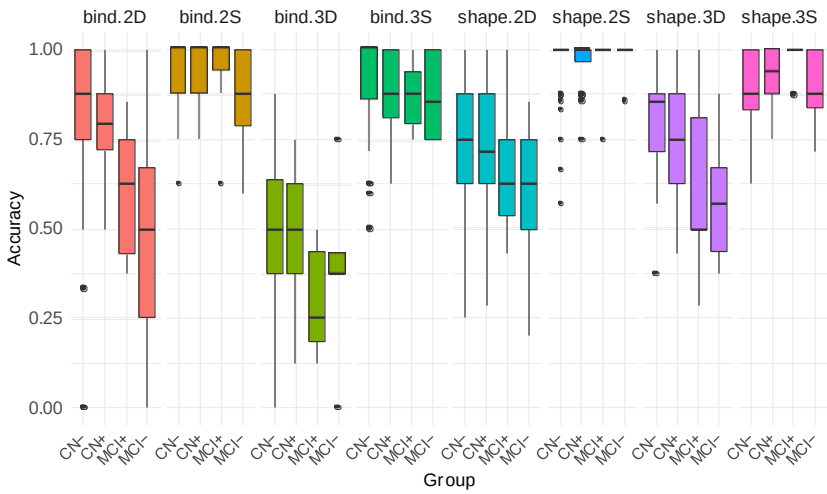

Figure: Task performances by task type and group (cognitive function × ptau181)

Pupillary Patterns Extracted by MFPCA

$$X_{ij}(t) = \mu(t) + \eta_j(t) + Z_i(t) + W_{ij}(t)$$

- $X_{ij}(t)$: baseline-adjusted pupil size at time t for i th subject and jth trial
- $\mu(t)$: overall mean pupil size curve
- $\eta_j(t)$: trial-specific shift from mean (can be set to zero)
- $Z_i(t)$: subject-specific deviation from mean function
- $W_{ij}(t)$: residual subject- and visit-specific deviation from the subject-specific mean

Pupillary Patterns Extracted by MFPCA

- Decompose the variability in pupil size using multi-level functional principal component analysis (MFPCA)

$$X_{ij}(t) = \mu(t) + \eta_j(t) + \sum_{k=1}^{\infty} \xi_{ik}\,\varphi_k^{(1)} + \sum_{l=1}^{\infty} \zeta_{ijl}\,\varphi_l^{(2)}$$

  - $X_{ij}(t)$: baseline-adjusted pupil size as function of time t for subject i and trial j
  - $\mu(t)$: overall mean pupil size as function of time t
  - $\eta_j(t)$: trial-specific shift from mean
- $\varphi_k^{(1)}$: level 1 PCs
- $\varphi_k^{(2)}$: level 2 PCs
  - ξ_{ik}, ζ_{jil}: PC scores

Pupillary Patterns Extracted by MFPCA

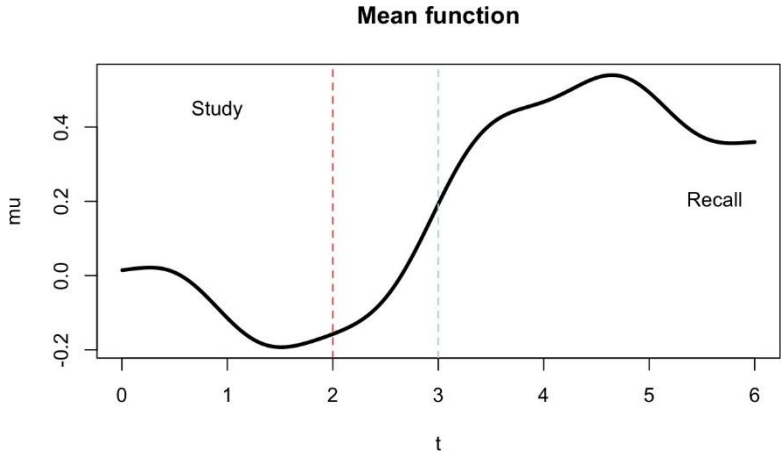

Figure: Overall mean pupil size curve of binding task

Pupillary Patterns Extracted by MFPCA

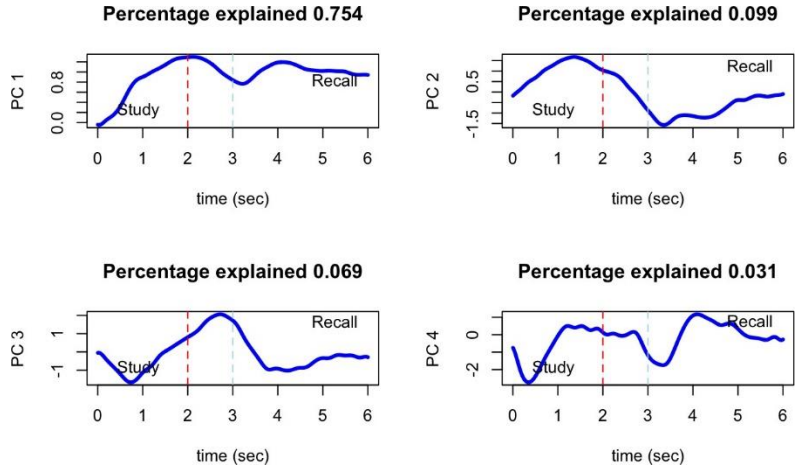

Figure: Top subject-level functional PCs of binding task

Pupillary Patterns Extracted by MFPCA

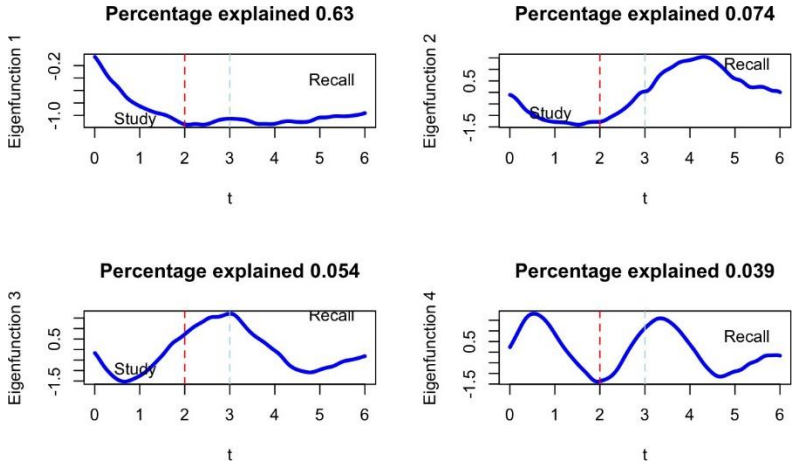

Figure: Top trial-level functional PCs of binding task

Regression of Task Accuracy on Groups, ET and Covariates

	Estimate	**Std. Error**	**z value**	**p value**
(Intercept)	7.18	0.87	8.22	<0.001
Set Size	-1.25	0.11	-11.43	<0.001
Answer S	2.07	0.12	17.05	<0.001
SEX	-0.13	0.13	-1.05	0.29
AGE	-0.04	0.01	-3.95	<0.001
Normal ptau+	-0.11	0.15	-0.72	0.47
MCI ptau+	-0.66	0.21	-3.1	0.0019
MCI ptau-	-0.65	0.2	-3.17	0.0015
Level1 PC1	-0.08	0.16	-0.46	0.64
Level1 PC2	-0.88	0.47	-1.85	0.06
Level2 PC1	-0.2	0.09	-2.16	0.03
Level2 PC2	0.91	0.27	3.33	<0.001

Future Directions

- Comprehensive stratified analysis
- Develop methods for integrating eye gaze and pupillary data
- Characterize modes and rates of cognitive decline in different groups using ET features
- ML methods with improved interpretability for complex functional data

Potential Applications in Clinical Trials

- Incorporate discoveries into clinical trials
- Potential regular testing for patients and on-going tracking in trials
- Monitor longitudinal changes and cognitive decline mode/rate
- Monitoring in the cognitive normal/biomarker negative/placebo group in trials
- Facilitate development of behavioral interventions

Acknowledgments

- Collaborators: Diane Jacobs, David Salmon, Karen Messer, Yuchen Qi, Elena K. Festa, William C. Heindel, Camille A. Marangi, Douglas R. Galasko, Bhrugu Bharathi, Briteny Escobedo
- Grant awards: NIH R01AG064002 (PI: Diane Jacobs)

Thank you!

- Please feel free to contact me at j2zou@ucsd.edu

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