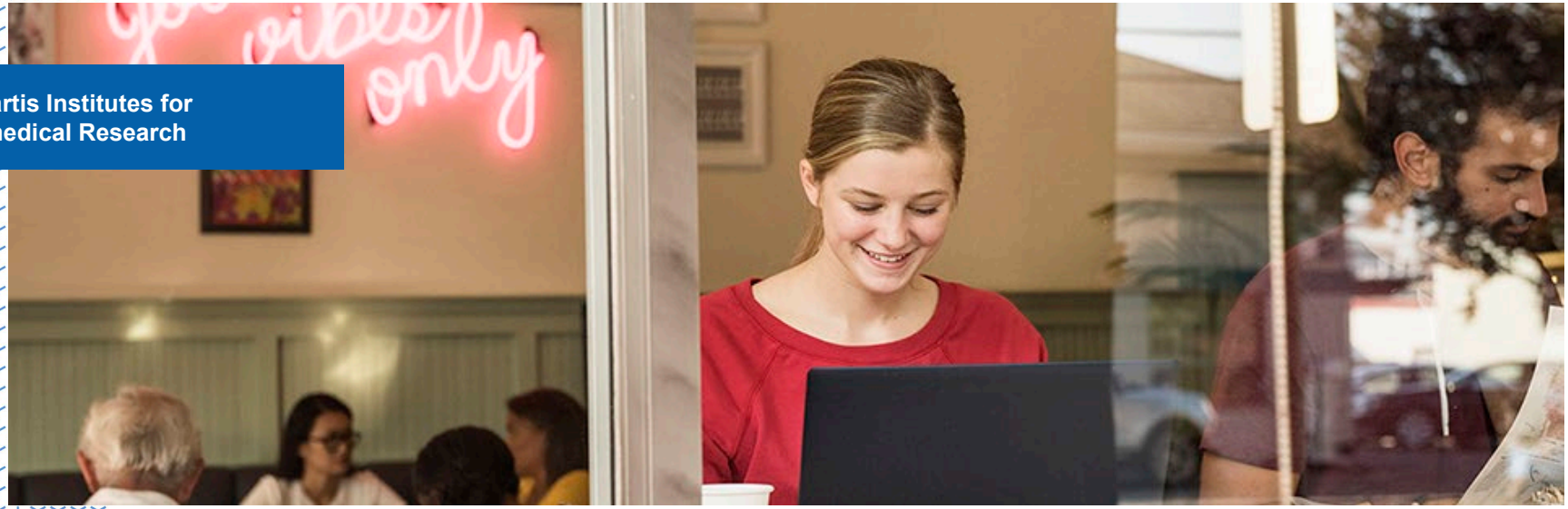
Novartis Institutes for Biomedical Research



Nextgen endpoints for clinical drug development

Kristin Hannesdottir and Jelena Curcic
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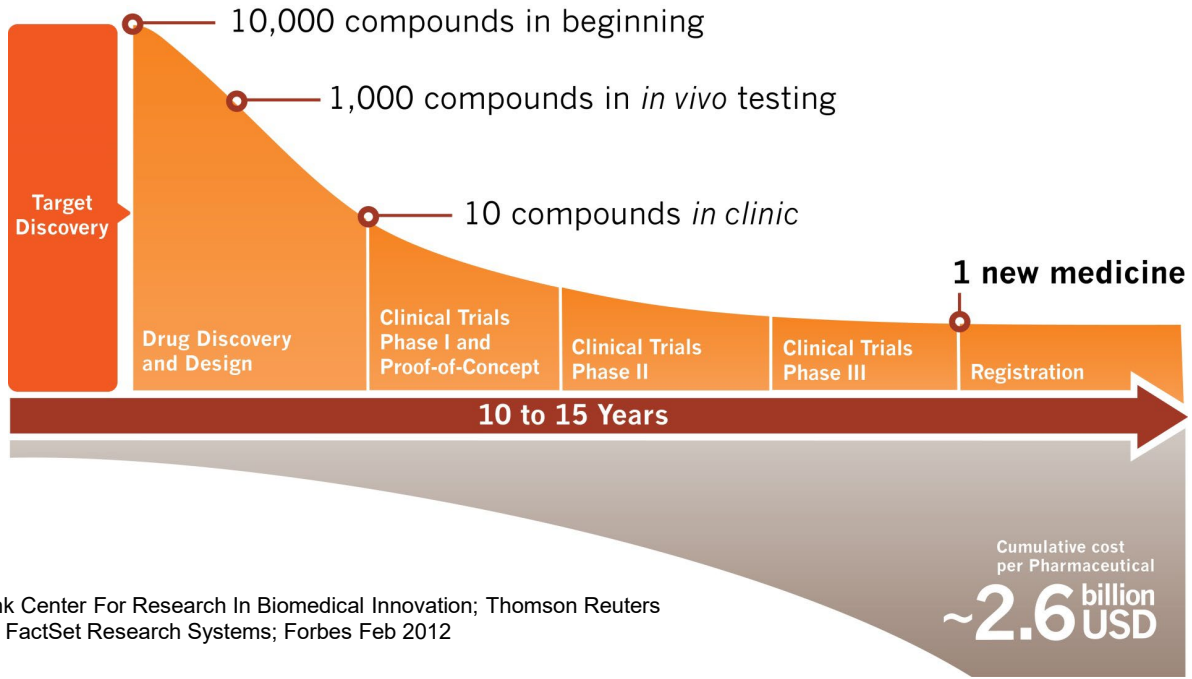
Disclosure

- Kristin Hannesdottir and Jelena Curcic are employees of Novartis and hold Novartis shares

Drug development is a lengthy, costly and risky undertaking

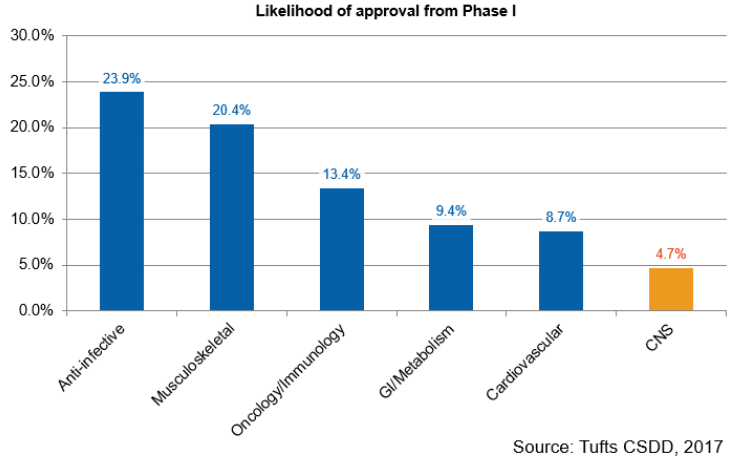


Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems; Forbes Feb 2012

Goal: Improve accuracy of clinical drug trials

Neuroscience has one of the lowest success rates

- NS endpoints are noisy → large sample size
- NS endpoints lack sensitivity → lengthy trials
  - Increasing sample size and length of trial is not enough → high failure rate remains



Source: Tufts CSDD, 2017

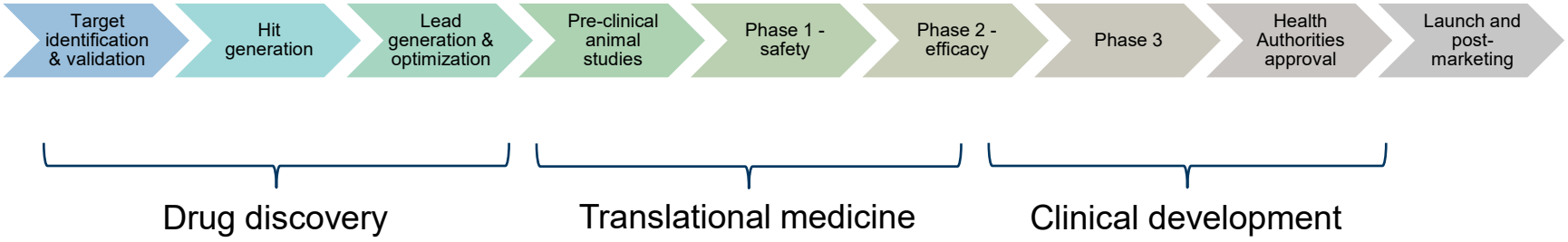
Reducing variability and increasing drug signal detection is key to more accurate trials

Two examples of how to achieve this:

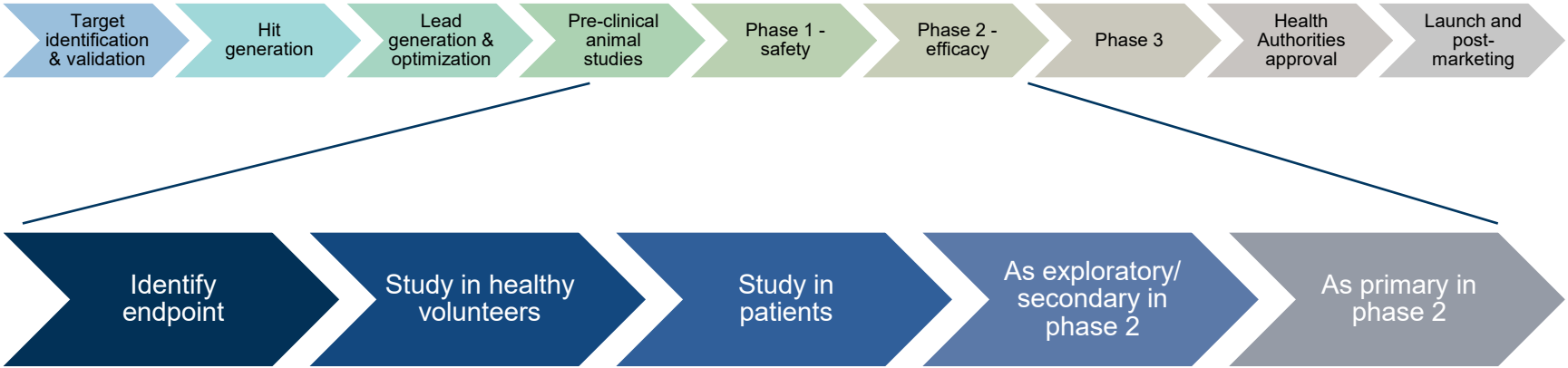
1. More **direct physiological** assessments with less variability
2. **More frequent** assessments to reduce variability

Drug development

Phases



Roadmap for novel endpoint methods



Curcic et al. 2022 JMIR Research Protocols - Description of the Method for Evaluating Digital Endpoints in Alzheimer Disease Study: Protocol for an Exploratory, Cross-sectional Study

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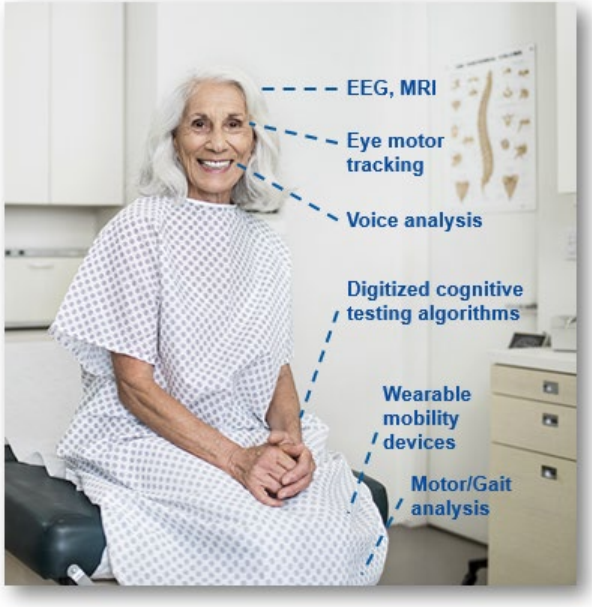
How can we increase endpoint accuracy?

1. Select established endpoints that are **psychometrically appropriate** for the indication and stage of disease
2. **Increase frequency** of assessments to reduce variability and increase effect size
3. **Digitally augment** endpoints to increase accuracy and strength of drug signal detection



The whole picture?

A drug trial may require in-clinic visits 4 weeks apart

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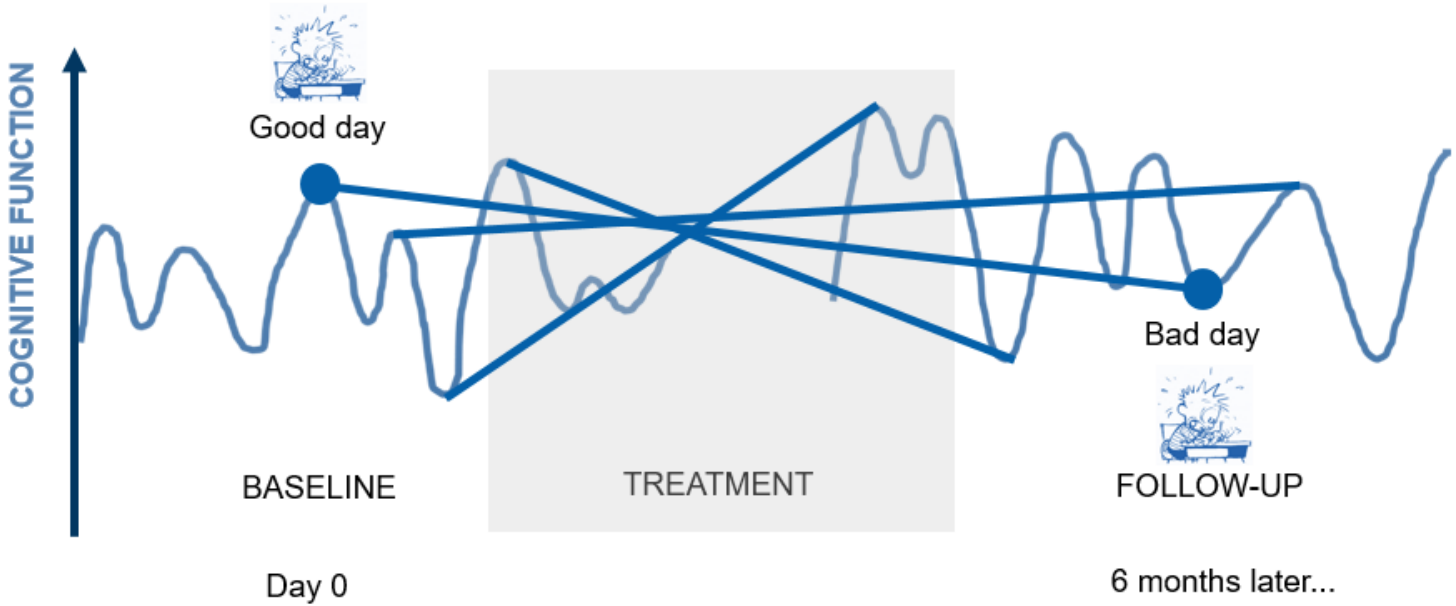
Increase frequency of assessments

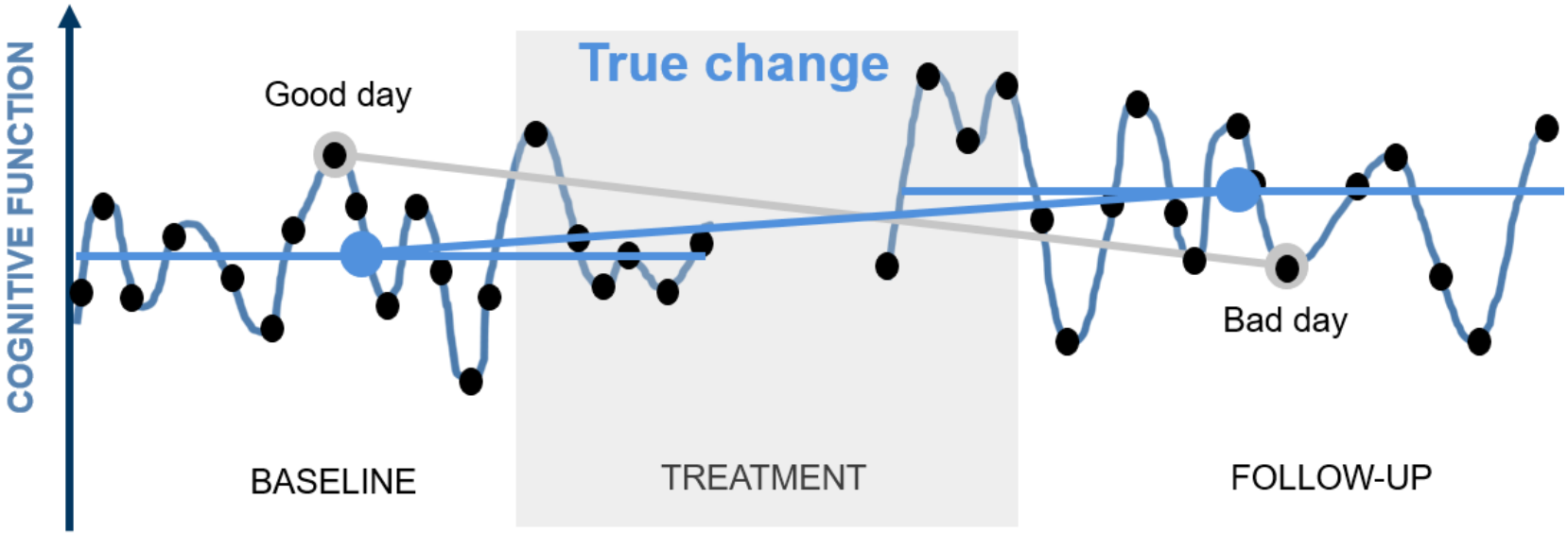
Single time-point, highly variable endpoints can lead to erroneous results:



Adapted from Hassenstab et al. 2017

Increase frequency of assessments

More frequent assessments capture true change:



Adapted from Hassenstab et al. 2017

MEDIA study: Digital augmentation of conventional endpoints in Alzheimer's disease

50 participants (aged 60-80 years, 66% male)

Control (n=13)
MMSE 29.5 (1.1)

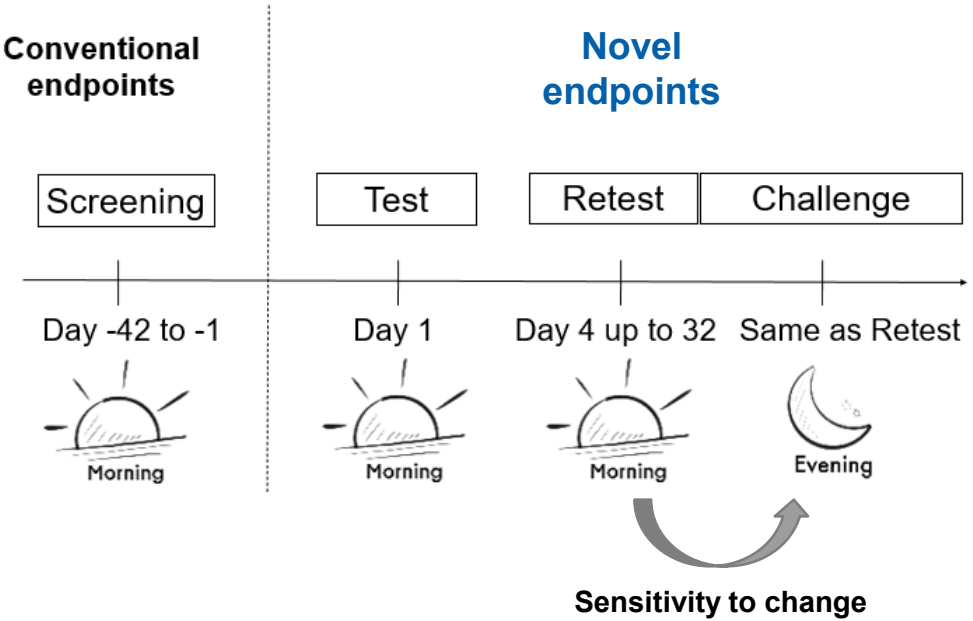
Pre-symptomatic AD (n=12)
MMSE 29.7 (0.7)

Prodromal AD (n=13)
MMSE 27.4 (2.2)

Mild AD dementia (n=12)
MMSE 21.8 (1.5)

Amyloid -

Amyloid +



Curcic J., et al. *A description of the MEDIA study: a method for evaluating digital endpoints in Alzheimer's disease.* JMIR Research Protocols, 2022 Jun 13, doi: 10/2196/35442

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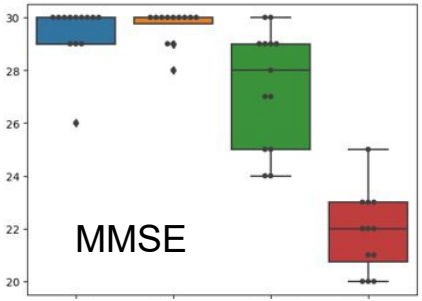
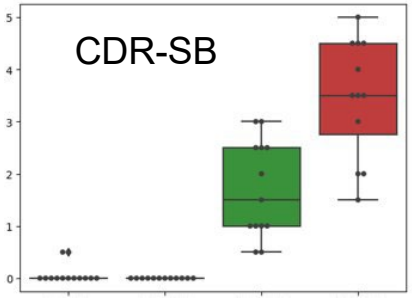
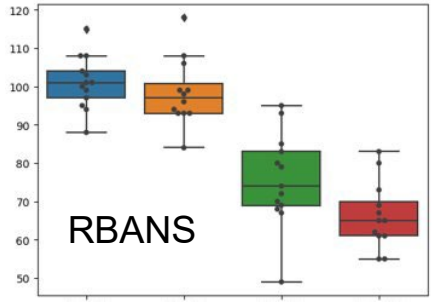
Baseline characteristics

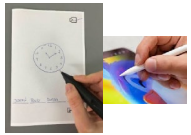
Demographics	Control N = 13	Pre-symtomatic N = 12	Prodromal AD N = 13	Mild AD dementia N = 12	Total N = 50
Age - Mean (SD)	68 (3.7)	72 (4.3)	71 (4.1)	69 (6.5)	**70 (4.9)**
Sex (male) – n (%)	9 (69.2)	7 (58.3)	9 (69.2)	8 (66.7)	**33 (66)**
Education – n (%)					
Higher education	9 (69.2)	4 (33.3)	4 (30.8)	3 (25)	**20 (40)**
Upper secondary education	4 (30.8)	6 (50.0)	5 (38.5)	6 (50)	**21 (42)**
Compulsory education		2 (16.7)	4 (30.8)	3 (25)	**9 (18)**



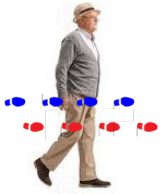




Digital augmentation in the MEDIA study



Digitized cognitive testing

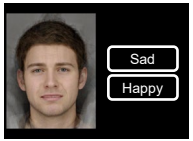


Cognition-motor dual-task paradigm

EEG activity

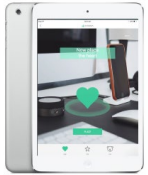
Oculo-motor activity

Retinal amyloid biomarkers



Social / emotional cognition

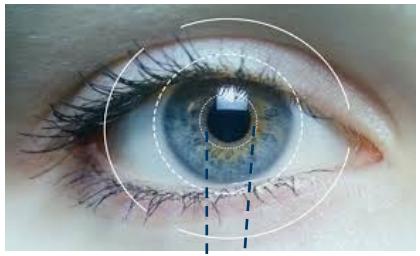
Computerized cognitive tests



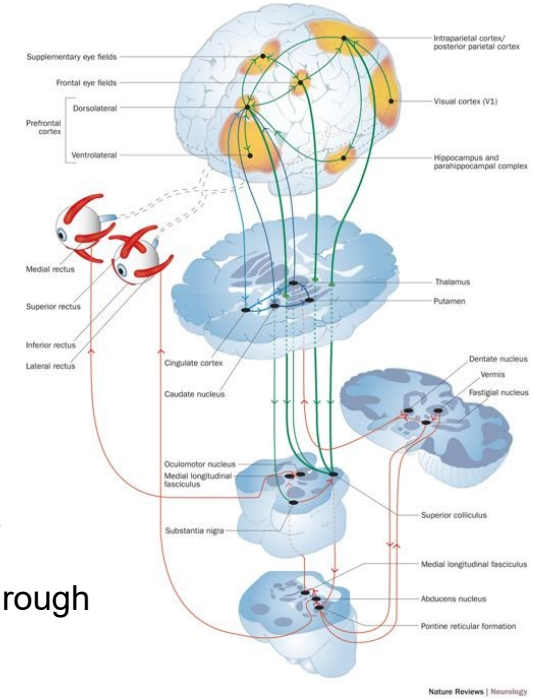
Augmented reality

Voice / speech biomarkers

Oculo-motor activity: A direct physiological measure of cognition?



- The eye as a biomarker (Lim et al., 2016)
- Original methods not suitable for clinical trials
- Cognitive testing during eye motor tracking through portable camera or virtual reality headset

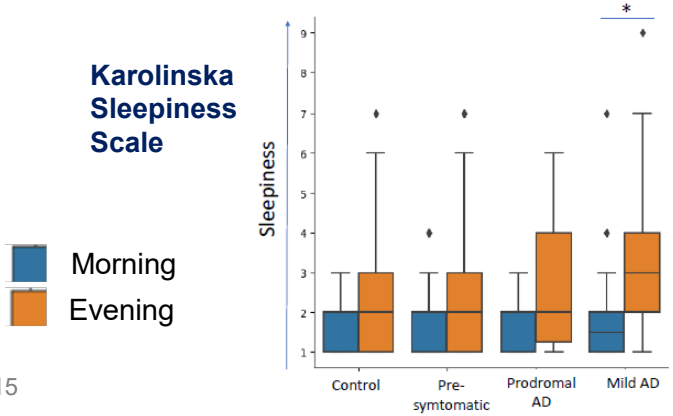


Fielding et al., 2015

Preliminary results: Oculo-motor activity

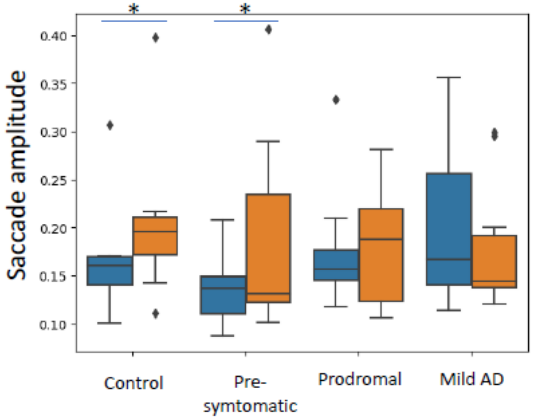
- Oculo-motor activity while participants read 50 grammatically similar sentences
- Cognitive fatigue induced different patterns of oculo-motor activity across cohorts
- Results suggest that oculo-motor activity may reflect changes in cognitive resources induced by a benign challenge model
- Further studies are needed to confirm the potential of eye-tracking during reading as a sensitive and objective measure for clinical drug trials
- **Distinguishes clinical stages of early AD**

Karolinska Sleepiness Scale



Saccade amplitude is related with working memory effort

In fatigued controls working memory effort is increased



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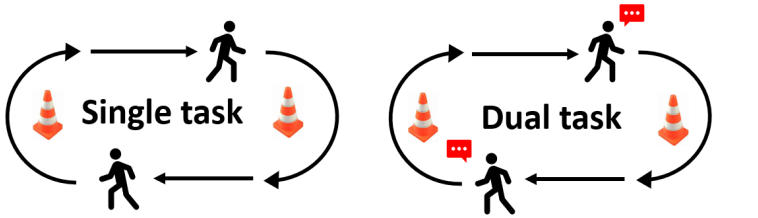
Gait/cognition dual tasking: A real life measure of cognition?

- In real life we rarely perform one task at a time
- Dual tasking overstrains cognitive capabilities resulting in gait performance decrements
- May detect presymptomatic stages of Alzheimer's disease (Nadkarni et al., 2017)

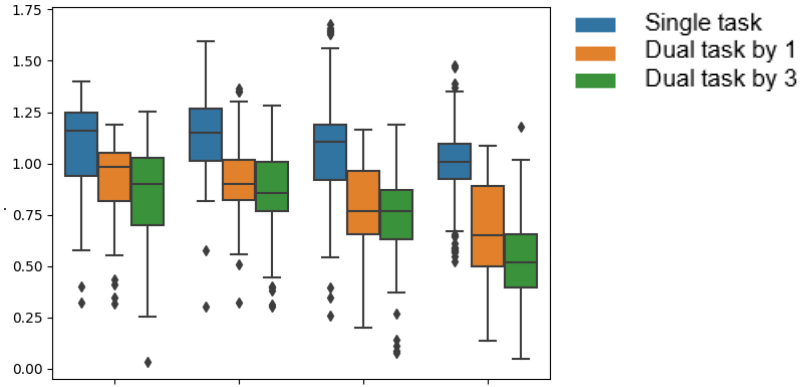
Dual tasking: preliminary results



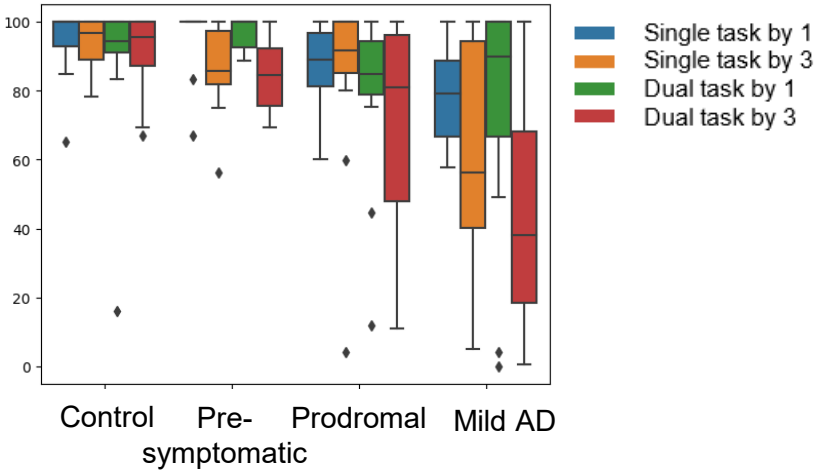
Task						
Cognitive	Rest	-1	-3	-3	-1	Rest
Motor	Walk	Sit	Walk	Sit	Walk	Walk

- All cohorts show a cognitive-priority trade-off when dual tasking
- The dual tasking paradigm is sensitive to changes in cognitive load

Walking speed



Correct response rate (CRR)



Closing remarks: why stronger endpoints?

Augment existing endpoints for improved accuracy → **reduce failed trials**

Greater understanding of the impact of disease on patient's lives → **clinical meaningfulness**

Reduce endpoint variability and increase effect size → **smaller, more efficient trials**

Briefer, at home assessments → **lower burden** to sites and trial participants

Augmented endpoints hold promise to streamline and increase accuracy of early clinical trials → de-risking late-stage development and ultimately **delivering medicines to patients faster**

Acknowledgements

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