**Interoceptive Accuracy Moderates the Glycaemic, Autonomic and Subjective
Response to a Glucose Load: A Test of the Predictive Coding Framework.**

Hayley A Young*, Chantelle M Gaylor, Danielle de Kerckhove, Heather Watkins, and
David Benton

Department of Psychology

Swansea University

Wales, UK

SA2 8PP

Phone : ++44 1792 295908

Email : h.a.young@swansea.ac.uk

* To whom correspondence concerning this article should be addressed.

Keywords: Interoceptive inference; Predictive coding; Phenotypic flexibility;
Glucoregulation; Mood; Hunger.

Abstract

Recently, interoception and homeostasis have been described in terms of predictive coding and active inference. Afferent signals update prior predictions about the state of the body, and stimulate autonomic mediation of homeostasis. Performance on tests of interoceptive accuracy (IAc) may indicate an individual's ability to flexibly assign precision to interoceptive signals, thus determining the relative influence of ascending signals and prior beliefs. Accordingly, individuals with high IAc should be more able to counter-regulate during the post prandial period. Eighty females were randomly allocated to consume glucose, an artificially sweetened drink, water or no drink. Before, and thirty minutes after a drink, IAc, heart rate and blood glucose were measured, and participants rated their hunger thirst and mood. A higher IAc was related to lower blood glucose levels, a decline in anxiety, and a higher heart rate, after consuming glucose. A higher IAc also resulted in a larger decline in hunger if they consumed either glucose or sucralose. These data provide the first empirical verification of the role of active inference in interoception and homeostasis. In addition, the approach highlights the utility of indices of interoceptive accuracy as composite markers of phenotypic flexibility.

Introduction

Interoception, the perception and interpretation of visceral afferent signals, underpins homeostatic functioning (1), and is an essential component in many theories of emotion (1-6). However, interoception is no longer viewed as a 'stimulus - response' system and several recent models have linked interoception and homeostatic/allostatic control, to predictive coding and active inference (2, 7-9).

According to these models, afferent visceral signals update prior predictions (previously learned expectations) about the state of the body, thereby driving autonomic mediation of homeostasis. Discrepancies between predicted and experienced interoceptive signals results in interoceptive prediction error (i.e. that part of incoming interoceptive sensation not accounted for by prior expectations). It has been proposed that interoceptive prediction error underlies emotion, especially anxiety (5, 10). Within the interoceptive system, the minimisation of prediction error is possible, either by modifying top-down predictions, or by changing the sensory signals through action, a process termed 'active inference' (11). The nature of the resulting modification depends on the relative influence of ascending signals and prior beliefs, which is determined by the precision or reliability attributed to them. However, although these frameworks have received theoretical support, to date they lack empirical verification.

If these models are correct, differences in interoceptive accuracy (IAc) should relate to changes in autonomic nervous system (ANS) functioning and subjective state following a homeostatic challenge. This is because deviation from homeostasis increases interoceptive prediction error, and counter-regulation minimises the

prediction error through active inference. It has been argued that those who perform well on tests of interoceptive accuracy may be better able to flexibly establish the precision of interoceptive signals (12). If this were the case it would be predicted that individuals with high IAc would be endowed with a greater metabolic flexibility during the post prandial period. The present study tested this hypothesis.

Importantly, variability in the response to glucose consumption is well documented (13). Moderating factors that have been identified include; glucose intolerance (14, 15), body mass index (16), and subjective (17) and objective sensitivity to hypoglycaemia (15, 18). According to the active inference framework, interoceptive inference defines the homeostatic set point (19). Therefore, if prior expectations indicate the persistence of either high or low blood glucose, then the set point at which interoceptive prediction error is experienced, and an awareness of a change in blood glucose occurs, may become chronically altered. This has the potential to explain the variability in the response to a glucose load.

Interestingly, it has been reported that glucose facilitation depended on initial levels of thirst (20). In addition, there are similar reports that changes in thirst mediated the effect of consuming water when mildly hypohydrated (21, 22). An increase in thirst was associated with a decline in energy, and an increase in anxiety and depression ratings; an effect that was reduced by drinking water. Thirst is a motivational subjective sensation that arises when interoceptive prediction error signals a need to restore a particular physiological set point. Although data on individual variation in thirst is limited (23), the association between thirst and aspects of mood support the role of interoceptive factors in moderating the affective response to food.

Of particular importance, is the report that individual differences in vagal tone, measured using heart rate variability (HRV), moderated the glycaemic and appetitive response to a glucose load (24). Lower HRV was related to greater blood glucose excursions; an effect attenuated by consuming a drink with a low glycaemic load. Again similar effects have been reported after consuming water; increased HRV was related to a better mood (25). Notably, heart rate and HRV are inversely related to interoceptive accuracy (26, 27), which is consistent with the role of interoception in homeostatic functioning. Those with higher HRV may be better able to counter-regulate during the postprandial period due to increased interoceptive processing. Taken together these findings suggest that differences in interoception might be key to understanding variability in the response to food. However, to the best of our knowledge heartbeat perception as an index of these individual differences remains unexplored.

Interestingly, a separate literature has recently redefined health as the ability of the mind and body to cope with daily-life challenges (28). In the context of metabolic health, this ability to adapt has been termed “phenotypic flexibility” (29); that is the ability to recover from excursions from the prescribed homeostatic levels. To the extent that tests of interoceptive accuracy measure an individual’s ability to flexibly ascribe precision to interoceptive signals (12), differences in interoceptive accuracy may be a composite functional marker of “phenotypic flexibility”. Indeed it has previously been argued that aberrant interoceptive processing represents core impairment across psychiatric disorders (30-34). It is proposed that differences in interoception drive symptom inter-correlation across psychiatric conditions, and thus give rise to the hypothetical ‘p factor’ (35). Given the maintenance of homeostasis is

considered a core function of interoceptive inference; it is surprising that such proposals have not yet been extended to encompass physical health. As such a second aim of the present study was to explore this possibility.

Taken together, there is strong theoretical support for the hypothesis that differences in interoceptive accuracy should relate to the glycaemic, autonomic, and subjective response to a glucose load. Specifically, it was predicted that those with high interoceptive accuracy would be better able to counter-regulate during the post prandial period. With this in mind, the present study examined the response to glucose, an artificially sweetened drink, water or no drink. These data provide the first empirical verification of the role of active inference in interoception and homeostasis. In addition, the approach highlights the utility of indices of interoceptive accuracy as composite markers of phenotypic flexibility.

Methods

Participants

The sample size was based on previous research that has considered the association between IAc and eating behaviour (36); eighty females between 18 and 33 years were recruited (Table 1). Participants were excluded if they had a metabolic or cardiovascular disorder, gastrointestinal problems, were pregnant, had a current diagnosis of a mood or eating disorder, and/or were taking medications or herbal supplements to manage body weight or control appetite. BMI ranged from 17.7 – 38.3 (average 23.3) kg/m^2 ; 5.2% were underweight ($\text{BMI} < 18.5$), 63.6% of the sample had a normal BMI between 18.6 and 24.9, 23.4% of the sample were overweight with a BMI between 25 and 30 whereas the remaining 7.8% of the

sample were obese with a BMI > 30. Participants were instructed to refrain from drinking alcohol and taking part in any physical activity within twenty four hours of the study and to abstain from consuming any food and drink for at least eight hours before attending the laboratory. All participants were tested in the morning between 9.00am and 1.00pm.

Table 1 here

Procedure

After providing their written informed consent, participants rated their mood, hunger and thirst. Participants then had their height, weight and fasting BG measured and conventional Ag/AgCl electrodes and transducers were applied and connected to a BIOPAC MP150 and ECG100C amplifier module (BIOPAC, USA). Participants then completed the interoception task as outlined below. Interbeat interval data were monitored throughout the interoception task with a sampling rate of 2000Hz. This study employed a parallel designed study as such the participants were then randomly allocated to receive water, sucralose, glucose or nothing. The random sequence was computer generated by HY who produced the solutions in sequentially numbered tumblers. Participants were allocated by CG in the order they were recruited. The subjects were blind as to the nature of the drinks consumed. With the exception of hunger ($p < 0.03$) and thirst ($p < 0.01$), at baseline the groups were well matched for subjective ratings, interoception, fasting blood glucose, and BMI (Table 1). Participants were given five minutes to consume the entire beverage following which they relaxed (either reading or watching TV) for thirty minutes, before they again rated their mood, hunger and thirst, completed the heartbeat perception

task, and a BG measurement was taken. Heart rate was recorded for a second time using the BIOPAC MP150 and ECG100C amplifier module (BIOPAC, USA). Finally, after sixty minutes another BG measurement was taken. The procedure was approved by Swansea University Department of Psychology ethics committee and was conducted in accordance with the principles laid down by the declaration of Helsinki 2013. All participants provided written informed consent.

Test drinks

Each drink was 500 ml provided in a clear plastic tumbler. The glucose drink contained 75 g of glucose dissolved in water. The sugar free beverage was sweetened with sucralose to produce a similar sweetness to the other drinks which was confirmed during previous experiments (24). These two drinks contained 10 ml of lemon juice to increase palatability. An equal volume of plain water was consumed in the water condition. Participants who consumed nothing were unaware that other participants had consumed a drink.

Interoceptive accuracy (IAc)

The heartbeat perception task was performed using the Mental Tracking Method (37) with intervals of 30, 35, 40, and 45 and 50 seconds that were separated by 30 second resting periods. During each trial R-R intervals were recorded and participants were asked to silently count their heartbeats without the use of an exteroceptive aid (such as taking one's pulse). At the end of each period participants reported the number of counted heartbeats. The participants were not informed about the length of the counting phases nor about the quality of their performance. The following transformation: $1 - \sum ((\text{Actual} - \text{Reported})) / (\text{Actual})$ was

used to calculate heartbeat tracking scores. These scores were then averaged to form a mean heartbeat tracking score (IAC). The interoception score varied between 0 and 1 with a higher score indicating better accuracy. This heartbeat tracking task is a standard measure used to assess the accuracy of the ability to detect interoceptive signals and was chosen to be consistent with the previous literature on interoception (26, 38, 39), and as it may specifically measure an individual's ability to selectively attend to interoceptive signals (12).

Blood glucose

Blood glucose was monitored from finger pricks using an ExacTech sensor (Medisense Britain Limited) that using an enzymic method, coupled with microelectronic measurement, which has been shown to be accurate.

Mood, Hunger and Thirst

Participants were asked to describe the way they felt 'at that moment' using visual analogue scales (VAS) with pairs of adjectives at the ends of 100 mm lines; Composed/Anxious, Elated/Depressed, Tired/Energetic, Not at all hungry/Extremely hungry and Not at all thirsty/Extremely thirsty (40).

Body mass index (BMI)

Body mass was measured using an electronic scale (Kern KMS-TM, Kenr and Sohn GmbH, Germany) that, to avoid problems associated with movement, took 50 assessments over a 5 second period to produce an average value. Height was measured using a portable stadiometer.

Results

Descriptive results

A one sample t test confirmed that the overall score for IAc was above chance level (Mean = 0.64, SD = 0.21), $t = 27.19$, $p < 0.0001$). Those who score above this level were considered to have good IAc whereas those below were considered to have poor IAc.

The effect of interoceptive accuracy (IAc) on changes in blood glucose (BG)

Initially it was considered whether the effect of consuming glucose, rather than rather than sucralose, water or nothing, on BG, varied according to individual differences in IAc. A 4 (Drink: Glucose, Sucralose, Water, Nothing) X 2 (IAc: High, Low) X 3 (Time: Fasting BG, 30 min BG, 60 min BG) repeated measures ANOVA was conducted. BMI and age were considered time independent covariants but neither contributed significantly to the model (BMI: $F = (1, 67) = 1.309$, $p = 0.257$, $\eta_p^2 = 0.019$, Age: $F = (1, 67) = 0.001$, $p = 0.979$, $\eta_p^2 = 0.001$).

As expected the interaction Time X Drink was significant ($F = (6, 134) = 38.628$, $p < 0.0001$, $\eta_p^2 = 0.638$): participants who consumed glucose had significantly higher BG levels after 30 and after 60 minutes compared to all other drinks (all $p < 0.0001$). Interestingly, the interaction Time X Drink X IAc also reached significance ($F = (6, 134) = 2.613$, $p < 0.020$, $\eta_p^2 = 0.105$). In those who consumed sucralose, water or nothing, BG did not differ at any time point depending on IAc (all $p > 0.4$). Similarly, IAc did not influence fasting BG across the entire sample ($p = 0.447$) or in the group who drank glucose ($p = 0.670$). After 30 minutes those with low IAc tended to have higher BG levels if they consumed glucose (Figure 1), although the effect did not

reach significance ($p = 0.145$). However, after 60 minutes the effect was significant ($p < 0.0001$); those with low IAc had higher BG levels. These findings suggest that individuals with higher IAc may be better able to counter-regulate their glycaemic response to a glucose load.

Figure 1 here

The effect of interoceptive accuracy (IAc) and glucose on heart rate (HR).

If interoceptive inference underpins homeostasis through changes in the ANS, differences in interoception should relate to HR changes following the consumption of a drink. Therefore, it was considered whether consuming glucose, rather than sucralose, water or nothing, influenced HR and whether this varied according to individual differences in IAc. A 4 (Drink: Glucose, Sucralose, Water, Nothing) X 2 (IAc: High, Low) X 2 (Time: Fasting HR, 30 min HR) repeated measures ANOVA was conducted. BMI and age were considered time independent covariants. Neither BMI ($F = (1, 67) = 0.786$, $p = 0.7896$, $\eta_p^2 = 0.001$) nor age ($F = (1, 67) = 0.786$, $p = 0.212$, $\eta_p^2 = 0.004$) were related to HR. There was a significant Time X Drink interaction ($F = (3, 67) = 9.264$, $p < 0.0001$, $\eta_p^2 = 0.293$). This effect reflected a decline in HR, from T1 to T2, in those who consumed sucralose ($p < 0.0001$), water ($p < 0.0001$) or nothing ($p < 0.0001$); the effect was absent in those who drank glucose ($p = 0.842$). There was also a significant Time X Drink X IAc interaction ($F(3,67) = 2.715$, $p < 0.05$, $\eta_p^2 = 0.108$). In those with high IAc, consuming glucose resulted in a higher HR than consuming water ($p < 0.02$) or nothing ($p < 0.01$). All other follow up tests were not significant (Figure 2). These findings suggest that consuming glucose results in a higher HR; an effect accentuated in those with higher IAc. Those high in

IAC may assign high precision to their ascending interoceptive signals, enhancing the recognition of interoceptive prediction error, and the modification of this error through engagement of the ANS (active inference).

Figure 2 here

The effect of interoceptive accuracy (IAC) and glucose on mood

From the interoceptive inference perspective, emotions are motivating signals that arise as a result of a discrepancy between expected and actual body states (interoceptive prediction error). If this is correct then differences in interoception should relate to the affective response to a drink (a homeostatic challenge that produces prediction error). Initially effects on ratings of anxiety (ANX) were considered. A 4 (Drink: Glucose, Sucralose, Water, Nothing) X 2 (IAC: High, Low) X 2 (Time: Fasting anxiety, 30 min anxiety) repeated measures ANOVA was conducted. BMI and age were considered time independent covariants. Neither BMI ($F = (1, 67) = 1.161, p = 0.285, \eta_p^2 = 0.017$) nor age ($F = (1, 67) = 2.991, p = 0.088, \eta_p^2 = 0.043$) were related to ANX. However, the Time X Drink X IAC interaction was significant ($F = (3, 67) = 3.160, p < 0.030, \eta_p^2 = 0.124$). In those who consumed glucose, those with high IAC experienced a decline in ANX ($p < 0.0001$); this effect was absent in those with low IAC ($p = 0.467$) (Figure 3). Assuming those high in IAC are better able to counter regulate after a homeostatic challenge (and thus minimise prediction error), this may explain the reduction in anxiety observed in this group.

The same analysis was conducted for ratings of depression (DEP). This time age ($F = (3, 67) = 5.090, p < 0.02, \eta_p^2 = 0.071$) contributed significantly to the model; older participants rated themselves as more depressed. However, BMI was without effect

($F = (3, 67) = 2.815$, $p < 0.098$, $\eta_p^2 = 0.040$). In addition, none of the interactions involving Drink or IAc reached significance: Time X Drink ($F = (3, 67) = 0.146$, $p = 0.932$, $\eta_p^2 = 0.007$) and Time X Drink X IAc ($F = (3, 67) = 0.785$, $p = 0.506$, $\eta_p^2 = 0.034$).

Similarly, when it came to ratings of fatigue, only age reached significance ($F = (3, 67) = 8.531$, $p < 0.005$, $\eta_p^2 = 0.113$) with older participants rating themselves as more tired. BMI did not relate to energy levels ($F = (3, 67) = 0.862$, $p < 0.3568$, $\eta_p^2 = 0.013$) and neither were any of the interactions involving Drink or IAc: Time X Drink ($F = (3, 67) = 1.496$, $p = 0.224$, $\eta_p^2 = 0.063$) and Time X Drink X IAc ($F = (3, 67) = 0.903$, $p = 0.444$, $\eta_p^2 = 0.039$).

Figure 3 here

The effect of interoceptive accuracy (IAc) and glucose on hunger and thirst

In the context of interoception, hunger and thirst are arguably the most motivationally relevant subjective feelings. A 4 (Drink: Glucose, Sucralose, Water, Nothing) X 2 (IAc: High, Low) X 2 (Time: Fasting anxiety, 30 min anxiety) repeated measures ANOVA was conducted. BMI and age were considered time independent covariants. Again age contributed significantly ($F = (1, 67) = 4.418$, $p < 0.03$, $\eta_p^2 = 0.062$) but BMI did not ($F = (1, 67) = 3.370$, $p < 0.07$, $\eta_p^2 = 0.048$). There was also a significant Drink X Time interaction ($F = (3, 67) = 4.775$, $p < 0.004$, $\eta_p^2 = 0.176$); those who drink glucose ($p < 0.01$) or sweetener ($p < 0.04$) experienced a significant decline in hunger. Conversely, those who consumed nothing had a significant increase in hunger ($p < 0.02$). There was no effect in those who consumed water ($p = 0.210$). In addition, the Time X Drink X IAc interaction was also significant ($F = (3, 67) = 2.642$, $p < 0.05$,

$\eta_p^2 = 0.106$). Essentially, the aforementioned effects were driven by those with high IAc. Those with high, but not low, IAc had a decline in hunger after glucose ($p < 0.001$) and sucralose ($p < 0.001$) ($p = 0.849$ and $p = 0.667$ respectively in those with low IAc). In addition, those with high, but not low, IAc had an increase in hunger after nothing ($p < 0.03$) ($p = 0.318$ in those with low IAc). No effects were observed in those who consumed water (high IAc $p = 0.223$, low IAc $p = 0.608$) (Figure 4). Given the decline in hunger was of a similar magnitude in those who consumed sucralose to those who consumed glucose it is possible that this effect represents sensitivity to sweet taste in those with high IAc, rather than an increase in blood glucose.

Figure 4 here

Similar effects were seen when thirst was considered. Neither the effect of BMI nor the effect of age was significant. However the Time X Drink interaction was ($F(3, 67) = 3.842$, $p < 0.01$, $\eta_p^2 = 0.147$). Those who consumed water were significantly less thirsty than those who consumed nothing, after a drink ($p < 0.01$). The Time X Drink X IAc interaction was also significant ($F = (3, 67) = 2.717$, $p < 0.05$, $\eta_p^2 = 0.108$). Participants who consumed nothing were significantly more thirsty than those who consumed glucose ($p < 0.04$), sucralose ($p < 0.05$) and water ($p < 0.002$), but only if they had high IAc ($p = 0.704$, $p = 0.786$, $p = 0.171$ respectively in those with low IAc).

The effect of changes in BG on changes in IAc

To determine whether cardiac and glucoregulatory interoception are functionally coupled the effects of changes in BG on heartbeat perception were determined. Partial correlation analysis (controlling for age and BMI) revealed an interesting pattern of results (Table 2). As reported in the previous analysis, in the glucose

condition a higher fasting IAc predicted better glucoregulatory control; that is a decline in glucose from thirty to sixty minutes post consumption ($r = -0.440$, $p < 0.05$). However, a positive correlation was observed between an increase in BG after 30 minutes and a change in IAc ($r = 0.482$, $p < 0.05$), although the effect was not significant after sixty minutes ($r = 0.295$, $p = 0.2$). Conversely, in both the water ($r = -0.536$, $p < 0.05$ after 60 minutes) and nothing conditions ($r = -0.536$, $p < 0.05$ after 30 minutes, $r = -0.468$, $p < 0.06$ after 60 minutes) negative correlations between changes in BG and changes in IAc were observed. Given that some individuals fell below fasting levels of glucose in both those conditions, these findings are also consistent with an increased interoceptive PE, which would increase attention allocated to interoceptive signals.

Table 2 here

Discussion

The primary objective of the present study was to empirically test predictions from recent theoretical models of interoceptive inference. It is reported that after consuming a glucose drink, those with better interoceptive accuracy (IAc) had lower blood glucose levels, reported a decline in subjective anxiety (but not depression or fatigue), and presented larger modifications of autonomic nervous system (ANS) functioning. In addition, those with high IAc had a decline in hunger after both glucose and sucralose. Taken together, these findings suggest that a high IAc facilitates the ability to counter-regulate during the post-prandial period.

From the perspective of interoceptive inference, a change in the internal states of the body, away from the inferred bodily state, leads to interoceptive prediction error (PE)

(41). If the precision assigned to interoceptive PEs is sufficient (i.e. they are considered reliable), PEs can either ascend into the brain to revise prior beliefs or descend to the periphery to make those prior beliefs come true by engaging autonomic reflexes (42). Assuming individuals who perform well on heartbeat tracking tasks do so because they can flexibly adjust the relative precision of their interoceptive priors and prediction errors (12), this may explain their greater autonomic response following a glucose load.

In the current context, a change in blood glucose, which is not fully predicted by interoceptive priors, gives rise to PE and is ultimately resolved by interoceptive active inference in the form of autonomic reflexes; this effect would be enhanced in those who assign high precision to this interoceptive PEs. In line with the present findings, a number of studies have previously reported greater autonomic reactivity in individuals with higher IAc. For example, those with good heartbeat perception showed a higher autonomic response when the experimenter's hand was moving at the boundary of their peripersonal space (43). In addition, those high in interoceptive accuracy also experienced stronger heart rate responses to pleasant and unpleasant stimuli (44). However, this is the first report that those with better heartbeat perception also exhibit greater autonomic reactivity to a homeostatic challenge, providing the first empirical evidence of the role of interoceptive inference in homeostatic control.

Interestingly, we also observed that those with higher IAc reported a decline in subjective anxiety if they consumed glucose. Numerous models have been proposed to account for the role of interoceptive inference in emotional experience. It was originally argued that emotions per se arise as a result of inferences about the

causes of interoceptive afferents, which is interoceptive inference itself (7). In addition, accounts concerning *emotional valence* suggest that emotion is the result of changes in free energy; a rise in free energy (equivalent to the sum total of PEs) producing negative emotion and a reduction in free energy (either by modifying top-down predictions or by changing the sensory signals through action) producing positive emotion. (45). More recently it has been proposed that *emotional arousal* is dependent on interoceptive precision (12). According to this perspective, people with high IAc are likely to experience feelings of generalized physiological arousal and as their interoceptive PEs are given high precision and these indicate changes in free energy. Indeed, individuals high in anxiety tend to perform better on heartbeat perception tasks (5, 46, 47). However, in the present study, those high in IAc reported a decline in anxiety after glucose; an effect that was absent in those with low IAc. Importantly, at baseline, there were no differences in anxiety that depended upon IAc, thus these findings could not be explained by regression to the mean. A plausible explanation for this finding is that although the interoceptive PEs of people with higher IAc may be cascaded up the interoceptive hierarchy, rather than being suppressed by low-level priors, they are able to effectively minimise this PE through active inference. This explanation is supported by their greater autonomic reactivity and better glycaemic regulation. If this interpretation is correct, a high IAc may lead to positive or negative emotional valence, depending on the context and an individual's ability/opportunity to minimise free energy. This will be an important consideration in future research.

This is the first study to link individual differences in heartbeat perception to glycaemic control; however, a limited neuroimaging literature has associated levels

of peripheral blood glucose to changes in insula activity (48, 49); an area of the brain often linked to heartbeat perception (50), that is thought to play a role in registering interoceptive PE (42). For example, Page et al. (48) reported that hypoglycaemia (between 3.3 and 4.4 mmol/ l) compared to euglycaemia, resulted in a preferential increase in insula (and striatum) activity, in response to images of high caloric foods. In line with models linking interoception and positive alliesthesia (51), there was also a corresponding increase in hunger and 'wanting', but not 'liking' these food items. Similar effects have been isolated specifically to the caudal dorsal mid-insula; a lower BG level ($> 4.4\text{mmol/l}$) was related to an increase in insula activation in response to food, but not non-food, items (49).

The above findings are consistent with the present study; after consuming water or not drinking a decline in BG was associated with an increase in heartbeat perception. On the other hand in those who consumed glucose, an increase in BG was associated with an increase in heartbeat perception. According to models of interoceptive inference, both an increase in BG and a decrease in BG would constitute a shift away from a homeostatic 'set-point', and thus potentially would increase interoceptive PE, explaining the present findings. To the extent that heartbeat perception and insula activation co-vary (52), the present findings support the role of the insula in the computation of interoceptive PE signals. A practical implication of this finding is that future studies utilising heartbeat perception tasks should carefully control the nutritional and homeostatic state of the participants.

Interestingly, individuals with low IAc when fasting were characterised by higher blood glucose levels after sixty minutes, suggesting that they were less able to regulate their glycaemic response. Importantly this finding did not depend upon

individual differences in BMI or age. Taken together with the present finding that an increase in BG led to an increase in HBP, it is plausible that individuals who are better able to attend to interoceptive changes are also better able to minimise PE, though active inference (in this case a probable counter-regulatory increase in insulin in order to restore BG levels).

Previously, individual differences in insulin resistance have been related to areas on the brain involved in interoception, including the insula. For example, in participants with depression who experienced an increase in appetite (but not those who experienced a decrease in appetite), HOMA-estimated insulin resistance was related to a heightened insula response to food cues (53). In addition, the ventral striatum – insula connectivity was enhanced in those with insulin resistance (54). Such findings have been used to support models of positive alliesthesia (51); that is hypersensitivity to bodily signals (e.g. hunger) increases the incentive value of environmental food cues that restore homeostasis; an effect that may be accentuated in those with poorer glucose tolerance. Indeed, we previously reported increased IAc in emotional eaters (26), which may underlie increased reward sensitivity in this population (55, 56). In addition, the present finding that IAc was associated with fasting hunger rating suggests that higher heartbeat perception is indeed related to hunger, which is also in line with a previous finding that changes in hunger following a 24 hour fast correlated with changes in heartbeat perception (57).

Although the association between insulin resistance and insula activity suggests aberrant interoceptive processes in these populations, they appear to contradict the present finding that those with poorer GT had lower, rather than higher IAc. With this in mind, an alternative although not mutually exclusive perspective is that

interoceptive insensitivity may also predispose towards obesity and insulin resistance though a reduction in satiety sensitivity (58). Indeed in the present study we observed that those with high IAc had a decline in hunger after both glucose and sucralose; an effect that was diminished in those with low IAc. In addition, Herbert and Pollatos (59) observed that normal weight participants exhibited better heartbeat perception as compared to overweight and obese participants. However, Herbert and Pollatos (59) did not measure insulin resistance, and the relation between glucose tolerance and IAc in the present study did not depend on BMI.

A further consideration is that the insula also plays a role in propagating prediction-error signals back to visceromotor regions to modify predictions (9). Thus the means of prediction error resolution (i.e. by modifying top-down predictions or by changing the sensory signals through action) in insulin resistance, remains to be determined. For instance, it is possible that reduced IAc in those with poorer glucose tolerance indicates that a greater precision is awarded to prior beliefs, relative to ascending prediction errors. For example, if high-level predictions about the persistence of high blood sugar become abnormally strong (i.e., high blood sugar becomes chronically expected), glucoregulatory control may be diminished and allostatic food-seeking behaviours may be enhanced. Conversely, if prior expectations indicate the persistence of low blood glucose, then the set point at which one becomes aware of low BG, possibly through the occurrence of autonomic or neuroglycopenic warning symptoms may be lowered – this may help understanding of disorders ranging from hypoglycaemia unawareness to eating disorders (in terms of dysfunctional signalling of hunger and satiety). Future research will need to consider this possibility.

A final question is why in the present study did those with high IAc have a decline in hunger after both glucose and sucralose? Importantly, our experimental design allowed us to infer the relative contribution of humeral (blood glucose), gustatory (sweet taste) and gastric (volume of liquid consumed) signals. The pattern of results suggests the influence of sweet taste was important in causing a decline in hunger after glucose and sucrose, but not water, in those with high heartbeat perception. Interestingly, Simmons et al. (49) identified that activity in the caudal dorsal mid-insula increased in response to food images and also in response to low blood glucose – using a gustatory mapping task the authors had previously identified this region of the insula as responsive to a sweet tastant in the same group of participants. These findings suggest overlapping representations of gustatory and interoceptive (low blood glucose) stimuli in the insula. Similar effects have been noted in this region of the brain when participants were asked to attend to sensation coming from their “heart”, “stomach”, or “bladder” (60). Using a fMRI-Adaptation paradigm Avery et al. (61) identified that the dorsal mid-insula exhibited repetition suppression following repeated interoception (heartbeat attention task) trials and also exhibited adapted responses to subsequent gustatory stimuli. This finding suggests that interoceptive and gustatory information is integrated within the insula rather than merely co-represented there. In addition, Murphy et al. (32) found that those with alexithymia, a condition often associated with impaired interoception (30), were less able to discriminate gustatory stimuli of different intensities. Taken together these findings may explain the present observation that those high in IAc had a greater decline in hunger in response to the drinks with a sweet taste. However, as hunger declined similarly in both the glucose and the sucralose

conditions, the influence of blood glucose and sweet taste did not appear to be additive in influencing hunger ratings.

Finally, the vast majority of experimental tests of interoception have focused on differences in cardiac perception (e.g. 37, 62, 63, 64), assumed to represent an indicator of general “interoceptive awareness”. However, it is not clear whether individual sensitivity for cardiac activity is indeed related to the sensitivity for other bodily perturbations. This raises important questions about the interpretation of the extant interoceptive literature, particularly concerning eating behaviour (e.g. 26, 39), where the ability to detect gastric and / or humoral signals may be equally, if not more, important. A minority of studies have assessed interoception in more than one domain simultaneously, generally reporting moderate relationships between sensitivity across axes. For example, Herbert, Muth (65) assessed the relationship between heartbeat perception and the amount of water a person could consume until reaching the point of individually perceived fullness. Cardiac awareness showed a moderate inverse relationship with ingested water volume. On the other hand Garfinkel, Manassei (66) recently found no association between cardiac and respiratory measures of interoceptive accuracy (i.e. heartbeat perception performance), however, cardiac and respiratory measures of interoceptive awareness (i.e. metacognitive insight into own interoceptive ability) were positively correlated.

The present findings lend some support to the suggestion that there is a general sensitivity for interoceptive processes across modalities. Heartbeat perception was related to the affective response to a glucose load, although effects were not consistent across mood dimensions; consuming glucose led to a decline in anxiety in

those with high IAc, no effects were observed for energy levels or depression. In addition, in relation to hunger, the evidence presented here suggests that good heartbeat perceivers may be more sensitive to gustatory influences than gastric fullness, although more research is needed to confirm this.

Conclusions

In conclusion, the present study provides the first empirical confirmation of the role of active interoceptive inference in the control of homeostasis. The finding that after a glucose load, a better interoceptive accuracy (IAc) was related to lower blood glucose levels, a decline in rating of anxiety, and larger modifications of autonomic nervous system (ANS) functioning, can be interpreted as being due to their proficiency in effectively minimise this PE through active inference; the consequence of being better able to flexibly assign precision to interoceptive signals (12). Given that recent conceptualisations of “health” emphasise resilience and the capacity to cope / adapt to daily challenges (28), including homeostatic challenges (29), the present findings point to IAc as an indicator of “phenotypic flexibility”. As such these data may provide mechanistic insight into the heterogeneity in the glycaemic, autonomic, affective and appetitive response to foods and pave the way towards personalized nutritional recommendations. Future research should consider whether aspects of habitual diet impinge upon measures of IAc, as this may indicate their potential to enhance homeostatic control by enhancing active interoceptive inference.

Contributions

HY and DB conceived and designed the methods and study. HW, CG and DDK ran the experiment and were responsible for data collection and entry. HY analysed and interpreted the data, and wrote the manuscript with input from DB.

Competing financial interests

The authors declare no competing financial interests.

Acknowledgments

We would like to thank Swansea University for supporting this research and Gary Freegard for helping set up the equipment used in this experiment.

References

1. Craig AD. Opinion: How do you feel? Interoception: the sense of the physiological condition of the body. *Nature reviews Neuroscience*. 2002;3(8):655.
2. Seth AK. Response to Gu and FitzGerald: Interoceptive inference: from decision-making to organism integrity. *Trends in cognitive sciences*. 2014;18(6):270.
3. Seth AK, Critchley HD. Extending predictive processing to the body: emotion as interoceptive inference. *Behavioral and Brain Sciences*. 2013;36(03):227-8.
4. Harshaw C. Interoceptive dysfunction: Toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychological bulletin*. 2015;141(2):311.
5. Paulus MP, Stein MB. Interoception in anxiety and depression. *Brain structure and Function*. 2010;214(5-6):451-63.
6. Klabunde M, Collado D, Bohon C. An interoceptive model of bulimia nervosa: A neurobiological systematic review. *Journal of Psychiatric Research*. 2017.

7. Seth AK. Interoceptive inference, emotion, and the embodied self. *Trends in cognitive sciences*. 2013;17(11):565-73.
8. Gu X, Hof PR, Friston KJ, Fan J. Anterior insular cortex and emotional awareness. *Journal of Comparative Neurology*. 2013;521(15):3371-88.
9. Barrett LF, Simmons WK. Interoceptive predictions in the brain. *Nature Reviews Neuroscience*. 2015;16(7):419-29.
10. Paulus MP, Stein MB. An insular view of anxiety. *Biological psychiatry*. 2006;60(4):383-7.
11. Pezzulo G, Rigoli F, Friston K. Active Inference, homeostatic regulation and adaptive behavioural control. *Progress in neurobiology*. 2015;134:17-35.
12. Ainley V, Apps MA, Fotopoulou A, Tsakiris M. 'Bodily precision': a predictive coding account of individual differences in interoceptive accuracy. *Phil Trans R Soc B*. 2016;371(1708):20160003.
13. Smith MA, Riby LM, van Eekelen JAM, Foster JK. Glucose enhancement of human memory: a comprehensive research review of the glucose memory facilitation effect. *Neuroscience & Biobehavioral Reviews*. 2011;35(3):770-83.
14. Owen L, Scholey A, Finnegan Y, Sünram-Lea SI. Response variability to glucose facilitation of cognitive enhancement. *British Journal of Nutrition*. 2013;110(10):1873-84.
15. Young H, Benton D. The glycemic load of meals, cognition and mood in middle and older aged adults with differences in glucose tolerance: A randomized trial. *e-SPEN Journal*. 2014;9(4):e147-e54.
16. Owen L, Sünram-Lea SI. Glucose facilitation of cognition: Factors responsible for variability in behavioural response. *Appetite*. 2008;50(2):564.

17. Gibson EL, Scevoli N. Individual differences in glucose facilitation of cognitive function. *Appetite*. 2014;83:353.
18. Young H, Benton D. The nature of the control of blood glucose in those with poorer glucose tolerance influences mood and cognition. *Metabolic brain disease*. 2014;29(3):721-8.
19. Seth AK. The cybernetic Bayesian brain: Open MIND. Frankfurt am Main: MIND Group; 2014.
20. Scholey AB, Sünram-Lea SI, Greer J, Elliott J, Kennedy DO. Glucose enhancement of memory depends on initial thirst. *Appetite*. 2009;53(3):426-9.
21. Benton D, Jenkins KT, Watkins HT, Young HA. Minor degree of hypohydration adversely influences cognition: a mediator analysis. *The American journal of clinical nutrition*. 2016;104(3):603-12.
22. Young HA, Benton D. The use of moderated mediated analysis to study the influence of hypo-hydration on working memory. *Nutricion hospitalaria*. 2016;33(3):71-5.
23. Brannigan M, Stevenson RJ, Francis H. Thirst interoception and its relationship to a Western-style diet. *Physiology & behavior*. 2015;139:423-9.
24. Young HA, Watkins H. Eating disinhibition and vagal tone moderate the postprandial response to glycemic load: a randomised controlled trial. *Scientific Reports*. 2016;6:35740.
25. Young HA, Johnston S, Benton D. Compensatory Autonomic Modulations Mediate Hypohydration Related Changes in Brain Functioning and Mood. *The FASEB Journal*. 2017;31(1 Supplement):298.3-.3.

26. Young, Williams C, Pink AE, Freegard G, Owens A, Benton D. Getting to the heart of the matter: Does aberrant interoceptive processing contribute towards emotional eating? *PLoS One*. 2017;12(10):e0186312.
27. Owens AP, Friston KJ, Low DA, Mathias CJ, Critchley HD. Investigating the relationship between cardiac interoception and autonomic cardiac control using a predictive coding framework. *Autonomic Neuroscience: Basic and Clinical*. 2018.
28. Young HA, Benton D. Heart-rate variability: a biomarker to study the influence of nutrition on physiological and psychological health? *Behavioural pharmacology*. 2018;29(2-):140.
29. Stroeve JH, Wietmarschen H, Kremer BH, Ommen B, Wopereis S. Phenotypic flexibility as a measure of health: the optimal nutritional stress response test. *Genes & nutrition*. 2015;10(3):13.
30. Brewer R, Cook R, Bird G. Alexithymia: a general deficit of interoception. *Royal Society Open Science*. 2016;3(10):150664.
31. Brewer R, Happé F, Cook R, Bird G. Commentary on “Autism, oxytocin and interoception”: Alexithymia, not Autism Spectrum Disorders, is the consequence of interoceptive failure. *Neuroscience & Biobehavioral Reviews*. 2015;56:348-53.
32. Murphy J, Catmur C, Bird G. Alexithymia is associated with a multidomain, multidimensional failure of interoception: Evidence from novel tests. *Journal of Experimental Psychology: General*. 2018;147(3):398.
33. Murphy J, Brewer R, Catmur C, Bird G. Interoception and psychopathology: A developmental neuroscience perspective. *Developmental cognitive neuroscience*. 2017;23:45-56.
34. Quattrocki E, Friston K. Autism, oxytocin and interoception. *Neuroscience & Biobehavioral Reviews*. 2014;47:410-30.

35. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science*. 2014;2(2):119-37.
36. Pollatos O, Georgiou E. Normal interoceptive accuracy in women with bulimia nervosa. *Psychiatry Research*. 2016;240:328-32.
37. Schandry R. Heart beat perception and emotional experience. *Psychophysiology*. 1981;18(4):483-8.
38. Ainley V, Tsakiris M. Body conscious? Interoceptive awareness, measured by heartbeat perception, is negatively correlated with self-objectification. *PloS one*. 2013;8(2):e55568.
39. Pollatos O, Kurz A-L, Albrecht J, Schreder T, Kleemann AM, Schöpf V, et al. Reduced perception of bodily signals in anorexia nervosa. *Eating behaviors*. 2008;9(4):381-8.
40. Lorr M, McNair DM, Fisher S. Evidence for bipolar mood states. *Journal of personality assessment*. 1982;46(4):432-6.
41. Gu X, FitzGerald T. Interoceptive inference: homeostasis and decision-making. *Trends Cogn Sci*. 2014;18(6):269-70.
42. Owens AP, Allen M, Ondobaka S, Friston KJ. Interoceptive inference: from computational neuroscience to clinic. *Neuroscience & Biobehavioral Reviews*. 2018.
43. Ferri F, Ardizzi M, Ambrosecchia M, Gallese V. Closing the gap between the inside and the outside: interoceptive sensitivity and social distances. *PLoS One*. 2013;8(10):e75758.
44. Pollatos O, Herbert BM, Matthias E, Schandry R. Heart rate response after emotional picture presentation is modulated by interoceptive awareness. *International Journal of Psychophysiology*. 2007;63(1):117-24.

45. Joffily M, Coricelli G. Emotional valence and the free-energy principle. *PLoS computational biology*. 2013;9(6):e1003094.
46. Garfinkel SN, Tiley C, O'Keeffe S, Harrison NA, Seth AK, Critchley HD. Discrepancies between dimensions of interoception in autism: implications for emotion and anxiety. *Biological psychology*. 2016;114:117-26.
47. Pollatos O, Traut-Mattausch E, Schandry R. Differential effects of anxiety and depression on interoceptive accuracy. *Depression and anxiety*. 2009;26(2):167-73.
48. Page KA, Seo D, Belfort-DeAguiar R, Lacadie C, Dzuira J, Naik S, et al. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. *The Journal of clinical investigation*. 2011;121(10):4161-9.
49. Simmons WK, Rapuano KM, Kallman SJ, Ingeholm JE, Miller B, Gotts SJ, et al. Category-specific integration of homeostatic signals in caudal but not rostral human insula. *Nature neuroscience*. 2013;16(11):1551.
50. Critchley HD, Wiens S, Rotshtein P, Öhman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nature neuroscience*. 2004;7(2):189-95.
51. Simmons WK, DeVile DC. Interoceptive contributions to healthy eating and obesity. *Current opinion in psychology*. 2017;17:106-12.
52. Schulz SM. Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis. *Phil Trans R Soc B*. 2016;371(1708):20160018.
53. Simmons WK, Burrows K, Avery JA, Kerr KL, Taylor A, Bodurka J, et al. Appetite changes reveal depression subgroups with distinct endocrine, metabolic, and immune states. *Molecular psychiatry*. 2018:1.
54. Ryan JP, Sheu LK, Critchley HD, Gianaros PJ. A neural circuitry linking insulin resistance to depressed mood. *Psychosomatic medicine*. 2012;74(5):476.

55. Gibson EL. The psychobiology of comfort eating: implications for neuropharmacological interventions. *Behavioural pharmacology*. 2012;23(5 and 6):442-60.
56. Gibson EL. Emotional influences on food choice: sensory, physiological and psychological pathways. *Physiology & behavior*. 2006;89(1):53-61.
57. Herbert BM, Herbert C, Pollatos O, Weimer K, Enck P, Sauer H, et al. Effects of short-term food deprivation on interoceptive awareness, feelings and autonomic cardiac activity. *Biological psychology*. 2012;89(1):71-9.
58. Stevenson RJ, Mahmut M, Rooney K. Individual differences in the interoceptive states of hunger, fullness and thirst. *Appetite*. 2015;95:44-57.
59. Herbert BM, Pollatos O. Attenuated interoceptive sensitivity in overweight and obese individuals. *Eating behaviors*. 2014;15(3):445-8.
60. Avery JA, Kerr KL, Ingeholm JE, Burrows K, Bodurka J, Simmons WK. A common gustatory and interoceptive representation in the human mid-insula. *Human brain mapping*. 2015;36(8):2996-3006.
61. Avery JA, Gotts SJ, Kerr KL, Burrows K, Ingeholm JE, Bodurka J, et al. Convergent gustatory and viscerosensory processing in the human dorsal mid-insula. *Human brain mapping*. 2017;38(4):2150-64.
62. Weiss S, Sack M, Henningsen P, Pollatos O. On the interaction of self-regulation, interoception and pain perception. *Psychopathology*. 2014;47(6):377-82.
63. Pollatos O, Herbert BM, Berberich G, Zaudig M, Krauseneck T, Tsakiris M. Atypical self-focus effect on interoceptive accuracy in anorexia nervosa. *Frontiers in human neuroscience*. 2016;10.
64. Shah P, Hall R, Catmur C, Bird G. Alexithymia, not autism, is associated with impaired interoception. *Cortex*. 2016;81:215-20.

65. Herbert BM, Muth ER, Pollatos O, Herbert C. Interoception across modalities: on the relationship between cardiac awareness and the sensitivity for gastric functions. *PloS one*. 2012;7(5):e36646.
66. Garfinkel SN, Manassei MF, Hamilton-Fletcher G, den Bosch YI, Critchley HD, Engels M. Interoceptive dimensions across cardiac and respiratory axes. *Phil Trans R Soc B*. 2016;371(1708):20160014.

Figures and Tables

Figure 1. The glycaemic response to consuming glucose in those with high or low IAc. $n = 20$. After sixty minutes, those with low IAc had significantly higher blood glucose levels than those with high IAc.

Figure 2. Change in HR from before to after consuming either glucose, sucralose, water or nothing in those with high or low IAc. N = 80. In those with high IAc, consuming glucose resulted in a higher HR than consuming water ($p < 0.02$) or nothing ($p < 0.01$).

Figure 3. Change in anxiety from before to after consuming either glucose, sucralose, water or nothing in those with high or low IAc. N = 80. In those who consumed glucose, those with high IAc experienced a decline in ANX ($p < 0.0001$); this effect was absent in those with low IAc ($p = 0.467$).

Figure 4. Change in hunger from before to after consuming either glucose, sucralose, water or nothing in those with high or low IAc. N = 80. Those with high, but not low, IAc had a decline in hunger after glucose ($p < 0.001$) and sucralose ($p < 0.001$) ($p = 0.849$ and $p = 0.667$ respectively in those with low IAc). In addition, those with high, but not low, IAc had an increase in hunger after nothing ($p < 0.03$) ($p = 0.318$ in those with low IAc). No effects were observed in those who consumed water (high IAc $p = 0.223$, low IAc $p = 0.608$).

	Glucose		Sucralose		Water		Nothing		Drink	IAc	IAc X Drink
	Low IAc	High IAc	Low IAc	High IAc	Low IAc	High IAc	Low IAc	High IAc			
Age	20.2(0.9)	20.7(0.8)	20.8(3.5)	19.9(0.9)	20.1(1.1)	21.4(2.2)	20.0(1.1)	22.8(4.7)	p=0.58	p=0.10	p=0.12
BMI	24.4(4.4)	24.5(5.6)	22.4(2.6)	22.1(3.3)	24.8(5.6)	23.7(3.8)	24.1(4.2)	25.0(4.8)	p=0.35	p=0.92	p=0.92
Fasting glucose	5.2(0.6)	5.1(0.4)	5.1(0.5)	4.9(0.9)	5.2(0.5)	5.2(0.4)	5.3(0.4)	4.9(0.5)	p=0.92	p=0.27	p=0.76
Fasting HR	72.5(5.9)	66.3(6.4)	76.3(13.0)	70.2(10.5)	74.1(13.3)	70.7(7.6)	72.4(6.8)	73.2(13.4)	p=0.65	p=0.11	p=0.68
Baseline anxiety	33.4(15.6)	33.1(19.1)	37.6(21.3)	33.2(24.6)	29.1(18.9)	29.2(22.8)	26.1(21.9)	28.8(18.4)	p=0.63	p=0.91	p=0.96
Baseline depression	35.2(18.9)	36.5(24.2)	44.2(14.4)	35.2(20.3)	36.9(14.9)	50.4(11.7)	34.3(25.9)	39.6(15.8)	p=0.57	p=0.52	p=0.32
Baseline tiredness	51.3(30.1)	66.2(14.6)	64.3(17.2)	64.4(30.8)	45.2(24.3)	67.0(17.2)	52.6(26.4)	51.5(25.3)	p=0.51	p=0.13	p=0.42
Baseline hunger	54.0(22.9)	63.6(24.7)	52.1(15.7)	68.0(31.6)	54.3(19.1)	69.7(13.6)	43.6(35.7)	52.0(26.9)	p=0.31	p<0.03	p=0.95
Baseline thirst	60.7(33.2)	82.8(13.1)	55.1(35.5)	64.0(33.2)	69.7(26.5)	86.3(10.7)	66.3(19.7)	80.2(14.7)	p=0.15	p<0.01	p=0.88

Table 1. Demographic and baseline scores for those who consumed glucose, sucralose, water or nothing and those with either high or low IAc. Participants were well match across groups, however, those with high IAc were more hungry and thirsty while fasted.

		Glucose			Sucralose			Water			Nothing		
	Fasting	Δ 30-F	Δ 60-F	Δ 60-30	Δ 30-F	Δ 60-F	Δ 60-30	Δ 30-F	Δ 60-F	Δ 60-30	Δ 30-F	Δ 60-F	Δ 60-30
Mean	5.13	4.76	3.91	-0.85	-0.20	-0.37	-1.17	-0.52	-0.74	-0.21	-0.34	-0.44	-0.10
Range	3.70-6.90	1.30-10.20	0.10-11.60	-8.30-0.30	-1.40-1.20	-1.60-1.00	-1.40-0.40	-1.30-0.60	-2.10-0.30	-1.00-0.40	-1.30-0.40	-1.90-0.50	-1.50-1.30
F IAc	-0.041	-0.179	-0.278	-0.440*	0.387	0.313	-0.168	0.253	0.202	0.064	-0.436	-0.061	0.212
Δ IAc	0.094	0.482*	0.295	-0.122	-0.289	-0.366	-0.025	-0.399	-0.569*	-0.536*	-0.536*	-0.468*	-0.156
F HR	0.042	0.336	0.163	-0.123	0.175	0.108	-0.115	-0.454*	-0.364	-0.118	0.487*	0.440*	0.157
Δ HR	-0.049	0.126	0.129	0.015	0.299	0.271	-0.097	0.531*	0.613**	0.463*	-0.072	-0.216	-0.183

Table 2: Results from the partial analysis that assessed the associations between change in blood glucose and changes in heartbeat perception. * $p < 0.05$.