

# **Cognitive Trajectories in DIAN: Relationships with Symptom Onset, Mutation Types, and Clinical Status**

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# Disclosures

No relevant disclosures

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## Consultant

- GLG Council
- Biogen

## Clinical Trials

- Cognition Core  
Director, DIAN-TU

# DIAN Aims: Cognition

- How is cognition different between Non-Carriers and Mutation Carriers?
  - Similar pattern to late-onset AD?
- Differences between CDR 0 Mutation Carriers and Non-Carriers?
- What is the influence of estimated years to symptom onset (EYO)?
- Differences between mutation types (PS1,PS2,APP)

# Current DIAN Cognitive Battery

## Episodic Memory

DIAN Word List Test

WMS-R Logical Memory

Pair Binding

## Attentional Control

Semantic Categorization

Simon Flanker Task

Consonant-Vowel,  
Odd-Even Switching Task

## Working Memory

Computation Span

Reading Span

WMS-R Digit Span

## Processing Speed

WAIS-R Digit Symbol

Trailmaking Test Part A

Trailmaking Test Part B

## Semantic Memory

Boston Naming Test

Category Fluency

Word Fluency

## DIAN-TU Composite

MMSE

DIAN Word List Test

WMS-R Logical Memory

WAIS-R Digit Symbol

# DIAN Participants at Baseline: Data Freeze 10

	Non-Mutation Carriers CDR = 0 (n = 174)	Mutation Carriers CDR = 0 (n = 157)	Mutation Carriers CDR = 0.5 (n = 64)	Mutation Carriers CDR >= 1 (n = 37)
Age (years)	38.9 (11.2)	34.8 (9.3)	43.7 (9.9)	49.0 (9.3)
Est. Years till Onset	-9.3 (11.6)	-12.9 (9.0)	-1.9 (6.9)	5.1 (4.3)
Sex (% Female)	59%	58%	56%	49%
APOE4 carriers (%)	27%	27%	31%	35%
PS1   PS2   APP (%)	65%   10%   25%	70%   12%   18%	80%   3%   17%	86%   0%   14%
Education (years)	14.6 (2.9)	14.6 (2.9)	13.6 (3.2)	13.0 (2.8)
MMSE	29.1 (1.2)	29.0 (1.2)	26.2 (3.1)	15.7 (7.2)

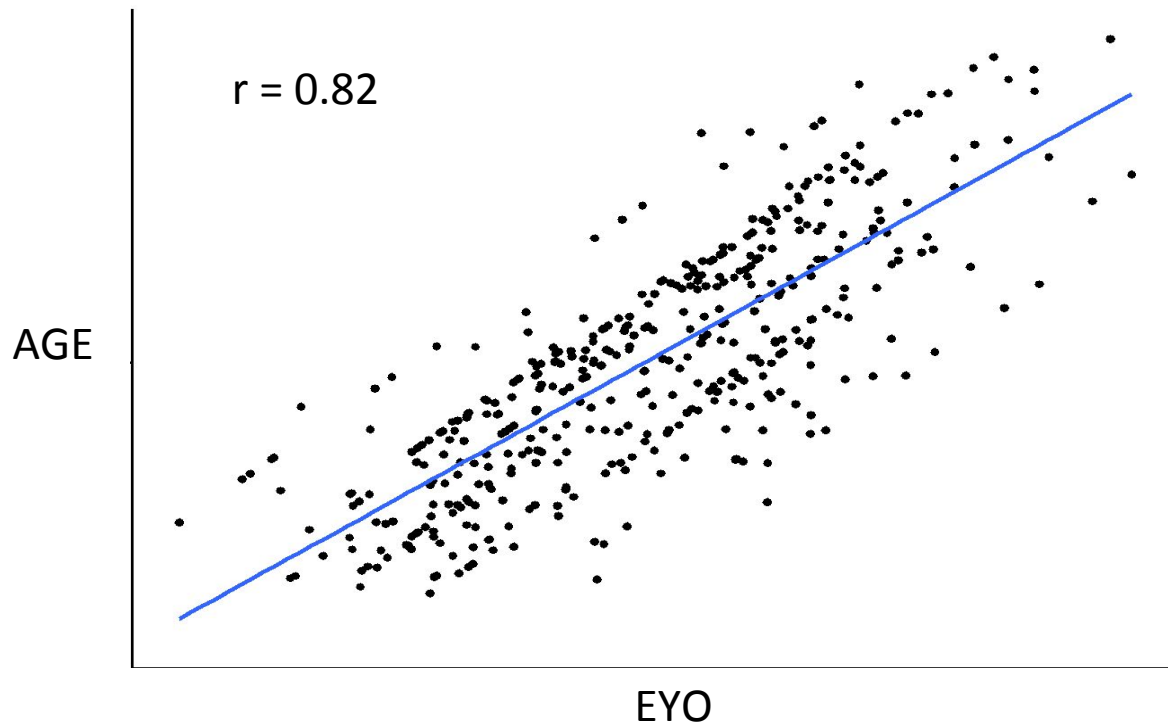
# DIAN Longitudinal Cognitive Data: Data Freeze 10

	Non-Mutation carriers CDR = 0	Mutation Carriers CDR = 0	Mutation Carriers CDR = 0.5	Mutation Carriers CDR >= 1	Totals
Completed One	174	157	64	37	432
Completed Two	83	84	46	22	235
Completed Three	20	19	30	7	76
Completed Four+	10	7	15	3	35

# Statistical Models

- Linear Mixed Effects Regression
  - Fixed Effects:
    - Estimated Years to Symptom Onset (EYO), Gender, Education
    - Group: Non-Carrier (CDR 0), Asymptomatic Mutation Carriers (CDR 0), Symptomatic Mutation Carriers (CDR >0)
    - Group\*EYO interaction
  - Random Terms:
    - Family membership, EYO, participant
  - $p$  values calculated with Satterthwaite approximations
  - Effect size: “Cohen’s D”
    - Baseline sample size used to estimate pooled variance

# Age vs EYO

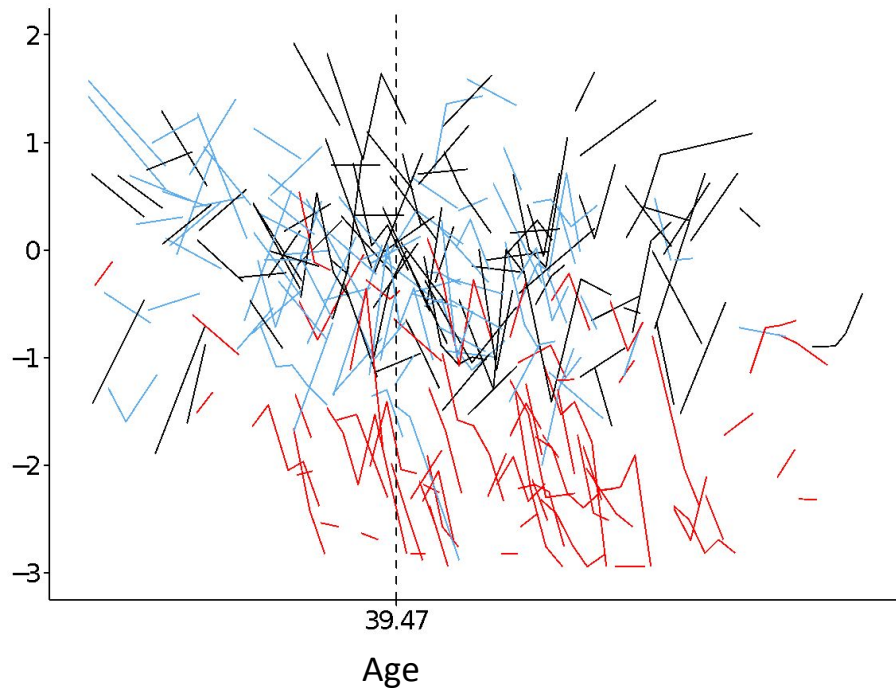




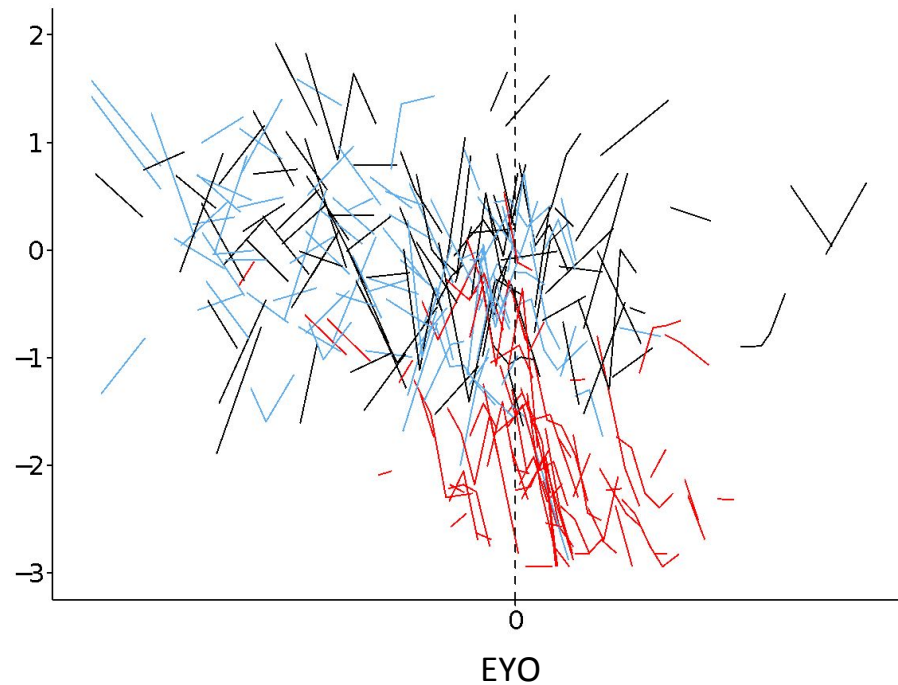
# Age vs EYO

— Non-Carriers — CDR 0 Carriers — CDR >0 Carriers

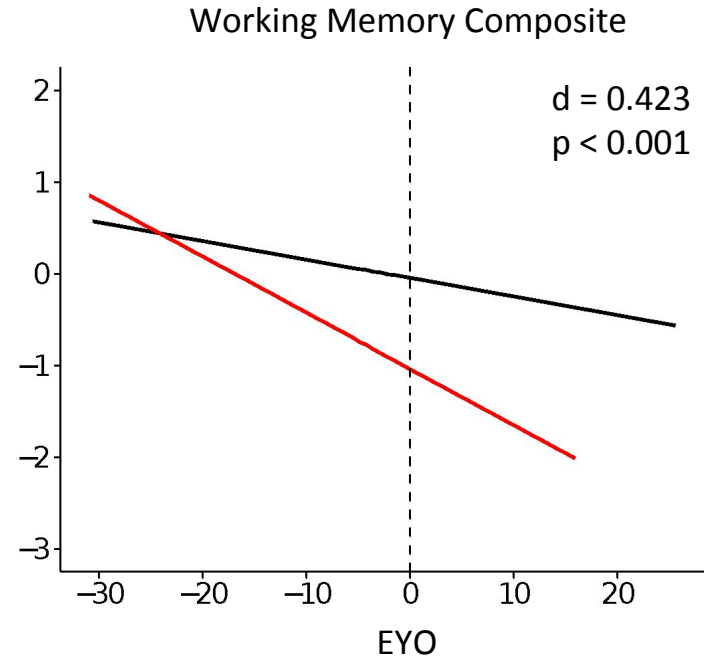
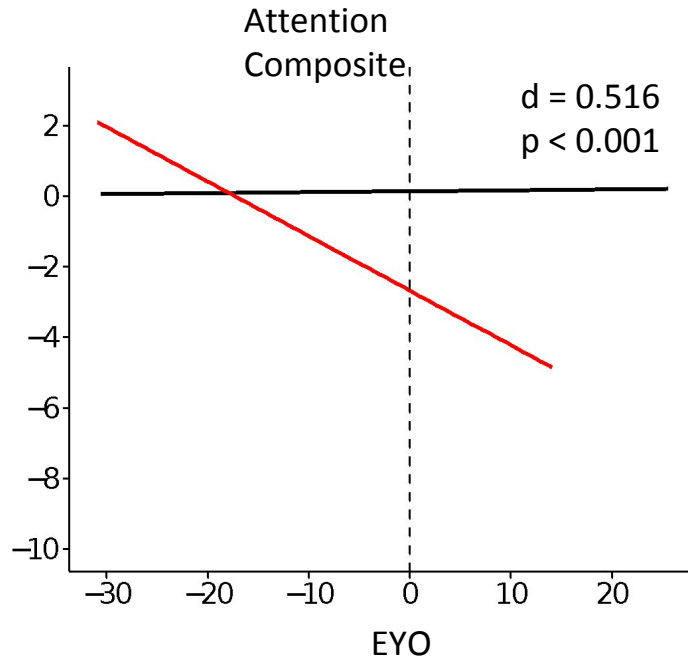
Episodic Memory Composite



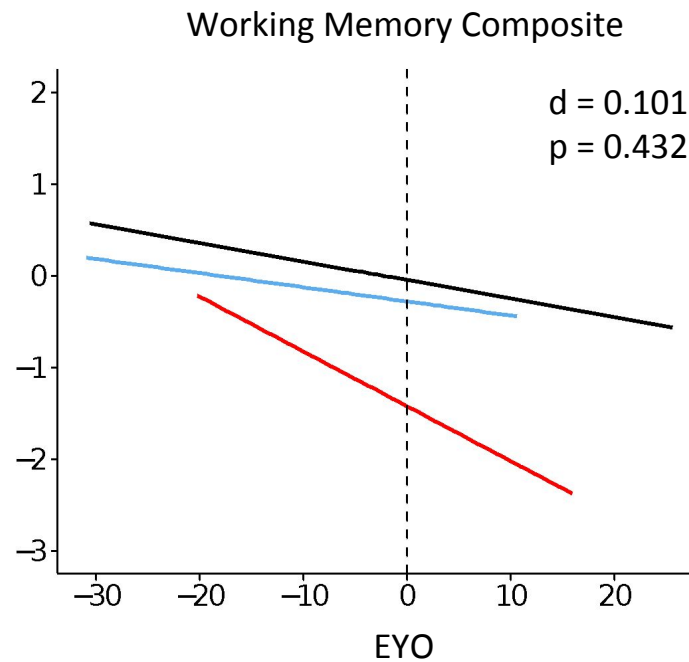
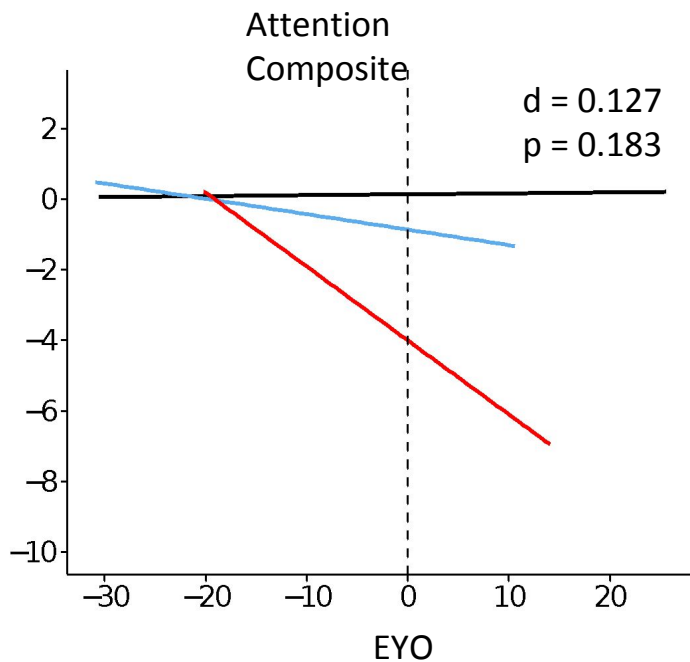
Episodic Memory Composite



# Cognitive Change across EYO: Carriers vs Non-Carriers



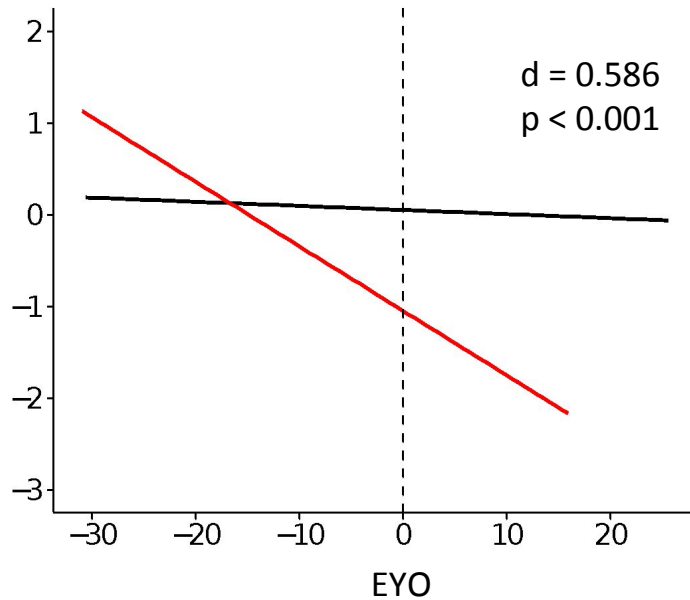
# Cognitive Change across EYO: Non-Carriers vs CDR 0 Mutation Carriers



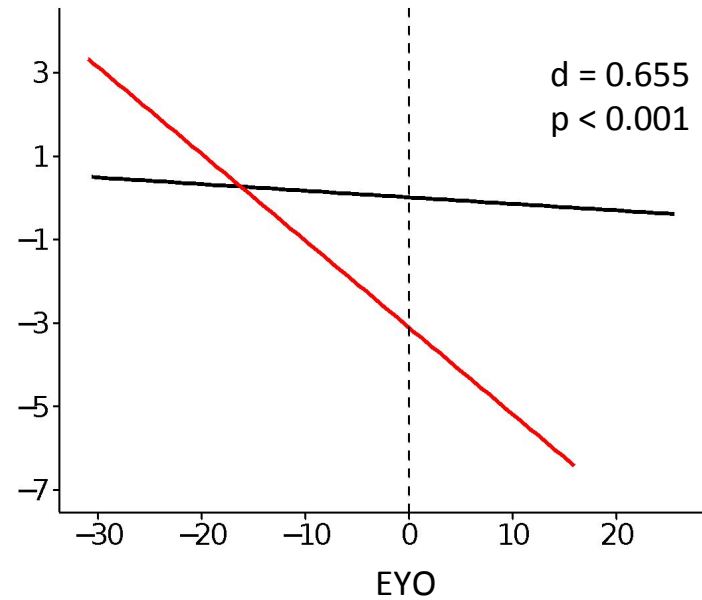
— Non-Carriers — CDR 0 Carriers — CDR >0 Carriers

# Cognitive Change across EYO: Carriers vs Non-Carriers

Semantic Memory Composite

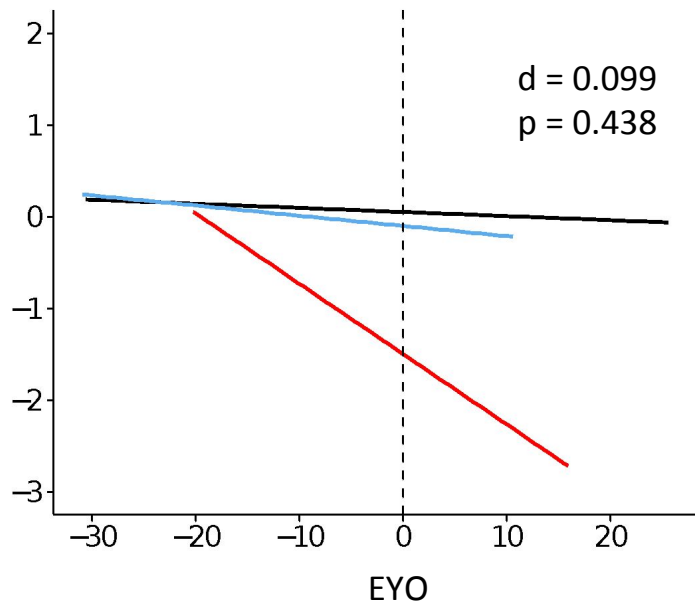


Processing Speed Composite

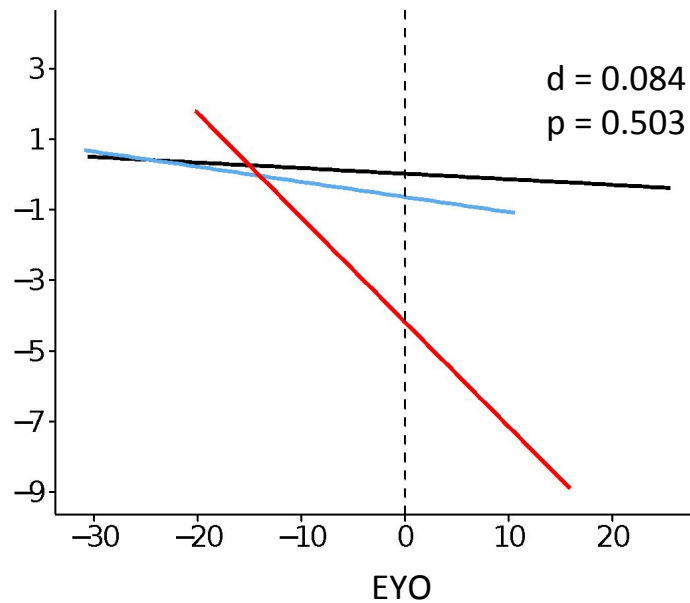


# Cognitive Change across EYO: Carriers vs Non-Carriers

Semantic Memory Composite



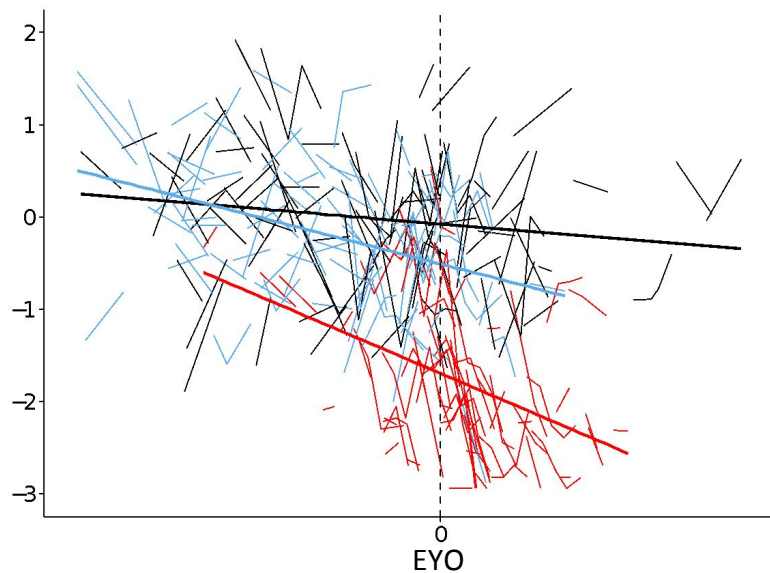
Processing Speed Composite



— Non-Carriers — CDR 0 Carriers — CDR >0 Carriers

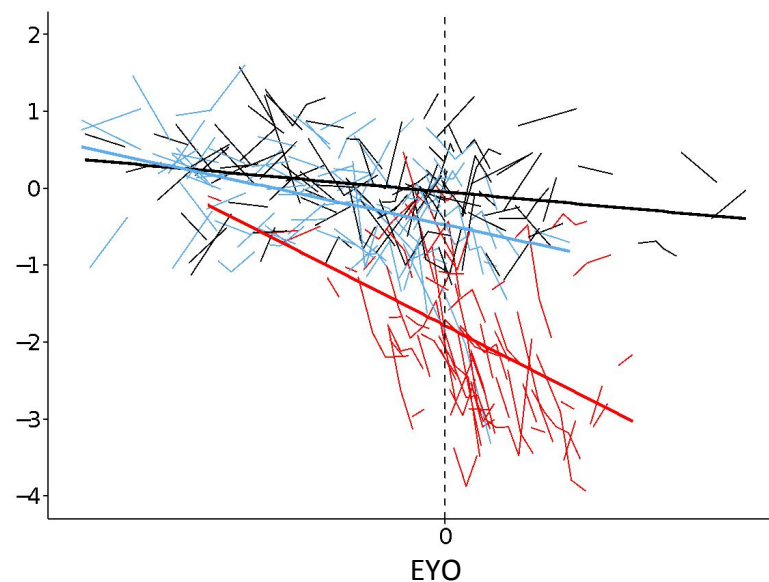
# Cognitive Change across EYO

Episodic Memory Composite



— Non-Carriers  
— CDR 0 Carriers  
— CDR >0 Carriers

DIAN-TU Composite

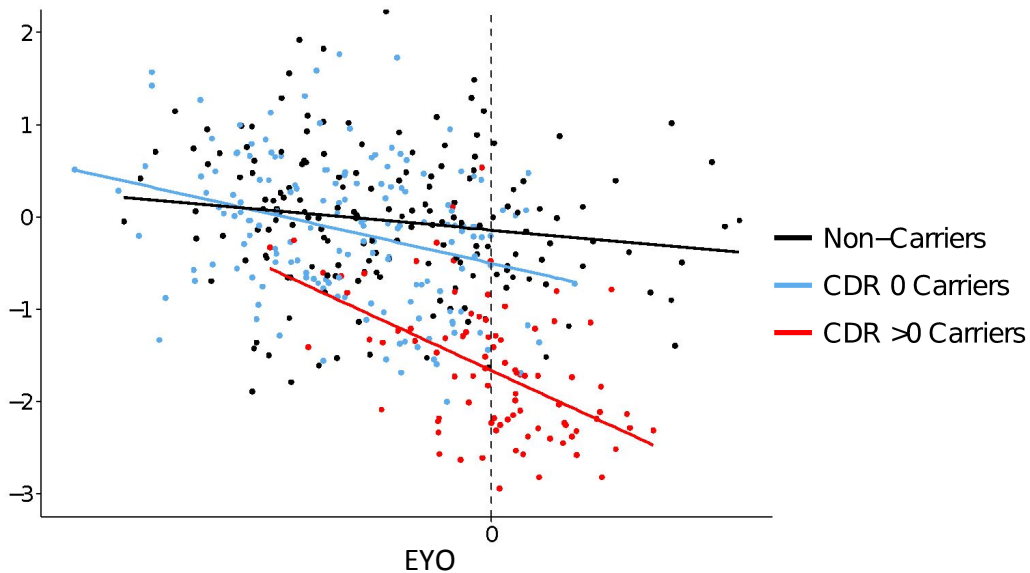


	N	Slope	<i>p</i>	Cohen's D
Non-Carriers	83	(ref)	(ref)	(ref)
CDR 0 Carriers	84	-0.030	0.019	0.321
CDR >0 Carriers	68	-0.070	<0.001	0.665

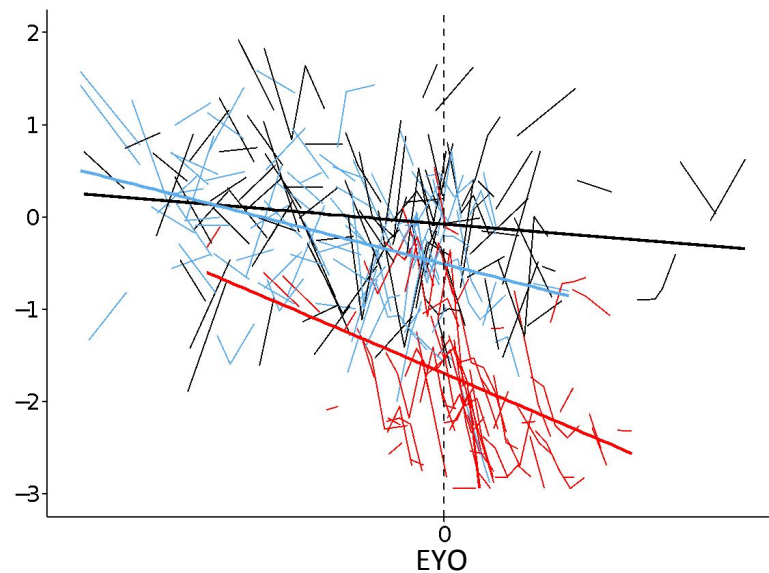
	N	Slope	<i>p</i>	Cohen's D
Non-Carriers	83	(ref)	(ref)	(ref)
CDR 0 Carriers	84	-0.012	0.043	0.262
CDR >0 Carriers	68	-0.102	<0.001	1.097

# Baseline vs. Longitudinal: Episodic Memory

Baseline (n = 420)



Longitudinal (n = 229)

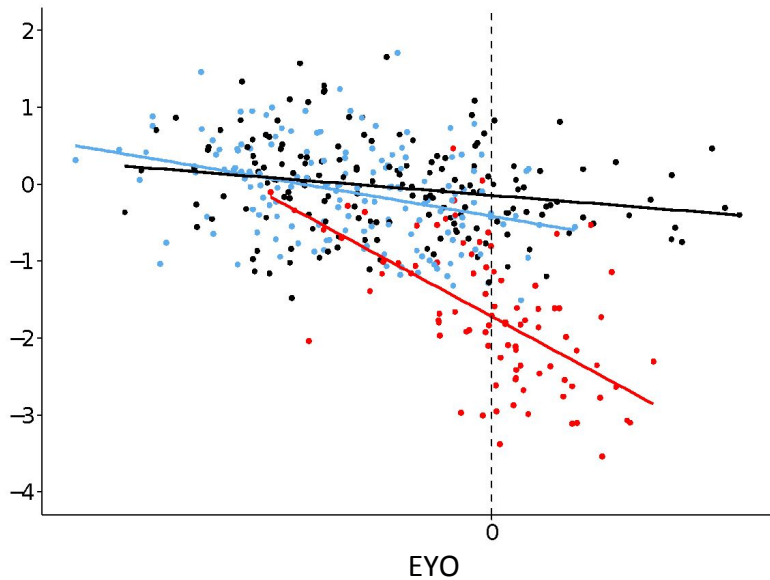


	N	Slope	$p$	Cohen's D
Non-Carriers	170	(ref)	(ref)	(ref)
CDR 0 Carriers	160	-0.031	0.068	0.150
CDR >0 Carriers	90	-0.056	<0.001	0.502

	N	Slope	$p$	Cohen's D
Non-Carriers	83	(ref)	(ref)	(ref)
CDR 0 Carriers	84	-0.030	0.019	0.321
CDR >0 Carriers	68	-0.070	<0.001	0.665

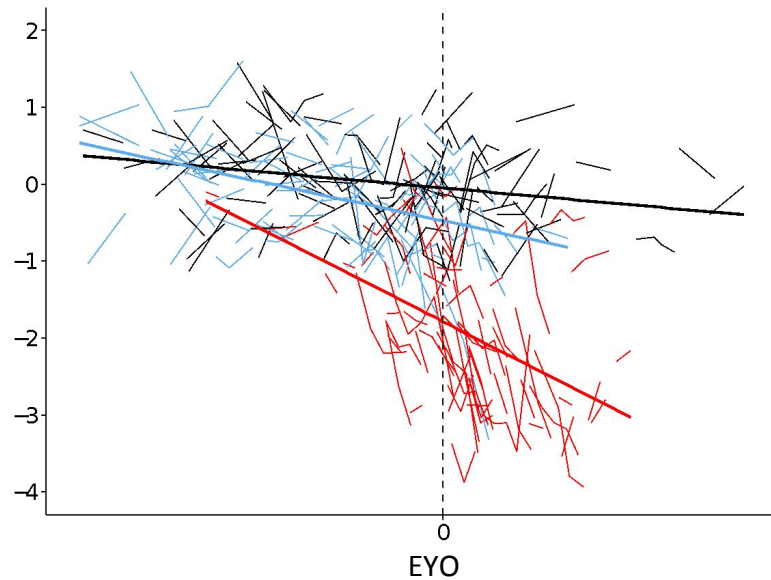
# Baseline vs. Longitudinal: DIAN-TU Cognitive Composite

Baseline (n = 420)



Longitudinal (n = 229)

— Non-Carriers  
— CDR 0 Carriers  
— CDR >0 Carriers



	N	Slope	<i>p</i>	Cohen's D
Non-Carriers	170	(ref)	(ref)	(ref)
CDR 0 Carriers	160	-0.021	0.081	0.151
CDR >0 Carriers	90	-0.078	<0.001	0.872

	N	Slope	<i>p</i>	Cohen's D
Non-Carriers	83	(ref)	(ref)	(ref)
CDR 0 Carriers	84	-0.012	0.043	0.262
CDR >0 Carriers	68	-0.102	<0.001	1.097



# Summary

- Widespread differences between Non-Carriers and Mutation Carriers across nearly all domains of cognition.
- Declines in episodic memory and DIAN-TU composite evident in asymptomatic mutation carriers
- Age and EYO highly correlated, but EYO is a better indicator of declines in cognition
- No differences in cognitive decline across mutation types
- Cross-sectional data appears mirror longitudinal data in DIAN

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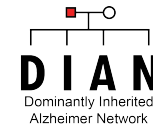
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**DIAN Participants and Families**

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Informatics – D Marcus  
Neuropathology – NJ Cairns

## DIAN Expanded Registry

E McDade  
E Ziegemeier  
D Levitch  
M Downey-Jones

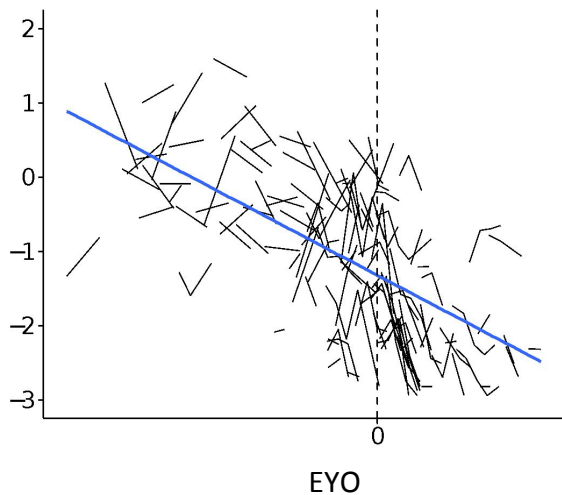
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## Performance Sites (PI)

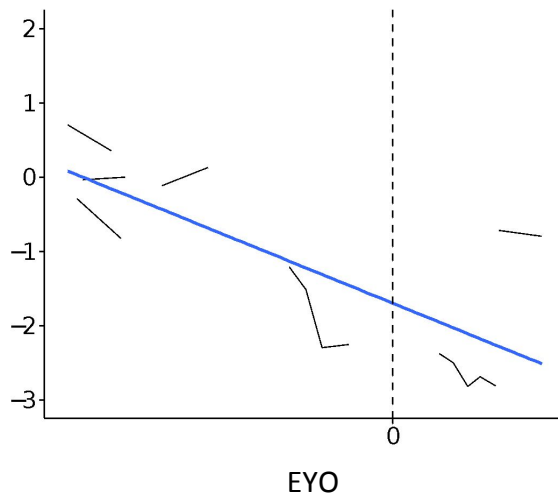
- **United States:** Washington Univ (Bateman), MGH/BWH (Chhattwal), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti/Farlow), USC (Chui/Ringman), U of Pittsburgh (Berman), Mayo Clinic, Jacksonville (Graff-Radford)
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- **Japan:** Hirosaki, Osaka City, Niigata and Tokyo (Mori)
- **Korea:** Asan Medical Center (Lee)

# Episodic Memory declines by Mutation Type

*PSEN1* (N=112)



*PSEN2* (N=7)



*APP* (N=28)

