Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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Digital biomarkers to support decentralized trials

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Daily behaviors

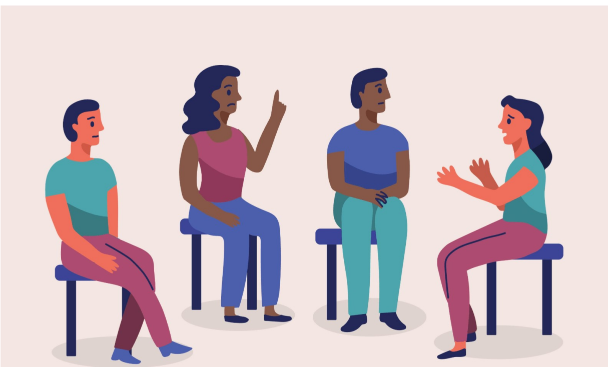
There exists hidden behavioral patterns that can teach us about neurological disease

Facial expression

Communication

Typing

Navigation



Driving

Writing

Reading

Walking

Posture

Gaze patterns

Reaching

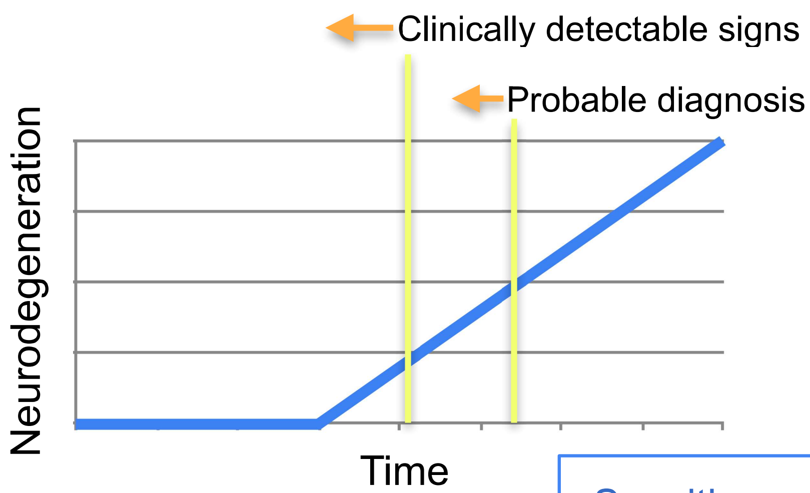
Speech

Crawling

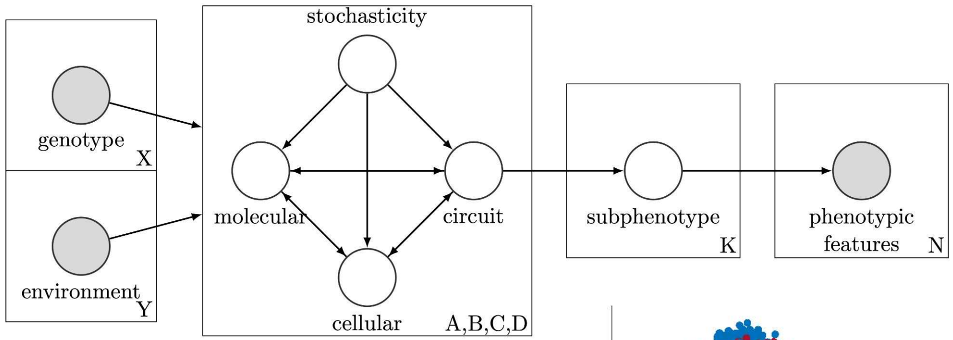
Digital tools can capture behavioral patterns

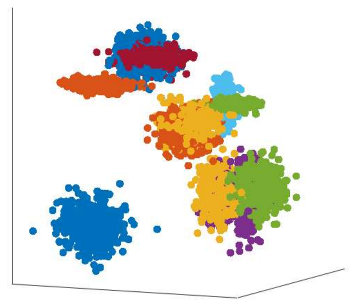
Clinical Utility of Identifying and Quantifying Patterns

Detection and Diagnosis

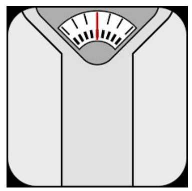


Pathophysiology





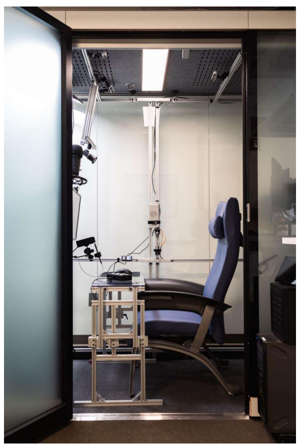
Sensitive and reliable measures of disease change



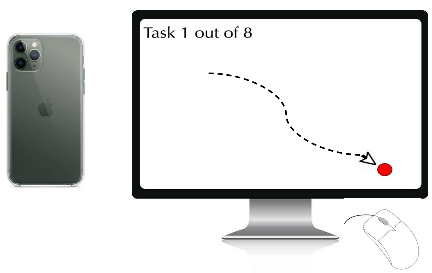
Digital Behavior Measurement Approaches

Active/Task-based Measurement

neurobooth

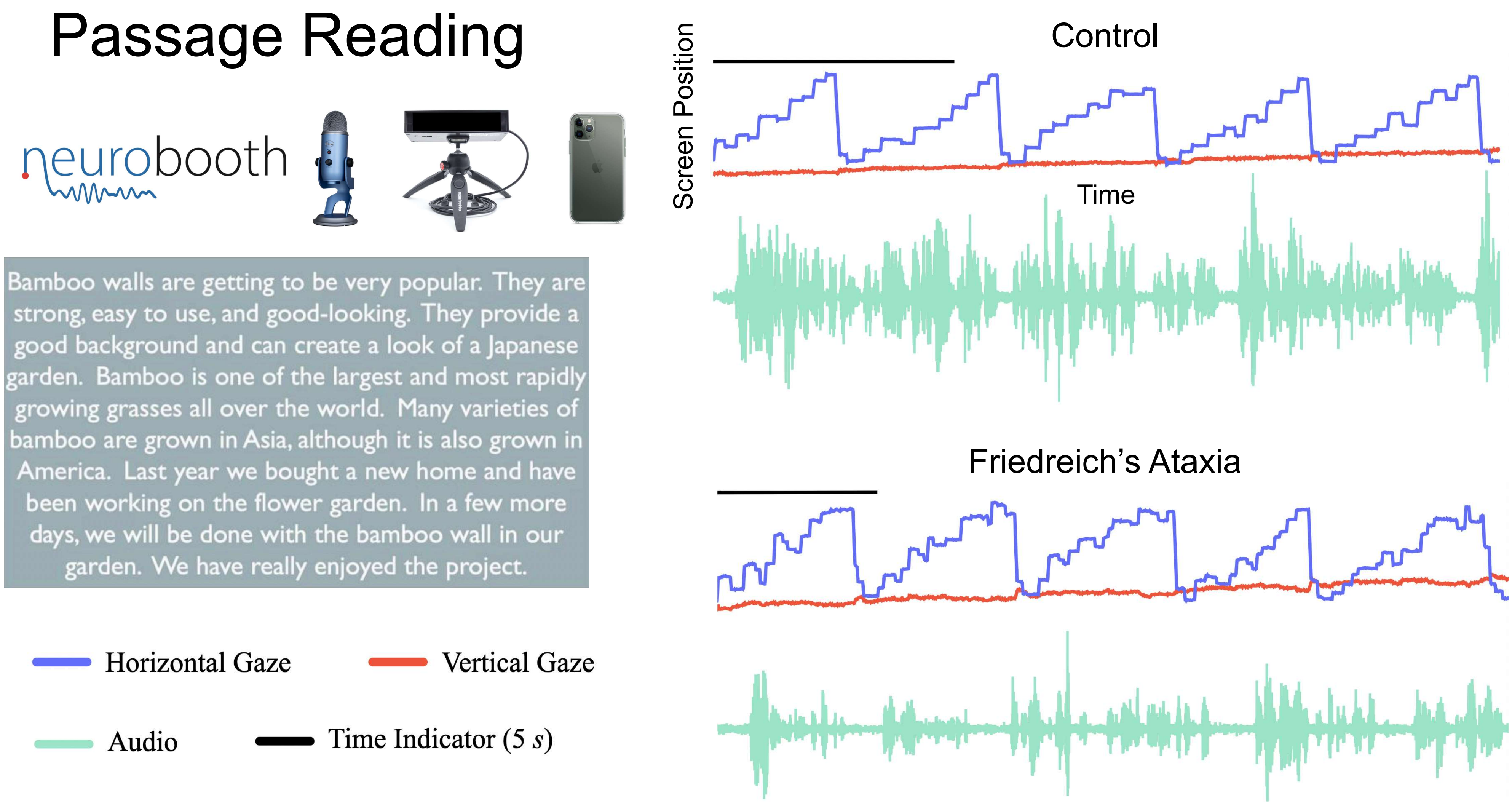


Can be remote:

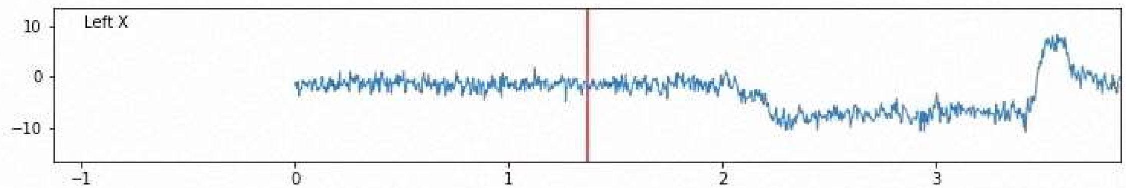


Passive/Continuous Measurement

- Highly scalable
- Doesn't require consistently performed motor tasks
- Ecologically valid
- Potential for highly reliable measures


Passage Reading
neurobooth
Bamboo walls are getting to be very popular. They are strong, easy to use, and good-looking. They provide a good background and can create a look of a Japanese garden. Bamboo is one of the largest and most rapidly growing grasses all over the world. Many varieties of bamboo are grown in Asia, although it is also grown in America. Last year we bought a new home and have been working on the flower garden. In a few more days, we will be done with the bamboo wall in our garden. We have really enjoyed the project.
Horizontal Gaze
Vertical Gaze
Audio
Time Indicator (5 s)
Control
Screen Position
Time
Friedreich's Ataxia

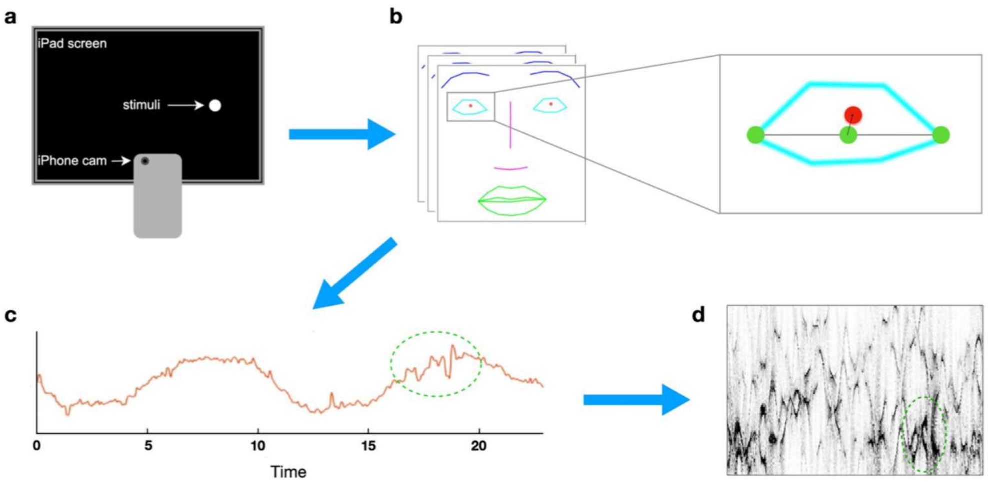
Oculomotor analysis from mobile phone video

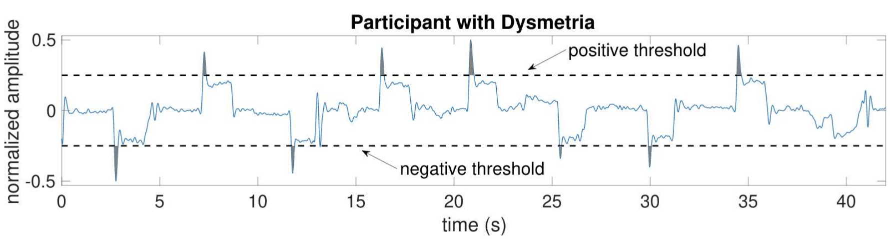


Oculomotor analysis from mobile phone video

Guillermo

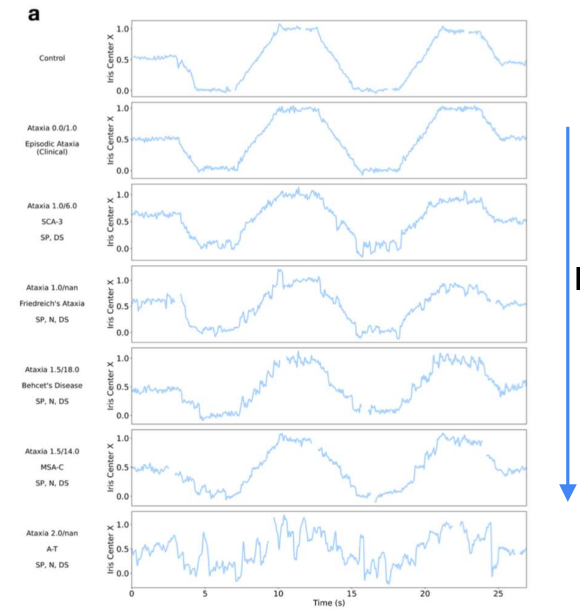
George



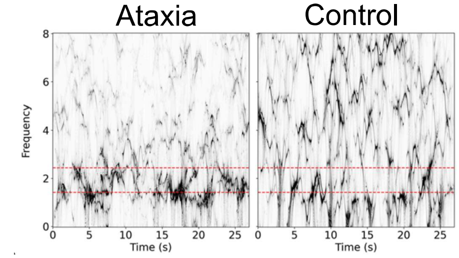


Azami et al. 2022, *IEEE Access*

Hamed

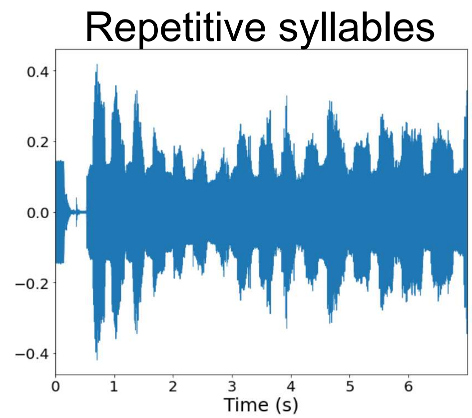


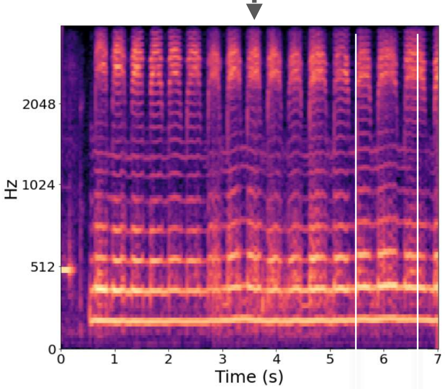
Increasing Ataxia Severity



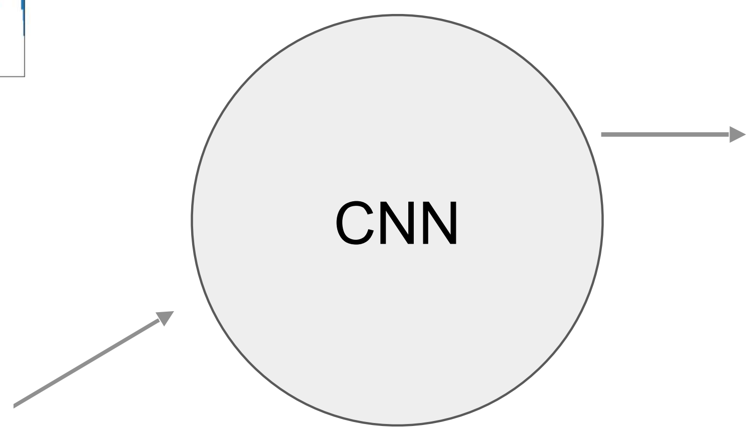
Chang et al. 2020, *Scientific Reports*

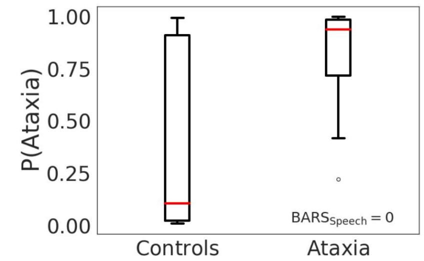
Detecting early speech changes in ataxias

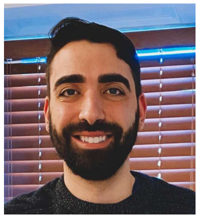




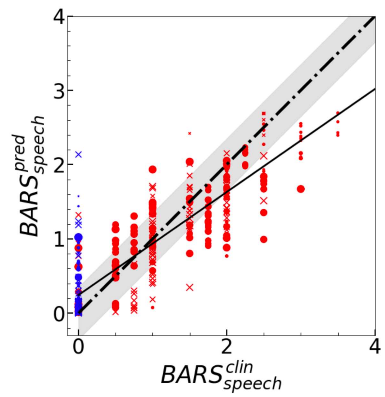
- In-clinic & Remote
- 450+ recordings from 200+ individuals
- Children and adults with ataxia

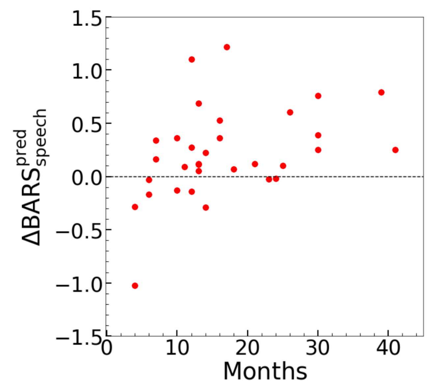


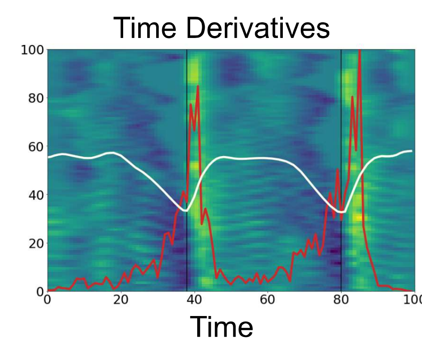




Kyriakos



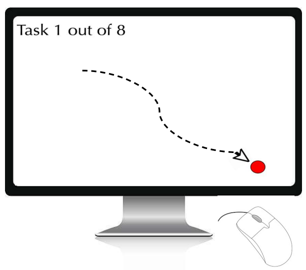


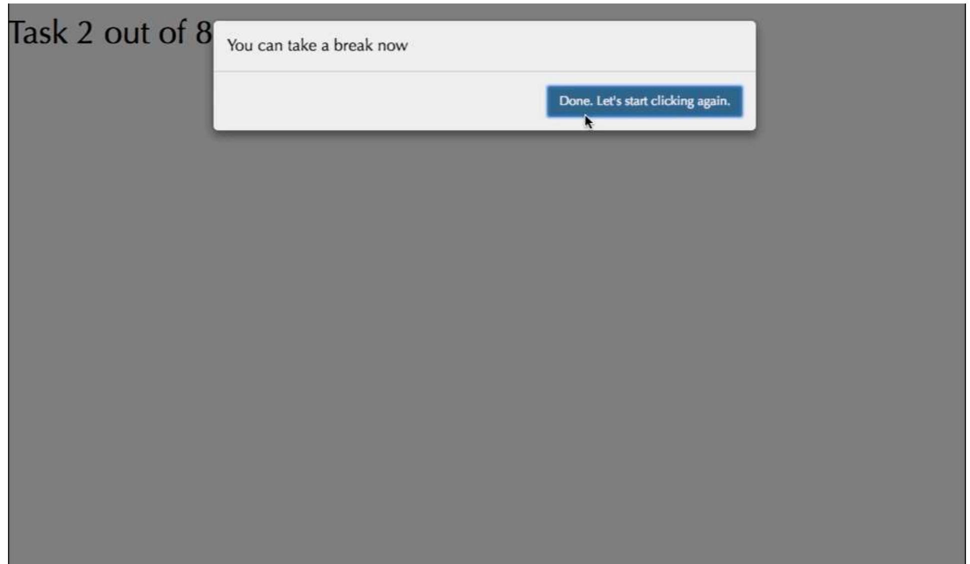


Vattis et al. 2023, *medRxiv*

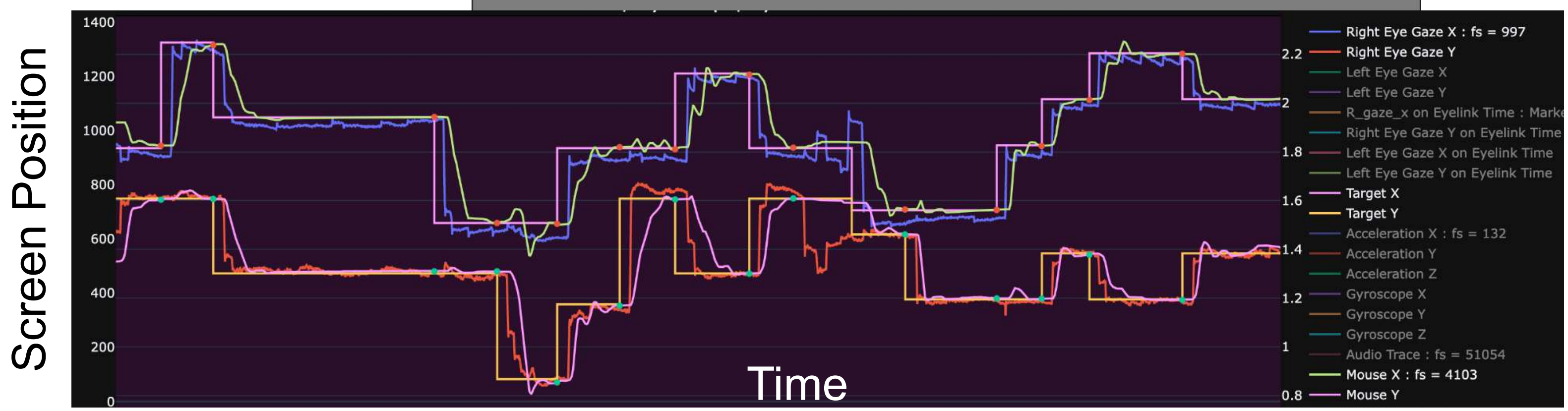
Computer Mouse Task

neurobooth



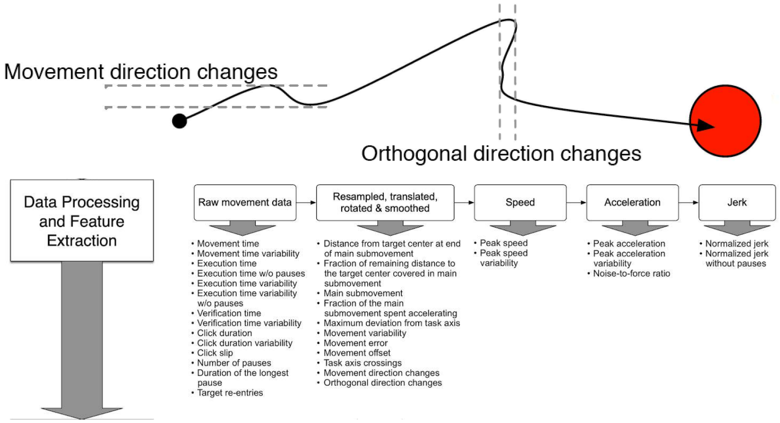


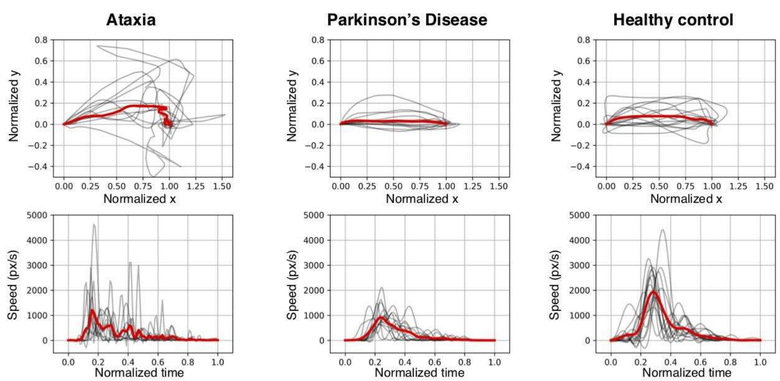
Krzysztof



Web-based Computer mouse task

Krzysztof

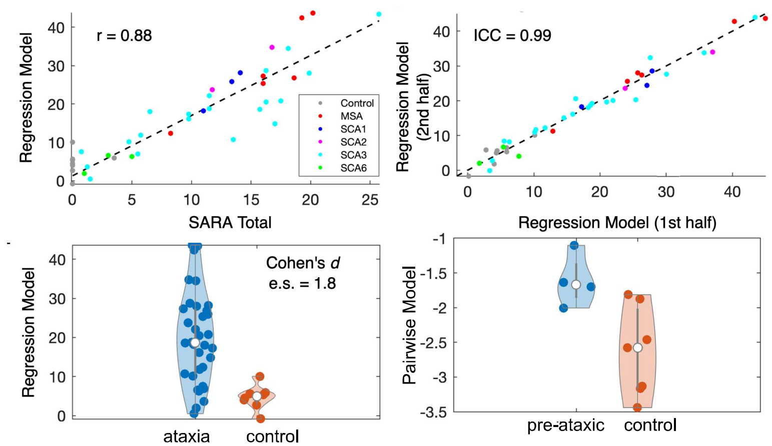




Gajos et al. 2020, *Movement Disorders*

Comparison (number in parentheses next to each class)	Number of features used	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Parkinsonism (46) versus healthy (29)	5	0.913	1.000	1.000	0.879
Ataxia (95) versus healthy (29)	4	0.926	0.897	0.967	0.788
Mild ataxia (16) versus healthy (29)	6	0.750	0.966	0.923	0.875

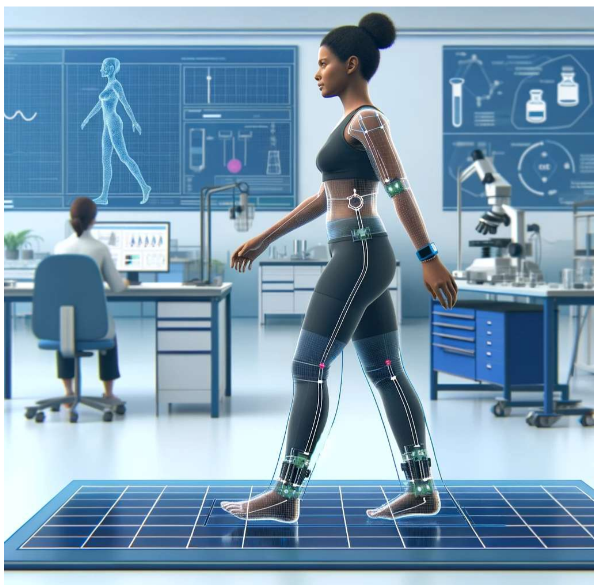
Nicole

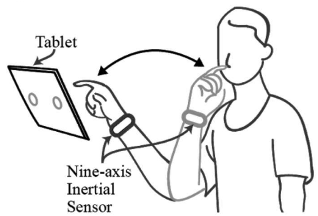


Eklund et al. 2023, *Brain Communications*

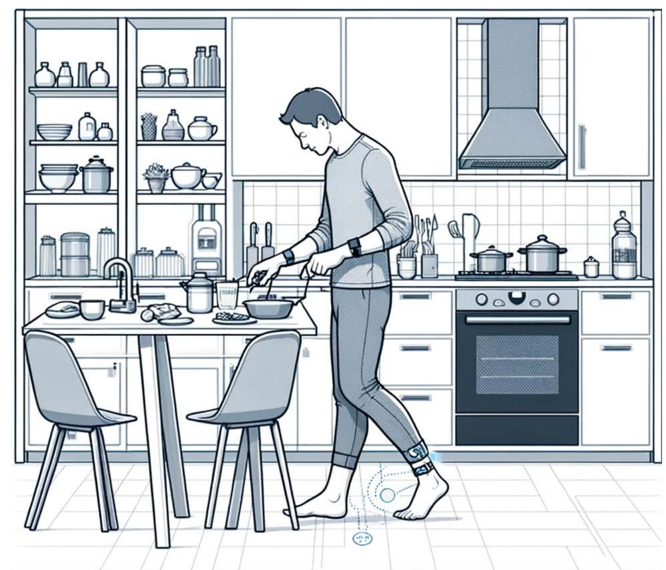
Passive Motor Phenotyping with Wearable Sensors

In-Clinic — Task-based





At-Home — Free-living



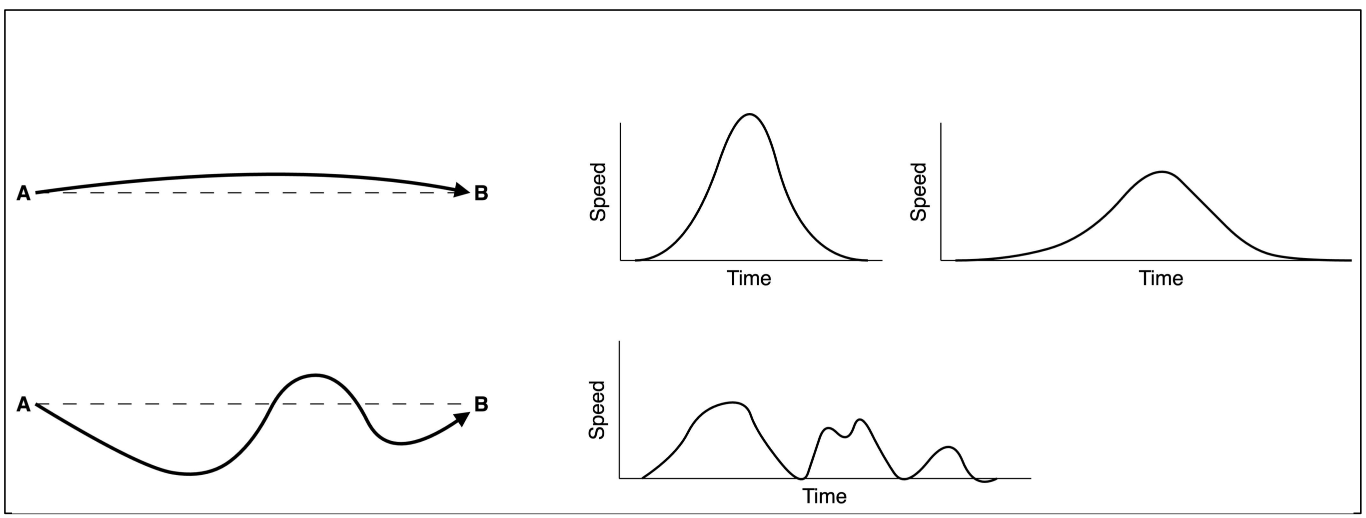
Types of measurements from sensors worn at home

- Step counts, ambulatory time
- Activity counts, time in light/moderate/vigorous activity, sedentary time, energy expenditure
- Stride velocity
- Acceleration time series statistics, power spectrum

→ Influenced by mood, fatigue, sleep quality, systemic illness, travel, device wear period

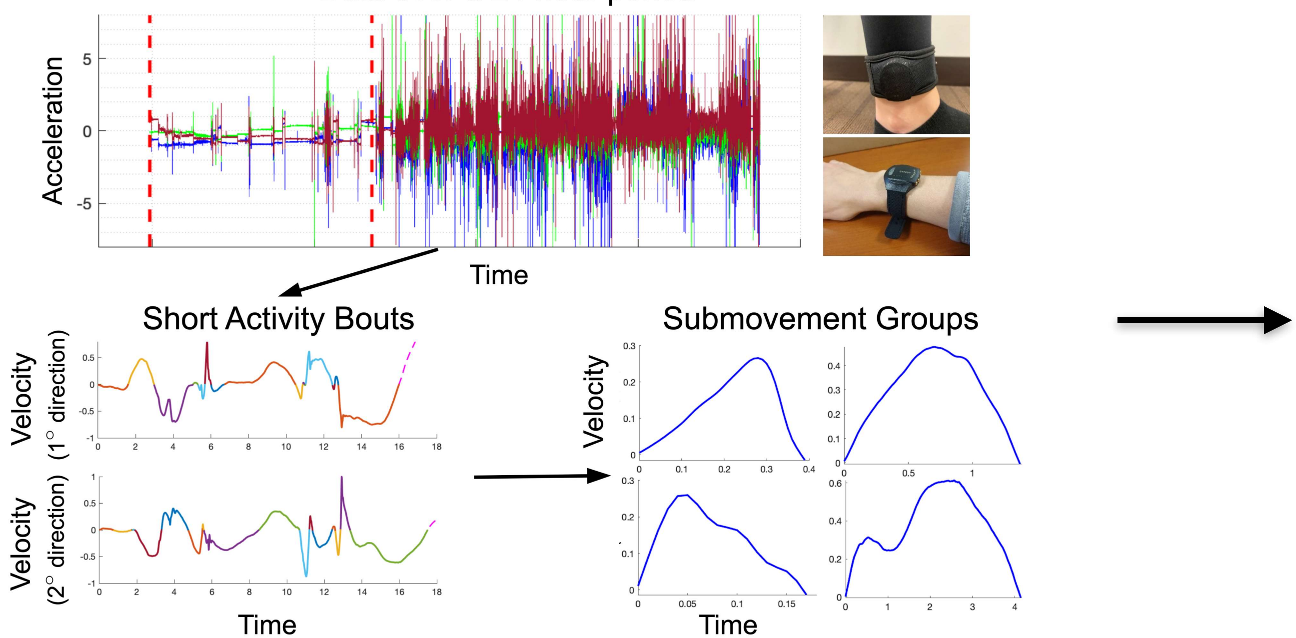
Can we create measures that are more specific for neurological disorders?

Submovements



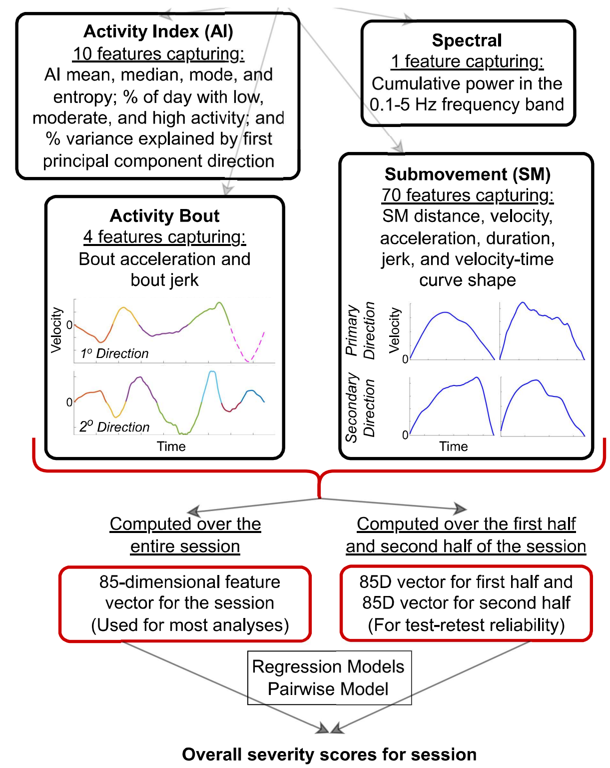
Submovements from Natural Behavior

Continuous Triaxial Accelerometer
Data over a 24 hour period



85 Movement Features

- Individual feature analysis
- Composite model analysis



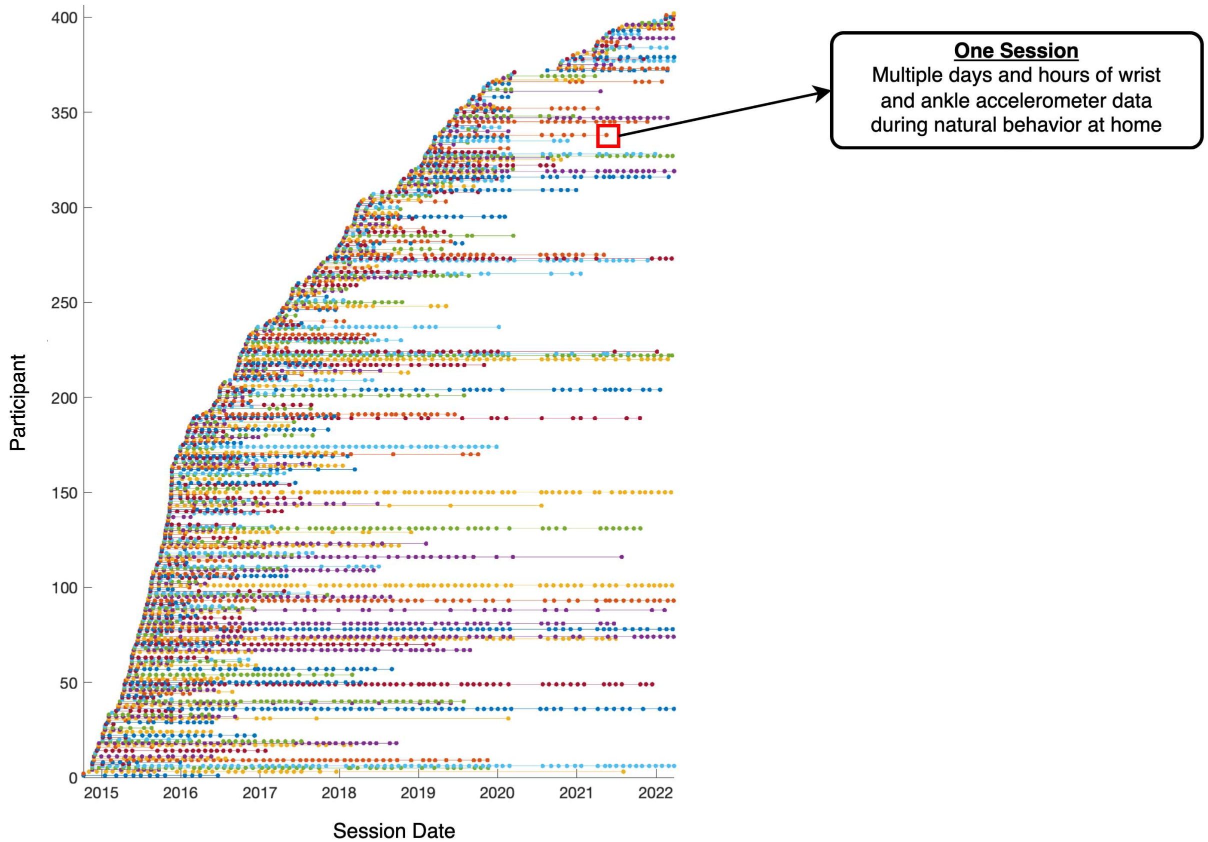
Gupta et al. 2022, *Cerebellum* - ataxia telangiectasia
Eklund et al. 2023, *Brain Communications* - SCAs and MSA-C
Gupta et al. 2023, *Nature Communications* - ALS
*Ongoing work in DRPLA, Friedreich's ataxia, UBTF

Amyotrophic Lateral Sclerosis (ALS)

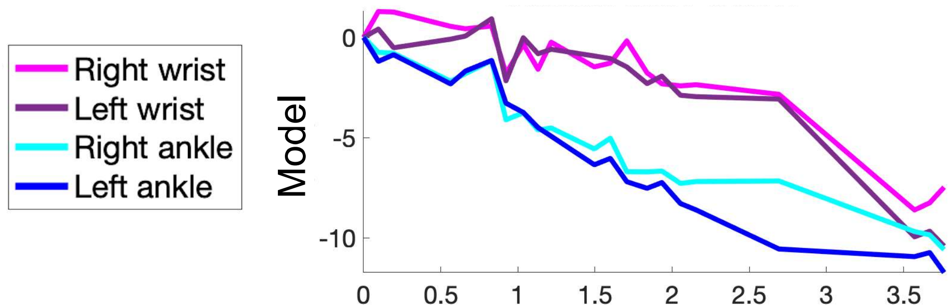
Longitudinal ALS dataset

376 ALS, 26 controls (188 ALS, 6 controls with longitudinal data)

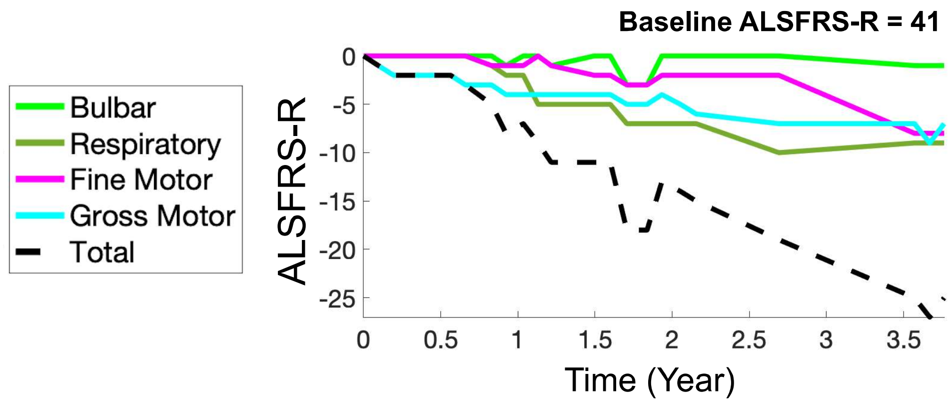
All Four Limbs @30 Hz



Longitudinal analysis of ALS data: one individual

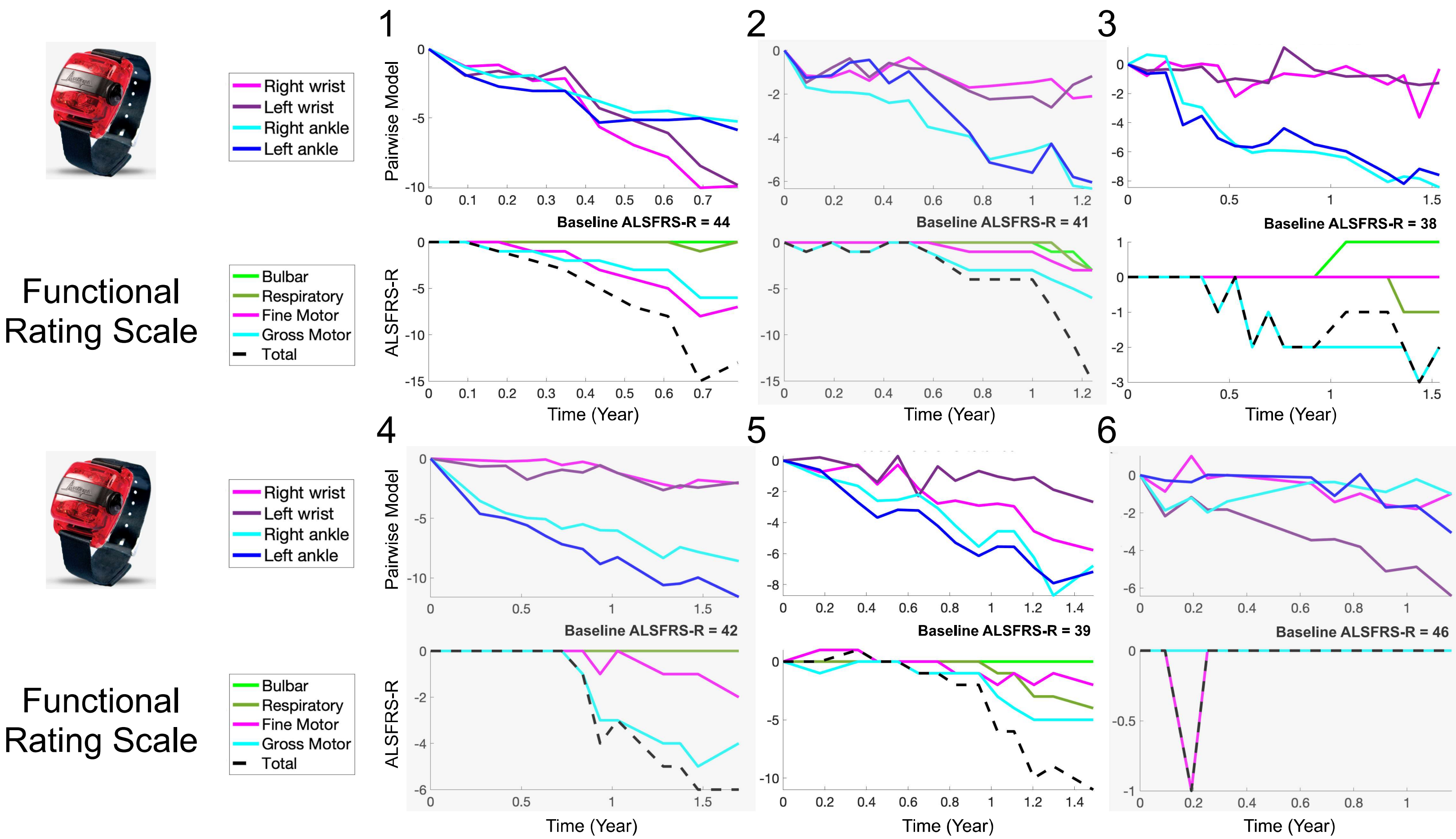


Functional
Rating Scale



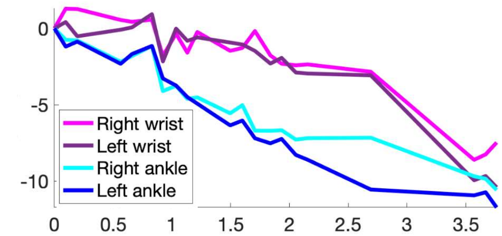
Gupta et al. 2023, *Nature Communications*

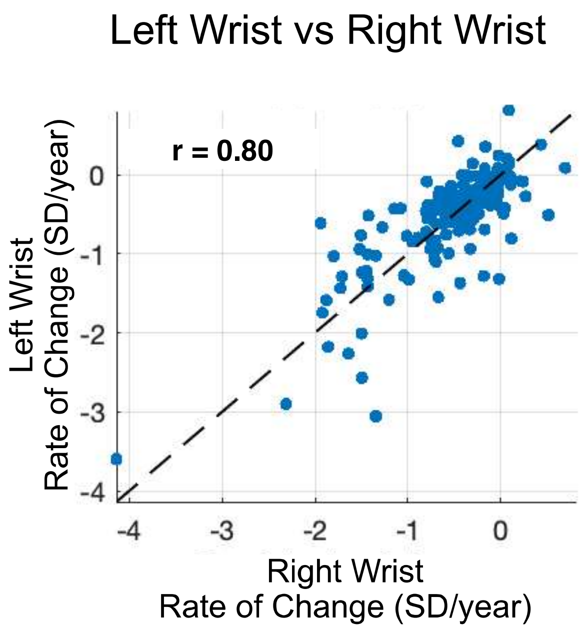
Longitudinal analysis of ALS data: 6 individuals

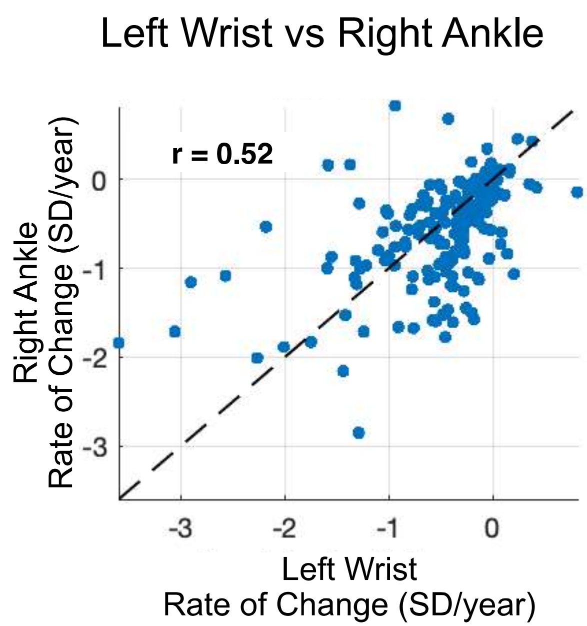


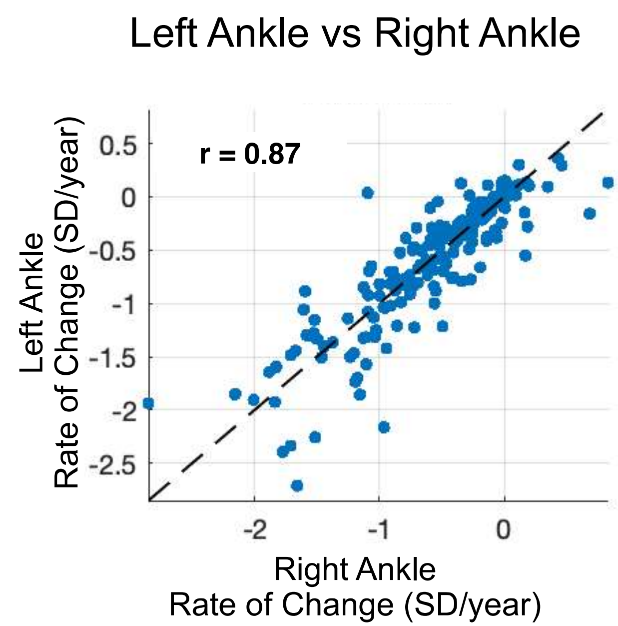
Four Sensor Rate of Change Comparison

* Each point represents an individual with ALS





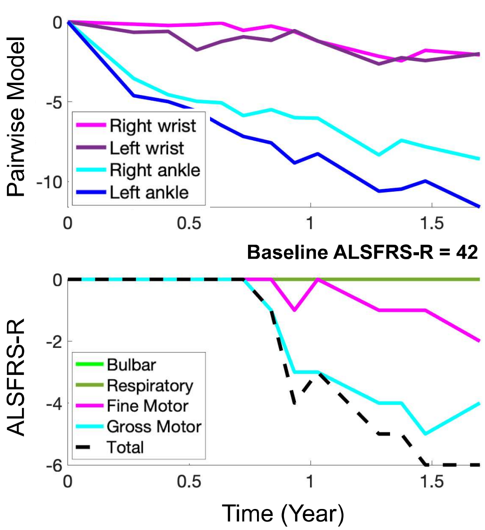




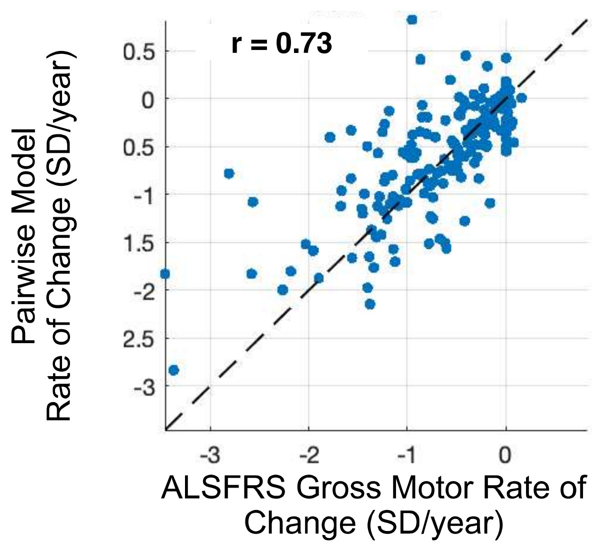
What information does the ankle and wrist sensor capture?

* Each point represents an individual with ALS

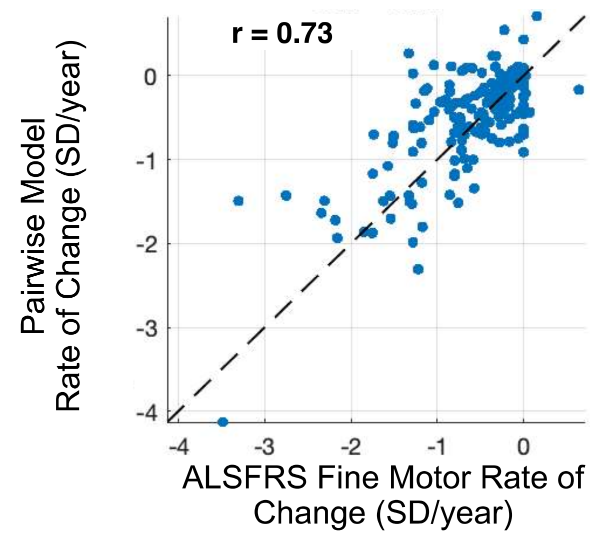
Individual Example



<u>Ankle</u> Captures <u>Gross</u> Motor Function

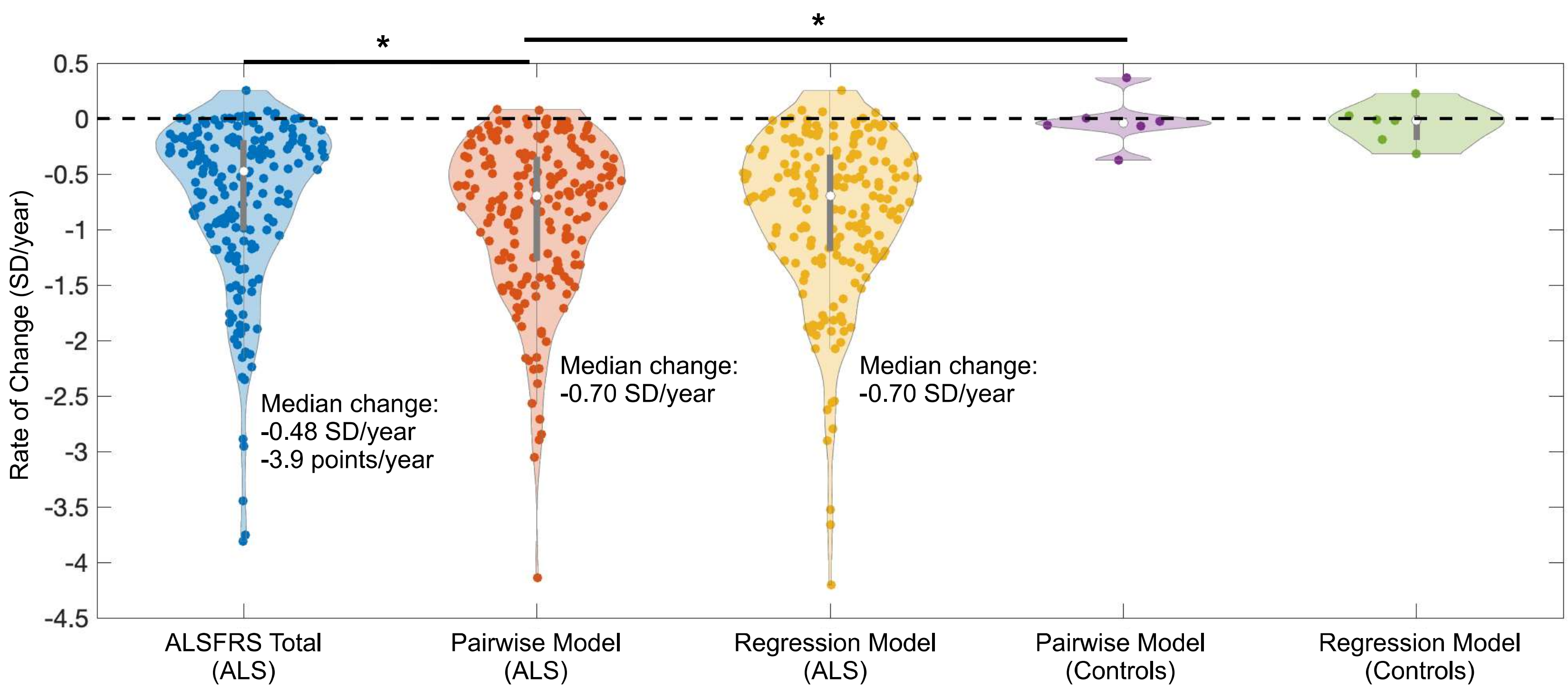


<u>Wrist</u> Captures <u>Fine</u> Motor Function



Personalize By Taking Limb with Fastest Progression

*Sample size estimates decrease from N=121 to N=76 with sensors-based outcome



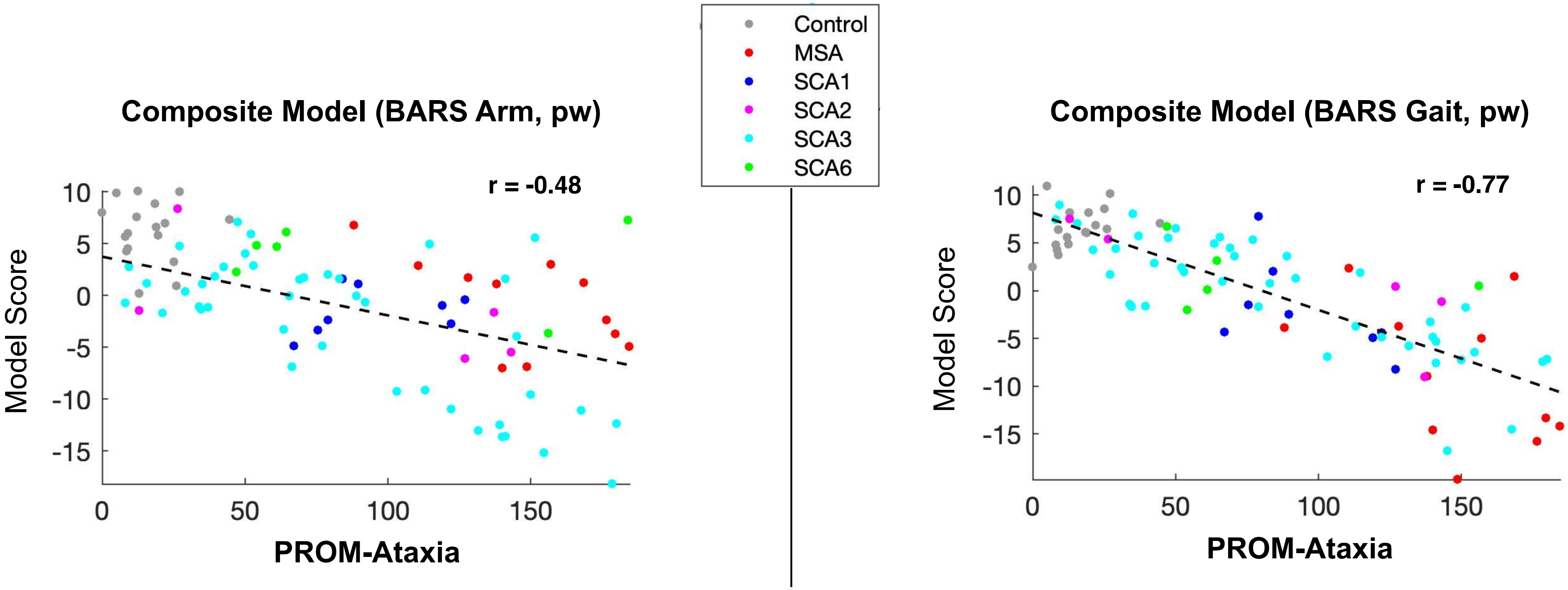
Functional
Rating Scale

Gupta et al. 2023, *Nature Communications*

Spinocerebellar ataxias (SCAs) and Multiple System Atrophy (MSA)

Agreement with Patient-Reported Function

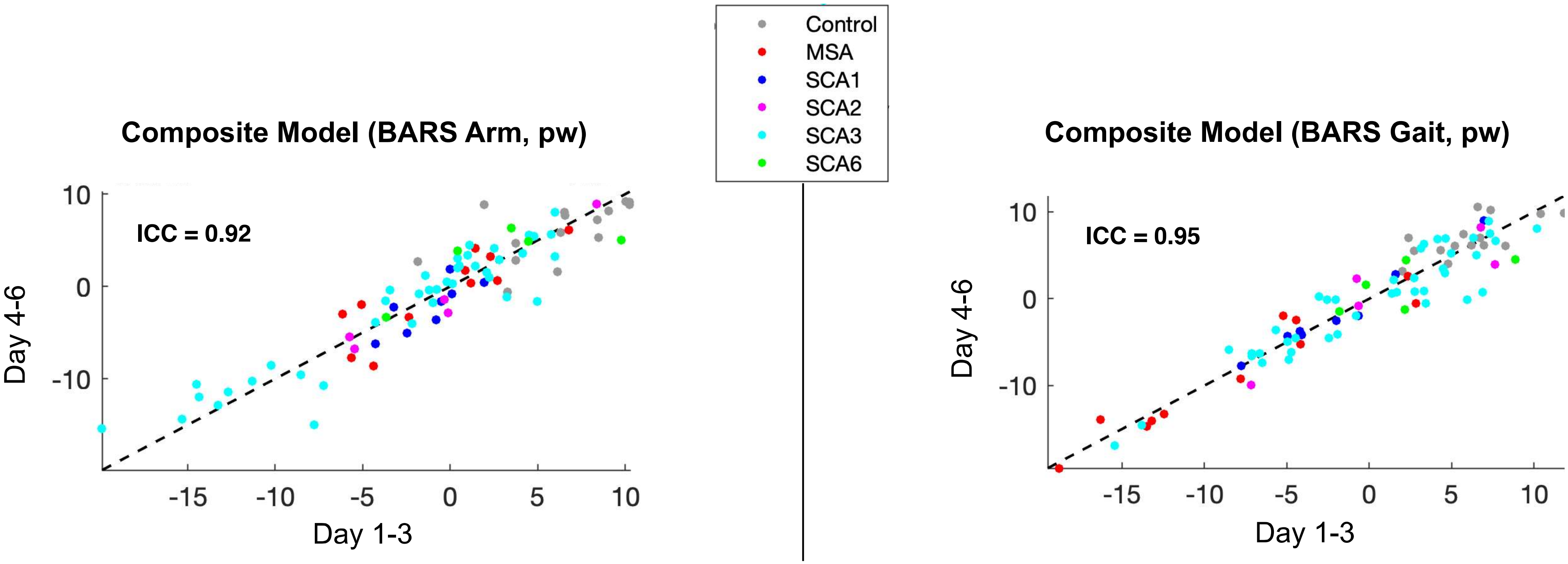
* Each point represents a person



Eklund et al. *Brain Communications* (2023)

Reliability within 1 week

* Each point represents a person

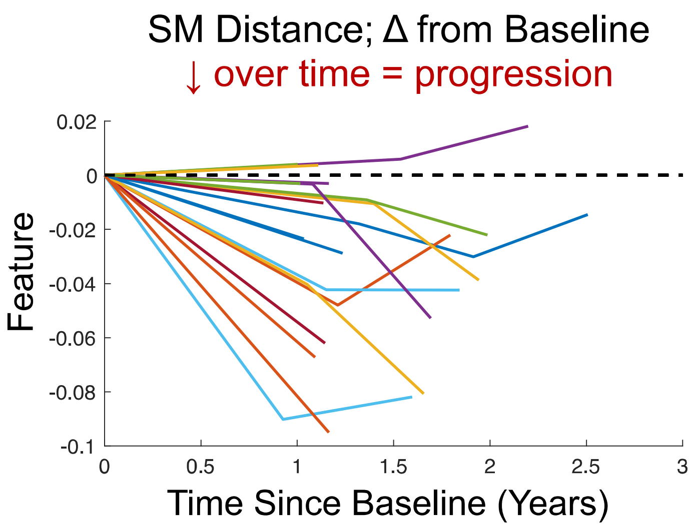


Eklund et al. *Brain Communications* (2023)

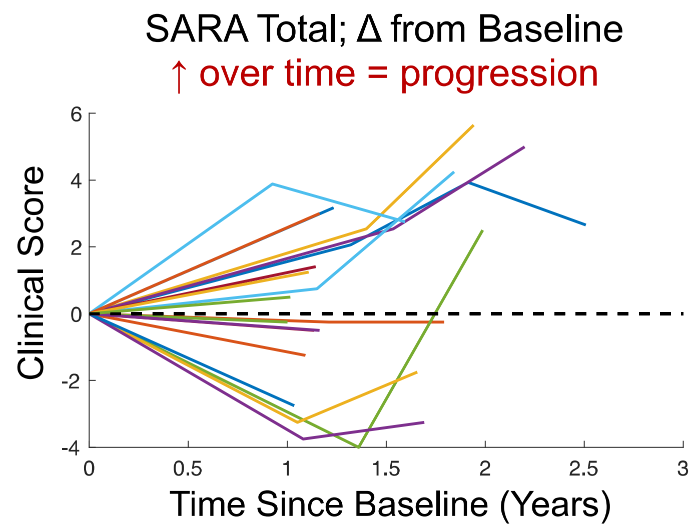
Sensitivity to disease progression

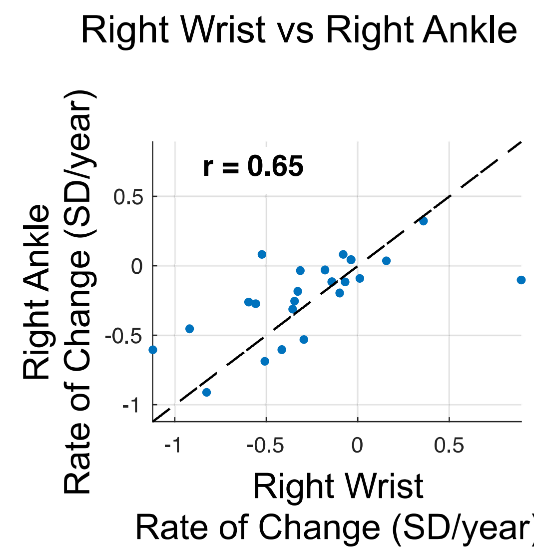
12 SCA3, 2 SCA1, 1 SCA2, 1 SCA6, 3 MSA-C, 4 Controls (N = 23)
SARA: 0.5-23 (10), Age: 30-70 (53), Sex(F/M): 10/9
6 preataxic individuals

<u>Sensor Measure</u>



<u>Clinical Rating Scale</u>

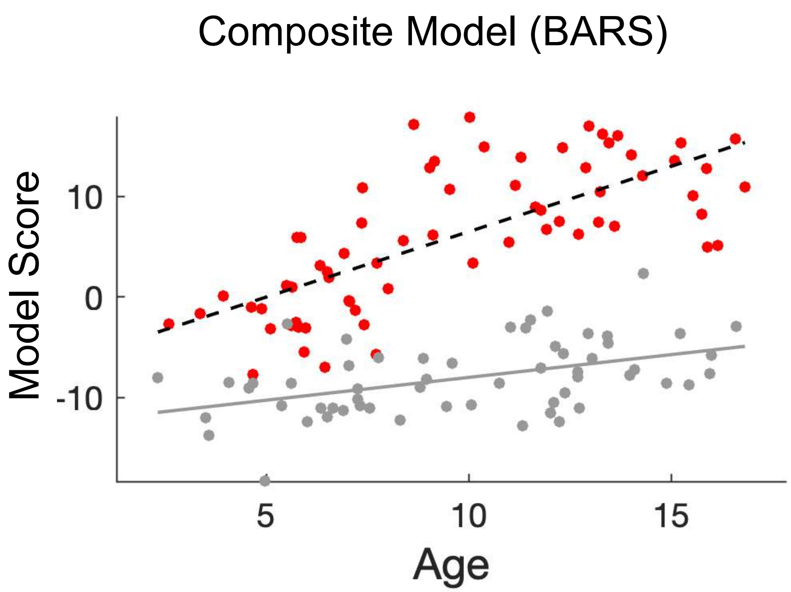


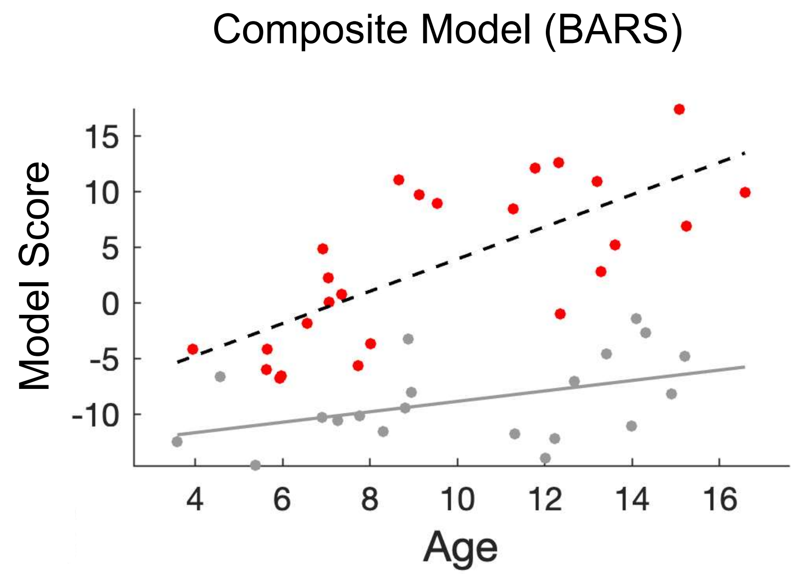


Pediatric Populations

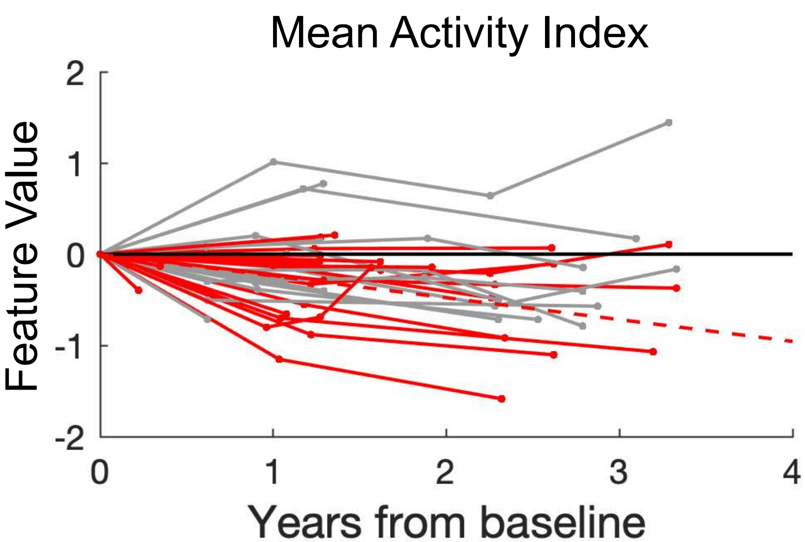
Ataxia-Telangiectasia (A-T)
Friedreich's ataxia (FA)
Dentatorubral-pallidoluysian atrophy (DRPLA)
Upstream Binding Transcription Factor-related neurodegenerative disease (UBTF)

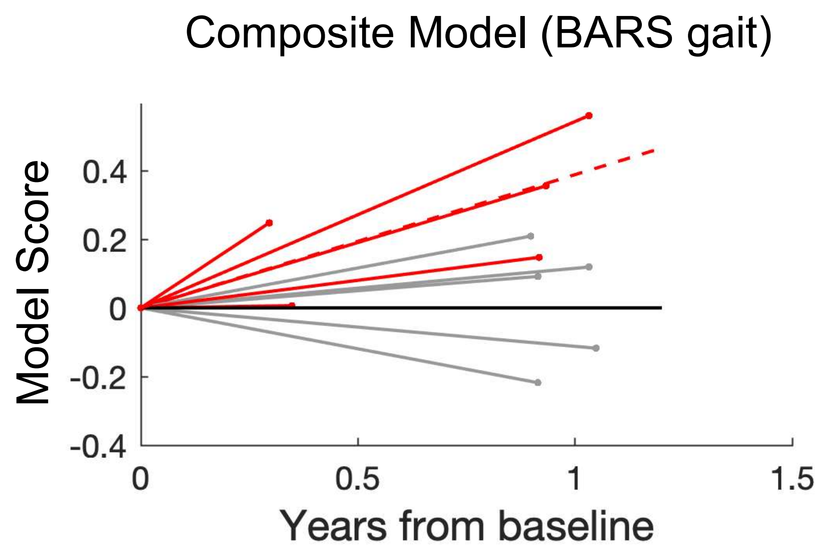
Comparison with control participants (Children with A-T)





Sensitivity to disease progression (Children with A-T)





Summary

- There are a variety of digital technologies and behavioral assessment approaches
    - E.g., Eye movement, speech, fine motor function, gross motor function
- Active/task-based versus passive/task-free assessments of behavior
- Methods for analyzing natural behavior are maturing
- There is potential to translate digital technologies across populations
    - However the most rapidly changing measures are usually disease-specific
- Increasing utility to collect at-home digital measures in natural history studies

Acknowledgements

Research Group

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Anna Luddy
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Brandon Oubre
Siddharth Patel
Larry White
Faye Yang

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Guillermo Sapiro, Duke
Ashkan Vaziri, BioSensics

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Albert Hung
Vikram Khurana, BWH
David Lynch, CHOP
Amanda Nagy
Jeremy Schmahmann
Christopher Stephen
Fernando Vieira, ALS-TDI
Anne-Marie Wills
Timothy Yu, BCH

A-T Children's Project · FARA Friedreich's Ataxia Research Alliance · CURE DRPLA · Dake Family Foundation · the orphan disease center · Massachusetts Life Sciences Center · Biogen · Massachusetts General Hospital · NIH National Institute of Neurological Disorders and Stroke · Broad Institute

Discussion