Autonomic Neuroscience: Basic and Clinical xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

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

Andrew P. Owens[a,b,c,*], Karl J. Friston[d], David A. Low[e], Christopher J. Mathias[f], Hugo D. Critchley[g,h,i]

[a] Lab of Action & Body, Department of Psychology, Royal Holloway, University of London, Egham, Surrey, UK
[b] Institute of Neurology, University College London, London WC1N 3BG, UK
[c] National Hospital Neurology and Neurosurgery, UCL NHS Trust, London WC1N 3BG, UK
[d] Wellcome Trust Centre for Neuroimaging, University College London, WC1N 3BG, UK
[e] School of Sport and Exercise Sciences, Liverpool John Moores University, Liverpool L3 2AB, UK
[f] Hospital of St John & St Elizabeth, London NW8 9NH, UK
[g] Psychiatry, Brighton and Sussex Medical School, Brighton BN1 9RR, UK
[h] Sussex Partnership NHS Foundation Trust, Brighton BN1 9RRUK, UK
[i] Sackler Centre for Consciousness Science, University of Sussex, BN1 9RR, UK

A R T I C L E I N F O

Keywords:
Active inference
Autonomic nervous system
Dysautonomia
Free-energy principle
Heart rate variability
Homeostasis
Interoception
Interoceptive (active) inference
Predictive coding

A B S T R A C T

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 (Damasio, 1999; Gray et al., 2012) and individuals with greater interoceptive accuracy experience emotions more deeply, particularly anxiety (Schandry, 1981). In a recent study examining previously reported anxiety in postural tachycardia syndrome (PoTS) and vasovagal syncope (VVS) patients (Eccles et al., 2015) (Owens et al., 2017), we described how interoceptive accuracy during head-up tilt (HUT) is anxiogenic in both PoTS and VVS patients compared to healthy controls (Owens et al., 2017). It has been proposed that predictions of experienced versus expected interoceptive signals can be a ‘bottom-up’ source of anxiety (Paulus and Stein, 2006). 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 (Owens et al., Under review-b). This hypothesis is supported by our finding that the insula detects discrepancies in predictions rather than actual changes in one's physical state (Gray et al., 2007).

* Corresponding author at: Lab of Action & Body, Department of Psychology, Royal Holloway, University of London, Egham, Surrey TW20 0EXU, UK.
E-mail address: andrew.owens@rhul.ac.uk (A.P. Owens).

https://doi.org/10.1016/j.autneu.2018.01.001
Received 22 September 2017; Received in revised form 20 December 2017; Accepted 4 January 2018
1566-0702/

In predictive coding terms, the mismatch between top-down predictions generated by the brain and sensory signals from the periphery constitute a 'prediction error' (Clark, 2013). 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 (Kanai et al., 2015). 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) (Friston, 2009; Friston, 2010), 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 (Seth et al., 2011; Seth and Critchley, 2013; Barrett and Simmons, 2015; Ondobaka et al., 2017; Quattrocki and Friston, 2014) (Owens et al., Under review-a), including how interoceptive afferent signals construct predictions about the state of the body that potentially dictate autonomic mediation of homeostasis (Gu et al., 2013; Gianaros et al., 2012) (Ondobaka et al., 2017). 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) (Brown et al., 2013), otherwise prediction errors would lead to revised predictions rather than action (Adams et al., 2013). 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 (Seth et al., 2011; Seth and Critchley, 2013; Barrett and Simmons, 2015; Ondobaka et al., 2017; Quattrocki and Friston, 2014), 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 (Pavlov, 1927). 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 (Waldstein et al., 1991) (Critchley et al., 2004) (Gray et al., 2012; Garfinkel et al., 2014).

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 (Owens et al., 2017).

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 ± 7.56 years), 20 patients with a confirmed prior diagnosis of PoTS (19 female, mean age 36 ± 10.84 years) and 20 patients with a confirmed prior diagnosis of VVS (13 female, mean age 37 ± 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 (Mathias et al., 2012; Freeman et al., 2011). VVS is the most common (~40%) form of syncope (Fenton et al., 2000) 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 (Schandry, 1981), ii) interoceptive sensibility (one's subjectively reported sensitivity to interoceptive sensation) and iii) interoceptive awareness (one's metacognitive awareness of one's