

PODE 2013 - POPULATION OPTIMUM DESIGN OF EXPERIMENTS

Improving cognitive testing with IRT and optimal design

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ALZHEIMER'S DISEASE



- Fatal disease
- Most common form of dementia
- Prevalence is 13% for age > 65 (US)
- Increasing problem in aging societies

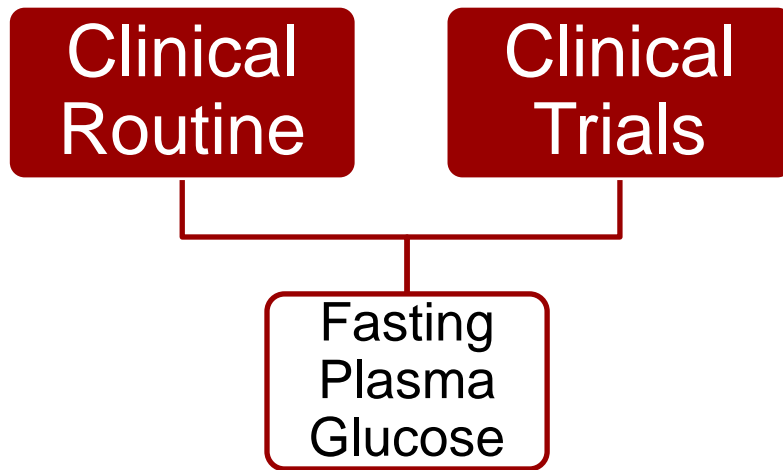
- Cause remains vastly unknown
- Only symptomatic treatment
- No cure

Why no/few treatments?

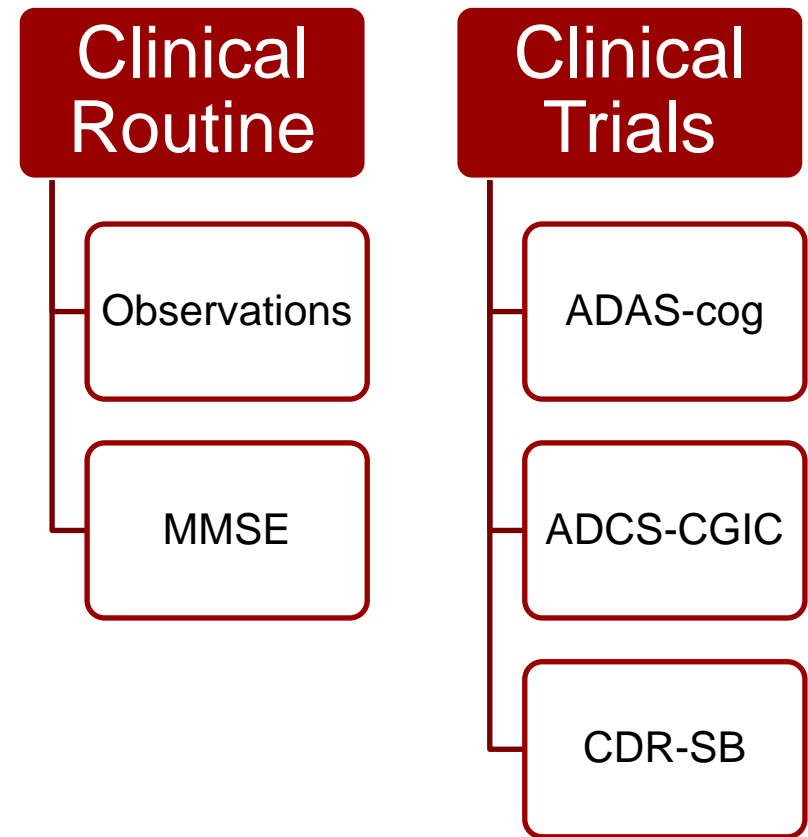


Diagnosis

Diabetes



Alzheimer's Disease





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ADAS-cog Score

- Cognitive subscale of Alzheimer's Disease Assessment Scale
- Cognitive assessment including broad range of sub-tests e.g.,

TASK BASED

Remembering Words

LAKE
CLOCK
FOREST
ANIMAL

Naming Objects



Commands



Construction



Ideational Praxis



Orientation



Alzheimer's Disease Cooperative Study
ADAS - Cognitive Behavior
SAMPLE FORM - Page 1 of 4

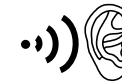
Center Name	Patient Number	Payroll Initials	Examiner Initials	Examination Date
P R				Month Day Year
1. WORD RECALL TASK: Indicate the total number of correct responses for each list.		T. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.		
Trial 1: 5 Trial 2: 7 Trial 3: 8		Trial 1: Trial 2: Trial 3:		
2. NAMING OBJECTS AND PRIZES: Check each object/prize named accurately or check "NONE".		9. LANGUAGE: Check level of impairment.		
<input type="checkbox"/> Clock <input type="checkbox"/> Spoon <input type="checkbox"/> None <input type="checkbox"/> Nail <input type="checkbox"/> Blank <input type="checkbox"/> Hammer <input type="checkbox"/> Whistle <input type="checkbox"/> Screen <input type="checkbox"/> Bathroom <input type="checkbox"/> Fruit <input type="checkbox"/> Comb <input type="checkbox"/> Tongue <input type="checkbox"/> Thumb <input type="checkbox"/> Index <input type="checkbox"/> Ring <input type="checkbox"/> Pinky <input type="checkbox"/> Middle		<input type="checkbox"/> None: patient speaks clearly and/or is understandable. <input type="checkbox"/> Very Mild: one instance of lack of understandability. <input type="checkbox"/> Mild: patient has difficulty ~25% of the time. <input type="checkbox"/> Moderate: patient has difficulty 25-50% of the time. <input type="checkbox"/> Moderately Severe: patient has difficulty more than 50% of the time. <input type="checkbox"/> Severe: often or always unintelligible; flared, but empty speech, such.		
3. COMMANDS: Check each command performed accurately or check "NONE".		9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment.		
<input type="checkbox"/> None <input type="checkbox"/> Point to the ceiling then to the floor. <input type="checkbox"/> Put the pencil on top of the book then pick it back. <input type="checkbox"/> Put the watch on the other side of the person and set aside the watch. <input type="checkbox"/> The watch should be worn with two fingers keeping your eyes shut.		<input type="checkbox"/> None: patient understands. <input type="checkbox"/> Very Mild: one instance of misunderstanding. <input type="checkbox"/> Mild: 3-4 instances of misunderstanding. <input type="checkbox"/> Moderate: requires several repetitions and rephrasing. <input type="checkbox"/> Moderately Severe: patient only occasionally responds correctly; i.e., yes - no questions. <input type="checkbox"/> Severe: patient rarely responds to questions appropriately; not due to poverty of speech.		
4. CONSTRUCTIONAL PRAXIS: Check each figure drawn correctly.		10. WORD FINDING DIFFICULTY: Check one response.		
<input type="checkbox"/> None: attempted but drew no forms correctly. <input type="checkbox"/> Patient drew no forms, substituted, wrote words. <input type="checkbox"/> Circle <input type="checkbox"/> Two overlapping rectangles <input type="checkbox"/> Rhombus <input type="checkbox"/> Cube		<input type="checkbox"/> None. <input type="checkbox"/> Very Mild: 1 or 2 instances, not clinically significant. <input type="checkbox"/> Mild: noticeable circumlocution or synonym substitution. <input type="checkbox"/> Moderate: loss of words without compensation or neologism. <input type="checkbox"/> Moderately Severe: frequent loss of words without compensation. <input type="checkbox"/> Severe: nearly total loss of content words; speech sounds empty; 1- to 2 word utterances.		
5. IDEATIONAL PRAXIS: Check each step completed accurately or check "NONE".		11. READING TEST ABSTRACTS: Check level of impairment.		
<input type="checkbox"/> None <input type="checkbox"/> Fold a letter. <input type="checkbox"/> Put letter in envelope. <input type="checkbox"/> Seal envelope. <input type="checkbox"/> Address envelope. <input type="checkbox"/> Indicate where stamp goes.		<input type="checkbox"/> None. <input type="checkbox"/> Very Mild: forgets once. <input type="checkbox"/> Mild: must be reminded 2 times. <input type="checkbox"/> Moderately Severe: must be reminded 3-4 times. <input type="checkbox"/> Moderately Severe: must be reminded 5-6 times. <input type="checkbox"/> Severe: must be reminded 7 or more times.		
6. ORIENTATION: Check each item answered correctly or check "NONE".				
<input type="checkbox"/> None <input type="checkbox"/> Full name <input type="checkbox"/> City <input type="checkbox"/> State <input type="checkbox"/> Month <input type="checkbox"/> Season <input type="checkbox"/> Place <input type="checkbox"/> Date <input type="checkbox"/> Place <input type="checkbox"/> Year <input type="checkbox"/> Time of day				

White: ADCS Copy Yellow: Worksheet Copy Pink: Clinica Monitor Copy

RATER ASSESSED



Ability to Speak



Ability to Understand

ADAS-cog Score



ADAS-cog Score Model

y_{ijk} Response of (category assigned to) subject i for item j at time ik
 M Number of test items in ADAS-cog assessment
 \hat{y}_{ik} ADAS-cog score

$$\hat{y}_{ik} \approx \sum_{j=1}^M y_{ijk}$$

Commonly used pharmacometric model:

$$\begin{aligned}\hat{y}_{ik} &= \theta_0 + \eta_{0i} + (\theta_1 + \eta_{1i}) \cdot t_{ik} + \varepsilon_{ik} \\ \eta_{0i}, \eta_{1i} &\sim \text{Normal}(0, \Omega) \\ \varepsilon_{ik} &\sim \text{Normal}(0, \sigma)\end{aligned}$$



ADAS-cog IRT Model

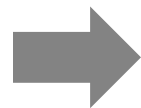
From now: consider only data from 1 time point (drop k index)

D_i Latent variable “cognitive disability” of patient i
 f_j Response function for test j

$$P(y_{ij} = x) = f_j(x, D_i)$$
$$D_i \sim \text{Normal}(0,1)$$

Instead of summary score, calculate

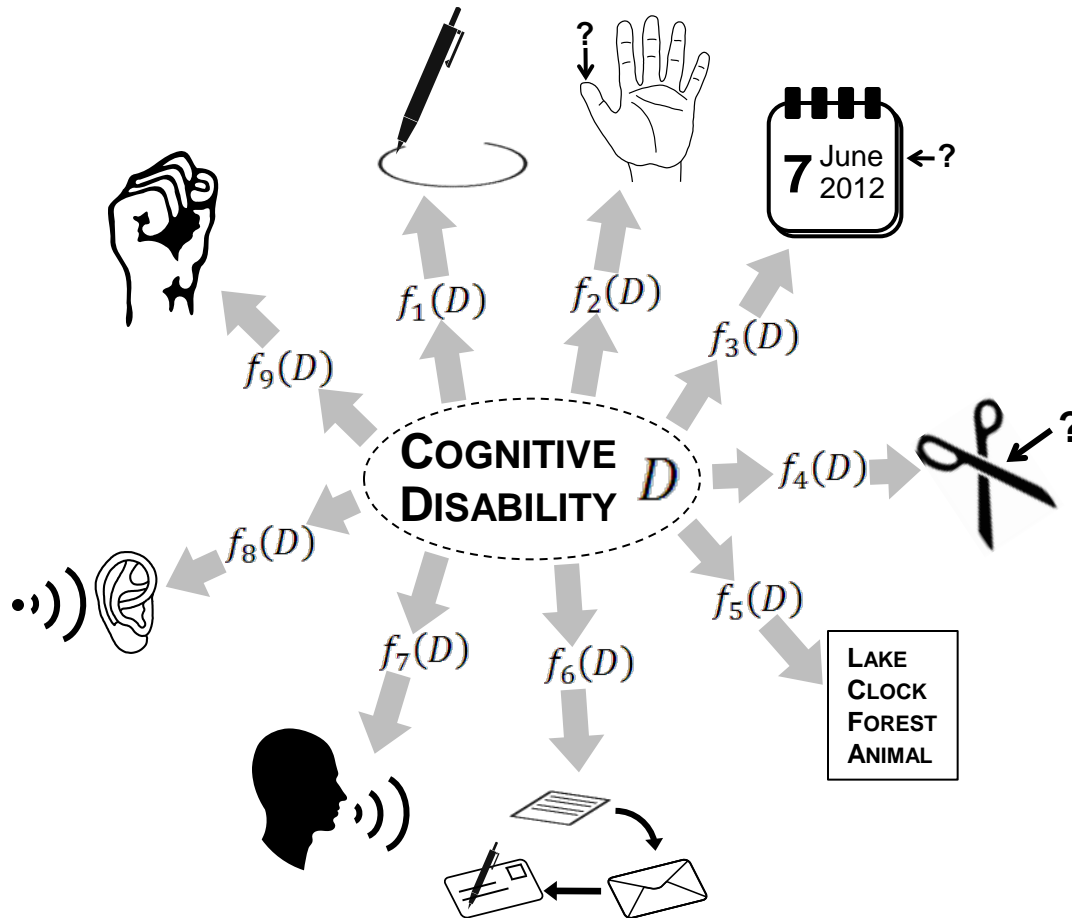
$$\hat{D}_i = \arg \max_D \sum_{j=0}^M \log f_j(y_j, D) + \log p(D; 0,1)$$



Item Response Theory



ADAS-cog IRT Model





ADAS-cog IRT Model

Latent variable model:

$$D_i \sim \text{Normal}(0,1)$$

Response Models:

$$g(\boldsymbol{\kappa}, D) = \kappa_1 + (\kappa_2 - \kappa_1) \frac{e^{\kappa_3(D - \kappa_4)}}{1 + e^{\kappa_3(D - \kappa_4)}}$$
$$\boldsymbol{\kappa} = (\kappa_1, \kappa_2, \kappa_3, \kappa_4)$$

Binary:

$$P(y_{ij} = 1) = g(\boldsymbol{\kappa}_j, D_i)$$

Count (binomial):

$$P(y_{ij} = l) = \binom{n}{l} g(\boldsymbol{\kappa}_j, D_i)^l (1 - g(\boldsymbol{\kappa}_j, D_i))^{n-l}$$

Count (generalized Poisson):

$$P(y_{ij} = l) = \frac{g(\boldsymbol{\kappa}_j, D_i)(g(\boldsymbol{\kappa}_j, D_i) + \delta l)^{l-1} e^{-g(\boldsymbol{\kappa}_j, D_i) - \delta l}}{l!}$$

Ordered categorical:

$$P(y_{ij} \geq l) = g(\boldsymbol{\kappa}_j, D_i)$$

$$P(y_{ij} = l) = P(y_{ij} \geq l) - P(y_{ij} \geq l + 1)$$

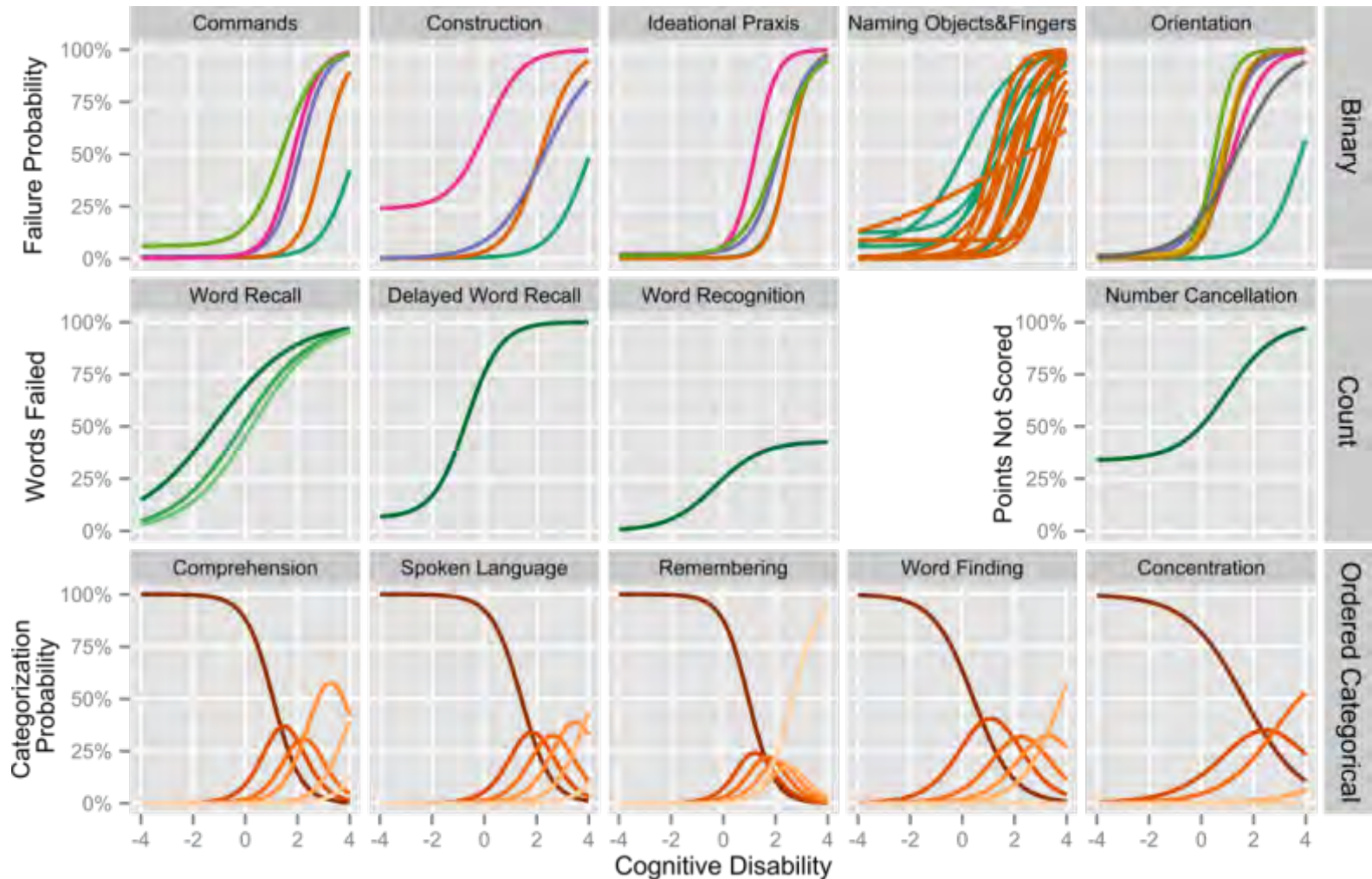


Parameter Estimation

- Test specific parameters $\mathbf{K} = (\kappa_1, \dots, \kappa_M)$ (167 in total) estimated from clinical trial databases
 - ADNI:
 - Observational study with normal, mild cognitively impaired (MCI) and mild AD subjects
 - Baseline ADAS-cog data from 819 subjects
 - CAMD:
 - Database with placebo arm data from clinical trials
 - First visit ADAS-cog data from 6 studies (1832 subjects)
- Estimation:
 - NONMEM 7.3 beta
 - LAPLACE method



Estimated Response Functions





Item Information

Which test item is most informative with respect to cognitive disability?

Calculate item information function:

$$I_j(D_i) = -E \left[\frac{\partial^2}{\partial D_i^2} \log f_j(y|D_i) \right]$$



Item Information - Binary Response

$$g(\boldsymbol{\kappa}_j, D) = \kappa_{j1} + (\kappa_{j2} - \kappa_{j1}) \frac{e^{\kappa_{j3}(D - \kappa_{j4})}}{1 + e^{\kappa_{j3}(D - \kappa_{j4})}}$$

$$P(y_{ij} = 1) = g(\boldsymbol{\kappa}_j, D_i)$$

$$P(y_{ij} = 0) = 1 - g(\boldsymbol{\kappa}_j, D_i)$$

$$l(\boldsymbol{\kappa}_j, D_i) = \frac{\partial}{\partial D_i^2} \log g(\boldsymbol{\kappa}_j, D_i)$$

$$= - \frac{\kappa_{j3}^2 e^{\kappa_{j3}(D_i - \kappa_{j4})} (\kappa_{j1} - \kappa_{j2}) (\kappa_{j1} - \kappa_{j2} e^{2\kappa_{j3}(D_i - \kappa_{j4})})}{(e^{\kappa_{j3}(D_i - \kappa_{j4})} + 1)^2 (\kappa_{j1} + \kappa_{j2} e^{\kappa_{j3}(D_i - \kappa_{j4})})^2}$$

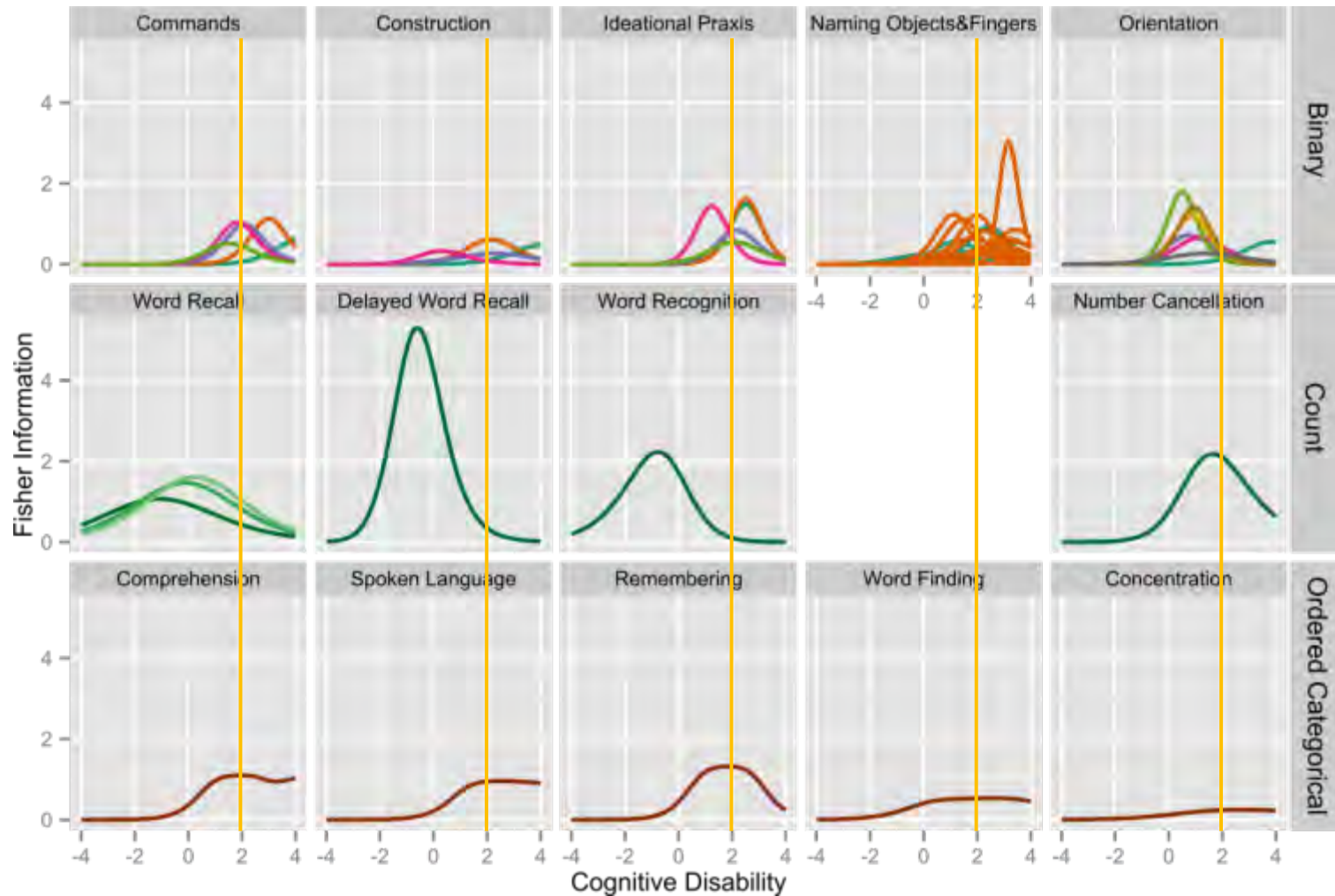
$$h(\boldsymbol{\kappa}_j, D_i) = \frac{\partial}{\partial D_i^2} \log (1 - g(\boldsymbol{\kappa}_j, D_i))$$

$$= - \frac{\kappa_{j3}^2 e^{\kappa_{j3}(D_i - \kappa_{j4})} (\kappa_{j1} - \kappa_{j2}) (\kappa_{j1} + e^{2\kappa_{j3}(D_i - \kappa_{j4})} - \kappa_{j2} e^{2\kappa_{j3}(D_i - \kappa_{j4})} - 1)}{(e^{\kappa_{j3}(D_i - \kappa_{j4})} + 1)^2 (\kappa_{j1} - e^{2\kappa_{j3}(D_i - \kappa_{j4})} + \kappa_{j2} e^{2\kappa_{j3}(D_i - \kappa_{j4})} - 1)^2}$$

$$J_j(\boldsymbol{\kappa}_j, D_i) = -g(\boldsymbol{\kappa}_j, D_i)l(\boldsymbol{\kappa}_j, D_i) - (1 - g(\boldsymbol{\kappa}_j, D_i))h(\boldsymbol{\kappa}_j, D_i)$$



Item Information Functions





Population Information

Subjects disability is unknown prior to assessment

- can't calculate individual information value
- calculate expected information for a population to be studied

$$\begin{aligned}\bar{J}_j &= E[J_j(D_i)] \\ &= \int_{-\infty}^{\infty} p(D_i; \mu_{\text{pop}}, \sigma_{\text{pop}}^2) J_j(D_i) dD_i\end{aligned}$$

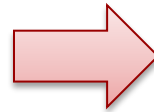
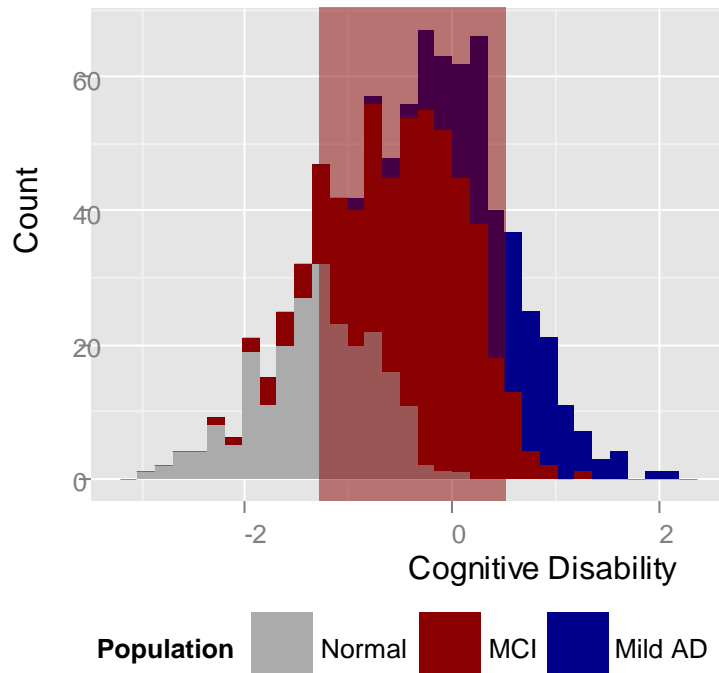
$p(x; \mu_{\text{pop}}, \sigma_{\text{pop}}^2)$...Probability density function for normal distribution with mean μ_{pop} and variance σ_{pop}^2

μ_{pop} and σ_{pop}^2 are estimated from ADNI data

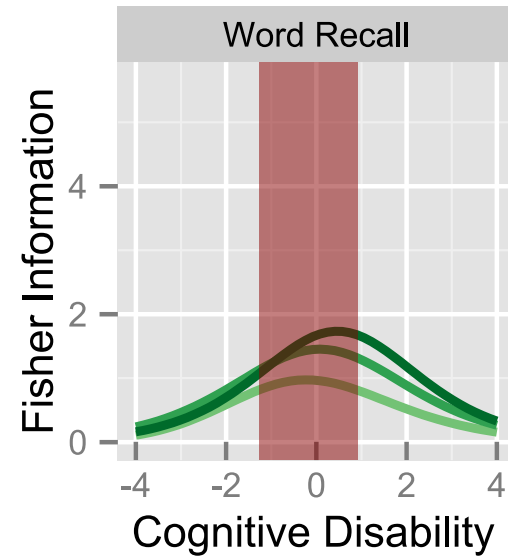


Population Information

Disability Distribution in ADNI



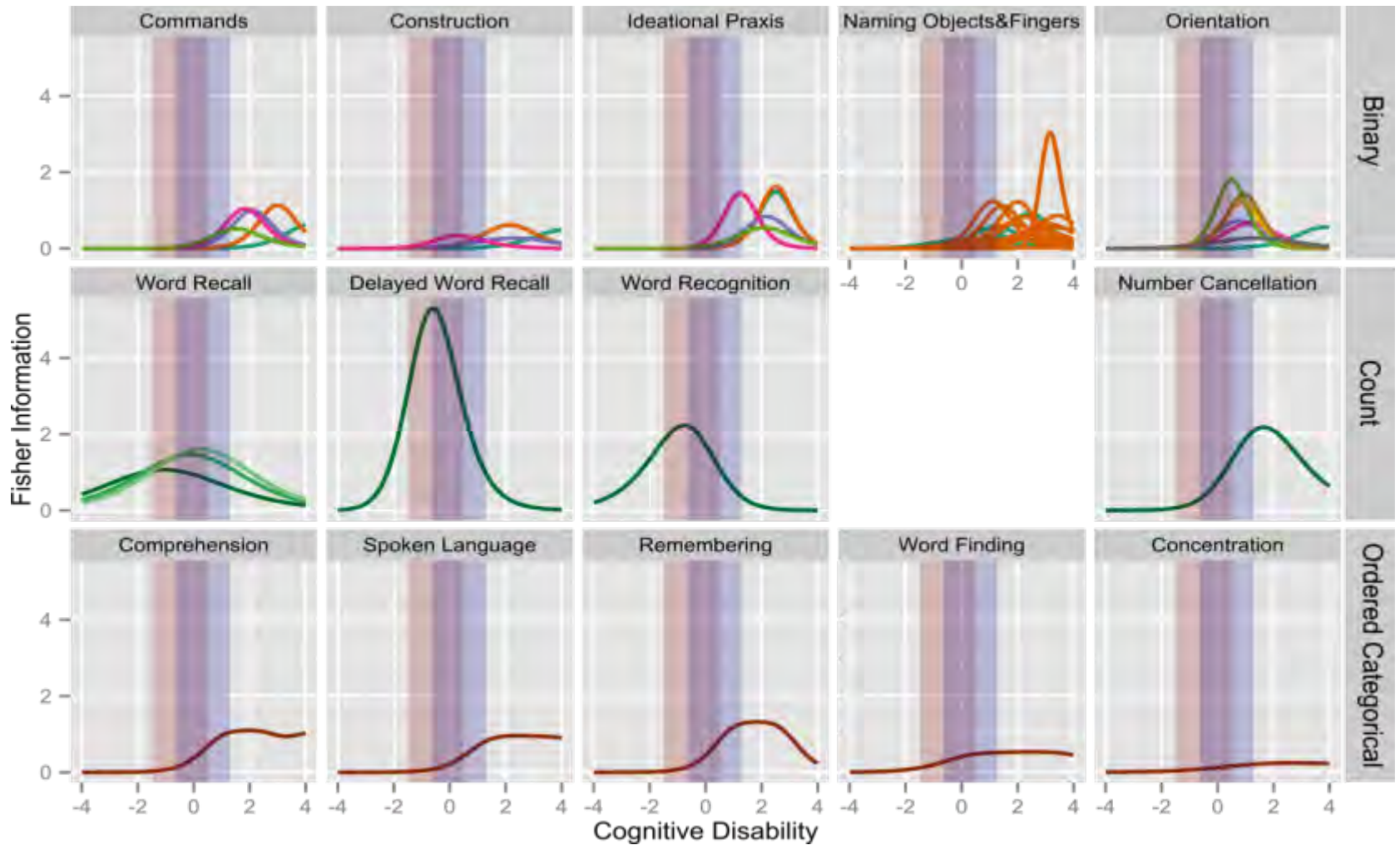
Item Information



Average Information
in Population: 3.81



Population Information





Component Ranking

MCI Population			
	Component	Information	%
1	Delayed Word Rec	4.61	29.9
2	Word Recall	3.82	24.8
3	Word Recognition	1.98	12.8
4	Orientation	1.98	12.8
5	Naming Obj&Fing	1.06	6.9

**87%
of total**

mAD Population			
	Component	Information	%
1	Orientation	4.92	22.7
2	Word Recall	3.79	17.5
3	Delayed Word Rec	3.26	15.0
4	Naming Obj&Fing	2.83	13.0
5	Number Cancellation	1.48	6.8



Adaptive Assessment

\mathbb{T}	Set of available cognitive tests
T_k	Set of already performed cognitive tests up to step k
y_k	Subject response at step k
\hat{D}_k	Disability estimate of subject after step k
σ_k^2	Associated variance of the estimate

Algorithm

$$\hat{D}_0 = 1, \sigma_0^2 = 1, k = 0$$

while $\sigma_k^2 > tol$ {

$$\tau^* = \arg \max_{j \in \mathbb{T} \setminus T_k} \int_{-\infty}^{\infty} p(x; \hat{D}_k, \sigma_k^2) \mathcal{I}_j(x) dx$$

$y_k =$ patient response to τ^*

$$T_k = T_k \cup \tau^*, k = k + 1$$

$$\hat{D}_k = \arg \max_D \sum_{j=0}^k \log f_j(y_j, D) + \log p(D; 0, 1)$$

$$\sigma_k^2 = \frac{d^2}{dD^2} \sum_{j=0}^k \log f_j(y_j, D) + \log p(D; 0, 1)$$

}



AD i.d.e.a.- Alzheimer's Disease

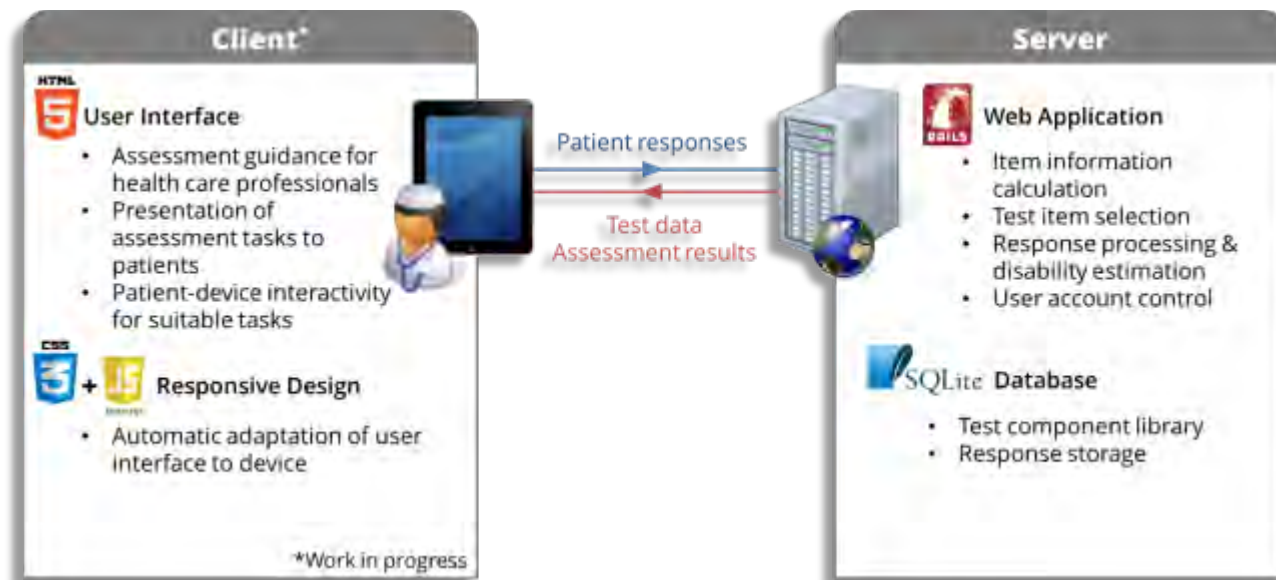
integrated dynamic electronic assessment



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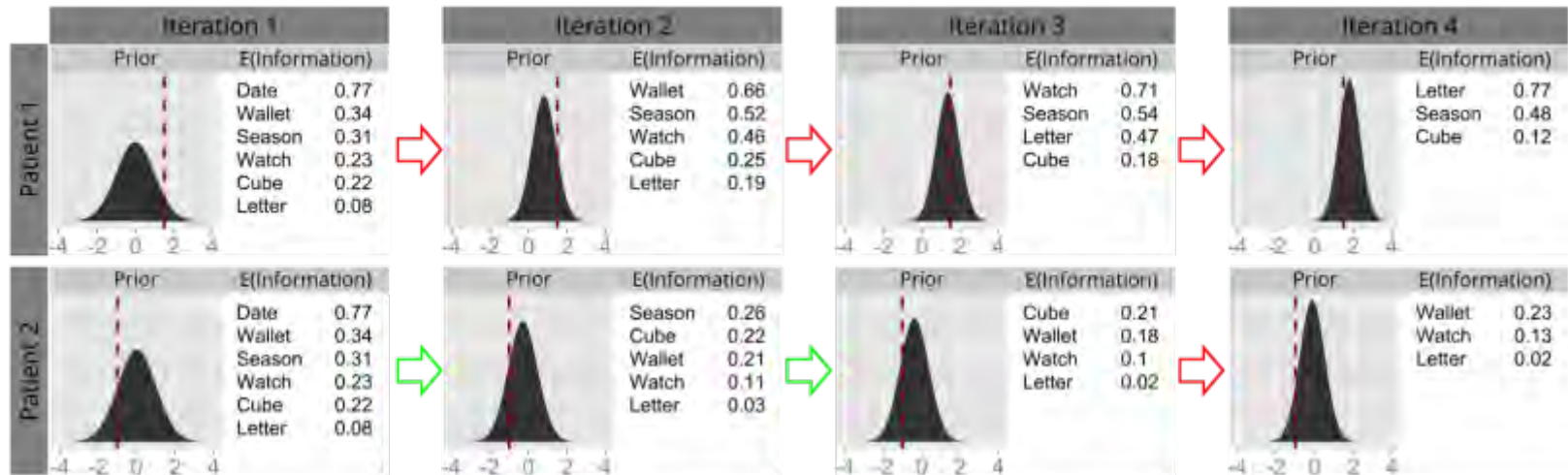
Aim: Implement adaptive testing algorithm in a web application

Architecture:





Algorithm Operation



Test items: Name Current Date
Name Current Season
Draw Cube

Fold Letter
Put Watch
Name Object "Wallet"

Legend: Patient Failed
 Patient Succeeded
 "True" Disability



Benefits of AD i.d.e.a.



AD i.d.e.a.

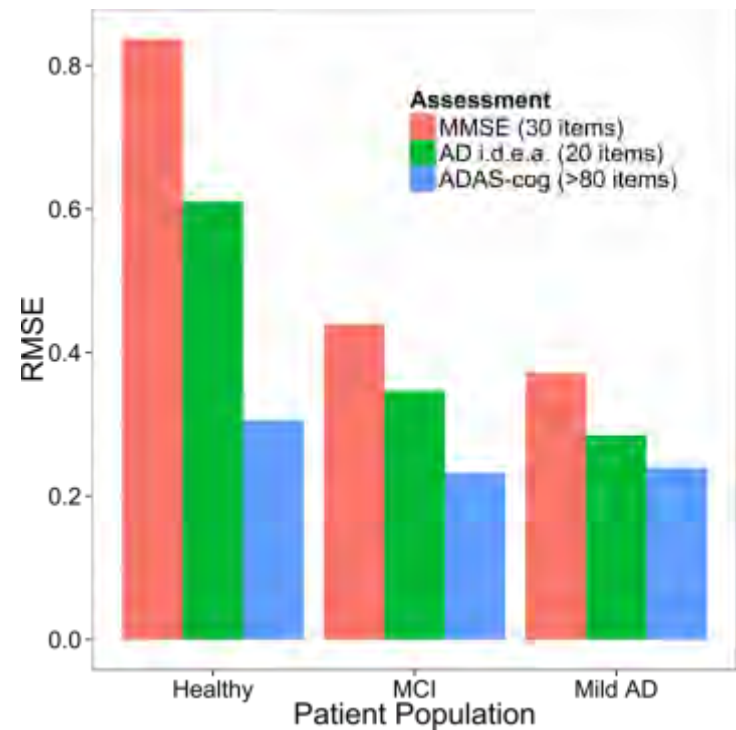
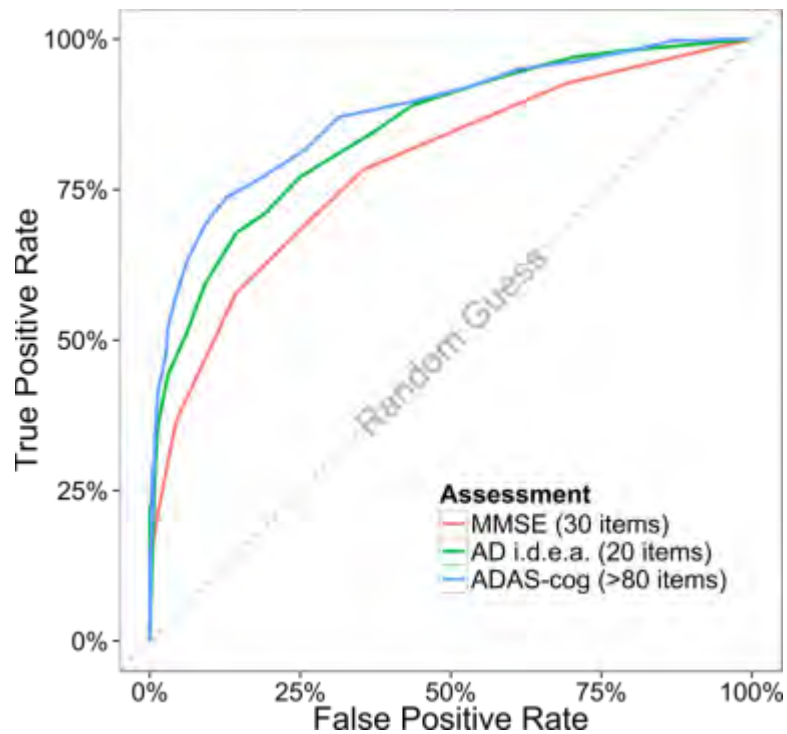
- ✓ Simplified testing procedure
- ✓ Decreased duration
- ✓ Increased sensitivity
- ✓ Assessment history
- ✓ Unique underlying scale

Clinical benefits

- + Routine cognitive testing
- + Improved diagnosis
- + More precise tracking
- + Integration of multiple existing assessments

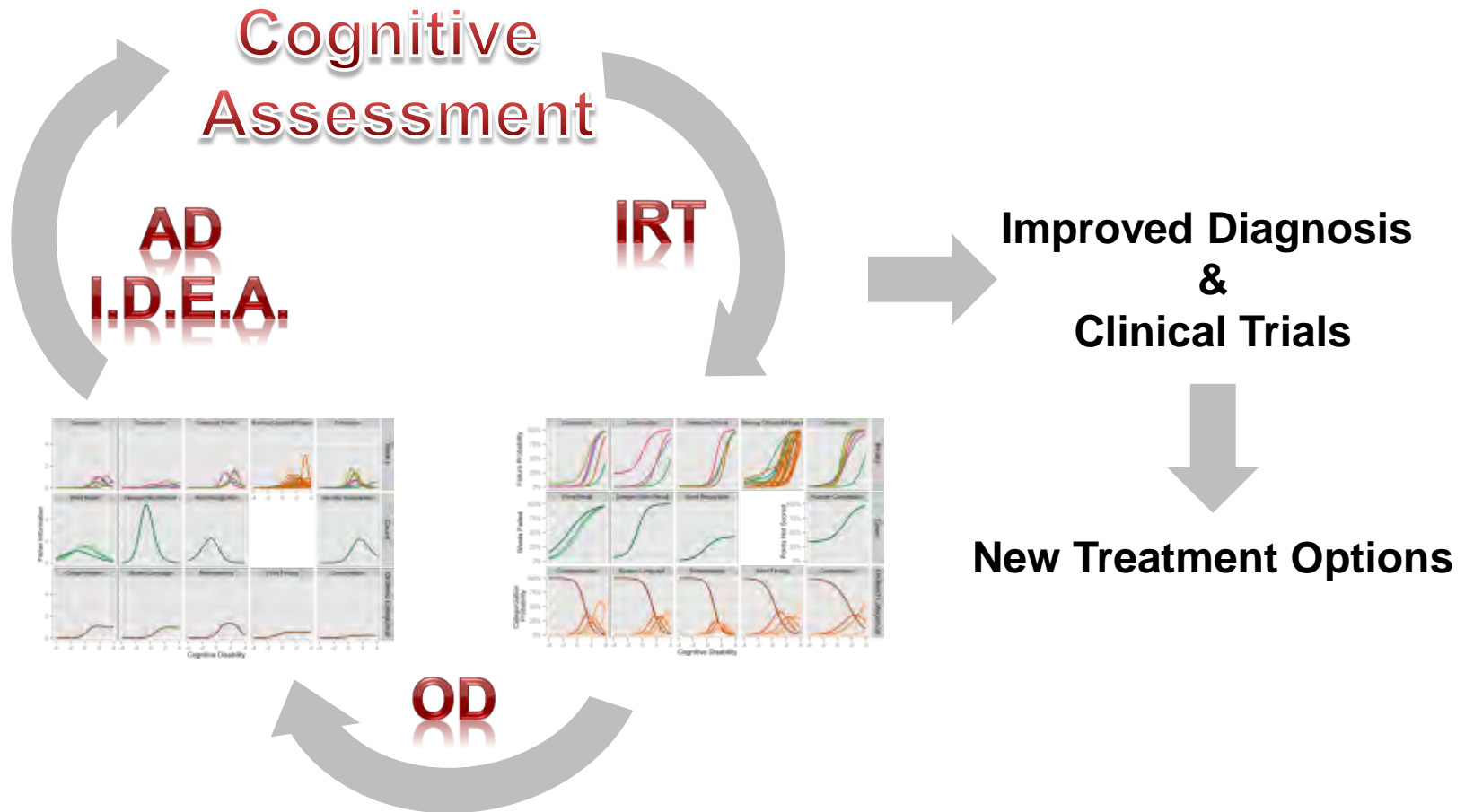


Algorithm Performance





Summary





Acknowledgements

- DDMoRe initiative



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