Synthesizing workshop and personal insights to propose next steps

Multimodal Biomarkers for CNS, Workshop, 14 March 2023
Session 5: Synthesis and Potential Next Steps
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NATIONAL ACADEMIES *Sciences Engineering Medicine*

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

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Disclosures

- Equity: Deliberate Solutions Inc, Topia Inc, and Vodafone Group plc.
- Salary: Chief Executive Officer, Deliberate Solutions, Inc.
- Deliberate's research support (incl. monetary and benefit-in-kind; active, pending or in-submission)
  - Federal: NIH, DARPA, NSF, PCORI
  - Other: Mount Sinai Health System, Boehringer Ingelheim, Columbia University (HITLAB)

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We’re at the start of multimodal biomarkers impacting CNS clinical development and care, and **we need to establish frameworks**

Observations

- **How do we develop MMB:**
  - Dataset creation: comprehensive, collected in SYNC and standardized
  - ‘Big data’ as a misunderstood concept
- **Navigating regulatory pathways: Deliberate’s case**
- **How do we evaluate and regulate MMB**
  - The problem of definition: composite vs multiplex (ML), discrete vs continuous
  - Novel evaluation tools

Suggested Next Steps

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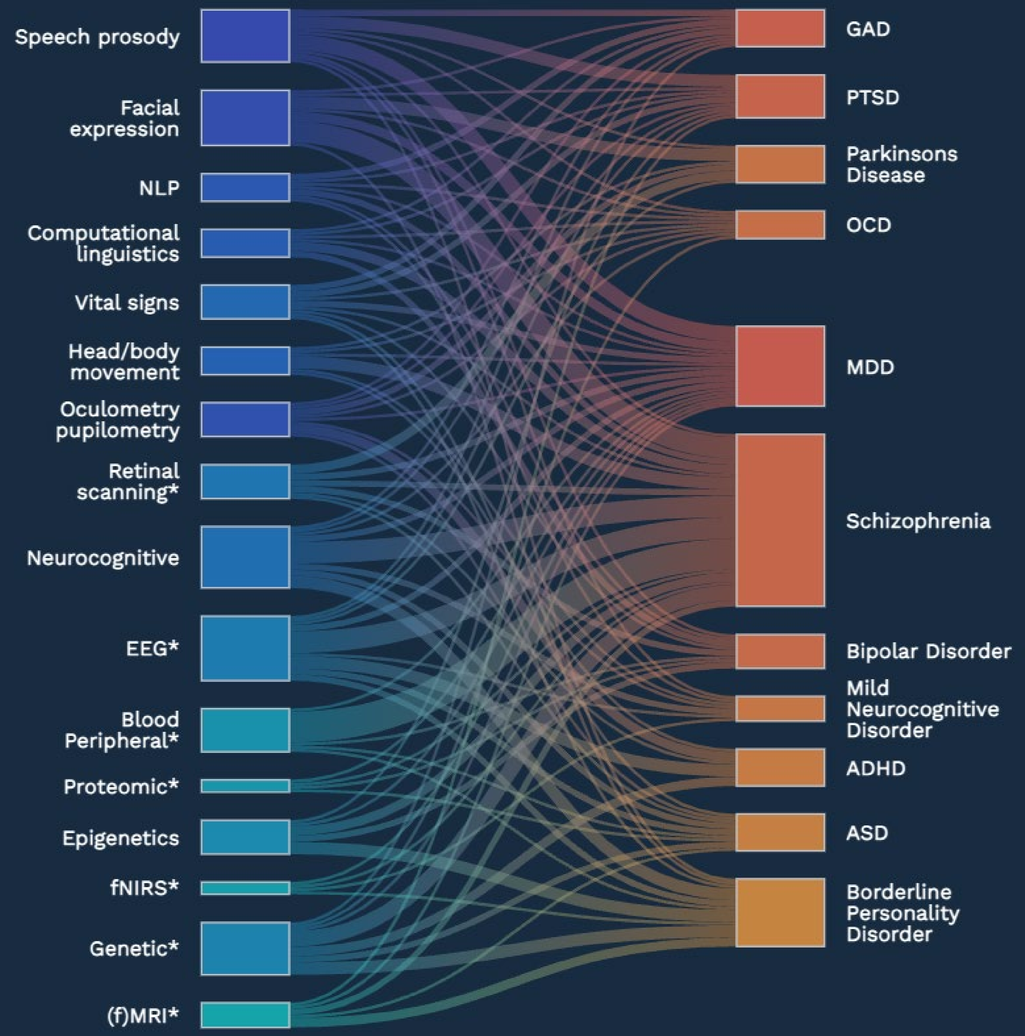
There is **compelling evidence** linking most biomarker domains with **CNS indications,** yet **multimodal approaches are lacking**



Note: This is an illustrative, non-comprehensive, review.
For an interactive version and full references see:

www.deliberate.ai/biomarker-indication

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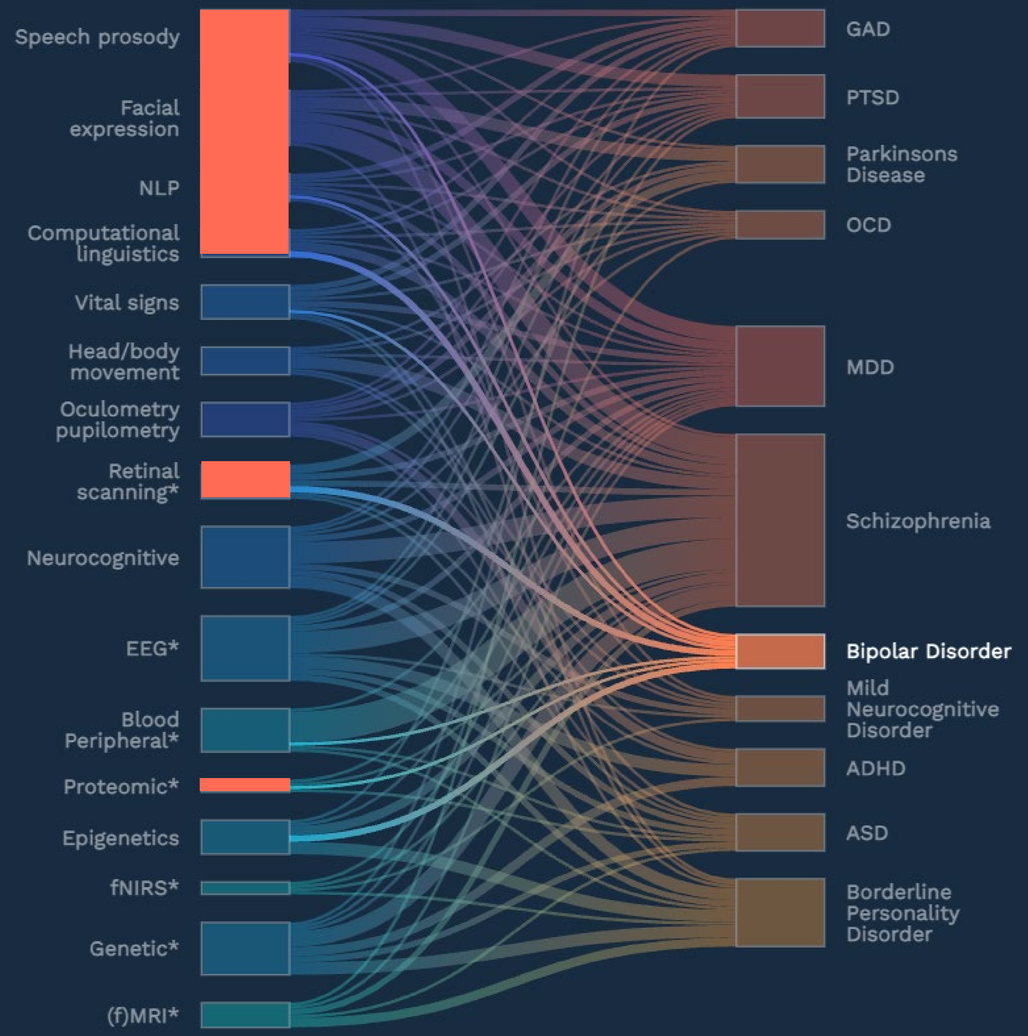

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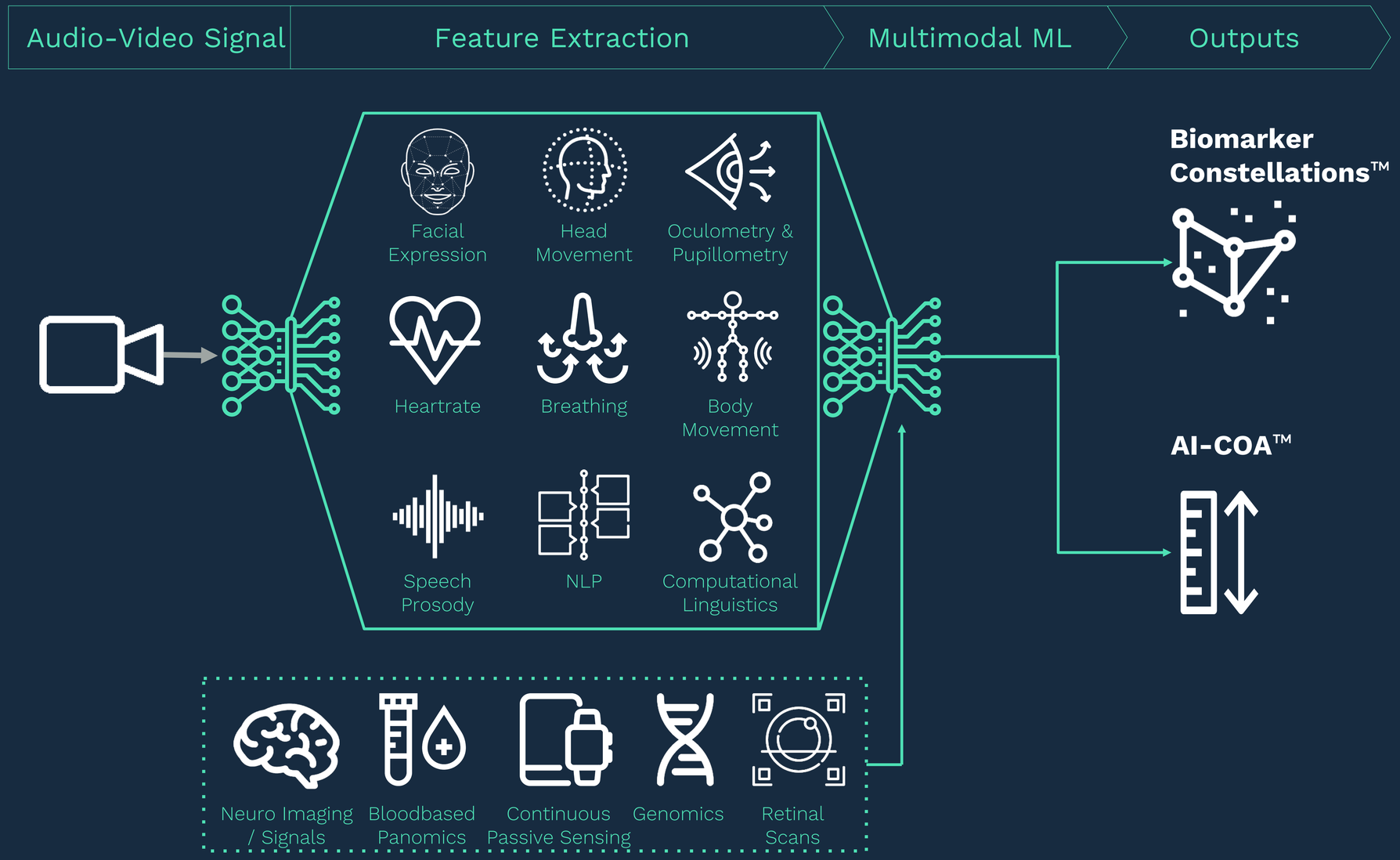
Our multimodal biomarker platform **multitude™**, provides **objective measures** that better **detect, predict and monitor** CNS indications



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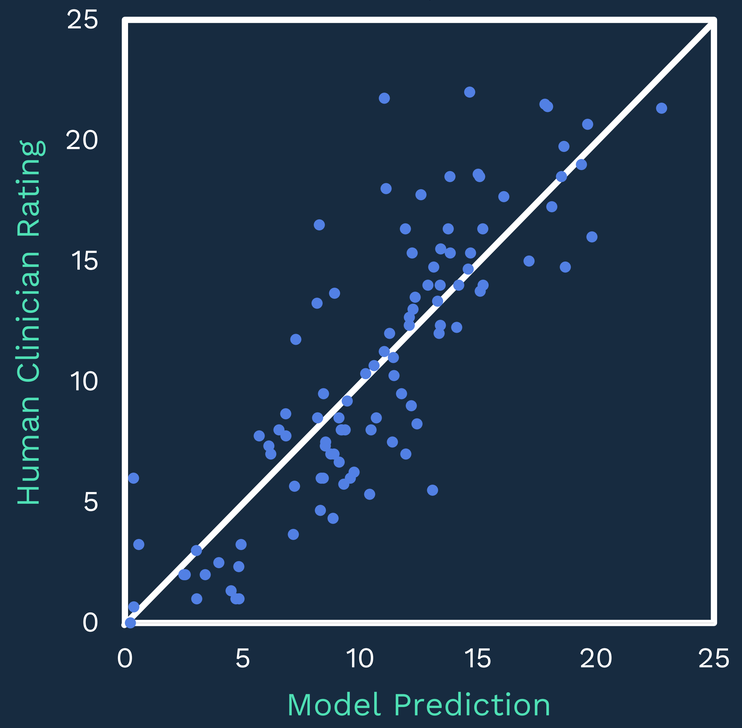
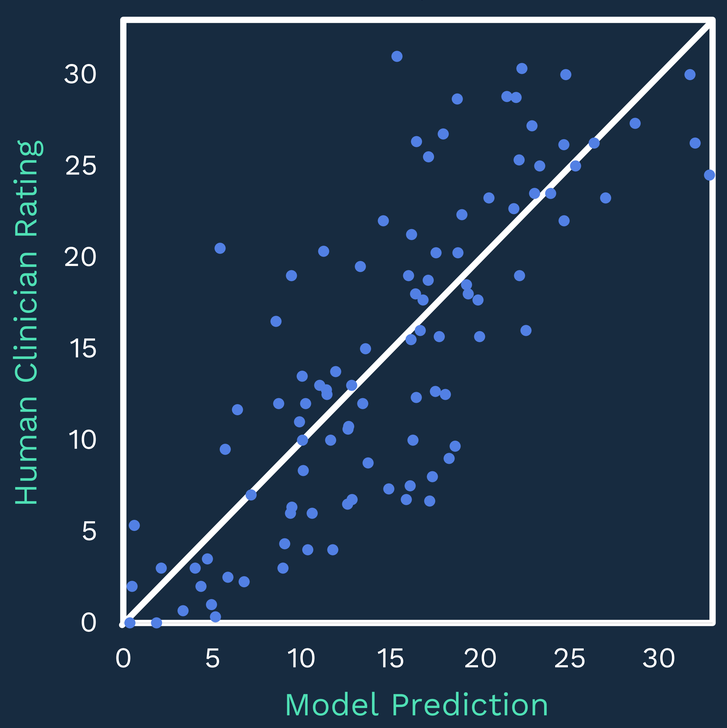
Depression and Anxiety **AI-COAs™ exceed typical rater reliability** and are LOI reviewable within FDA ISTAND

Performance of Depression and Anxiety AI-COA™
(10-fold cross validation)

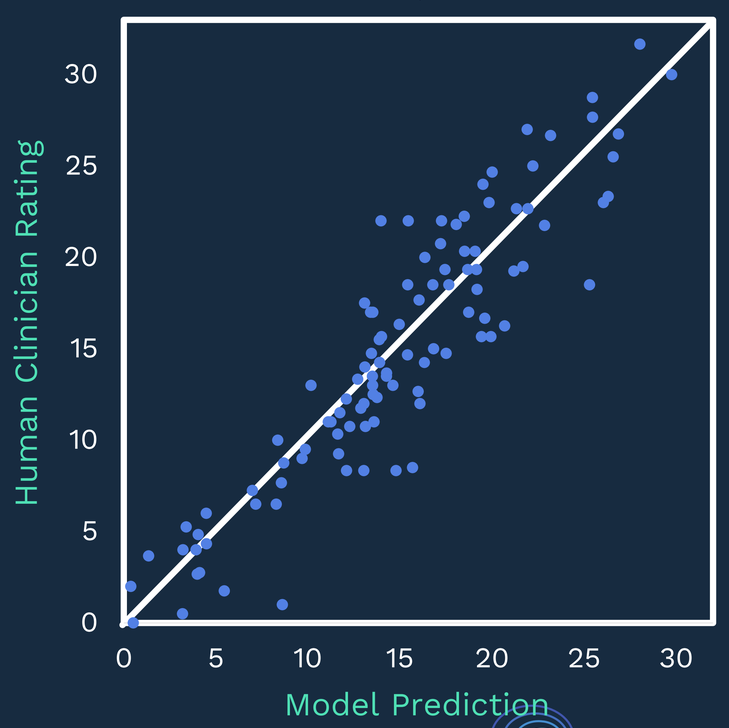
HAM-D17
ICC: 0.86
RMSE: 2.99 | MAE: 2.32



MADRS
ICC: 0.82
RMSE: 5.10 | MAE: 4.09



HAM-A
ICC: 0.92
RMSE: 2.90 | MAE: 2.332



For comparison: typical rater reliability seen in trials is 0.7-0.8 ICC

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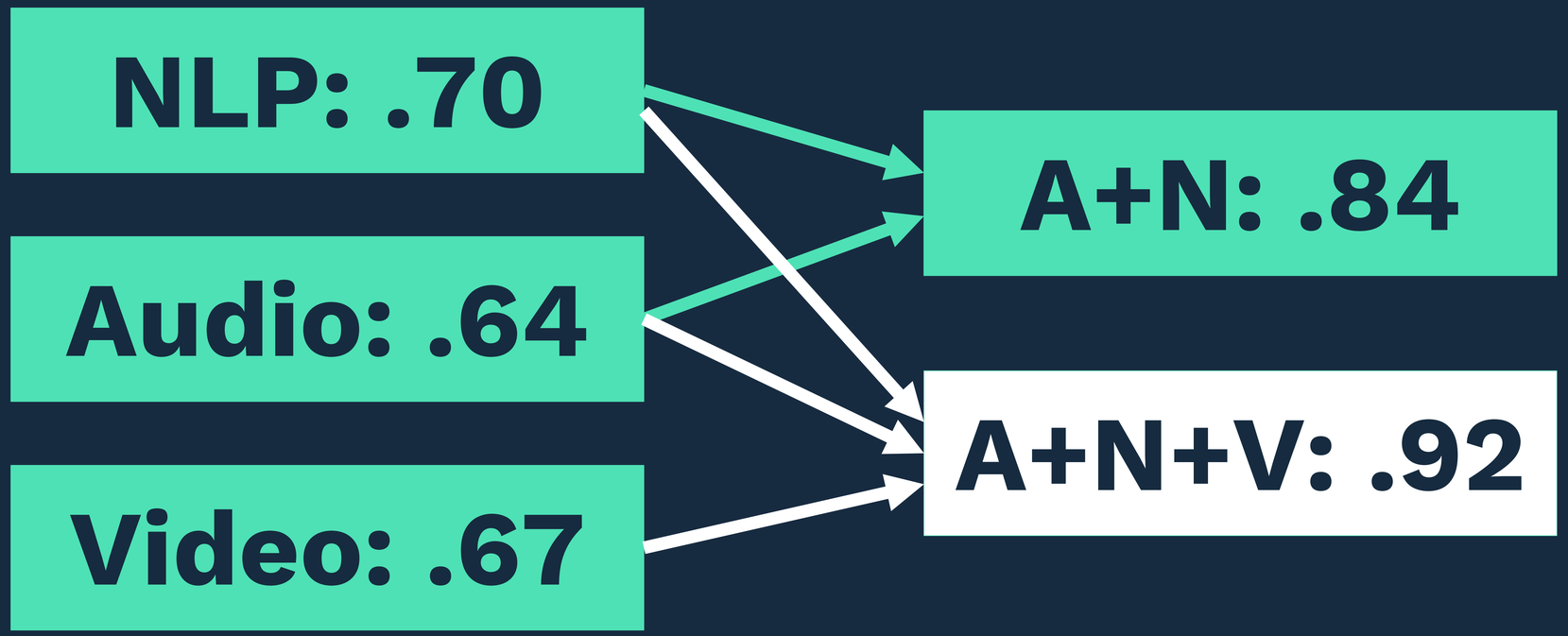
Multimodal models are significantly more powerful than unimodal ones in clinical outcome prediction (example: HAM-A)



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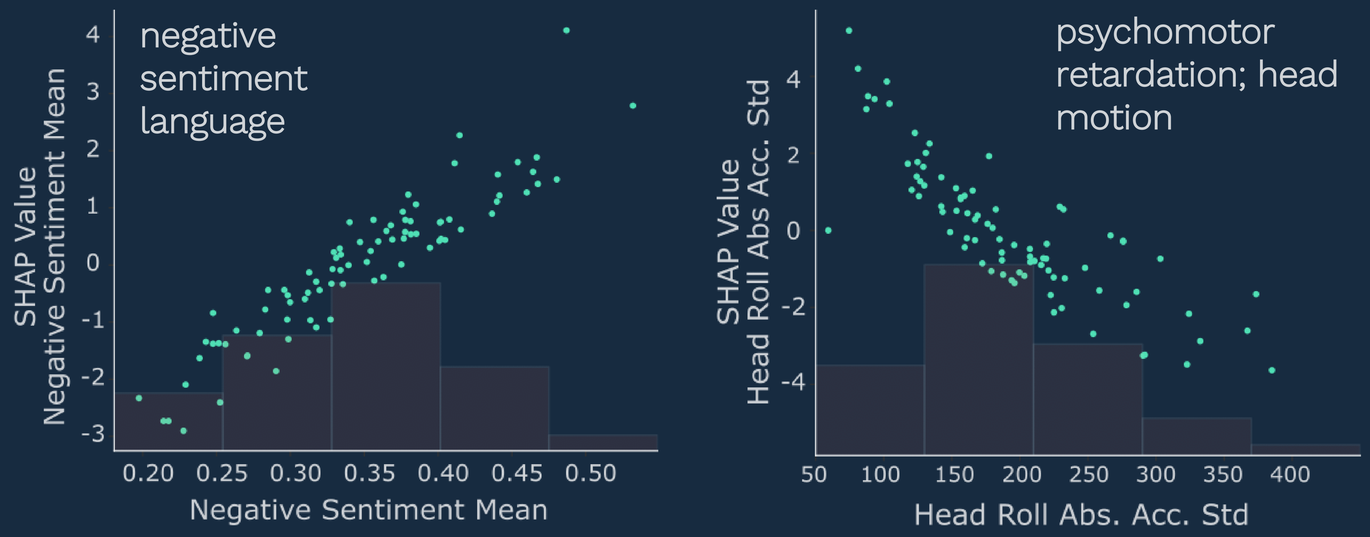
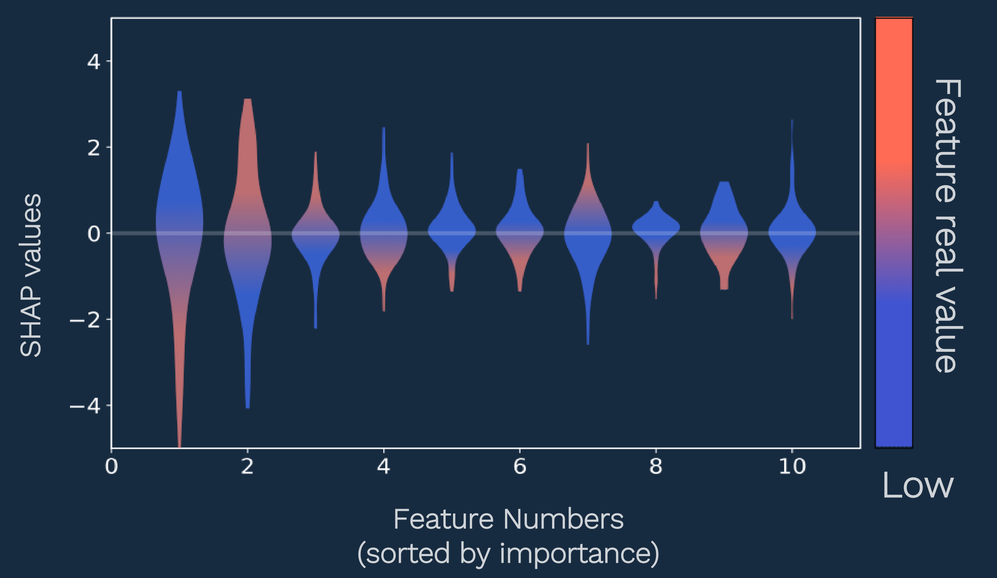
AI-COAs™ provide interpretable results, with shapley analysis across the model and for each assessment.

Shapley Values describe relative feature importance to model prediction

Example individual feature impact on model results



Feature model impact comparison



Note: for Violin chart (right), a) the color distribution reflects the normalized real feature values input into the model, b) the width of a violin represents the frequency of SHAP values in the sample, and c) the length of a violin represents the range of SHAP values in the sample

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Suggested Next Steps

1. **Generate required datasets:**
   - Industry consortia
   - NIH set-aside funding
   - Augment real-world datasets with 'additional' data signals
2. **Provide guidance/requirement (NIH) for consistent data acquisition methods**
3. **Increase regulatory clarity:**
   - FDA Guidance on how MMB will be reviewed (what analysis to present) and best practices on generating evidence

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