A neurometabolic signature in the frontal cortex explains individual differences in effort-based decision-making

CBMM Journal Club

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Introduction

Background

- Effort-based decision-making is a critical aspect of human behaviour, influencing **how individuals weigh the costs of actions against potential rewards**

- **Motivation drives individuals** to engage in tasks that may require significant physical or mental effort.

Introduction

Importance

- Understanding the **neurobiological underpinnings** of motivation and effort can provide insights into **individual differences** in behaviour.
- Variability in **effort aversion** can impact well-being, success, and is a symptom in various brain **pathologies**.
- The specific neurobiological components influencing effort-based decision-making remain **poorly understood**.
- Prediction using **multivariate** analyses (previously only univariate)

Introduction
Objectives

- To investigate the neurometabolic signature in the frontal cortex associated with individual differences in effort-based decision-making.

- To explore how this signature correlates with motivation levels and effort exertion.

▸ **Research Questions:**

  - What specific neurometabolic factors influence effort-based decision-making?

  - How do these factors vary among individuals with different motivational drives?

Methodology

Demographics

- N_i=75… 6 exclusions ➡ N=69, 34 female/35 male.
- 25 ≤ age ≤ 40
- Right-handed
- Fluent in French. Experiment took place at EPFL.
- Excluded for not completing tasks (2) or outliers consistently choosing the effortful option (4)

Methodology

Techniques and tools

- 7T ^{1}H-MRS (Proton Magnetic Resonance Spectroscopy): MR technique capable of detecting, identifying and quantifying biochemical compounds or metabolites in the brain tissue.

- Machine Learning: identify patterns related to effort-based DM.
  Pattern = metabolite concentration in ROI x *individual differences in DM*

- Blood sampling: essential for baseline metabolites

Methodology

Design and controls

- Between-subjects design
- Circadian rhythms: all experiments started at 02:00pm
  75 initial participants, 1 per day = 15 weeks (!!) @ 5 days/week for data acquisition
- Weight and BMI: to ensure participants of similar bodily mass and metabolic rates
- No eating 1.5h before experiment
- Individual calibration: identifying each person’s indifference points, mental and physical
  Level of effort they were willing to accept in exchange for a given monetary incentive

Methodology

Procedure

- Localisation of VOI in ROI
- Task-training (instructions, testing for task comprehension)
- Mental and Physical tasks
- Choose between fixed low-effort ($) or high effort ($$$)
  3 high effort options calculated per participant during calibration
- Execute. Repeat. 54 trials × 4 blocks.

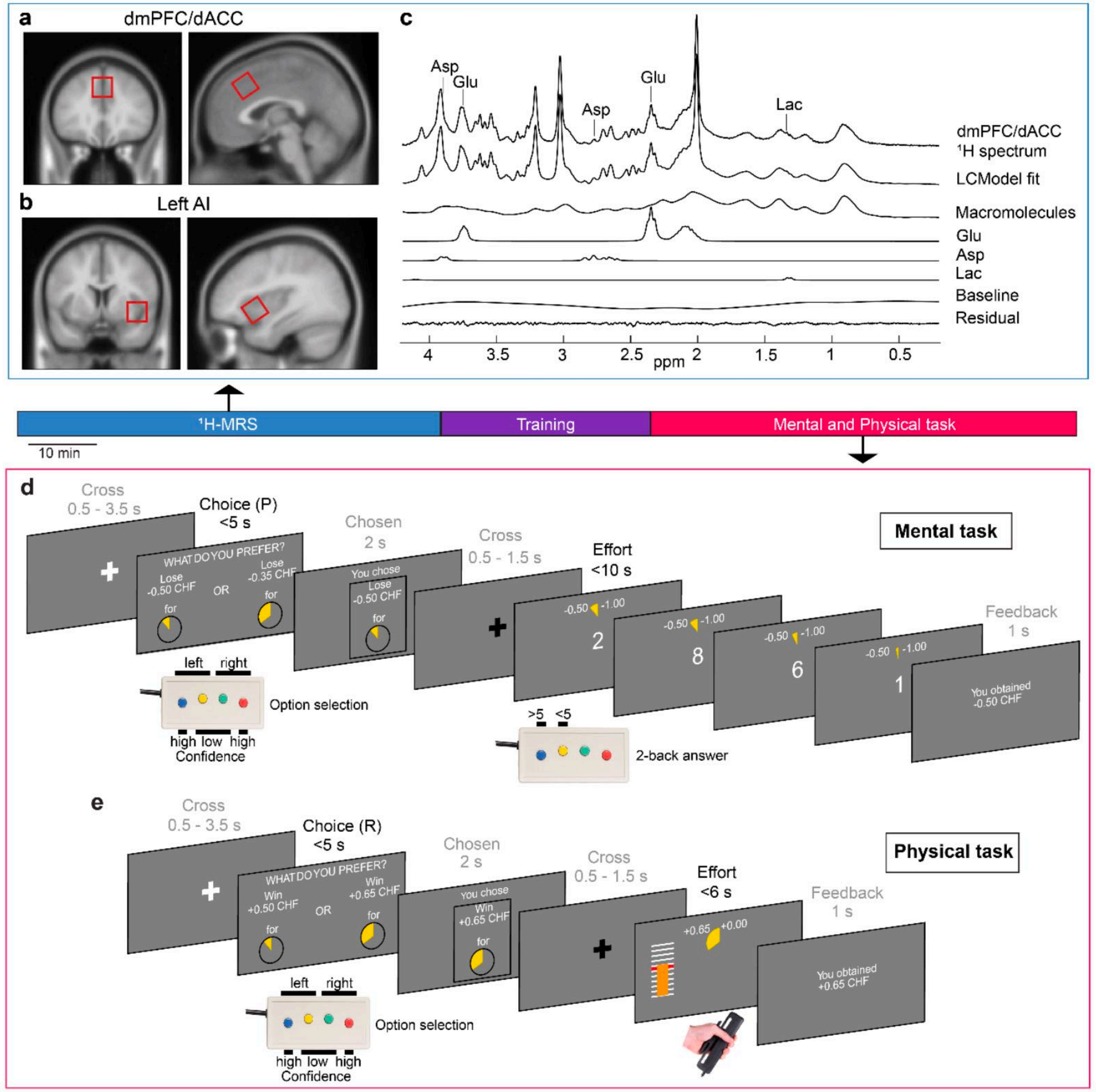


Fig. 1: Overview of experimental design

Methodology

Mental vs Physical tasks

Mental	Physical
2-back	Squeeze
Was the stimulus you saw 2-back superior or inferior to 5?	*Maintain 55% maximal voluntary contraction for a given duration*
Effort measured in number of stimuli to solve	Effort measured in duration
Max effort task: *solve the maximum number of stimuli as measured during calibration*	Max effort task: *maintain maximum squeeze as measured during calibration for given duration*

Methodology

Incentives

- Base: 70 CHF *(121 AUD)*
- Every extra hour: +10 CHF *(17 AUD)* No exact info on average duration, but fig.1 says ~150min
- Every maximal effort task: +4 CHF *(7 AUD)* 10 maximal effort tasks were proposed
- Average payout: 204 ± 17.4 CHF *(353 ± 30 AUD)*

Methodology

Metabolites and ROI

- Aspartate
- Lactate
- Glutamine
- Glutathione…

Neuronal health, energy metabolism, cell signalling

- dmPFC
- dACC
- Ant.Insula

Assessing cost-benefit trade-offs

Lesions = ↑ effort aversion

Involved in mental and physical effort

Salience network

Results

Behavioural tasks

- Calibrating for participants led to 95% and 98% successful trials for mental effort and physical effort, respectively
- Choosing high physical effort (HPE) task correlated with ↑ and more intense handgrip
- Choosing high mental effort (HME) task correlated with ↑ number of errors and ↑ cognitive efficiency$(t) = \frac{\text{Number(correct)}}{\text{Total trial time}}$

→ Task created is effective in quantifying motivational dynamics

Results

Metabolic data

- Glutamate, aspartate and lactate:
  - were significant metabolites in predicting high mental effort (HME) choices,
  - accounted for up to 40% of the variance in HME decisions
- Glutamate had a quadratic association with mental effort choices, meaning both high and low concentrations are problematic (though, a sweet spot does exist)
- ↑ $[Glu]_{dmPFC}$ = ↑ sensitivity to mental effort
- ↑ [Asp] = ↑ aversion to mental effort
- ↑ $[Lac]_{dACC}$ = ↓ motivation for high-effort tasks

Results

Machine Learning and multivariate analyses

- **Can metabolite concentrations predict the proportion of HME and HPE choices?**
    - Gradient tree boosting regression model using metabolite concentrations as regressors
    - 9 relevant features for HME, 4 relevant features for HPE
    - Train/Validate/Test approach: CVLOO 80% train/validate (N=55) and 20% test (N=14)
    - Training using XGBoost to fit linear response functions to HME and HPE, with Bayesian optimisation for hyperparameter tuning
    - RMSE for prediction error

Results

Machine Learning and multivariate analyses

- HPE prediction was a failure: not above chance-level, explaining only <5% of the variance using metabolite concentrations in all three regions
- Similar results when using only metabolite concentrations from Ant.Ins (no figures provided)
- In contrast, HME prediction was a good fit, explaining 31% of the variance

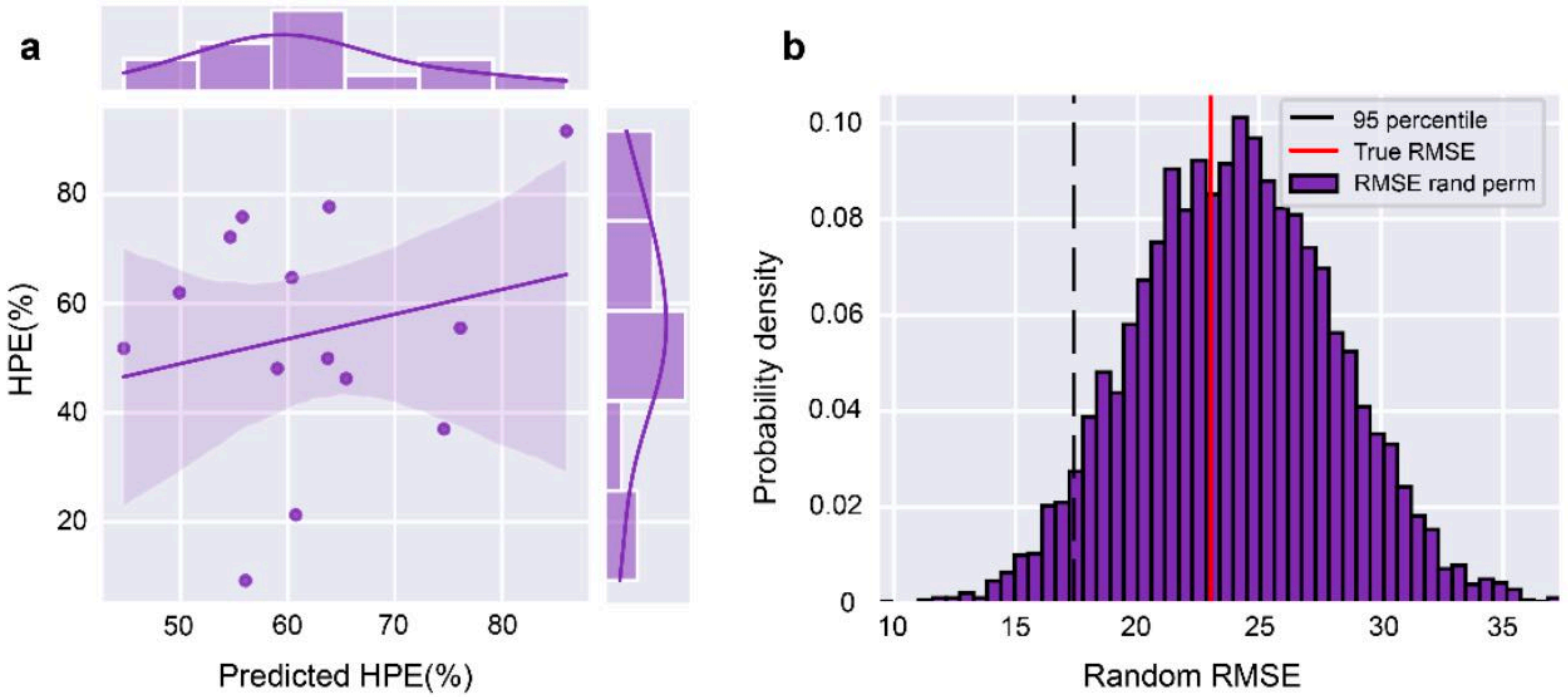
Results

HPE prediction

High Physical Effort
dmPFC/dACC
metabolites

Testing set:
r = 0.22, p = 0.22

Permutation test:
True RMSE = 23.00%
95th percentile
RMSE = 17.38 %



From Fig.2

Results

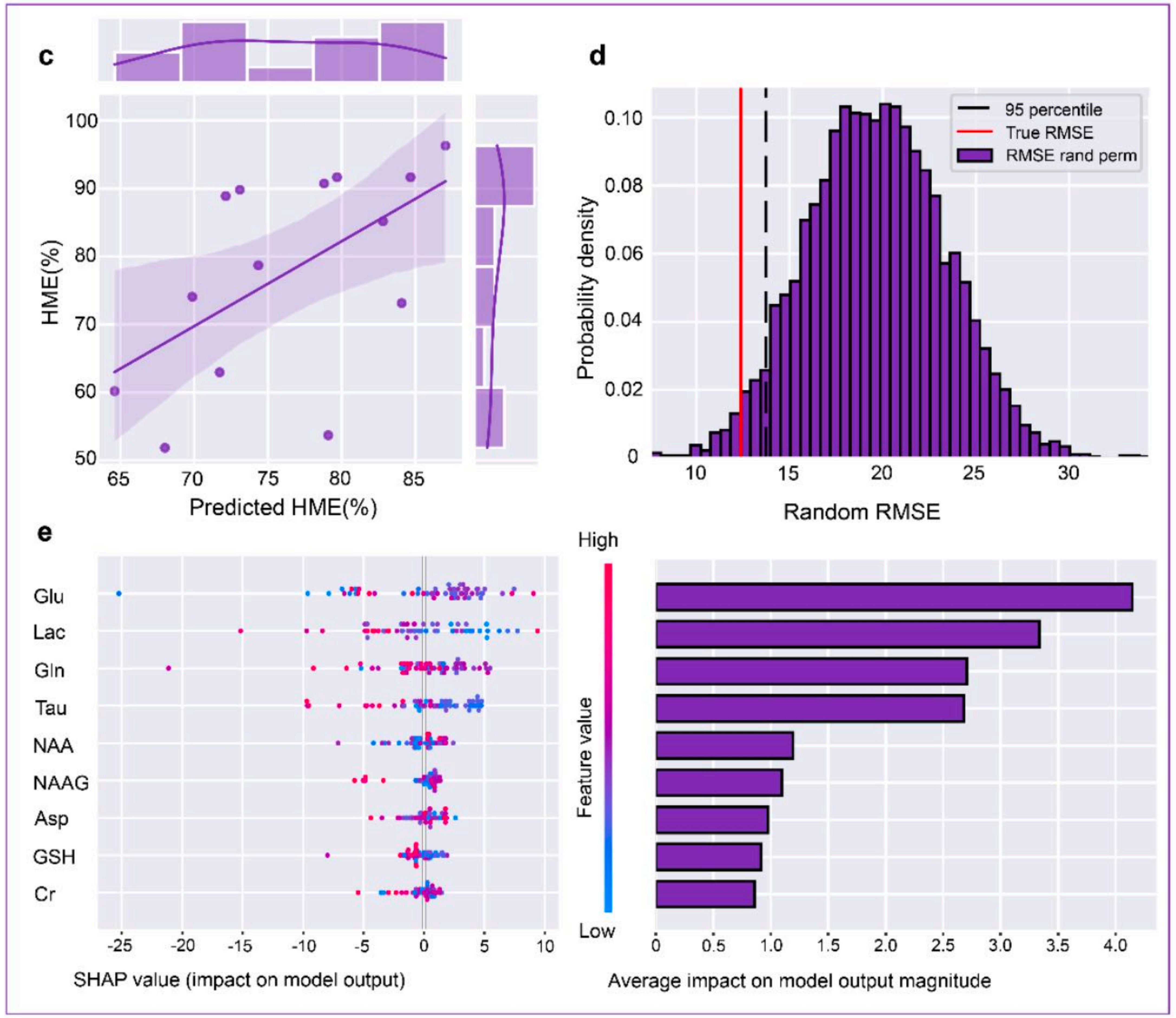
HME prediction (dmPFC/dACC)

High Mental Effort
dmPFC/dACC
metabolites

Testing set:
r = 0.56, p = 0.02

Permutation test:
True RMSE = 12.37%
95th percentile
RMSE = 13.72 %

Features



From Fig.2

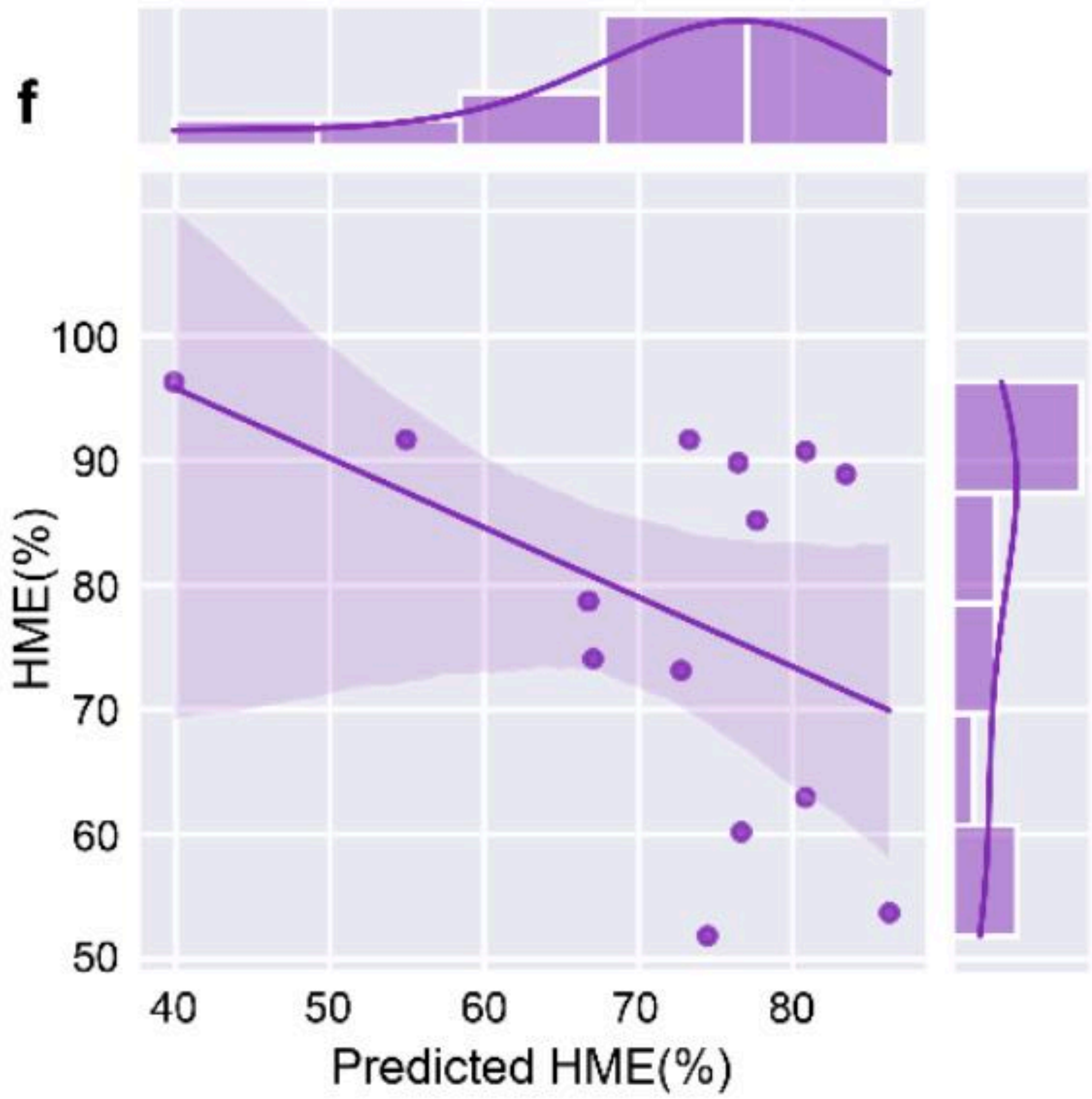
Results

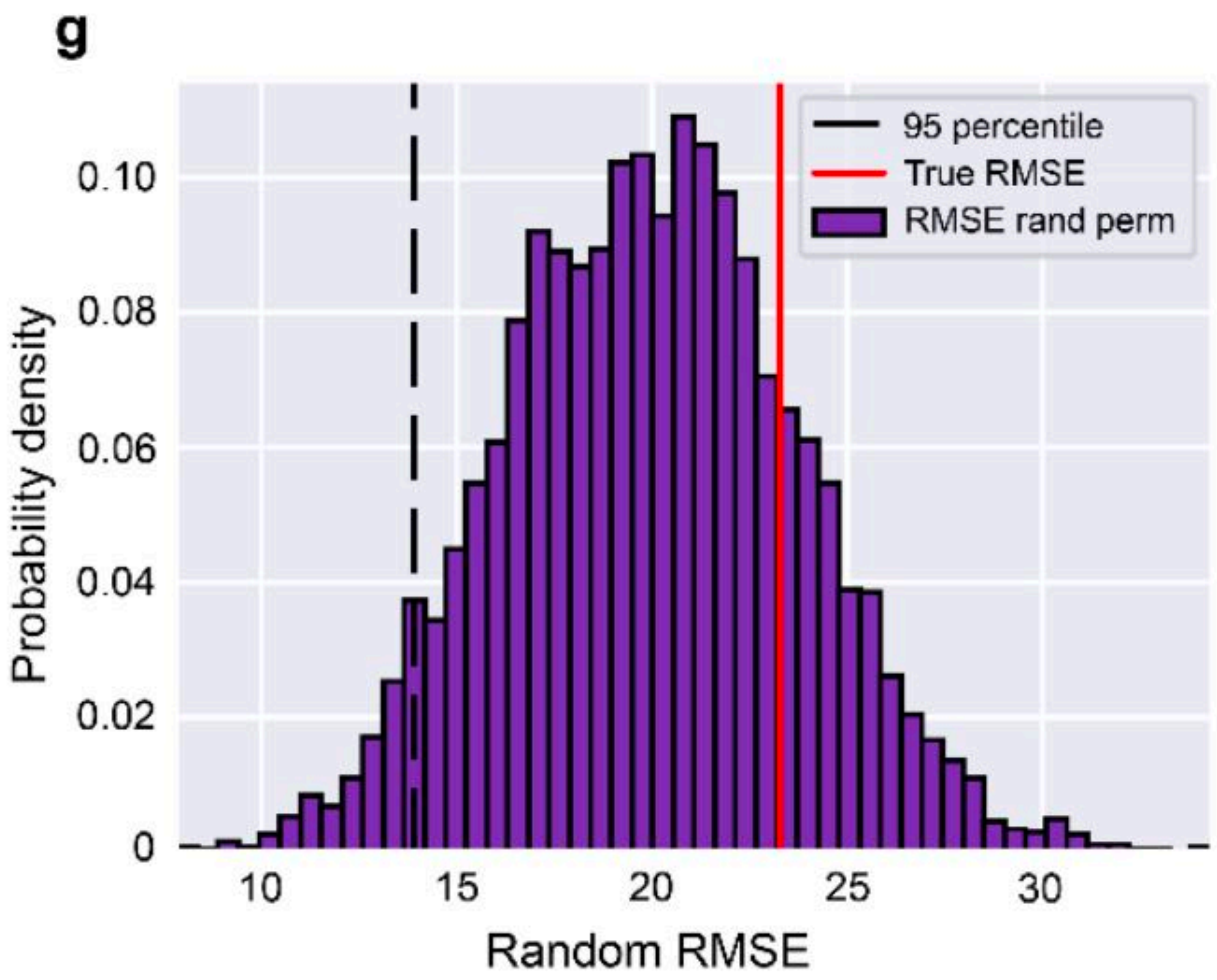
HME prediction (Ant.Ins)

High Mental Effort
AI metabolites

Testing set:
r = -0.47, p = 0.06

Permutation test:
True RMSE = 23.28%
95th percentile
RMSE = 13.89 %

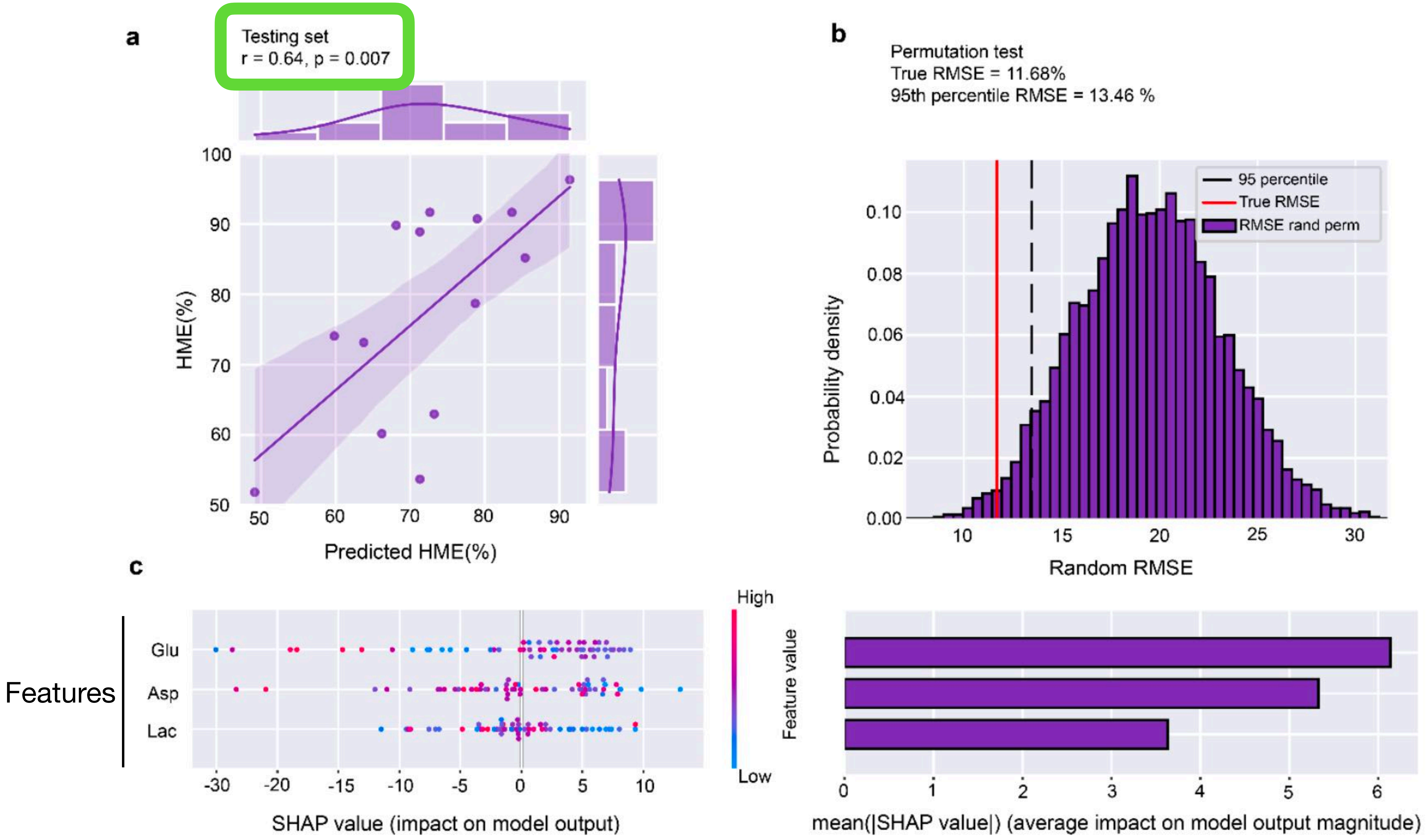




From Fig.2

Results

Improving HME prediction (dmPFC/dACC)



From Fig.6

Results

[Glu] in dmPFC/dACC and proportion of HME choices

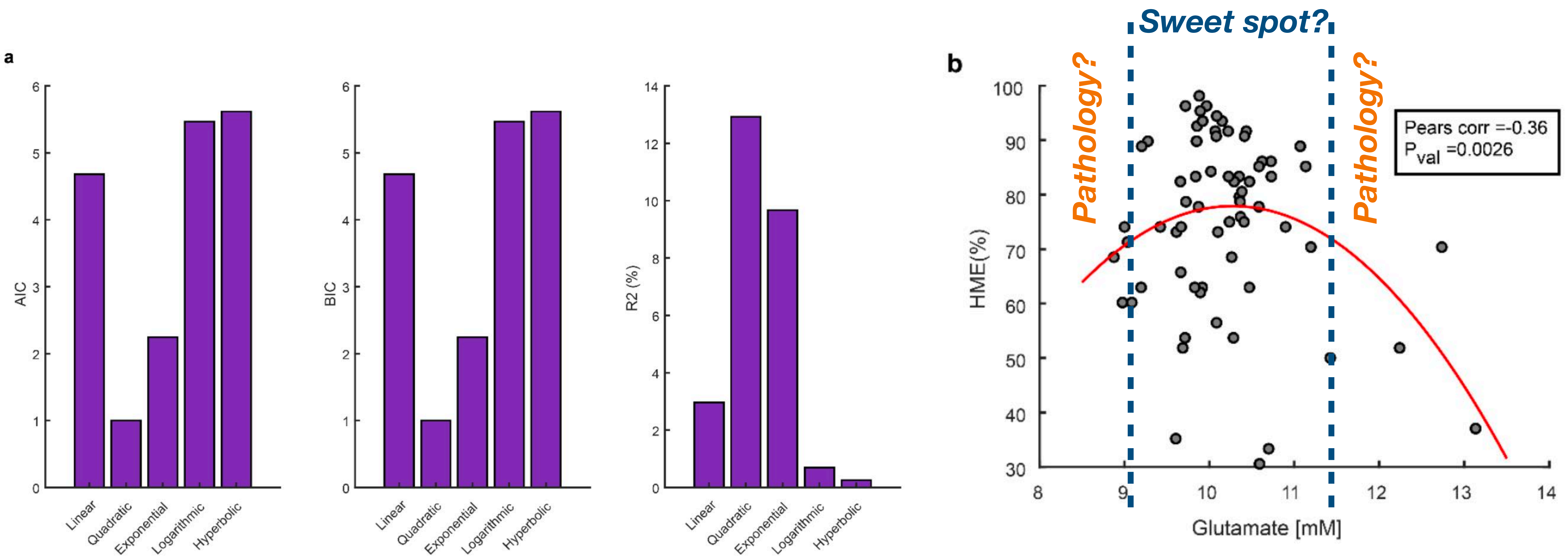


Fig.S4 (Supplementary Material)

→ Glutamate is involved in motivational disorders, schizophrenia

→ **Results suggest there is an optimal interval of [Glu] in dmPFC/dACC for decreasing effort aversion for mental tasks**

Results

Is the model the right fit?

Model 5: kI + kE + Bias + kTime integrated

$$\Delta SV(t) = kI * \Delta I(t) - \Delta E(t) * \left(kE + kF * T_{integrated}(t)\right)$$

$$kF * T_{integrated}(t) = kFp * \sum_{t=0}^{T} AUC(t) - kFm * Efficiency(t)$$

$$Efficiency(t) = \frac{Number_{correct\ answers}}{Total\ trial\ time}(t)$$

$$AUC(t) = \int_{t=0}^{T} exerted\_force(t)$$

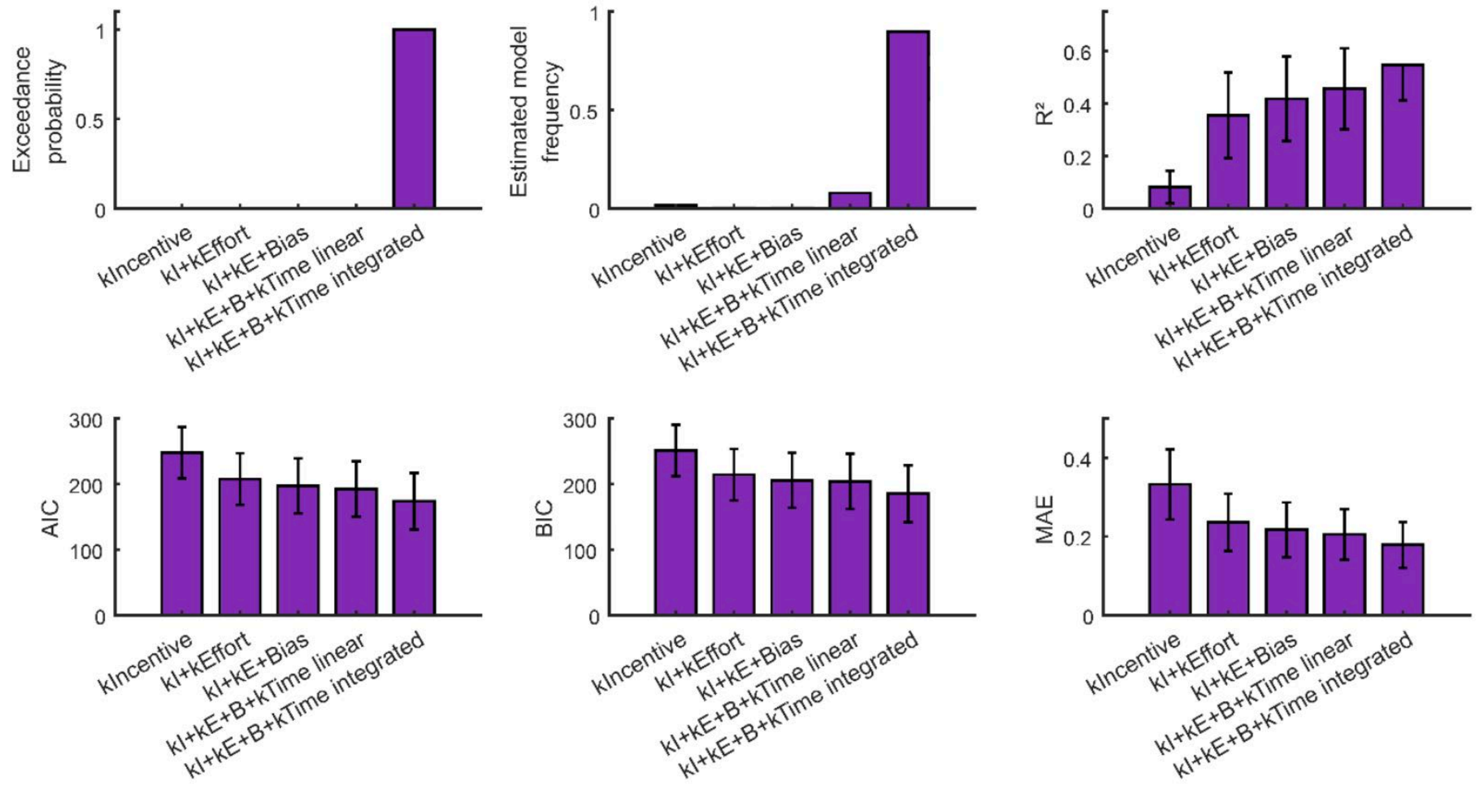
$$Pr_{High\ effort\ choice}(t) = \frac{1}{1 + e^{-\Delta SV(t) + bias}}$$

From Supplementary Material

- $\Delta SV(t)$: subjective value of offer at trial t
- ΔI is the difference in rewards (ΔR) or punishment (ΔP)
- E: Effort

  E_m: Mental Effort — E_p: Physical Effort
- F: Fatigue

  F_m: Mental Fatigue — F_p: Physical Fatigue
- k: sensitivity



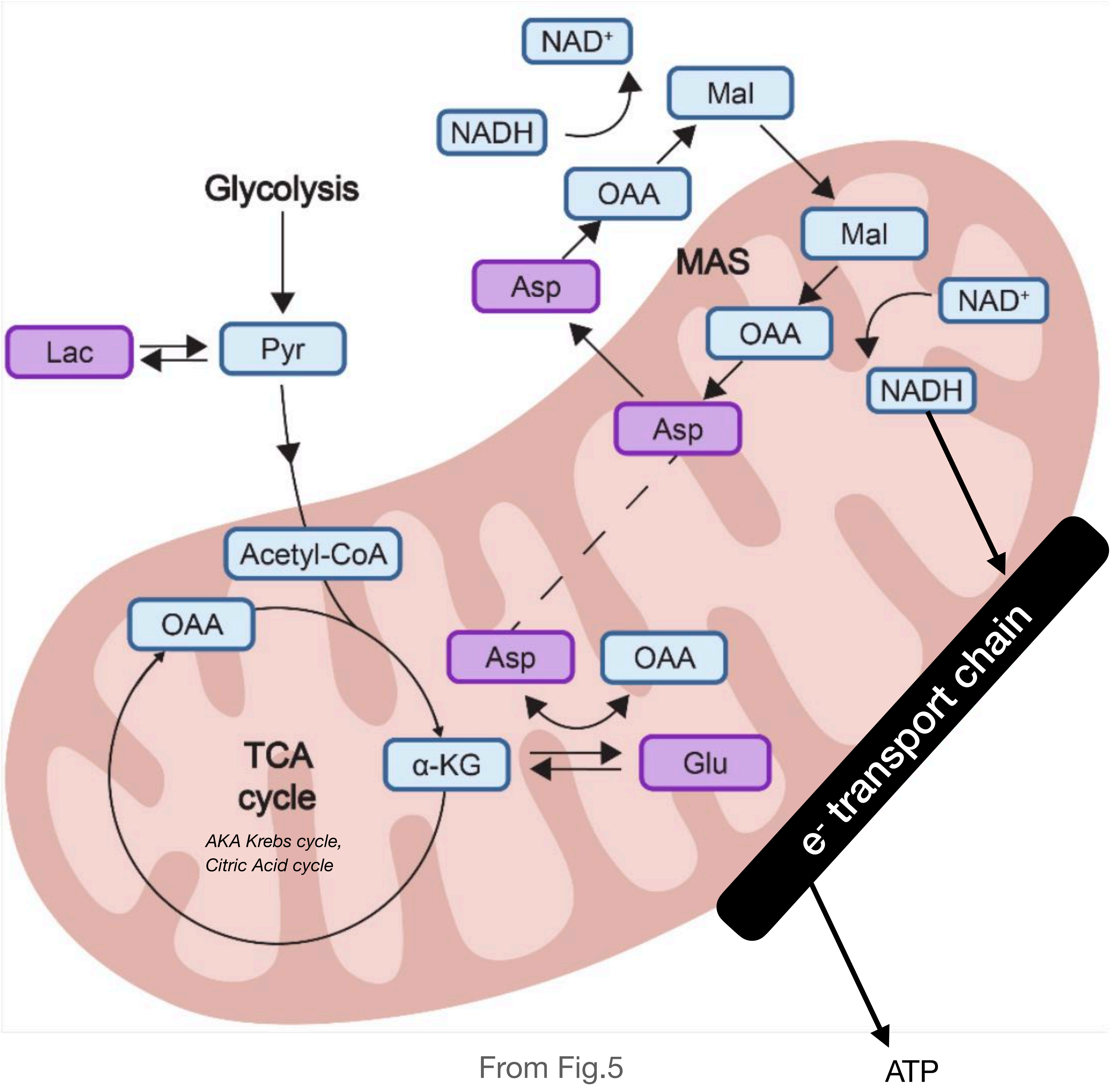
From Fig.S5 (Supplementary Material)

Results

Metabolites for neurophysiology

- Brain consumes energy from many sources of ATP, not only glucose
- Glycolysis creates only 2 molecules of ATP, TCA cycle creates 2 molecules but ETC creates **34 molecules of ATP**
- These metabolites are precursors to energy creation and even sometimes neurotransmitters.
- Their **importance cannot be understated** for neuronal activity in effort-based decision-making tasks

Mitochondria: cellular respiration



From Fig.5

Thank you 😁 🧠 ⚛️

Barakat, A., Clairis, N., Brochard, J., Pessiglione, M., Godin, J., Cuenoud, B., Xin, L., & Sandi, C. (2024). A neurometabolic signature in the frontal cortex predicts individual differences in effort-based decision-making. *bioRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2024.01.23.576854