Measuring dystonia motor severity objectively

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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

before
intervention
(meds, BoNT, DBS, TMS, PT, placebo, etc.)

after
Pivotal to trial outcomes: measuring SEVERITY

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after

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?

- signs
- symptoms

- Function
- Disability
- QoL

(i.e. concept(s) of interest (COI))
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)
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} 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:
  - 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?

- Treatment outcome variability
- Measurement variability
- Measured treatment outcome variability
What if we could circumvent the variability of subjective measures?
OBJECTIVE measures: definitions
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How do we define “objective”? each measurement does not depend on human judgement
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How do we define “objective”?: each measurement does not depend on human judgement

Terminology can be problematic:
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  - “technology-based objective measures” (TOMs, Espay 2016 Mov Disord; to distinguish from subjective methods labeled as “objective”?)
OBJECTIVE measures: definitions

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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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FULL PAPER
Flexible Electronics

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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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• Less physically obtrusive
  (vs. markers, EMG electrodes, etc.)
• minimizes observer effect!
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- 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
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Scope:
- BSP and CD: videos from clinical exam
- LD: videos from laryngoscopic exam
CMOR for eye closure in BSP

A

Eye closure time (%)

BFM (video)

B

Eye closure time (%)

GDRS (video)

C

Eye closure time (%)

JRS (video)

Peterson et al. 2016 Neurology
CMOR for CD: head deviation
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Zhang 2022 Annals Clinical Translational Neurology
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 use the term “ET-plus”? (e.g. if the head tremor is “jerky”)
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?
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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
Measuring severity: the patient perspective

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Combine PRO’s *and*

Video-based objective measures
Combine PRO’s and Video-based objective measures

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

- Synergies

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

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

A. Ideal therapeutic response.

B. Short duration therapeutic response.

C. Dose Failure.

D. Progressive decrementing effect.

*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 ?)
All assessments depend on the “tasks”

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**especially for the dystonias**; the moment-to-moment motor features depend on:
- sensory input
- attention
- task
All assessments depend on the “tasks”

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

one FDA clinical outcome assessments (COA) category:
- PerfO: performance outcome
  - based on "standardized task(s) according to a set of instructions"
Collaborators and Sponsors

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DoD CDMRP
Thank you

David Peterson
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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)
... So once we define a patient population for a trial...

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

...how should we assess trial outcome?

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