Application of Item Response Theory to ADAS-cog Scores Modeling in Alzheimer's Disease

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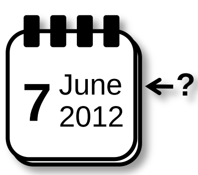
Make a fist

Draw a circle



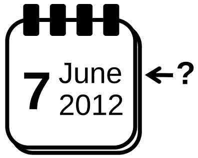
Name current month

ADAS-cog Assessment

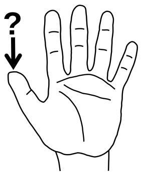
- Cognitive subscale of Alzheimer’s Disease Assessment Scale
- Cognitive assessment including broad range of sub-tests e.g.,


“Make a fist”

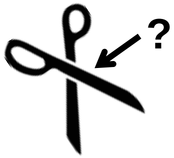

“Draw a circle”



“Name current month”



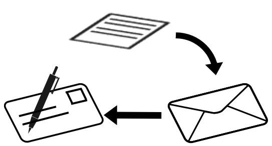
“Name finger”

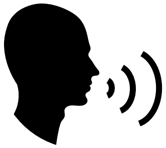


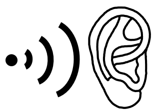
“Name object”

LAKE
CLOCK
FOREST
ANIMAL

“Remember those words”


“Fold→put in envelop→address→ stamp”


Ability to speak


Ability to understand

Rosen et al. 1984

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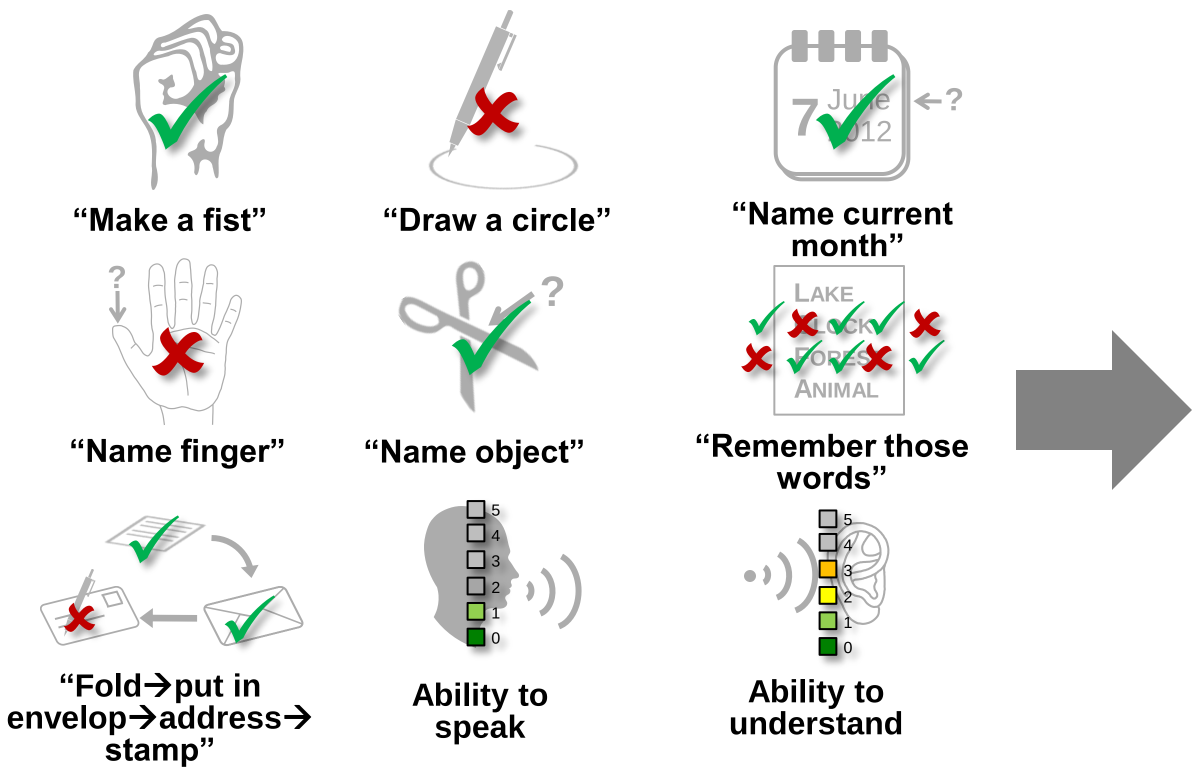
ADAS-cog Assessment

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



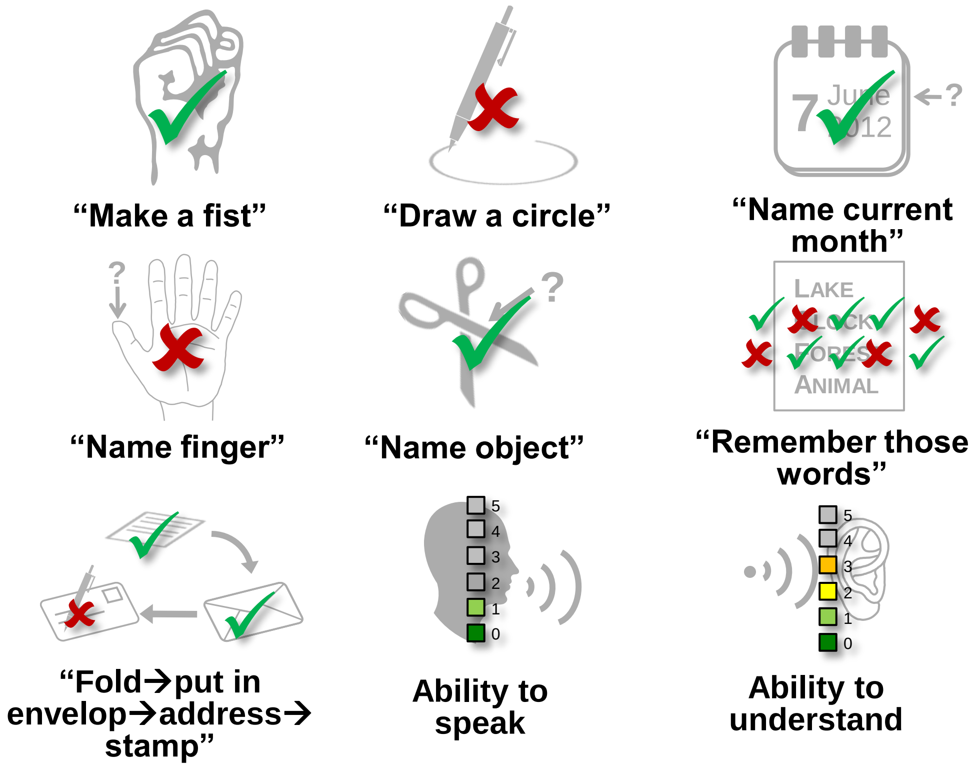
- Primary outcome
- Range 0-70
- $\Sigma_{AD}\uparrow \rightarrow$ AD severity $\uparrow$

ADAS-cog Score Σ_{AD}

Rosen et al. 1984

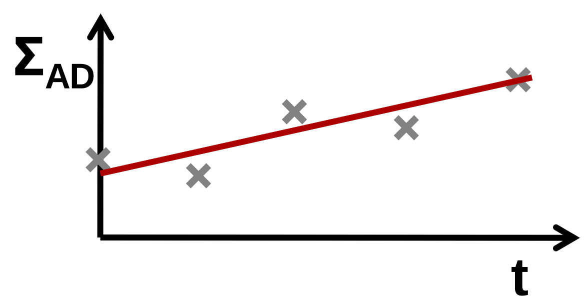
ADAS-cog Assessment

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



- Primary outcome
- Range 0-70
- $\Sigma_{AD}\uparrow \rightarrow$ AD severity $\uparrow$

ADAS-cog Score Σ_{AD}

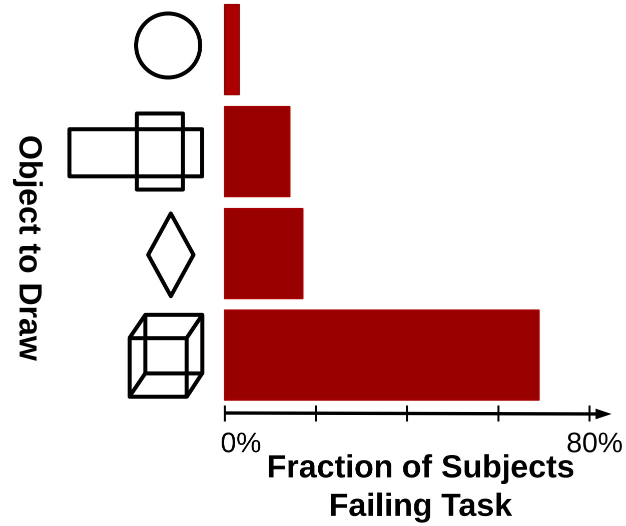


Rosen et al. 1984

Score Properties

- Tasks have varying difficulty e.g., construction or drawing task

Non-linear scale



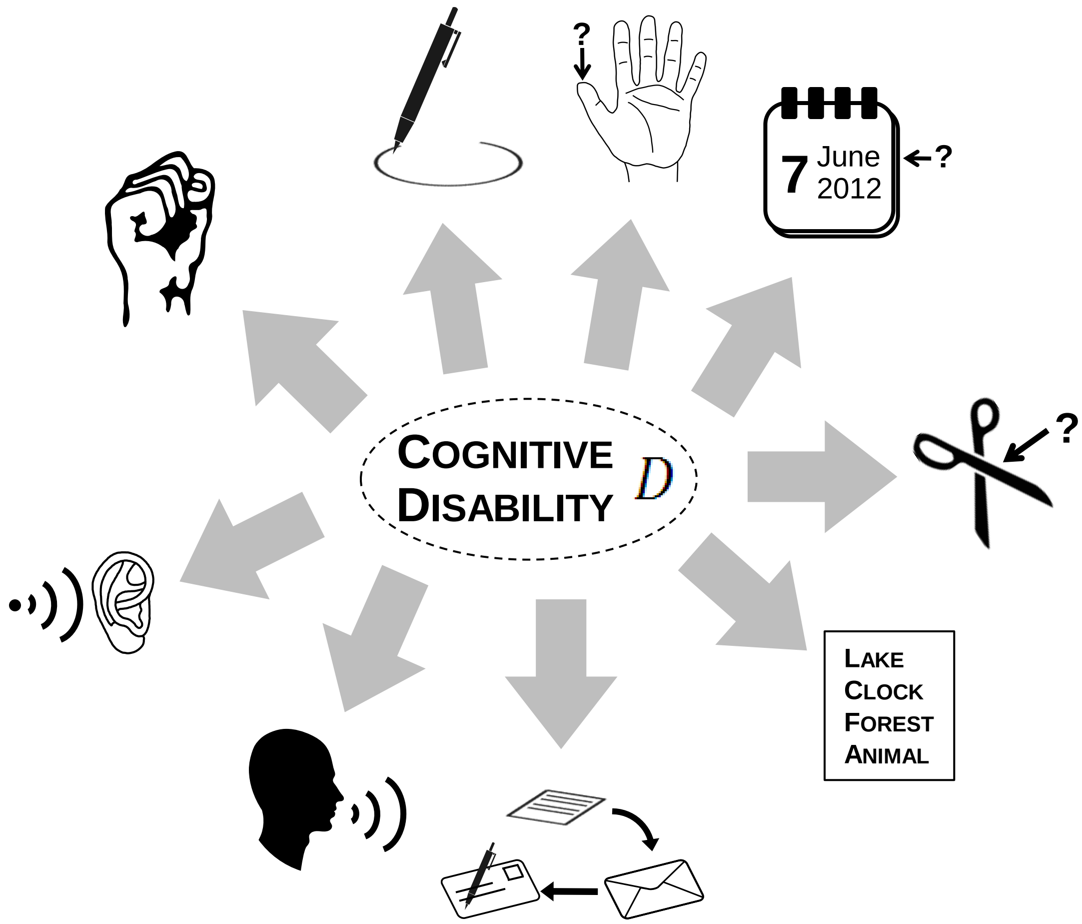
- Imputation necessary if subject refuses task or physician omits it

Bias

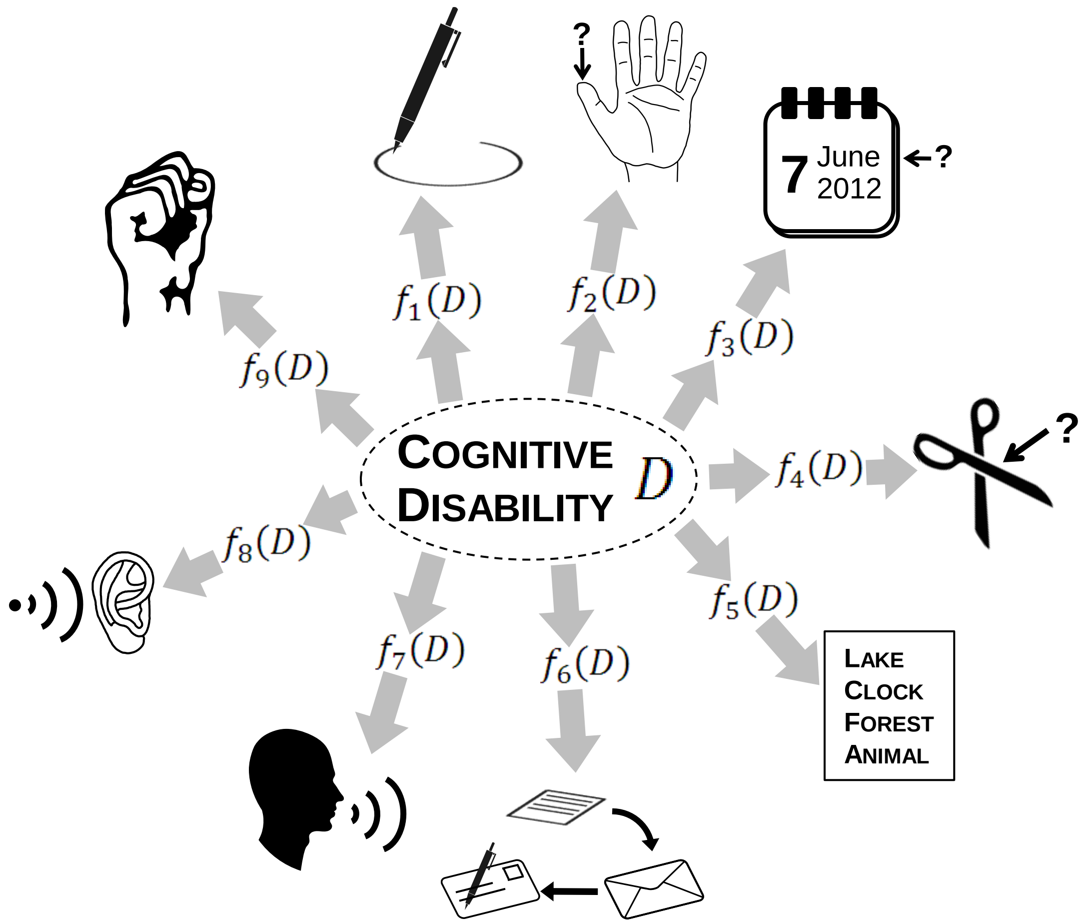
- ADAS-cog in study A ≠ ADAS-cog in study B
  - Different test versions (ADAS-cog$_{11}$, ADAS-cog$_{mod}$, ADAS-cog$_{13}$, ADAS-cog$_{MCI}$)

Hard to pool data

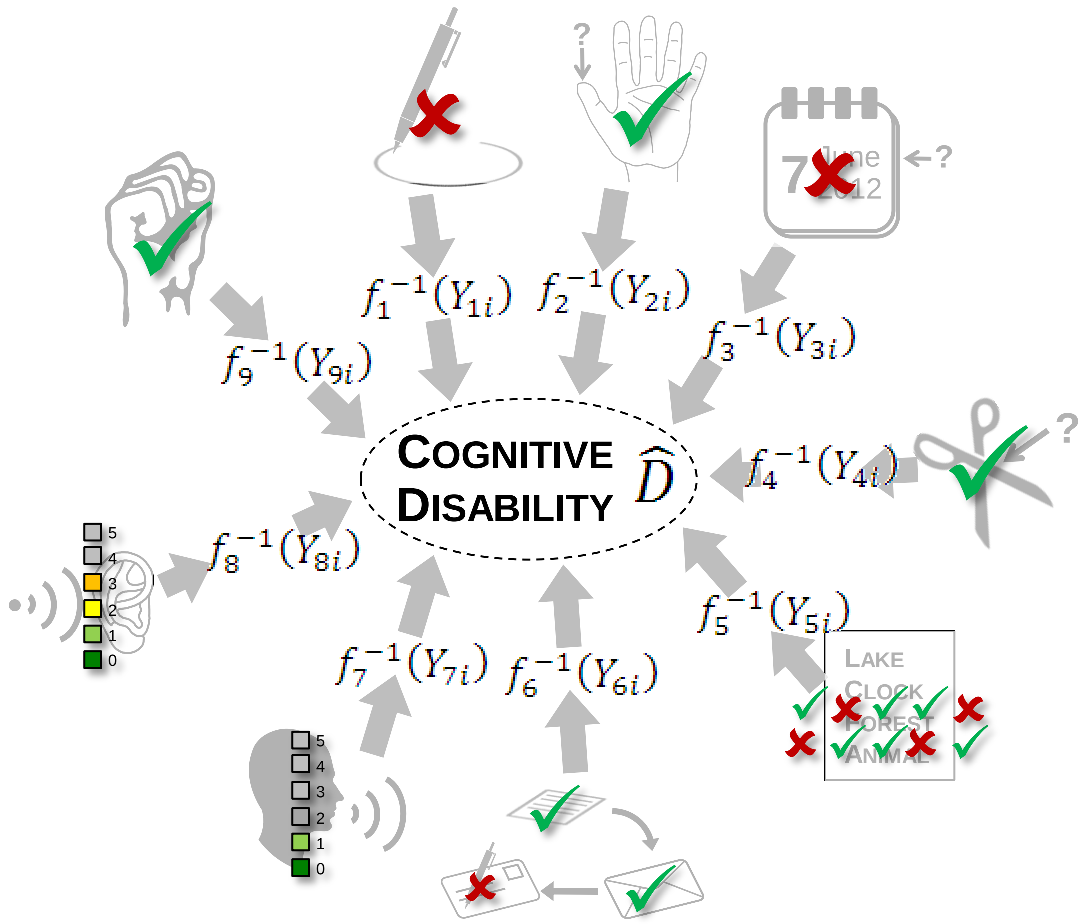
Cognitive Disability



Cognitive Disability



Cognitive Disability



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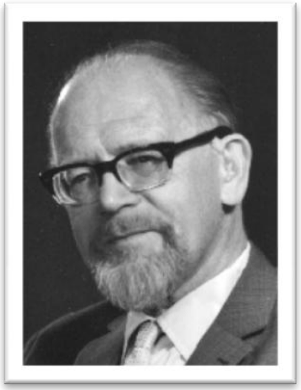
Item Response Theory



Georg Rasch

Paul Lazarsfeld

Statistical framework to score tests or surveys consisting of several dichotomous (or polytomous) responses

Developed around 1950 by Rasch and Lazarsfeld

Assumption:

Individual responses for each item depend on a hidden variable (trait or ability)

- Describes the probability of a certain test outcome as the function of a person's ability
- Directly estimates the most likely ability, instead of summary scores

Used in psychometrics for the development of high-stakes tests

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Project Outline

- **Assumption:**

Outcome of each test in the ADAS-cog assessment depends on unobserved variable “cognitive disability”

- **Approach:**
  1. Develop IRT model for ADAS-cog assessment using data from clinical trial databases
  2. Apply ADAS-cog IRT model to longitudinal clinical trial data
  3. Investigate benefits of IRT model

Baseline Model

Data

ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

- Observational study with normal, mild cognitively impaired (MCI) and mild AD subjects
- Baseline ADAS-cog data
- 819 subjects

CAMD CRITICAL PATH INSTITUTE

- Database with placebo arm data from clinical trials
- First visit ADAS-cog data from 6* CAMD studies (Phase II & III)
- 1832 subjects

>150000 data entries in total

http://www. adni-info.org
http://www.c-path.org

**Studies with item level data as of November 2011*

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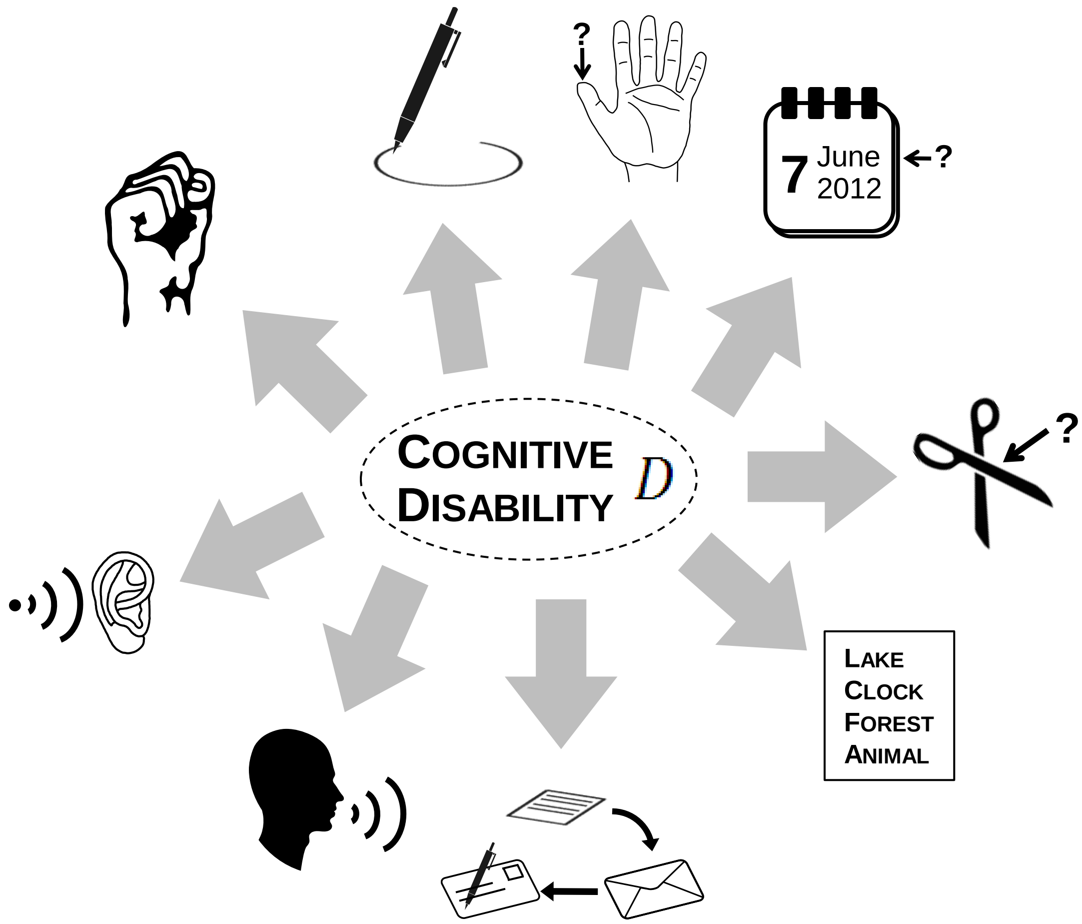
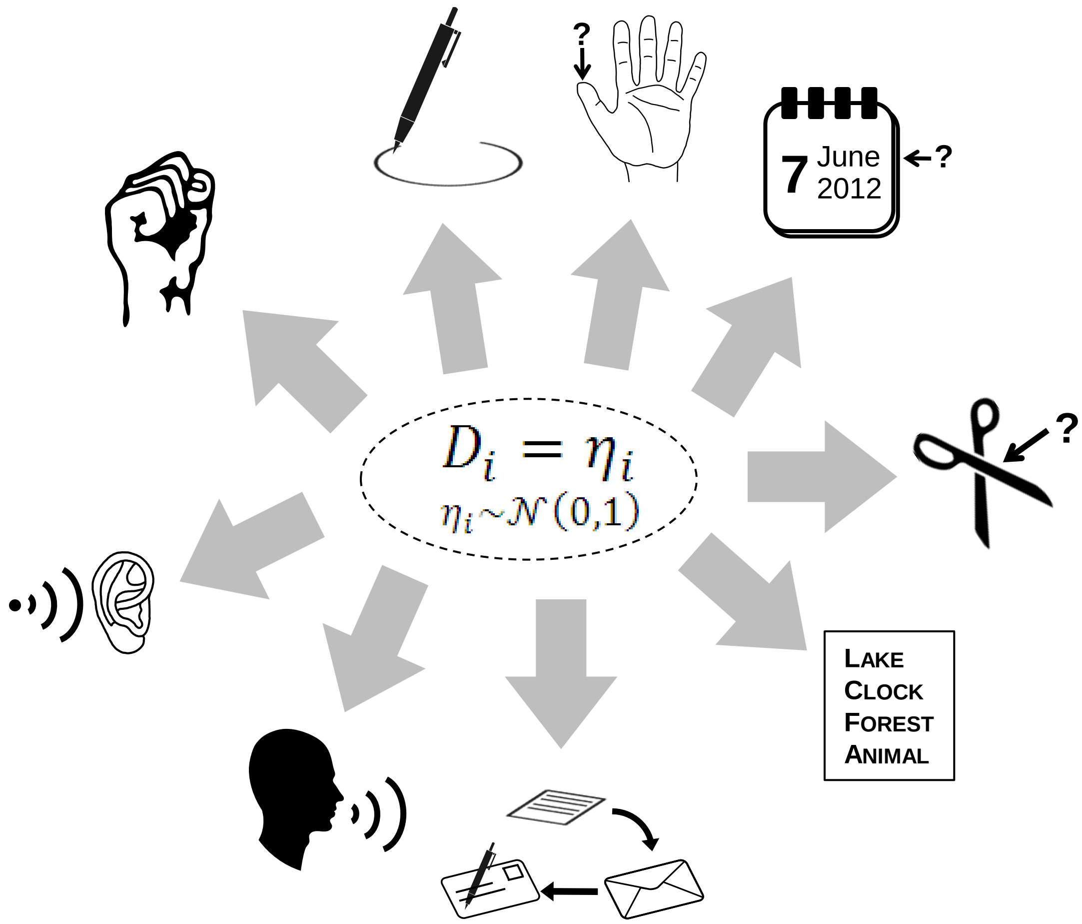
Model



Model



$D_i = \eta_i$
$\eta_i \sim \mathcal{N}(0,1)$
?
7 June 2012
?
?
Lake
Clock
Forest
Animal

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Model

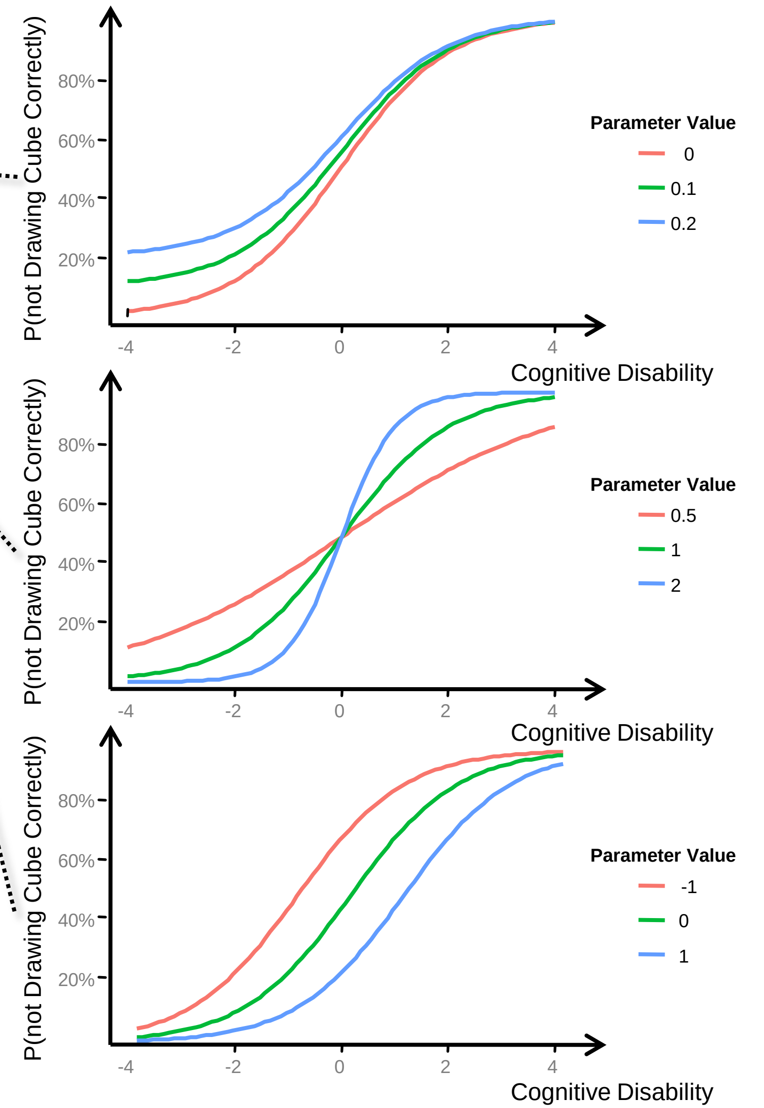
Test specific

$$P(Y_{ji} = 1) = c_j + (1 - c_j)\frac{e^{a_j(D_i - b_j)}}{1 - e^{a_j(D_i - b_j)}}$$

Binary

Subject specific

$$D_i = \eta_i$$
$$\eta_i \sim \mathcal{N}(0, \omega^2)$$



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Model

$$P(Y_{ji} = 1) = c_j + (1 - c_j)\frac{e^{a_j(D_i - b_j)}}{1 - e^{a_j(D_i - b_j)}}$$

Binary (x 39)

$$\begin{cases} p_{ij} = c_j + (1 - c_j)\dfrac{e^{a_j(D_i - b_j)}}{1 - e^{a_j(D_i - b_j)}} \\ P(Y_{ji} = k) = \dbinom{n}{k} p_{ij}^{k}(1 - p_{ij})^{n-k} \end{cases}$$

Binomial (x 3)

$$D_i = \eta_i$$

$$\eta_i \sim \mathcal{N}(0, \omega^2)$$

Generalized Poisson (x 1)

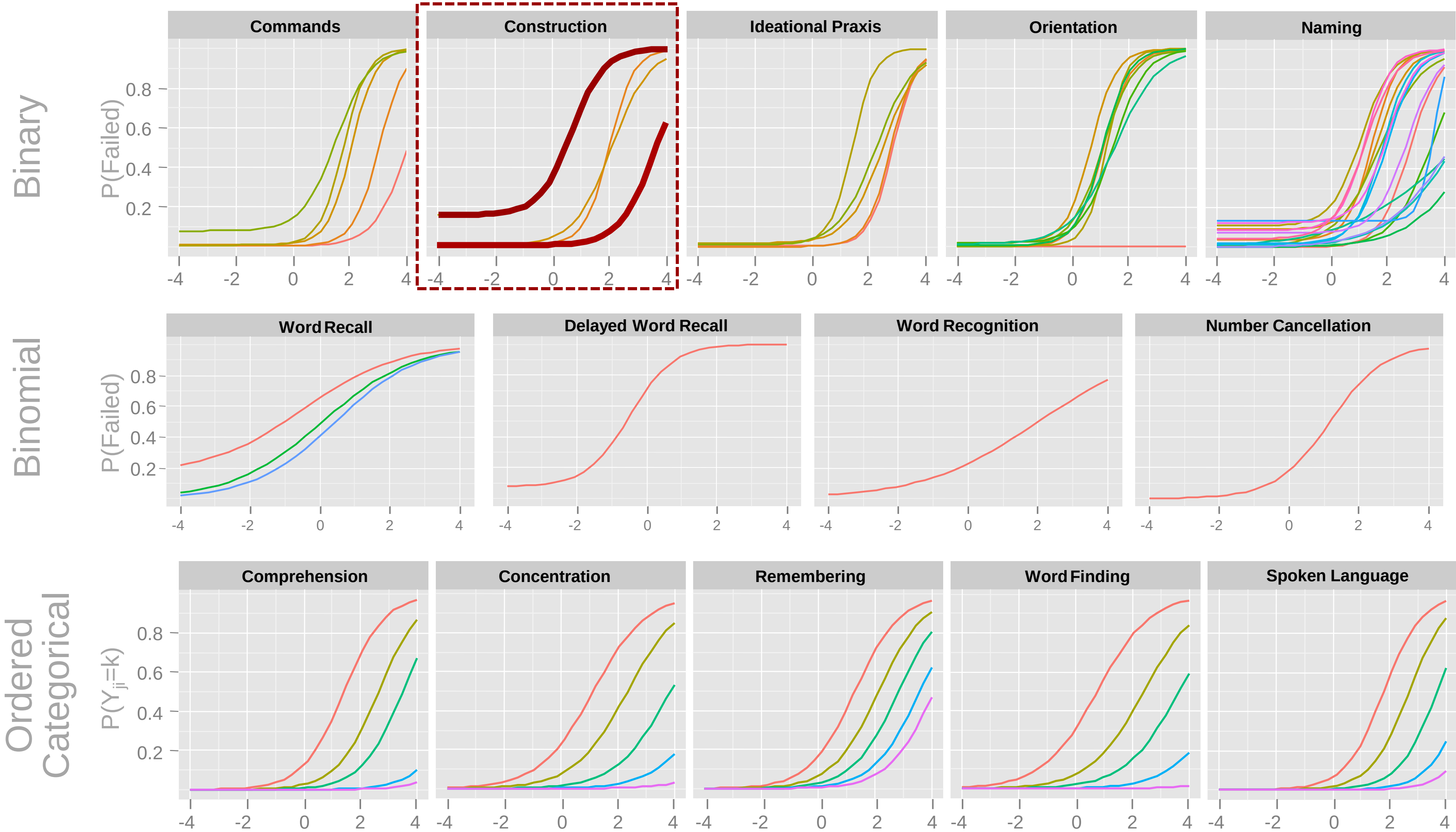
Ordered Categorical (x 5)

$$\begin{cases} P(Y_{ji} \geq k) = \dfrac{e^{a_j(D_i - b_j)}}{1 - e^{a_j(D_i - b_j)}} \\ P(Y_{ji} = k) = P(Y_{ji} \geq k) - P(Y_{ji} \geq k + 1) \end{cases}$$

167 Parameters

- 166 fixed effect
- 1 random effect

Results


Binary
Binomial
Ordered Categorical
P(Failed)
$P(Y_{ji}=k)$
Commands
Construction
Ideational Praxis
Orientation
Naming
Word Recall
Delayed Word Recall
Word Recognition
Number Cancellation
Comprehension
Concentration
Remembering
Word Finding
Spoken Language

Longitudinal Model

Data

- Placebo arm of Phase III study with mild to moderate AD patients
- 18 month with 6 ADAS-cog assessments
- 322 subjects

84907 observations in total

Model

$$P\left(Y_{ji}=1\right)=c_j+\left(1-c_j\right)\frac{e^{a_j\left(D_i-b_j\right)}}{1-e^{a_j\left(D_i-b_j\right)}}$$

Binary (x 39)

$$\begin{cases} p_{ij}=c_j+\left(1-c_j\right)\dfrac{e^{a_j\left(D_i-b_j\right)}}{1-e^{a_j\left(D_i-b_j\right)}} \\ P\left(Y_{ji}=k\right)=\binom{n}{k}p_{ij}^{k}\left(1-p_{ij}\right)^{n-k} \end{cases}$$

Binomial (x 3)

$$D_i=\eta_i$$
$$\eta_i \sim \mathcal{N}\left(0,\omega^2\right)$$

Ordered Categorical (x 5)

$$\begin{cases} P\left(Y_{ji}\geq k\right)=\dfrac{e^{a_j\left(D_i-b_j\right)}}{1-e^{a_j\left(D_i-b_j\right)}} \\ P\left(Y_{ji}=k\right)=P\left(Y_{ji}\geq k\right)-P\left(Y_{ji}\geq k+1\right) \end{cases}$$

Generalized Poisson (x 1)

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Model

$$P(Y_{ji}=1)=c_j+(1-c_j)\frac{e^{a_j(D_i-b_j)}}{1-e^{a_j(D_i-b_j)}}$$

$$\begin{cases} p_{ij}=c_j+(1-c_j)\dfrac{e^{a_j(D_i-b_j)}}{1-e^{a_j(D_i-b_j)}} \\ P(Y_{ji}=k)=\binom{n}{k}p_{ij}^k(1-p_{ij})^{n-k} \end{cases}$$

Binary (x 39)

Binomial (x 3)

$$D_i(t)=D_{0i}+\alpha_i t$$

$$D_{0i}=\theta_1+\eta_{1i}$$

$$\alpha_i=\theta_2(1+\eta_{2i})$$

$$\eta_x\sim N(0,\Omega)$$

Ordered Categorical (x 5)

Generalized Poisson (x 1)

$$\begin{cases} P(Y_{ji}\geq k)=\dfrac{e^{a_j(D_i-b_j)}}{1-e^{a_j(D_i-b_j)}} \\ P(Y_{ji}=k)=P(Y_{ji}\geq k)-P(Y_{ji}\geq k+1) \end{cases}$$

5 Parameters

- 2 fixed effect
- 2 random effect
- 1 covariance

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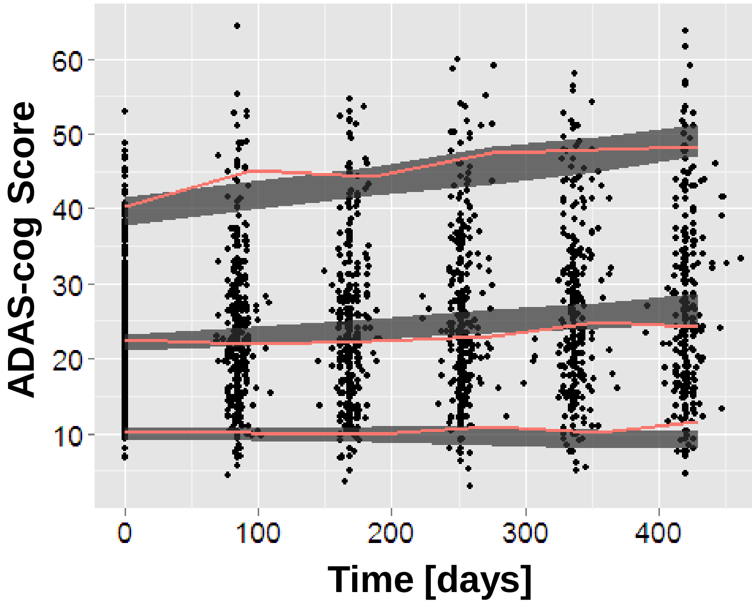
Results

- All parameters estimated precisely (assessed through - Hessian of log-likelihood)
- Corresponding to baseline ADAS-cog value of 22.2 points and yearly increase of 3.5 points

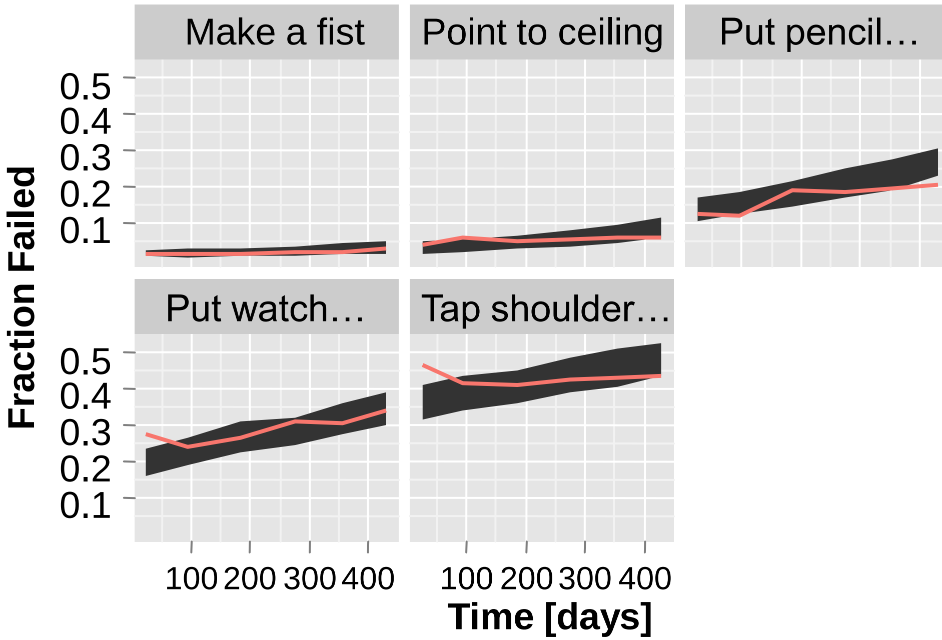
Parameter	Value	RSE
Baseline θ_1	0.96	4.2 %
Slope θ_2	$8.80 \cdot 10^{-04}$	8.7 %
IIV Baseline ω_1	0.71	5.4 %
IIV Slope ω_2	1.3	8.9 %
Cor(η_1,η_2)	0.528	10.1 %

Diagnostics

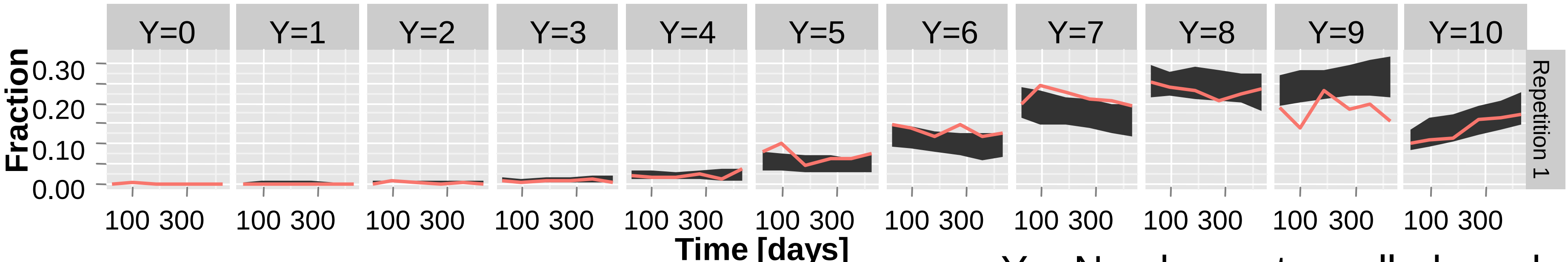
Summary Score



Commands Test



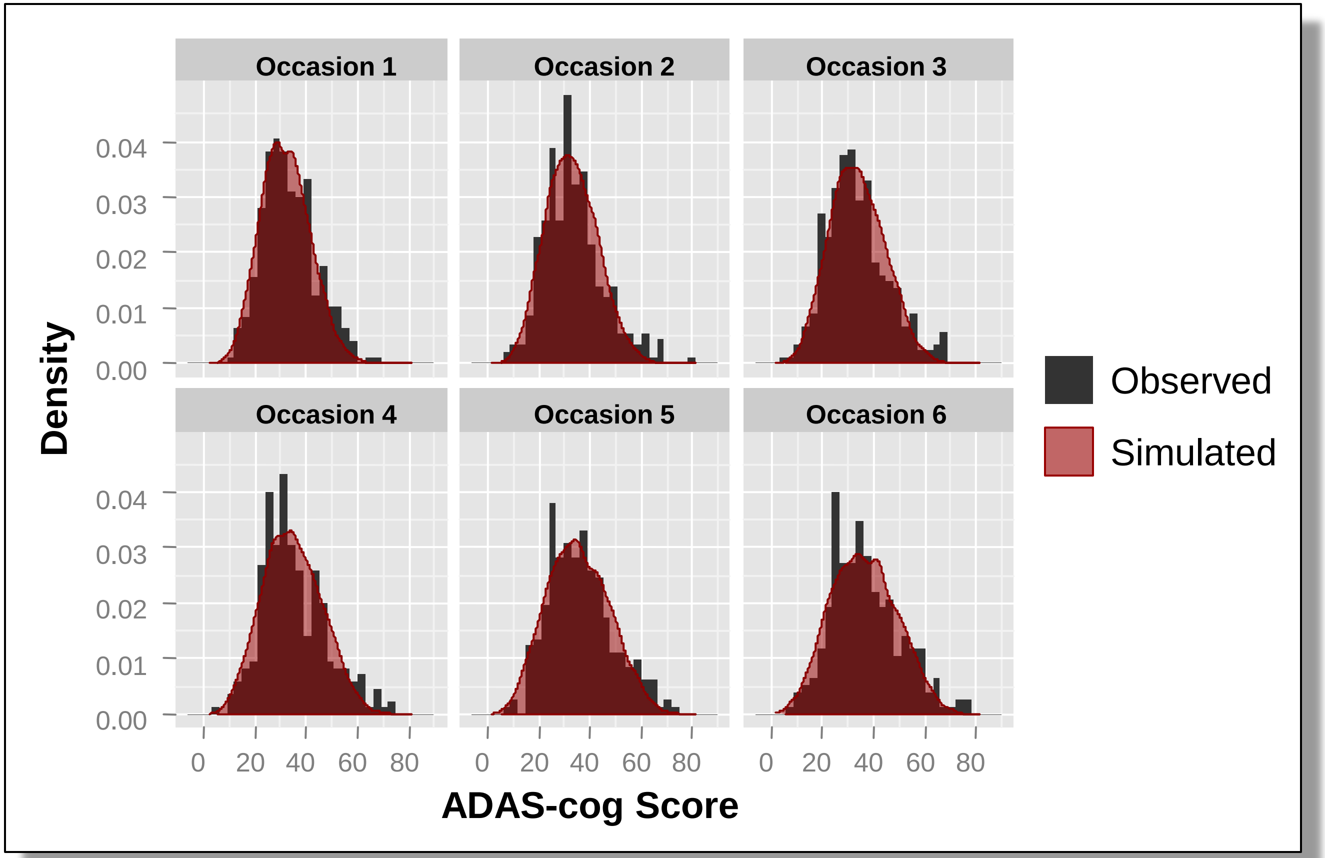
Word Recall Test



Y = Number not recalled words

Benefits of the IRT Approach

Handle the True Nature of the Score



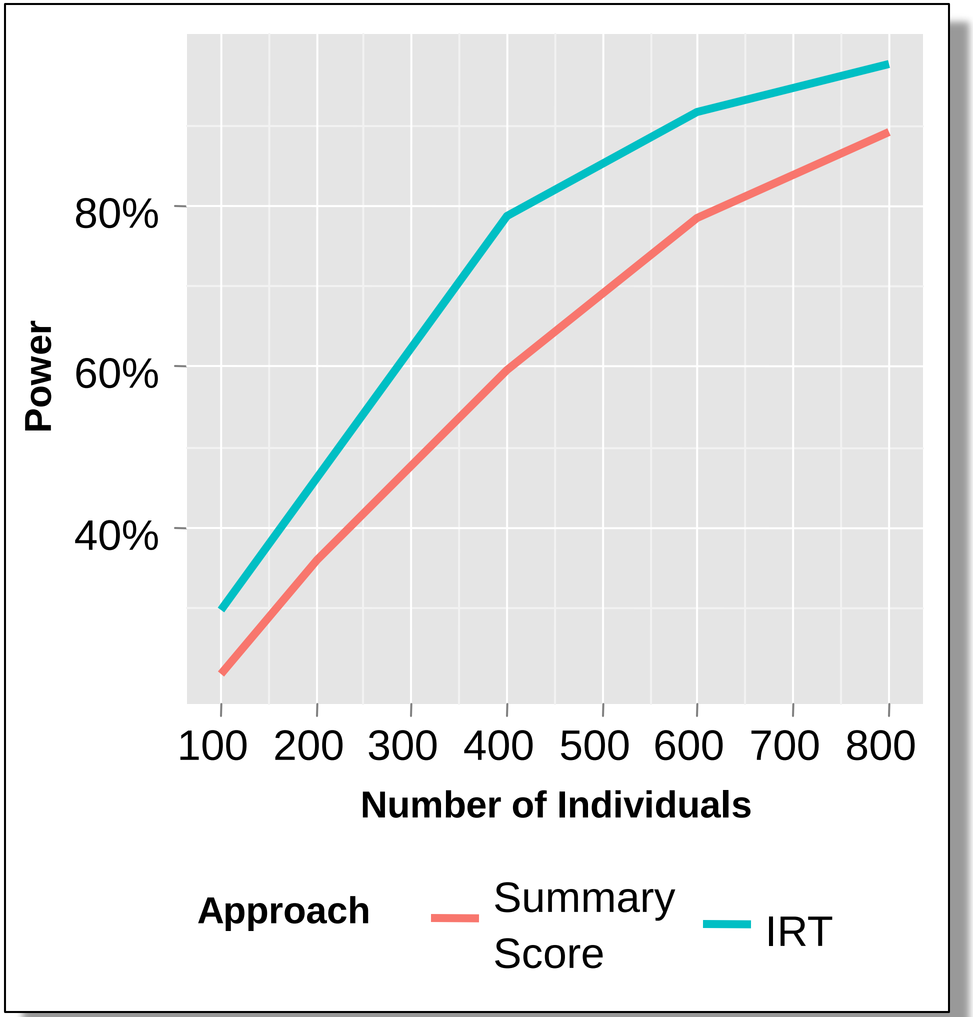
- Bounded nature of each subcomponent is taken into account

→ Summary score distribution is more natural

Increased Power

- Method:
  1. Simulation from longitudinal IRT model with disease modifying drug effect of 20 % (n=500)
  2. Estimation with full and reduced IRT model
  3. Estimation with full and reduced Summary Score model

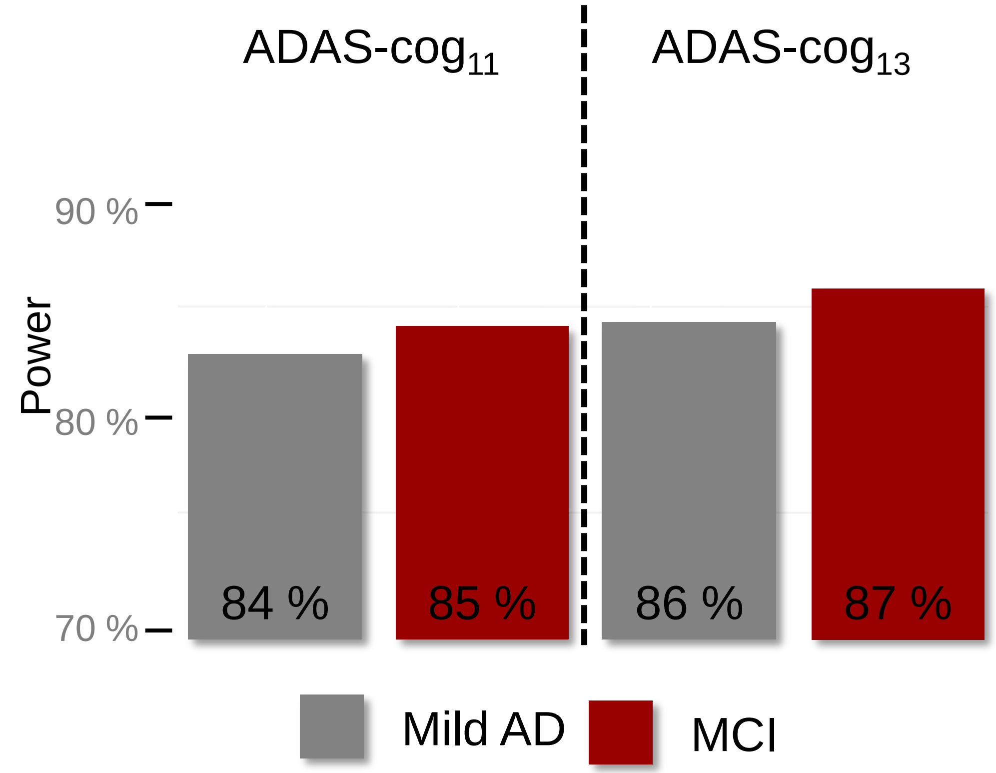
➔ Increased Power when using IRT model



Improved Clinical Trial Simulations

- Approach delivers test & subject specific parameters

➔ Simulate different populations & different ADAS-cog assessments



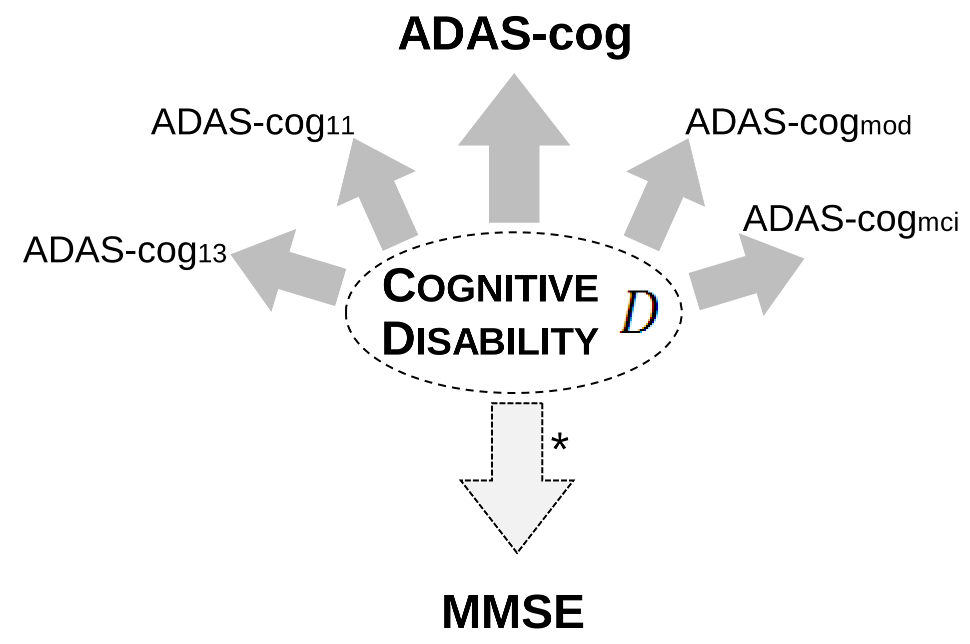
*600 Subjects (300/300), 20% drug effect DM

Integrating Information Across Trials

- Combination of data across trials easily possible

- Other cognitive tests like MMSE can be related to same hidden variable

  ➔ MMSE assessments become additional observations



* Work in Progress

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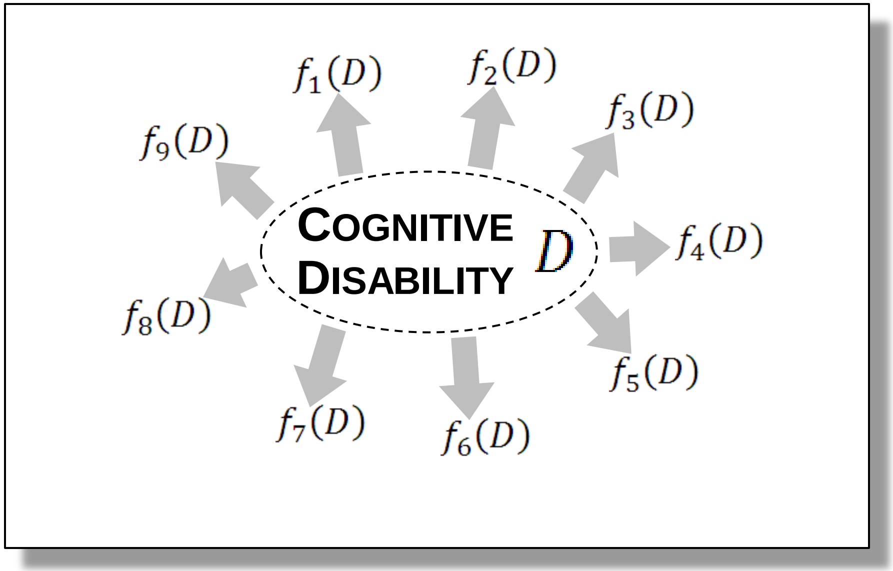
Advanced Optimal Trial Design

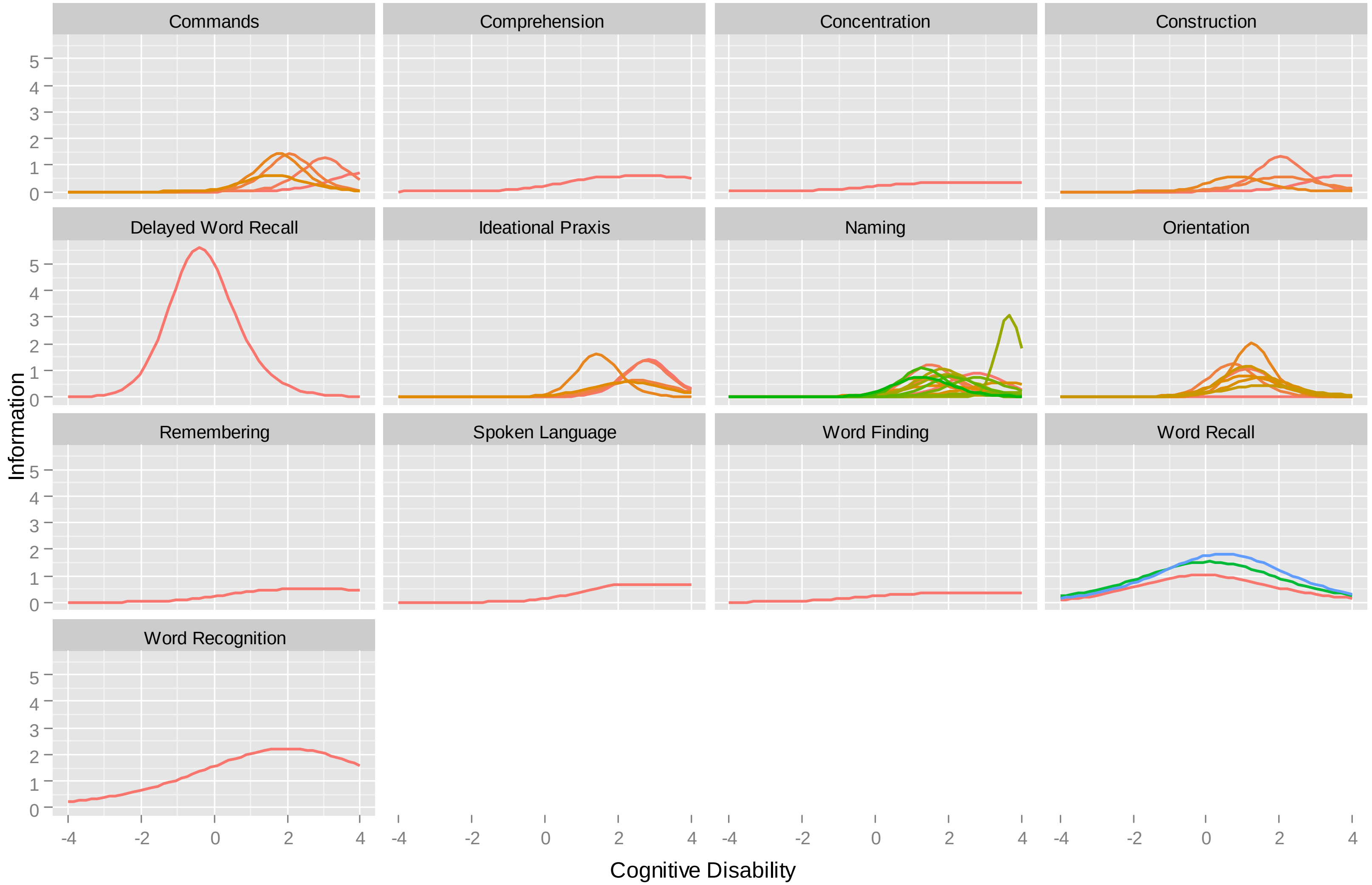


- Each response function is dependent on D
- Calculate Fisher Information for each item:

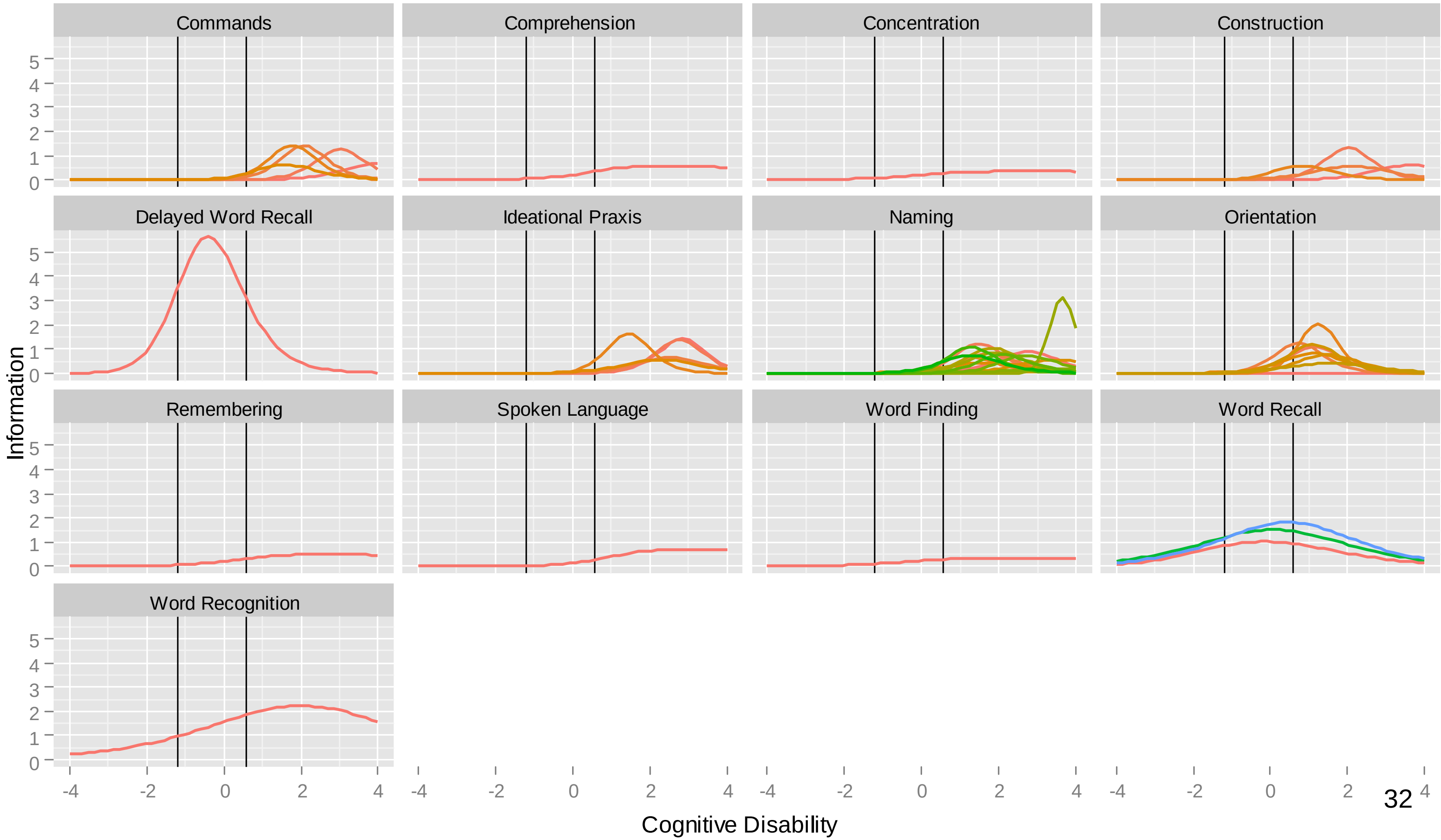
$$\mathcal{I}(D) = -E\left(\frac{\partial^2}{\partial D^2}\log f_j\left(Y_j,\theta\right)|\theta\right)$$

- Measure of information content in each item

Item Information



Information for a MCI Study



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Component Ranking for MCI Study

Test	Information
Delayed Word Recall	4.651539
Word Recall	3.842586
Orientation	1.655941
Word Recognition	1.285888
Naming	0.840697
Number Cancellation	0.414947
Construction	0.291493
Word Finding	0.20777
Ideational Praxis	0.184183
Concentration	0.177565
Remembering	0.164553
Comprehension	0.162216
Commands	0.157477
Spoken Language	0.104431

- Allows adaptation of the test to a specific population
- Test can be performed quicker with little change in information content

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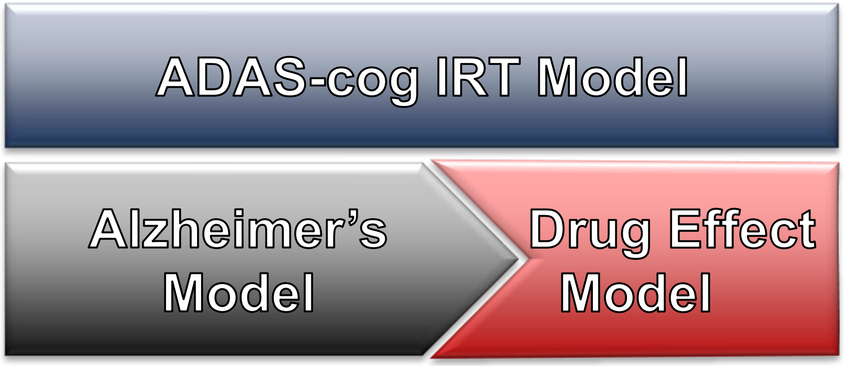
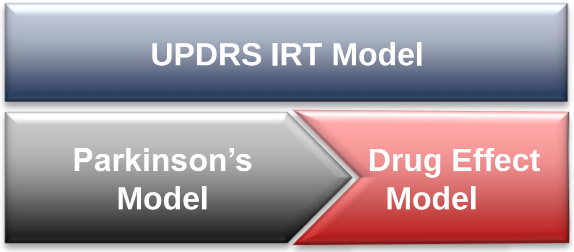
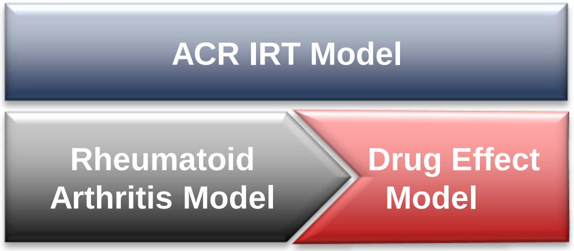
Summary



Extension:





Advantages

- Treat true nature of data (better simulation properties)
- Increased drug effect detection power
- More flexible clinical trial simulations
- Possibility to optimize test design
- Implicit mechanism for missing sub-scores

Acknowledgements

- Colleagues in Uppsala

- Pfizer colleagues in Groton