PODE 2013 - POPULATION OPTIMUM DESIGN OF EXPERIMENTS

Improving cognitive testing with IRT and optimal design

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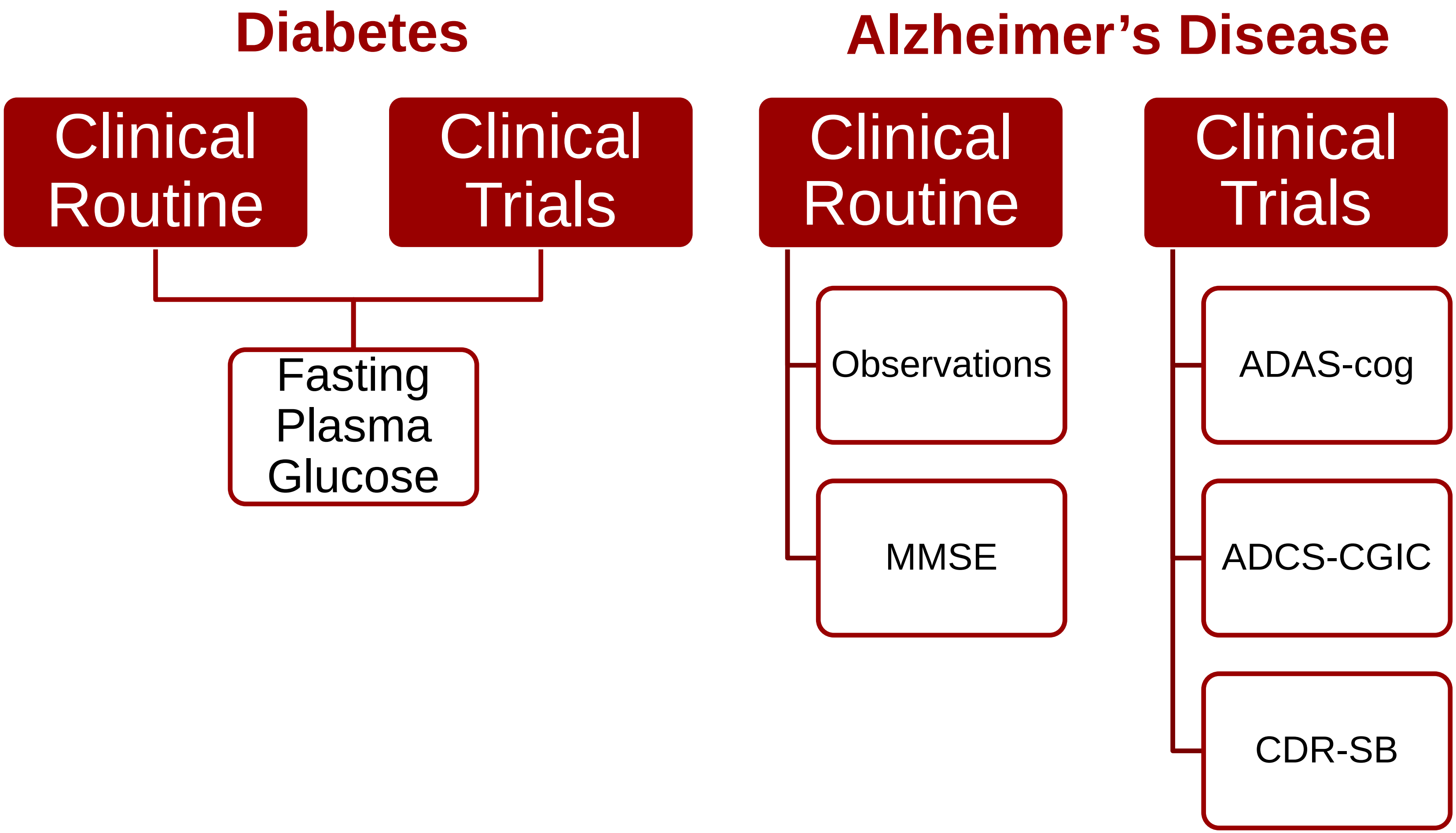
Alzheimer's Disease

- 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
Clinical Routine
Clinical Trials
Fasting Plasma Glucose
Clinical Routine
Observations
MMSE
Clinical Trials
ADAS-cog
ADCS-CGIC
CDR-SB

ADAS-cog Score

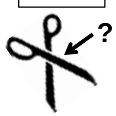
- Cognitive subscale of Alzheimer’s Disease Assessment Scale
- Cognitive assessment including broad range of sub-tests e.g.,

TASK BASED

Remembering Words

LAKE
CLOCK
FOREST
ANIMAL

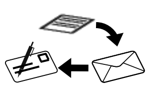
Naming Objects



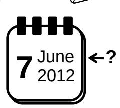
Commands

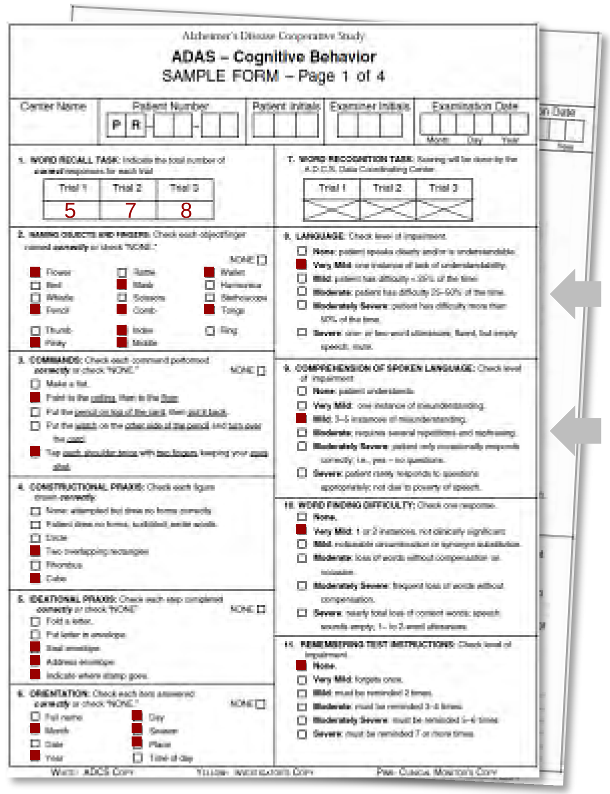
Construction

Ideational Praxis

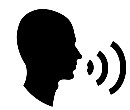


Orientation

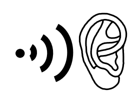




RATER ASSESSED



Ability to Speak



Ability to Understand

⋮

ADAS-cog Score

Rosen et al. 1984

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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:

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

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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

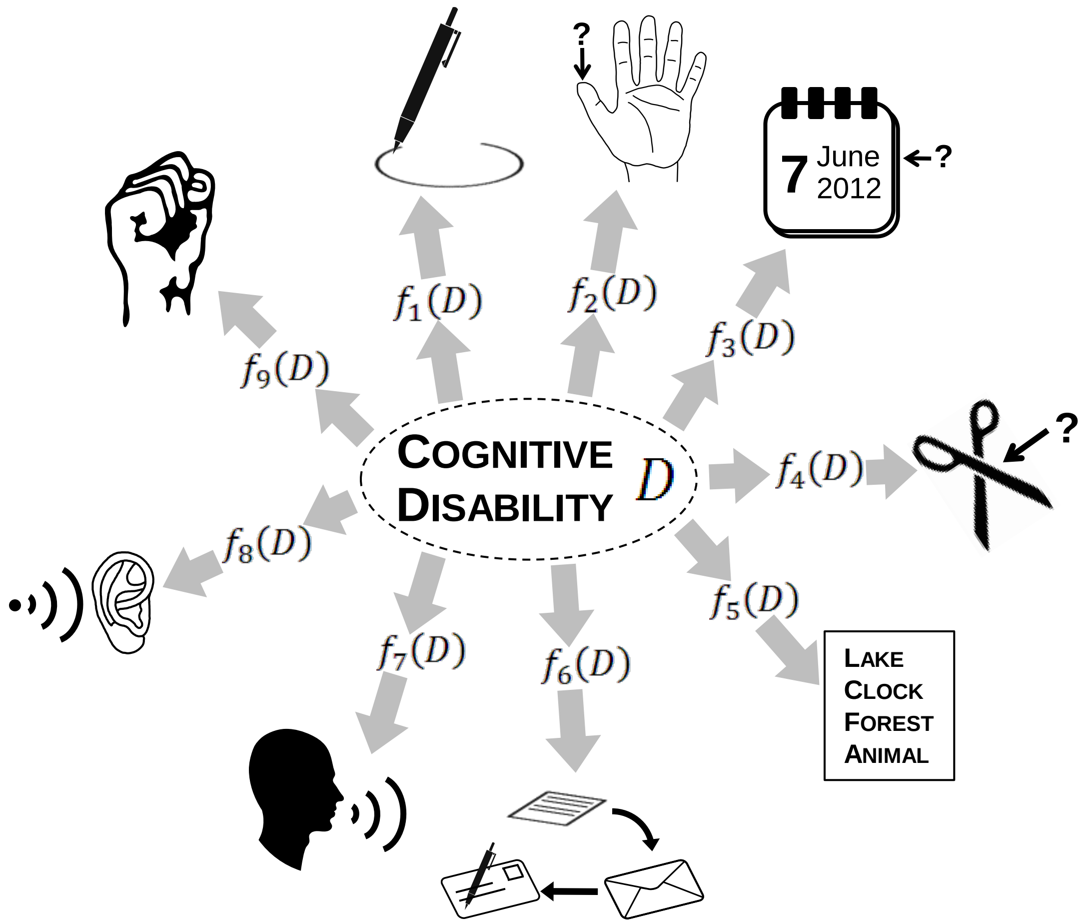
$$\mathrm{P}\left(y_{ij} = x\right) = \mathrm{f}_j(x, D_i)$$
$$D_i \sim \mathrm{Normal}(0,1)$$

Instead of summary score, calculate

$$\widehat{D}_i = \arg\max_D \sum_{j=0}^{M} \log \mathrm{f}_j\left(y_j, D\right) + \log \mathrm{p}(D; 0,1\ )$$

→ Item Response Theory

ADAS-cog IRT Model



ADAS-cog IRT Model

Latent variable model:

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

Response Models:

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

$$\boldsymbol{\kappa} = (\kappa_1, \kappa_2, \kappa_3, \kappa_4)$$

Binary:

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

Count (binomial):

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

Count (generalized Poisson):

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

Ordered categorical:

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

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

Parameter Estimation

- Test specific parameters $\mathbf{K} = (\boldsymbol{\kappa}_1, \dots, \boldsymbol{\kappa}_M)$(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

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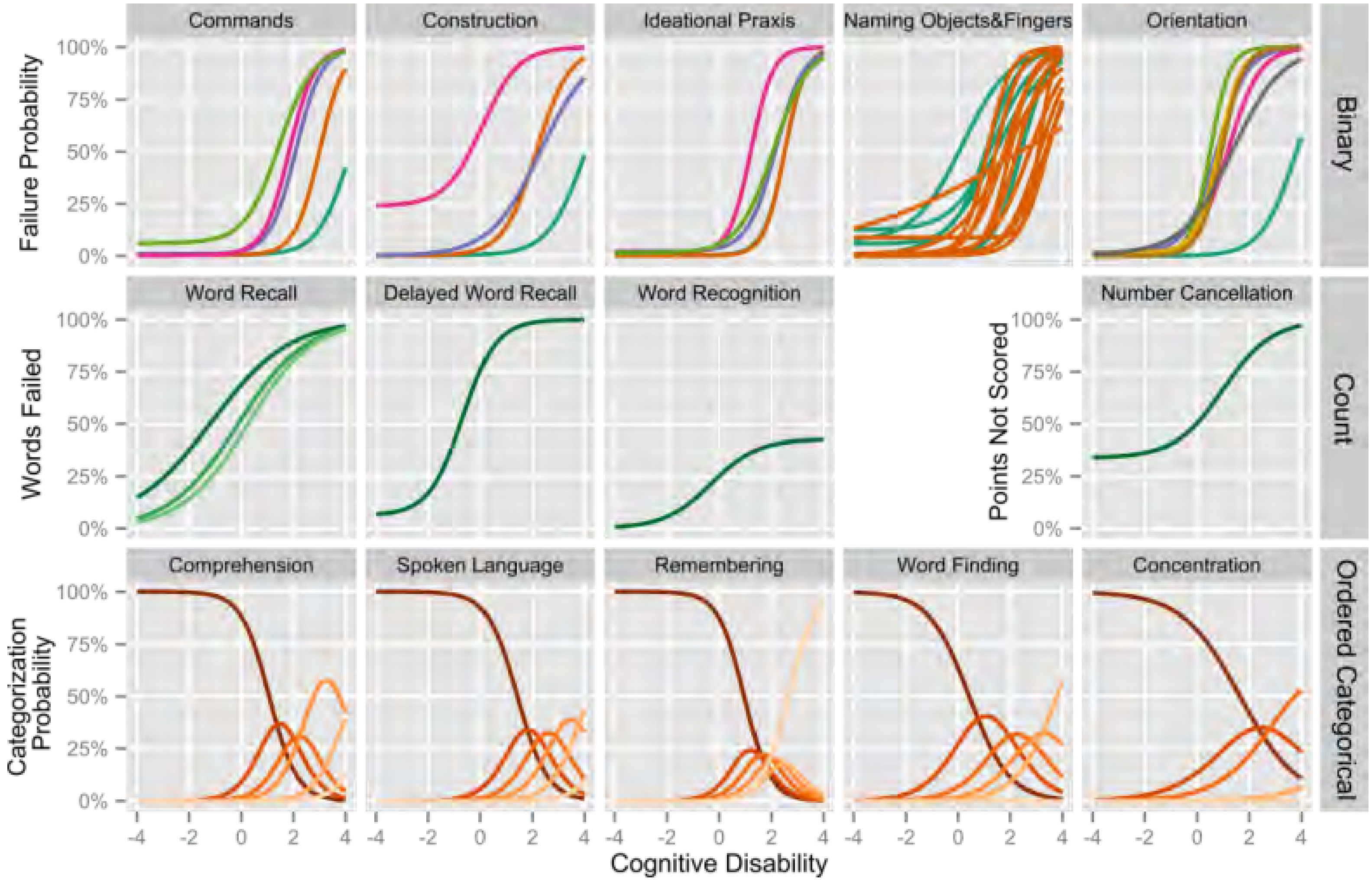
Estimated Response Functions



Item Information

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

Calculate item information function:

$$\mathcal{J}_j(D_i) = -\mathrm{E}\left[\frac{\partial^2}{\partial D_i^2}\log \mathrm{f}_j(y|D_i)\right]$$

Item Information - Binary Response

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

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

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

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

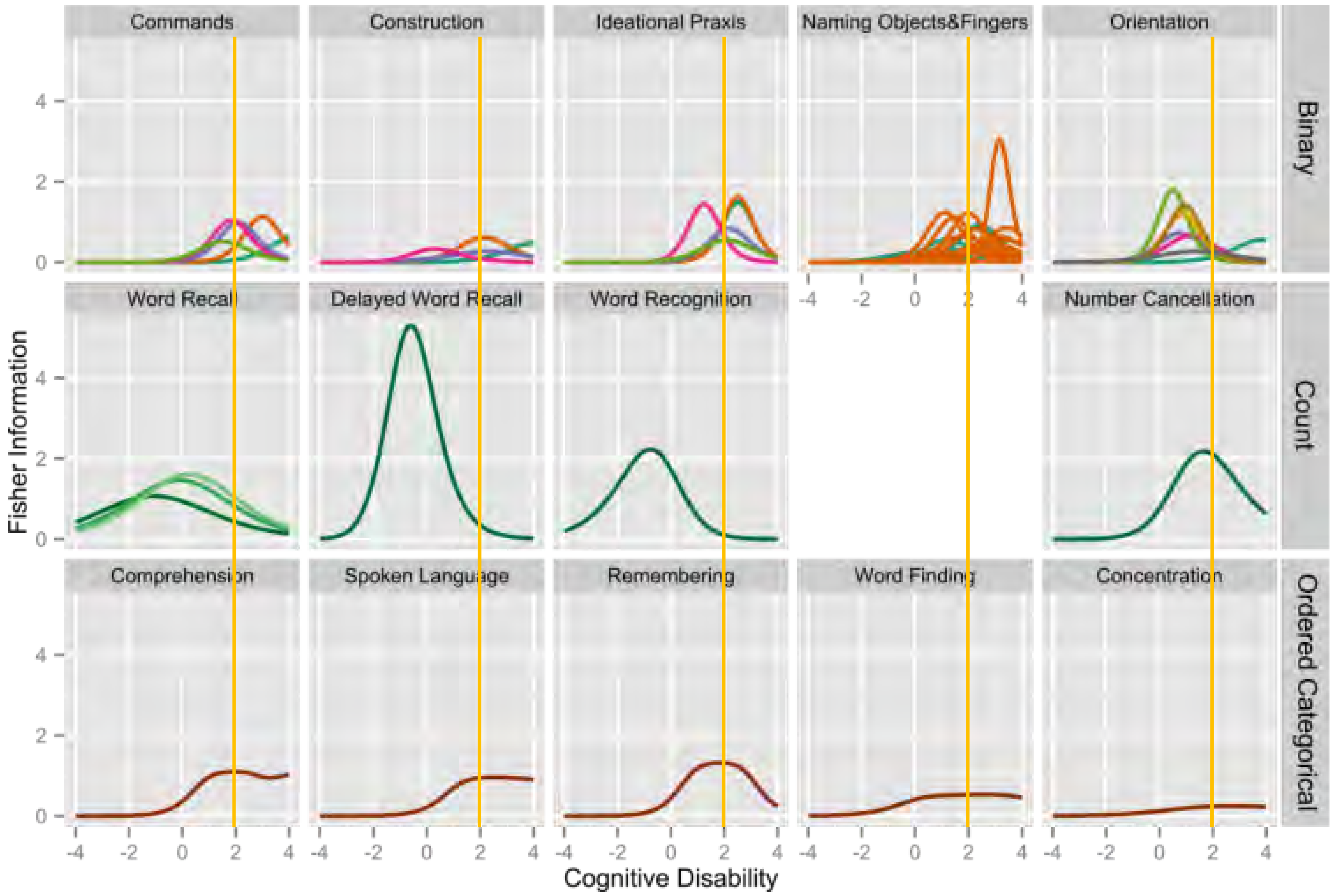
$$= -\frac{\kappa_{j3}^2 e^{\kappa_{j3}(D_i-\kappa_{j4})}(\kappa_{j1} - \kappa_{j2})\left(\kappa_{j1} - \kappa_{j2} e^{2\kappa_{j3}(D_i-\kappa_{j4})}\right)}{\left(e^{\kappa_{j3}(D_i-\kappa_{j4})} + 1\right)^2 \left(\kappa_{j1} + \kappa_{j2} e^{\kappa_{j3}(D_i-\kappa_{j4})}\right)^2}$$

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

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

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

Item Information Functions



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Population Information

Subjects disability is unknown prior to assessment

→ can't calculate individual information value

→ calculate expected information for a population to be studied

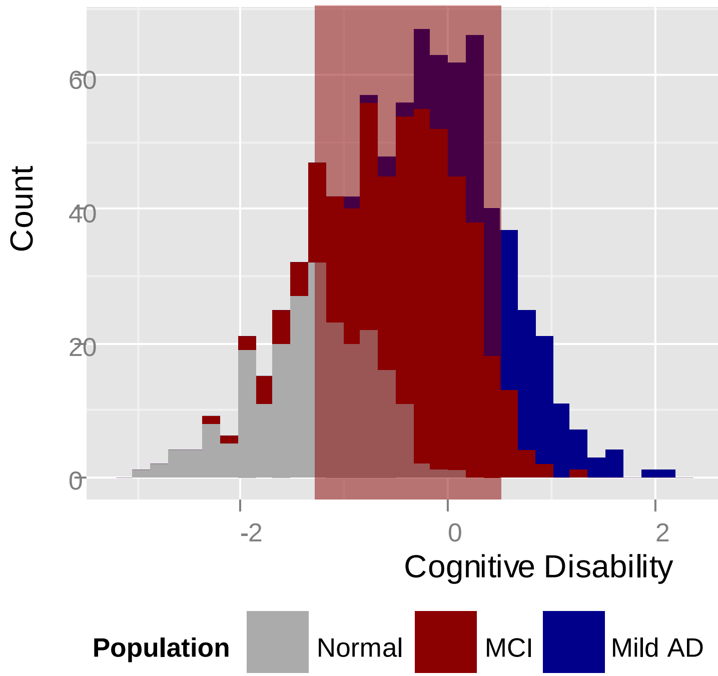
$$\bar{\mathcal{I}}_j = \mathrm{E}\left[\mathcal{I}_j(D_i)\right] = \int_{-\infty}^{\infty} \mathrm{p}\left(D_i; \mu_{\mathrm{pop}}, \sigma_{\mathrm{pop}}^2\right) \mathcal{I}_j(D_i)\, dD_i$$

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

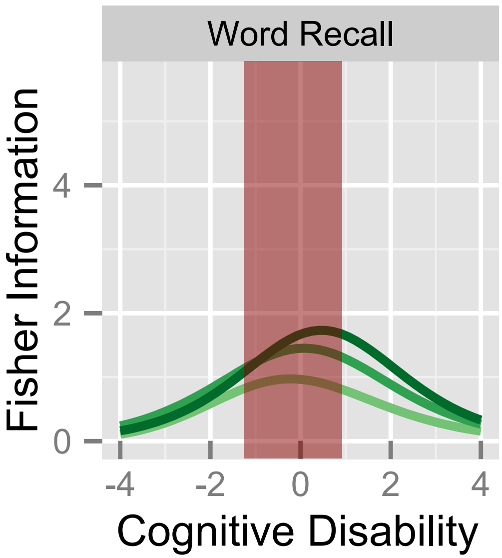
μ_{pop} and σ_{pop}^2 are estimated from ADNI data

Population Information

Disability Distribution in ADNI

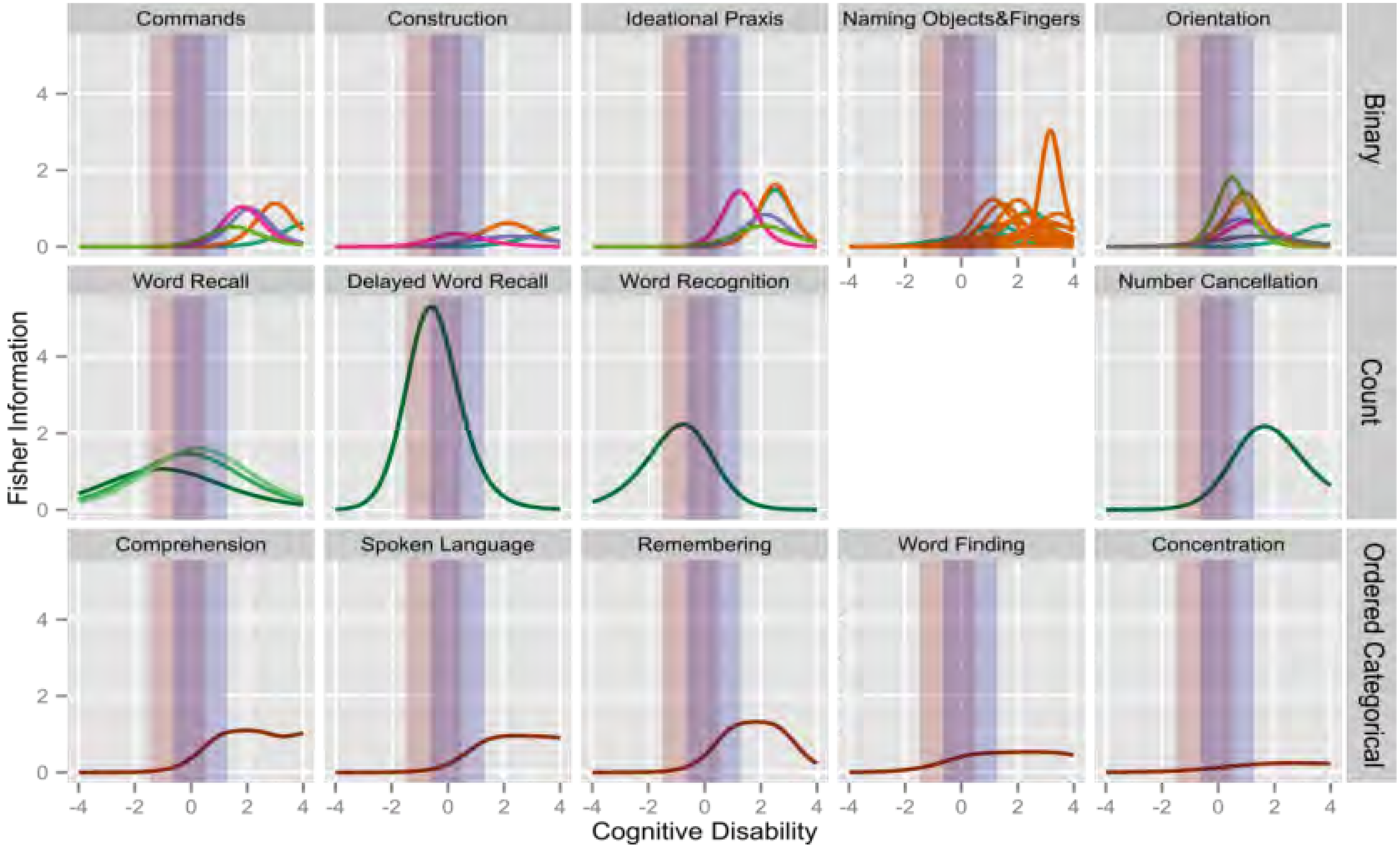


Item Information



Average Information in Population: 3.81

Population Information



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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
$\widehat{D}_k$	Disability estimate of subject after step k
σ_k^2	Associated variance of the estimate

Algorithm

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

$$\text{while } \sigma_k^2 > tol \, \{$$

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

$$y_k = \text{patient response to } \tau^*$$

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

$$\widehat{D}_k = \arg\max \sum_{j=0}^{k} \log \mathrm{f}_j\left(y_j, D\right) + \log \mathrm{p}(D; 0,1\ )$$

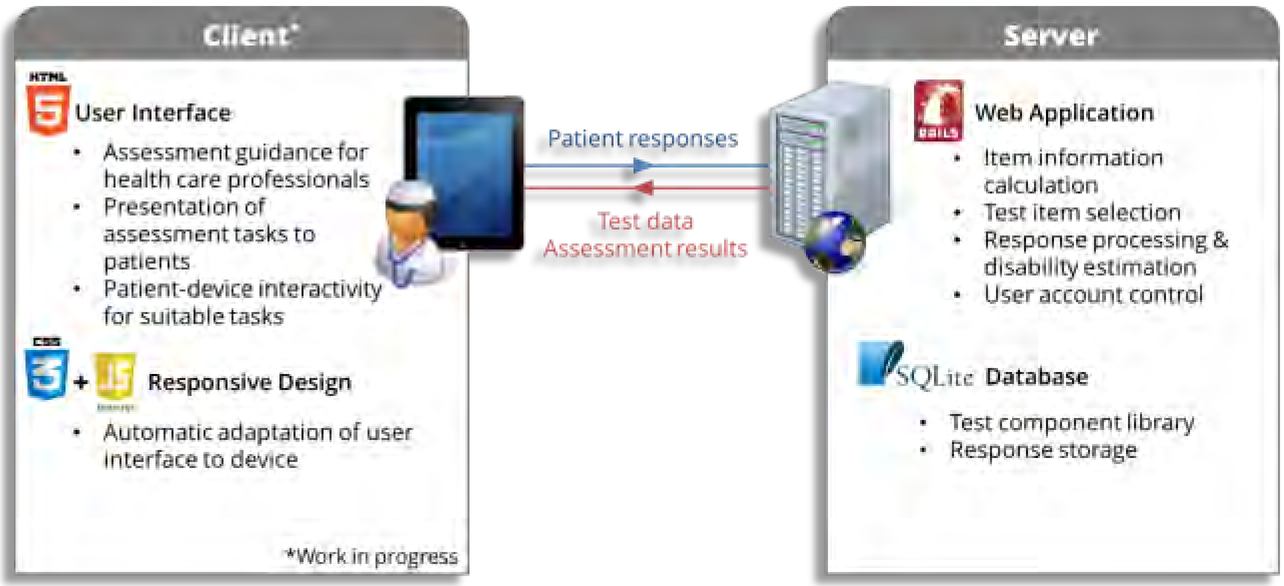
$$\sigma_k^2 = \frac{d^2}{dD^2} \sum_{j=0}^{k} \log \mathrm{f}_j\left(y_j, D\right) + \log \mathrm{p}(D; 0,1\ )$$

$$\}$$

AD i.d.e.a.- Alzheimer's Disease integrated dynamic electronic assessment

Aim: Implement adaptive testing algorithm in a web application

Architecture:



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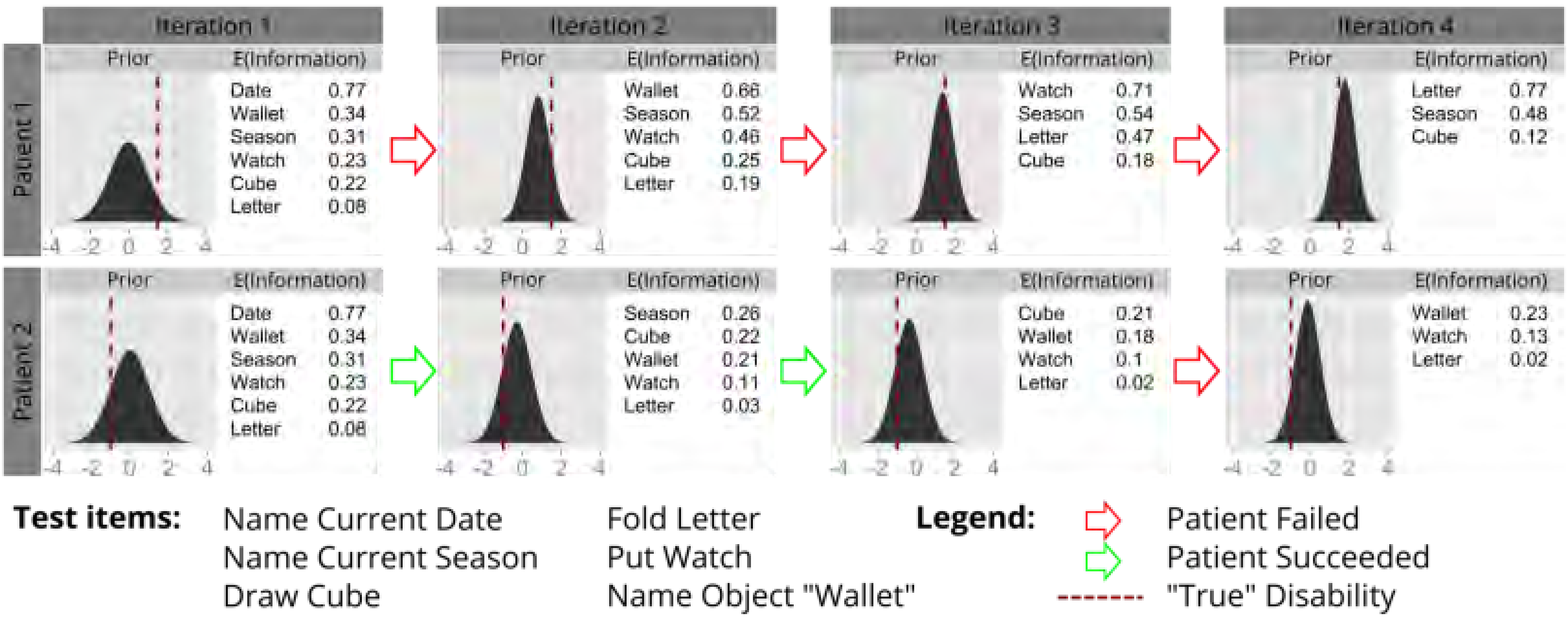
Algorithm Operation



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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

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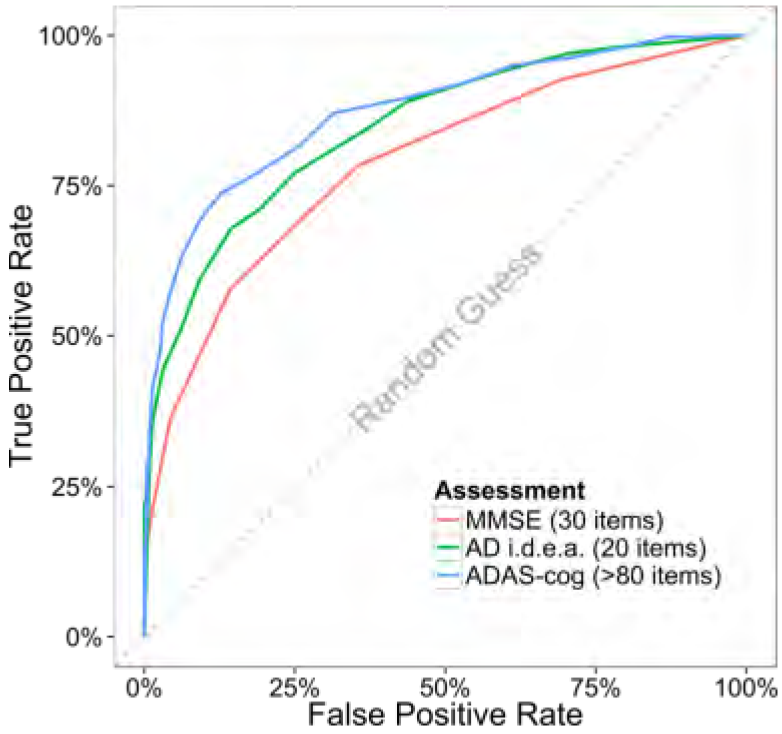
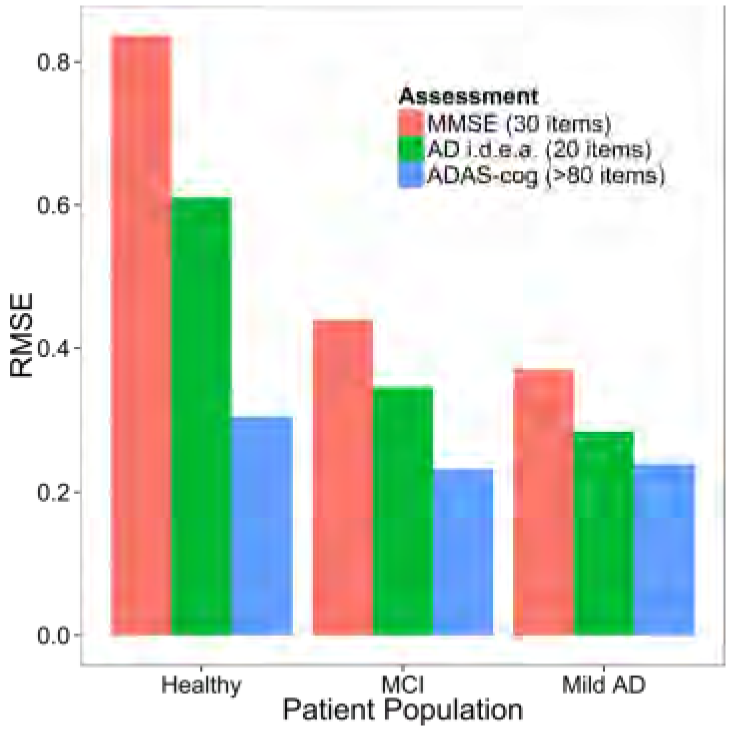
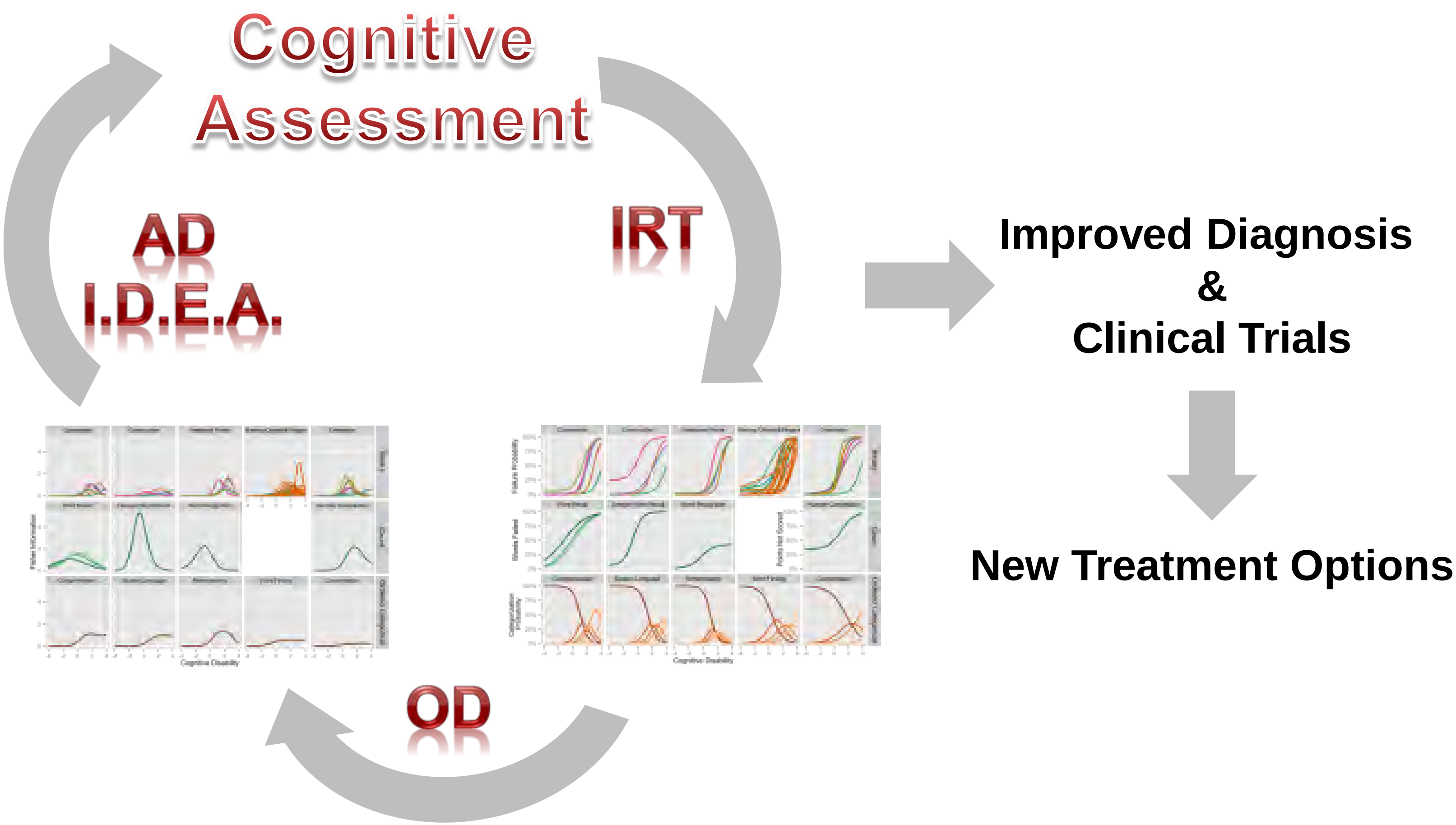
Algorithm Performance





Summary


Cognitive Assessment
IRT
AD I.D.E.A.
OD
Improved Diagnosis
&
Clinical Trials
New Treatment Options

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Acknowledgements

- DDMoRe initiative

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