Predicting individual variations in mental effort-based decision-making using machine learning: Neurometabolic signature in the dorsomedial prefrontal cortex/dorsal anterior cingulate cortex

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Abstract

Exploring why individuals vary in their willingness to exert effort in decision-making is fundamental for understanding human behavior. Our study focuses on the dorsomedial prefrontal cortex/dorsal anterior cingulate cortex (dmPFC/dACC), a crucial brain region in motivation and decision-making, to uncover the neurobiological factors influencing these individual differences. We utilized 7T proton magnetic resonance spectroscopy (^{1}H-MRS) to analyze metabolite concentrations in the dmPFC/dACC and anterior insula (AI) of 75 participants, aiming to predict individual variability in effort-based decision-making. Employing computational modeling, we identified key motivational parameters and, using machine learning models, pinpointed glutamate, aspartate, and lactate as crucial metabolites predicting decision-making to exert high mental effort, signifying their role as potential biomarkers for mental effort decision-making. Additionally, we examined the relationships between plasma and brain metabolite concentrations. Our findings provide novel insights into the neurometabolic underpinnings of motivated behavior, offering new perspectives in the field of cognitive neuroscience and human behavior.

Introduction

Motivation drives individuals to overcome the inherent costs of actions to achieve desired outcomes, such as obtaining rewards or avoiding punishments (Chong et al., 2016; Pessiglione et al., 2018). This process, fundamental to human behavior, involves making decisions based on cost-benefit trade-offs between the rewards involved in an action and the effort required to reach them. However, there is striking variability in how individuals approach effortful decisions. Some readily engage in physically or mentally demanding tasks for potential gains or to avoid adverse outcomes, while others may show reluctance or inability to engage similarly, which can significantly impact their well-being, longevity, and success in life (Duckworth et al., 2015; Epstein & Silbersweig, 2015; Kanfer et al., 2017). Moreover, a pronounced aversion to effort exertion is a key symptom in various brain pathologies (Le Heron et al., 2018; Pessiglione et al., 2018). While such diversity in motivational drive reflects a significant aspect of human cognition, our understanding of the neurobiological underpinnings of these inter-individual differences remains limited.

Neurobiologically, motivation and effort-based decision-making are closely linked to the functioning of specific brain regions, particularly the dorsomedial prefrontal cortex/dorsal anterior cingulate cortex (dmPFC/dACC) (Bartra et al., 2013; Clairis & Lopez-Persem, 2023; Lopez-Gamundi et al., 2021; Pessiglione et al., 2018; Soutschek et al., 2022). The dmPFC/dACC plays a pivotal role in regulating motivated behavior and exerting mental and physical effort, with its activation being crucial in these cognitive processes (Chong et al., 2017; Kurniawan et al., 2021). Lesions in this area can lead to increased effort aversion (Le Bouc et al., 2023) and even akinetic mutism, a state characterized by a lack of initiative to act (Darby et al., 2018), further underscoring its importance. However, our understanding of the specific components (e.g., neural, metabolic, and others) within the dmPFC/dACC that influence effort-based decision-making is still limited. Investigating these neural factors is vital for developing strategies to enhance motivation, thereby empowering individuals to achieve their goals and maximize their potential.

Recent advances emphasize the importance of brain bioenergetic and metabolic processes for brain function, behavior, and cognition (Morella et al., 2022; Ülgen et al., 2023; Yellen, 2018). While initial studies predominantly focused on glucose as the resource-limiting energy source for demanding cognitive processes (Baumeister, 2003; Gailliot, 2008; Gailliot & Baumeister, 2007), such as decision-making, recent research has revealed not only that brain glucose might not be as limited as was originally proposed (Dang, 2016; Job et al., 2013; Lange & Eggert, 2014; Vadillo et al., 2016). Moreover, neurons utilize various energy substrates, not just glucose, to support neural activity (Lutas & Yellen,

2013) and, consequently, meeting cognitive demands (Yellen, 2018). These concepts collectively reinforce the notion that cognitive processes, including motivation and decision-making, are closely linked to the brain's metabolic state. Understanding this relationship is crucial for insights into the mechanisms that regulate these cognitive functions. However, our understanding of how metabolism influences motivational processes and decision-making is still in its early stages.

Proton magnetic resonance spectroscopy (^{1}H-MRS) is emerging as a powerful non-invasive tool in this context, enabling the quantification of brain metabolites and providing insights into the neurochemical state of specific brain regions. Metabolites are measurable through ^{1}H-MRS, such as glucose, glutamate, lactate, aspartate, N-acetylaspartate (NAA), creatine, and others. These metabolites play crucial roles in neuronal health, energy metabolism, and cellular signaling, all key for neural function and behavior production. Understanding how the concentrations of these metabolites correlate with effort-based motivated behavior processes can offer valuable insights into the neurometabolic underpinnings of these cognitive functions. Previous studies have offered initial insights linking specific metabolites in specific brain regions to individuals' performance in motivation and decision-making tasks (Jocham et al., 2012; Strasser et al., 2020; Wiehler et al., 2022; Yoon et al., 2016). However, virtually all the studies linking metabolite concentrations, acquired through ^{1}H-MRS, to behavior or cognition have focused on individual metabolites using univariate analyses, whether in patient or healthy populations. This approach has led to a fragmented understanding, potentially overlooking how the combined influence of multiple metabolites contributes to motivated behavior. Addressing this gap employing multivariate statistical methods can provide a more comprehensive view of the neurochemical bases of motivated behavior, given the interconnected nature of metabolic pathways.

In this study, we leveraged the critical role of the dmPFC/dACC in assessing cost-benefit trade-offs in effortful tasks to predict individual differences in decision-making for effort-based motivated behavior. We utilized ultra-high field 7 Tesla (7T) ^{1}H-MRS to measure metabolite concentrations in the dmPFC/dACC, our target region, and in the anterior insula (AI) to assess the specificity of our findings. The AI, a part of the salience network known for its response to aversive stimuli like punishment (Litt et al., 2011; Seeley et al., 2007), served as a comparative region. Additionally, we conducted metabolomic analyses of blood samples. To gauge participants' willingness to exert physical and mental efforts, we created an effort-based decision-making task where subjects chose between low and high-reward options, that required varying levels of effort. These tasks involved obtaining rewards or avoiding punishment and alternating between mental and physical effort. We applied computational modeling to extract key parameters influencing effortful decisions in our task (Bonnelle

et al., 2015; Pessiglione et al., 2018). We subsequently employed machine learning models to explore whether specific dmPFC/dACC metabolite combinations could predict effortful choices and parameters of motivated behavior. Our study offers new insights into how dmPFC/dACC metabolic processes relate to motivated behavior components, potentially identifying novel biomarkers and therapeutic targets for motivation-related cognitive functions, especially in the context of mental effort and perception.

Results

Our study was designed to explore how individual variation in 7T ^{1}H-MRS measured metabolites in the dmPFC/dACC (see **Fig. 1A,C**) can predict differences in physical and mental motivated behavior (**Fig. 1D-E**) across individuals. Additionally, we performed ^{1}H-MRS scans in the AI to assess the specificity of our predictive findings (**Fig. 1B**).

Behavioral Task

To assess motivated behavior, participants performed a behavioral task comprising 216 trials in 4 blocks. To ensure task feasibility and remove any risk assessment, we calibrated the task individually before the start. Each trial required choosing between two options, differing in monetary incentives and effort levels (**Fig. 1D-E**). After each decision, participants had to perform the task at the chosen effort level. This step was critical to ensure that decisions genuinely reflect the effort levels offered, rather than risk discounting. Indeed, participants completed the selected effort in 95 ± 3.7% of mental effort trials and 98 ± 3.4% of physical effort trials. Increased task difficulty led to reduced high-effort/high-reward choices in both physical and mental tasks (**Fig. S1A,D**), indicating effort aversion. Higher difficulty led also to more effort, shown by greater and steeper handgrip force in the physical task (**Fig. S1B-C**), and more errors and cognitive load in the mental task (**Fig. S1E-F**). These findings validate the task's effectiveness in measuring motivation for both physical and mental efforts.

dmPFC/dACC Metabolites as Predictors of Motivated Behavior

To determine if dmPFC/dACC metabolite levels can predict the proportion of high mental effort (HME) and high physical effort (HPE) effort choices made by participants, we employed a gradient tree boosting regression model with metabolite concentrations as regressors. Our feature selection process, applied to 18 features including metabolites and standard ratios (detailed in Supplementary Materials), identified 9 features relevant for HME and 5 for HPE prediction (**Fig. 2**). To enhance data robustness and minimize overfitting, we adopted a train/validation/test approach with cross-validation leave-one-out (CVLOO) design, splitting data into training/validation and testing sets with an 80% ratio, resulting in training/validation (N = 55) and testing (N = 14) datasets. We trained an

extreme gradient boosting trees (XGBoost) to fit linear response functions to HME and PHE, utilizing Bayesian optimization for hyperparameter tuning. The prediction error was quantified using the root mean square error (RMSE).

For the PHE data, the model showed a medium fit in training and validation (train RMSE = 0.47%, validation RMSE = 17.34%). However, the test set revealed a borderline result (test RMSE = 19.51%, r = 0.5, p = 0.06), explaining only 25% of the variance (**Fig. 2A**). A permutation test with 5000 permutations indicated that these borderline significant results were not above chance level (95th percentile = 13.72 > model RMSE = 12.37) (**Fig. 2B**), leading us to discard PHE prediction from further analysis.

In contrast, for the MHE data, the model developed demonstrated a good fit (train RMSE = 0.05%, validation RMSE = 13.06%) and a consistent result in the unbiased estimate that is the test set (test RMSE = 12.37%, r = 0.56, p = 0.036), explaining 31% of the variance (**Fig. 2C**). The permutation test with 5000 permutations confirmed that our model's predictions significantly exceeded chance level (95^{th} percentile = 13.72 > model RMSE = 12.37) (**Fig. 2D**). These results support our hypothesis that dmPFC/dACC metabolite concentrations can predict inter-individual variation in motivated behavior, specifically demonstrating their predictive power in the context of mental effort tasks.

To understand the impact of individual metabolites in the XGBoost model for predicting HME, we analyzed the Shapley Additive exPlanations (SHAP) values. The identified features included in descending order of their importance (determined by the magnitude of each feature's SHAP value) are glutamate (Glu), lactate (Lac), glutamine (Gln), taurine (Tau), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), aspartate (Asp), glutathione (GSH) and creatine (Cr) (**Fig. 2E**). Thus, glutamate and lactate emerged as the top discriminating features. However, our SHAP analysis of the data distribution for each predictive feature/metabolite revealed that specific metabolite concentrations do not always have a linear relationship with HME. Indeed, neither glutamate (r = -0.19, p = 0.12) nor lactate (r = -0.13, p = 0.27) demonstrated a linear relationship with HME. Particularly for glutamate, extreme values – either low or high – were negatively associated with HME, indicating a non-linear relationship. To further investigate this, we employed Bayesian model comparison to determine the best formula linking glutamate with HME. The model that most accurately predicted HME featured an inverted U-shape relation, based on the mean-centered squared score of glutamate concentrations (r = 0.36, p = 0.0026), as supported by both the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (**Fig. S3**).

To determine if the metabolites relevant for HME are specific to the dmPFC/dACC region, we similarly assessed the ability of AI metabolite concentrations to predict HME. We applied the same model

training process used for the dmPFC/dACC to AI metabolite concentrations. However, this AI-based model did not achieve statistical significance in predicting HME in our test set ($r = -0.47$, $p = 0.11$) (**Fig. 2F**), nor in the permutation test (95th percentile = 13.89% > model RMSE = 23.28%) (**Fig. 2G**). These results underscore the specificity of the XGBoost model for the dmPFC/dACC in accurately predicting HME, thereby emphasizing the distinct predictive value of the dmPFC/dACC metabolic landscape in motivated behavior.

Dissecting Performance: Computational Modeling of Motivated Behavior

Thus far, our analysis has demonstrated the capability of dmPFC/dACC metabolites to predict HME using XGBoost. However, since motivation, and by extension HME, is a complex construct composed of multiple elements like reward sensitivity, effort aversion, etc. (Bonnelle et al., 2015; Chong et al., 2016; Pessiglione et al., 2018), the specific behavioral components influenced by metabolism in this brain region remain to be elucidated. To dissect HME into these distinct motivational components and enhance our mechanistic understanding, we employed computational modeling in our task. This approach aligns with previous studies that have shown the efficacy of computational methods in deepening our understanding of behavioral mechanisms and uncovering neurobiological correlates otherwise not observable (Corrado & Doya, 2007; Nassar & Frank, 2016; Pessiglione et al., 2018). This approach helped us extract idiosyncratic participant parameters, including sensitivities to reward (kR) and punishment (kP), to mental and physical effort (kEm/kEp), mental facilitation over time (kFm), physical fatigue (kFp), and overall intrinsic motivation (bias). Adhering to established best practices in modeling (Wilson and Collins 2019), our approach's validity and robustness are clearly demonstrated in Figures 3A and 3B. Parameter recovery, assessed by comparing simulation parameters with those optimized, was successful in 80% of simulations for all the parameters, except for kFm which was recovered in 46% of simulations, a reasonable result (**Fig. 3A**). No spurious correlations ($-0.5 < r < 0.5$, Palminteri et al., 2017) were detected between parameters (**Fig. 3B**), allowing for independent and sensitive recovery of each of the seven parameters. This indicates that our model was capable of independently and sensitively recovering each of the seven parameters.

Further validation was performed by challenging our model against variants with fewer parameters through several model comparison techniques, including exceedance probability, estimated model frequency, AIC and BIC (**Fig. S4**). These unanimously highlighted the importance of all the extracted parameters (i.e., kR, kP, kEm, kEp, kFm, kFp, and bias) in describing participants' behavior, despite the penalization of each additional parameter in the comparison process. Importantly, our model closely mirrored participant choices (median absolute error of 17.8 ± 6%, goodness of fit $R^2 = 0.56$) (**Fig. 3C-**

D), effectively capturing the tendency of participants to choose more effortful options when monetary incentives were higher or the associated effort was less demanding.

dmPFC/dACC Metabolites Specifically Predict Sensitivity to Mental Effort

Next, we sought to determine whether dmPFC/dACC metabolites could predict any of the five idiosyncratic parameters characterizing HME modeling, derived from the computational modeling above. Specifically, we applied a separate XGBoost regression model to each parameter to investigate their predictability based on metabolite concentrations. Given that cognitive effort is often perceived as aversive, which influences action avoidance (Vogel et al., 2020), we initially focused on predicting sensitivity to mental effort (kEm) from metabolite concentrations. The dataset was split into 80% for training/validation (N=53) and 20% for testing (N = 14), with hyperparameter tuning conducted using hyperopt. The model showed a good level of accuracy in predicting kEm (range = 2.13, train RMSE = 0.16, validation RMSE = 0.42), and the test set yielded a modest prediction error (test RMSE = 0.4, r = 0.56, p = 0.037) (**Fig. 4A**), accounting for 30% of kEm's variance. This was confirmed by a permutation test, which indicated predictions significantly above chance level (95th percentile = 0.45 > model RMSE = 0.4) **(Fig. 4B**). Notably, other parameters involved in mental-effort decision making such as reward sensitivity (kR), punishment sensitivity (kP), mental facilitation (kFm), and bias were not predictable using this model (kR: r = -0.21, p = 0.23; kP: r = -0.24, p = 0.21; kFm: r = -0.09, p = 0.53; bias: r = 0.07, p = 0.41).

To elucidate the impact of the five metabolites identified through our feature selection on kEm prediction, we examined their SHAP values (**Fig. 4C**). This analysis highlighted aspartate and lactate as the most discriminating features. Notably, aspartate exhibited a significant positive linear correlation with kEm (r = 0.41, p = 0.0007) (**Fig. S2A**). Although lactate was the second most important feature, it alone did not significantly correlate with kEm (r = 0.063, p = 0.62).

Refining the Predictive Model for Mental Effort Decision-Making with Essential Biomarkers

So far, our work has yielded two effective XGBoost models for predicting HME and kEm, utilizing 9 and 5 dmPFC/dACC metabolites, respectively. In our quest to unravel the neurometabolic foundations of motivation for mental effort, we next focused on further embracing parsimony. Given that overly complex models could hinder understanding and generalizability, our goal was to refine our models to strike a balance between simplicity and explanatory (Vandekerckhove et al., 2015), and thus aimed to develop a streamlined model with a minimal yet effective set of features. This strategy is consistent with the established approaches in cognitive neuroscience and machine learning, where impactful

models typically achieve high predictive accuracy with as few parameters as necessary (Takahashi et al., 2020).

First, we explored whether a robust prediction of HME could be made based on a selected few key metabolites. However, simply choosing the top two (i.e., glutamate and lactate; **Fig. S5A-C**) or top three (i.e., glutamate, lactate, and glutamine; **Fig. S5D-F**) predictors from our SHAP analysis did not yield a significant prediction.

Given that the simple selections of top metabolites (glutamate and lactate) in our initial trials did not yield significant predictions, we pursued a novel approach, inspired by the movement in machine learning toward integrating biological context to enhance model relevance and interpretability (Zampieri et al., 2019). Taking into account that Asp ranked top in the kEm model but rather low in the HME model, possibly due to its biosynthetic relationship with Glu and Gln (Holten & Gundersen, 2008) [note that these three metabolites are intertwined in the TCA cycle (**Fig. 5**)], we hypothesized that machine learning's tendency to minimize correlated features might have undervalued Asp's contribution in the HME model. Our data confirmed significant intercorrelations among these metabolites (**Fig. S4D**), suggesting that Asp, despite its lower ranking, could still hold unique predictive information. Notably, Lac, with no strong association with either Glu ($r = 0.03$, $p = 0.77$) or Asp ($r = 0.19$, $p = 0.11$), maintained its distinct variance. This led us to re-evaluate the potential of Glu, Asp, and Lactate concentrations in the dmPFC/dACC for predicting HME and their role as biomarkers for mental effort decision-making.

Thus, we trained again a XGBoost model and used again a train/validation/test analysis design with a cross-validation leave-one-out (CVLOO) design. Data were split into training/validation into an 80% ratio, creating training/validation ($N = 55$) and testing ($N = 14$) data sets. To fit a linear response function to HME, we used XGBoost and the RMSE as a metric of error percentage. The model resulted in a good fit on the training (RMSE = 0.34%) and validation (RMSE = 15.94%) sets. (**Fig. 6A,B**) and a consistent result in our unbiased model estimate, the test set (RMSE = 11.4%, $r = 0.64$, $p = 0.014$), explaining up to 40% of the variance (**Fig. 6C**). The permutation test with 500 permutations confirmed that our model's predictions significantly exceeded chance levels (95^{th} percentile = 13.46 > model RMSE = 11.68). The results support the idea that a few dmPFC/dACC metabolite concentrations can predict participants' willingness to perform mental effort.

Analyzing the impact of glutamate, aspartate, and lactate on the model's prediction of HME using SHAP values revealed complex relationships, similar to our results from our initial model predicting HME. Specifically, glutamate and lactate did not exhibit linear correlations with HME (glutamate: $r = -0.19$, $p = 0.12$; lactate: $r = -0.13$, $p = 0.27$). Notably, extreme glutamate values were negatively

associated with HME, still suggesting a quadratic relationship. In contrast, aspartate showed a strong negative linear correlation with HME (r = -0.37, p = 0.0018) (**Fig. S2A**).

Plasma and brain concentrations

Next, in order to explore if there is a relationship between our top identified metabolites in dmPFC/dACC predictive of HME with relevant plasma components, we examined if plasma concentrations of glutamate, aspartate, and lactate correlate with their levels in the dmPFC/dACC (**Fig. S6**). Furthermore, we also examined if plasma concentrations of glutamine correlated with its dmPFC/dACC counterpart levels, as glutamate is present in much lower concentration than its precursor in blood (Smith, 2000). We also performed the same analyses for the AI (our comparison brain region). Our analyses revealed no significant correlation between the plasma and dmPFC/dACC or AI concentrations of glutamate and aspartate. Interestingly, lactate displayed region-specific correlations, being significant in the dmPFC/dACC (r = 0.27, p = 0.023) but not in the AI (r = 0.14, p = 0.36). Conversely, glutamine showed a strong positive association in both brain regions (r = 0.54, p = $1.5 \cdot 10^{-5}$ in dmPFC/dACC; r = 0.34, p = 0.014 in AI), indicating a more global brain-plasma relationship.

Discussion

There are considerable individual differences in the propensity of individuals to opt for high-effort choices in incentivized effortful tasks. Despite the significant role of motivation in numerous life outcomes (Duckworth et al., 2015; Epstein & Silbersweig, 2015; Kanfer et al., 2017), the neurobiological underpinnings behind these individual differences remain largely unexplored. Our study bridges this gap by identifying specific neurometabolic factors in the dmPFC/dACC — a region critical to effort-based decision-making (Chong et al., 2017; Clairis & Lopez-Persem, 2023; Kurniawan et al., 2021; Le Bouc et al., 2023; Lopez-Gamundi et al., 2021b; Pessiglione et al., 2018; Soutschek et al., 2022)— that underlie individual variations in the decision to exert mental effort.

Departing from previous research that focused on individual metabolites (Grachev et al., 2001; Jocham et al., 2012; Strasser et al., 2020; Wiehler et al., 2022; Yoon et al., 2016; Yücel et al., 2007), our multivariate approach yields a more comprehensive understanding of neurometabolic processes in mental effort and decision-making. Our initial machine learning model successfully predicted human high mental effort (HME) selection, identifying nine key metabolites as crucial discriminants from over twenty analyzed using ^{1}H-MRS in the dmPFC/dACC. The high-field (7T) ^{1}H-MRS was pivotal in our study, as it offers superior spectral resolution than lower magnetic field scanners, thus enabling the differentiation of key metabolites, including glutamate and glutamine that, along with lactate, emerged as top discriminants in our model. However, attempts to model high physical effort (HPE)

and predict mental effort using anterior insula metabolites were inconclusive, emphasizing the unique role of dmPFC/dACC metabolites in mental effort prediction. This specificity is remarkable, given the functional correlation between the dmPFC/dACC and the anterior insula within the salience network (Litt et al., 2011; Seeley et al., 2007; Uddin, 2015; Uddin et al., 2019). Subsequently, aspartate and lactate were identified as key in predicting mental effort sensitivity (kEm), with their elevated levels related to greater aversion to mental effort. Notably, this model highlights kEm as the only predictable motivational component from our task, among the several components extracted via computational modeling. This suggests that sensitivity to mental effort (and, consequently, aversion to effort) is a central cognitive process through which dmPFC/dACC metabolism influences decisions involving high mental effort, emphasizing the significance of these metabolites in the context of motivation and cognitive effort.

Our final model, which aimed for both simplicity and explanatory power, incorporated biological context to identify a combination of glutamate, aspartate, and lactate in the dmPFC/dACC as sufficient discriminants for high mental effort propensity. This final model, explaining up to 40% of HME variance, balances parsimony with predictive strength and reflects the individual and collective significance of glutamate, aspartate, and lactate in mental effort decision-making. The prominent roles of aspartate and lactate in both HME and kEm model predictions highlight their importance in understanding the motivation for mental effort, likely through their relation to mental effort sensitivity (kEm).

The intricate roles of these three dmPFC/dACC metabolites provide insights into their potential contribution to high mental effort. They play essential metabolic roles in cellular processes, including glycolysis (lactate) and the TCA cycle (glutamate, aspartate), contributing to neuronal energy and synaptic signaling. Importantly, the three are interconnected (see **Fig. 5**), with lactate contributing to glutamate and aspartate biosynthesis (Waagepetersen et al., 1998), while glutamate and aspartate have a bidirectional relationship, supporting each other's production (McKenna et al., 1996; Schousboe et al., 2014). Moreover, glutamate, released by neurons, can be taken up by astrocytes and converted into lactate (Juaristi et al., 2019; Pellerin & Magistretti, 2012; Waagepetersen et al., 1998). Thus, the combined role of these three metabolites in predicting HME suggests that their interplay within a metabolic network fine-tunes dmPFC/dACC neural computations related to mental effort. The brain may consider the region's metabolic state when determining mental effort feasibility and desirability.

However, understanding the contributions of the three predicting metabolites to HME is challenging. Only aspartate showed a linear association with HME, with elevated levels linked to reduced mental effort decisions (HME) and increased aversion to mental effort (kEm). This finding's robustness is further supported by negative correlations between dmPFC/dACC aspartate levels and both kEm and several performance measures indicating lower cognitive efficiency with higher aspartate levels **(Fig. S8**). Aspartate, an amino acid, plays an integral role in brain metabolism and mitochondria (Schousboe et al., 2014) and serves as a precursor to glutamate (see above). Its involvement in neuronal activity has been further underscored in studies showing its transient decreases following neuronal stimulation (Bednařík et al., 2015, 2018; Mangia et al., 2007). These multifaceted functions underscore its vital significance in brain metabolism, neurotransmission and, consequently, its potential implications for cognitive processes, particularly in situations demanding high mental effort. Hypothetically, dysfunction at the TCA cycle level leads to the accumulation of aspartate in the dmPFC/dACC, subsequently impacting motivated behavior.

Instead, glutamate displayed an inverted U-shaped relationship with HME. Intermediate glutamate levels were associated with increased mental effort, while both excessively low and excessively high levels were linked with reduced mental effort choices. Glutamate, also an amino acid and key neurotransmitter and metabolic component (Schousboe et al., 2014), plays a dual role in the brain. Both low and high glutamate concentrations can impair cellular functions (Matute et al., 2007; Zhou & Danbolt, 2014), emphasizing the importance of maintaining an optimal balance for proper cognitive function. Notably, we also found that, in the dmPC/dACC, the Glu/Asp ratio, potentially reflecting the TCA cycle and mitochondrial function, correlated positively with high mental effort and negatively with sensitivity to mental effort, highlighting the importance of maintaining a proper balance between glutamate and aspartate concentrations for mental effort regulation.

Regarding lactate, its concentration in the dmPFC/dACC was related to HME and kEm, only when considered alongside other metabolites, as no mathematical function was found to describe this as a univariate relationship. Interestingly, the SHAP analyses hinted that in the absence of a linear association, there may be a certain threshold beyond which elevated lactate levels might detrimentally influence mental effort decisions. Lactate has recently emerged from just being considered as a waste product from stressed muscles and cells (Jorfeldt et al., 1978; Rabinowitz & Enerbäck, 2020) to be regarded as a key player in brain energy metabolism and glutamate production (Magistretti & Allaman, 2018; Rabinowitz & Enerbäck, 2020; Schurr, 2017). It acts as a crucial energy source for neurons, particularly during periods of intense neuronal activity (Magistretti & Allaman,

2018). Lactate's dynamic regulation is essential for supporting cognitive processes and maintaining proper brain function (Dienel & Hertz, 2001; Shulman et al., 2001; Theriault et al., 2023).

Lactate is a recognized metabolic marker for mitochondrial dysfunction in the brain (Barker et al., 2005; Bianchi et al., 2007; Schmiedel et al., 2003). Elevated lactate levels indicate impaired mitochondrial function, characterized by a shift towards glycolytic metabolism and reduced oxidative phosphorylation. This elevation serves as a biomarker for mitochondrial dysfunction and energy metabolism disturbances in brain pathologies (Ernst et al., 2017; Li et al., 2022; Machado-Vieira et al., 2017) as, under normal conditions with intact mitochondrial metabolism, lactate does not accumulate in the brain (Bianchi et al., 2007; Schmiedel et al., 2003) but serves as an energy source for neurons (Magistretti & Allaman, 2018; Pellerin et al., 1998). However, in the presence of mitochondrial dysfunction, a shift to extramitochondrial glycolysis leads to lactate accumulation (Ernst et al., 2017). As lactate is a tightly controlled molecule, whose fundamental role is to uncouple the glycolysis and the TCA cycle, its influence may most likely be seen in other intricate metabolic pathways (Rabinowitz & Enerbäck, 2020; Waagepetersen et al., 1998), including potential changes in glutamate and, thereby, aspartate levels. Given our results suggest that higher baseline dmPFC/dACC lactate concentrations tended to have a negative impact on mental effort, despite lactate's energy-providing role, our findings suggest that high lactate levels, possibly due to some mitochondrial dysfunction, could adversely affect motivation.

Therefore, of the number of metabolites collected from each participant, the most discriminating variables contributing to motivated behavior in our mental effort task include features that were related to energetic pathways. Energy is of peculiar importance as, notably, the dmPFC/dACC selected in our study, is one of the regions with the highest energy consumption of the brain (Castrillon et al., 2023; Raichle & Mintun, 2006). At a regional level, regions like the dmPFC/dACC that expanded most during human evolution show an excessive energy demand compared to the rest of the brain. Furthermore, the dmPFC/dACC also shows higher aerobic glycolysis (Vaishnavi et al., 2010), suggesting that this region is capable of intense and sudden energy expenditure. One could thus hypothesize that a higher concentration of metabolites (glutamate, aspartate, and lactate) would mean more available energy, and thus result in increased levels of motivation. However, aspartate and a combination of lactate and glutamate concentration, influence negatively motivated behavior. Here, we hypothesize that our measures of aspartate and lactate concentrations display an accumulation due to an imbalance in mitochondria of the TCA function. This could be an explanation for the decreased willingness to perform mental efforts in subjects with higher baseline levels of dmPFC/dACC aspartate,

lactate, and glutamate. However, this is but one hypothesis that would remain to be tested in future studies.

The multivariate approach in our study also identified the importance of other metabolites, such as glutathione and taurine related to antioxidant pathways, and glutamine, although to a lesser extent. Previous research has demonstrated that glutathione levels in the nucleus accumbens positively affect physical endurance by protecting against oxidative stress (Zalachoras et al., 2022), while glutamine levels were found to negatively correlate with physical effort perception in the nucleus accumbens (Strasser et al., 2020). These findings suggest that metabolic pathways impacting motivated behavior may vary across different brain areas, emphasizing the potential for targeted interventions to address motivational deficits in various contexts.

Interestingly, metabolite concentrations are considered to remain constant across multiple days and even across years for most metabolites, as shown by the intra-class correlation coefficient (Lally et al., 2016; Ross et al., 2006), supporting the view that the inter-individual differences in metabolism and motivated behavior measured in our study reflect general differences across individuals that could be related to genetic or environmental (nutrition, climate, development, etc.) factors that are relatively stable over time. To minimize any other influence on the metabolic state of our participants (age, circadian rhythm, meal), we only included individuals between 25 and 40 years old (i.e., after the brain development and before neurodegeneration) and always started the experiment at 2 pm to minimize the potential effects of hunger/digestion and circadian rhythm on our metabolic measurements. However, such concentrations are not immutable and can be altered in several manners, including through nutritional supplementation and modifications to the microbiome. This opens the door to potential interventions in diseases where motivation is affected (Kochalska et al., 2020; Lyoo et al., 2003).

When exploring the relationship between brain and plasma concentrations, we found that the concentrations of our biomarkers in the brain are generally independent of plasma concentrations, except for lactate, which exhibited a positive correlation in the dmPFC/dACC. Validating findings in the literature, the concentration of glutamate in the dmPFC/dACC and AI is observed to be largely independent of plasma levels, with plasma representing only a fraction of the brain concentration (Smith, 2000). To the best of our knowledge, the relationship between aspartate concentration in the plasma and the brain has never been described. Similar to glutamate, aspartate levels in the dmPFC/dACC and AI remain independent of plasma concentration, with concentration a hundred times lower in plasma compared to the brain. In contrast, metabolites such as lactate and glutamine demonstrate concentrations in the blood that closely mirror those in the brain, suggesting potentially

distinct dynamics in the brain uptake of these metabolites (Cruzat et al., 2018). In our study, lactate concentration in plasma displayed a significant correlation only with brain concentrations in the dmPFC/dACC, an area known for higher energy consumption. In comparison, glutamine transport appears to be global, as plasma concentrations showed a significant relationship with concentrations in the dmPFC/dACC. Taken together, our targets of interest appear to be largely unaffected by plasma concentrations.

While effort is typically viewed as something to be minimized, it can also enhance the value of outcomes and even drive our choices (Gheza et al., 2023; Inzlicht et al., 2018; Zerna et al., 2023). Stable individual differences in cognitive motivation — the tendency to engage in and enjoy effortful cognitive activities — have been documented with self-report measures and recently reinforced by empirical evidence (Crawford et al., 2022). This research indicates the presence of a trait-level cognitive motivation in the population, characterized by a consistent propensity to undertake and derive pleasure from cognitively demanding tasks. Cognitive effort, typically avoided as aversive, can be intrinsically valued, particularly when linked to rewards (Clay et al., 2022). This is in contrast to individuals with certain psychological or neurological conditions, who demonstrate a diminished willingness to exert cognitive and physical effort (Ang et al., 2023; Horne et al., 2021; Le Bouc et al., 2023; Vinckier et al., 2022; Westbrook et al., 2023). The reluctance in these cases is often linked to altered reward sensitivity rather than an increased perception of effort (Le Heron et al., 2018). Importantly, in our study, we implemented a process of standardizing tasks' effort demands across participants, drawing inspiration from a critical methodological advancement highlighted in recent cognitive effort research (Fleming et al., 2023).

In conclusion, the present study emphasizes the major role of metabolites in dmPFC/dACC of healthy participants, namely glutamate, aspartate, and lactate, to predict the amount of effort participants are willing to produce and their perception of it. Thus, in addition to highlighting the importance of these metabolic pathways, our study contributes to bridging the gap between motivated behavior and neurometabolism in healthy adults. Future studies will help to understand the precise role and interactions at the molecular level of the metabolites identified here. For instance, one could causally manipulate the levels of these metabolites in the dmPFC/dACC equivalent of animal models, to better disentangle the impact of each metabolite. Moreover, nutritional interventions aiming at modifying the dmPFC/dACC levels of glutamate, aspartate, and lactate in humans could prevent and help treat pathologies related to motivational alterations but further studies are first needed to verify whether nutritional intake of glutamate, aspartate, and/or lactate precursors can causally influence dmPFC/dACC levels of these metabolites, and have a positive impact.

Limitations of the study

The borderline nature of the results of our model to predict HPE underscores the necessity for further investigation into the involvement of dmPFC/dACC metabolites in the computation of physical effort decisions. Furthermore, the model was able to result in significant predictions but it was trained on a limited sample size. In the future, it will be important to benchmark the prediction capacity of our model and show its generalization capacity to both new datasets and other mental effort paradigms.

Conclusions

Our study breaks new ground within the emerging field that underscores the crucial role of bioenergetic and metabolic processes in influencing brain function and cognitive behaviors. Our holistic approach represents a significant advancement in understanding the intricate metabolic interplay in cognitive neuroscience. Unlike traditional univariate analyses, our machine learning approach considers the collective impact of these metabolites, highlighting the complex relationship between metabolic processes and cognitive functions. By integrating multiple metabolites, our model provides a more comprehensive view of how brain bioenergetics and metabolism influence cognitive functions and motivation. The identified dmPFC/dACC metabolites have the potential to serve as biomarkers for mental effort. This study contributes to the emerging field emphasizing the role of bioenergetics and metabolism in brain function and cognitive behavior, opening new avenues for exploring their impact on mental health.

Methods

Participants

The results presented in this section are part of a larger study that aims at investigating inter-individual differences in motivated behavior. Here, we specifically analyzed a subset of the collected data that pertains to metabolite concentrations and behavioral measures.

A total of 75 healthy (N = 40 females) right-handed volunteers participated in this study, approved by the Cantonal Ethics Committee of Vaud (CER-VD), Switzerland. Participants were recruited through the Université de Lausanne (UNIL) LABEX platform, as well as through online and printed announcements in the city of Lausanne. Participants were required to speak French fluently (B2 minimum). Furthermore, they underwent a screening process to identify any exclusion criteria, including being between 25 and 40 years old, not regularly using drugs or medications, having no history of neurological disorders, and not having any contraindications to MRI scanning, such as pregnancy, claustrophobia, a tattoo near the neck, or metallic implants. All participants provided signed informed consent before taking part in the study. Prior to their lab visit, participants completed inclusion/exclusion criteria and several online questionnaires via an online platform using Qualtrics (Qualtrics, Provo, UT, USA). Using the MADRS-S, a depression questionnaire, and to ensure we acquired a wide range of behavior and sufficient inter-individual variability, we collected as many participants with a MADRS-S score lower than 4 and higher than or equal to 4 (Ntini et al., 2020; Yee et al., 2015). Two participants did not finish the behavioral experiment due to technical issues. Furthermore, four participants always selected the effortful option in at least one of the two tasks, which made it impossible to fit our model on their behavior, leaving us with a final sample size of 69 subjects for our first and third machine learning model (34 females; age = 30.5 ± 3.9 years; weight = 67.9 ± 12.6 kg; BMI = 22.8 ± 3.1). For our second machine learning model, 2 more participants were filtered due to aberrant values (higher than mean+3SD) for the behavioral parameter kEm. After removing these participants, the final sample for the second model contained 67 subjects (34 females; age = 29.9 ± 3.9 years; weight = 67.7 ± 12.5 kg; BMI = 22.8 ± 3).

Participants received a payment of 70 CHF for completing the task, an additional 10 CHF per hour spent in the experiment, and a fixed amount of 4 CHF for each time they performed a physical or mental maximal performance, performed 10 times. Finally, participants also received payment based on their choices and performance during the indifference point measurement and in the main task. On average, participants earned 204 ± 17.4 CHF for their participation in the study.

Experimental procedure

Participants were invited to participate in our study, which always started at 2 pm to control for any metabolic difference that could be driven by the circadian rhythm. Participants were also required to eat at least 1h before coming to avoid any metabolic fluctuation that could be related to food digestion. First, blood samples were collected at the "Point Santé" in EPFL and the "centre médical des arcades" by healthcare professionals. Next, baseline metabolite concentrations were acquired by proton magnetic resonance spectroscopy (^{1}H-MRS), both in the dmPFC/dACC and the AI (**Fig. 1A-C**). Then, participants were trained out of the scanner to perform the behavioral task. During training, participants performed their maximum voluntary contraction (MVC) and maximum number of correct responses (MNCR), used to account for interindividual differences, by calibrating task difficulty both in physical and mental tasks. In addition, the perceived value of the incentive was assessed by identifying the indifference points, corresponding to a 50% chance of accepting a certain level of effort for a given monetary incentive. The behavioral task explores different aspects of motivated behavior while capturing a wide range of interindividual differences (**Fig. 1D**). On every trial, participants were asked to choose between a fixed low incentive/low effort option and a high incentive/high effort option, varying in both effort and incentive levels. After their choice selection, the selected option was displayed and continuous (for high confidence) or dotted (for low confidence) lines reflected the level of confidence. Then after their selection, participants always had to perform the selected effort. Incentives were either monetary loss or gain. Effort was either physical, implying to exert a force equal or superior to 55 % of the participant's MVC during a varying amount of time depending on the level of effort selected, or mental, implying to perform different numbers of correct responses in a 2-back task, depending on their MNCR. The complete set of explanations is reported in the Supplementary Materials.

MRS acquisition and preprocessing

Proton magnetic resonance (^{1}H-MR) spectra were collected using a 7 Tesla/68 cm MR scanner (Magnetom, Siemens Medical Solutions, Erlangen, Germany) with a single-channel quadrature transmitter and a 32-channel receive coil (Nova Medical Inc., MA, USA). To optimize the magnetic field homogeneity, shim components were adjusted using FASTMAP (Gruetter, 1993) for both first and second-order. LCModel was used for analysis (Provencher, 1993), and all spectra were corrected for phase shifts and averaged, with a basis set that included simulated metabolite spectra and an experimentally measured macromolecule baseline (Schaller et al., 2014) in the chemical shift range of 0.2 to 4.2 ppm. An unsuppressed water spectrum was acquired and used as an internal reference for absolute metabolite quantification in LCModel.

An MP2RAGE image was acquired and used to calculate the tissue composition within the MRS voxel. Furthermore, the MP2RAGE image was then segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) in SPM12 toolbox (Wellcome Trust Center for NeuroImaging, London, UK) with the MarsBaR package (https://marsbar-toolbox.github.io/) (Brett et al., 2002), creating the VOI mask. Metabolite concentrations were adjusted for the CSF fraction, assuming water concentrations of 43,300 mM in GM, 35,880 mM in the WM, and 55,556 mM in the CSF. In addition, to ensure all voxels were positioned correctly, we computed a density map of metabolites measurement, highlighting the precision of our voxel positioning, based on our MP2RAGE image and VOI mask (**Fig. S7**).

Following metabolite quantification in LCModel and correction, any computed metabolite concentrations with a Cramér-Rao lower bounds (CRLB) higher than 30 % were rejected. In addition, any participants with metabolite concentrations higher than the mean ± 3SD were removed as outliers. Then, the metabolites ratios were computed, namely glutamine to glutamate (Gln/Glu), glutamate to γ-aminobutyric acid (Glu/GABA), and creatine to phosphocreatine + creatine (Cr/(PCr+Cr)). Finally, using the Python package sklearn.*IterativeImputer*, the missing dataset values were filled by multivariate imputation.

Motivated behavior modeling

Participants' choices were fitted with a softmax model using Matlab's VBA toolbox (https://mbb-team.github.io/VBA-toolbox/) which implements Variational Bayesian analysis under the Laplace approximation (Daunizeau et al., 2014). The algorithm provides an estimate of the posterior density over the model parameters, starting from Gaussian priors.

We compared five models, each increasing in complexity (**Fig. 2S**). In our models, we modeled the complete behavior of participants in order to compare physical and mental effort types. To reduce the risk of overfitting, and improve robustness, all models' components were kept linear. By assessing how each model accounted for each participant's choice we captured seven different components of motivated behavior, namely sensitivity to reward (kR), punishment (kP), physical (kEp) and mental effort (kEm), physical fatigue (kFp) and mental facilitation (kFm), and a bias term (bias). These sensitivities were used to compare subjective values across options. We found that participants' choices were best predicted by our fifth model (Fig. 2S), composed as follows:

$$\Delta SV(t) = kR * \Delta R(t) + kP * \Delta P(t) - \Delta Ep(t) * \left(kEp + kFp * \sum_{t=0}^{T} AUC(t)\right) - \Delta Em(t) * \left(kEm + kFm * \frac{N_{correct\ answers}(t-1)}{effort\ time(t-1)}\right)$$

Where ΔSV is the subjective value of the varying option discounted by the subjective value of the fixed option. ΔR and ΔP represent the difference in the monetary incentives (reward or punishment)

between the varying option and the fixed option, ΔE represents the difference in effort level between the varying option and the fixed option, the area under the curve (AUC) represents the total force exerted in a given trial during a physical block, $N_{correct\ answers}(t-1)$ represents the number of correct answers provided in the previous trial and effort time(t-1) represents the time it took to complete the effort in the previous trial, during a mental block. When a block was specific to an effort, or a trial specific to an incentive type, its counterpart was set to 0. Finally, ΔSV is then taken as input in a *softmax* function:

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

Where $P_{High\ effort}(t)$ represents the probability of choosing the high effort/high incentive option for a given ΔSV at trial t. Apart from the bias parameter (*bias*), all parameters were positively constrained through a log(1+exp(x)) transformation. Priors were uninformative and practically flat with a null mean, and a sigma set to 100, accounting for high fluctuations in ΔI between participants, due to IP calibration and forced positivity. Finally, apart from the bias, parameters were boxcox transformed to reduce skewness and increase normality (Bicego & Baldo, 2016).

Feature selection and extreme gradient boosting trees (XGBoost).

Feature selection plays a crucial role in developing predictive models, as it simplifies the model by removing redundant features and mitigates overfitting, particularly for small sample sizes with limited generalization ability. To avoid bias in test predictions, feature selection was conducted on the training dataset for both models. Features with a Pearson correlation coefficient smaller than 0.1 with the target variable were removed. As a second round of feature selection, the training set was further divided into train and validation sets. Sklearn *AdaBoostRegressor* package was used to train models using cross-validation leave-one-out (CVLOO) and predicted target variables. The selected features were those that yielded the smallest validation error. The resulting metabolites were given to train both machine learning algorithms.

We employed *XGBoost* to predict the number of high-effort options performed by participants (models 1 and 3) and the mental effort perception, extracted with the behavioral model (model 2) using a selected set of metabolite concentrations. We used the *XGBRegressor* function from the Python *XGBoost* package to fit both models. XGBoost includes several adjustable hyperparameters. We optimized the step size shrinkage (eta), maximum depth of the tree (max_depth), minimum sum of instance weight (min_child_weight), and regularization parameters (gamma, lambda, alpha)

through Bayesian optimization with the *hyperopt* Python package (Bergstra et al., 2013). We assessed our model's prediction performance by correlating the predicted and true values of the target variables in a holdout sample that was not utilized in the model learning process. The train and test datasets were loaded into data frames using the *pandas* Python package and evaluated using model assessment metrics computed with the *numpy* Python package. Additionally, we computed the SHAP values using the *shap* Python package (Lundberg et al., 2019).

Figures

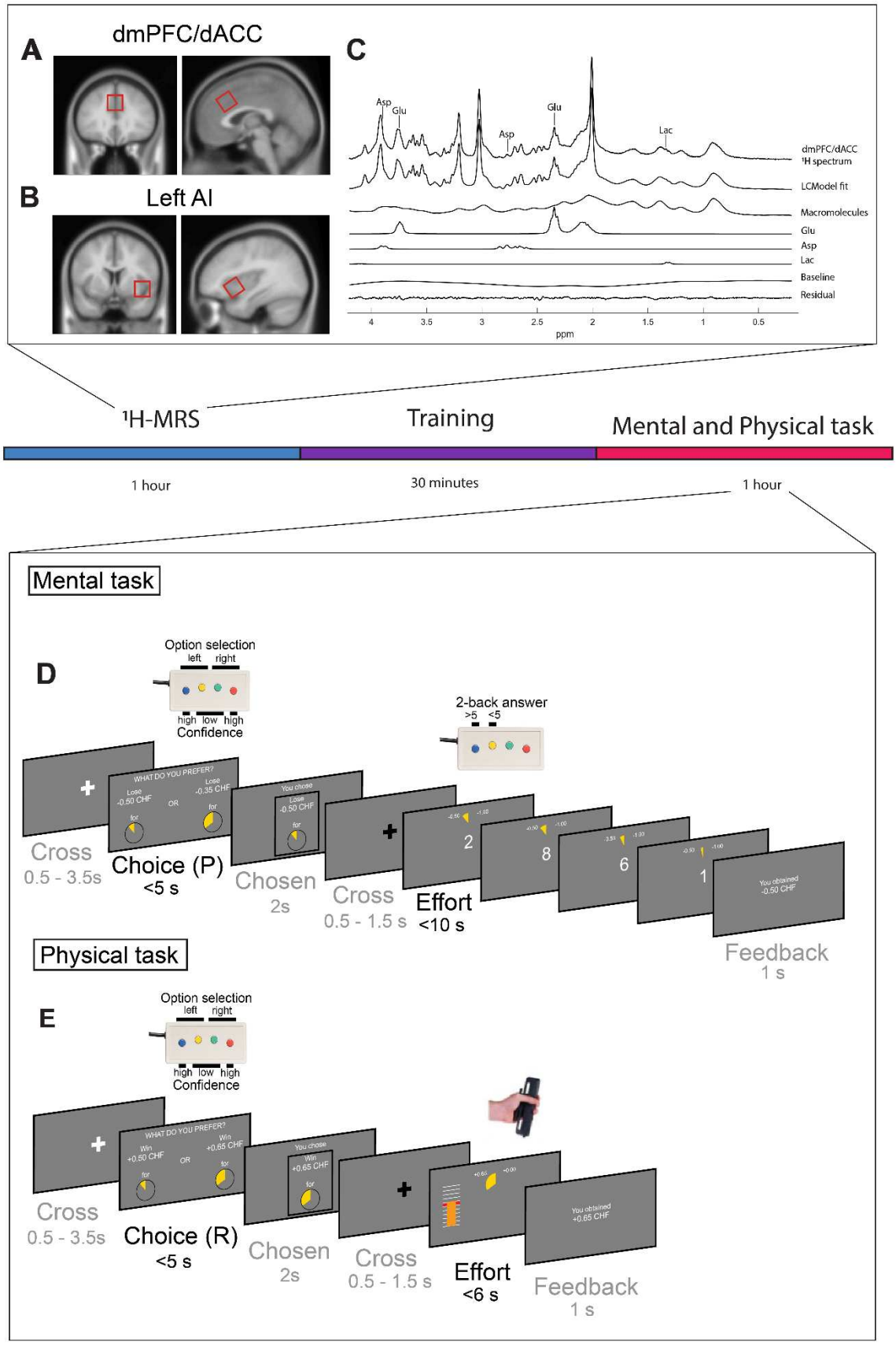

Fig. 1 Experimental design. **A-B** dmPFC/dACC and AI voxel positioning (20x20x20mm^3) in the coronal and sagittal cut. The voxel in this image is positioned on the average anatomical scan of the participants included in the study (N=69). **C** Representative ^{1}H MR spectrum acquired with the semi-adiabatic SPECIAL sequence at 7 Tesla, as well as the corresponding LGCModel spectral fit, macromolecules, baseline, residual fit, and individual fit for glutamate (Glu), aspartate (Asp) and lactate (Lac). **D-E** behavioral task design. After a fixation cross with a jitter, participants had up to 5 seconds to choose which option they wanted to select. One option was fixed and the other varied the incentive and the effort level. Incentives were either expressed as rewards, or as punishments. Reward and punishment trials were intermixed, while physical and mental effort trials were performed in separate blocks. During the choice period, each option was associated with a reward or a punishment and a different level of effort. The selected option was displayed through short feedback (2s). Then a fixation cross with a jitter allowed to disentangle the decision-making process from the effort period, while allowing the participant to prepare for the effort to perform. During the mental effort period (**D**), participants had to perform a certain number of correct answers depending on their calibration and on the selected effort option, within 10s. At the end of each trial, feedback on the performance was displayed. During the physical effort period (**E**), participants needed to maintain their force higher than the threshold, based on their calibration and the selected effort option, within 5s.

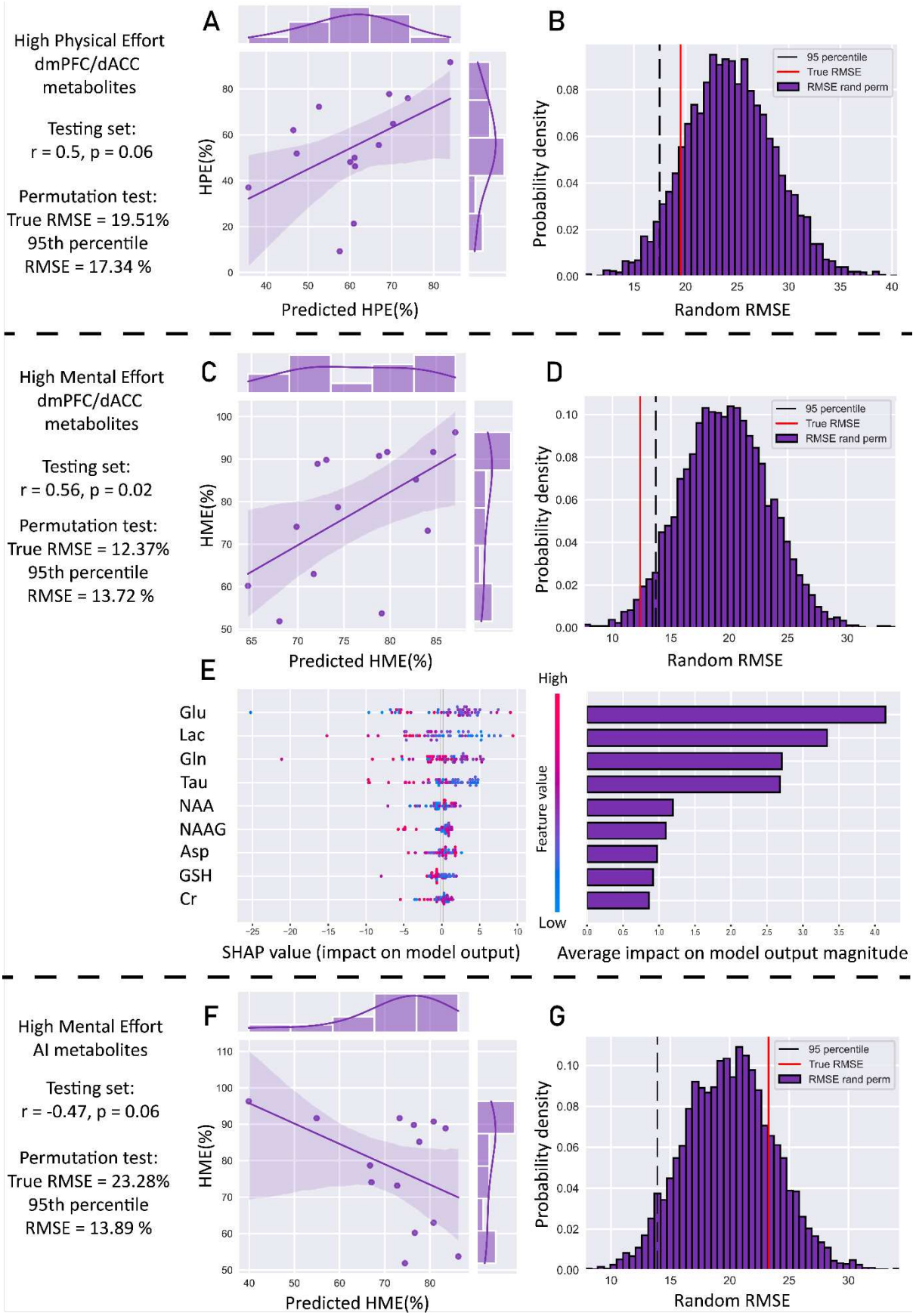

Fig. 2 Model prediction of the percentage of high-effort choices, based on metabolites concentration in the dmPFC/dACC and AI. A Trained on dmPFC/dACC metabolites, correlation between the XGBoost model's prediction of HPE and the true

percentage of HPE for the test set (r = 0.5, p = 0.06), using the following features: lactate (Lac), Glycine (Gly), Phosphocreatine/total creatine (PCr/(Pcr+Cr)), γ-aminobutyric acid (GABA), Glutamate/GABA. **B** Permutation test by permuting labels randomly and repeating the procedure, using the 95th percentile as a (threshold 95th percentile = 17.34% < model RMSE = 19.51%). **C** Trained on dmPFC/dACC metabolites, correlation between the XGBoost model's prediction of HME and the true percentage of HME for the test set (r = 0.56, p = 0.02). **D** Permutation test by permuting labels randomly and repeating the procedure, using the 95th percentile as a threshold (threshold 95th percentile = 13.72% > model RMSE = 12.37%). **E** SHAP values and importance for the trained model were calculated for each subject. After feature automatized feature selection, nine features remained: glutamate (Glu), lactate (Lac), glutamine (Gln), taurine (Tau), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), aspartate (Asp), glutathione (GSH), creatine (Cr). **F** Trained on AI metabolites, correlation between the XGBoost model's prediction of HME and the true percentage of HME for the test set (r = -0.47, p = 0.06). **G** Permutation test by permuting labels randomly and repeating the procedure, using the 95th percentile as a threshold (threshold 95th percentile = 13.89% < model RMSE = 23.28%). The model resulted in critical failure in prediction, due to its inverse prediction in the test set.

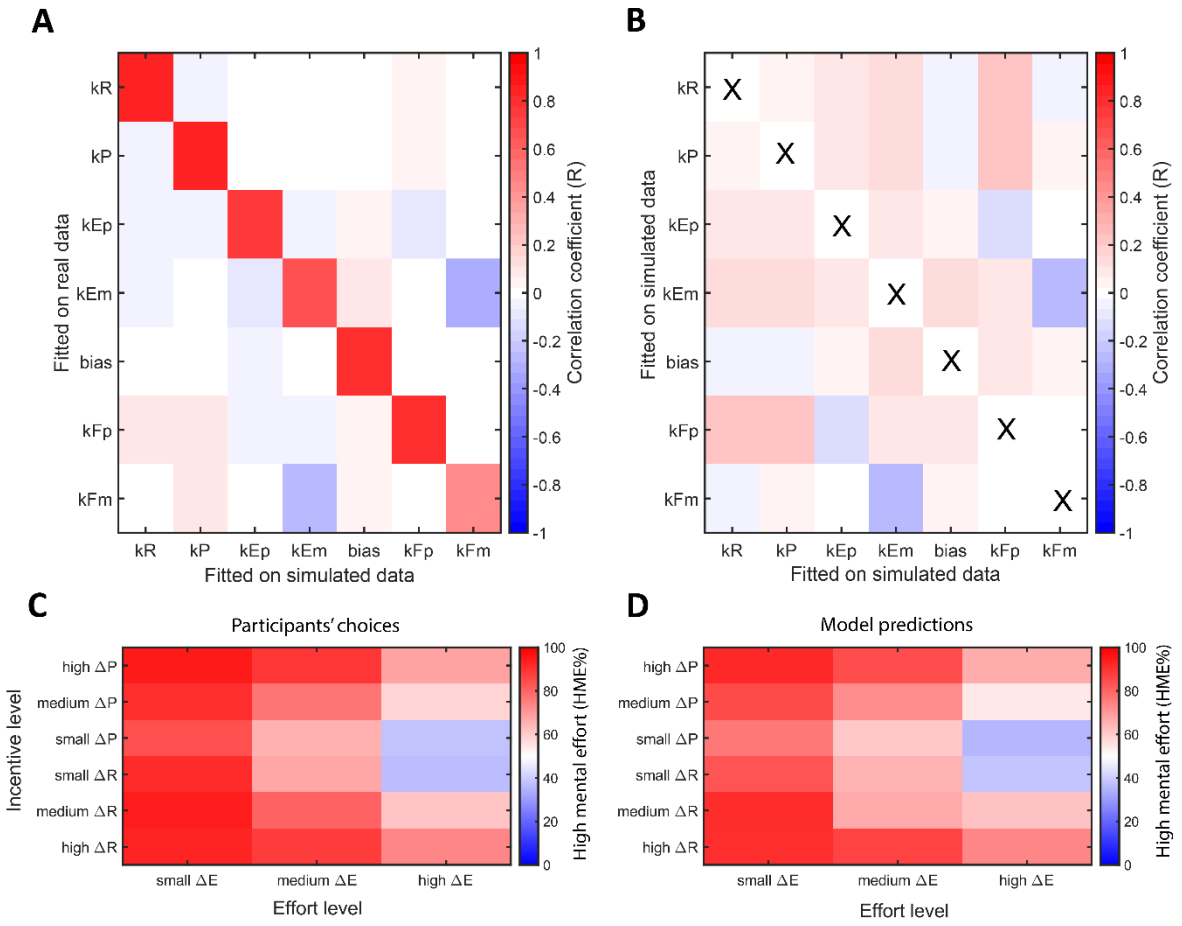

Fig. 3 Characterizing model recovery, parameters independence, as well as motivated behavior across mental effort. A Confusion matrix to test model recovery. We get our parameters recovery by choosing random parameters, using them to simulate data, and then fitting the model on the simulated data, which are then compared to the original parameters used. Our model shows high recovery in all parameters and moderate recoverability for kFm. **B** Autocorrelation matrix to investigate parameters' identifiability based on 30'000 simulations. The highest correlation can be found between kEm and

kFm (r = -0.21). **C** Percentage of high effort taken per participant in function of the amount of mental effort and incentive presented. **D** Model's predictions on the amount of HME in function of the amount of incentive and effort involved.

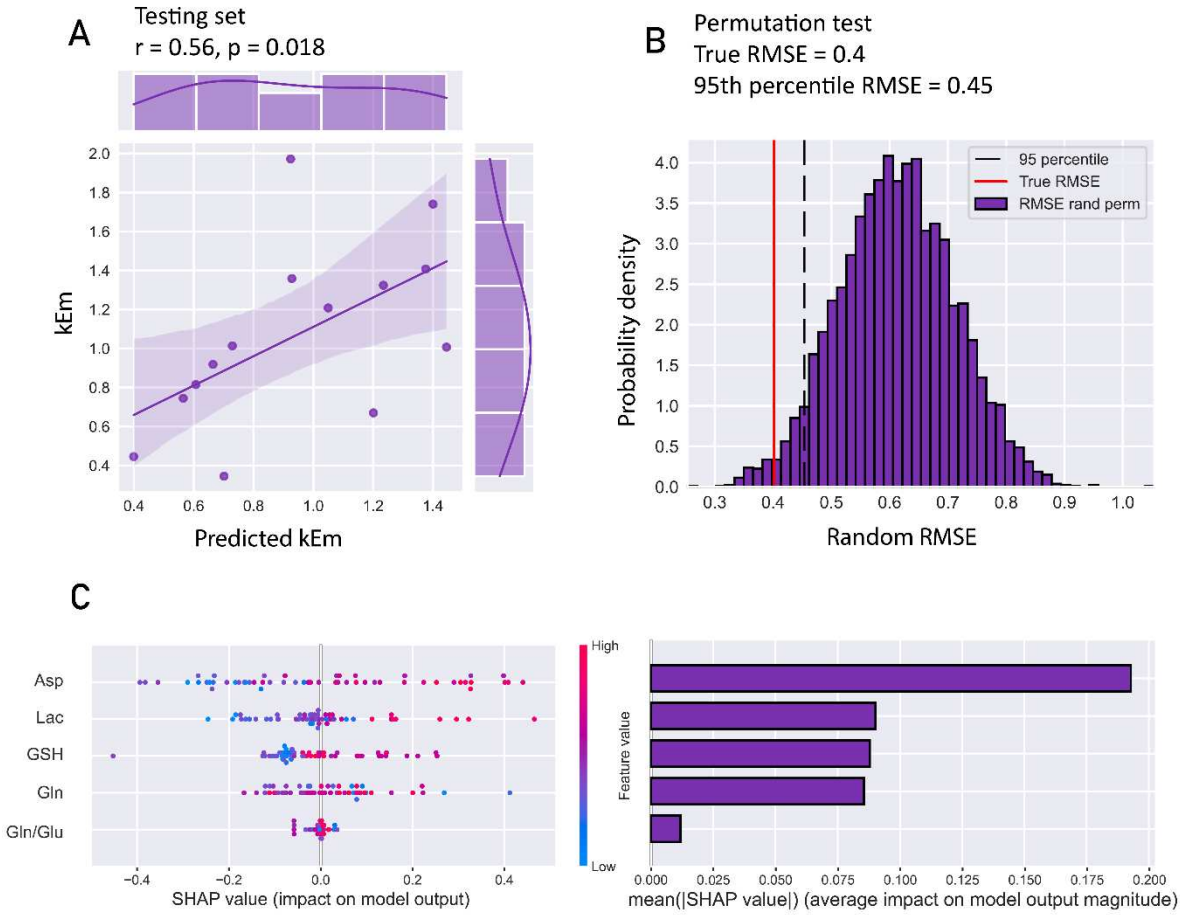

Fig. 2 Model prediction of sensitivity to mental effort from metabolites concentration in the dmPFC/dACC. A Correlation between the XGBoost model's prediction and sensitivity to mental effort for the test set (r = 0.56, p = 0.018). **B** Permutation test by permuting labels randomly and repeating the procedure, using the 95th percentile as a threshold (threshold 95th percentile = 0.45 > model RMSE = 0.4). **C** SHAP values for the trained model were calculated for each subject. After automatized feature selection, five remained: aspartate (Asp), lactate (Lac), glutathione (GSH), glutamine (Gln), and Gln/Glu ratio.

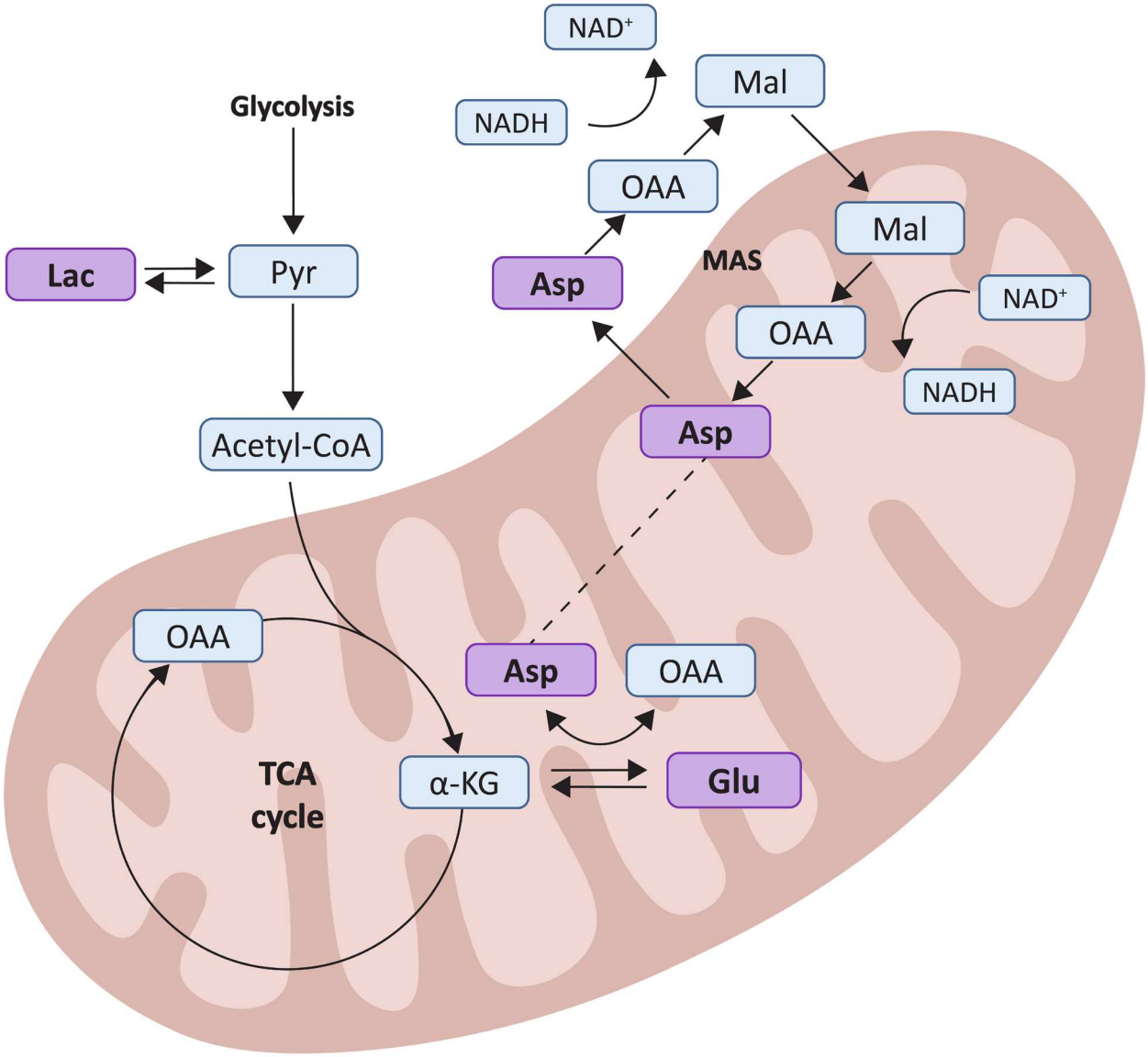

Fig. 5 Simplified schematic of the tricarboxylic acid (TCA) cycle and malatate-aspartate shuttle (MAS) in mitochondria and its relationship of aspartate, glutamate and lactate. Alpha-ketoglutarate (α-KG), malate (Mal), aspartate (Asp), pyruvate (Pyr) lactate (Lac), oxaloacetate (OAA), glutamate (Glu), acetyl-coenzyme A (acetyl-CoA), nicotinamide adenine dinucleotide (NAD^+/NADH). In bold and purple are highlighted our metabolites of interest.

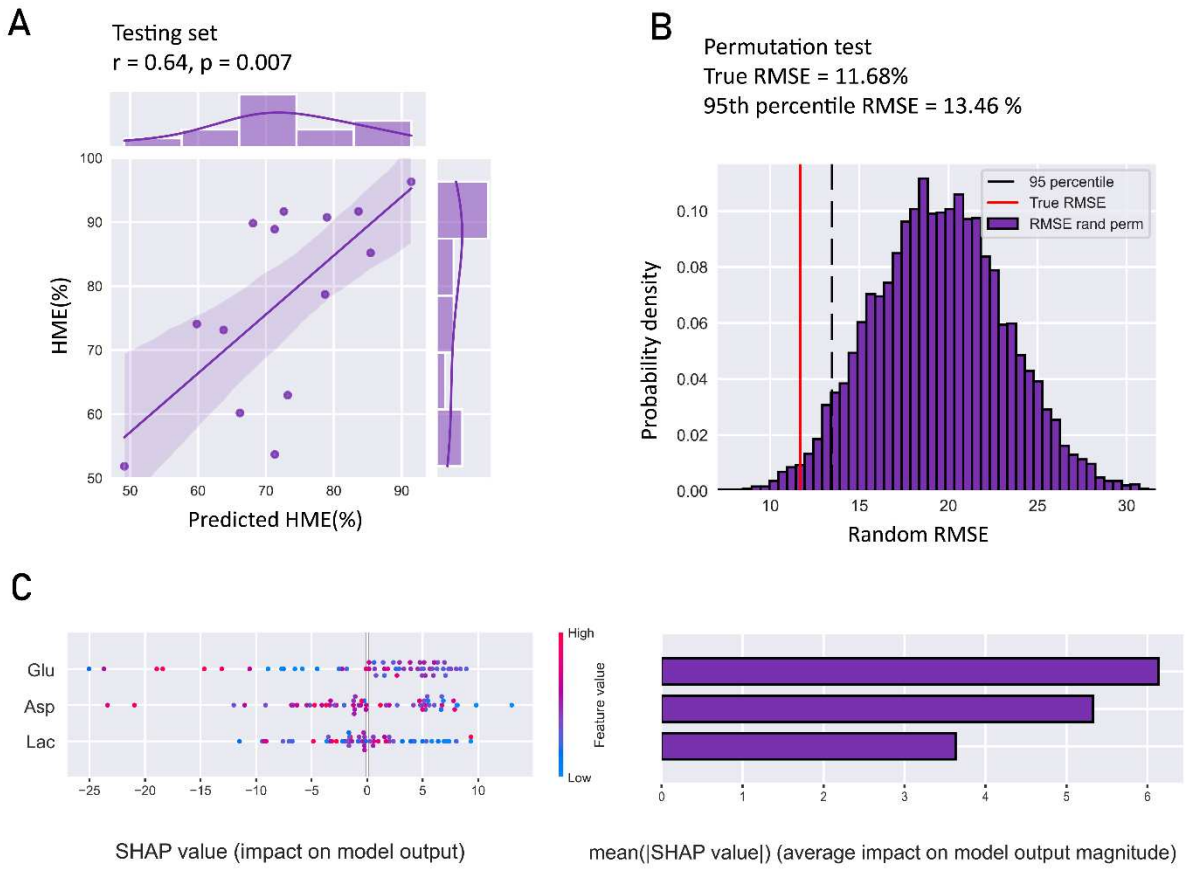

Fig. 6 Model prediction of the percentage of high-effort choices during the mental task, based on metabolites concentration in the dmPFC/dACC, using only glutamate, aspartate, and lactate metabolites. A Correlation between the XGBoost model's prediction and the percentage of times high mental effort (HME) was chosen) for the test set (r = 0.64, p = 0.007). **B** Permutation test by permuting labels randomly and repeating the procedure, using the 95th percentile as a threshold (threshold 95th percentile = 13.46% > model RMSE = 11.68%). **C** SHAP values for the trained model were calculated for each subject.

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Conflict of interest

The authors declare no conflicts of interest.

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