

The Course of Cognitive Decline in Familial Alzheimer's Disease due to *PSEN1* and *APP* Mutations

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Cognitive Decline in Familial AD:

Outline

- Cognitive decline in late-onset AD
 - Challenges to studying it
- Familial AD as a model
- A brief literature review
- Our studies
 - Phase I: Cross-sectional study in Mexico
 - Longitudinal word list recall findings
 - Phase II: Ongoing studies at UCLA
 - Complex Reaction Time Test



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Pre-Clinical AD

- AD pathology precedes cognitive changes by years
(Katzman, '88)
- Many therapies directed at preventing or slowing AD are under development
- It is important to select persons at greatest risk for AD for treatment trials
- A full understanding of incipient AD will help us understand the pathogenesis of the illness and diagnose it early
- The preclinical state is challenging to study because you do not know who is and who is not going to develop AD in the future

Pre-Clinical AD

- Much knowledge about early AD obtained from case-control and prospective studies in the elderly
- These studies suggest early decline in:
 - Episodic memory (Chen, '01)
 - Executive function (Spieler, '96, Collete, '99)
 - Slowed choice reaction time (Pate, 94)
- Such studies have limitations-
 - Confounded by effects of normal aging
 - Confounded by illnesses, medications associated with aging
 - Uncertainty of ultimate diagnosis
 - Longitudinal studies problematic
 - Loss to follow-up, etc.
 - Problems with inter-group variability
 - Educational, vocational, genetic background

Autosomal Dominant Early-Onset Familial AD (FAD)

- \approx 2% of AD cases are autosomal dominant
- Most due to mutations in 1 of 3 genes
 - Amyloid precursor protein (APP) on chromosome 21
 - Presenilin-1 (PS1) on chromosome 14
 - \approx 65% of FAD cases
 - Presenilin-2 (PS2) on chromosome 1
- Essentially fully penetrant
 - Age of onset can be consistent within families, allowing one to calculate an “adjusted age” (Fox et al, '97, Murrell et al '06)
- By comparing mutation carriers (MCs) and their non-mutation carrying kin (NCs) prior to overt dementia we may identify early disease characteristics

Cognitive Decline in FAD: A Brief Literature Review

- A single subject at-risk for FAD had verbal memory deficits 26 months prior to presenting for a subjective memory complaint (Newman et al, '94)
- 63 persons at-risk for FAD followed for 6 years (Fox et al, '98)
 - In 10 subjects who became demented, early decline in verbal memory and performance IQ were noted

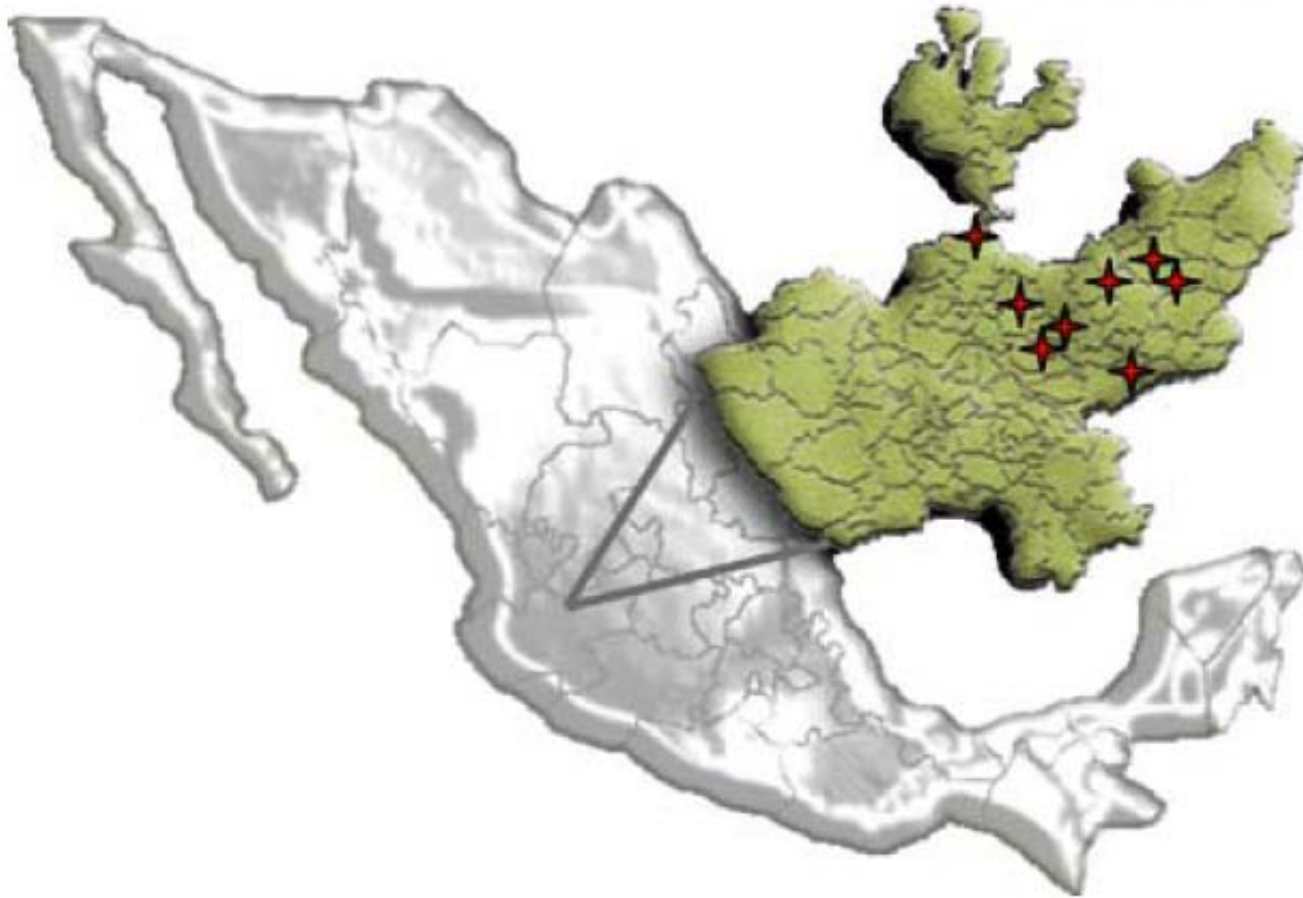
Cognitive Decline in FAD: A Brief Literature Review

- Comparing 40 carriers of the E280A *PSEN1* mutation to 82 non-carriers in Columbia (Ardila et al, '00)
 - More verbal memory intrusion errors in mutation carriers
 - Among 10 of the 40 with memory complaints
 - Deficits found in multiple verbal and non-verbal memory tests as well as the MMSE, digit symbol, language measures
- Among 14 persons in Mexico at-risk for FAD (Diaz-Olavarrieta et al, '97)
 - 6 had memory deficits of whom 4 additionally had visuospatial deficits and 3 had language deficits

Pre-Clinical *PSEN1* Mutation Carriers: Phase I, Methods (Ringman et al, '05)

- 77 members of 10 Mexican families w/*PSEN1* mutations
- Exclusionary criteria:
 - Overtly demented (n = 7), beyond median age of AD Dx in family (n = 13), incomplete data (n = 6)
- 51 at-risk subjects received, either at the INNN in Mexico or in their own home:
 - Clinical Interview
 - Neuropsychological Battery
 - Computerized Reaction Time Testing
 - *PSEN1* and *ApoE* genotyping
- Of 51 subjects:
 - 40 were from 9 families with the A431E *PSEN1* substitution (Yescas et al '06, Murrell et al '06)
 - 11 were from a single family with the L235V *PSEN1* substitution

State of Jalisco:
Area: 80,137 km²
Population: 6.3 million



(Yescas, Alonso, et al,
Neurogenetics, '06)

Fig. 1 Map of Mexico, with the State of Jalisco *highlighted*. The *stars* denote the location of the counties/cities from which eight of the Ala431Glu mutation families are from. The remainder family is from the State of Jalisco; however, the city of origin is unknown

Pre-Clinical *PSEN1* Mutation Carriers: Neuropsychology

- At-risk subjects received a comprehensive neuropsychological battery in Spanish_(Ostrosky-Solis)
 - MMSE, Trails Making Tests A&B, Letter Cancellation Test, Wechsler Memory Scale – R Subtests (information, orientation, mental control, logical memory-immediate recall, digit span, visual memory, associative learning), Rey-O Figure, 10-Word List Learning Test-immediate and delayed recall (n=48), Boston Naming Test, Category Fluency, Letter Fluency, WAIS Block Design Test
- The performance of carriers and non-carriers of *PSEN1* mutations compared by ANOVAs co-varying for mutation in family (A431E vs. L235V), family of membership

Pre-Clinical *PSEN1* Mutation Carriers: Subject Characteristics

	+ <i>PSEN1</i> Mutation	- <i>PSEN1</i> Mutation	
# Subjects	30	21	
Mean age	28.9 (18-43)	29.2 (18-47)	p=.873
% Female	60.0%	76.2%	p=.366
Education- Mn. Years	11.1 (6-17)	12.7 (7-18)	p=.067

Pre-Clinical *PSEN1* Mutation Carriers: Neuropsychology

Mean scores	+ <i>PSEN1</i> Mutation (n=30)	- <i>PSEN1</i> Mutation (n=21)	
MMSE	28.0 (23-30)	29.2 (27-30)	p=.004
TMT- A (time in seconds)	49.9 (18-95)	39.0 (20-67)	p=.028
TMT- B (time in seconds)	123.0 (54-275)	72.5 (45-110)	p<.001

Pre-Clinical *PSEN1* Mutation Carriers: Neuropsychology

Mean scores	+ <i>PSEN1</i> Mutation (n=30)	- <i>PSEN1</i> Mutation (n=21)	
10-Word list, # of words recalled after delay	6.3 (0-9)	7.5 (5-10)	p=.029
WAIS Block Design	32.5 (18-46)	37.0 (27-46)	p=.029

Presenilin-1 Mutation Present?

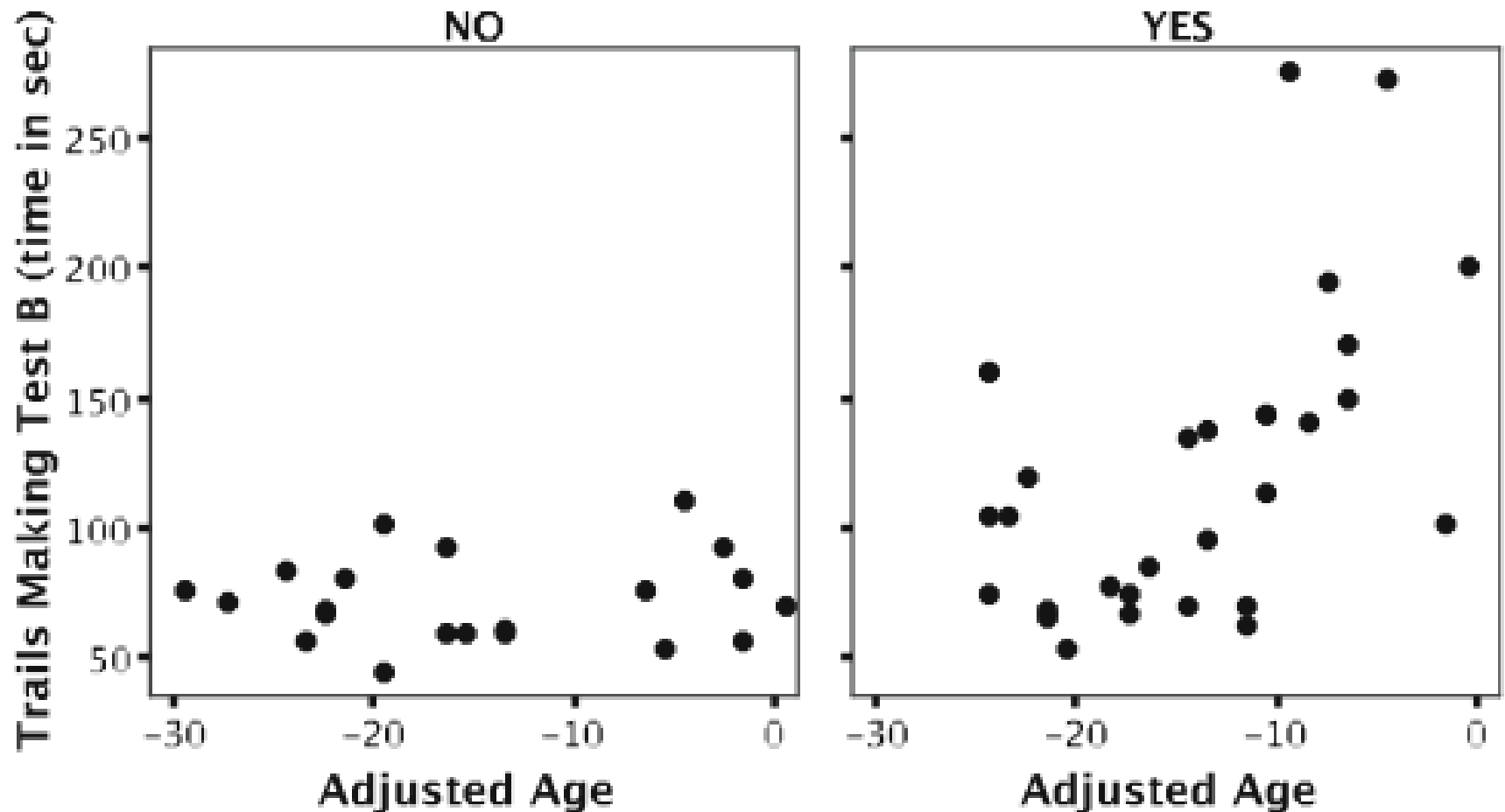


Figure. Time to complete Trails Making Test B in PS1 mutation carriers and noncarriers. Subjects' ages are in number of years younger than the median age at dementia diagnosis in their family.

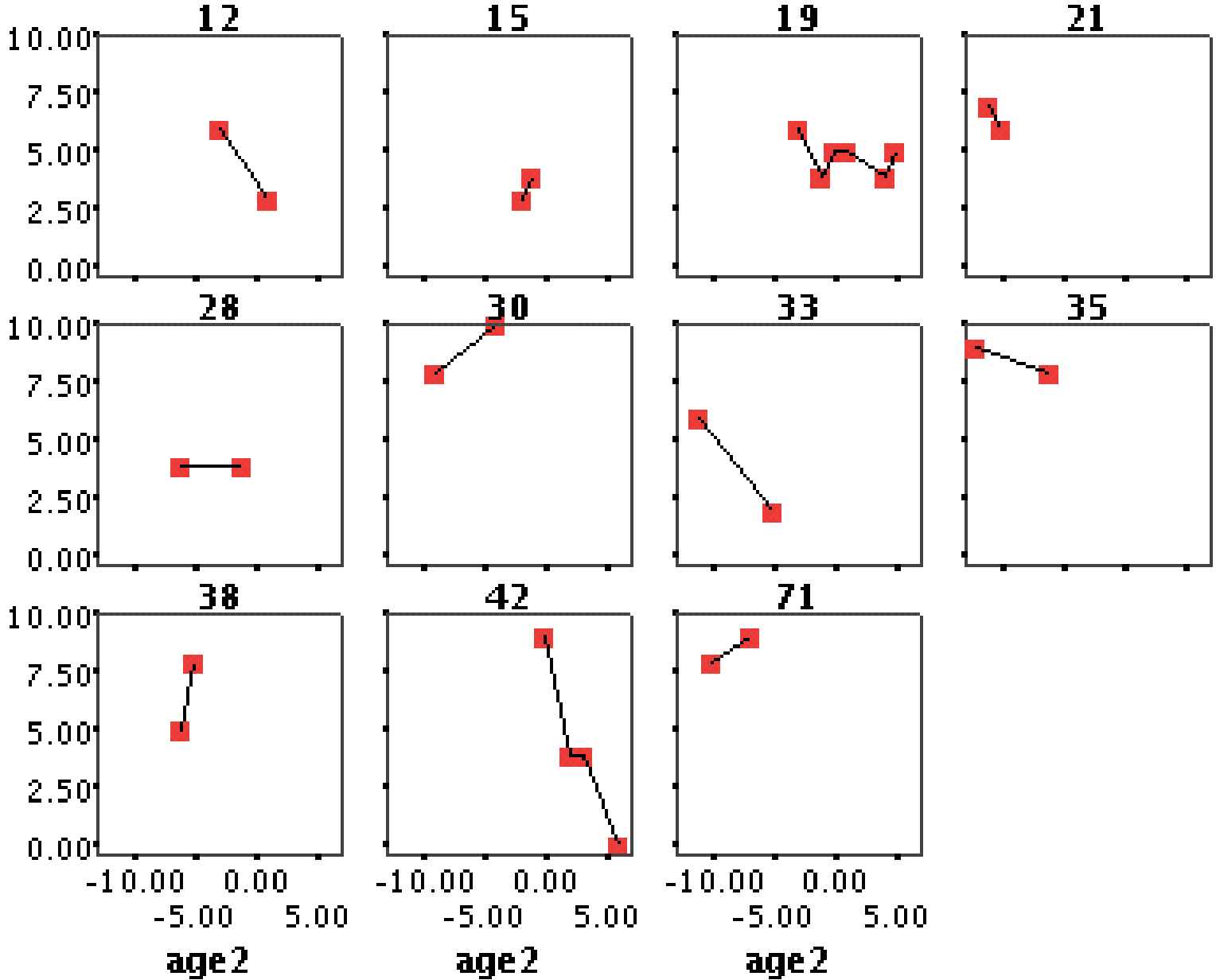
Neuropsychology of Pre-Clinical *PSEN1* Mutation Carriers: Phase I Results

- MMSE, Trails A & B, Delayed Recall of a 10 word list, and WAIS Block Design performance affected in preclinical *PSEN1* mutation carriers
- When the group was divided into tertiles according to relative age, differences were only seen in the oldest tertile
 - Mean age = 38.5, age relative to family-specific typical age of dementia diagnosis = 5.6 years
- *ApoE* genotype did not exert a significant effect in this study

Neuropsychology of Pre-Clinical *PSEN1* Mutation Carriers: Longitudinal Data

- 11 presymptomatic *PSEN1* mutation carriers who were within 15 years of age of dementia diagnosis in their family underwent neuropsychological testing on at least two occasions
- On delayed recall of a 10 word list:
 - A mean decline of 0.15 words/year observed
- Only 5 of 11 subjects were examined over the time in which dementia diagnosis might be expected to occur

Number of words recalled out of 10 after a brief delay



Age in relation to median age of dementia Dx in Family

Pre-Clinical FAD Mutation Carriers: Phase II, Methods

- 42 Mexican or Mexican-American persons with or at-risk for inheriting *PSEN1* or *APP* mutations were admitted to the UCLA CRC where they underwent:
 - Clinical assessment: CDR, med. history, etc.
 - Cognitive assessments:
 - Spanish English Neuropsychological Assessment Scale (SENAS)
 - Additional word list and verbal prose memory tests
 - Wisconsin Card Sorting Task, Color Trails
 - A subset received items from the Ostrosky-Solis battery
 - Imaging, Genetic, Biochemical, Psychiatric assessments
- When including subjects with CDR = 0.5, deficits in the WCST, Color Trails, delayed recall of a paragraph are seen *(preliminary, unpublished results)*

Pre-Clinical FAD Mutation Carriers:

Mild Cognitive Impairment? (Ringman et al, '09)

- Does MCI, as described by R. Petersen ('99, '04), apply to persons inheriting FAD mutations?
 - 22 non-demented FAD mutation carriers underwent Spanish-language neuropsych testing
 - Composite z scores for language, visuospatial, verbal memory, and frontal/executive function domains calculated
 - 7 met criteria for MCI:
 - 3 w/single domain amnesic
 - 2 w/multiple domain amnesic
 - 1 w/frontal/executive, visuospatial
 - 1 w/visuospatial
 - 1 w/single domain language
 - 1 w/single domain frontal/executive
 - Self-report of memory complaints was not a good predictor of memory impairment in this population

Pre-Clinical FAD Mutation

Carriers: Reaction Time

- Cognitive processing slows with age_(Salthouse)
- Cognitive processing slows in AD, particularly complex processing_(Pirozzolo et al., '81)
- Computerized reaction time (RT) testing allows us to measure this sensitively
- 67 at-risk subjects performed a computerized battery of 6 different reaction time tests of various complexities

Pre-Clinical FAD Mutation

Carriers: Reaction Time

1) Simple Reaction Time Test

- Subjects push a single key as quickly as possible after the appearance of a target

2) Complex Choice Reaction Time Test

- A picture and a word appear simultaneously on the computer screen
- If the picture and word are the same, subjects press a “yes” key, if not, the “no” key
- On a subset of trials, an auditory cue signals subjects to do the opposite

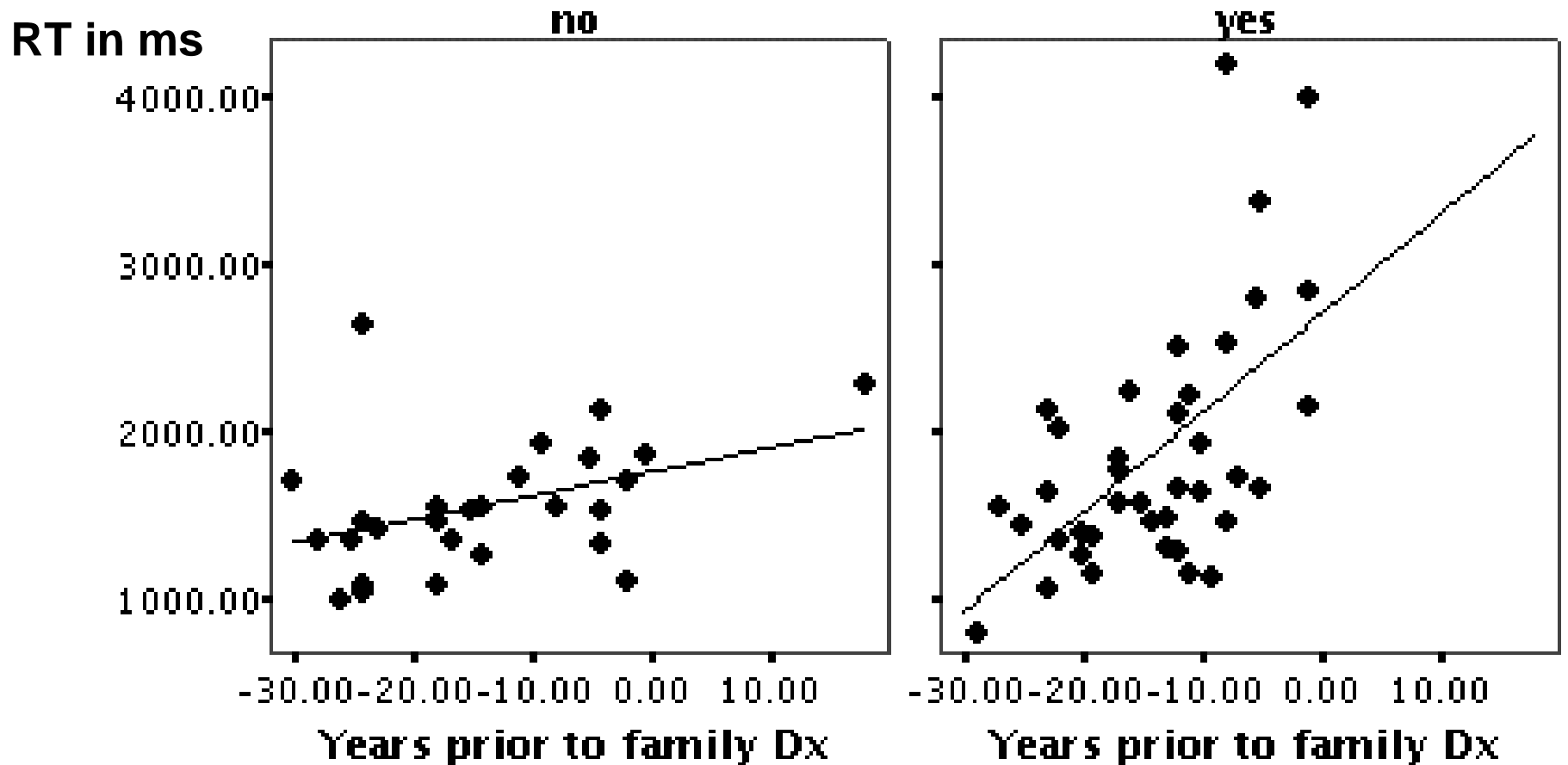
Pre-Clinical FAD Mutation

Carriers: Reaction Time

- Simple Reaction Time
 - No difference in accuracy or median RT
 - No correlation w/ age in either group
- Complex Choice Reaction Time
 - Significant slowing of median RT in mutation carriers compared to non-carriers
 - 1.9 seconds vs. 1.6 seconds, $p=.028$
 - Positive correlation between relative age and RT
 - In non-carriers: $r = 0.41$, $p = 0.03$
 - In carriers: $r = 0.57$, $p < 0.001$

Complex Reaction Time in FAD Mutation Carriers

FAD Mutation Present?



Cognitive Decline in FAD: Conclusions

- Cognitive decline in early FAD similar to that seen in late-onset AD
 - Memory deficits are early
 - Consistent with concept of amnesic MCI
 - Executive dysfunction also occurs early
 - Slowing of complex cognitive skills occurs
 - Trials Making Test B
 - Complex Reaction Time Test
- Using neuropsychological testing, it is possible to detect cognitive decline around 5 years prior to diagnosable dementia
- Much of the findings regarding cognitive decline in FAD are generalizable to late-onset AD

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