Metabolism and the mind: Investigating the link between glucose control and reinforcement learning in humans

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Running title: *Glucose control and reinforcement learning*

Keywords: interoception; glucose tolerance; reward learning; computational psychiatry; metabolic psychiatry; depression

Word count: 3825

Abstract

Background: Signals from the body profoundly influence cognition. This process is known as interoception, and has been extensively studied in the cardiac, respiratory, and gastric domains; in contrast, metabolic influences remain poorly understood. Here, we focus on the link between glucose control and cognition, motivated by the observation that there is substantial, unexplained comorbidity between type-2 diabetes and depression. In rodents, insulin modulates dopamine signalling in the ventral striatum. We therefore hypothesised that, in humans, differences in glucose control would be associated with altered reward learning.

Methods: To test this hypothesis, we recruited 48 participants from the general population, who each completed a glucose tolerance test, a monetary reward learning task known to relate to dopamine function, and mental health questionnaires. We fitted an established reinforcement learning model to the task data in order to obtain computational parameters characterising participants' learning, and then examined the associations between these parameters and their glucose control.

Results: We discovered that poorer glucose control was associated with greater reliance on recent rewards during learning which was, in turn, associated with higher depression symptoms. There was also more modest evidence for the association between glucose control and depression symptoms.

Conclusions: Together, our results identify a specific neurocognitive process, reward learning, by which metabolic information may influence cognition, and which may explain the link between metabolic diseases like type-2 diabetes and depression.

Introduction

Neuroscientists have studied the ways in which physiological signals are processed by the brain since Sherrington (1), who first coined the term 'interoception'. Since then, the field has grown substantially, and researchers have identified a range of bodily signals—including heart rate, breathing and core temperature—that influence cognition and emotion (2,3). Individual differences in interoception have also been linked to several common mental health conditions, including anxiety, depression and psychosis (4). Understanding how bodily signals shape cognition is therefore critical not only for elucidating normal brain function, but also for uncovering the mechanisms underlying psychiatric illness.

One domain of bodily signals which remains somewhat overlooked, however, is that of metabolic information. The brain plays a central role in energy regulation: it must monitor energy availability and, weighing the benefits of pursuing potentially rewarding activities against their anticipated energetic costs (5; 6), adjust behaviour and cognition accordingly. But how does the brain achieve this, and how does this metabolic interoception shape decision-making? Existing human studies on metabolism and cognition have largely focussed on eating behaviour and food rewards (e.g. 7, 8, 9). However, the high comorbidity between metabolic disorders and depression (10, 11) indicates that metabolic signals may influence decision-making more broadly. In particular, it has been suggested that the neural systems regulating energy balance overlap with those which control reward learning and motivation (12, 13, 14). In the current study, we set out to test whether metabolic signals have domain-general effects on cognition – i.e. whether they shape decisions even in tasks unrelated to food or eating.

Evidence from rodent experiments strongly supports this possibility. Insulin, a key metabolic hormone, readily crosses the blood-brain barrier (15), and insulin receptors are densely expressed on dopaminergic neurons in the ventral striatum, a region critical for reward learning and motivation (16). Blocking insulin signalling in this area disrupts flavour and place preference learning (17), while brain-wide insulin receptor knock-out induces depression-like behaviour on the tail-suspension and forced-swim tests (18). These studies

illustrate what happens when brain insulin signalling is impaired, which is an important aspect of human type-2 diabetes. While this condition is primarily characterised by reduced peripheral insulin sensitivity, which affects blood glucose regulation, this develops in tandem with reduced neuronal insulin sensitivity (19). Together, these results suggest that insulin signalling might be an important link between metabolic and cognitive function, influencing variation in blood glucose control, reward learning and affective symptoms.

Disrupted reward learning is a well-established feature of several mental health disorders. In humans, this is often studied within the framework of computational psychiatry, which has shown that impairments in reward processing are associated with depression symptoms, particularly anhedonia (20, 21, 22). The precise computational mechanisms are debated, with some studies implicating altered reward learning rates (23, 24, 25, 26), while others emphasise reduced reward sensitivity (27, 28, 29). Given the heterogeneity of depression, it is likely that multiple pathways—each with distinct computational signatures—contribute to these effects (30). To characterise these mechanisms, we used an established paradigm, the Probabilistic Selection Task, and fitted well-validated reinforcement learning models (31, 32, 33).

To assess glucose control, we used an oral glucose tolerance test (OGTT), in which participants consume a concentrated glucose solution and their glucose level is monitored as it rises and returns to baseline. A higher and more prolonged glucose spike reflects poorer glucose control, which is a marker for peripheral insulin resistance and elevated risk of type-2 diabetes (34). To enhance the OGTT we used a continuous glucose monitor (CGM) – a relatively new technology that provides glucose estimates every two minutes, in contrast to the 15-minute resolution of traditional finger-prick testing (35).

The primary aim of this study was to investigate the relationship between glucose control and reward learning. Specifically, we hypothesised that participants with poorer glucose tolerance—as indexed by incremental area under the curve (iAUC)—would show lower test-phase accuracy and altered learning parameters in computational models. Evidence for this relationship would suggest that metabolic signals shape decision-making in a domain-

general way, with potential implications for understanding comorbidity between metabolic and psychiatric disorders.

Methods and materials

Preregistration

This study was preregistered on the Open Science Foundation (https://doi.org/10.17605/OSF.IO/UQ58Z); there were no deviations from this protocol. The task code, raw data and analysis scripts are stored at https://osf.io/b9z5v/.

Procedure

Participants attended the lab in the morning following an overnight fast (i.e. 7–14 hours without food or drinks except water, and no exercise or nicotine). A continuous glucose monitor was attached to the back of the left arm and allowed to calibrate for one hour. We then began the oral glucose tolerance test: participants consumed 50g of glucose dissolved in 250ml of water, and their blood glucose was monitored over the next two hours. In this time, participants completed a reward learning task on the computer, followed by several mental health questionnaires. Any remaining time could be spent sitting quietly (e.g. reading, or working on a laptop). The study concluded at the end of the two-hour monitoring window.

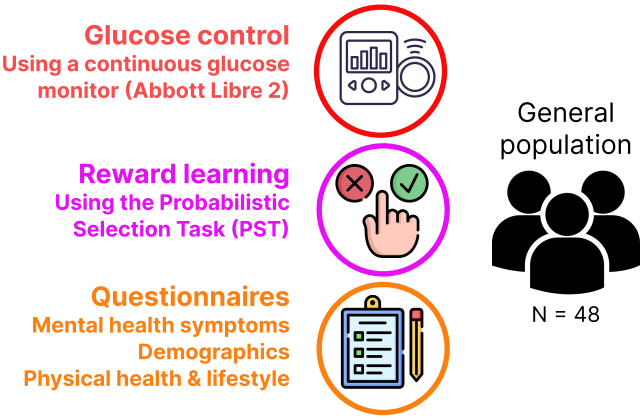


Figure 1. The study design. We first administered an oral glucose tolerance test, quantifying participants' ability to regulate their blood sugar levels. Next they completed a reward learning task (to which we were subsequently able to fit a computational model and extract

parameters representing their learning rates and decision-noise). Finally, participants completed a set of mental and physical health questionnaires.

Participants

We recruited 56 participants from the general population around Cambridge. Eligible participants were aged 18-60, fluent in English and not taking medications known to affect glucose regulation (e.g. insulin, steroids). We did not otherwise exclude individuals with mental or physical health conditions.

Following preregistered exclusion criteria or technical issues, 8 participants were excluded: 4 failed attention checks during the questionnaires and 4 were because of connectivity issues with the CGMs. This left 48 participants in the final sample, exceeding our preregistered minimum of 46 (calculated to detect an effect size of $r = 0.4$ with 80% power at alpha = 0.05). Given the absence of prior studies linking glucose iAUC to cognitive performance, this moderate effect size (36) was chosen as a pragmatic benchmark, balancing statistical sensitivity with practical feasibility. It is consistent with individual differences research using a comparable probabilistic reward learning paradigm, where associations between reward learning and continuous traits (e.g., depression symptoms) typically fall in the range of r = 0.3–0.5 (e.g. 24, 26). The study was approved by the Cambridge Psychology Research Ethics Committee (PRE.2022.078), and all participants provided written informed consent. Summary characteristics are shown in Table 1, with further detail in Supplementary Table S1.

Table 1. Demographic characteristics of the sample

Sample size	48
Age: mean (SD, range)	41.2 years (14.6, 18-60)
Sex	
- Male	12
- Female	36
BMI: by group	
- < 18.5	2
- 18.5 - 25	26
- 25 - 30	8
- > 30	12
BMI: mean (SD, range)	25.6 kg/m^2 (5.69, 17.6-39.3)

Measures

Oral Glucose Tolerance Test (OGTT)

We followed the method described by (37) for using CGMs in the OGTT. A Freestyle Libre 2 sensor (Abbott Laboratories) was applied to the back of the participant's left arm and allowed to calibrate for one hour. Participants then consumed 50g of glucose dissolved in 250ml of water (within 2 minutes). Glucose levels were tracked for two hours post-ingestion.

The main outcome of interest was the incremental area under the curve (iAUC), which comprises the area below the curve but above the fasting concentration of glucose. This metric, commonly employed in human research (37, 38), was preferred over total or net AUC as it accounts for individual differences in fasting glucose.

We computed iAUC using the trapezoid rule: for each pair of glucose readings, y_1, y_2, at timepoints t_1, t_2, $area = \frac{(y_1+y_2)}{2} \times (t_2 - t_1)$. If either reading was below baseline, we used linear interpolation to calculate only the positive area; if both were below baseline, the interval was excluded. Finally, the incremental areas were summed to give the overall iAUC – a higher iAUC indicates poorer glucose control.

We also report some validation analyses using fasting glucose, which was the initial CGM reading taken prior to participants consuming the glucose drink (i.e. after the overnight fast).

CGMs have been validated for people without diabetes (39, 40), and recent studies report good agreement between CGMs and venous sampling iAUCs (r = 0.73; 41), with mean bias < 5% (42), supporting their use in cognitive neuroscience studies.

Reward Learning Task

To assess reward learning, we used the Probabilistic Selection Task (PST; 32, 33), incorporating the affect ratings from (31). A schematic of the task is provided in Figure S1. Participants chose between pairs of Japanese Hiragana symbols, each associated with a different reward probability (20%, 30%, 40%, 60%, 70%, or 80%). Symbol-outcome mappings were randomised.

After instructions (including a mandatory comprehension check), participants completed a training phase comprising six blocks of sixty trials. Symbols were presented in fixed pairs (80%–20%, 70%–30%, 60%–40%). Feedback followed each choice: “Correct! You won 25 points”, “Incorrect”, or “No response detected”. Participants also rated their momentary happiness, confidence or engagement on that trial using a sliding scale. At the end of each block, they also rated their fatigue.

In the test phase (60 trials), all symbol pairings were shown twice. No feedback was given, and participants were instructed to choose the symbol that “felt most correct” on each trial.

Mental and Physical Health Questionnaires

We administered seven self-report symptom scales assessing depression (PHQ9; 43), anxiety (BAI and GAD-7; 44, 45), anhedonia (SHAPS; 46), apathy (AES; 47), impulsiveness (I-8; 48) and physical activity (GPPAQ; 49). The BAI contained an 'easy' attention check ("Press 'not at all'"), while the I-8 and AES each included a 'hard' check (do they "work forty hours a day" and have they "used a computer"). Participants were excluded if they failed the easy check, or both hard checks. We also asked additional questions about lifestyle and physiological variables, including smoking status, sleep quality and (for female participants) menstrual phase. At the end of the questionnaires, participants confirmed whether they had done the overnight fast (with reassurance that their payment would be unaffected). All participants responded 'yes'.

Preregistered analyses

Our preregistered primary hypothesis was that participants' glucose control would be associated with reward learning. We tested this both model-agnostically (by correlating glucose iAUC with accuracy on the PST) and using computational modelling. For the latter, we fitted a well-established hierarchical reinforcement learning model (33) using Hamiltonian MCMC in *Stan* (50).

On each trial, the probability of choosing symbol i over j was modelled as a logistic function of the difference in their expected values (Q-values), scaled by the participant's outcome sensitivity (β).

$$p_{choose_i} = logistic\left(\beta \times \left(Q_i - Q_j\right)\right)$$

Following each choice, the Q-value of the chosen option was updated via a Rescorla-Wagner rule:

$$Q(t+1) = Q(t) + \alpha\left(R(t) - Q(t)\right)$$

We tested two model variants: one with a single learning rate (α),and one with separate learning rates for positive and negative prediction errors (reward and loss learning rates). In previous studies, the reward learning rate parameter been linked to dopamine function (32,

33).

Note we did not include separate reward and punishment sensitivities, as had been anticipated in our preregistration, as this led to model non-identifiability due to trade-off with the corresponding learning rates.

Both models fitted well (no divergences, split-Rhat < 1.1, E-BFMI > 0.3, maximum treedepth < 10; 51), and posterior predictions visually matched the empirical data. Parameter recovery analyses indicated very good correlations between observed and recovered parameters (r = 0.94, 0.95 and 0.90 for reward learning rate, loss learning rate and outcome sensitivity parameters respectively), validating our use of these models in our analysis here (see Figure S3).

Approximate leave-one-out cross-validation strongly favoured the two learning-rate model, which we used in all subsequent analyses (details of fitting, priors and model comparison are in the Supplement). We extracted individual estimates of reward learning rates and correlated these with glucose iAUC. As MCMC yields posterior distributions rather than point estimates, we computed correlations across all (4000) posterior draws, giving posterior distributions for each correlation. We report both the posterior mean and the 90% highest density interval (HDI) – a commonly used interval in Bayesian analysis that balances sensitivity and interpretability (52). Correlation strength is interpreted using standard thresholds: ~ 0.1 (small), ~ 0.3 (moderate) and ~ 0.5 (large) (36).

Other exploratory analyses (associations between glucose iAUC and questionnaire measures) were conducted using Bayesian regressions implemented in *rstanarm* (53).

CGM validation dataset and analyses

Although CGMs are well-validated for tracking within-subject fluctuations, their use for measuring between-subject differences is newer. To assess its validity, we ran confirmatory regressions testing whether fasting glucose and iAUC were associated with age and adiposity. To increase power, we combined data from this study (N=48) with data from a later study using the same OGTT protocol (N=52; https://osf.io/rcusg/), yielding a combined validation sample of N=100.

Results

Validation analyses

As CGMs are a relatively new method in cognitive neuroscience, we first validated their use by examining associations between key glucose metrics (iAUC and fasting glucose) and established predictors of glucose tolerance (age and adiposity). We replicated these analyses in larger, combined dataset that included CGM data from a subsequent study (see Methods for details). The results, plotted in Figure 2, showed that iAUC was positively associated with age in both our primary dataset (mean-β = 0.03, 90% HDI: 0.007, 0.06) and in the combined dataset (mean-β = 0.02, 90% HDI: 0.006, 0.04). Fasting glucose was also associated with age in the combined dataset (mean-β = 0.01, 90% HDI: 0.001, 0.02), though this effect was not significant in the smaller sample (mean-β = 0.01, 90% HDI: –0.005, 0.03).

iAUC showed no consistent association with adiposity (measured as the effect of weight after controlling for height: mean-β = 0.01, 90% HDI: 0.01, 0.04; mean-β = –0.002, 90% HDI: –0.02, 0.01), but fasting glucose concentration was associated with adiposity in both datasets (mean-β = 0.02, 90% HDI: 0.005, 0.03; mean-β = 0.02, 90% HDI: 0.01, 0.03).

Taken together, these results suggest that our preregistered primary outcome, glucose iAUC, may not fully capture glucose tolerance. Fasting glucose showed more consistent associations with known metabolic risk factors and may offer a more stable indicator. While iAUC remains valuable as a measure of glucose dynamics, it may benefit from being complemented by more stable measures such as fasting glucose. We therefore include fasting glucose as a sensitivity analysis in our subsequent results, where it successfully replicates our key findings.

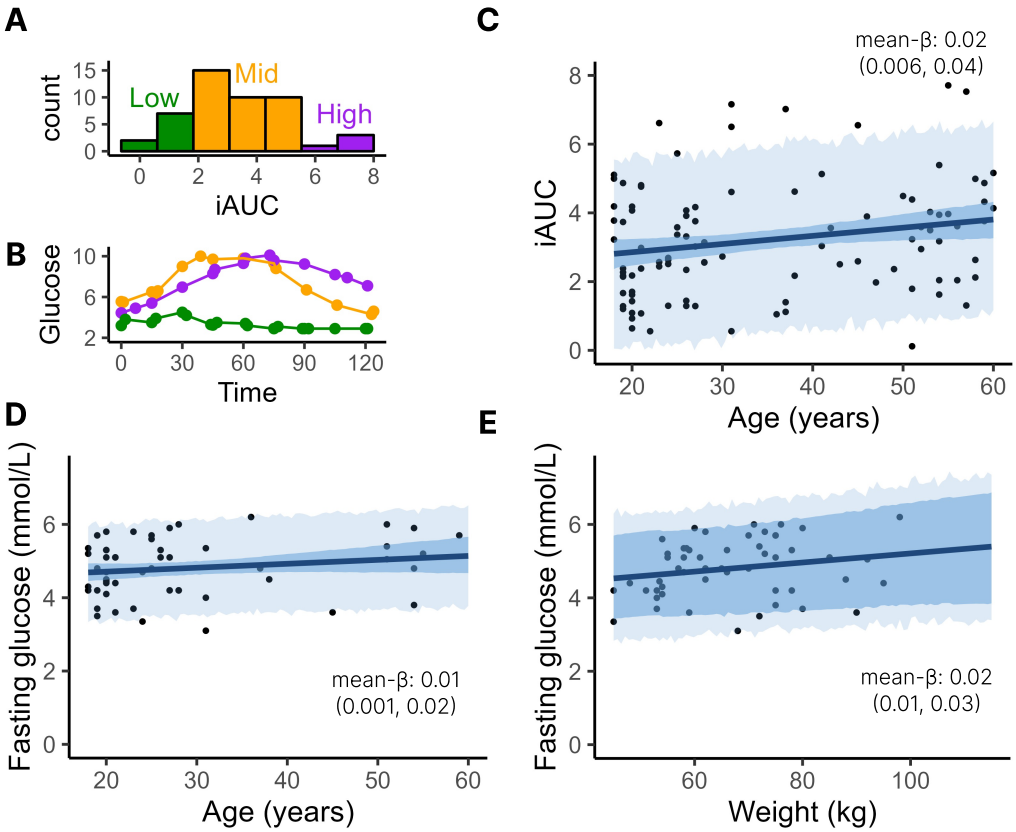


Figure 2. CGM parameters and their associations with known metabolic risk factors. A) Histogram of glucose iAUC values. B) Glucose dynamics for three example participants with low, medium and high iAUCs. C–E) Results of the validation analyses. All plotted relationships show regression terms whose 90% highest density interval (HDI) did not cross zero, indicating credible effects. C) Shows the relationship between age and glucose iAUC, D) between age and fasting glucose, and E) between adiposity (weight adjusted for height) and fasting glucose. Plots show the posterior mean regression line (solid), the 90% HDI for the regression line (dark shading), and the 90% HDI for predicted observations (light shading). Empirical data are plotted in black for reference.

Primary analysis: Glucose control correlates with reward learning

As preregistered, we tested the hypothesis that glucose control is associated with reward learning. Using a validated reinforcement learning model (31), we estimated each participant's reward learning rate and correlated it with their glucose iAUC. This correlation was significant (posterior mean-r = 0.32, 90% HDI: 0.23, 0.40), indicating that participants with poorer glucose control tended to update their behaviour more rapidly following

rewards (Figure 3). The full posterior distribution was above zero, providing strong evidence for a positive correlation.

A similar association was found for the loss learning rate (mean-*r* = 0.23, 90% HDI: 0.16, 0.31), whereas outcome sensitivity was not reliably linked to iAUC (66% HDI overlapped zero).

Given the limitations of iAUC as a standalone measure (see above), we repeated these analyses using fasting glucose. The results were virtually identical: both reward and loss learning rates were positively correlated with fasting glucose (mean-*r* = 0.31, 90% HDI: 0.22, 0.40; and mean-*r* = 0.31, 90% HDI: 0.21, 0.41, respectively).

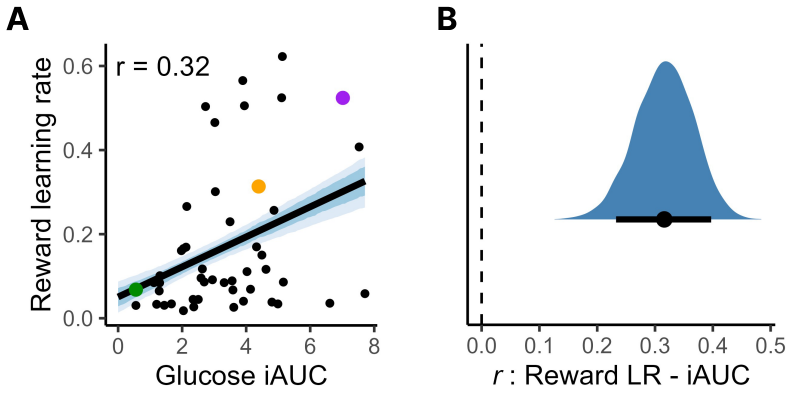


Figure 3. Graphs of the correlation between glucose iAUC and reward learning rate. Participants with higher iAUC (indicating worse glucose tolerance) tended to have higher reward learning rates. Panel A) plots the relationship as a regression (black line, with the 66% and 90% HDIs in blue shading). The example participants with low/medium/high iAUC, identified in Figure 1, are highlighted here in green, orange and purple respectively. Panel B) shows the full posterior distribution of the correlation in blue, with the mean and 90% HDI plotted in black beneath.

We found no evidence that glucose iAUC predicted overall task accuracy (in either training or test phases; 66% HDIs overlapped zero), suggesting that glucose control relates not to overall performance, but to how participants update their choices. To explore this, we tested for a relationship between glucose iAUC and win-stay behaviour. We observed

modest evidence for such a link (mean-r = 0.14, 90% HDI: –0.10, 0.38); although the interval overlapped zero, the posterior probability that the correlation was positive was nevertheless 85%, which is still partially supports an effect.

Exploratory analyses

We also explored the associations between model parameters, glucose control, and mental health symptoms. Reward learning rate showed small positive associations with several symptom measures: depression (PHQ9 score: mean-*r* = 0.18, 90% HDI: 0.03, 0.33; Figures 4a, 4b), anhedonia (SHAPS score; mean-*r* = 0.19, 90% HDI: 0.05, 0.33) and apathy (AES score; mean-*r* = 0.19, 90% HDI: 0.06, 0.32).

Glucose control showed a weaker and less conclusive link to depression symptoms (r = 0.18, 90% HDI: –0.06, 0.42; Figures 4c, 4d), but the posterior probability of a positive correlation was still relatively high (89%), consistent with a possible association (52). No reliable associations were found between glucose control and other mental health measures (66% HDIs for anxiety, anhedonia, apathy and impulsiveness all overlapped zero).

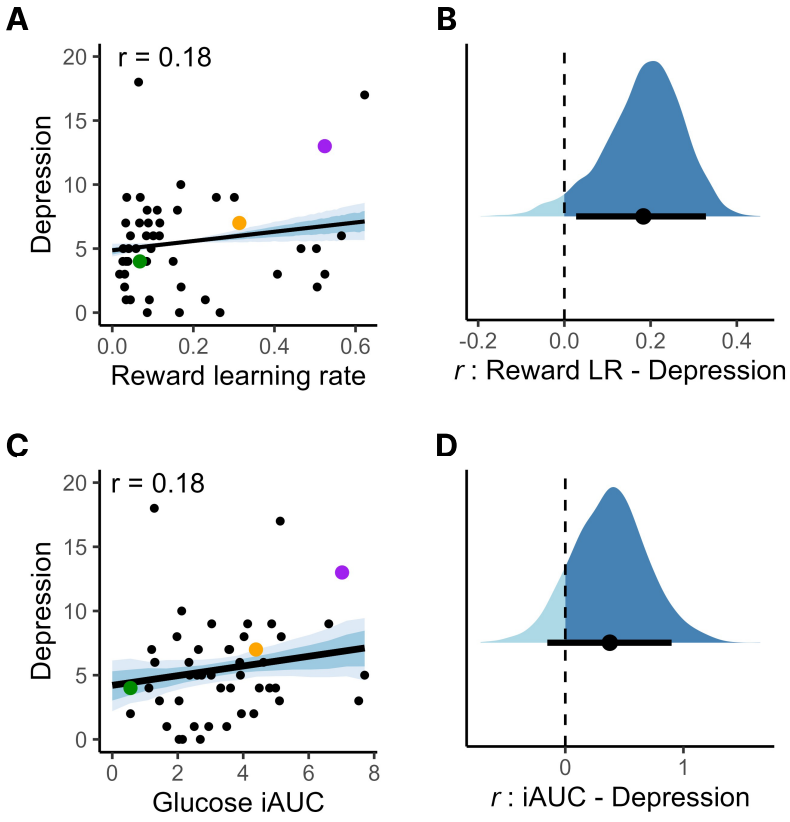


Figure 4. Correlations of depression symptoms with reward learning rate and glucose iAUC. A & B) Higher reward learning rate was associated with worse depression symptoms (PHQ9 score). C & D) There was also a weaker, though generally positive, relationship between depression symptoms and glucose iAUC (note that the 90% HDI for this effect crossed zero – see discussion in main text). Plots A & C) plot these relationships as regressions (black line, with the 66% and 90% HDIs in blue shading). The example participants with low/medium/high iAUC, identified in Figure 1, are highlighted here in green, orange and purple respectively. Plots B & D) display the full posterior distributions in blue, with the means and 90% HDIs plotted in black beneath.

Changes in affect ratings

Participants' subjective affect ratings declined slightly over the course of the training phase. Using Bayesian mixed-effects regression, we estimated that happiness ratings started at 57.6% on the first trial, and subsequently declined by 0.08 percentage points per trial (90% HDI: 0.04, 0.12); confidence ratings started at 37.8% and declined by 0.11

percentage points per trial (90% HDI: 0.06, 0.16); and engagement ratings started at 65.9% and declined by 0.21 percentage points per trial (90% HDI: 0.14, 0.27).

We also examined whether these declines were modulated by glucose control or learning rate. Higher reward learning rates were associated with a slower decline in engagement over time (interaction β = 0.42, 90% HDI: 0.05, 0.80). No other significant effects were found.

Discussion

In a general population sample (N=48), poorer glucose control was associated with greater reliance on recent rewards during decision-making, which in turn predicted higher depression scores. While the findings are correlational and do not establish causality, they do point to a specific neurocognitive profile linked with metabolic ill-health: individuals with higher learning rates tended to have worse glucose control.

Compared to other interoceptive domains, much less is known about how metabolic information shapes cognition. Most prior research has focussed primarily on insulin's role in eating behaviour (e.g., 54). Here, we show there is a broader interaction with decision-making processes. The link between glucose tolerance and increased reward learning rates suggests variation in how participants weigh recent versus past outcomes, rather than a simple difference in level of performance (an interpretation supported by our model-agnostic analysis). This pattern aligns with theories proposing a role for metabolic state in modulating reinforcement learning (e.g., 12).

Individual differences in learning rates may reflect variation in dopaminergic signalling (32, 33), which is in turn modulated by central insulin. In animals, striatal insulin receptor sensitivity alters dopamine release and reward learning (17, 18). In humans, intranasal insulin affects resting-state activity in dopaminergic regions including the striatum and prefrontal cortex (55, 56, 57) and may offer a tool for probing causal effects on reward learning (58, 59). Future work could combine such interventions with computational modelling to test these mechanisms more directly.

Our results also point to new opportunities for mental health research. Depression and type-2 diabetes are highly comorbid, a fact which has led some authors to speculate that they may share underlying mechanisms (11 ,15, 60). Based on our results, one possibility is that central insulin resistance causes changes in reward learning, which then contributes to the reward and motivational deficits seen in depression. If so, then improving insulin sensitivity could be an effective means of reducing depression symptoms. This suggestion is supported by several findings from the literature. For example, (61) found that an acute

dose of the GLP-1 agonist liraglutide (which enhances peripheral insulin secretion, as well as having direct effects on brain reward pathways) led to improved motivation for participants with lower baseline insulin sensitivity. This converges with preliminary evidence from randomised controlled trials that GLP-1 agonists reduce depression symptoms (62).

A separate line of research has shown that both exercise (63, 64, 65) and dietary interventions (66, 67, 68) can have significant antidepressant effects. In both cases the underlying mechanism remains as yet poorly-understood, however one compelling explanation—supported by our results here—is that improved global insulin sensitivity mediates their antidepressant effects (e.g., see discussion in [69]).

Interestingly, our findings differ from (70), who reported lower learning rates in individuals with reduced peripheral insulin sensitivity. However, their task focussed on sensory rather than reward learning, and used a different computational model (the Hierarchical Gaussian Filter vs. Q-learning in the present study). More importantly, (70) studied selected groups (lean and obese), while we sampled from the general population without selecting for metabolic health. Our transdiagnostic approach aimed to maximise generalisability (71), but likely included fewer individuals with severe insulin resistance. This may be critical, as previous work has identified an inverted-U relationship between adiposity and brain reward responses (72), and similar non-linearities may exist between insulin sensitivity and learning. It is also worth noting that insulin transport across the blood-brain barrier is saturable (73), meaning that increases in peripheral insulin do not translate linearly to CNS insulin levels. This may contribute to individual differences in learning effects and could underlie non-linear relationships between peripheral insulin sensitivity and reward processing. These complex relationships highlight the need for further studies using unified tasks and models across a wide range of metabolic profiles.

Some limitations should be acknowledged. First, while the OGTT offers a practical and widely-used index of glucose control, it does not directly assess insulin sensitivity. Gold-standard alternatives such as the hyperinsulinemic-euglycemic clamp, or the HOMA-IR (74) require venous sampling and are less suitable for cognitive neuroscience setting, in

particular due to safety considerations around inducing hyperinsulinemia. Given these constraints, we selected the OGTT as the most feasible approach, although this necessarily limits our ability to draw specific inferences about insulin resistance; therefore, we focus here on the measurement of glucose control instead. Similarly, metabolic regulation is influenced by a range of other physiological systems (e.g., hormonal axes like cortisol or ghrelin, gut microbiota, and stress pathways) that were not measured here. Future work could incorporate such indices to better characterise the multifactorial basis of metabolic-cognitive interactions.

Second, our glucose control measures have technical limitations. Traditionally, the OGTT uses a fixed glucose dose, which may not scale proportionally with body size (75), and CGMs can yield noisier data within the first 24 hours due to local inflammatory effects (76, 77). Nevertheless, our replication of key findings using fasting glucose mitigates these concerns and illustrates the value of including complementary metabolic measures.

Third, our sample was mainly female (36:12 F:M) and the average BMI (25.6kg/m^2) was slightly lower than that of the UK general population (27.6kg/m^2; [78]), both of which may affect generalisability. Future studies could adopt a systematic sampling strategy to achieve gender balance, or even oversampling particular metabolic phenotypes (e.g., individuals with obesity or insulin resistance) to improve both representativeness and interpretability.

Finally, while we have highlighted one possible pathway—from impaired glucose control to altered learning and mood—the relationship is likely bidirectional (79), raising the possibility of positive feedback loops in which neurocognitive and metabolic processes reinforce one another. The current study was correlational and cannot support directional conclusions. Therefore, clarifying the causal structure of these associations will be an important goal for future work.

In conclusion, we have identified an association between glucose control, reward learning and depression symptoms. While these results are correlational and preliminary, they offer initial evidence that metabolic signals may influence reward processing beyond food-related behaviour, potentially shaping broader processes of learning and mood. Given the

complexity of metabolic regulation and the limitations of our sample and design, further research will be essential to clarify the directionality, mechanisms, and generalizability of these effects. Nevertheless, these findings highlight an underexplored relationship between metabolic and cognitive processes, with implications for understanding and treating comorbid mental and metabolic disorders.

Acknowledgements

This work was funded by UK Medical Research Council (MC_UU_00030/12) and Wellcome Trust (226490/Z/22/Z) awards to CLN. MKS was supported by a British Association of Psychopharmacology Summer Internship.

Author contributions. *Experimental design*: HAF, MKS & CLN; *Data collection*: HAF, MKS, IL & AW; *Data analysis and drafting manuscript*: HAF; *Editing manuscript*: HAF & CLN; *Final approval:* HAF, MKS, IL, AW & CLN.

Disclosures

The authors have nothing to disclose.

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SUPPLEMENTARY INFORMATION

Metabolism and the Mind: Investigating the Link Between Glucose Control and Reinforcement Learning in Humans

Fleming *et al.*

Supplement

Probabilistic Selection Task Schematic

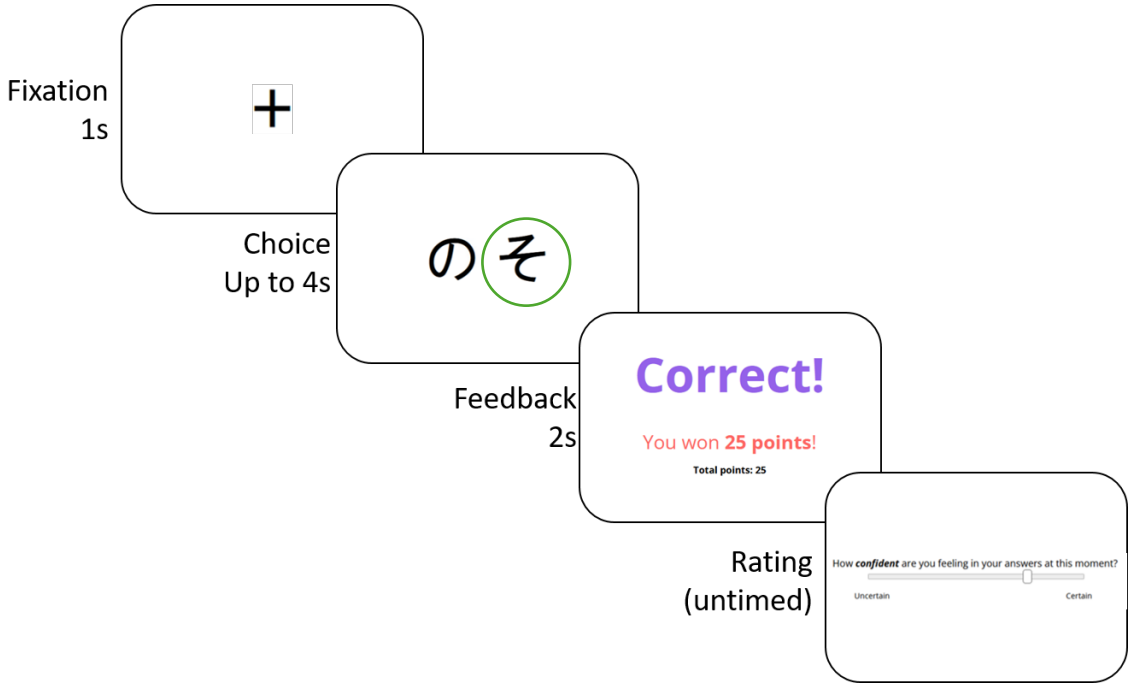


Figure S1. Schematic of the Probabilistic Selection Task. After an initial fixation period, participants were shown a pair of symbols (drawn from a set of six), and had to choose one by pressing the left or right arrow key. These symbols were associated with 20%, 30%, 40%, 60%, 70% or 80% chance of reward. In the training phase participants were then shown a feedback screen indicating whether they had won the reward (+25 points) or not. During the final test phase this screen was omitted. Finally, participants were asked a question about their current affective state.

Computational modelling: Further details

Full model specification

The full implementation of the model is provided at the OSF repository for this study, https://osf.io/b9z5v/. Below we set out the essential mathematical equations:

Learning

During the training phase, the values of the options (denoted by Q) were modelled using a Rescorla-Wagner learning rule, which augmented the value in Q by the prediction error weighted by the participant's learning rate, α:

$$Q_i(t) = Q_i(t-1) + \alpha\big(R - Q_i(t-1)\big)$$

In the two learning rate model, two different learning rates were applied, depending on whether a reward or loss was experienced on each trial.

After the training phase, during the test phase, there was no more feedback and so the Q values were no longer updated and were held constant for the remaining test trials.

Action selection

The response on each trial (choose stimulus *i*, choose stimulus *j*, or make no response) was modelled as being drawn from a categorical distribution:

$$response \sim categorical\begin{pmatrix} p_i \times (1 - p_{ignore}) \\ p_j \times (1 - p_{ignore}) \\ p_{ignore} \end{pmatrix}$$

Where p_i is the probability of choosing stimulus *i* over *j,* and is given by the difference between the Q-values of options i and j, multiplied by the sensitivity β and then passed through a logistic function. The complement p_j was simply $1 - p_i$.

$$p_i = logistic\left(\beta \times \left(Q_i - Q_j\right)\right)$$

The (few) trials where participants made no response at all were modelled by the parameter p_{ignore}.

Link functions

Both the learning rate and 'ignore' parameters were passed through logistic functions to ensure they fitted within the range 0-1, prior to being used in the learning/action stages of the model.

Priors

The model was specified hierarchically, i.e. the participant-level parameters (indexed 1…N) were themselves drawn from population-level distributions, as set out below.

$$\alpha_n \sim normal(\alpha_\mu, \alpha_\sigma)$$
$$\alpha_\mu \sim normal(0,1)$$
$$\alpha_\sigma \sim exponential(1)$$

$$\beta_n \sim normal(\beta_\mu, \beta_\sigma)$$
$$\beta_\mu \sim normal(0,2)$$
$$\beta_\sigma \sim exponential(1)$$

$$ignore_n \sim normal(ignore_\mu, ignore_\sigma)$$
$$ignore_\mu \sim normal(-2,1)$$
$$ignore_\sigma \sim exponential(1)$$

Model fitting and comparison

We fitted two versions of this computational model, one which contained just a single learning rate for each participant (as written out above; termed the Base model) and another which used two learning rates, one for reward trials and another for losses (referred to as the 'Base + 2LR' model). Both models were coded in Stan and fitted using Hamiltonian MCMC, with 4 chains for 1000 warmup and 1000 sample iterations. Both models fitted well (no divergences, split-Rhat < 1.1, E-BFMI > 0.3, maximum treedepth < 10; [1]), and posterior predictions visually matched the empirical data.

We compared their relative performance using approximate leave-one-out cross-validation (2). As shown in Figure S2 below, this substantially favoured the Base + 2LR model, which was ahead by approximately 16 standardised units of distance. Therefore this model was used for all subsequent analyses.

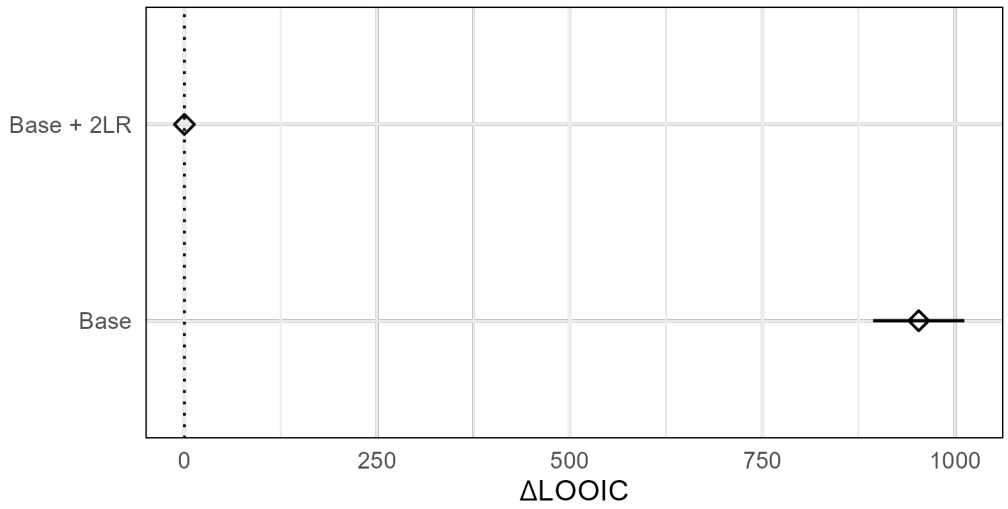


Figure S2. Model comparison showing substantially better approximate leave-one-out cross-validation performance for the model with two learning rates (Base + 2LR) compared with the single learning rate (Base) model.

Parameter recovery analyses

Parameter recovery was assessed by simulating new data from the empirical parameter estimates for each participant, refitting the model to these simulated datasets and comparing the recovered parameters to the originals. Recovery was very good: for reward learning rate, loss learning rate and outcome sensitivity, the correlations between empirical and recovered parameters were r = 0.94, 0.95 and 0.90 respectively (Figure S3).

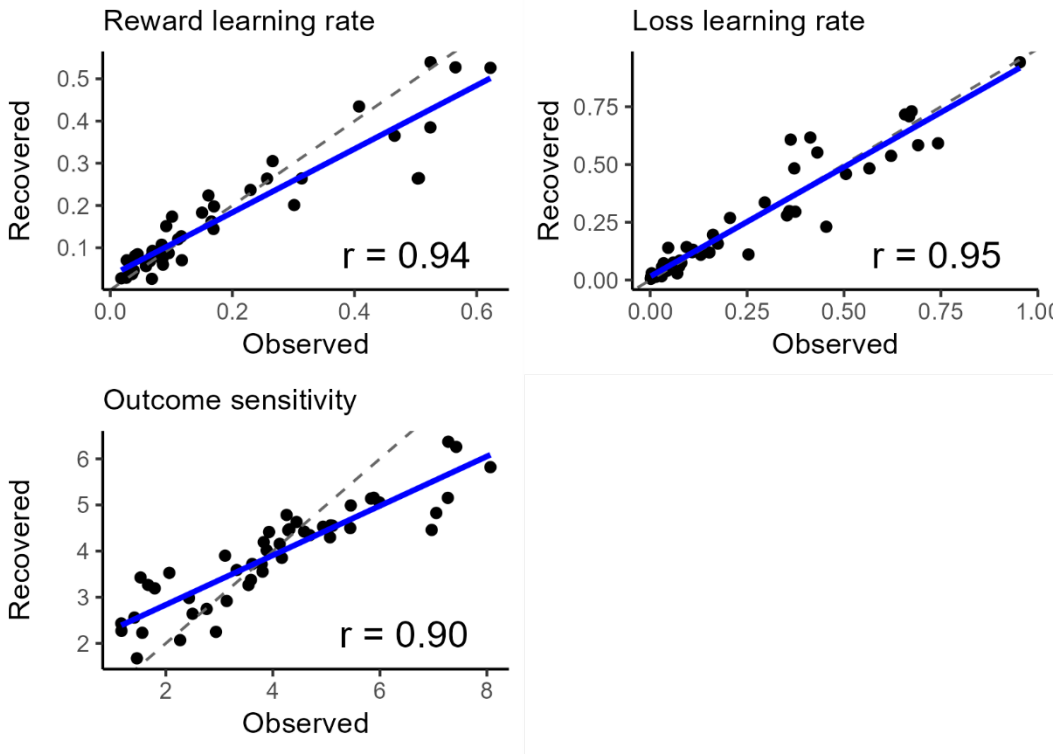


Figure S3. Parameter recovery results. All three parameters showed good recovery, with correlations of *r* = 0.94, 0.95 and 0.90 for reward learning rate, loss learning rate and outcome sensitivity respectively. Dashed grey line indicates perfect recovery (y = x), while the solid blue line shows the calculated regression line.

Supplementary results

To validate the reward learning task, we checked whether people's behaviour was consistent with previous studies. As shown in Figure S4A, all participants gradually learned the correct responses over the six blocks of the training phase (F[5,235] = 18.5, $p < .001$, $\eta^2_{partial} = 0.28$), and performed better on the 80-20 vs 70-30 vs 60-40 pairs (F[2,94] = 32.2, $p < .001$, $\eta^2_{partial} = 0.41$). In the subsequent test phase, performance was worse for novel pairs compared with those on which participants had trained (t[47] = 4.52, $p < .001$, $d = 0.65$), and we likewise saw performance declining over 80-20 vs 70-30 vs 60-40 trial types, $F(2,94) = 7.29$, $p = .001$, $\eta^2_{partial} = 0.13$ (Figures S4B and S4C). Participants' behaviour therefore matched the same patterns seen in the original studies with this task (3,4).

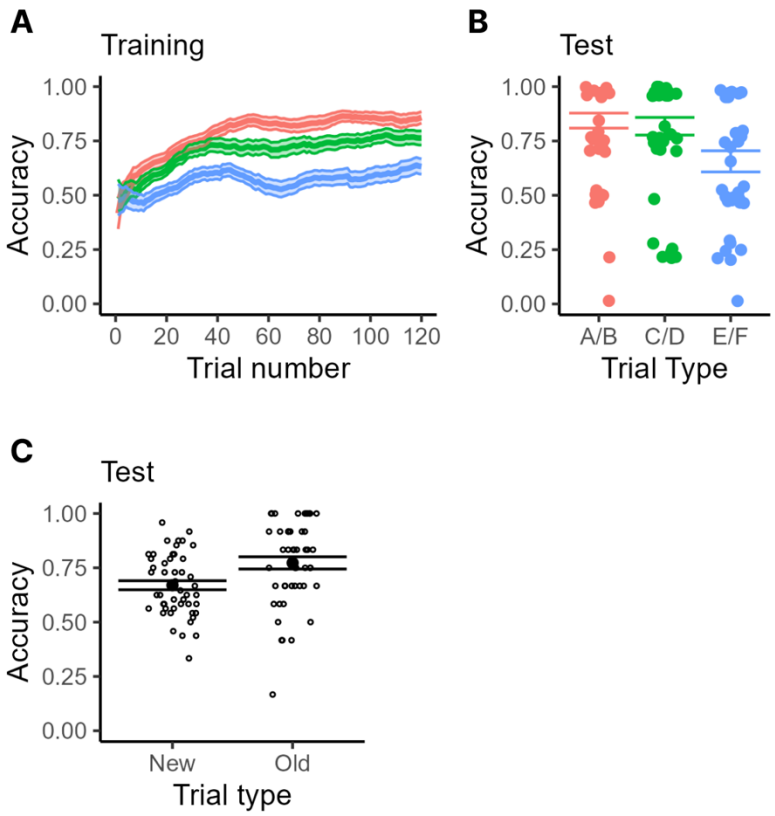


Figure S4. Performance on the Probabilistic Selection task during the training and test phases. A) Average performance over the course of the training, split by trial type. During training, participants gradually learned the correct responses, although performance was markedly better for the 80/20 (A/B) trial type compared with 70/30 (C/D) and 60/40 (E/F) trial types. B) Average accuracy during the test phase for just the trial types which had been trained previously. C) Average accuracy during the test phase for the trained vs. novel trial types. In B) and C) we show participants' individual data points, and the overall average±SE (error bars).

Full list of conditions and medications taken

Table S1. List of diagnosed conditions and medications taken by participants included in the final analysis (N=48).

Diagnosis	
Neurological disorder	0
Psychiatric disorder (ever diagnosed)	14
- Generalised or social anxiety disorder	9
- Major depressive disorder	3
- Other	2
Other chronic conditions	6
- Type 2 diabetes	1
- Inflammatory	2
- Other	3
Medication	
- Contraceptive pill	5
- Antidepressant (any)	4
- Antihypertensive	3
- Proton pump inhibitor	3
- Painkillers	2
- HRT	2
- Antispasmodic	1

Correlation between fasting glucose and iAUC

Fasting glucose was defined as the initial CGM reading taken prior to participants consuming the glucose drink (i.e., after the overnight fast). In our sample, fasting glucose and iAUC were modestly correlated (r = 0.15, p = 0.30). This correlation is rarely reported in previous studies, but in the available literature varies it varies from r = 0.41 to r = 0.68 (5,6).

Table S2. Comparison of the correlations between fasting glucose and iAUC, in the current and previous studies.

Study	**Correlation between fasting glucose and iAUC** *(r)*
Current study	0.15
Borg et al., 2010	0.68
Kjøllesdal et al., 2014	0.41

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