

Computational phenotyping for de-risking neuro-psychiatry drug development

Latent computational parameters derived from behavioral and neural data provide objective readouts across clinical conditions



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1 CNS clinical trials fail far more often than trials of other drugs

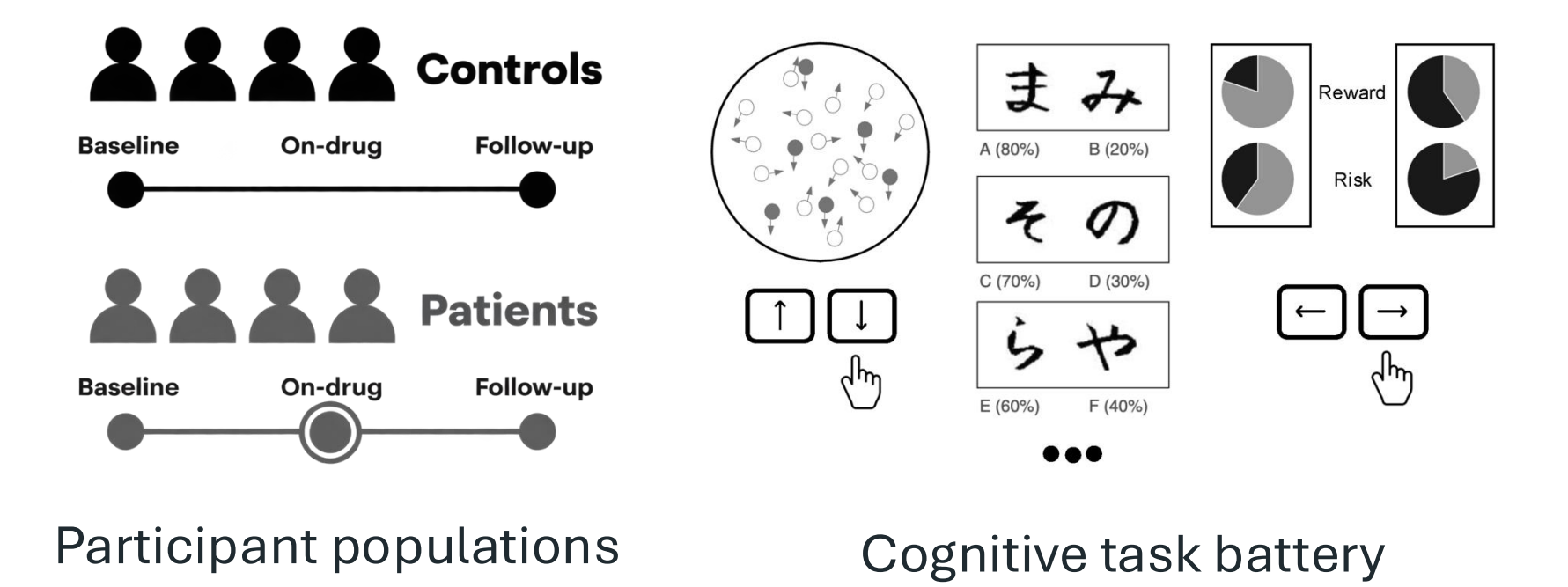


Tufts CSDD Impact Report 2014.

The cause: Difficulty in quantifying treatment response; absence of objective measure.

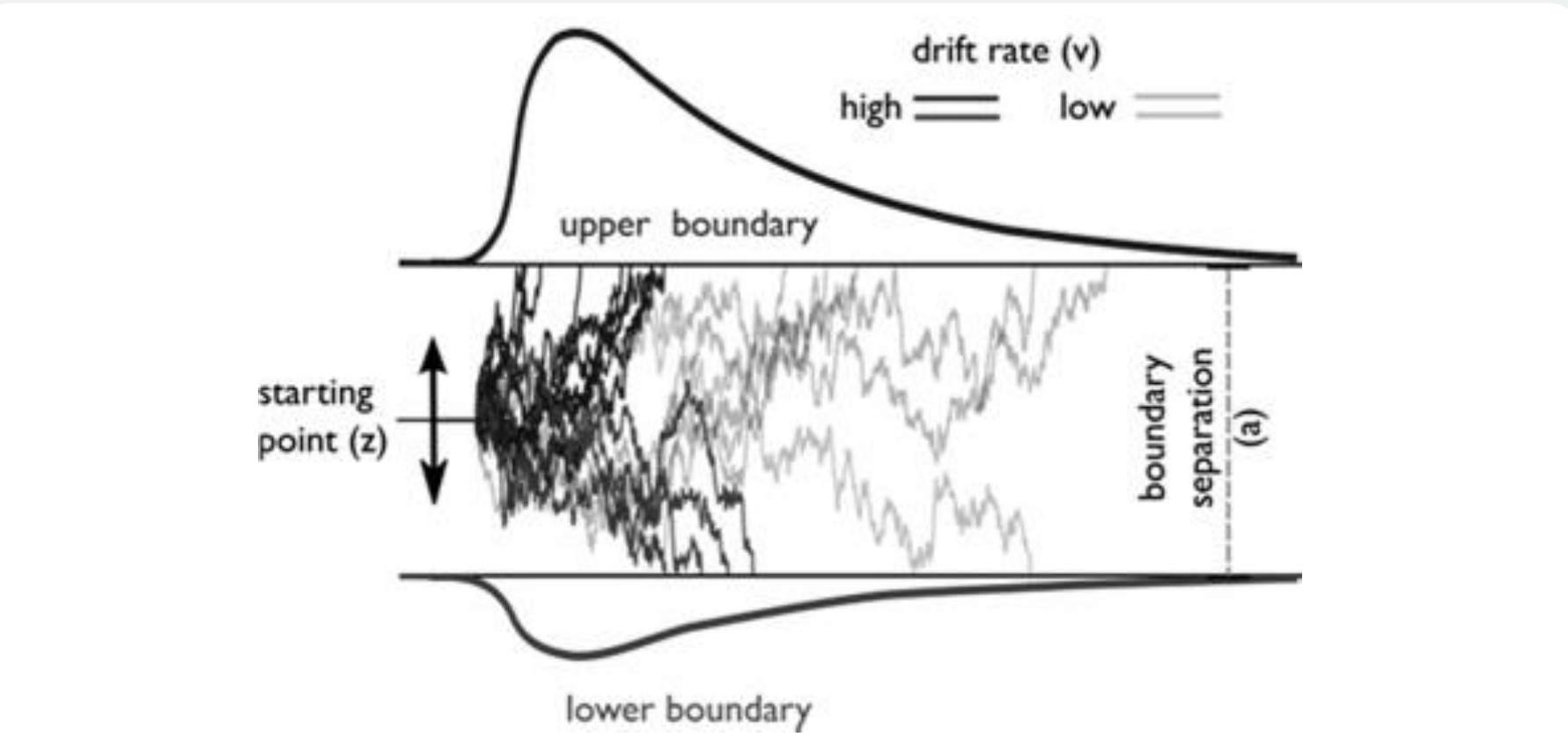
Sensitivity: Failing to detect/quantify a true treatment effect. Aggregate measures, rating scales, subjective measures show low sensitivity.
Construct validity: The measure fails to characterize the diagnostic/engagement mechanism. Data-driven measures show poor mechanistic validity.

2 Computation links brain, mind and pathology

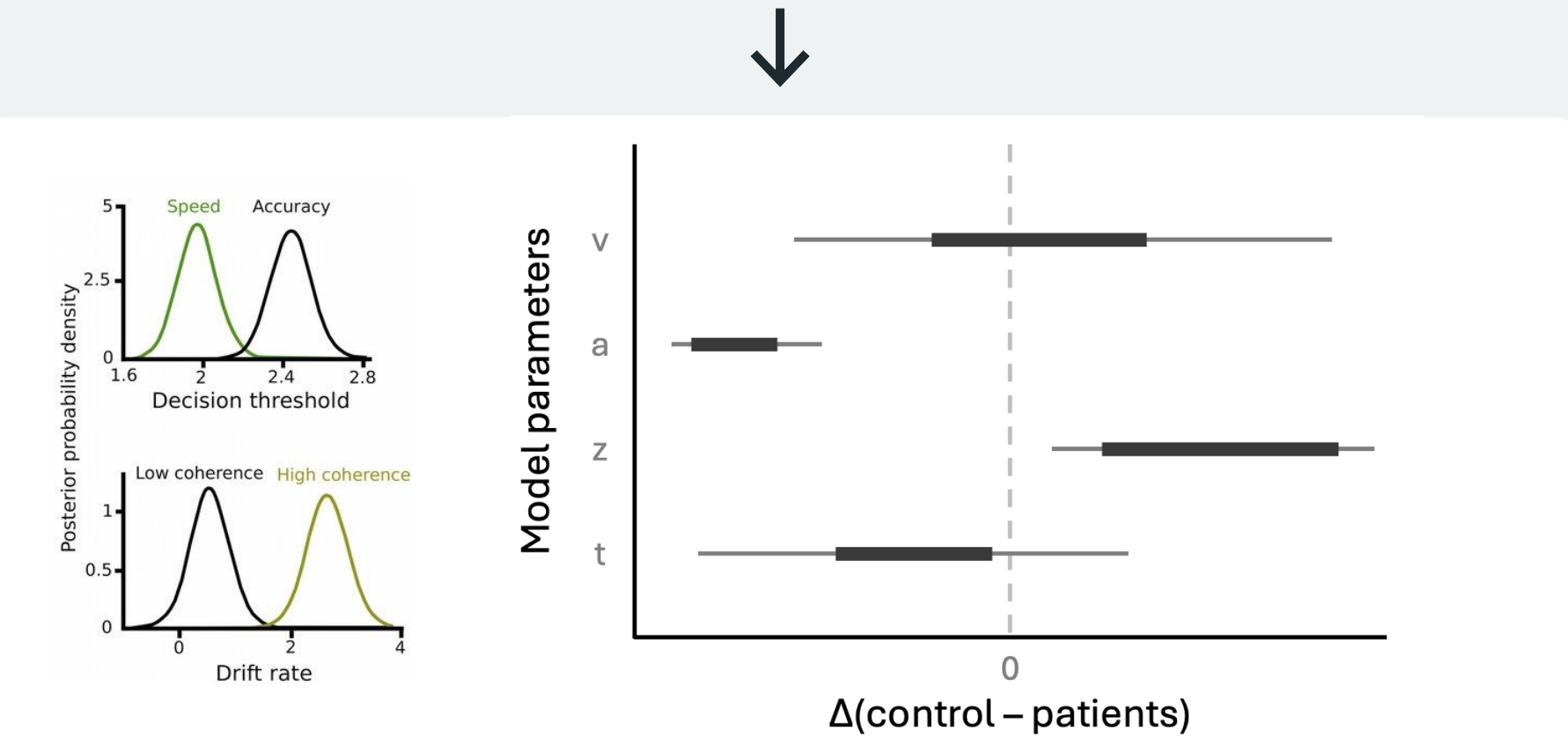


Specialized neurocognitive tasks characterize underlying brain mechanisms in control and patient populations.
Eg: CANTAB measures proxy treatment effects; typical clinical studies stop here.

However, aggregate measures suffer from limited sensitivity and heterogeneity-driven mis-characterization of brain mechanisms.

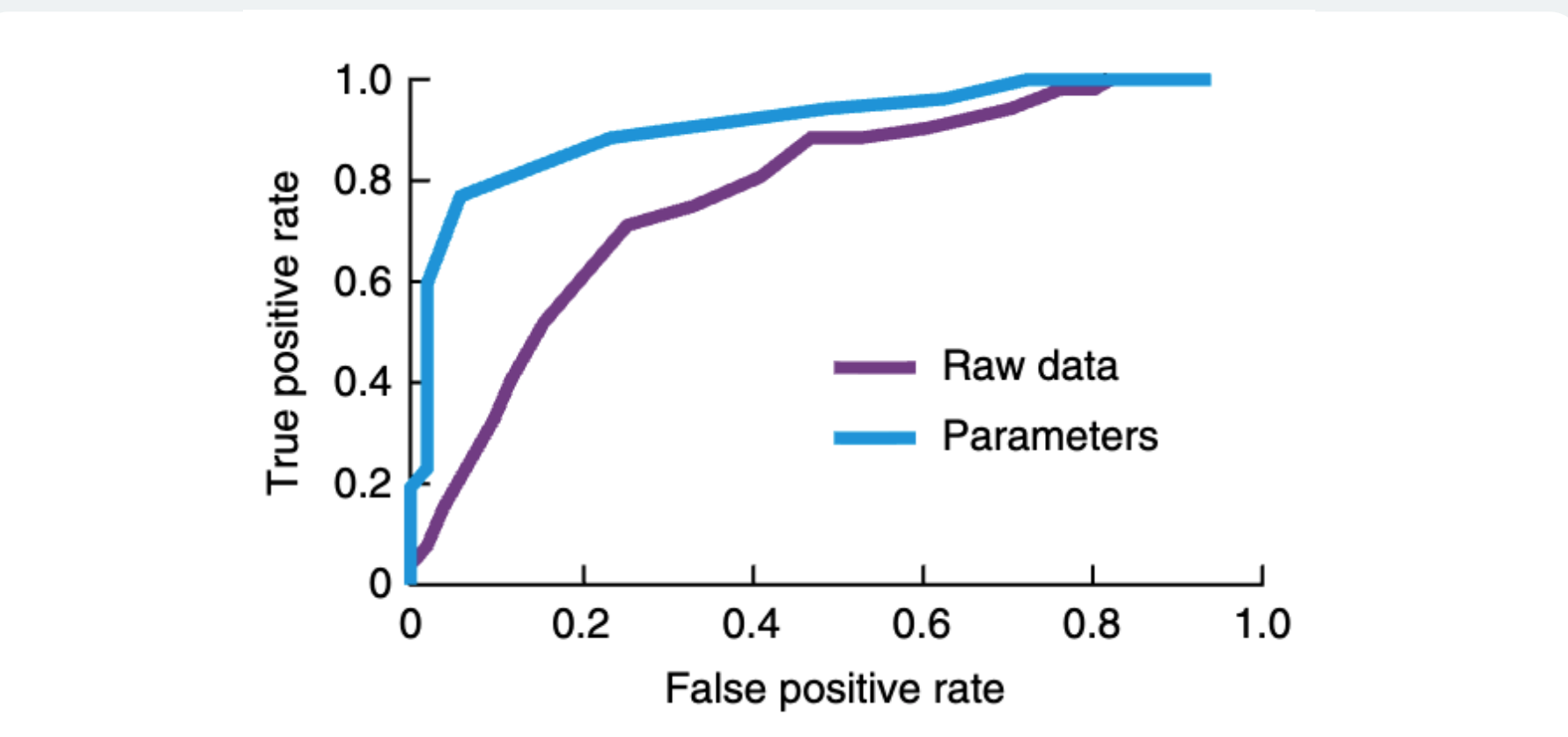


Mechanistic models of neurocognitive mechanisms index sensitivity and heterogeneity.
Eg: DDM, a mechanistic model of decision making.



Parameter-level readout separates patient groups and subpopulations, quantifies drug effects.
Mechanistic models help derive low-dimensional, interpretable endpoints.

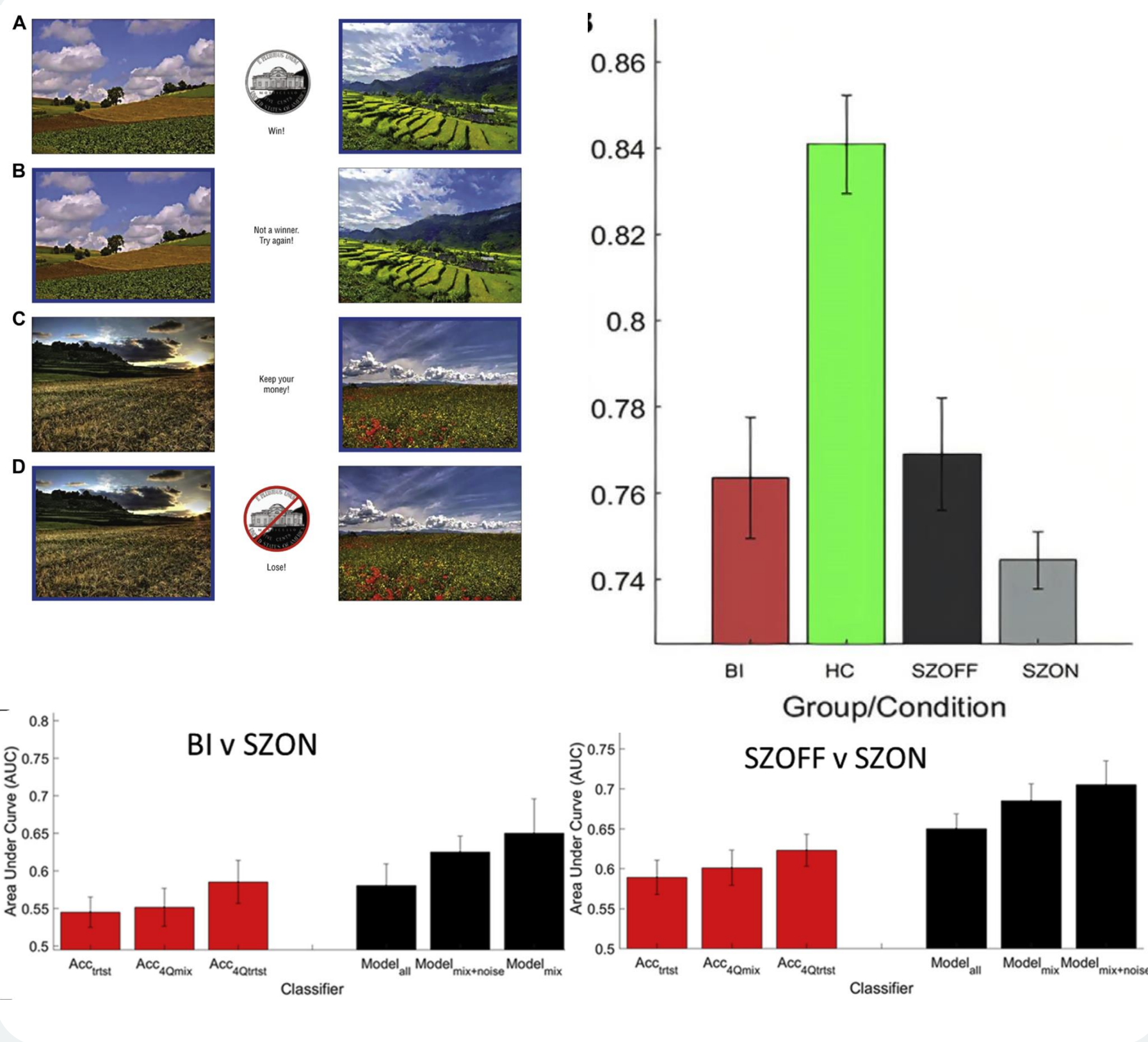
Diagnostic classification for clinical conditions. Theory-driven mechanistic models improve clinical prediction over purely data-driven approaches.



(Huys et al. 2016)

CASE STUDIES

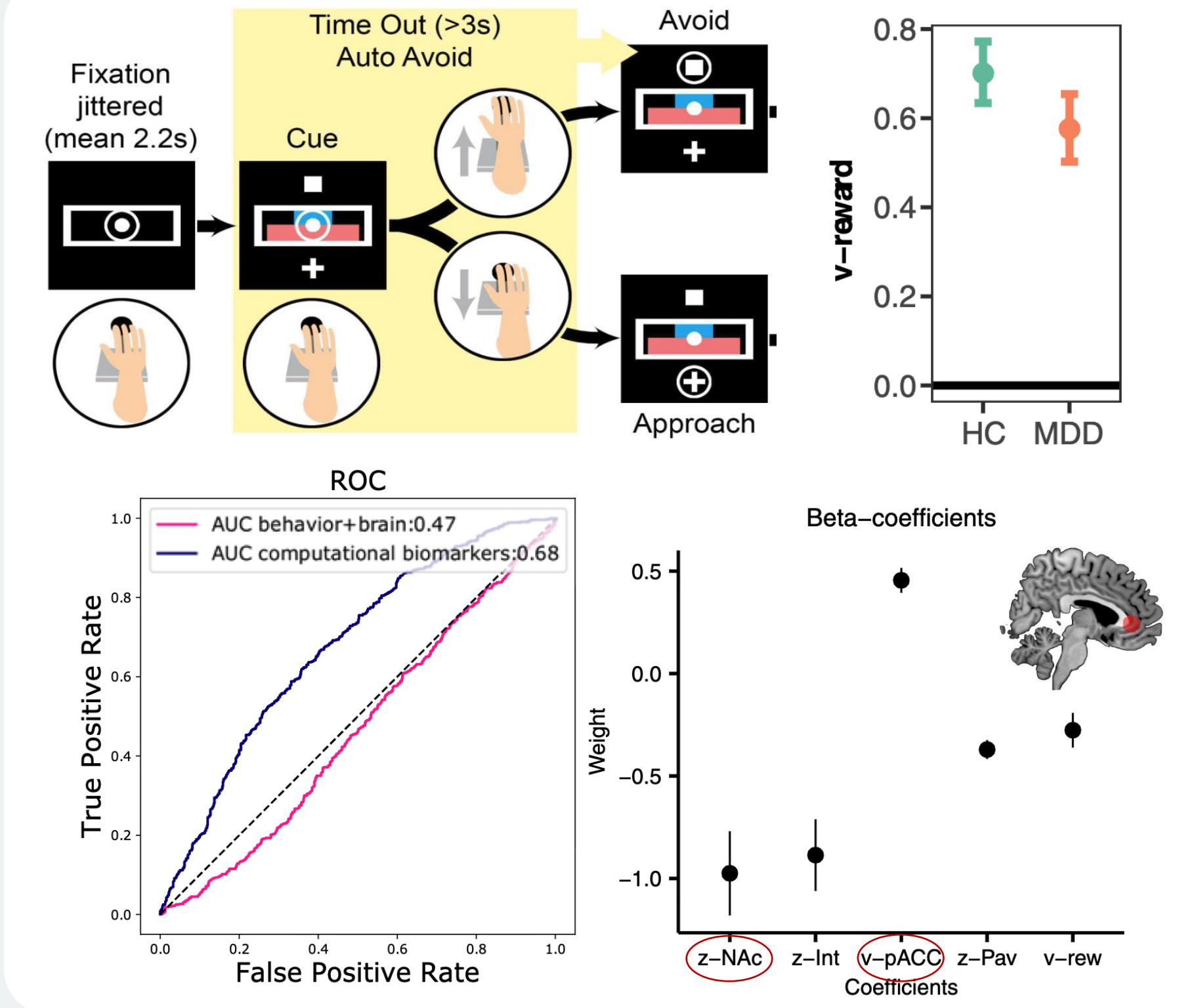
Improving patient classification by characterizing RL differences in SCZ and BP



In contrast to behavioral measures, computational models identified lesser dependence on value learning in SCZ relative to BP group.

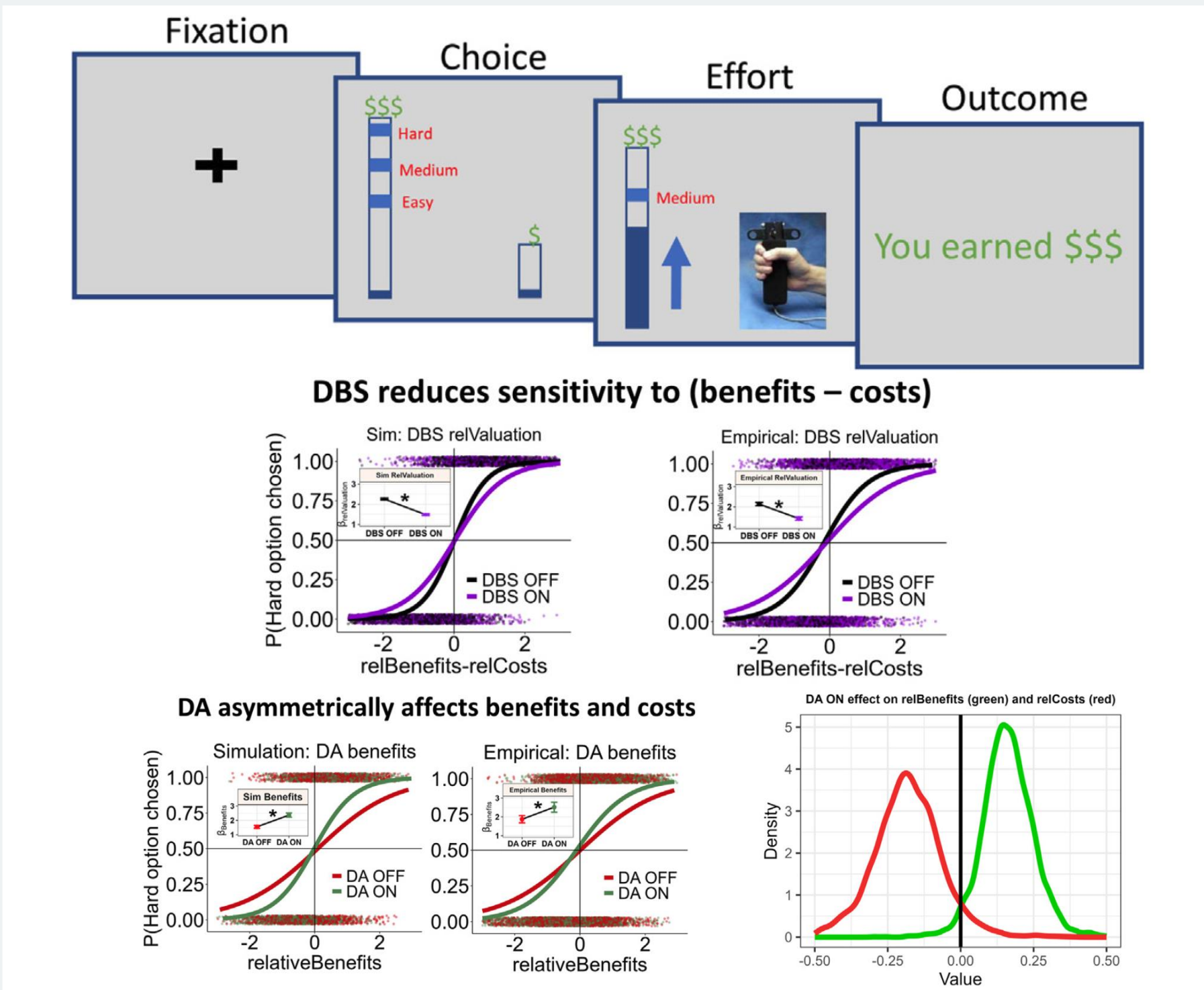
(Geana et al. 2022; see Wiecki et al. 2016 for HD phenotyping)

Computational phenotyping of approach-avoidance conflict in MDD



MDD was associated with reduced reward sensitivity. Individual parameters were linked to clinical measures of MDD and were useful for classifying diagnosis/treatment. (Pedersen et al. 2021)

Proof-of-concept modeling disentangles separable mechanisms of impulsivity within one clinical diagnosis: PD

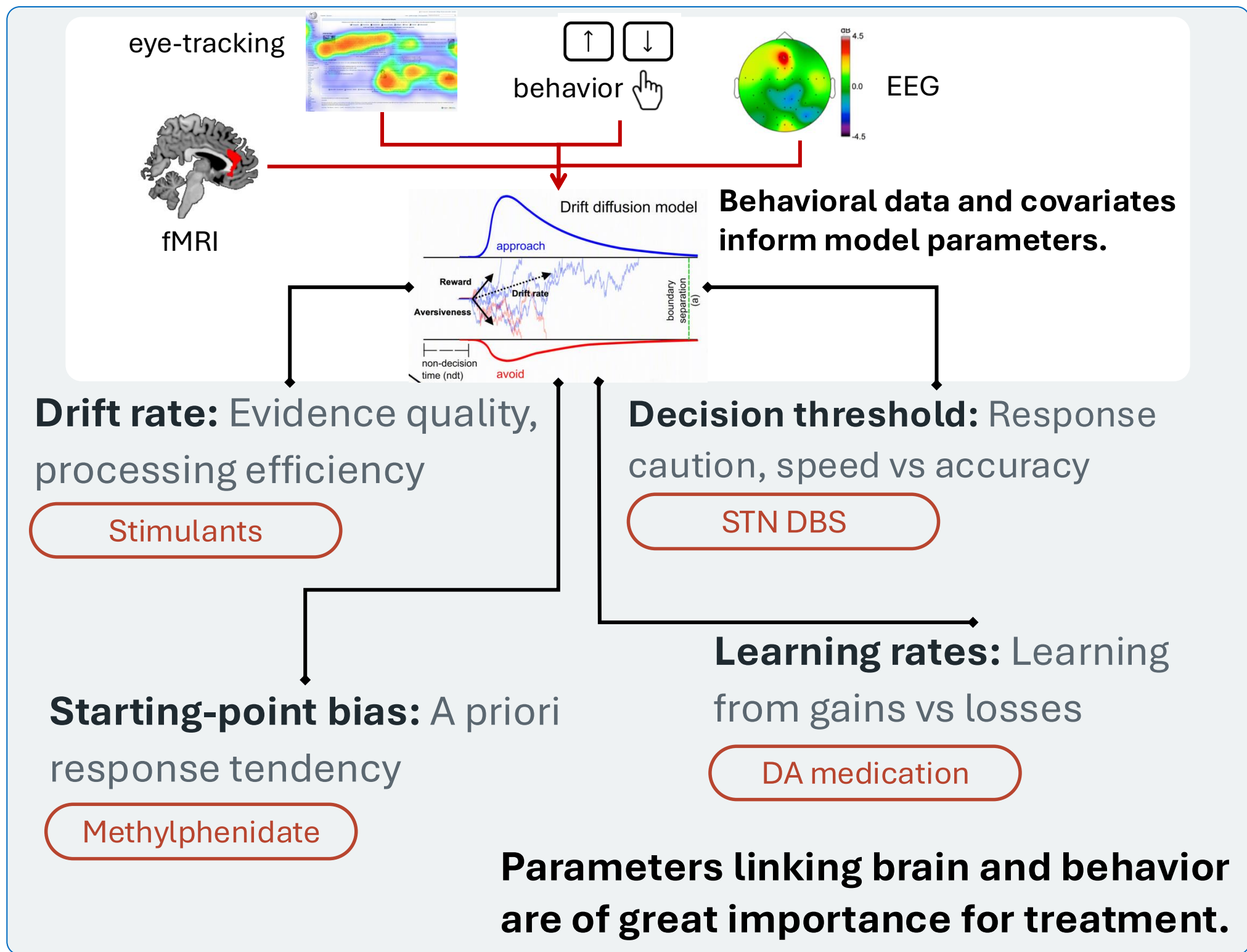


DA asymmetrically affects costs and benefits while DBS reduces decision threshold. (Pagnier et al. 2024)

Other studies including ongoing retrospective reanalysis and use in randomized trials.

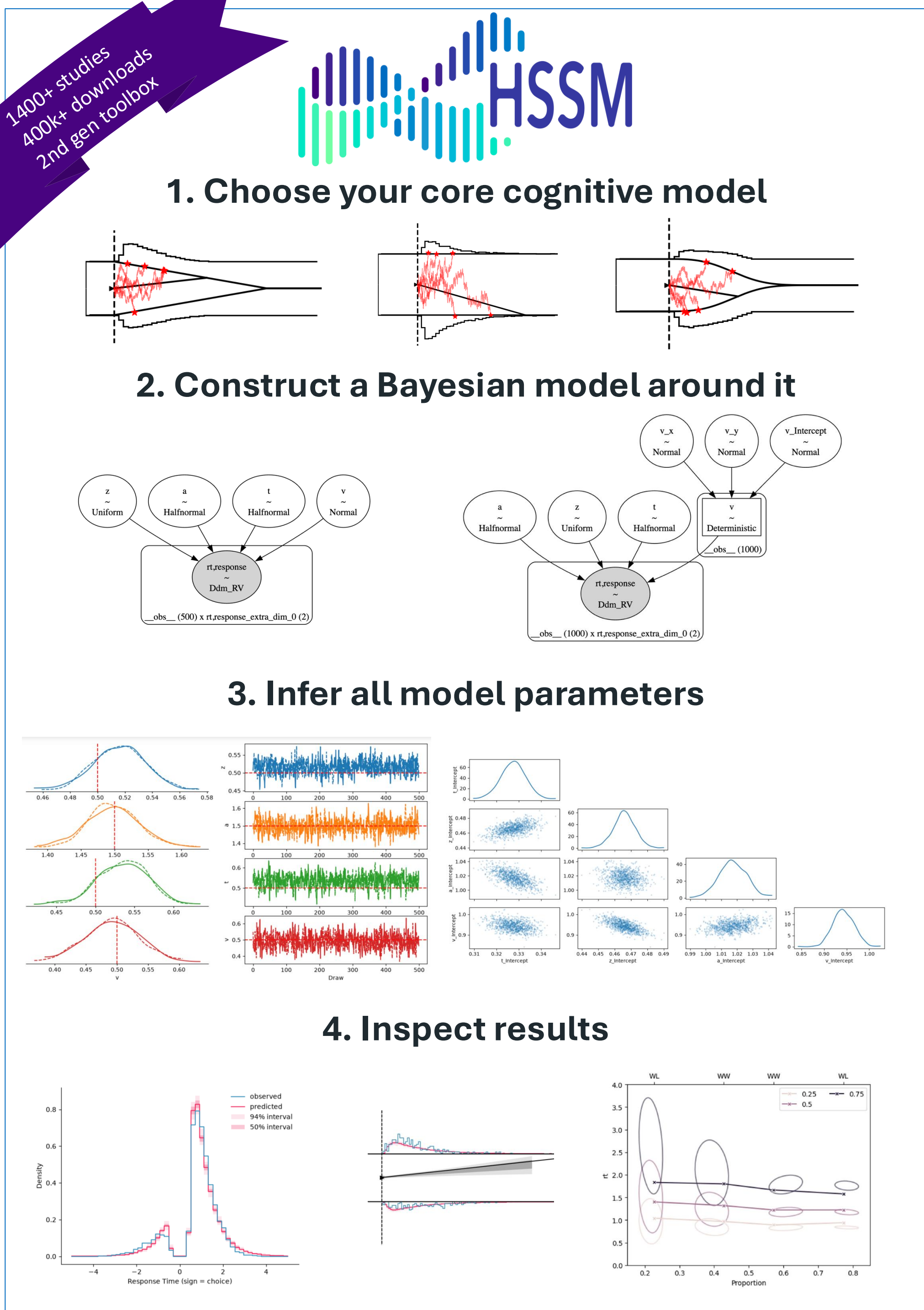
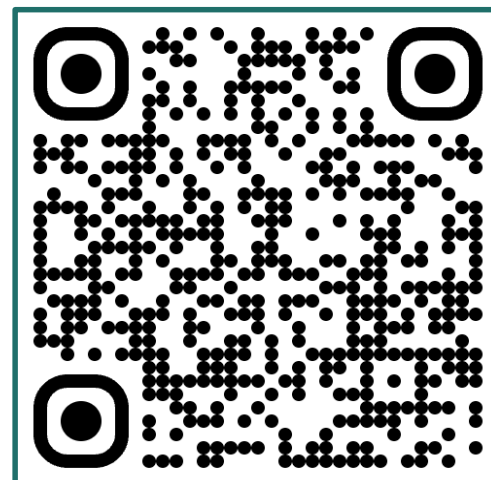
MDD antidepressant assignment (bupropion and sertraline); phenotyping of learning and memory in SCZ; Roche RG7203 proof-of-mechanism; and more!

3 Parameters index mechanisms that drugs and stimulation move



4 From research finding to trial endpoint

Task: Behavioral battery, no rater, multi-site ready.
Model: Hierarchical Bayesian model of choice, RT with (neural) covariates; treatment and site as regressors.
Contrasts: Posterior treatment effects on each parameter estimated jointly.
Validation: Calibration, posterior predictive checks, convergence, prior sensitivity.
Report: Parameter-level treatment contrasts with full posteriors, sensitivity and power projection.
Regulatory fit: Exploratory endpoint in Phase 1b/2a, alongside primary COAs. Qualification path via FDA ISTAND, context of use per indication and task. Consistent with FDA draft guidance on Bayesian methodology (Jan 2026).



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