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Investigating the relationship between cardiac interoception and autonomic cardiac control using a predictive coding framework

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Number of words in abstract: 250
Number of words in main text: 3383
Number of tables: 4
Number of figures: 1

Key words: active inference, autonomic nervous system, dysautonomia, free-energy principle, heart rate variability, homeostasis, interoception, interoceptive (active) inference, predictive coding

Abstract

Predictive coding models, such as the 'free-energy principle' (FEP), have recently been discussed in relation to how interoceptive (afferent visceral feedback) signals update predictions about the state of the body, thereby driving autonomic mediation of homeostasis. . This study appealed to 'interoceptive inference', under the FEP, to seek new insights into autonomic (dys)function and brain-body integration by examining the relationship between cardiac interoception and autonomic cardiac control in healthy controls and patients with forms of orthostatic intolerance (OI); to (i) seek empirical support for interoceptive inference and (ii) delineate if this relationship was sensitive to increased interoceptive prediction error in OI patients during head-up tilt (HUT)/symptom provocation. Measures of interoception and heart rate variability (HRV) were recorded whilst supine and during HUT in healthy controls (N=20), postural tachycardia syndrome (PoTS, N=20) and vasovagal syncope (VVS, N=20) patients. Compared to controls, interoceptive accuracy was reduced in both OI groups. Healthy controls' interoceptive sensibility positively correlated with HRV whilst supine. Conversely, both OI groups' interoceptive awareness negatively correlated with HRV during HUT. Our pilot study offers initial support for interoceptive inference and suggests OI cohorts share a central pathophysiology underlying interoceptive deficits expressed across distinct cardiovascular autonomic pathophysiology. From a predictive coding perspective, OI patients' data indicates a failure to attenuate/modulate ascending interoceptive prediction errors, reinforced by the concomitant failure to engage autonomic reflexes during HUT. Our findings offer a potential framework for conceptualising how the human nervous system maintains homeostasis and how both central and autonomic processes are ultimately implicated in dysautonomia.

1 Introduction

An individual's interoceptive (afferent visceral feedback) accuracy moderates the degree to which bodily events are linked to cognitive-affective processes (1, 2) and individuals with greater interoceptive accuracy experience emotions more deeply, particularly anxiety (3). In a recent study examining previously reported anxiety in postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) patients (4) (5), we described how interoceptive accuracy during head-up tilt (HUT) is anxiogenic in both PoTS and VVS patients compared to healthy controls (6). It has been proposed that predictions of experienced versus expected interoceptive signals can be a 'bottom-up' source of anxiety (7). Therefore, if one were to feel dizzy or tachycardic whilst being aware that these physical sensations were abnormal or symptoms of illness, anxiety would be created about one's discordant body state (8). This hypothesis is supported by our finding that the insula detects discrepancies in predictions rather than actual changes in one's physical state (9).

In predictive coding terms, the mismatch between top-down predictions generated by the brain and sensory signals from the periphery constitute a 'prediction error' (10). Predictive coding, therefore suggests that top-down predictions are used to form prediction errors that are passed back up cortical (and subcortical) hierarchies to update or revise predictions in higher hierarchical levels. The implicit message passing therefore comprises a descending top-down stream of predictions that are reciprocated by an ascending bottom up stream of prediction errors. The influence of a prediction error's signalling as it ascends the cortical hierarchy is based upon its reliability, i.e., 'precision' or inverse variance. Precision-weighting reflects the balance between prediction and prediction error, therefore a high confidence in prior beliefs means that sensory precision is, effectively, attenuated (11). In other words, if sensory input is judged to be imprecise or unreliable, such as vision in the dark, more precision or confidence will be placed in prior expectations – or knowledge of the environment – to ensure optimal perception. In predictive coding, this balance is mediated by differential weighting of prediction errors at different levels of the (interoceptive) hierarchy, in proportion to their estimated precision. Computationally, this means precision-weighted prediction errors are passed from one level to the next, where precise prediction errors at any particular level have more influence on other levels.

Predictive coding models, such as the 'free-energy principle' (FEP) (12, 13), propose that the brain recognises the causes of afferent sensory input using probabilistic (Bayesian) inference to support adaptive responses. The brain endeavours to maximise the evidence for its model of the environment by minimising prediction error (i.e., free-energy or surprise), because the greater the prediction error, the greater the deviation from homeostasis. In other words, by minimising prediction errors, states of the world (and the body) generating sensations must conform to predicted state of affairs. This can be achieved either by changing top-down predictions or by changing the sensory signals through action, a process termed 'active inference' under the FEP, e.g., moving one's sense organs closer to an object that cannot initially be identified.

Recently, predictive coding, and the FEP in particular, have been conceptualised in relation to interoception (14-18) (19), including how interoceptive afferent signals construct predictions about the state of the body that potentially dictate autonomic mediation of homeostasis (20, 21) (17). In this currently hypothetical context, descending predictions would only elicit autonomic responses if the ascending prediction error is not cancelled out by an attenuation of sensory precision (sensory attenuation) (22), otherwise prediction errors would lead to revised predictions rather than action (23). Prediction error in the sensory perceptual system can be modified by changing predictions only, but in the motor system and (potentially) autonomic nervous system (ANS), prediction error can also be discharged by engaging peripheral reflexes and behaviours that alter the sensory signal at its origin.

Although the FEP's potential role in interoception has only recently been considered (14-18), we suggest classical conditioning could be interpreted as an early example of interoceptive inference. Pavlov demonstrated, not only that an unconditioned interoceptive prediction error (food) induces homeostatic autonomic responses (salivation), but that through the encoding of another exteroceptive signal (a bell), the same autonomic reflex can be induced by top-down predictions (24). Pavlov's study illustrates how interoceptive signals contribute to the largely preconscious reflexive regulation of homeostasis and allostasis via the ANS. Moreover, during psychological stress, top-down influences can perturb normal baroreflex function, causing heart rate (HR) and blood pressure (BP) to increase in the absence of allostatic demand. This indicates that the circuitry supporting the baroreflex represents

an important level at which afferent interoceptive cardiac signals interact with descending central activity that encodes expected (predicted) or desired physiological states. Likewise, baroreceptor signalling of cardiovascular arousal ascends the neuraxis to influence conscious perception, cognition and emotion (25) (26) (2, 27).

This pilot study therefore sought empirical support for interoceptive inference in healthy controls, PoTS and VVS patients by asking if homeostatic afferent interoceptive signals – from the viscera – related to autonomic mediation of homeostasis. We hypothesised that if interoceptive inference underpins homeostasis via the ANS, correlations between interoceptive measures and autonomic function should exist. Moreover, these correlations would be sensitive to dysautonomic symptom provocation in PoTS and VVS patients during HUT comparative to healthy controls, when interoceptive prediction error increases as deviation from homeostasis increases but baroreceptor dysfunction prohibits reflexive autonomic allostatic adaption. This should be expressed as a distinct and inverse correlative pattern in PoTS and VVS compared to controls at rest, based on our previous findings that, compared to control subjects, interoceptive accuracy during HUT inversely correlates with anxiety in PoTS and VVS(6).

2 Materials and methods

2.1 Ethics and participants

All experimental procedures received national and institutional ethical approval (NRES Committee London - Harrow, University College London Healthcare Trust Research and Design Office, Imperial College London AHSC Joint Research Compliance Office) and conducted in accordance with the declaration of Helsinki. We recruited 20 healthy controls (13 females, mean age 35 $\pm$ 7.56 years), 20 patients with a confirmed prior diagnosis of PoTS (19 female, mean age 36 $\pm$ 10.84 years) and 20 patients with a confirmed prior diagnosis of VVS (13 female, mean age 37 $\pm$ 13.00, 19 vasodepressor, 1 cardioinhibitory). Autonomic diagnoses were made at the Autonomic Unit, National Hospital for Neurology and Neurosurgery (University College London Hospitals) or the Autonomic and

Neurovascular Medicine Unit, St Mary's Hospital (Imperial College Healthcare Trust) prior to testing. Written informed consent was provided by all participants prior to participation.

PoTS is defined by an abnormal increase in HR on standing or HUT in association with symptoms of palpitations, dizziness, functional impairment in the absence of a significant orthostatic drop in BP (28, 29). VVS is the most common (~40%) form of syncope (30) and is caused by excessive postural vasodilatation and/or bradycardia, resulting in cerebral hypoperfusion and subsequent loss of consciousness. PoTS and VVS represent two of the most common forms of orthostatic intolerance (OI). These patients represent distinct forms if dysautonomia expressed through aberrant cardiovascular (baroreflex) control related to posture. In PoTS, this relates to aberrant cardiovascular sympathoexcitation and in VVS, loss of consciousness is preceded by excessive parasympathoexcitation and the withdrawal of sympathetically-mediated vasoconstriction. However, some forms of VVS are associated with preserved muscle sympathetic nerve activity.

2.2 Interoception protocol

Measures of interoception included i) interoceptive accuracy (one's objective interoceptive ability) scores, which were collected using a heartbeat tracking task (3), ii) interoceptive sensibility (one's subjectively reported sensitivity to interoceptive sensation) and iii) interoceptive awareness (one's metacognitive awareness of one's own interoceptive abilities) (31), i.e., if someone has good interoceptive awareness, the level of their (objective) interoceptive accuracy will match their (subjective) interoceptive sensibility (31). Interoceptive accuracy scores were obtained by counting the R-waves in event-marked electrocardiogram (ECG) traces and averaging the below measure over three tracking periods per exercise (Table 1).

$$1 - (|nbeats_{real} - nbeats_{reported}|) / ((nbeats_{real} + nbeats_{reported})/2).$$

Interoceptive sensibility was measured from the participant's subjective confidence score for performance in each heartbeat tracking task using a visual analogue scale (1 = not confident at all to 10 = very confident indeed). Interoceptive awareness scores were quantified as the strength of

correlation between the measures of interoceptive accuracy and interoceptive sensibility. Importantly to the neurobiological model of interoceptive inference (14, 16), these dimensions of interoception, while originating in beat-to-beat signalling from cardiac and arterial baroreceptors (32, 33), have cortical representations, notably within anterior insular cortex (AIC) (26, 34), a site of descending control of baroreflex function (21).

Using the fast fourier transformation (FFT) nonparametric method, which is typified by discrete peaks of the frequency bands, we continuously recorded HR and quantified cardiovascular autonomic control from heart rate variability (HRV) and associated high (0.15-0.4 Hz) and low (0.04 to 0.15 Hz) frequency components. High frequency (HF-HRV) is a sensitive measure of parasympathetic modulation of the RR interval and cardiac coupling to respiratory changes. Low frequency (LF-HRV) HRV was, until relatively recently, believed to depict sympathetic cardiac influences (35) however, this has been called into question (36, 37), as studies have shown that endogenous fluctuations in LF-HRV provide information about sympathetic regulation of BP. Moreover, recent studies have positively correlated LF-HRV and baroreceptor sensitivity (36, 38) as well as reduced LF-HRV and baroreflex-cardiovagal failure (39). HRV data was collected using PowerLab 16/30, AD Instruments, Oxford, United Kingdom. Data was checked for erroneously detected R-peaks before analysis. The ambient temperature of the examination room was maintained at 19℃.

The protocol was comprised of two stages (table 1): (i) supine (10 mins) and HUT (10 mins). Heartbeat tracking task epoch lengths (25, 35, 45 secs) for interoception tasks were taken from previous studies that identified optimum task timeframes (40, 41) and then randomised during the protocol. Different timeframes were used to prevent habituation, retain attention and discourage participants from merely counting seconds. Participants were asked to not take their pulse and to confirm that they could not feel their pulse against any clothing or apparatus. A minimum 3 mins baseline period was inserted between each stage of the protocol to allow haemodynamic profiles to return to baseline.

Tests	Supine baseline	Head-up tilt
Purpose of test(s)	To acquire normative hemodynamic data	To assess orthostatic tolerance and increase prediction error in OI subjects
Description of test	Minimum of 10 mins supine rest during beat-to-beat heart rate variability collection	10 mins 60° head-up tilt, during which the bed the subject is securely laying on is tilted to 60° (head upward)
Autonomic measures	Heart rate Low-frequency heart rate variability High- frequency heart rate variability	Heart rate Low-frequency heart rate variability High- frequency heart rate variability
Interoceptive measures	Objective interoceptive accuracy Subjective interoceptive sensibility Metacognitive interoceptive awareness	Objective interoceptive accuracy Subjective interoceptive sensibility Metacognitive interoceptive awareness

Table 1. **Overview of interoceptive inference protocol. This table outlines the exercises, interoceptive measures and autonomic variables during testing. This pilot study sought initial empirical support for interoceptive inference in healthy controls, postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) patients by examining if homeostatic afferent interoceptive signals relate to autonomic mediation of homeostasis. If interoceptive inference underpins autonomically mediated homeostasis, correlations between interoceptive measures and autonomic function should exist and these correlations should be sensitive to dysautonomic symptom provocation in forms of orthostatic intolerance (OI) during head-up tilt (HUT), when interoceptive prediction error increases, but baroreceptor dysfunction prohibits reflexive autonomic allostatic adaption. This should increases in prediction error should be expressed as a distinct and inverse correlative pattern in PoTS and VVS compared to controls at rest, based on our previous findings**

2.3 Statistical analysis

Statistical analysis was performed online using SPSS (version 20). Descriptive statistics are presented as mean (± 1 SD) for normally distributed data. Quantitative variables were compared across multiple time points using analysis of variance and at single time points by independent t-tests for two groups. Data were corrected for multiple comparisons and Pearson correlation coefficients were used to study pairwise correlations between normally distributed variables. Spearman correlation analysis was used for analysis of variables or non-normally distributed variables. Preliminary analyses were carried out to assess if there was a violation of the assumptions of normality, linearity, and homoscedasticity. Using Cohen's effect size (ES) statistic (42), a correlation coefficient of .10 represented a weak association; a correlation coefficient of .30 was considered a moderate correlation and a correlation coefficient of .50 or larger represented a strong correlation. Statistical significance was specified as a 2-tailed p-value of <0.05.

3 Results

3.1 Interoceptive accuracy

Compared to controls, patients with PoTS and VVS displayed lower interoceptive accuracy (Figure 1). This was reduction was not significant in PoTS patients but VVS patients showed significantly lower interoceptive accuracy at baseline and during HUT.

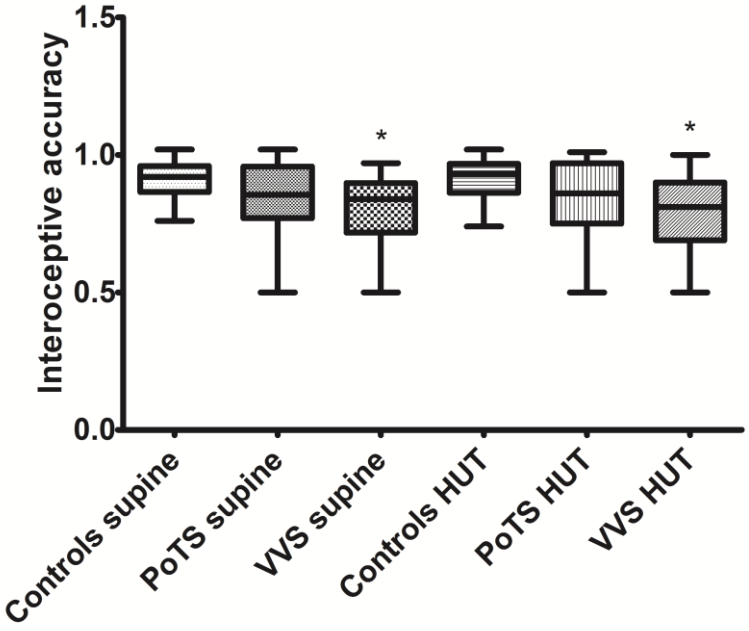


Figure 1. Interoceptive accuracy scores were collected whilst supine and during head-up tilt (HUT) from patients with the postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) vs healthy controls. ± = standard deviation, * = statistically significant (p=.05)

3.2 Interoceptive sensibility

There were no between-group differences in interoceptive sensibility (table 2).

Interoceptive sensibility	Supine	HUT
Healthy controls	5.0 ± 4.5	3.7 ± 7.8

Postural tachycardia syndrome	5.2 ± 1.8	5.1 ± 1.7
Vasovagal syncope	4.2 ± 2.1	3.9 ± 2.3

Table 2. Interoceptive sensibility scores were collected whilst supine and during head-up tilt (HUT) from patients with the postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) vs healthy controls. ± = standard deviation

3.3 Interoceptive awareness

There were no between-group differences in interoceptive awareness (table 3).

Group	Interoceptive Awareness
Healthy controls	.29 ± .37
Postural tachycardia syndrome	.22 ± .53
Vasovagal syncope	.22 ± .42

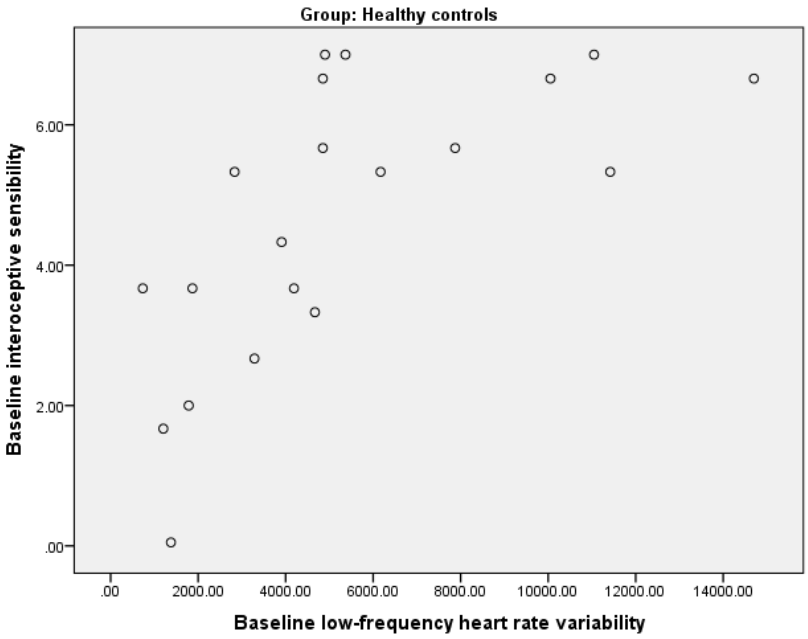
Table 3. Group interoceptive awareness scores were equated for from patients with the postural tachycardia syndrome and vasovagal syncope vs healthy controls. ± = standard deviation

3.4 Interoception and heart rate variability

A Pearson product-moment correlation was conducted to evaluate the relationship between cardiac interoception (as measured by interoceptive accuracy, interoceptive sensibility and interoceptive awareness) and autonomic cardiac control (as measured by LF-HRV and HF-HRV). Preliminary analyses showed that there was no violation of the assumptions of normality, linearity, and homoscedasticity. There were strong, positive correlations between healthy controls' supine LF-HRV (r_s= .816, p=.001), HF-HRV (r_s= .676, p=.002) and interoceptive sensibility (Table 4). There were moderate, negative correlation between PoTS patients' HF-HRV (r_s= -.457, p=.043) and interoceptive awareness. There was a strong negative correlation between VVS patients' HF-HRV (r_s= -.658, p=.015) and interoceptive awareness. Thus, the positive correlations between interoception and autonomic outflow in control participants was reversed in PoTS and VVS patients under orthostatic engagement

of the baroreflex, when interoceptive prediction error increases as deviation from homeostasis increases but baroreceptor dysfunction prohibits reflexive autonomic allostatic adaptions.

2a



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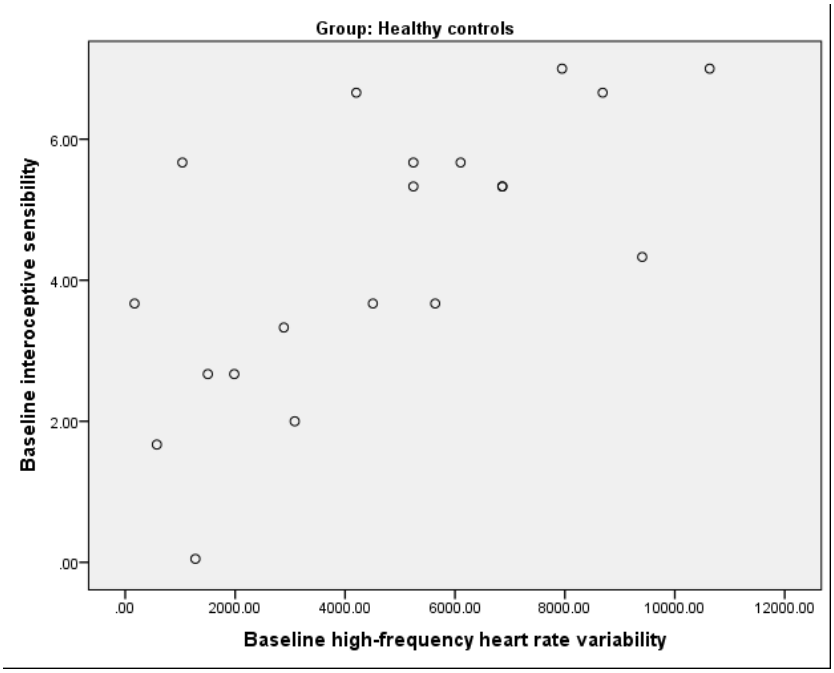

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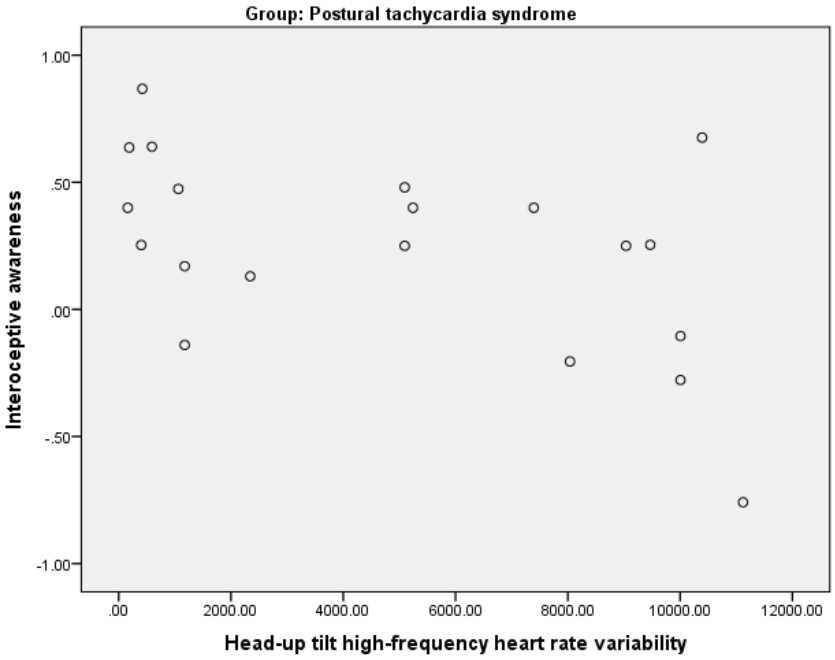

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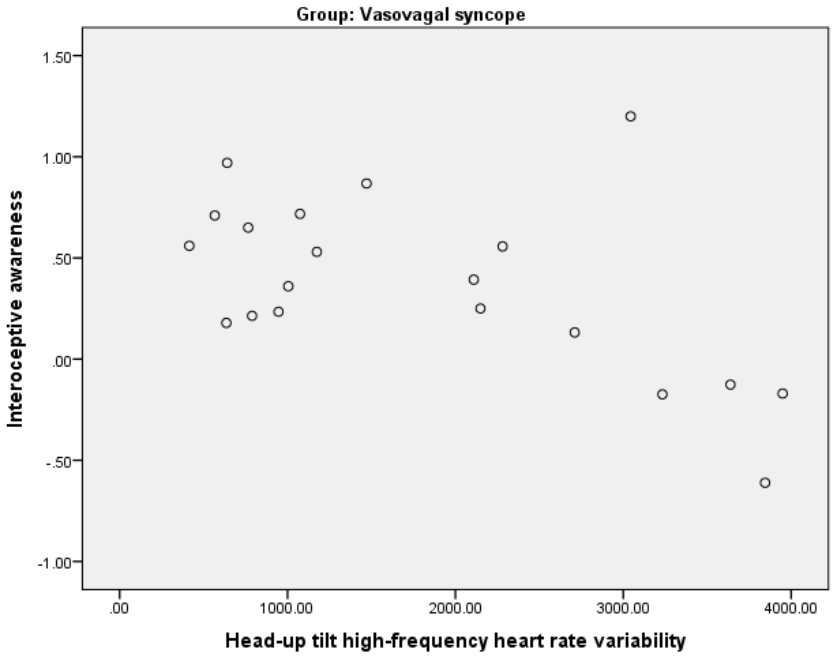

Figures 2a, b, c, d Give an overview of how interoceptive inference may subjugate autonomic reflexes, as measured by high frequency and low frequency heart rate variability Correlations between cardiac interoceptive measures and autonomic cardiac control were found in healthy controls (fig 2a and 2b) whilst supine and orthostatic intolerance patient groups during increased interoceptive prediction error (head-up tilt) (figs 2c and 2d). Interoceptive accuracy is an objective interoceptive measure gained from the subject's performance during a heartbeat tracking task. Interoceptive sensibility represents subjective confidence in one's own interoceptive accuracy. Interoceptive awareness is a metacognitive measure of the degree to which objective interoceptive accuracy relates to interoceptive sensibility

4 Discussion

This study sought empirical support for the interoceptive inference hypothesis by examining the relationship between measures of cardiac interoception and autonomic cardiac control and to delineate if these correlations would be sensitive to autonomic symptom provocation in PoTS and VVS patients during HUT, when dysautonomia would increase interoceptive prediction error, comparative to healthy controls

From the perspective of interoceptive inference, the lower interoceptive accuracy in the patient groups can be interpreted as a failure to appropriately 'contextualise' autonomic precision or gain, i.e., unlike healthy controls - where cardiovascular autonomic arousal normally increases interoceptive accuracy (43) - the opposite occurred in both OI patient groups. In other words, normal interoceptive inference normally adjusts the gain of sympathetic and parasympathetic drives so that they are context-sensitive but in PoTS and VVS, a failure of precision would present as context-sensitive failures of autonomic reflexes, such as a postural HR increase exceeding that necessitated for cardiac output to maintain organ perfusion or loss of consciousness due to cerebral hypoperfusion.

If top-down regulation of precision is expressed in attentional selection of precise sensory information, a failure to attenuate or contextualise precision translates into a failure to attend accurately to ascending interoceptive signals. At a primary level of analysis, our results indicate that attention to interoceptive cues is ineffective in OI because the underlying neuromodulatory mechanisms that flexibly regulate synaptic gain within the central autonomic network (CAN) are compromised, for which there is recent evidence (44, 45). This argument suggests that patients may experience difficulty in withdrawing attention from the interoceptive domain, and is supported by observations of bodily hypervigilance in PoTS and VVS patients (46, 47) (6). Our data on reduced interoceptive accuracy is comparable to sensory attenuation in the somatosensory domain, such that the same psychophysiological phenomena

that underlie somatosensory attenuation produces an underestimation of self-generated internal sensations (see figure 1).

This offers a formal explanation for the paradoxical increased bodily hypervigilance but reduced interoceptive accuracy we recently found in a related study (6). Under predictive coding framework, fluctuations in interoceptive prediction error typically go unnoticed because they are resolved by autonomic reflexes. Only when unresolved prediction errors are large enough to ascend to higher levels of the interoceptive hierarchy are they available for conscious perception. Active inference accounts propose that responses to prediction error depend upon how the brain selects or attends to afferent sensory signals (48). Both OI patient groups underestimated their HR at rest and during symptom and interoceptive prediction error provocation. This implicit failure to appropriately attend to interoceptive signals suggests that relevant (autonomic/cognitive) control networks, most-likely involving the insula and anterior cingulate cortex (49), are unable to select afferent inputs (50). This might contribute to the reported cognitive difficulties in PoTS (51-53) and explain why patients with PoTS and VVS report symptoms of indecisiveness and distractibility compared to healthy controls (47) (6).

We hypothesised that if interoceptive signals drive autonomic mediation of homeostasis, interoceptive and autonomic measures would correlate. Additionally, symptom provocation in OI patients would be expressed as an inverse correlative pattern, based on our previous findings that interoceptive accuracy inversely correlates with anxiety in PoTS and VVS compared to healthy controls (6). The correlations between interoceptive measures and HRV could support interoceptive inference's hypothesis. The strong positive correlations between supine interoceptive sensibility and LF-HRV and HF-HRV in healthy controls is consistent with interoception's homeostatic role, i.e., more accurate interoception means better autonomic responsivity. In principle, a failure to attenuate or contextualise ascending interoceptive prediction error would preserve interoceptive accuracy under autonomic stress, however, PoTS and VVS patients cannot adequately use their interoceptive prediction errors to engage autonomic reflexes during HUT due to autonomic dysfunction. In this situation, these patients are less able to produce reactive changes in autonomic outflow, so prediction errors must be resolved through

central interoceptive processes rather than autonomic function, producing an inverted correlative pattern to controls under orthostatic challenge but leaving metacognitive autonomic awareness unchanged between controls and OI subjects, as observed. This may also explain why interoceptive awareness was the interoceptive measure that correlated with HRV amongst both PoTS and VVS patients. The fact that interoceptive sensibility and awareness rather than interoceptive accuracy – the most commonly used interoceptive measure in research – correlated with HRV, supports Garfinkel and colleague's (31) proposal that most interoceptive experiments may be using the least relevant measure of interoception.

Two recent neuroimaging studies relate to the potential aberrant central correlate for interoceptive disruptions in OI. The first showed left insula volume reductions in PoTS patients correlate with affective symptoms (44). The second reported reduced right insula volumes correlated with BP falls during HUT in VVS patients (45). The insula is part of the CAN (54) and vital for autonomic and interoceptive processes (26). The involvement of the insula in PoTS and VVS neuropathophysiology is unlikely to be the result of age-related neurodegeneration, as these forms of OI typically manifest in adolescence and early adulthood (28, 55), as reflected by the participants' mean ages of 32 and 24 years in these studies respectively. The AIC is suggested to coordinate a relaying of tactile (56) and interoceptive prediction errors (20) and to encode interoceptive representations of self and others, as well as being implicated in error-based learning of affect and uncertainty (57). Therefore, insula abnormalities in OI could have a bearing on interoceptive inference and associated peripheral systems. We have found some support for this in VVS (58). Using voxel-based morphometry, we established a hierarchical predisposition for VVS, in which VVS subjects had reduced medulla, midbrain and left caudate volumes in comparison to healthy controls. Additionally, caudate volume predicted anxiety, faint frequency and HF-HRV. Together, these findings indicate the mapping of the interoceptive inference hierarchy, starting with subcortical structures, such as striatum, and homeostatic brainstem regions that channel prediction error as they ascend the cortical hierarchy and predictions generated by the brain that descend the cortical hierarchy via the peripheral cardiovascular hub of the baroreflex.

This study had several limitations. Neuroimaging would have allowed for more robust investigation of interoceptive processing of autonomic feedback, and importantly, potentially provided direct assessment of prediction error signatures. Physiological measures, such as cardiovascular fitness and body mass index were not standardized across subjects, the former having been previously positively correlated with interoceptive accuracy. A further limitation is the small number of subjects in the study, lack of respiratory measurement in relation to HF-HRV and the lack of blood pressure measurement to provide a robust marker of sympathetic nerve activity. Unfortunately, beat-to-beat blood pressure monitoring was not possible during the heartbeat tracking task, due to the possible confounding effect of the finger cuff used for digital photoplethysmography. It is also important to consider other explanations for our findings than predictive coding, such as non-cardiac mechanoreceptors in varying locations (e.g., thoracic or cutaneous mechanoreceptors) providing greater sensory input to OI phenotypes compared to controls.

4.1 Conclusion

This study appealed to interoceptive inference to offer new insights into autonomic (dys)function and brain-body integration in healthy subjects and in individuals for whom autonomically mediated homeostasis is intermittently compromised. The diminished interoceptive accuracy in PoTS and VVS can be interpreted as a failure to contextualise autonomic precision, as normal interoceptive inference adjusts the gain of sympathetic and parasympathetic reflexes so that they are context-specific and maintain homeostasis. Correlations between cardiac interoception and HRV are interpreted in terms of between-participant differences in gain afforded to interoceptive prediction errors. The negative correlations between interoceptive measures and HRV during HUT in PoTS and VVS can be interpreted as an inappropriate preservation of interoceptive precision that goes hand-in-hand with a failure to engage autonomic reflexes. This study considered how interoceptive afferents construct predictions about the state of the body, offering a new approach to studying the interactions between the central and autonomic nervous systems' mediation of homeostasis.

Competing interests:

Dr Andrew Owens reports no disclosures
Prof Karl Friston reports no disclosures
Dr David Low reports no disclosures
Prof Christopher Mathias reports no disclosures
Prof Hugo Critchley reports no disclosures

Acknowledgments:

We would like to thank all those who participated in and supported this study. APO was funded by a research fellowship from the Autonomic Charitable Trust and the St Mary's Development Trust.

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