The genesis and presentation of anxiety in disorders of autonomic overexcitation

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Abstract

Introduction: We investigated the genesis and presentation of previously–reported anxiety in disorders of autonomic overexcitation in relation to interoception, body vigilance and trauma to test our hypothesis that patients with the postural tachycardia syndrome (PoTS), vasovagal syncope (VVS) and essential hyperhidrosis (EH) represent atypical anxiety phenotypes in whom affective symptoms are more related to apprehension and vigilance of physiological (interoceptive) feedback than neurotic or trauma-related factors.

Methods: The Anxiety Sensitivity Index, Body Vigilance Scale, Self-consciousness Scale, Childhood Trauma Events Scale and heartbeat tracking tasks were completed by 23 healthy controls, 21 PoTS, 20 EH and 20 VVS patients. Interoceptive accuracy (IA) was assessed during supine rest (9mins), isometric exercise (3mins), cold pressor (90s) and head up tilt (HUT) (9mins)

Results: In comparison to controls, PoTS, VVS and EH patients reported increased symptoms of somatic anxiety but not of social anxiety/self-consciousness or trauma. Autonomic patients' IA was diminished and consistently underestimated even during autonomic arousal compared to controls. Controls and EH IA negatively correlated with somatic anxiety/hypervigilance, whereas PoTS and VVS IA and somatic anxiety/vigilance positively correlated.

Conclusions: Affective symptoms in PoTS, VVS and EH appear to be driven by anxiety and vigilance of physical sensations/symptoms, rather than trauma or neurosis. Increased somatic vigilance/anxiety in PoTS and VVS may be due to interoception being anxiogenic in these cohorts. Diminished interoception may be due to a common central dysregulation, as both sudomotor and cardiovascular forms of autonomic dysfunction had comparable IA deficits. These findings provide a possible therapeutic pathway for psychological symptoms in PoTS, VVS and EH.

Keywords: hyperhidrosis, vasovagal syncope, postural tachycardia syndrome, interoception, anxiety.

Introduction

Postural tachycardia syndrome (PoTS), vasovagal syncope (VVS) and essential hyperhidrosis (EH) are forms of intermittent dysautonomia; a set of conditions characterised by temporary dysregulation of normative autonomic function, in which sympathetic and/or parasympathetic responses evoked by day-to-day physiological challenges exceed what is required to maintain homeostasis and cause functional impairments that impact quality of life (QoL). Intermittent dysautonomia is typically expressed as orthostatic intolerance (OI) or thermoregulatory dysfunction (Mathias and Bannister, 2013). Postural tachycardia syndrome (PoTS) is defined by an excessive increase in heart rate (HR) (+30 BPM or HR >120 BPM) with palpitations and dizziness occurring within 10 mins of standing upright (orthostasis) or head-up tilt (HUT), but without orthostatic hypotension (systolic blood pressure [SBP] fall of > 20 mmHg or > 10mmHg diastolic blood pressure [DBP]) (Freeman et al., 2011). Vasovagal syncope(VVS) is the most common (~40%) form of syncope (Fenton et al., 2000), caused by excessive postural vasodilatation and/or bradycardia. VVS can be provoked both by physiological challenges, including injury, prolonged standing, dehydration or heat stress, and by psychological/emotional challenges. Essential hyperhidrosis (EH) is defined by excessive sweating, typically on the palms of the hands, soles of feet and axillae. EH can also be provoked both by mild exertion, mild heat stress and psychological/emotional challenges (Lai et al., 2014).

Autonomic symptoms are commonly experienced by patients with psychiatric diagnoses. These symptoms may be comparable to PoTS, VVS and EH, including sweating, faintness or palpitations. However, clinical diagnostic criteria of an autonomic disorder are rarely met (Ruchinskas et al., 2002, Lkhagvasuren et al., 2011). Conversely, comorbid, typically sub-clinical psychological (cognitive-affective) symptoms are common in patients with PoTS, VVS and EH (Giada et al., 2005, Gracie et al., 2006, Ruchinskas, 2007, D'Antono et al., 2009, Rios-Martinez et al., 2009). Patients with PoTS are more likely to report anxiety and panic symptoms. Both PoTS and panic disorder share psychological and physiological symptoms (Esler et al., 2004) but PoTS symptoms are attributable to a breakdown of peripheral autonomic reflexes (Masuki et al., 2007), in contrast panic disorder's psychogenic sympathoexcitation (Coupland et al., 2003). Many patients with PoTS express maladaptive cognitive errors, including catastrophizing, which can add to functional disability and reinforces anxiety and somatic hypervigilance (Benrud-Larson et al., 2003). Alongside comorbid anxiety and depressive symptoms, patients with PoTS often describe poor sleep quality, fatigue (Bagai et al., 2011) and 'brain fog' (Ocon, 2013, Ross et al., 2013). Psychometry may reveal deficits in cognitive functioning, including impaired attention, short-term memory and recall abilities (Raj et al., 2009, Anderson et al., 2014). However, the psychological morbidity in patients with PoTS appears secondary to the primary autonomic pathology (Khurana, 2006, Masuki et al., 2007, Raj et al., 2009).

Depression, anxiety and blood-injection-injury phobia are common in VVS (Graham, 1961, McGrady et al., 2001, Luborsky et al., 1973, Karaca et al., 2007) and anxiety has been associated with increased risk of syncope during HUT (Cohen et al., 2000) and greater syncope burden (Lerma et al., 2013). VVS patients who do not respond to treatment are more anxious and depressed, report more negative thoughts regarding physical harm or death, and experience increased avoidance/protection coping behaviour and rumination (Gracie et al., 2006).

Among patients with EH, rates of anxiety are higher and underlying deficits in emotional processing, characterised by increased levels of alexithymia (inability to identify and describe emotions) are noted (Ak et al., 2013). Patients with EH report poorer QoL and increased social anxiety compared to patients with other dermatological diagnoses (Lessa Lda et al., 2014). Thoracic sympathectomy can cause compensatory hyperhidrosis but may still improve subjective symptoms and QoL (Ramos et al., 2006). In summary, affective/emotional and sudomotor factors can be difficult to dissociate in EH.

Influential theories acknowledge the key contribution of peripheral physiological changes in the experience of emotions (James, 1894, Damasio, 1994). For example, 'somatic markers', such as a racing heart and breathlessness, enhances anxiety symptoms. The signalling and processing of internal bodily sensations, particularly those relayed by viscerosensory afferent nerves conveying autonomic state, is termed 'interoception'. Interoception contributes to homeostatic control through autonomic reflexes (e.g. baroreflex) and/or behavioural change. Correspondingly, the degree to which a person is sensitive to interoceptive signals is linked to emotional experience: e.g., people better at laboratory tests of heartbeat detection (judging when one's heart is beating) may experience emotions, notably anxiety, with greater intensity (Schandry, 1981, Wiens et al., 2000) (Critchley et al., 2004). An individual's interoceptive accuracy (IA) moderates emotional and motivational behaviour (Damasio, 1999, Gray et al., 2012).

IA is a potential vulnerability factor for anxiety disorders (Dunn et al., 2010a), however, a more comprehensive account incorporates notions of attribution, expectation and prediction about bodily arousal. Discrepancies between expected and actual homeostatic signals (interoceptive prediction errors) contribute to anxious feelings. This effect can be exacerbated by imprecise interoceptive predictions and prior beliefs (Paulus and Stein, 2006). For example, an interoceptive prediction error occurs that is large-enough to reach conscious awareness when we feel dizzy, tachycardic or too hot, especially in a situation in which we consider these autonomic responses as inappropriate, based on previous experience and environmental

information, such as observing others in the same environment but in an apparently dissimilar autonomic state. The interoceptive prediction error signals a disruption of homeostasis, creating a central high-order response, e.g., anxiety or behaviour modification (Garfinkel et al., 2014, Owens et al., under review, Ondobaka et al., 2015). Consistent with this proposal are observations that patients with autonomic failure, who cannot generate centrally driven states of autonomic arousal, show attenuation of some high-order emotional responses (Chauhan et al., 2008, Heims et al., 2006). Correspondingly, in patients with PoTS, VVS and EH, autonomic hyperactivity and interoceptive signals can interact in the over-expression of mood and anxiety symptoms (Eccles et al., 2015). One small study of patients with PoTS examined interoceptive ability but did not show differences from controls in cardiac IA (Khurana, 2014). However, patients with PoTS described more experience of different types of palpitations during testing, suggesting increased attention to cardiothoracic symptoms.

In this study, we investigated individual factors underlying the genesis and presentation of anxiety symptoms in disorders of transient autonomic overexcitation. Specifically, we examined how, interoceptive accuracy (IA), body vigilance and trauma interact with the expression of exaggerated autonomic responses in patients with PoTS, VVS and EH. Our central hypothesis was that apprehension and vigilance of interoceptive feedback provide better explanatory power for affective symptoms in these patients, than neurotic or trauma-related factors. We measured individual differences in IA using heartbeat detection tasks, both at rest and during autonomic arousal, and we assessed anxiety, body vigilance and history of trauma using questionnaires.

Methods

Participants

All experimental procedures were ethically approved by University College London Healthcare Trust Research and Design Office and the Imperial College London Research Ethics Committee. We recruited twenty-one patients with an established diagnosis of PoTS (19 female, mean age 36 years), twenty patients with diagnosis of VVS (13 female, mean age 37 years, 19 vasodepressor, 1 cardioinhibitory) and twenty patients with diagnosis of EH (5 female, mean age 46 years) alongside twenty healthy controls (13 females, mean age 35 years). Autonomic diagnoses were made after investigation 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). Written informed consent was provided by all participants prior to participation.

Interoception protocol

Ambient temperature of the treatment room was maintained at 20°C throughout testing for all participants. Heart rate (HR) was recorded continuously (PowerLab 16/30, AD Instruments, Oxford, United Kingdom) and analysed offline.

During the 3rd, 6th and 9th minutes of supine baseline, participants carried out a heartbeat tracking task (Schandry, 1981), silently counting each heartbeat during an epoch of pseudorandom duration (21, 26, 36, 25, 35 or 45 seconds). Epoch length was taken from previous studies that have identifying optimum task windows (Pollatos et al., 2009, Dunn et al., 2010b). Participants were instructed to not manually take or touch their pulse and to declare that they could not feel their pulse against any clothing or apparatus. This task was repeated twice more. The paradigm was repeated during various manoeuvres that increase sympathetic nerve activity (SNA): 3 mins supine isometric exercise (33% MVC), 90 seconds supine cold pressor applied to the hand and 9 mins head up tilt (HUT). Pressor manoeuvres are reliable and robust clinical assessment of vasomotor integrity (Khurana and Setty, 1996, Mathias et al., 2013, Mathias, 2003). 3 mins baseline was allowed between each stage of the protocol to allow hemodynamics to return to normal. As well as increasing SNA, both pressor exercises have central components; nociceptive in the case of the cold pressor and the recruitment of central command to maintain handgrip during isometric exercise (Victor et al., 1995). HUT is a pure measure of vasomotor integrity in response to orthostasis. HUT was terminated if syncopal, pre-syncopal or orthostatic-related symptoms were recorded or reported by the participant.

IA scores were yielded by counting the R waves in the event-marked electrocardiogram (ECG) traces and averaging the following equation over the 3 tracking tasks of each stage of the protocol (supine baseline, isometric exercise, cold pressor, HUT):

$$1 - (|n\text{beats}_{real} - n\text{beats}_{reported}|)/((n\text{beatsreal}+n\text{beats}_{reported})/2).$$

Self-report measures

Self-report measures were completed prior to testing. These were designed to measure anxiety sensitivity, body vigilance, history of childhood trauma and self-consciousness (table 1).

Questionnaire name	***Description***
Anxiety Sensitivity Index	An 18 item questionnaire designed to assess apprehension of anxiety-related sensations based on beliefs about their harmful consequences (Reiss et al., 1986).
Body vigilance scale (BVS)	Examines the tendency to selectively attend to physiological changes in one's body (Schmidt et al., 1997). The BVS also collects information specific to some of the prevailing

	symptoms of PoTS, VVS and EH, e.g., 'palpitations (PoTS), chest pain/discomfort (PoTS), numbness/tingling (PoTS, VVS), shortness of breath/smothering (PoTS), faintness (PoTS, VVS), vision changes (VVS), feelings of unreality (VVS), dizziness (PoTS, VVS), hot flash (EH), sweating/clammy hands (EH).'
Childhood traumatic events scale (CTES)	A 7 point scale questions, e.g., 1 = not at all traumatic, 4 = somewhat traumatic, 7 = extremely traumatic, assessing traumatic events in childhood before age 17 and also in adulthood (Pennebaker and Susman, 1988). Trauma is an important aspect for consideration as it can have acute and sustained dysregulating effects on autonomic biochemistry.
Self-consciousness Scale (SCS-R) (revised)	A 23 item questionnaire designed to assess private and public self-consciousness and social anxiety (Scheier and Carver, 1985).

Table 1. The Anxiety Sensitivity Index, Body vigilance scale, Childhood traumatic events scale and Self-consciousness Scale (Revised) (SCS-R) were used to profile anxiety symptoms in postural tachycardia syndrome (PoTS), vasovagal syncope (VVS) and essential hyperhidrosis (EH)

Statistical analysis

Statistical analysis was performed online using SPSS version 18. Descriptive statistics are presented as mean (± 1 SD) for normally distributed data. Quantitative variables were compared between groups using an ANOVA when there were more than two groups or by independent t-tests for 2 groups. When necessitated, non-parametric tests were used to compare between two groups (Mann Whitney U Test) and when the analysis involved more than two groups to be compared, a Kruskal-Wallis test was used. Pearson correlation coefficients were used to study pairwise correlations between normally-distributed variables. Spearman rank order correlations were used for analysis of relationships of qualitative variables or non-normally distributed variables. Mixed model repeated measures ANOVA was used for comparison of data collected over more than two different time points in 2 or more different participant groups or 2 or more conditions in the same participant group. Statistical significance was defined as a 2-tailed p value of <0.05.

Results

Interoceptive accuracy (IA)

Within-subjects analysis of interoceptive accuracy (IA) during isometric exercise, cold pressor and HUT was compared to supine baseline values to analyse the effect of autonomic arousal on IA. In the current study, IA during did not change significantly in either control or clinical participants during experimentally-induced autonomic arousal.

Between-group analysis of IA found that, relative to controls, patients with PoTS, VVS and EH consistently underestimated the number heartbeats during heartbeat counting tasks. In patients with PoTS, IA was poorer during isometric exercise and cold pressor in comparison to

controls (figure 1). VVS IA was also poorer during baseline, isometric exercise and HUT. EH IA was poorer during baseline, isometric exercise and HUT relative to controls.

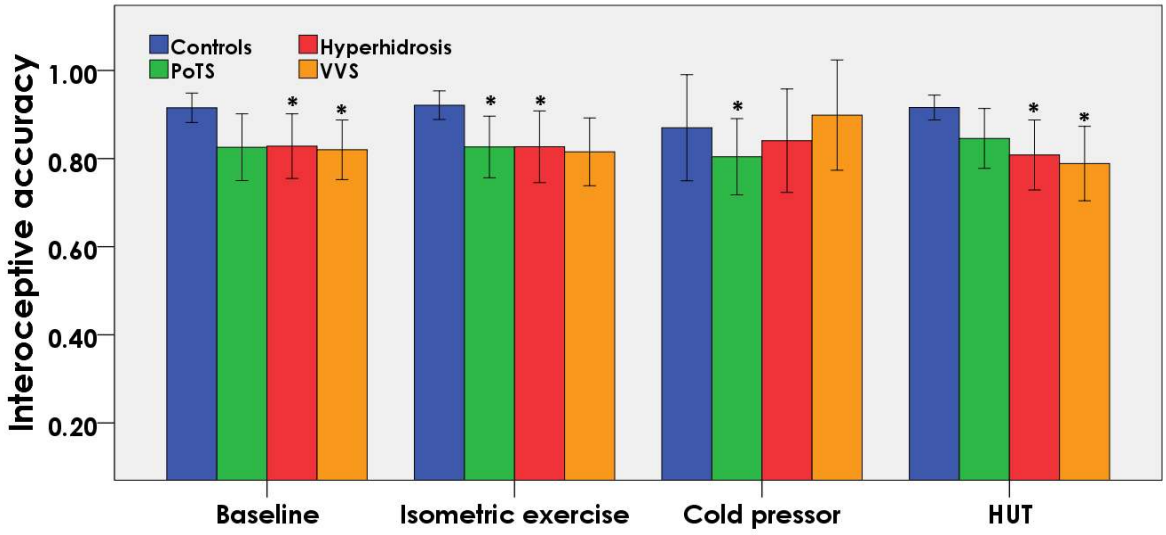

Figure 1. Interoceptive accuracy during supine baseline, isometric exercise, cold pressor and head up tilt (HUT) vs controls. PoTS = postural tachycardia syndrome; EH = essential hyperhidrosis, VVS = vasovagal syncope. Error bars = +/- standard deviation, * = statistically significant (*p*=0.05)

Self-report measures

Anxiety Sensitivity Index (ASI)

Patients with PoTS were more sensitive to anxiety than controls on the Anxiety Sensitivity Index (Figure 2). In particular, all three patient groups consistently scored higher than controls on the item, 'It scares me when I feel faint'.

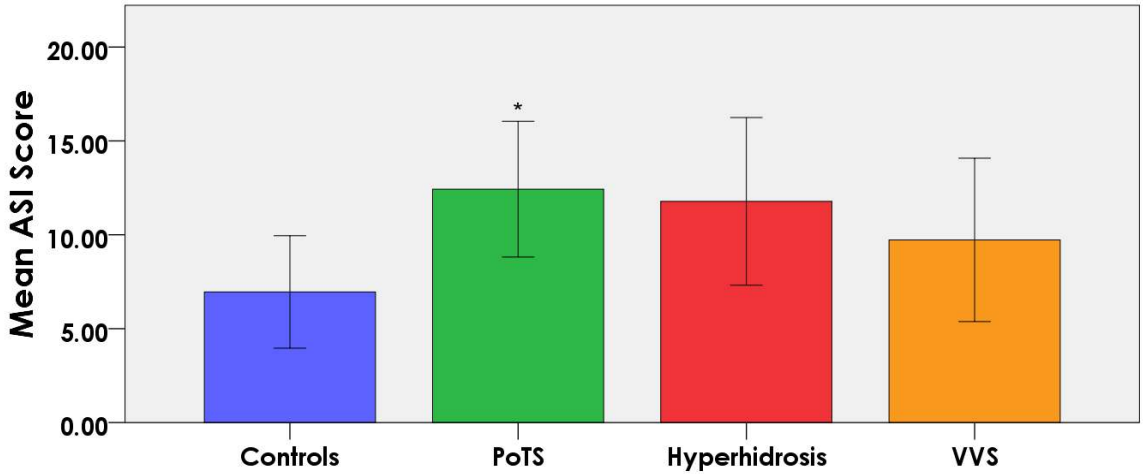

Figure 2. Anxiety Sensitivity Inventory (ASI) mean item scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and vasovagal syncope (VVS) patients Vs healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=0.05)

Body Vigilance Scale (BVS)

The PoTS group was the only clinical cohort to demonstrate higher global BVS scores in comparison to controls (figure 3). This group of patients also reported the greatest number of significantly increased individual items on the BVS (figure 4).

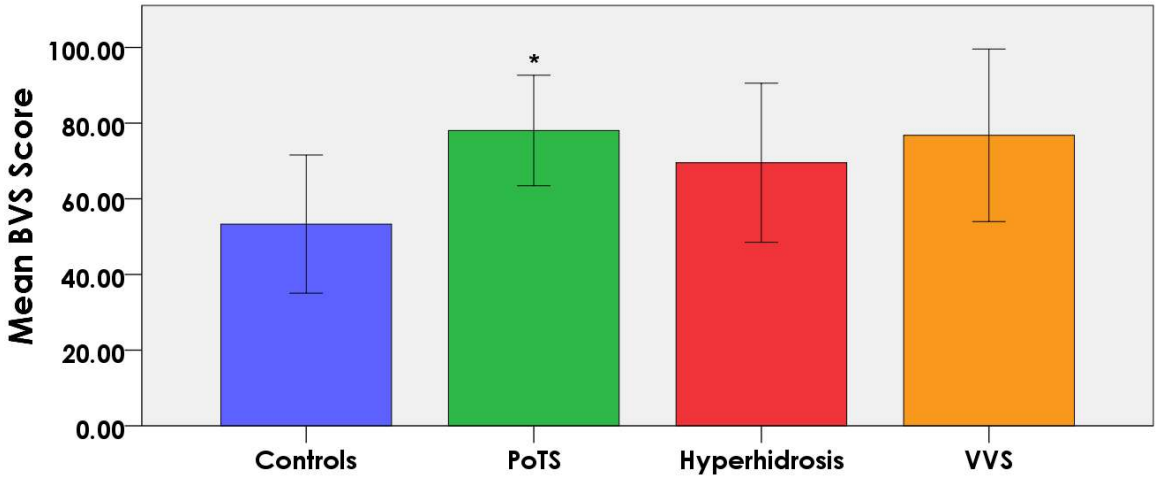

Figure 3. Body Vigilance Scale (BVS) mean item scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and vasovagal syncope (VVS) patients Vs healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=0.05)

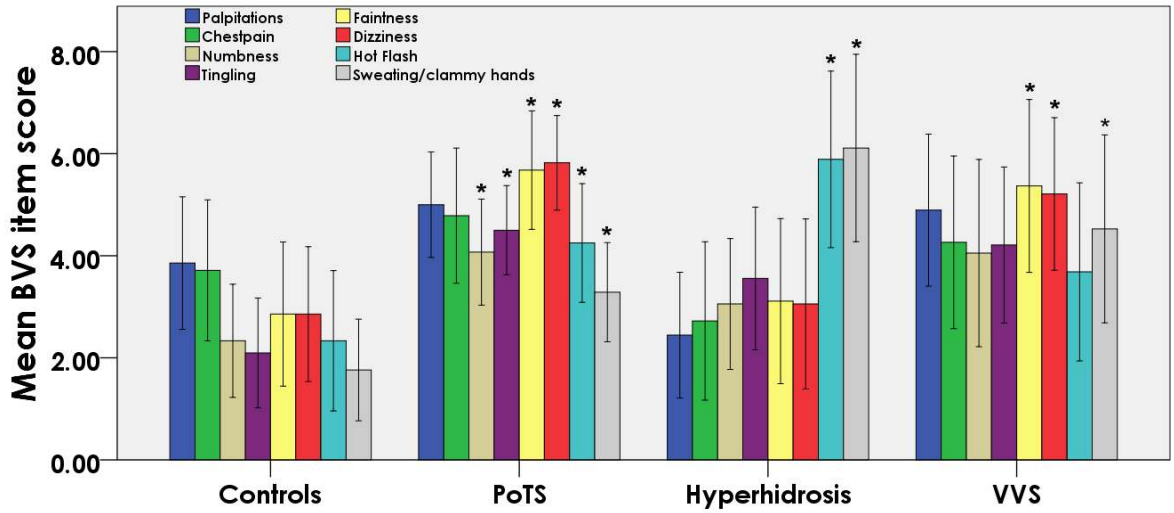

Figure 4. Body Vigilance Scale mean item scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and vasovagal syncope (VVS) patients Vs healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

Childhood Traumatic Events Scale (CTES)

There were no significant between-group differences in childhood or adult trauma (figure 5).

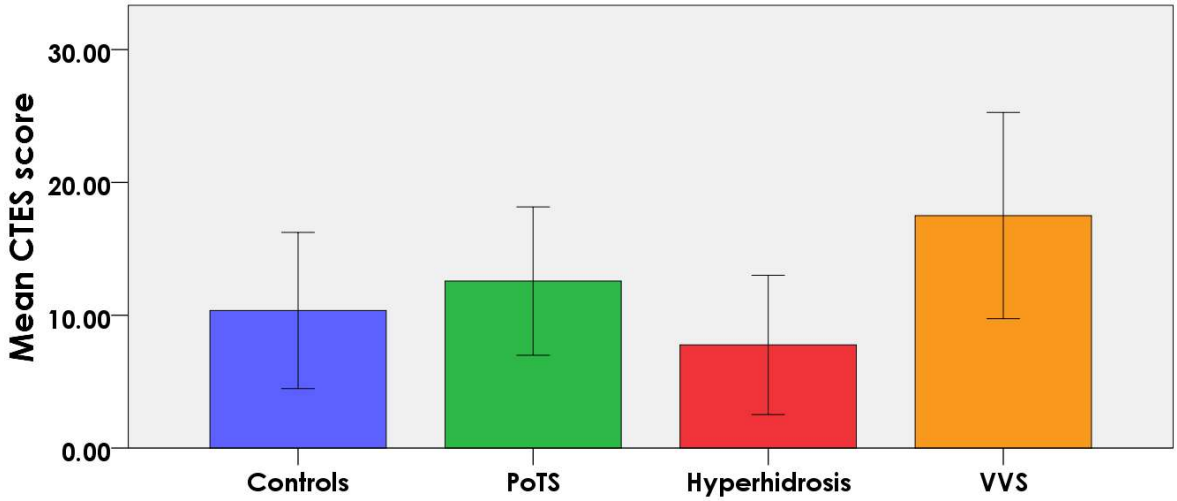

Figure 5. Childhood Traumatic Events Scale scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and vasovagal syncope (VVS) patients in comparison to healthy controls. Error bars = +/- standard deviation

The Self-Consciousness Scale-revised (SCS-R)

There were no significant differences in overall SCS-R scoring (figure 6).

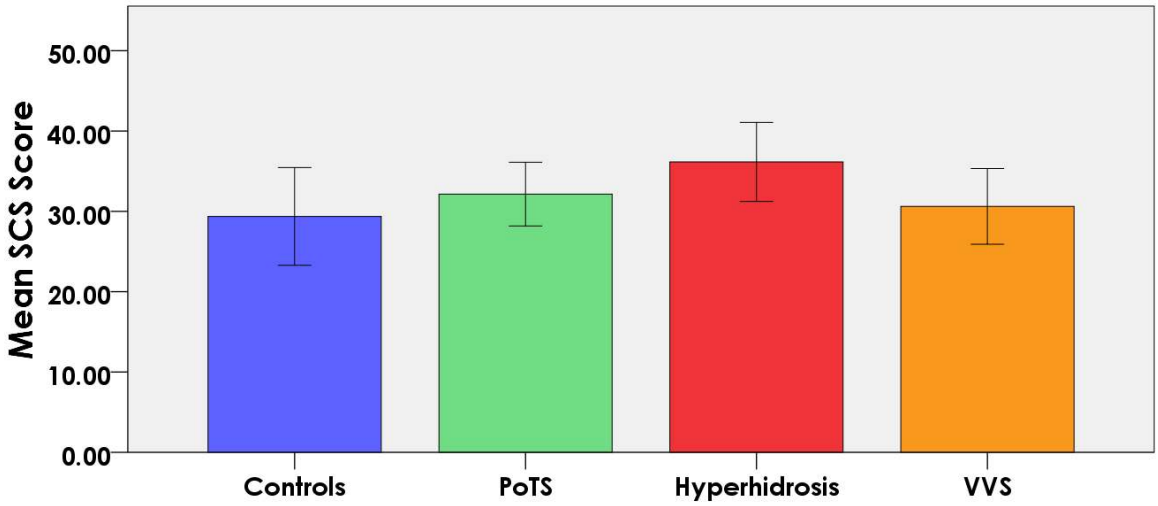

Figure 6. Mean Self-Consciousness Scale scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and vasovagal syncope (VVS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (p=0.05)

With the exception of ASI scores for the patients with PoTS, the intermittent dysautonomic patient groups reported similar levels of social anxiety, self-consciousness and trauma as the control group. However, the three patient groups differed from controls in the degree to which they focused on bodily symptoms. PoTS patients reported vigilance of a broad spectrum of OI, neuropathic and thermoregulatory sensations and symptoms. In contrast, VVS and EH subjects increased somatic vigilance was more specific to the primary symptoms of their autonomic

condition: Patients with VVS endorsed items relating to vigilance of presyncopal sensations, while patient with EH endorsed items relating to heat, sweating and skin sensation.

Self-report and interoception correlations

We further examined the contribution of individual differences in interoceptive ability/accuracy to the expression of anxiety symptoms in intermittent dysautonomia. We used correlation analyses to identify relationships between IA and scores on each of the questionnaires. Across all four study cohorts, IA correlated most strongly with BVS scores when compared to ASI, SCS or CTES data, for illustrative purposes individual correlations are presented to enable a descriptive understanding of these data. In the healthy control group, IA (negatively) correlated most strongly with the BVS item of 'nausea' (figure 7).

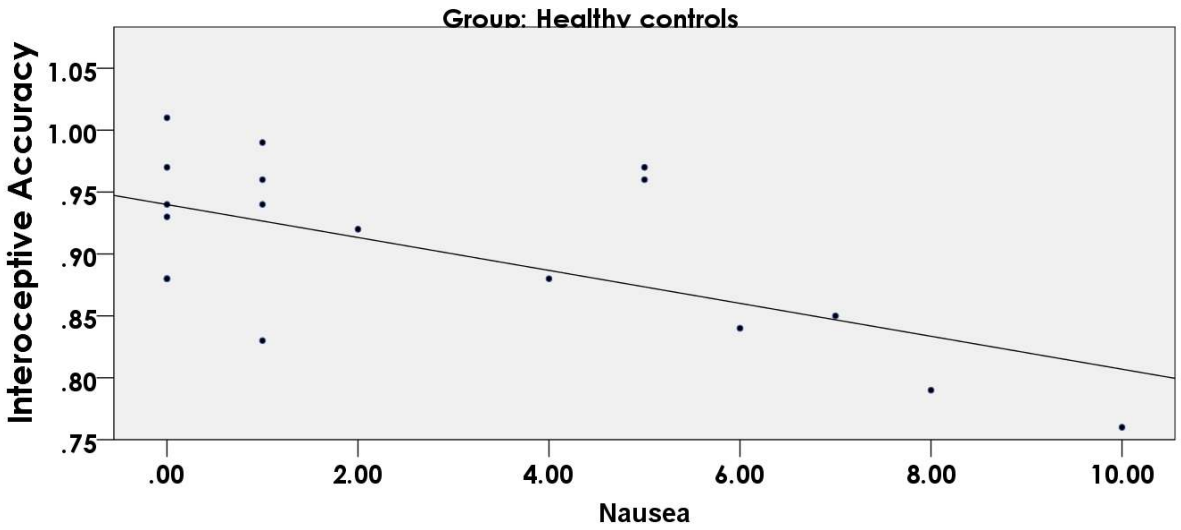

Figure 7. Scatterplot of the negative correlation (r_s= -0.620) between healthy controls interoceptive accuracy and somatic vigilance of nausea.

In the PoTS group, IA was most strongly (positively) correlated with the BVS item of *'shortness of breath'* (figure 8).

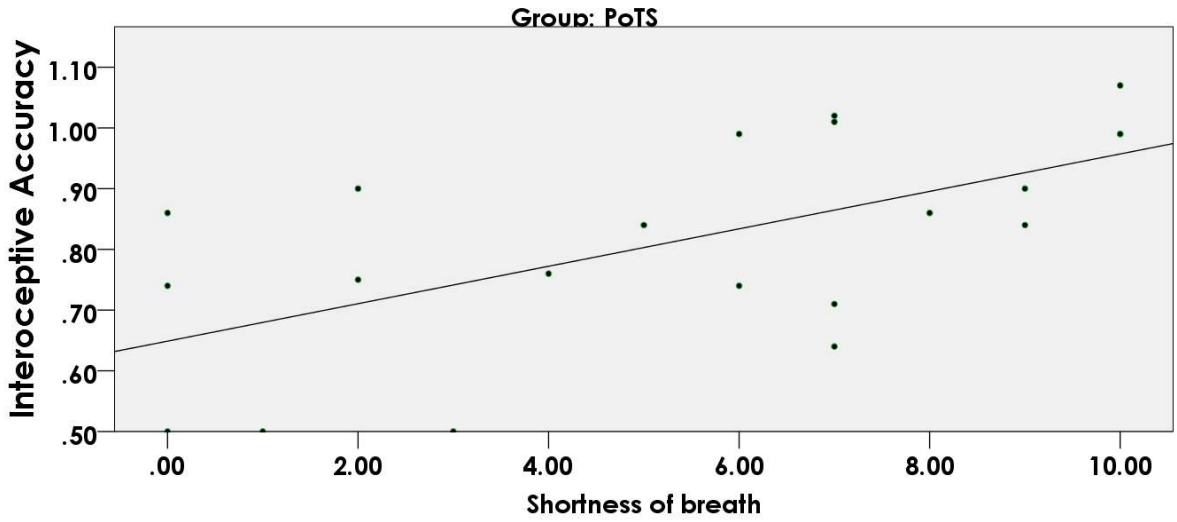

Figure 8. Scatterplot of the positive correlation (r_s= .616) between postural tachycardia syndrome (PoTS) subjects' interoceptive accuracy and somatic vigilance of dyspnea.

In the VVS group, IA was most strongly (positively) correlated with the BVS item of *'chest pain'* (figure 9).

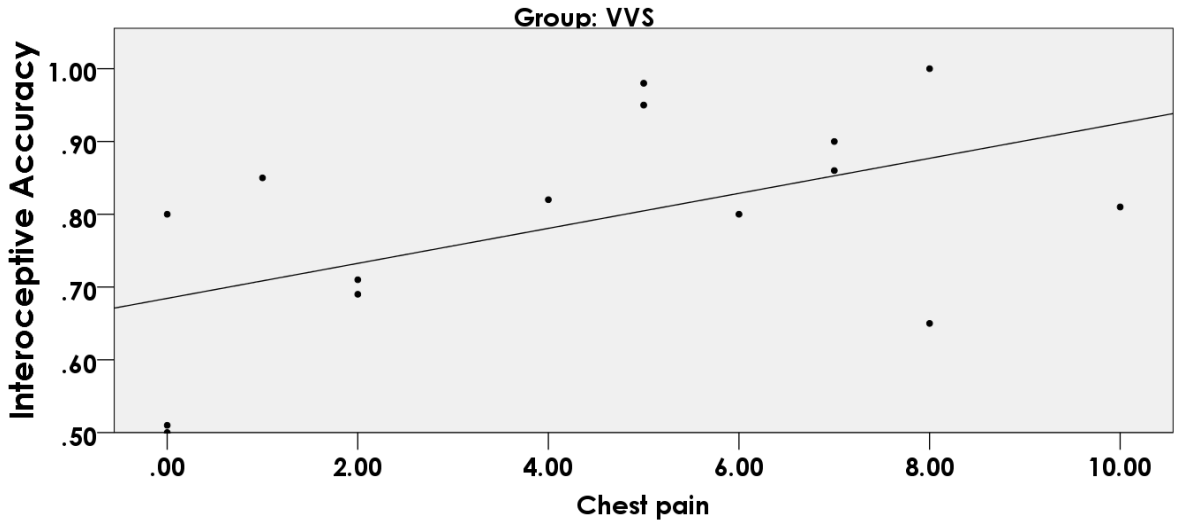

Figure 9. Scatterplot of the positive correlation (r_s= .546) between vasovagal syncope (VVS) subjects' interoceptive accuracy and somatic vigilance of chest pain.

In the EH group, IA was most strongly (negatively) correlated with the BVS item of *'how much time do you spend each day "scanning" your body for sensations (e.g., sweating, heart palpitations, dizziness)?'* (figure 10).

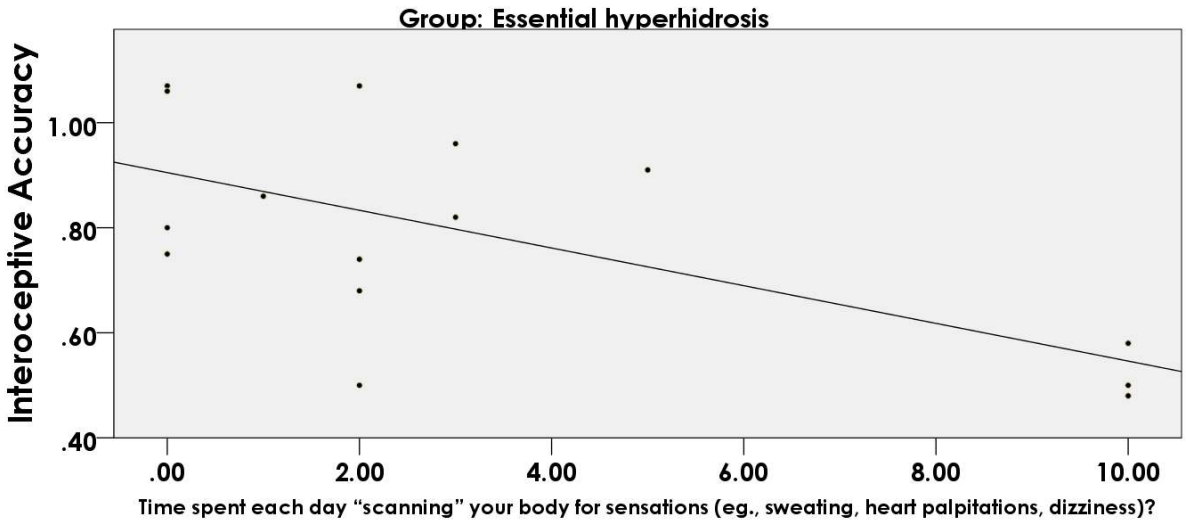

Figure 10. Scatterplot of the negative correlation (r_s= -0.620) between essential hyperhidrosis subjects' interoceptive accuracy and somatic vigilance scanning their bodies for sensations.

Discussion

This study examined psychological factors underlying the genesis and presentation of anxiety symptoms in disorders of transient dysautonomia that are characterised by autonomic over-excitation in relation to interoception, body vigilance and trauma. We tested our hypothesis

that patients with PoTS, VVS and EH represent atypical anxiety phenotypes, in whom affective symptoms are more aligned with apprehension and vigilance of interoceptive feedback than neurotic or trauma-related factors.

There were no significant between group differences in the incidence of adult or childhood trauma, indicating that the increased anxiety reported by patients with PoTS, VVS and EH in the current study was not the result of trauma.

Pre-syncope and neuropathic symptoms were reported to a greater extent by patients with PoTS, suggesting that somatic hypervigilance may be characteristic of PoTS and reflect the broader pathophysiological of the various PoTS phenotypes (Benarroch, 2012). The establishment of somatic hypervigilance may underpin the more enduring nature of PoTS symptoms in comparison to VVS and EH symptoms. PoTS patients did not, however, report significant hypervigilance to chest palpations and chest pain. While this may seem counterintuitive, it is consistent with the observed attenuation of IA in PoTS. Moreover, PoTS involves multiple organ systems (e.g., gastrointestinal, bladder, rheumatological) and may require patients to attend to many interoceptive signals from the viscera, rather than just palpitations. Together, the multi-system and chronic nature of PoTS symptoms could also contribute to the greater level of anxiety sensitivity in this group.

That VVS patients reported being more sensitive and paying more attention to changes in their body can be considered from the perspective that these symptoms are often a somatic marker of an imminent syncopal episode, therefore signifying the need for contingent behaviour to avoid trauma.

Overall, somatic vigilance was increased in the three patient groups The spectrum of somatic hypervigilance symptoms was broader in PoTS, whereas it's increased levels in VVS and EH related directly to syncopal or thermoregulatory symptoms, respectively. This supports recent findings from our group that anxiety and depression-related symptoms are increased in PoTS, VVS and EH, but that these emotional symptoms are directly related to sensitivity to physical and cognitive symptoms (Owens et al., 2015), as opposed to typical psychosocial or neurotic factors that commonly underlie generalised and social anxiety or panic disorders. Nevertheless, anxiety disorders occur with greater frequency in these patients and somatic hypervigilance is likely to represent both a vulnerability factor and a maintenance factor for affective symptoms.

EH patients were more concerned with how they presented themselves, most likely due to the social stigma that is applied to inappropriately or profusely sweating. However, other items

and global self-consciousness scales did not differ significantly between groups, indicating normative levels of social anxiety, self-consciousness and introspection in the clinical groups. This indicates that the psychological symptoms experienced by PoTS, VVS and EH patients are not related to trauma or neuroticism but rather the physiological, homeostatic and attentional dysregulation caused by their intermittent autonomic disorder, as supported by anxiety symptoms being firmly aligned with the vigilance and anxious apprehension of somatic events and visceral sensations.

Cardiovascular arousal reportedly increases interoception(Schandry et al., 1993). However, IA did not improve during the cardiovascular arousal engendered by pressor manoeuvres or HUT in neither the controls or patient groups. One account may be that the level of heightened cardiac output evoked during these tests was not large enough for the increased firing of cardiopulmonary mechanoreceptors to be large enough to ascend the cortical hierarchy in order to reach conscious awareness. In fact, cardiovascular arousal appears to impair IA in PoTS, VVS and EH. Similarly, anxious individuals typically overestimate their heartbeats (Essau and Jamieson, 1987), in contrast to our patients with intermittent dysautonomic who underestimated their heartbeats throughout testing, despite increased somatic vigilance and autonomic over-reactivity. This contextual impairment of IA further supports the conclusion that the increased anxiety in PoTS, VVS and EH is atypical.

The IA data implicates the contribution of dysregulated central processing of excessive afferent feedback for these deficits, as both sudomotor and cardiovascular forms of autonomic dysfunction consistently underestimated their heartbeats during the heartbeat tracking tasks. One explanation may be found in two recent neuroimaging studies in PoTS and VVS. First, patients with PoTS show reductions in (left) insula volume that correlate with affective symptoms (Umeda et al., 2015). Second, patients with VVS show reductions in (right) insula volume that correlate with BP falls on HUT (Kim et al., 2014). This implication of the insula in PoTS and VVS neuropathophysiology is not likely due to age-related neurodegeneration because of the patients' ages - 32 and 24 years respectively. The insula is part of the central autonomic network (Benarroch, 1993) and supports autonomic, interoceptive and nociceptive function. Thus, activation of the insula cortex, particularly the right anterior insula, correlates with IA and anxiety in healthy controls (Critchley et al., 2004) and is strongly implicated in the clinical expression of anxiety disorders (Paulus and Stein, 2006). Anterior insula, particularly on the right, also enables conscious access to the representation of internal bodily state (Critchley et al., 2004). Speculatively, greater neuropathophysiological involvement of right insula may explain, in part, why patients with VVS in particular underperformed in tests of IA (even poorer than patients with PoTS).

Insula cortex is proposed as a comparator of expected versus experienced internal bodily state. Thus, unexpected interoceptive signals are 'bottom up' sources of anxiety (Paulus and Stein, 2006). In predictive coding terms, discrepancies between the brain's top-down predictions of bottom-up sensory signals is a 'prediction error'. The 'free energy principle' (Friston, 2010) is a predictive coding model that proposes neuronal activity encodes expectations about the causes of afferent sensory input and that these expectations minimise prediction errors (free energy/surprise). Error minimization may be achieved by the prediction error ascending back up the neuraxis. This signal amends 'top-down' predictions about the sensory signal, or engages motor or autonomic reflexes that act upon the (external and/or internal) environment to reduce the prediction error from the 'bottom-up' (Friston and Frith, 2015). Recently, there has been growing interest in the concept of interoceptive (active) inference as a way of understanding autonomic control of homeostasis and emotion (Seth and Critchley, 2013, Seth et al., 2011, Ondobaka et al., 2015, Owens et al., under review). Interoceptive inference may explain why PoTS, VVS and EH patients underestimated their heartbeats, as large prediction errors require the recruitment of cognitive control networks (Seeley et al., 2007) to alter the weight of dysregulating afferent inputs. This also offers a formal explanation for PoTS patients not reporting palpations or chest pain as symptoms of significant somatic hypervigilance. This cognitive demand may also contribute to the previously reported attentional difficulties in PoTS (Ocon, 2013, Raj et al., 2009, Ross et al., 2013),(Owens et al., 2015), EH and VVS (Owens et al., 2015).

Somatic vigilance, rather than trauma, anxiety sensitivity, social anxiety/self-consciousness, was most strongly correlated with IA. The more interoceptively accurate controls and hyperhidrotics were at rest and during autonomic arousal, the less time they spent scanning their body for physical symptoms, indicating interoception's homeostatic role. This pattern was reversed in both OI groups, i.e., IA was positivity correlated with somatic vigilance and worry in patients with PoTS and VVS. This suggests that heighted psychological aspects of interoception contributes to anxiety in these conditions. It may be noteworthy that in typical anxiety disorders, catastrophic cognitions driven by visceral feedback tend to centre on cardiac sensations (Willem Van der Does et al., 2000, Domschke et al., 2010).

Our study had a number of limitations, including the small number of control and clinical participants that were recruited. Data-analyses were not corrected for multiple comparisons nor was functional neuroimaging undertaken, which could provide greater mechanistic insight into the functional integrity of central interoceptive processing in intermittent dysautonomia.

Conclusions

Affective symptoms in patients with PoTS, VVS and EH, appear to be driven by interoception of somatic symptoms and sensations, rather than trauma or neurosis. The greater levels of somatic vigilance in PoTS and VVS may be due to interoception being anxiogenic rather than homeostatic in these groups. PoTS, VVS and EH patients' diminished interoception may be due to a common central dysregulation, as both sudomotor and cardiovascular forms of autonomic dysfunction had comparable IA deficits. Recent MRI studies in OI suggest these interoceptive deficits may, at least in part, be mediated by structural differences within insula, However, further neuroimaging studies, particularly in EH, are required to confirm this. Another central contribution may be interoceptive inference of large prediction errors of excessive autonomic activity requiring alterations in how interoceptive signals are attended to, potentially contributing to the attentional symptoms in PoTS, VVS and EH. Our findings suggest a possible therapeutic pathway for psychological symptoms and impaired QoL in intermittent autonomic disorders, wherein behavioural therapeutic strategies target somatic anxiety and mindfulness techniques to address affective and attentional symptoms.

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