Patient-Centric Measures of Free-living Gait in ALS using Digital Health Technologies

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ActiGraph

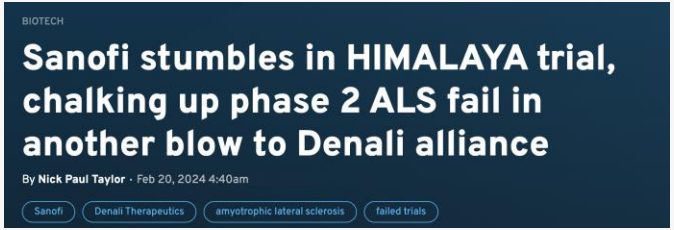
Introduction

ALS

- A progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord
- Loss of **speech, mobility, and respiratory** functions

ALS Drug Development

- **Limited success and patient satisfaction** with respect to disease progression and symptomatic relief*.
- **Lack of objective, sensitive, and patient-centric** measures
- An urgent need for the clinical outcome measures that can increase **the probability of success** of clinical trials in ALS


BIOTECH

Sanofi stumbles in HIMALAYA trial, chalking up phase 2 ALS fail in another blow to Denali alliance

By Nick Paul Taylor · Feb 20, 2024 4:40am

Sanofi | Denali Therapeutics | amyotrophic lateral sclerosis | failed trials

After 24 weeks, Sanofi assessed the change from baseline on an ALS severity scale, ALSFRS-R.

Actigraphy

- Hip-worn accelerometry outcomes were able to capture the functional decline (van Eijk, et al., 2019; Holdom et al., 2023)
- Wrist-worn activity measures were related with future decline in fine-motor function (Holdom et al., 2023)
- Functional mobility – **walking is meaningful**
- Wrist-derived gait measures can **increase compliance, adherence and reduce clinical trial costs**

*The Voice of the Patient, ALS drug dev survey, the ALS association, Oct, 2019

Objectives

1. Can wrist-based DHT measures of gait **distinguish between ALS** and the controls?
2. Can wrist-based DHT measures of gait **track the ALS progression**?
3. How to the wrist-based DHT measures of gait **correlate with the clinical measure**?

Study overview

Natural History Study

Assessing functional decline in ALS using actigraphy

PI: Frederik Steyn, PhD

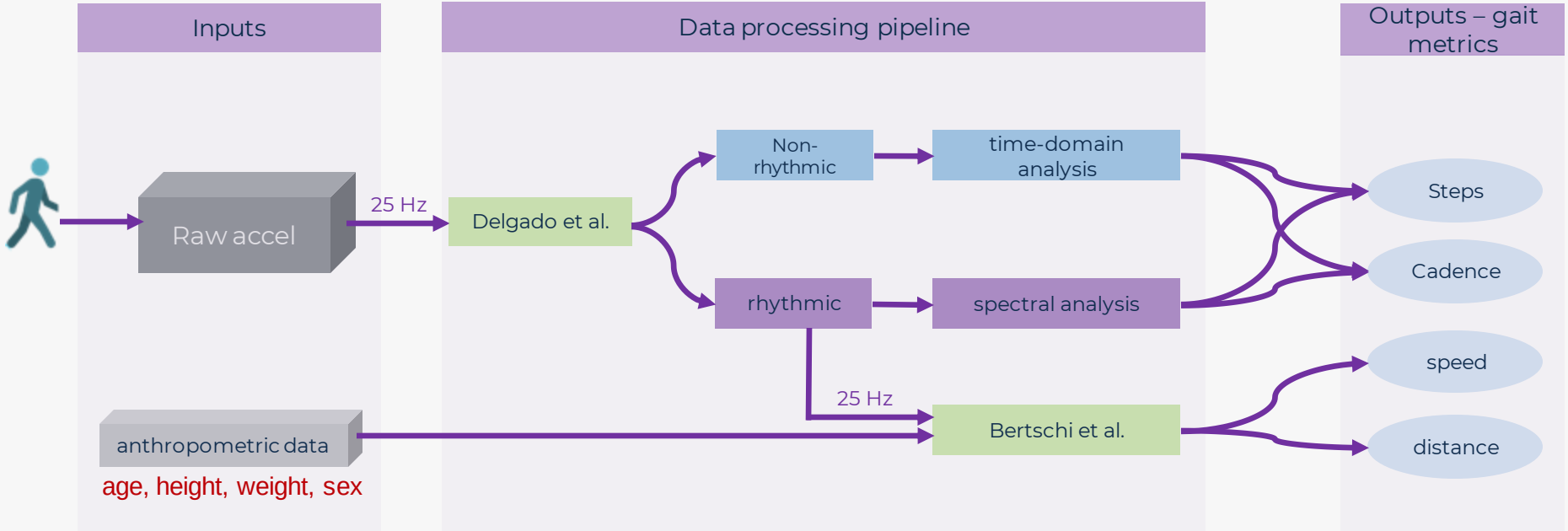
THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Objective – To observe the progression of the disease, and potentially differentiate patient subtypes.

Procedures

- **GT9X** on their **non-dominant wrist** (accelerometer)
- Continuous recording for **7-8 days.**
- **104 ALS and 54 controls** (since 2015)
- Multiple collection periods **(sessions)**
- Sessions are separated by **3-4 months**

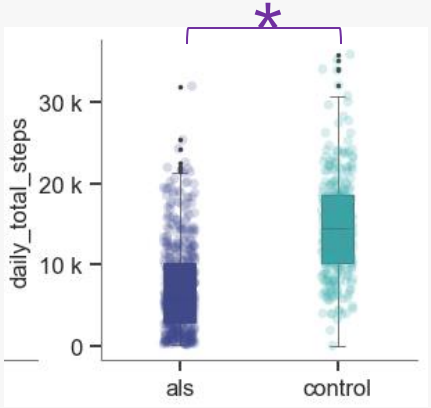
Algorithm and measures



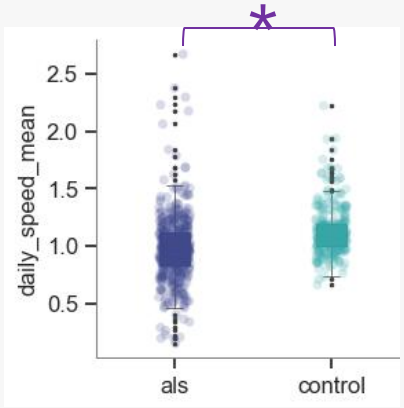
Q1: Can wrist-based DHT measures distinguish between ALS and the controls?

Session 0, Days 2-6, Controls = 58, ALS = 104

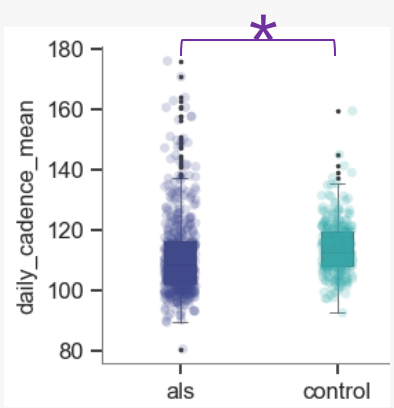
Step count



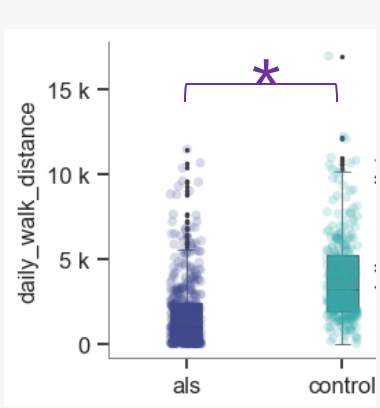
Gait speed (m/sec)



Cadence (steps/min)



Distance (m)

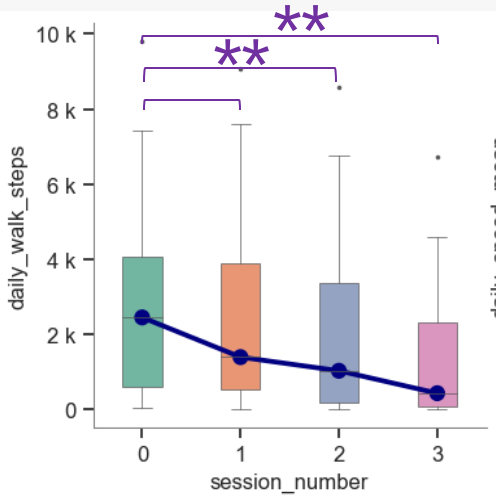


* $p < 0.05$

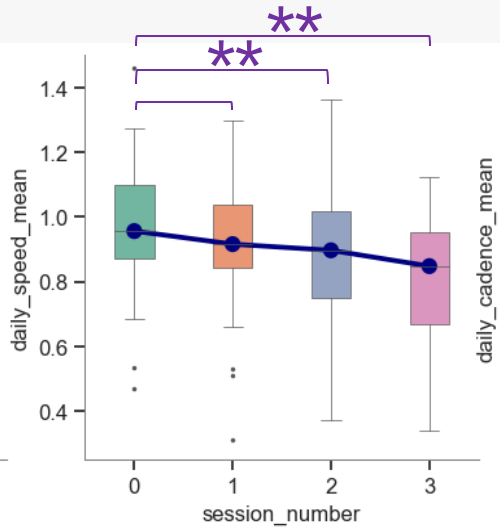
Q2: Can DHT-derived measures track the ALS progression?

Session 0-3, Days 2-6, N = 34 ALS,
Each session separated by 3-4 months

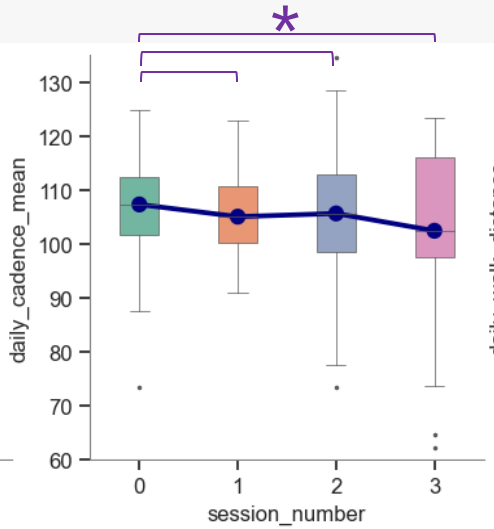
Step count



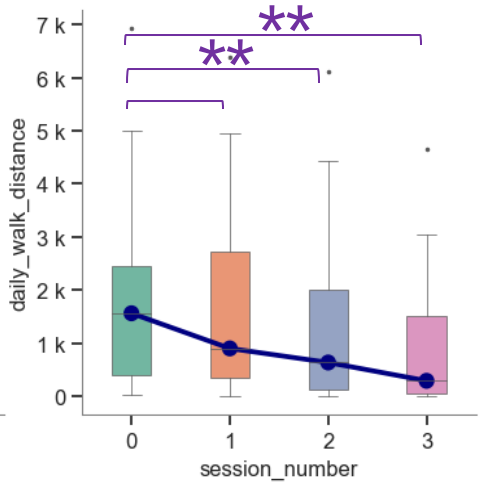
Gait speed (m/sec)



Cadence (steps/min)



Distance (m)



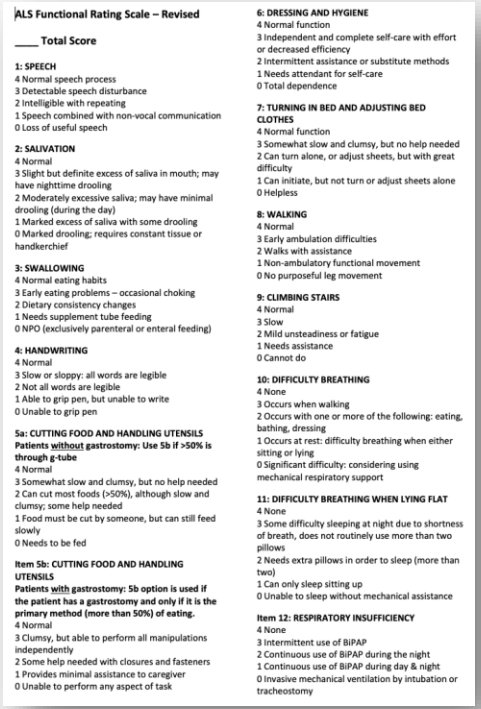
speed_50: ** at Sessions 2 & 3
speed_95: ** at Session 3

cadence_50: no significance change
cadence_95: * at Session 3

* $p < 0.05$, ** $p < 0.005$

Q3: How to the DHT measures correlate with the clinical measure?

ALS Functional Rating Scale – revised (ALSFRS-R)



ALS Functional Rating Scale – Revised

____ Total Score

1: SPEECH
4 Normal speech process
3 Detectable speech disturbance
2 Intelligible with repeating
1 Speech combined with non-vocal communication
0 Loss of useful speech

2: SALIVATION
4 Normal
3 Slight but definite excess of saliva in mouth; may have nighttime drooling
2 Moderately excessive saliva; may have minimal drooling (during the day)
1 Marked excess of saliva with some drooling
0 Marked drooling; requires constant tissue or handkerchief

3: SWALLOWING
4 Normal eating habits
3 Early eating problems – occasional choking
2 Dietary consistency changes
1 Needs supplement tube feeding
0 NPO (exclusively parenteral or enteral feeding)

4: HANDWRITING
4 Normal
3 Slow or sloppy; all words are legible
2 Not all words are legible
1 Able to grip pen, but unable to write
0 Unable to grip pen

5a: CUTTING FOOD AND HANDLING UTENSILS
Patients without gastrostomy: Use 5b if >50% is through g-tube
4 Normal
3 Somewhat slow and clumsy, but no help needed
2 Can cut most foods (>50%), although slow and clumsy; some help needed
1 Food must be cut by someone, but can still feed slowly
0 Needs to be fed

Item 5b: CUTTING FOOD AND HANDLING UTENSILS
Patients with gastrostomy: 5b option is used if the patient has a gastrostomy and only if it is the primary method (more than 50%) of eating.
4 Normal
3 Clumsy, but able to perform all manipulations independently
2 Some help needed with closures and fasteners
1 Provides minimal assistance to caregiver
0 Unable to perform any aspect of task

6: DRESSING AND HYGIENE
4 Normal function
3 Independent and complete self-care with effort or decreased efficiency
2 Intermittent assistance or substitute methods
1 Needs attendant for self-care
0 Total dependence

7: TURNING IN BED AND ADJUSTING BED CLOTHES
4 Normal function
3 Somewhat slow and clumsy, but no help needed
2 Can turn alone, or adjust sheets, but with great difficulty
1 Can initiate, but not turn or adjust sheets alone
0 Helpless

8: WALKING
4 Normal
3 Early ambulation difficulties
2 Walks with assistance
1 Non-ambulatory functional movement
0 No purposeful leg movement

9: CLIMBING STAIRS
4 Normal
3 Slow
2 Mild unsteadiness or fatigue
1 Needs assistance
0 Cannot do

10: DIFFICULTY BREATHING
4 None
3 Occurs when walking
2 Occurs with one or more of the following: eating, bathing, dressing
1 Occurs at rest: difficulty breathing when either sitting or lying
0 Significant difficulty: considering using mechanical respiratory support

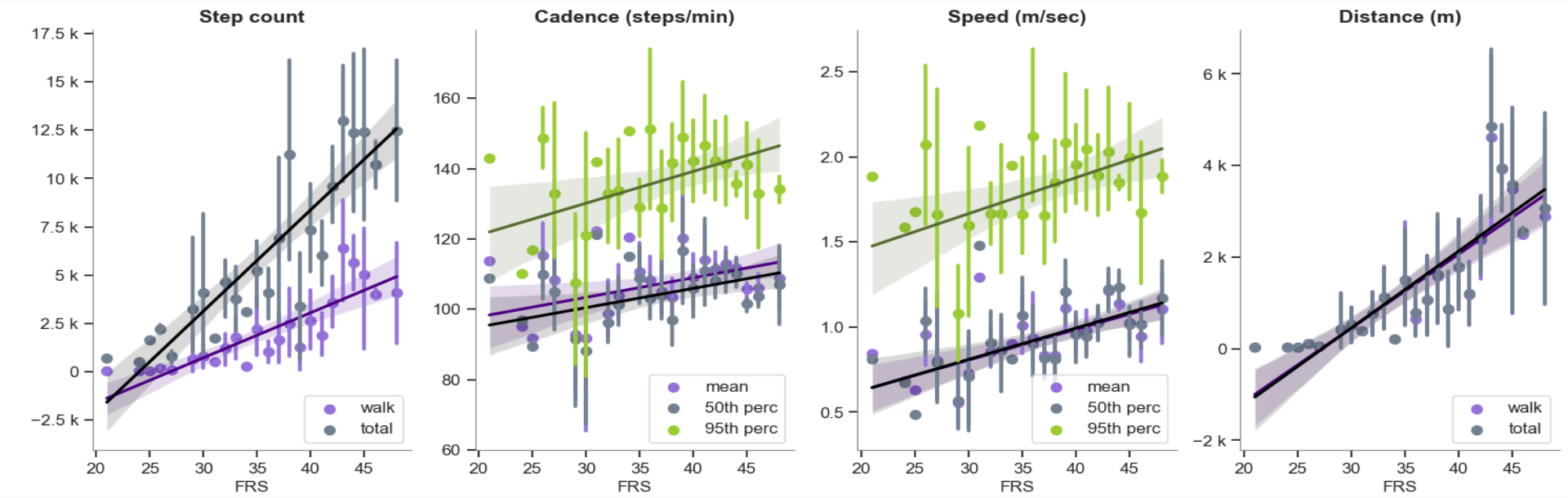
11: DIFFICULTY BREATHING WHEN LYING FLAT
4 None
3 Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2 Needs extra pillows in order to sleep (more than two)
1 Can only sleep sitting up
0 Unable to sleep without mechanical assistance

Item 12: RESPIRATORY INSUFFICIENCY
4 None
3 Intermittent use of BiPAP
2 Continuous use of BiPAP during the night
1 Continuous use of BiPAP during day & night
0 Invasive mechanical ventilation by intubation or tracheostomy

Each item: 0 to 4 (normal), max score: 48

- **High score – higher functional status**
- **Functional areas:**
  - Speech
  - Salivation
  - Swallowing
  - Handwriting
  - Cutting food and handling utensils
  - Dressing and hygiene
  - Turning in bed and adjusting bed clothes
  - Walking, climbing stairs
  - Breathing, respiratory

Q3: How to the DHT measures correlate with the clinical measure?



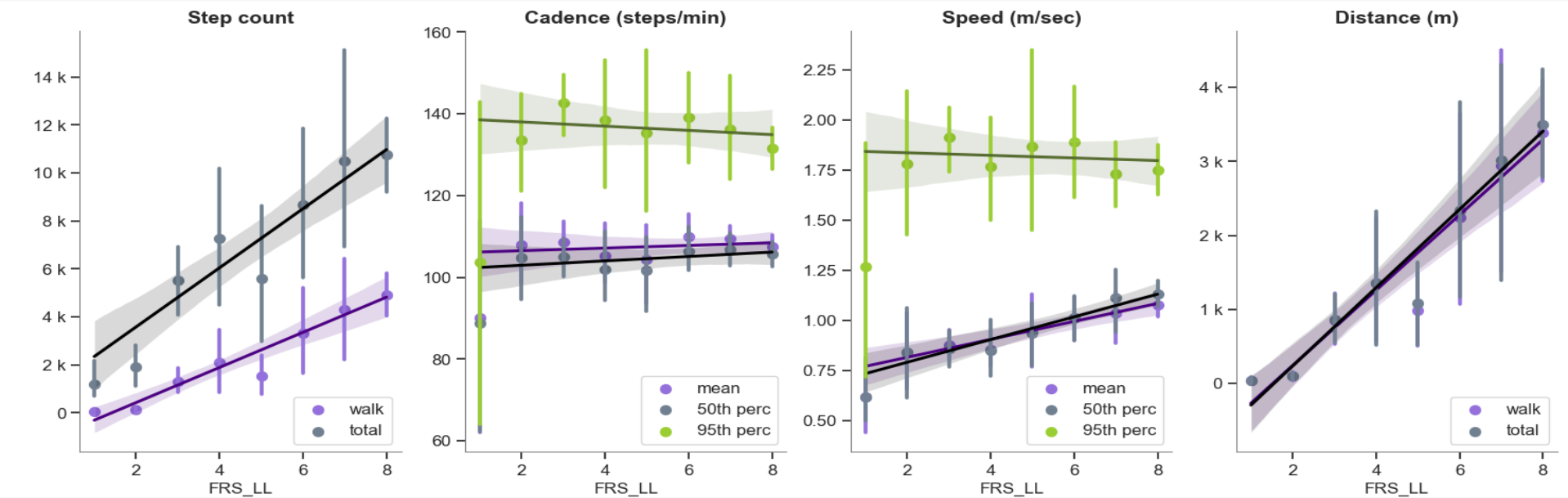
Pearson r=0.61, p=0.0
Pearson r=0.54, p=0.0

Pearson r=0.23, p=0.02
Pearson r=0.24, p=0.01
Pearson r=0.24, p=0.02

Pearson r=0.39, p=0.0
Pearson r=0.43, p=0.0
Pearson r=0.26, p=0.01

Pearson r=0.54, p=0.0
Pearson r=0.53, p=0.0

Q3: How to the DHT measures correlate with the clinical measure?



Pearson r=0.56, p=0.0
Pearson r=0.65, p=0.0

Pearson r=0.09, p=0.38
Pearson r=0.05, p=0.59
Pearson r=-0.05, p=0.6

Pearson r=0.47, p=0.0
Pearson r=0.42, p=0.0
Pearson r=-0.03, p=0.76

Pearson r=0.66, p=0.0
Pearson r=0.65, p=0.0

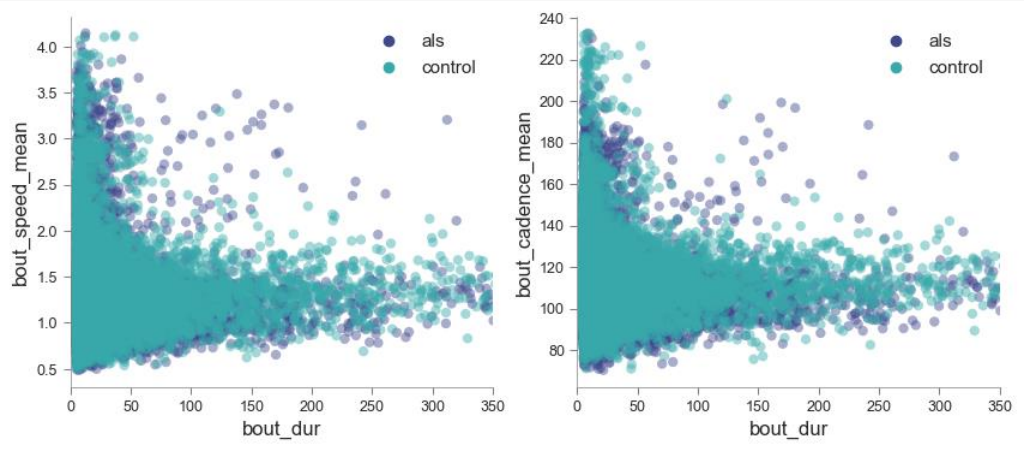
Gait bouts

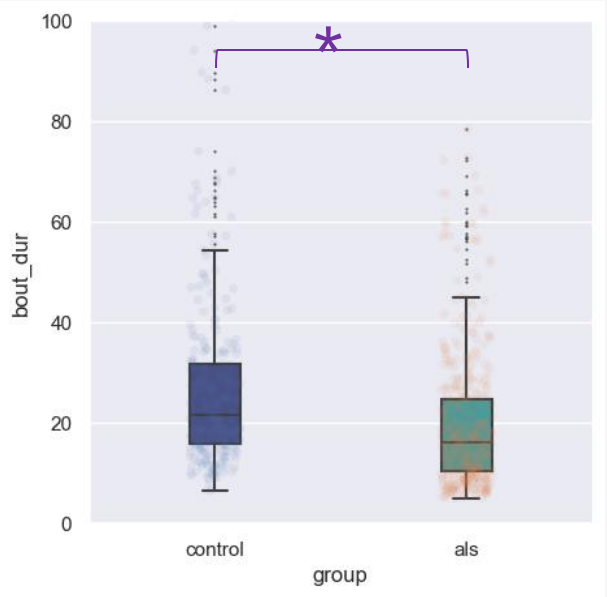
Removing the ‘noise’ in the data?

Bout-level metrics

Subject ID	Date	Bout ID	Bout Duration (sec)	Steps	Cadence*	Speed*	Distance
id1	date1	0			*50th (median) and 95th percentiles are also provided		
id1	date1	1					

***Bout** - a continuous walking segment detected by the algorithm*





Summary

1	Can DHT-derived measures distinguish between the ALS and the controls?	**Yes:** step counts, distance, speed (mean, median), cadence (mean and median)
2	Can DHT-derived measures track the disease progression?	**Yes:** step counts, distance, speed (mean, median), cadence (mean and median) 95th perc of speed, cadence only at session 3
3	How to the DHT-derived measures correlate with clinical measures ?	**All measures are significantly correlated with ALS-FRS** Step count, distance (**high effect size**) Gait speed (**medium effect size**) Cadence measures (**low effect size**)

Next steps

Statistical analyses

- How reliable the outcome measures are based on the variability in the data ?
- How much data is enough for getting the desired measures?
- How should we aggregate the data to improve the effect sizes?

Questions?

ADDS 2024

Thank You for Your Time.

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