Differences in glucose control are associated with altered reward learning in humans

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Abstract

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 much more poorly understood. Here, we focus on the link between glucose regulation 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, and so we hypothesised that, in humans, differences in insulin sensitivity might be associated with altered reward learning. To test this hypothesis, we recruited 48 participants drawn from the general population, who each completed a glucose tolerance test (a measure of insulin sensitivity), a monetary reward learning task, and several mental health questionnaires. We discovered that poorer glucose control is associated with greater reliance on recent rewards during learning. We also found that poorer glucose control and greater reliance on recent rewards both predicted higher depression symptoms. 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

Neural processing is energetically expensive (1). In order to manage its resources strategically, the brain needs to track metabolic information from the body, and modify cognition and behaviour accordingly. Which metabolic signals are monitored, and how these interact with ongoing cognitive processes, however, remains unknown.

A possible mechanism is suggested by the location of insulin receptors in the brain. These are richly expressed on dopaminergic neurons in the ventral striatum (2), an area involved in reward learning and motivation (3), and circulating insulin readily crosses the blood-brain barrier (2), making it a likely candidate for communicating metabolic information to the brain. We therefore hypothesised that differences in insulin sensitivity might be associated with altered reward learning. If so, this might provide a neurocognitive mechanism explaining the comorbidity of insulin resistance and depression (4).

This hypothesis and our methods were preregistered prior to data collection. Participants (N = 48) were drawn from the local general population, in order to characterise metabolic and cognitive function along continuous dimensions. In the following sections, we first confirm that poorer glucose control is associated with worse depression symptoms (extending existing clinical findings to the general population). We then show that a computational decision-making parameter, the reward learning rate, is also correlated with both glucose control and depression symptoms.

Results

Impaired glucose control is associated with depression symptoms

Figure 1 shows the study design, and sample characteristics are in Table 1. Participants arrived in the morning following an overnight fast. We first administered an oral glucose tolerance test (OGTT), a standardised measure of insulin resistance. Following the method in (5), we used continuous glucose monitors (CGMs; Freestyle Libre 2, Abbott Laboratories), which sample interstitial glucose every five minutes, providing rich data while also being well tolerated by participants. The outcome was the incremental area under the curve (iAUC) over the two hours of the OGTT – higher iAUC indicates poorer insulin sensitivity.

While the OGTT was underway, participants completed the behavioural task and mental health questionnaires. Using Bayesian regression models (with age and sex as covariates), we estimated with 95% certainty that glucose iAUC had a positive relationship with depression (PHQ9 scores). The standardised regression coefficient was 0.22, implying that a 1-point increase in PHQ9 would require a 128 mmol/L x min increase in iAUC. Glucose control was not associated with the other self-report measures (66% HDIs for anxiety, anhedonia, apathy and impulsiveness all overlapped zero).

Thus, insulin resistance was associated with increased depression symptoms. This replicates and extends observations from patient studies (2,4) to the general population.

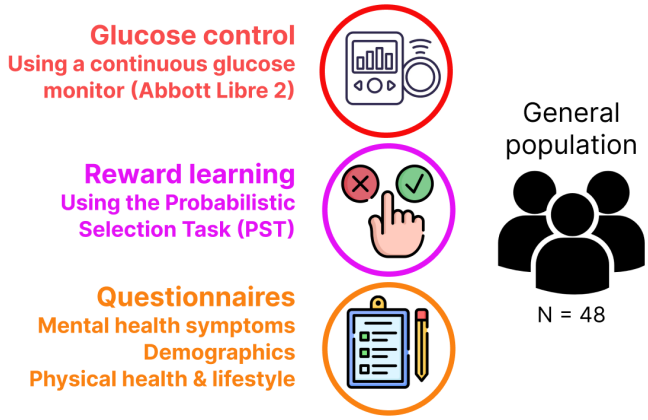

Figure 1. The study design.

***Table 1**. Demographics of the participants*

Demographics	N = 48 included in the analysis
Age, mean (years)	41.2 (SD=14.6; range = 18-60)
Sex	
- Male	12
- Female	36
BMI (kg/m^2)	
- < 18.5	2
- 18.5 - 25	26
- 25 - 30	8
- > 30	12
BMI range	17.6 – 39.3

Impaired glucose control is associated with greater reward learning rates

To assess participants' reward learning we used the Probabilistic Selection Task (PST; [6,7]). In this task, participants are shown pairs of symbols (coded A–F), and must learn which are consistently associated with rewards, while ignoring occasional misleading feedback. Symbols A and B were the most deterministic (80% of feedback was reliable) and E and F were the least (60%).

All participants learned the correct responses over the six blocks of the training phase ($F[5,235] = 18.5$, $p < .001$, $\eta^2_{partial} = 0.28$), but performed better on AB vs CD vs EF pairs ($F[2,94] = 32.2$, $p < .001$, $\eta^2_{partial} = 0.41$). In a subsequent test phase, performance was worse for novel pairings compared with those on which participants had trained ($t[47] = 4.52$, $p < .001$, $d = 0.65$), and we again saw performance declining over AB vs CD vs EF trial

types, $F(2,94) = 7.29$, $p = .001$, $\eta^2_{partial} = 0.13$. Participants' behaviour therefore corresponded with previous studies (6,7).

Our preregistered primary analysis was to assess the relationship between decision-making and glucose control, using both model-agnostic and model-based methods. While we did not see an association between overall accuracy and glucose tolerance, the computational modelling allowed us to investigate the decision-making mechanisms in greater detail. We fitted a hierarchical reinforcement learning model that has been previously validated for this task (6,7). The model had three main parameters: separate positive and negative learning rates (which quantify the influence of new vs. previous feedback), and a noise term.

We computed the correlation between each parameter and the glucose iAUC values using their full posterior distributions. We found that both the positive and negative learning rates were almost certainly associated with glucose tolerance (the entire posterior distributions were above zero; Figure 2). Specifically, the posterior means of these correlations were $r = 0.32$ (90% HDI: 0.23,0.40) and $r = 0.23$ (90% HDI: 0.16,0.31) respectively. In other words, participants with poorer glucose control were more influenced by recent outcomes than participants with better glucose control. Decision-making noise was not associated with glucose control (the 66% HDI of the correlation crossed zero).

Reward learning rate is positively associated with depression symptoms

Finally, we examined the correlations between these same parameters and mental health symptoms. Reward learning rate was not only positively associated with depression scores (PHQ9) with 96% certainty (posterior mean correlation of $r = 0.18$, 90% HDI: 0.03,0.33; Figure 2); it was also correlated with both anhedonia and apathy symptoms ($r = 0.19$, 90% HDI: 0.05,0.33; and $r = 0.19$, 90% HDI: 0.06,0.32, respectively).

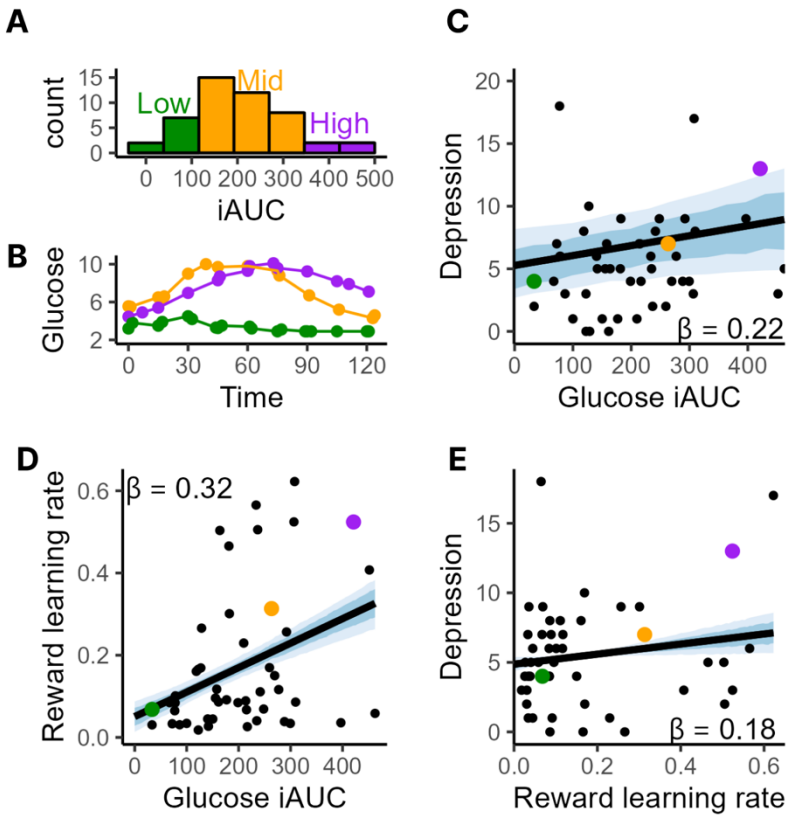

Figure 2. Associations between glucose control, reward learning and depression symptoms (PHQ9). A) Histogram of glucose iAUC values. B) Three indicative participants with low/medium/high iAUCs. C, D & E) Pairwise associations, with the same participants highlighted. Black points = empirical data; black line = mean regression line; blue shading = 66%/90% HDIs.

Discussion

We investigated the relationship between glucose control, reward learning and mental health in a sample of 48 participants from the general population. Poorer glucose control was associated with greater reliance on recent outcomes during the behavioural task; in turn, reliance on recent rewards was associated with higher scores for depression. Together, our results identify a specific neurocognitive mechanism, reward learning, by which insulin resistance and cognition are linked.

In comparison to other interoceptive domains, we know much less about how metabolic information shapes cognition. While previous research has primarily focussed on how insulin affects eating behaviour (e.g., 8), here we have identified an interaction with decision-making more generally. The increased reward learning rates with insulin resistance imply a difference in how participants weigh new versus previous outcomes they have experienced; they weren't simply performing the task better or worse (as our model-agnostic analysis showed) but, rather, exhibited a specific difference in the trial-by-trial process of learning.

Learning rates are thought to be related to dopamine levels (6,7). This implies that our results might be explained by differences in dopamine signalling as a consequence of variation in striatal insulin receptor sensitivity. Studies combining pharmacological interventions (for example, administering insulin) with computational modelling could allow this causal hypothesis to be tested directly.

These 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 (2, 9). Based on our results, one possibility is that insulin resistance causes changes in reward learning, which then contributes to the reward and motivational deficits seen in depression. A tantalising implication is that increasing insulin sensitivity might therefore improve depression symptoms (which may, for example, explain the antidepressant effects of exercise).

Several limitations should be mentioned. First, participants were recruited from the general population, and were not selected for any particular health characteristics. This improves generalisability, and accords with a dimensional approach to studying cognitive traits (10), but it also means we had relatively few participants with severe metabolic or mental ill-health. This is potentially important as previous work has shown an inverted-U relationship between adiposity and brain reward responses (11), and the same may hold true for insulin sensitivity. Further studies will be needed to explore how reward learning is affected in patients. Secondly, while we have hypothesised that insulin sensitivity may be driving neurocognitive changes which then contribute to depression, epidemiological studies show that the relationship between metabolic illness and depression is bidirectional (12); therefore, it is probably also true that altered reward learning affects lifestyle behaviours which impact metabolism (producing a positive feedback cycle). Further research will need to disentangle these processes.

In conclusion, we have identified a neurocognitive mechanism, reward learning, linking glucose control and depression. Altogether, these results point to an important and underexplored mechanism by which metabolic information shapes cognition.

Methods

This study followed our preregistration (https://doi.org/10.17605/OSF.IO/UQ58Z) without any deviations. This repository contains all code and data for reproducing the study and analyses.

Participants arrived in the morning following an overnight fast. We first conducted an oral glucose tolerance test (OGTT), followed by a decision-making task (the Probabilistic Selection Task; [7]), and six self-report symptom scales covering depression, anxiety, anhedonia, apathy, impulsivity, and physical activity. Full details are in the supplement.

To analyse the task data, we fitted a well-established reinforcement learning model with three main parameters: separate positive and negative learning rates, and a noise parameter. Model comparison substantially favoured this model over a simpler model with

a single learning rate. The model comparison, and full model equations, are detailed in the supplement.

Acknowledgments

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Supplementary Methods

This study was preregistered on the Open Science Framework (https://doi.org/10.17605/OSF.IO/UQ58Z), and there were no deviations from this protocol. The associated repository contains all task code, raw data, and full scripts for reproducing the study and our analyses.

In total we tested 56 adults from the local general population. Prior to recruitment we asked participants about any drugs they were regularly taking, and we only tested participants who were not taking drugs known to substantially affect blood sugar regulation. There were no other health-related recruitment criteria. Of the 56 participants who were tested, 8 were excluded (four because they failed the attention checks, see the section on the questionnaires below, and four because of signal dropout from the CGMs), leaving 48 in the final analysis. This exceeded our preregistered minimum sample size of 46. This study was approved by the Cambridge Psychology Research Ethics Committee (PRE.2022.078). All subjects provided written informed consent prior to taking part.

In addition to the demographics reported in Table 1, we also collected relevant data on participants' health characteristics: fourteen participants reported having been diagnosed with a psychiatric disorder at some point in their life (9 reported generalised or social anxiety disorder, 3 major depression, and 2 other). There were no reports of any history of neurological disorders. Six participants reported other chronic conditions: one type-2 diabetes (controlled by diet alone), 2 reported inflammatory conditions, and 3 reported other chronic conditions. Five participants were taking a contraceptive pill, 4 were taking antidepressants, 3 were taking antihypertensives, 3 were taking proton pump inhibitors, 2 were taking painkillers, 2 were taking HRT and 1 was taking an antispasmodic. Two participants reported familiarity with Japanese Hiragana characters.

Glucose Tolerance Test

Participants attended the lab in the morning following an overnight fast. After a briefing and taking informed consent, we commenced the oral glucose tolerance test (OGTT). We followed the method described by Suez et al. (1): after taking a baseline reading while

participants were still fasted, we then gave participants a drink consisting of 50g of glucose dissolved in 250ml of water, and monitored the change in their glucose levels over the following two hours, during which time participants were seated and still. Our dependent measure from the OGTT was the incremental area under the curve, which comprises all area below the curve but above the fasting concentration of glucose. We calculated this using the trapezoid rule.

Prior to the main analysis, we checked the CGM data and verified it was of sufficient quality. On average we obtained 18 readings per person (range: 11–42), and all participants provided a final reading within 2 minutes of the 2-hour cut-off time. iAUC values varied substantially across subjects (range 33.3–463 mmol/L x min; this is consistent with the values reported by Suez et al. [1]; 67–413 mmol/L x min).

Probabilistic Selection Task

In the Probabilistic Selection Task (originally devised by Frank et al. [2,3]; and here incorporating the affect ratings as described by Dercon et al. [4]), participants chose between pairs of Japanese Hiragana symbols, which each have different probabilities of leading to a reward (gaining 25 points). In total there were six symbols each associated with either 20%, 30%, 40%, 60%, 70% or 80% chance of receiving the reward (the symbols were assigned to these contingencies randomly at the start of the task).

After an initial instruction phase (which included a comprehension test that participants had to pass in order to proceed), participants completed a learning phase consisting of six blocks of sixty trials each. During this training phase, the symbols were always presented in the same pairs: 80% and 20%, 70% and 30%, and 60% and 40% (with the left/right order of symbols on the screen counterbalanced across trials). After making their choice, participants were shown the outcome of the trial: either a screen saying ‘Correct! You won 25 points’, followed by the running total of their points collected so far; a screen simply saying ‘Incorrect’; or a screen saying ‘no response detected’. They were then asked a question about their current feelings, from the following set: “How happy are you at this moment?”, “How confident are you feeling in your answers at this moment?” and “How engaged are you feeling at this moment”. They answered these questions using a horizontal

sliding scale. Finally, at the end of each block participants were also asked “How fatigued do you feel compared to the beginning of this block?”, again answered using a sliding scale.

After the training phase, participants completed a test phase, in which the symbols were no longer shown in fixed pairs but instead every possible permutation was shown twice each (yielding 30 unique trial types, and 60 total trials, in this phase). In this phase participants no longer received feedback on their choices – after making their selection, they were immediately asked the affect question, and then the trial ended. Participants were therefore told at the start of this phase simply to choose whichever symbol felt ‘most correct’.

Questionnaires

Questionnaires were presented on a computer using the software jsPsych. Participants were first asked a range of demographic questions: their age, sex, height, weight and whether they smoked; whether they had been diagnosed with diabetes (and if so, what type); whether they had any neurological, mental health or other chronic health conditions, and what medication they took; whether they menstruated and, if so, when their last period ended; and how long/well they had slept the night before.

Participants next completed six cognitive and health questionnaires: the Patient Health Questionnaire Depression Scale (PHQ-9; 5), the Generalised Anxiety Disorder questionnaire (GAD-7; 6), the Beck Anxiety Inventory (BAI; 7), the Snaith-Hamilton Pleasure Scale (SHAPS; 8), the Impulsive Behaviour Short Scale (I-8; 9), the General Practice Physical Activity Questionnaire (GPPAQ; 10), and the Apathy Evaluation Scale (11). The BAI contained an ‘easy’ attention check at the end (instructing participants to “Press not at all” for that question). The I-8 contained a ‘hard’ attention check (asking participants how often they ‘work forty hours a day’), as did the AES (asking whether they have used a computer before).

Finally, participants were also asked whether they had indeed fasted overnight as required – it was emphasised to them that they would still be paid the same regardless of their answer to this question, and that it was important they were truthful.

Analysis and Computational Modelling

The associations between glucose iAUC and our self-report measures were estimated using Bayesian linear regression models coded in R using the *rstanarm* package (12). All models included age and sex as covariates. We did not include BMI as a covariate because adiposity is a causal influence on glucose iAUC rather than a confounder, and therefore controlling for it would lead to misleading results (Moriarty et al., 2023). We examined the recommended diagnostics (i.e. no divergences, split-Rhat < 1.1, E-BFMI > 0.3, maximum treedepth < 10; 13) and found no problems with any of the models.

Our primary analysis of the Probabilistic Selection Task used hierarchical reinforcement learning models, which have been frequently used and are well validated for this task (2,3). We started by fitting a basic Q-learning model, described by the following equations.

On each trial, the model compares the subjective value of the stimuli shown on the left versus right side of the screen (on the first trial, these Q-values are initialised at zero). This difference is scaled by an inverse temperature parameter, β, which governs choice stochasticity, and then passed through a logistic function to compute the probability of choosing the left over the right stimulus. This probability is combined with a second parameter, p_{ignore}, to give a vector of probabilities corresponding to choosing the stimulus on the left, choosing the stimulus on the right, or making no response at all on that trial. Finally, this vector is provided to a categorical distribution which generates the response, $y \in$ {choose-left, choose-right, no-response}, on that trial.

$$p_{left} = logistic(\beta \times (Q_{left} - Q_{right}))$$

$$\theta = \begin{bmatrix} p_{left} \times (1 - p_{ignore}) \\ (1 - p_{left}) \times (1 - p_{ignore}) \\ p_{ignore} \end{bmatrix}$$

$$y \sim categorical(\theta)$$

Once feedback is received, the model updates the stored value of the item that was chosen by adding the prediction error to the existing value, weighted by the learning rate α. In the test phase (i.e. where there was no feedback), this step was omitted.

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

The three subject-level parameters were given hierarchical priors, with a logistic link-function where appropriate. We conducted prior predictive checking to determine sensible values for the population-level priors (code for reproducing these checks is included in the study repository).

$$\alpha_{subject} = logistic\left(LR_{subject}\right)$$
$$LR_{subject} \sim normal(LR_{\mu}, LR_{\sigma})$$
$$LR_{\mu} \sim normal(0,1)$$
$$LR_{\sigma} \sim exponential(1)$$

$$\beta_{subject} \sim normal(\beta_{\mu}, \beta_{\sigma})$$
$$\beta_{\mu} \sim normal(0,2)$$
$$\beta_{\sigma} \sim exponential(1)$$

$$p\_ignore_{subject} = logistic\left(\xi_{subject}\right)$$
$$\xi_{subject} \sim normal(\xi_{\mu}, \xi_{\sigma})$$
$$\xi_{\mu} \sim normal(-2,1)$$
$$\xi_{\sigma} \sim exponential(1)$$

We fitted this model, which we termed the 'Base' model, using Hamiltonian MCMC, coded in the *Stan* language using *cmdstanr* (14), with 4 chains run for 1000 warmup iterations and 1000 sample iterations each.

This base model was augmented by adding separate learning rates for positive and negative outcomes, which we refer to as the Base+2LR model. Both models fitted well according to the standard diagnostics (i.e. no divergences, split-Rhat < 1.1, E-BFMI > 0.3, maximum treedepth < 10; 13). We also visually confirmed that the posterior predictions of the models matched the patterns shown in the empirical data. We compared the two models based on their estimated out-of-sample predictive accuracy, using the *loo* package in Stan (15). We found that the Base+2LR model performed substantially better (with an expected log predictive density which was 16 standard errors ahead) and so we selected this model for further analysis.

Having selected a best fitting model, we then examined the associations between the model parameters and both the glucose iAUC values and the self-report questionnaires. To do this, while preserving the information contained in the full posterior distribution, we computed the correlations of these measures for each sample from the posterior individually. This then allows us to assess the full posterior distributions of the correlations obtained from the model. To do this, we again plotted the posterior distributions and, in the main text, we report the posterior means, 90% HDIs and, where relevant, the posterior probability that the correlation is not zero.

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