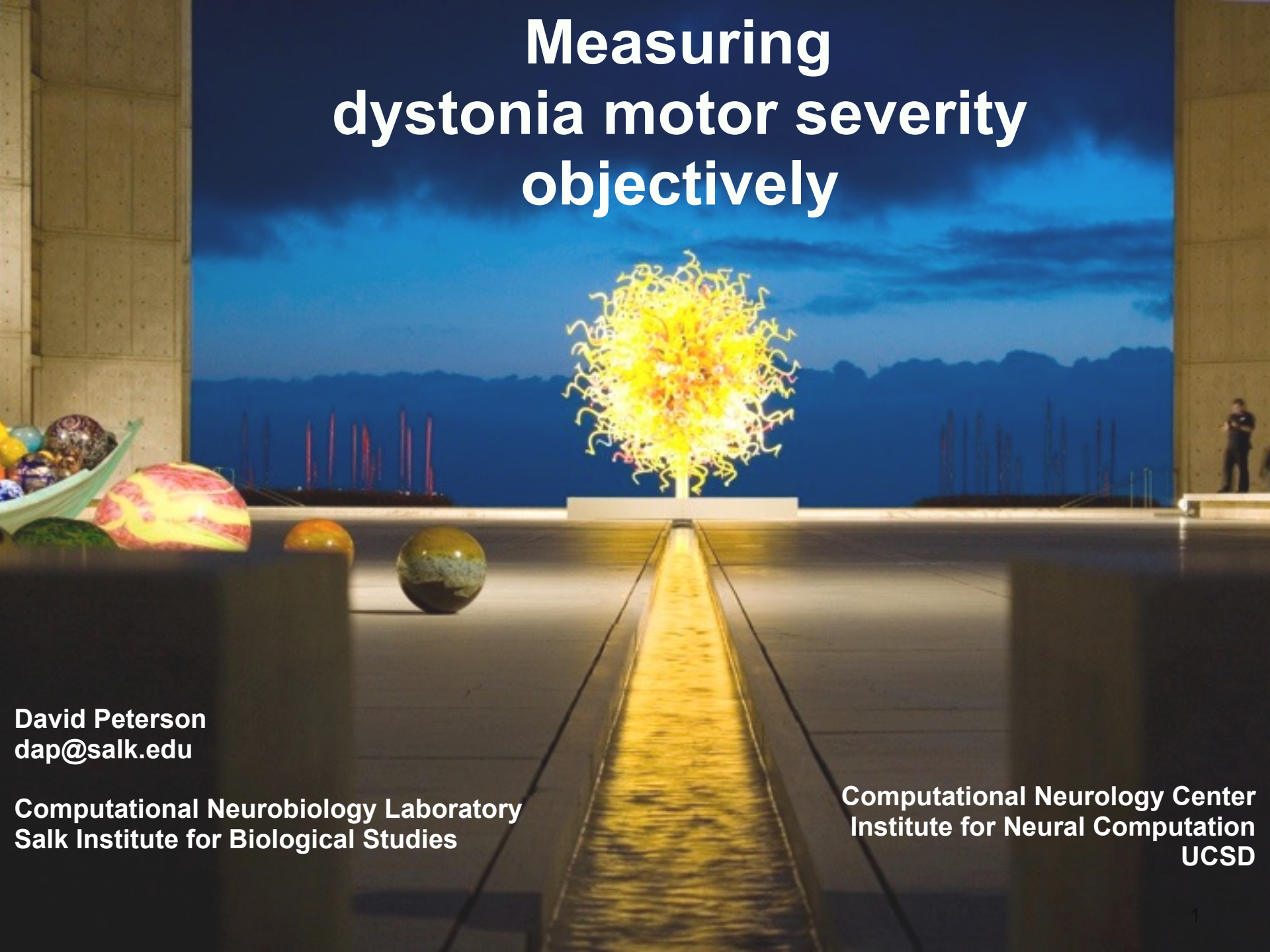


Measuring dystonia motor severity objectively



David Peterson
dap@salk.edu

Computational Neurobiology Laboratory
Salk Institute for Biological Studies

Computational Neurology Center
Institute for Neural Computation
UCSD

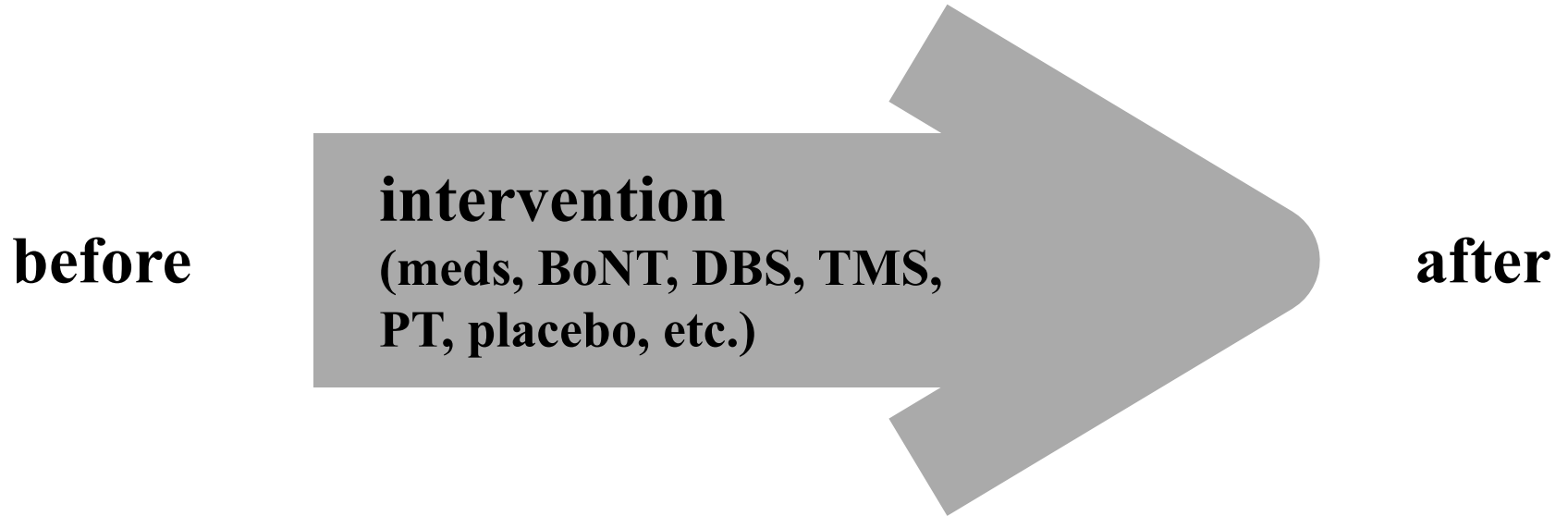


Why do we care?

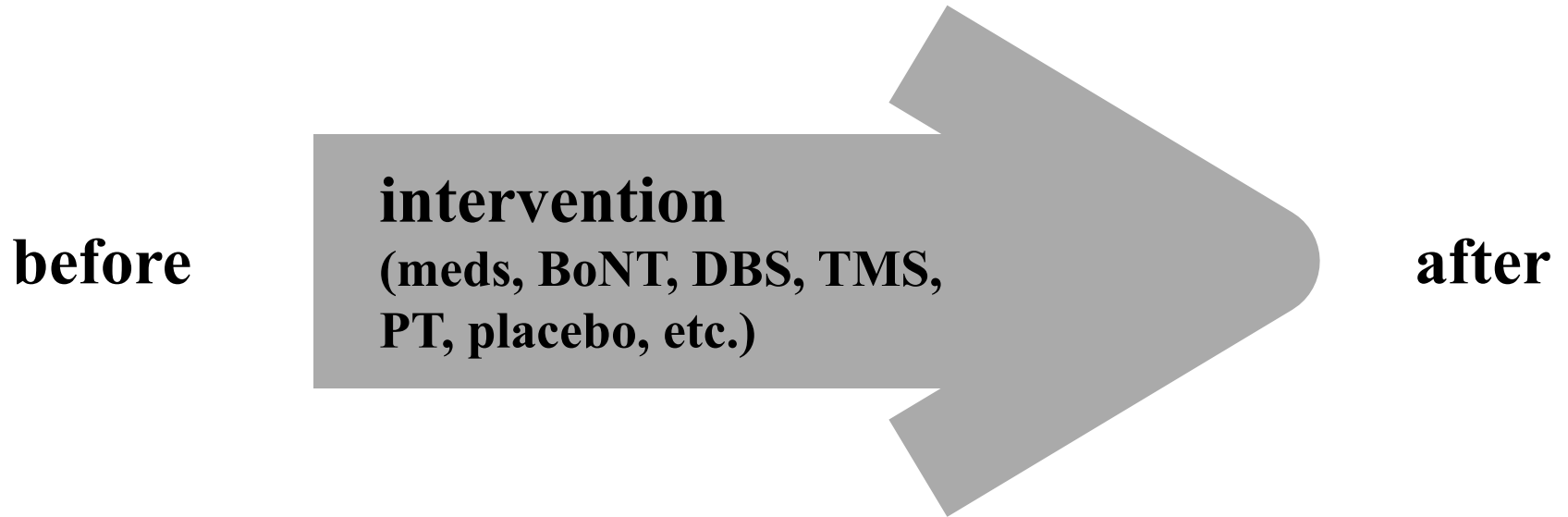
Why do we care?

- All in the service of improved treatment...
- Long term: Human research on mechanisms
 - (do the -omics, imaging, neurophys, etc. correlate with motor severity?)
- Short term: Trial outcomes

Pivotal to trial outcomes: measuring SEVERITY

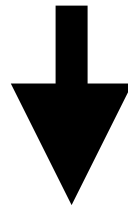
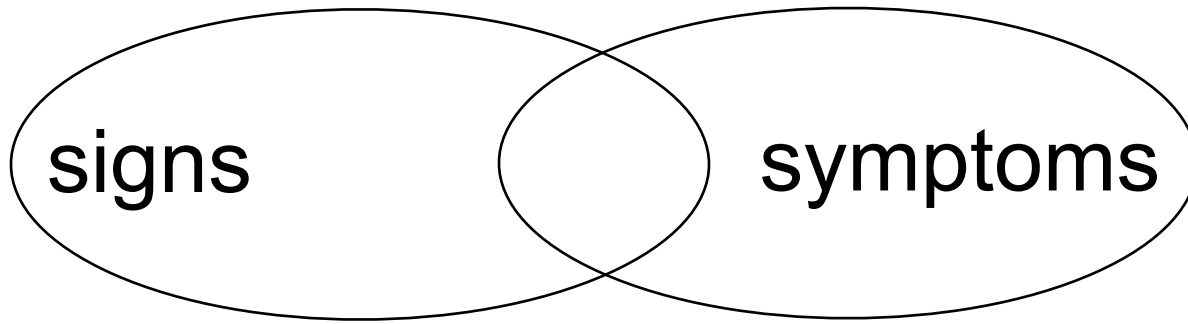


Pivotal to trial outcomes: measuring SEVERITY



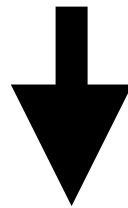
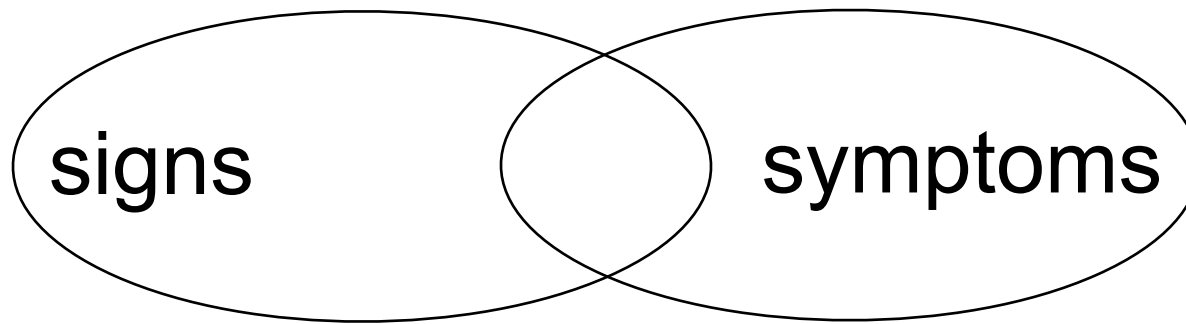
1. Compare before and after
(e.g. TWSTRS(before) - TWSTRS(after))
2. After intervention, assay “change”
(e.g. PGI-C)

Measuring severity of WHAT?



- **Function**
- **Disability**
- **QoL**

Measuring severity of WHAT?



- **Function**
- **Disability**
- **QoL**

(i.e. *concept(s) of interest (COI)*)

Measuring severity: HOW/WHO?

FDA categories of *clinical outcome assessments* (COAs) based on **WHO** is doing the measuring:

- ClinRO: **clinician** reported outcome
 - (i.e. clinical rating scales)
- ObsRO: **observer** reported outcome
 - (someone other than health professional or patient)
- PRO: **patient** reported outcome
 - (a.k.a. patient centered outcomes, PCOs)

Rating scales are subjective

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all based on
human
judgment

Rating scales are subjective

- ClinRO: **clinician** reported outcome
- ObsRO: **observer** reported outcome
- PRO: **patient** reported outcome



all based on
human
judgment

- Human judgment is intrinsically **subjective**
 - Affected by training, experience, etc.
 - Not necessarily wrong, just highly **variable**

The variability of subjective measures has consequences

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- It gets conflated with treatment outcome variability:

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The variability of subjective measures has consequences

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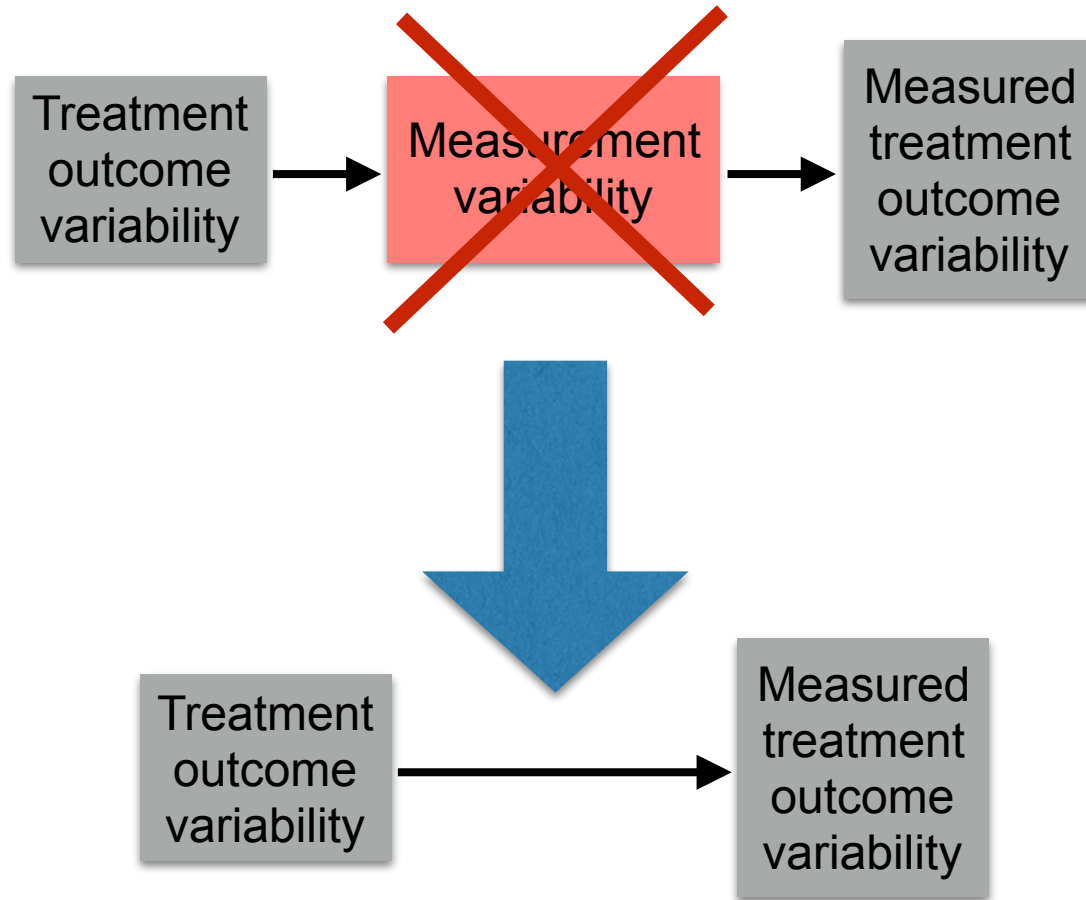


- Variability reduces intra- and inter-rater reliability
 - Within individual trials
 - Intra-rater: before / after treatment
 - Inter-rater: multi-site trials
 - Across different trials
 - Meta analyses
- Variability decreases statistical power, thereby requiring higher Ns (and trial costs), longer delays, higher risk

What if we could circumvent the variability of subjective measures?



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OBJECTIVE measures: definitions

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How do we define “objective”? each measurement does **not** depend on human judgement

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- “technology-based objective measures” (TOMs, Espay 2016 Mov Disord; to distinguish from subjective methods labeled as “objective”?)

OBJECTIVE measures: definitions

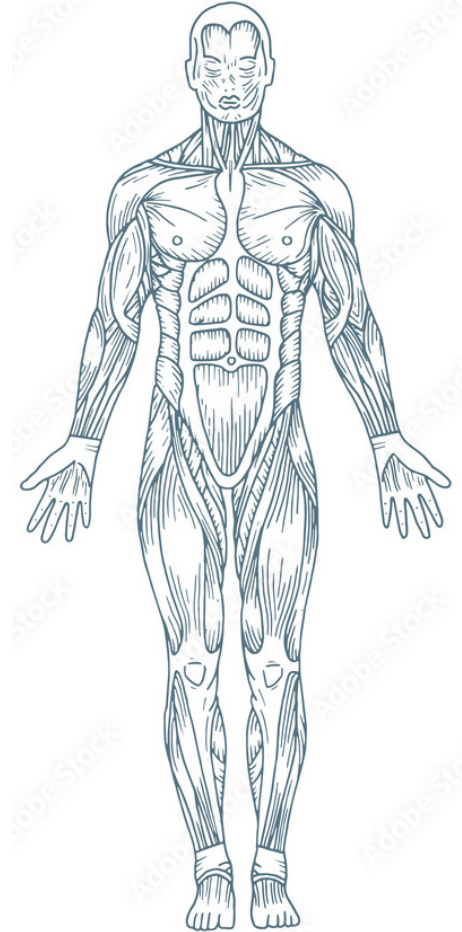
How do we define “objective”? each measurement does **not** depend on human judgement

Terminology can be problematic:

- “technology-based objective measures” (TOMs, Espay 2016 Mov Disord; to distinguish from subjective methods labeled as “objective”?)
- “digital methods”
 - e.g. “digital health technology” (FDA)
 - *but* digital implementations of subjective measures, e.g. “electronic CRSs”; apps being developed for PROs, etc.)
 - how about a ruler?

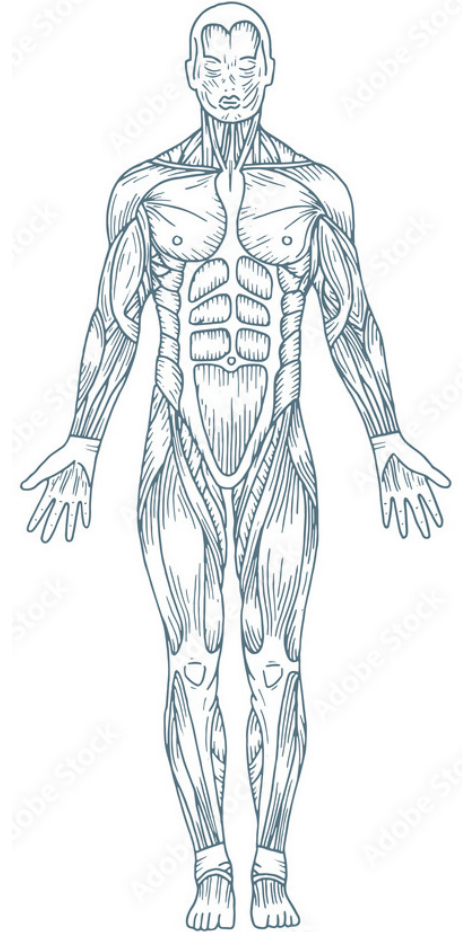
Objective measures for dystonia

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Objective measures for dystonia

- kinematics
 - optical,
 - reflective, and/or
 - electromagnetic markers
- IMUs (inertial measurement units)
 - accelerometers
 - gyroscopes
- EMG
- Video
 - 3d/depth
 - 2d



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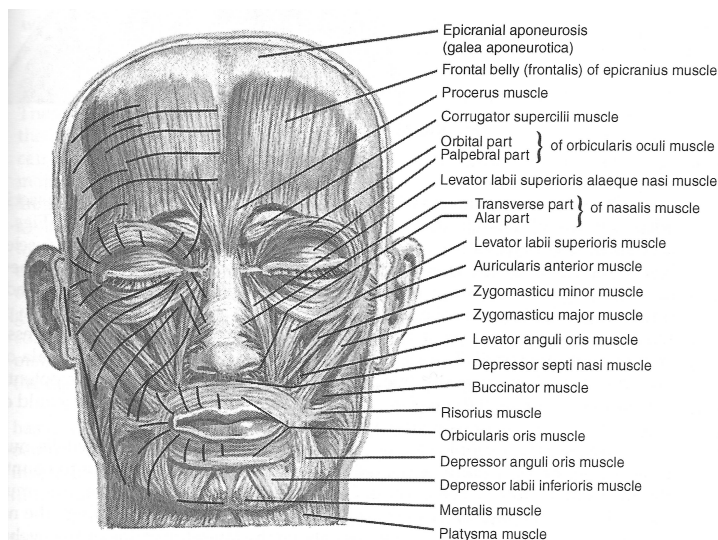
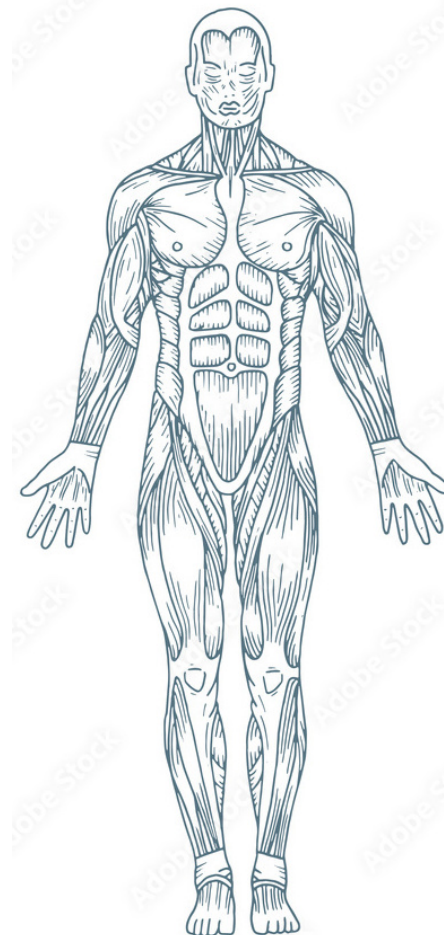


FIGURE 24.1 Superficial facial muscles, anterior view.



“Wearables” are becoming less obtrusive

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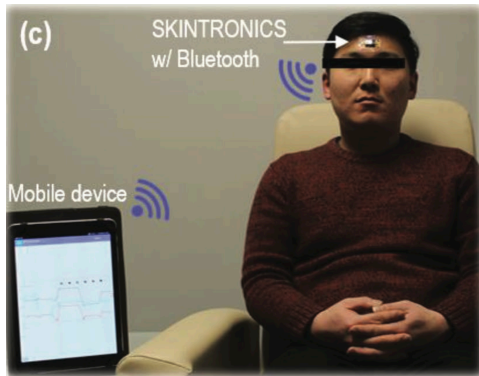
Soft Nanomembrane Sensors and Flexible Hybrid Bioelectronics for Wireless Quantification of Blepharospasm

Musa Mahmood, Shinjae Kwon, Gamze Kilic Berkmen, Yun-Soung Kim, Laura Scorr, H. A. Jinnah
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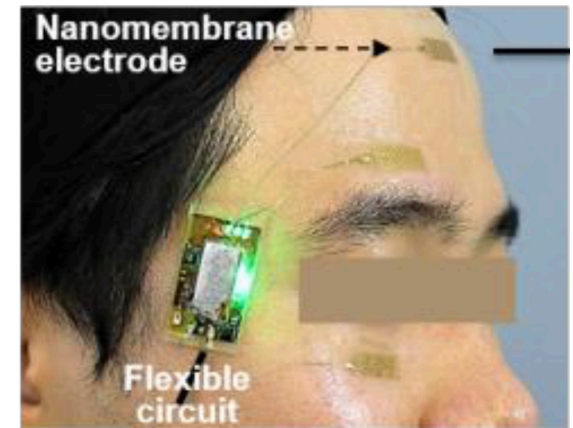
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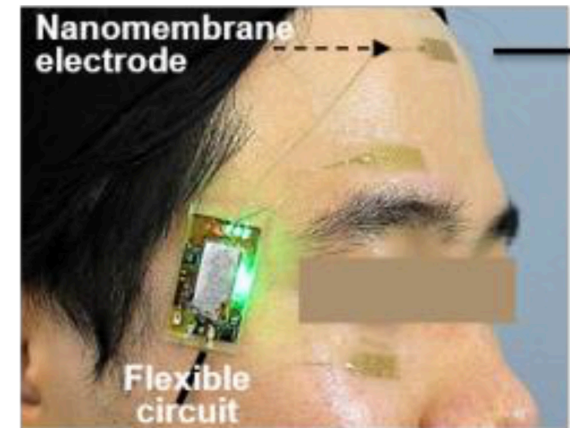
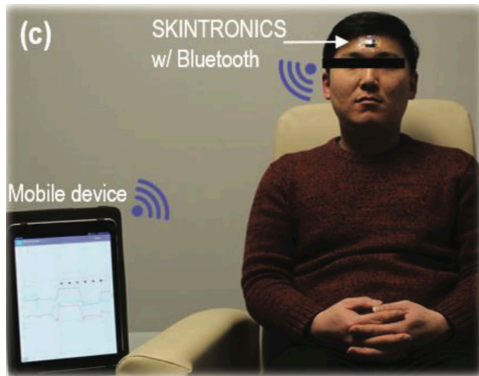
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FULL PAPER

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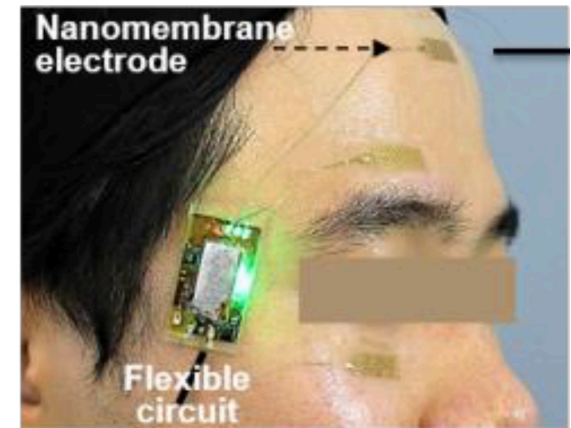
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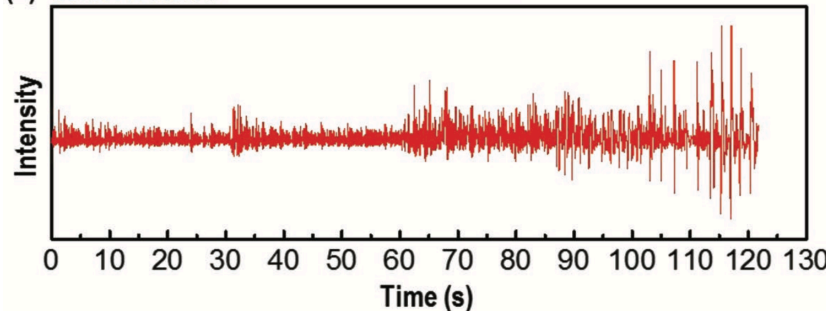
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(b) SKINTRONICS



Advantages of Video (vs. IMUs, EMG, etc.)

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- Clinical utility
 - Pervasive in movement disorders
 - Minimal additional resource requirements
 - equipment
 - expertise
 - time

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(vs. markers, EMG electrodes, etc.)
 - minimizes observer effect!
- Enables telehealth, remote access, more frequent assays during ADLs

Analyzing videos with computer vision (instead of human vision)

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Overall Approach:

- Develop software...
 - ... the Computational Motor Objective Rater, CMOR)
 - ... that leverages advances in AI (e.g. computer vision and machine learning/deep learning)
- Test CMOR's convergent validity with clinical ratings severity

Analyzing videos with computer vision (instead of human vision)

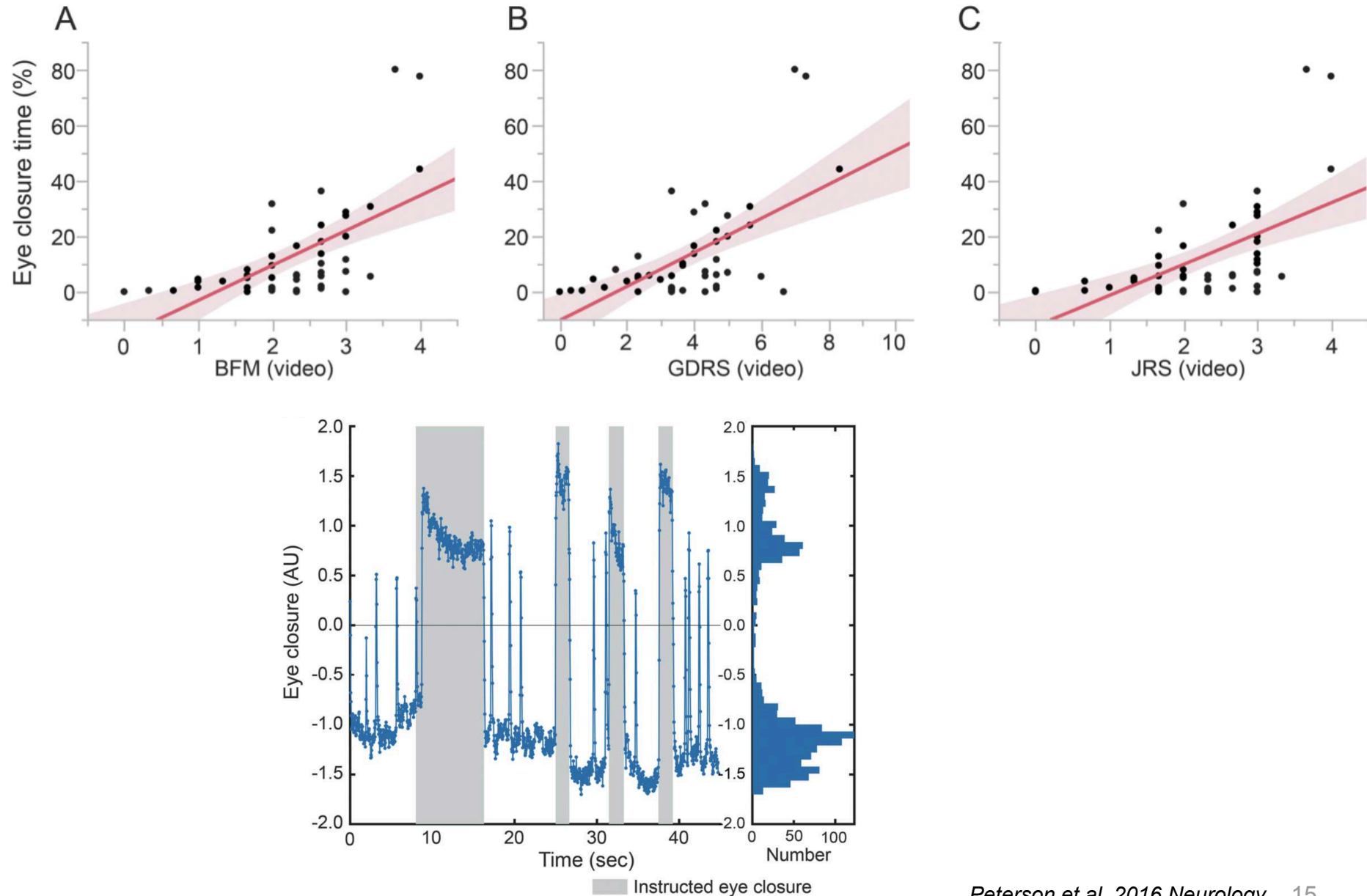
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Scope:

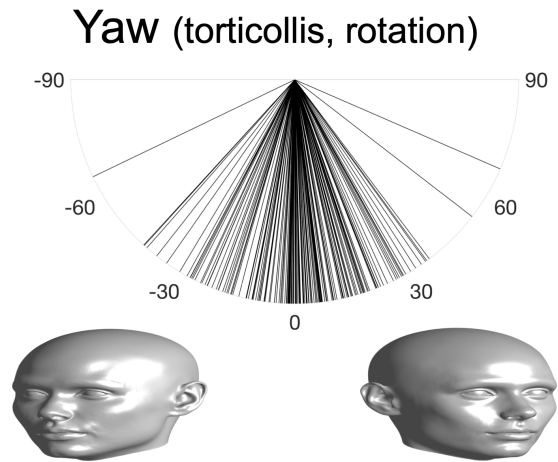
- BSP and CD: videos from clinical exam
- LD: videos from laryngoscopic exam

CMOR for eye closure in BSP

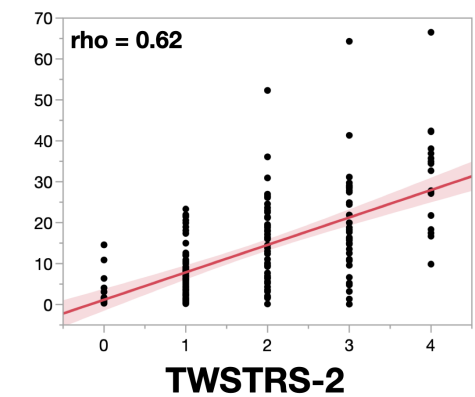
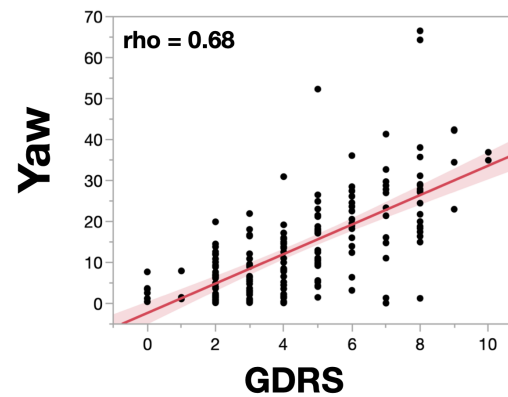
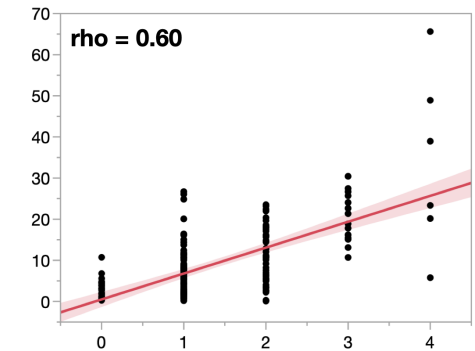
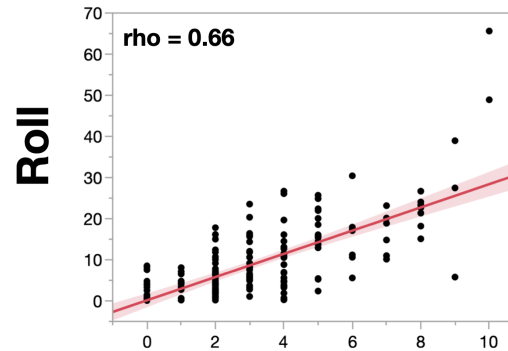
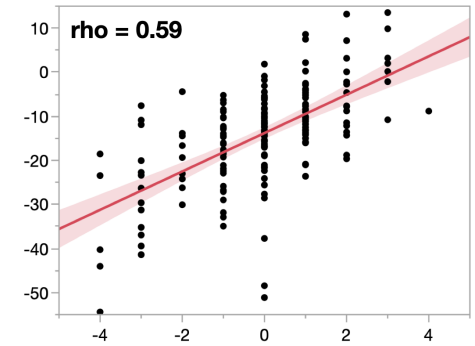
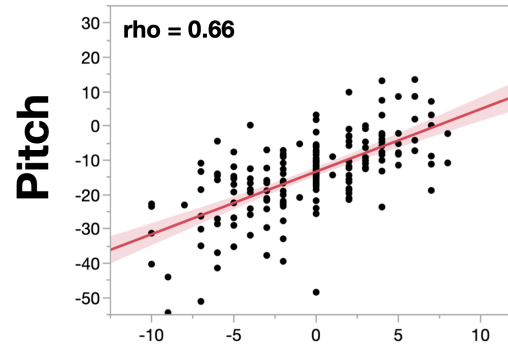
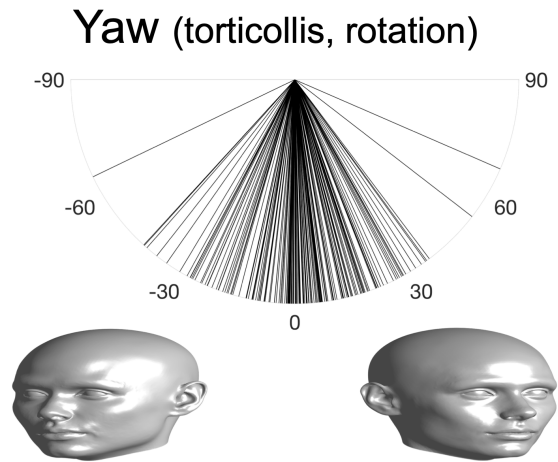


CMOR for CD: head deviation

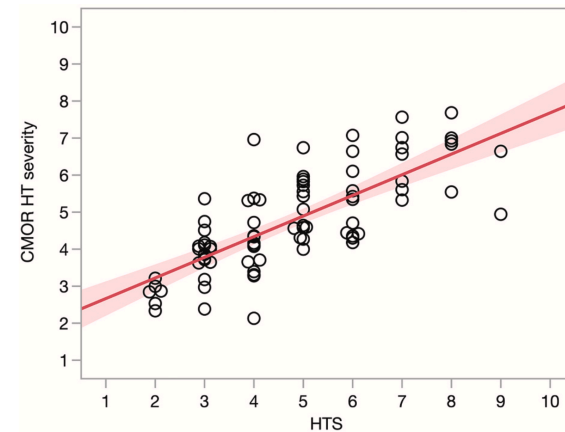
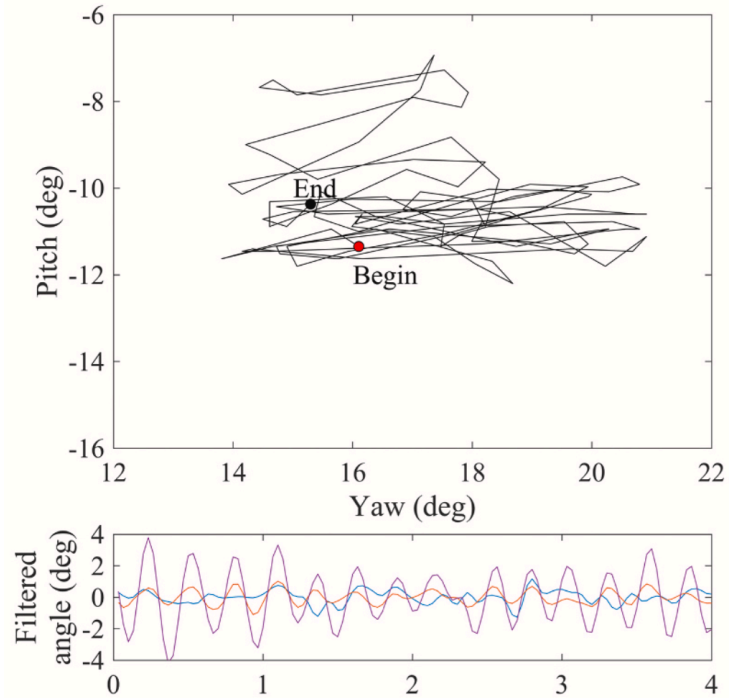
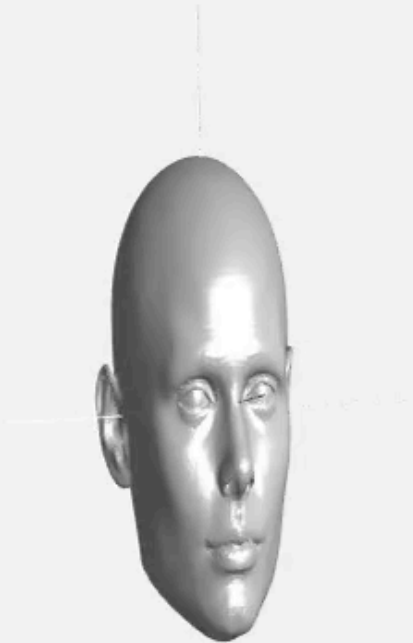
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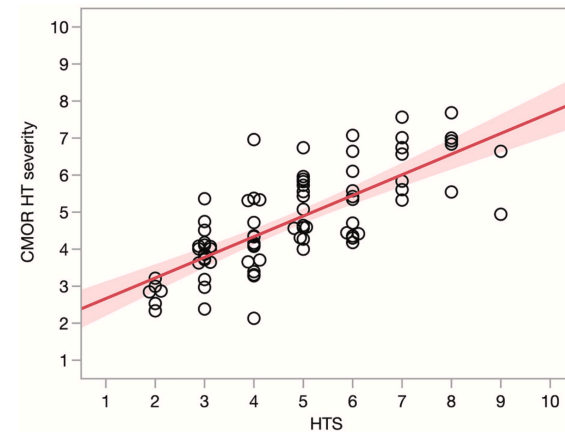
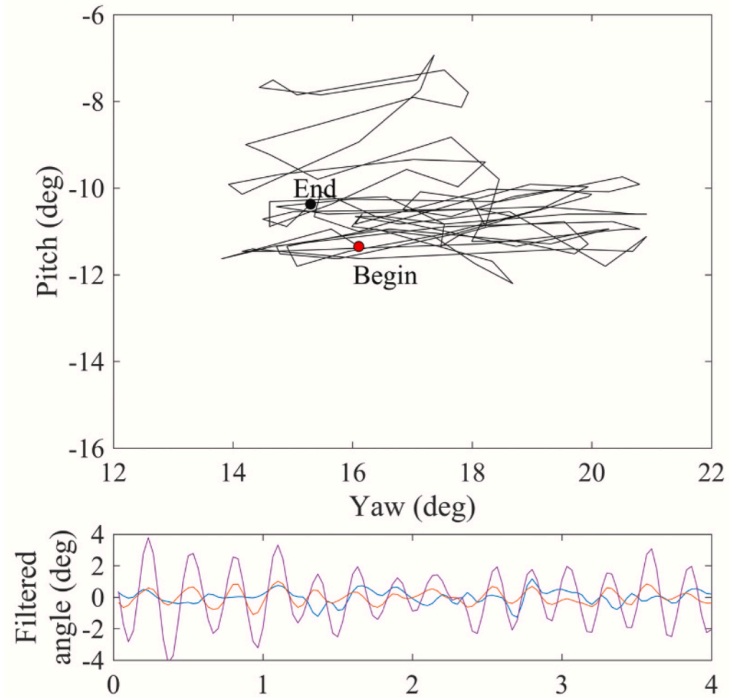
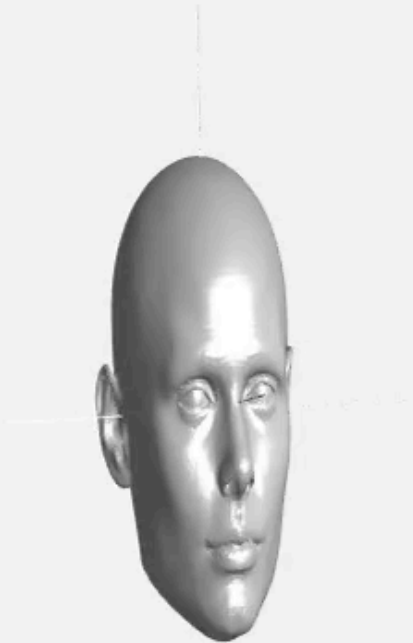


CMOR for CD: head tremor



Vu 2022 J Neurol Sci

CMOR for CD: head tremor



Vu 2022 J Neurol Sci

Managing complexity: the case of head tremor “subtypes”

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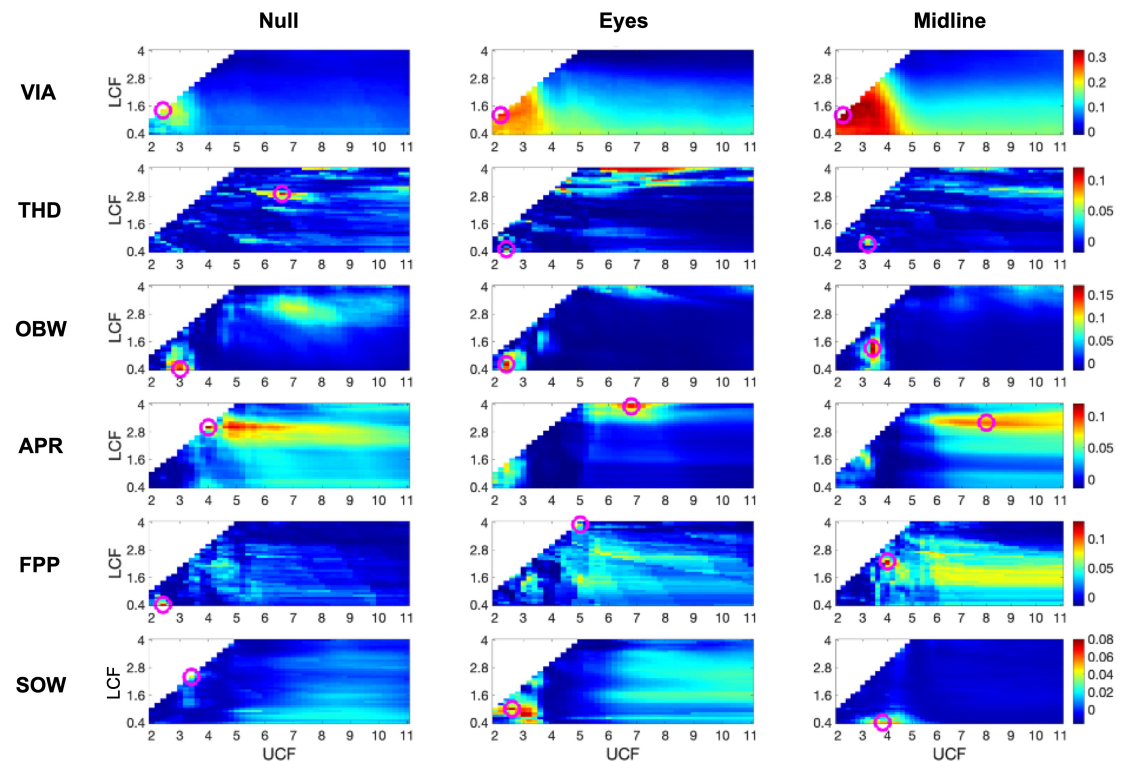
Should we
use the term
“ET-plus”?
(e.g. if the
head tremor
is “jerky”)

Managing complexity: the case of head tremor “subtypes”



“task” and analytic parameters
matter!

Should we
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CMOR for glottal dynamics in LD

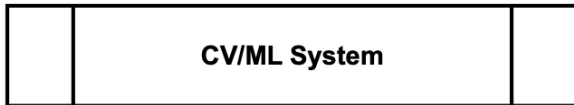
CMOR for glottal dynamics in LD

Can we predict ADSD voice quality by extracting glottal geometry from laryngoscopic video recordings?

How do dynamic features in the geometry of the glottis relate to voice quality in ADSD ?

CMOR for glottal dynamics in LD

RGB Frame



Scored Mask



(units in pixels)

Area = 1326

Minor axis length = 12

Shape = minor / major = 0.08

Major axis length = 149

Can we predict ADSD voice quality by extracting glottal geometry from laryngoscopic video recordings?

How do dynamic features in the geometry of the glottis relate to voice quality in ADSD ?

Peterson et al. 2022 J Speech Lang Hear Res

Objective measures in a BSP trial

Objective measures in a BSP trial

- Addex Pharmaceuticals
 - Allosteric modulators (AMs) for several CNS indications
 - dipraglurant: mGlu5 negative allosteric modulator (NAM)
 - PD LIDs
 - exploratory Phase 2 PCT in BSP
 - with the current IR formulation
 - assessments include clinical ratings, PROs, and objective measures:
 - CMOR and Skintronics
- *ClinicalTrials.gov Identifier: NCT05027997*
- <https://www.addextherapeutics.com/en/pipeline/researches/dipraglurant-dystonia/>

Measuring severity: the patient perspective

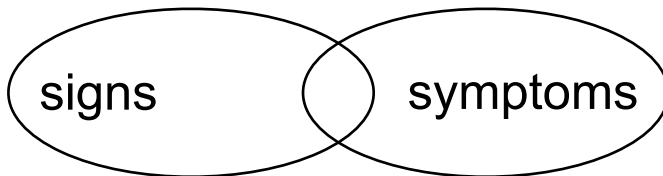
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Combine PRO's *and* Video-based objective measures

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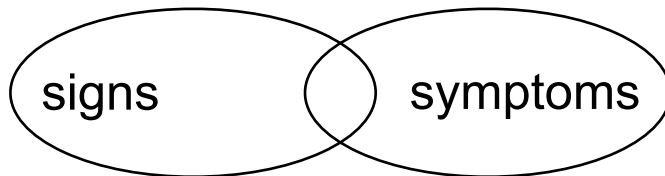
- BOTH enable measurement outside the clinic
 - Greater frequency
 - At home, in daily life settings
 - Patient-centered
- Synergies



Combine PRO's *and* Video-based objective measures

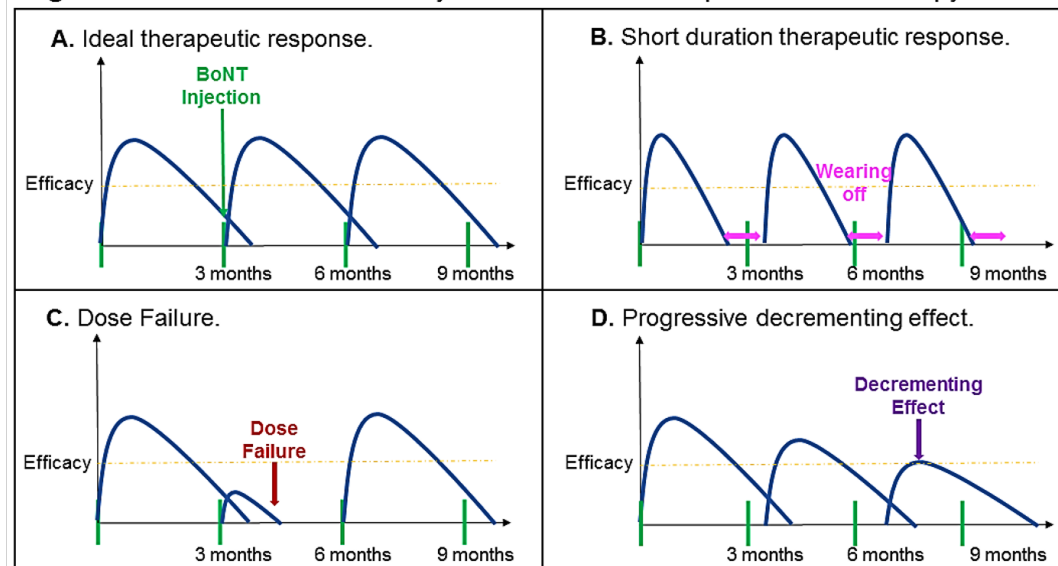
- BOTH enable measurement outside the clinic
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 - Patient-centered

- Synergies



In *context of use* involving BoNT cycles, we need more frequent measures

Figure 2. Fluctuations in severity over time and complications of therapy.



Pirio Richardson and Jinnah 2019 Expert Opinion Drug Discovery

All assessments depend on the “tasks”

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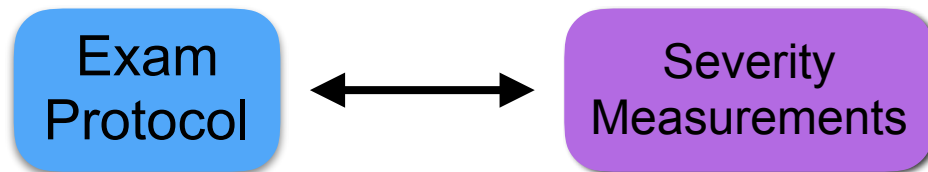
we need to be careful about **WHAT** is happening **during** the measurements (part of the COU ?)

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we need to be careful about **WHAT** is happening **during** the measurements (part of the COU ?)

especially for the dystonias; the moment-to-moment motor features depend on:

- sensory input
- attention
- task

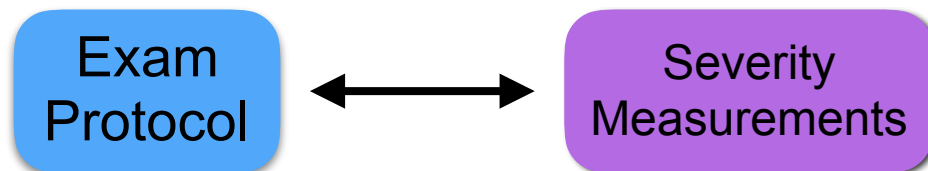


All assessments depend on the “tasks”

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especially for the dystonias; the moment-to-moment motor features depend on:

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one FDA clinical outcome assessments (COA) category:

- PerfO: performance outcome
 - based on "standardized task(s) according to a set of instructions"

Collaborators and Sponsors

DMRF

Dystonia Coalition

**NIH NCATS
(U54-NS11602)**



**Benign Essential
Blepharospasm
Research Foundation**

**NIH NIMH
(5T32-MH020002)**

DoD CDMRP



Buz Jinnah, Emory

**Joel Perlmutter and Jo Wright,
WUSTL**

**Mark Hallett,
NINDS**

**Giovanni Defazio,
Antonella Macerollo
U Bari**

Marni Bartlett, Apple

**Terry Sejnowski
CNL, Salk**

**Jake Whitehill,
Worcester Polytechnic**

**Cindy Comella, Glenn Stebbins
Rush University Medical Center**

Brian Berman, U Colorado

A photograph of a modern building at sunset. The sun is low on the horizon, creating a bright orange and yellow glow that reflects on a wet, polished surface in the foreground. The building's architecture is characterized by dark, angular, and somewhat irregular shapes, creating a sense of depth and perspective. The sky is filled with soft, wispy clouds, and the overall atmosphere is serene and contemplative.

Thank you

David Peterson
dap@salk.edu

US-based clinical trials: FDA terminology

US-based clinical trials: FDA terminology

- **CO*:**
 - *clinical outcome assessments (COAs) ...*
 - *... measuring concepts of interest (COIs)*
 - *... in contexts of use (COUs)*

... So once we define a patient population for a trial...

i.e. a *context of use* (COU)

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i.e. a *context of use* (COU)

...how should we assess trial outcome?

i.e. the *clinical outcome assessment* (COA)