The Psychophysiology of Dysautonomia

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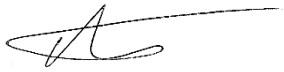
Declaration

I, Andrew Owens confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.



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Abstract

Modern theories of emotion emphasise the role of homeostatic requirements in motivating and shaping behaviour and link emotions with motor and autonomic responses to define physiological, behavioural and neurobiological phenomena initiated by the emotional valence and relevance of a stimulus. Intermittent dysautonomia is a transient but recurrent dysregulation of autonomic nervous system function, such as orthostatic intolerance (postural tachycardia syndrome, vasovagal syncope) or thermoregulatory dysfunction (essential hyperhidrosis). The sympathetic and parasympathetic nervous systems often work antagonistically and with organ specificity, producing definable patterns of activity, yet despite the coupling of emotion with autonomic function, the evidence for robust emotion-specific patterns remains elusive. Although psychiatric patients may report symptoms akin to intermittent dysautonomia, such as sweating, faintness or palpitations, autonomic diagnostic criteria are rarely met. However, comorbid psychological symptoms, such as subclinical anxiety and depression, are often reported in intermittent dysautonomia. Recent neuroimaging techniques have elucidated the interrelationship of autonomic and neurobiological pathophysiology and the perturbation of autonomic neuroanatomy by peripheral autonomic function and dysfunction. This thesis will investigate the complex interplay between brain and body in intermittent dysautonomia and healthy controls in order to improve our understanding of the common cognitive-affective symptomatology in vasovagal syncope (VVS), the postural tachycardia syndrome (PoTS) and essential hyperhidrosis (EH) that can complicate diagnosis and treatment. Moreover, organic conditions that provide such an overrepresentation of comorbid psychological symptoms may provide insight into cognitive-affective processes beyond autonomic medicine.

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Abbreviations

Acc = anterior cingulate cortex

Ach = acetylcholine

ADH = antidiuretic hormone

AF = autonomic failure

AI = anterior insula

AMS = autonomic (neurally) mediated syncope

ANS = autonomic nervous system

ASI = anxiety sensitivity index

BAI = Beck anxiety inventory

BDI = Beck depression inventory

BEES = Balanced emotional empathy scale

BP = blood pressure

BVS = body vigilance scale

CAS = Cardiac anxiety scale

CDR = cardiac defence response

CP = cold pressure

CTES = childhood traumatic experiences scale

DBP = diastolic blood pressure

DPD = depersonalization disorder

EDS iii = Ehlers-danlos syndrome iii

EH = essential hyperhidrosis

FMD = functional movement disorder

FNS = functional neurological symptoms

FS = functional syncope

HF-HRV = high frequency heart rate variability

HG = isometric hand grip exercise

HR = heart rate

HRV = heart rate variability

HUT = head up tilt

IA = interoceptive accuracy

IAPS = International Affective Picture System

JHS = joint hypermobility syndrome

LF-HRV = low frequency heart rate variability

MSA = multiple system atrophy

MTL = medial temporal lobe

NA = noradrenaline

NTS = nucleus of the solitary tract

OR = orienting response

PAF = pure autonomic failure

PAG = periaqueductal gray

PFC = prefrontal cortex

PNS = parasympathetic nervous system

PoTS = postural tachycardia syndrome

RAS = renin-angiotensin system

SBP = systolic blood pressure

SCI = spinal cord injury

SCS = self-consciousness scale

SNA = sympathetic nerve activity

SNS = sympathetic nervous system

SAI = state anxiety inventory

VAS = visual analogue scale

Chapter 1. Introduction with aims

'Homeostasis' refers to the maintenance of a bodily steady-state for optimal health and functionality. Homeostatic feedback and feedforward systems operate across central and visceral mechanisms in response to physiological requirements, generating corrective metabolic, cardiovascular or behavioural actions. Homeostatic regulation is facilitated via the autonomic nervous system (ANS) and its unique ability to mediate activity of bodily organs, glands and blood vessels via peripheral efferent neurons (see figure 1). The sympathetic nervous system (SNS) acts to increase effector organ activity predominantly via the catecholamines, noradrenaline (NA) and adrenaline at the neruoeffector junction. The parasympathetic nervous system (PNS) promotes vegetative activity mainly via acetylcholine (Ach), such as the slowing of heart rate (HR) or facilitation of food digestion by increasing gut motility.

Figure 1. Autonomic innervation of human organs. Sweat glands (not shown) are supplied by cholinergic fibres. From Jänig (1995).

To counteract venous pooling and maintain cerebral perfusion during orthostasis (standing), cardiopulmonary mechanoreceptors and arterial baroreceptors in the aortic arch and carotid sinus detect changes in vascular contraction and send afferent signals to the brainstem, upregulating peripheral sympathetic nerve activity (SNA), thereby, increasing peripheral vascular resistance, venous tone and HR so that the necessary arterial pressure to adequately perfuse neural tissue is reached (Smit et al., 1999). Behaviour-dependent increases in blood pressure (BP) are both enabled and moderated by the baroreflex (Janig and Habler, 2003, Dampney et al., 2013, Dampney et al., 2002). Failure of these autonomic reflexes can lead to transient loss of consciousness (TLoC) due to cerebral hypoperfusion.

Human consciousness and cognition is dependent on sympathetic, parasympathetic and sensory innervation of the cerebral vasculature to mediate cerebral perfusion, however, the complexity of neurovascular coupling allows for the breakdown of cerebral perfusion. Intracranial pressure and local arterial pressure maintain cerebral perfusion pressure (difference between intracranial pressure and mean arterial pressure (Van Lieshout et al., 2003)) at 80 mmHg and excessive increases or decreases (<50 mmHg) are prevented by autoregulation of cerebral blood flow (CBF), regardless of peripheral variations in BP (Van Lieshout et al., 2003). However, cerebral perfusion pressure is dependent on system arterial pressure, itself dependent on cardiac output and peripheral vascular resistance, therefore a reduction in either of these peripheral factors can cause reductions in cerebral perfusion pressure. Should cerebral perfusion pressure drop below 70 mmHg, the brain becomes

inadequately perfused with oxygen and other metabolites, predisposing to a transient loss of consciousness (TLoC) (Rosner et al., 1995).

To ensure biochemical reactions are efficient, the human body's' optimum core temperature is 37°C. Some cerebral activities, such as stress, shock or sleep also effect thermoregulation (Collins, 2013). Following the perception of thermal discomfort, thermoregulatory behaviour can be initiated to maintain thermostasis. Perceived changes in skin temperature and thermal discomfort induce behavioural modifications (Schlader et al., 2009). The spinothalamic tract and other afferents provide feedback to the thalamus and posterior hypothalamus, which assumes the role of a central 'thermostat'. Cutaneous thermoception is relayed to second-order thermal sensory neurons in the dorsal horn via dorsal root ganglia and glutaminergic third-order cool-sensitive neurons of the lateral parabrachial nucleus and lateral subnucleus. Conscious thermoception is relayed to the cortex and thalamus via dorsal horn neurons.

The body's main defence against hyperthermia is heat loss via evaporation from the skin and respiratory passages, thus transferring heat from the body to the environment. Cholinergic sympathetic sudomotor neurons innervate 2-4 million eccrine glands that secrete a hypotonic saline solution during heat stress. Sweat evaporation cools the surrounding skin, which then cools the local cutaneous blood flow. Body temperature can also be regulated via skin blood flow (see figure 2).

Figure 2. Diagram of thermoregulatory skin blood flow. NE = noradrenaline, NPY = neuropeptide Y, NO = nitric oxide, CGRP = calcitonin gene–related peptide, SP = substance P, NKA = neurokinin A. From Charkoudian, 2003

Vasoconstriction during cold stress conserves heat and lessens peripheral blood flow. Hypothermia is defined as a core temperature of $\leq$35°C. Cold responsive neurons in the caudal portion of the raphe pallidus and dorsomedial nucleus of the hypothalamus that initiate cold-defence behaviours are inhibited by hypothalamic warm sensitive neurons. Preoptic warm-sensitive neurons also synapse with shiver-promoting dorsomedial hypothalamic neurons which, via shivering premotor neurons in the rostral raphe pallidus and ventral horn, provide efferents to skeletal muscle α and γ motor neurons to invoke shivering. Cutaneous vasoconstriction sympathetic tone is modulated by noradrenaline (NA) and neuropeptide Y (NPY) (both post-ganglionic), serotonin and glutamate.

Central autonomic networks within the spinal cord, brainstem and hypothalamus mediate cardiovascular and thermoregulatory autonomic outflows (Benarroch, 1993). The ventromedial prefrontal cortex (vmPFC) is involved with PNS and antisympathetic activity (Gianaros et al., 2004; Matthews et al., 2004) and supragenual areas of the mid and anterior

cingulate are associated with SNS activity. Haemodynamic changes are global autonomic responses requiring input from the cortex, limbic forebrain and midbrain (Saper, 2002) (Morrison, 2001). Dorsal anterior cingulate cortex (Critchley et al., 2003) and insula cortex (Critchley et al., 2000a, Critchley et al., 2000b) activity reflects engagement of sympathetic activity coupled to mental and physical behaviours. Increased activity in the medial prefrontal cortex (mPFC), anterior and posterior insula and ventroposterior thalamus occurs during respiration, isometric exercise and valsalva manoeuvre (King et al., 1999).

Activity in the anterior cingulate cortex (Acc), insula, medial temporal lobe (MTL), ventral PFC (vPFC) and mPFC, medial thalamus, cerebellum, midbrain and pons increases during cold pressor and valsalva manoeuvres (Harper et al., 2000) and increases in BP are positively correlated with right dorsal Acc activity. These findings indicate sympathetic responses are lateralized to the right hemisphere (Oppenheimer et al., 1992) and the left insular cortex is involved in parasympathetic cardiovascular regulation.

Hypothalamic, pontine and medullary sympathetic and parasympathetic nuclei interact with homeostatic representations to generate physically or behaviourally-induced organ-specific autonomic responses (Saper, 2002). HR changes are predicted by amygdala and dorsal Acc activity (Janig and Habler, 2003) and during threat/stress induction, amygdala function predicts cardiac contractility (Dalton et al., 2005). The amygdala and other limbic structures supply a descending efferent drive to the hypothalamus and brainstem for congruent autonomic responses to emotion-related behaviour (Saper, 2002).

The nucleus of the solitary tract (NTS) receives baroreceptor afferents that synapse with the rostral ventrolateral medulla to set efferent pressor tone (see figure 3). Reduced baroreceptor tone has been associated with Acc, amygdala and anterior insula (AI) function, whereas initiation of baroreflexes increases activity in lateral PFC (lPFC) and posterior insula (Kimmerly et al., 2005).

Figure 3. Brainstem nucleai, including the nucleus tractus solitarius (NTS), involved with baroreflex and pressor function. Nucleus tractus solitarius = NTS, caudal ventrolateral medulla = CVLM, rostral ventrolateral medulla RVLM, dorsal motor nucleus of the vagus = DMNX, circumventricular organs =CVO, paraventricular nucleus = PVN), supraoptic nucleus SON. From Albaghdadi, 2007

Autonomic disease and dysfunction (dysautonomia) can be classified as either fixed or intermittent (Mathias and Bannister, 2013). Fixed ANS disorders cause autonomic failure (AF) as the lesion is fixed and usually irreversible, such as in spinal cord injury (SCI) or pure autonomic failure (PAF). The lesion may also be progressive, as in Parkinson's disease with AF or multiple system atrophy (MSA). AF is characterised by a postural fall in BP which is defined as orthostatic

hypotension (OH) when the fall is over 20 mmHg systolic BP (SBP) and/or 10 mmHg DBP. Fixed ANS disorders commonly present in patients of >40 years, whereas intermittent ANS disorders can present in all ages.

Intermittent dysautonomia is a temporary but recurrent dysregulation of normative autonomic function attributable to a specific factor, such as orthostatic intolerance (OI) or thermoregulatory dysfunction. Thermoregulatory dysautonomia may occur due to a systemic (malignancy, shock), metabolic (diabetes mellitus, menopause) or febrile illness (infection), as well as neurological disorders (stroke, Parkinsons disease) and can be focal or generalised in nature. Cardiovascular intermittent dysautonomia relates to orthostatic intolerance (OI), though factors such as food digestion, dehydration and exercise can also exacerbate symptoms. Sudomotor and cardiovascular intermittent dysautonomia often present in adolescence/early adulthood and with strong positive family histories (Kaufmann et al., 2003, Iodice et al., 2010).

The postural tachycardia syndrome (PoTS) is the most common form of OI (170 cases per 100,000) (Schondorf et al., 1999) and is characterised by an excessive HR increase of +30 bpm or HR >120 bpm without OH within 10 mins of orthostasis or head up tilt (HUT) (Freeman et al., 2011a). PoTS can be broadly divided into hyperadrenergic or neuropathic phenotypes (Benarroch, 2012), however, dysfunction of the noradrenaline transporter gene promoter region (Esler et al., 2006), infection (Schondorf and Low, 1993), deconditioning (Parsaik et al., 2012), hypovolemia and/or poor orthostatic cerebral autoregulation (Ocon et al., 2009b) have also been implicated in PoTS pathophysiology. Around 70% of PoTS patients are diagnosed with the heritable rheumatological condition, Ehlers-Danlos Syndrome iii/joint hypermobility type (Mathias et al., 2012), which also leads to vascular abnormalities that exacerbate orthostatic-related symptoms (Benarroch, 2012, Mathias et al., 2012).

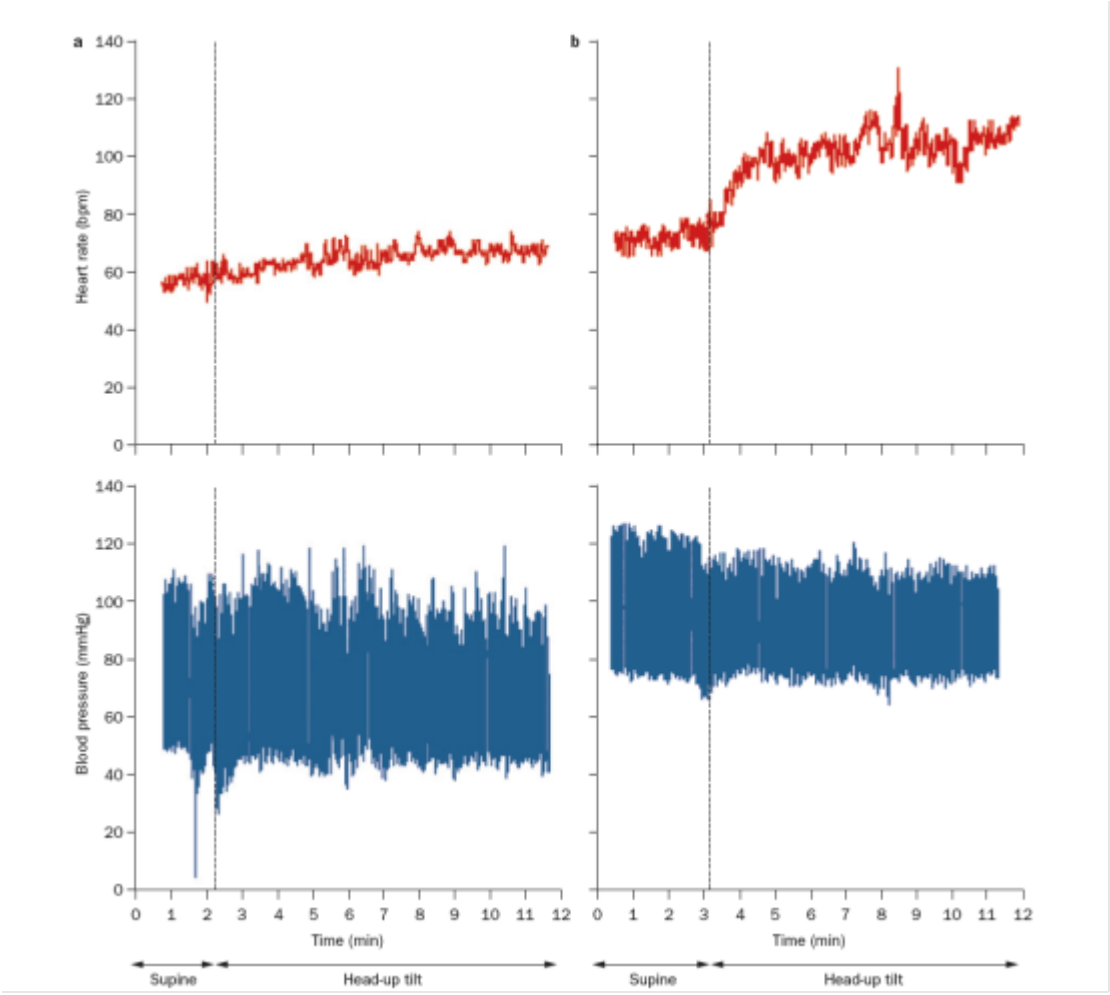


Figure 4. Supine and head up tilt blood pressure and heart rate profiles of a (a) healthy individual and (b) a patient with PoTS. The vertical dashed line indicates the onset of postural change (head-up tilt). Excessive tachycardia is observed after the onset of head-up tilt in the PoTS patient. PoTS, = postural tachycardia syndrome. From Mathias et al., 2012

Autonomic (neurally) mediated syncope (AMS) is a group of syncopal (fainting) phenotypes that are caused by the breakdown of autonomic reflexes. The three forms of AMS are;

I. Carotid sinus hypersensitivity (CSH)
II. Situational syncope (SS)
III. Vasovagal syncope (VVS)

VVS is caused by vasodilatation and/or bradycardia and predominantly occurs in females under 40 years, as opposed to CSH typically occurs in those >50 years of age due to exaggerated baroreceptor activation (Humm and Mathias, 2010). VVS typically first presents in late adolescence/early adulthood, whereas syncope in the elderly is predominately cardiogenic or due to OH (Vaddadi et al., 2007). VVS constitutes around 40% of syncopal events, making it the most common cause of syncope (Fenton et al., 2000). VVS is a paroxysmal malfunction of baroreflexes and the autonomic instability of a vasovagal episode is defined by prodromal sympathoexcitation that precedes parasympathetoexciation (vasodilatation, reduced cardiac output) (Medow et al., 2008, Barcroft and Edholm, 1945).

Despite the wealth of laboratory and ambulatory equipment available, the cause of 10-26% of syncope cases remains unexplainable (Brignole et al., 2005, Krahn et al., 1995, Krahn et al., 1998) and psychiatric illness is more prevalent in these patients with unexplained syncope, particularly if syncopal episodes are recurrent and/or include multiple somatic symptomology (Kapoor et al., 1995). 'Psychogenic pseudosyncope' (PSS) is the occurrence of apparent syncope (unresponsiveness and loss of postural tone) during normal physiological indices that would not result in cerebral hypoperfusion. There is currently a paucity of literature on PSS (van Dijk and Wieling, 2013) and direct observation of pseudosyncope in a clinical setting is rare (Luzza et al., 2004). Moreover, symptoms of OI, particularly pre-syncope, are commonly reported in functional somatic disorders (Kroenke and Rosmalen, 2006). During a PSS episode, the vast majority of patients close their eyes and resist eyelid opening (Tannemaat et al., 2013), periods of apparent unconscious are also significantly longer than AMS patients and occur more frequently than in AMS.

Conversion or medically unexplainable symptoms during autonomic testing remains under-researched and inadequately understood. One may also question the clarity, objectivity and accuracy of the term 'psychogenic pseudosyncope' due to the fact that actual episodes of VVS can be psychogenic, such as the site of blood, frustration or humiliation. Therefore, the term 'functional syncope' (FS) will be used in this thesis, rather than the less objective, inaccurate and repetitive term of psychogenic pseudosyncope.

FS appears to be a conversion disorder yet it is often reported or described with little attempt to try and unpick the psychophysiological mechanisms that may be involved in its presentation, therefore, **specific aim # 1** of this thesis will;

(i) review the historical profiles of FS patients to better understand the condition,
(ii) investigate any underlying autonomic or dysatuonomic aspects to FS,
(iii) describe the presentation and incidence of FS during autonomic testing

Essential hyperhidrosis (EH) is diagnosed when an individual's excreted sweat exceeds that required to normalise body temperature and causes significant functional impairment (see figure 5). The aetiology of EH remains unknown but the condition is defined by excessive local or generalised sweating, typically on the palms of the hands, soles of feet and axillary. The prevalence of the condition has been estimated to be 2-3% (Lai et al., 2014, Moraites et al., 2014). Eccrine glands are primarily implicated in EH, with the exception of axillary EH, which appears to have a more diffuse pathophysiology (Lonsdale-Eccles et al., 2003, Bovell et al., 2001).

Figure 5. (Left panel) Palmar hyperhidrosis and (right panel) generalised hyperhidrosis

Although psychiatric patients may report symptoms akin to intermittent dysautonomia, e.g., sweating, faintness or palpitations, autonomic diagnostic criteria are rarely met (Ruchinskas et al., 2002, Lkhagvasuren et al., 2011). However, attentional and secondary psychological symptoms are often reported in AMS, EH and PoTS (Giada et al., 2005, Gracie et al., 2006, Ruchinskas, 2007, D'Antono et al., 2009, Raj et al., 2009, Vazquez et al., 2011, Rios-Martinez et al., 2009).

Like PoTS, comorbid EDSiii/JHT and anxiety is significantly more common in young females (Martin-Santos et al., 1998). Investigations of functional disability in PoTS have found day-to-day limitations closely related to catastrophising thoughts, which also mediate anxiety and somatic hypervigilance (Benrud-Larson et al., 2003), another common anxiety trait in PoTS (Raj et al., 2009, Masuki et al., 2007, Raj, 2006). Cognitive function can be impaired in PoTS (Anderson et al., 2014, Raj et al., 2009). Inattention has been found to decrease with illness duration, likely due to adaptive or treatment responses. Furthermore, hyperactive traits were absent in childhood, suggestive of a causal role in these cognitive symptoms that often present in PoTS. that poor quality sleep, daytime sleepiness and fatigue have also common in PoTS (Bagai et al., 2011) is noteworthy.

Cohen et al (Cohen et al., 2000a) found that anxiety scores were positively correlated with positive (symptomatic hypotension and/or bradycardia) HUT. Anxiety has also been associated with greater syncope burden (Lerma et al., 2013). Though emotional stress may increase BP and HR, vascular resistance is not typically influenced by psychological factors, however, in an episode of emotionally-induced VVS, BP, HR and peripheral resistance fall profoundly (Mosqueda-Garcia et al., 2000). Abnormally high levels of depression, anxiety and

blood/injury phobia are common in VVS (Graham, 1961, McGrady et al., 2001, Luborsky et al., 1973, Karaca et al., 2007), with syncopal episodes often proceeding anticipation of real or fantasised physical harm in a social context, where fight/flight was perceived as unacceptable. Psychosocial threats, such as humiliation and mortification, to which the fainter feels they cannot escape can also provoke vasovagal episodes (Sledge, 1978). VVS patients who do not respond to treatment are more anxious and depressed than VVS treatment responders, report more negative thoughts regarding threats to physical harm or death, as well as higher levels of avoidance/protection coping and rumination (Gracie et al., 2006). VVS predisposition relates to differences in brainstem neuroanatomy that regulate baroreflex BP control and cardiovascular homeostasis (Beacher et al., 2009).

EH remains a neglected area of study. Although the aetiology of the condition remains uncertain, patients commonly report anxiety (Karaca et al., 2007), though it remains unclear whether anxiety is a prodromal symptom of EH or *vice versa* (Noppen et al., 1997, Ruchinskas, 2007). Anxiety in moderate rather than severe cases of axillary and craniofacial hyperhidrosis cases to be the most anxious (Braganca et al., 2014) and surgical interventions for EH typically involve thoracic sympathectomy, which often causes compensatory sweating yet still apparently improves psychosocial distress (Ramos et al., 2006). Such convoluted findings make delineating emotional and sudomotor factors in EH challenging. Therefore, **specific aim # 2** of this thesis will

(i) thoroughly and systematically investigate cognitive-affective symptoms in EH, AMS and PoTS to
(ii) decipher if these psychological symptoms are related to dysautonomia symptoms that functionally overlap with physical manifestations of anxiety and panic
(iii) or are trait-like phenomena independent of dysautonomia.

Theories of emotion connect affect with motor, neurobiological and autonomic responses to define a spectrum and time course (used to define emotions from moods) of phenomena initiated by the valence and arousal of a stimulus, which can be internal or located in the environment (LeDoux, 1992, McTeague et al., 2012). Emotional processing and decision-making are now not only seen as interrelated but complimentary (Bechara and Damasio, 2005). The ANS provides a key role in cognitive-affective processes as central processing of autonomic feedback influences behaviour in order to both avoid punishment and maximize reward, as evidenced by autonomic arousal reflecting behavioural learning (Bechara et al., 1997b, Damasio et al., 1991, Critchley et al., 2001a, Coricelli et al., 2005).

Regardless of whether a stimulus evokes a defensive or appetitive response, the two primary reflexes of increased sensory processing and preparation for mobilisation remain the same (Lang and Davis, 2006) across valances. This overlap, along with methodological

inconsistencies (e.g., experimental protocols, knowledge of the ANS, length of time responses were monitored), may explain the lack of validated emotion-specific autonomic signatures to date (Lang, 1994, Kreibig, 2010). Much of this research was influenced by the James-Lange theory, which proposes that physiological responses differentiate emotion from non-emotion (Lange and James, 1922) and that certain emotions are attached to the central interpretation (interoception) of bodily states, which are primarily defined by varying patterns of autonomic activity. The '*Somatic Marker Hypothesis*' (Damasio, 1999) emphasises how homeostatic requirements motivate and shape behaviour, for example, individuals are more mindful of palatable sensory signals when hungry. Such theories of brain-body integration posit that the sensitivity of the brain to bodily responses governs the intensity of emotional experience (Paulus, 2013).

'Interoception' is the processing of afferent visceral nerve activity, which informs autonomic mediation of homeostasis and contributes to emotion, behaviour and cognition at varying levels of consciousness, from baroreceptors modulating cardiac responses to fluctuations in BP to maintain cerebral perfusion, to discarding an item of clothing as an act of behavioural thermoregulation. An individual's interoceptive accuracy (IA) moderates the degree to which somatic events are linked to cognitive-affective processes (Damasio, 1999, Gray et al., 2012) and individuals with greater IA experience emotions more deeply, particularly anxiety (Schandry, 1981). Interoception is therefore a fundamental process of central and visceral homeostatic and allostatic integration, as evidenced by the recent finding that interoceptor (arterial baroreceptors) activity influences cognitive-affective processes on a preconscious level (Garfinkel et al., 2014) or that the sight or smell of food causes the release of insulin (Teff, 2011). In hypochondriasis, anxiety disorders and somatisation disorders, patients report somatic hypervigilance and somatosensory amplification (Barsky, 1992, Rief et al., 1998, Ludewig et al., 2005, Anderson and Hope, 2009), indicating anxiety shifts attention to interoceptive events.

Figure 6. Schematic of afferent interoceptive pathways in the human central nervous system.

Predictions of experienced versus expected interoceptive error signals of bodily events can be a 'bottom up' source of anxiety (Paulus and Stein, 2006). Therefore, if one were to feel dizzy, tachycardic or too hot or sweaty whilst being aware that the situation did not require these aberrant allostatic adaptions, the processing of these interoceptive error signals would create anxiety at the discordant bodily states. This hypothesis is supported by evidence that the insula detect discrepancies in predictions of one's physical state rather than actual changes in physical state (Gray et al., 2007), and that these error code predictions then influence behaviour and mood. Therefore, to investigate the potential influences of intermittent cardiovascular (PoTS, AMS) and sudomotor (EH) autonomic overactivity on brain-body integration processes, such as interoception, **specific aim # 3** of this thesis will;

I. assess somatic hypervigilance in AMS, EH and PoTS in comparison to controls.
II. assess empathy (an emotion influenced by interoception (Grynberg and Pollatos, 2015) that predicts autonomic arousal during emotional stimulation (Bogdanov et al., 2013) in AMS, EH and PoTS in comparison to controls.
III. define the subjective measure of interoceptive sensibility, objective measure of interoceptive accuracy (IA) and metacognitive measure of interoceptive awareness in AMS, EH and PoTS in comparison to healthy controls.
IV. assess heart rate variability (HRV) to examine autonomic variability and how this relates to brain-body integration in AMS, EH and PoTS in comparison to healthy controls.

The ANS is the primary mediator of efferent and afferent nerve traffic between the brain and the periphery and provides a potential framework to explore the associations between autonomic activity and affective disorders (Thayer et al., 1996, Thayer et al., 2000). It also leads one to consider what happens to cognitive-affective processes in conditions of exaggerated autonomic responsivity (Eccles et al., 2015). Phylogenetic defence responses have evolved to protect from physical harm, e.g., eye blink to air puff or limb shock withdrawal (Darwin, 1872/1998). These innate defence responses, particularly fight/flight, share many autonomic characteristics with intermittent forms of dysautonomia.

- **Freezing/hypervigilance** – All movement except oculomotor and respiratory is suspended (Blanchar and Blanchar, 1969). This response makes it more difficult to localise prey for movement-dependent predators.
- **Fight or flight** – a heightened defence response to threat. The SNS enables physiological responses to escape or repel the heightened danger, including:
    - Increased heart rate (PoTS)
    - Bladder relaxation (VVS)
    - Face flushing (EH)
    - Xerostomia (PoTS)
    - Shaking (PoTS, VVS)
    - Sudomotor activation (EH)
- **Tonic immobility** (TI) – has been well-documented in animals as 'sham death' and is an end-stage strategy (Monassi et al., 1999). In humans, TI typically occurs during sexual assault and is often preceded by peritraumatic fear and perceived inescapability (Bovin et al., 2008).

Despite the inconsistencies in defining emotion-specific autonomic signatures (Hodgson and Rachman, 1974, Rachman and Hodgson, 1974), a reliable and robust early response to a novel stimulus, especially unpleasant, is cardiac deceleration (Fanselow, 1994). Cardiac deceleration is a peripheral component of the 'orienting response' (OR), which is a series of involuntary sensory, motor and autonomic adjustments in response to an emotionally salient stimulus (see figure 7). These adjustments of SNS and PNS activity ensure optimal perception of

the stimulus, including inhibition of conditioned and unconditioned reflexes (Pavlov, 1953, Hedger et al., 2015) to '*increase analyser sensitivity*' (Sokolov, 1963a). The OR is the first response provoked by any novel stimulus and its magnitude depends on the evocative potential of the stimulus.

Figure 7. Diagram of the cardiac deceleration orienting response (left panel) and the skin conductance orienting response (right panel). From Bach et al., 2007

Electroencephalogram (EEG) and respiratory components of the OR represent novelty, peripheral vasoconstriction ORs reflect stimulus intensity and cardiac deceleration indicates stimulus detection (Barry, 2009). Moreover, the degree of cardiac deceleration predicts subsequent memory performance (Buchanan et al., 2006). Greater ORs are proposed to represent greater emotional significance of the stimulus and greater interoceptive accuracy (IA) is associated with increased subjective emotional experience, therefore, it is possible that a relationship may exist between IA and ORs and could provide an insight into holistic brain-body integration. However, this has not been investigated.

The non-muscular visceral components of the OR are autonomically mediated but there have been no investigations into whether dysautonomia affects ORs or related processes. This is worthy of investigation because the functional and organ-specific autonomic patterns that maintain homeostasis are permanently compromised in autonomic failure (AF) and intermittently compromised in conditions of OI, such as PoTS and AMS. In addition, many of these patients report comorbid affective, functional and cognitive symptoms not attributable to autonomic pathophysiology or neuropathophysiology (Heims et al., 2006a, Guaraldi et al., 2014, Ross et al., 2013, Ocon et al., 2009b, Stewart et al., 2012). From a clinical autonomic perspective, some unanswered questions remain, such as, (i) how do ORs compare at supine rest and during orthostasis, (ii) and between healthy controls and patients with compromised baroreflex function, particularly as PoTS and AMS have an over-representation of comorbid cognitive-affective symptoms? (iii) Would investigating the possible relationship between IA and ORs provide an insight into brain-body integration or these patients' common comorbid psychological symptoms, as greater ORs are proposed to represent greater emotional significance of the stimulus and greater IA is associated with increased emotional experience? **Therefore, specific aim # 4** of this thesis will investigate;

(i) the effects of orthostatic stress on ORs in PoTS and AMS in comparison to controls

(ii) explore any interactions between ORs and IA.

Chapter 2. Literature review & specific aims

2. Homeostasis

Although homo sapiens have developed rich and complex emotional lives, we exist within environments that place stresses on our bodies. In 1865, French physiologist, Claude Bernard defined the term 'homeostasis' to describe the maintenance of an internal steady-state environment within the body for optimal health and functionality. Homeostatic feedback and feedforward systems operate across central and visceral mechanisms in response to physiological requirements, generating corrective metabolic, cardiovascular or behavioural actions.

2.1. The autonomic nervous system

Homeostatic regulation is facilitated via the autonomic nervous system (ANS) and its unique ability to mediate activity of bodily organs, glands and blood vessels via peripheral efferent neurons. The term 'autonomic' derives from the fact that, with the exception of the sexual glands, autonomic nerve function is beyond conscious control. Autonomic neurons from the central (CNS) and peripheral nervous systems can be subdivided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS acts to increase effector organ activity predominantly via the catecholamines, noradrenaline (NA) and adrenaline at the neruoeffector junction. The PNS promotes vegetative activity mainly via acetylcholine (Ach), such as the slowing of heart rate (HR) or facilitation of food digestion by increasing gut motility.

Figure 8. Schematic of the main autonomic ganglia neurotransmitters. The acetylcholine receptor at all ganglia is the nicotinic subtype but postganglionic sympathetic and parasympathetic cholinergic receptors sites are of the muscarinic subtype. Ach = acetylcholine, NA = noradrenaline, Adr = adrenaline

2.1.1. The sympathetic nervous system

The SNS is essential for maintaining blood pressure (BP) and cerebral perfusion (see figure 9), which is vital for cognition and consciousness. Central SNS neurons synapse with peripheral sympathetic neurons via sympathetic ganglia (see Figure 1). Sympathetic preganglionic neurons are situated in the intermediolateral cell column of the spinal cord (Guyton, 1991). Preganglionic sympathetic neurons are cholinergic, secreting ACh to affect postganglionic neurons, most of which are adrenergic.

2.1.2. The parasympathetic nervous system

The PNS acts to conserve energy and facilitate recuperation and digestion by reducing effector organ function. Parasympathetic fibres predominantly exit the CNS via sacral spinal nerves and cranial nerves (Guyton, 1991). Three quarters of parasympathetic nerve fibres are located in the vagus nerve, where they innervate thoracic and gastrointestinal (GI) tissue. Pre-and-postganglionic parasympathetic nerve terminals are cholinergic.

2.1.3. Cardiovascular autonomic function

A homeostatic challenge to our bodies' equilibrium occurs whenever we stand upright (orthostasis). During the first 10-15 seconds of orthostasis, gravity attracts approximately 750ml of blood flow to the leg, pelvic and abdominal capacitance veins, known as venous pooling. To counteract venous pooling and maintain cerebral perfusion, cardiopulmonary mechanoreceptors and arterial baroreceptors in the aortic arch and carotid sinus detect changes in vascular contraction and send afferent signals to the brainstem, upregulating peripheral sympathetic nerve activity (SNA), which increases peripheral vascular resistance, venous tone and HR so that the necessary arterial pressure to adequately perfuse neural tissue is reached (see figure 9) (Smit et al., 1999).

Figure 9. Central and peripheral responses to orthostasis. From Mosqueda-Garcia et al, 2000.

Behaviour-dependent increases in BP are both enabled and moderated by the baroreflex (Janig and Habler, 2003, Dampney et al., 2013, Dampney et al., 2002). Failure of these autonomic reflexes can lead to transient loss of consciousness (TLoC) due to cerebral hypoperfusion. BP is an amalgamation of vascular resistance and cardiac output and is centrally mediated by three main groups of sympathetic efferent neurons that innervate blood vessels, cardiac tissue and the adrenal cortex and medulla;

- *Barosensitive neurons;*
    - ⇒ are activated by mental stress,
    - ⇒ responsible for short-term BP fluctuations (Janig and Habler, 2003)
    - ⇒ are under the control of arterial baroreceptors,
    - ⇒ have a dominant role in both short and long-term BP regulation,
    - ⇒ reside in and are regulated by the rostroventral lateral medulla (RVLM) (Dampney et al., 2002), spinal cord, hypothalamus and the nucleus of the solitary tract (NTS)
    - ⇒ innervate the kidney

- ⇒ are downregulated during arterial stretch or volume expansion
- ⇒ increase HR and noradrenaline (NA) release from adrenal chromaffin cells, which constricts non-dermal resistance arterioles
- ⇒ are activated by cutaneous nociceptors (Janig and Habler, 2003, Coote, 2005).

- *Glucosensitive cardiovascular neurons;*
  - ⇒ control adrenaline release from the adrenal medulla
  - ⇒ are activated by physical exertion and hypoglycaemia.

- *Thermosensitive neurons:*
  - ⇒ consist primarily of cutaneous vasoconstrictor neurons
  - ⇒ are activated by hyperventilation, hypothermia and emotional arousal (Janig and Habler, 2003, Vallbo et al., 2004, Dampney et al., 2002)

BP control also involves a number of neurohormones, such as antidiuretic hormone (ADH), noradrenaline (NA), adrenaline and the renin-angiotensin system (RAS). These neurohormones bring about vasoconstriction and water retention. During orthostasis, NA and to a lesser extent, adrenaline release increases, inducing vasoconstriction and increasing peripheral resistance (Mathias et al., 2013). Peripheral vasoconstriction is also influenced by renin, which is converted from angiotensin released from renal arterioles and promotes the release of aldosterone from the adrenal cortex. Plasma volume is maintained by water and sodium re-absorption within the kidney, which is promoted by aldosterone. As with adrenergic neurotransmitters, orthostasis also encourages the release of renin (Laszlo et al., 2001). The pituitary gland releases ADH, also known as vasopressin, which is involved in a feedback arc with variation of baroreflex responses and blood osmolarity (Robertson, 2001).

2.1.3.1. Cerebral perfusion & autoregulation

As bipeds with evolved neocortices, human consciousness and cognition is dependent on sympathetic, parasympathetic and sensory innervation of the cerebral vasculature to mediate cerebral perfusion, however, the complexity of this neurovascular coupling allows for the breakdown of cerebral perfusion. Intracranial pressure and local arterial pressure maintain cerebral perfusion pressure (difference between intracranial pressure and mean arterial pressure (Van Lieshout et al., 2003)) at 80 mmHg and excessive increases or decreases (<50 mmHg) are prevented by autoregulation of cerebral blood flow (CBF), regardless of peripheral variations in BP (Van Lieshout et al., 2003). However, cerebral perfusion pressure is dependent on system arterial pressure, itself dependent on cardiac output and peripheral vascular resistance, therefore a reduction in either of these peripheral factors can cause reductions in

cerebral perfusion pressure. Should cerebral perfusion pressure drop below 70 mmHg, the brain becomes inadequately perfused with oxygen and other metabolites, predisposing to a transient loss of consciousness (TLoC) (Rosner et al., 1995).

2.1.3.2. Cutaneous blood flow

In the periphery, vasodilation of blood vessels in non-glabrous skin occurs when cutaneous and core temperatures increase, such as during exercise or stress (Kellogg, 2006). Cutaneous vasodilation is mediated at the effector junction by nitric oxide, neuropeptide P (NPY), histamine, vasoactive intestinal peptide (VIP) and prostanoids (McCord et al., 2006). This increase in skin blood flow is biphasic (Nicotra et al., 2006);

I. **Neurogenic phase** (fast responding, peaking after a few minutes) – axon-reflex mediated skin blood flow increase peaks, initiated by activity of sensory nerves and modulated by sympathetic nerves (Hornyak et al., 1990)
II. **Phase Two** (peaking around 30mins) - mediated by endothelial nitric oxide and other endogenous mediators

2.1.4. Thermoregulatory autonomic function

To ensure biochemical reactions are efficient, the human body's' optimum core temperature is 37°C. A number of peripheral, central and behavioural mechanisms aid thermoregulation, however, some cerebral activities, such as stress, shock or sleep also effect thermoregulation (Collins, 2013).

2.1.4.1. Thermoception

Following the perception of thermal discomfort, thermoregulatory behaviour can be initiated to maintain thermostasis, increase temperature (e.g., voluntary locomotor activity, involuntary locomotor activity) or decrease temperature (e.g., removing clothing, adjusting ambient temperature, cessation of locomotor activity, water consumption) to negate the intervention of autonomically-mediated thermoregulatory mechanisms (Benzinger, 1969, Flouris and Cheung, 2009). Perceived changes in skin temperature and thermal discomfort induce behavioural modifications (Schlader et al., 2009) at rest (Nakamura et al., 2008) and during exercise (Tucker et al., 2006, Tatterson et al., 2000). Initiation of thermoregulatory behaviour is uniform in terms of skin, rectal temperature and thermal comfort, when exposed to hot (45 °C) (Schlader et al., 2009) and cold environments (Flouris and Cheung, 2009). Behavioural thermoregulation generally precedes endocrine and autonomic thermostatic mechanisms (Mundel et al., 2007).

Brain thermoregulatory centres include, the dorsalmedial hypothalamus (Dimicco and Zaretsky, 2007), amygdala (Kanosue et al., 2002), insula (Verhagen et al., 2004), cingulate, primary and secondary somatosensory cortex and orbitofrontal cortex (Craig et al., 1994). Within the preoptic-anterior hypothalamus (POAH), skin, viscera, and spinal cord reside cool and warm-sensitive thermoreceptor neurons. The spinothalamic tract and other afferents provide feedback to the thalamus and posterior hypothalamus, which assumes the role of a central 'thermostat'. Cutaneous thermoception is relayed to second-order thermal sensory neurons in the dorsal horn via dorsal root ganglia and glutaminergic third-order cool-sensitive neurons of the lateral parabrachial nucleus and lateral subnucleus. Warm-sensitive neurons located in the dorsal horn, project to third-order neurons in the lateral parabrachial nucleus in the lateral reticular formation, where cranial nerve efferents include the vagus nerve (Morrison and Nakamura, 2011).

Conscious thermoception is relayed to the cortex and thalamus via dorsal horn neurons. Glutamatergic cool-sensitive neurons of the external lateral subnucleus of the lateral parabrachial nucleus (LPBel) synapse with GABAergic interneurons in the median preoptic (MnPO) area to inhibit action potentials in warm-sensitive neurons of the medial preoptic (MPO) subnucleus, mediating control of cutaneous vasoconstriction (CVC), shivering and thermogenic brown adipose tissue (BAT). BAT sympathoexcitatory neurons in the dorsomedial hypothalamus are inhibited by preoptic warm-sensitive neurons. Glutamate, serotonin (5-HT) and vesicular glutamate transporter 3 (VGLUT3) act as BAT neuromodulators to control BAT sympathetic outflow and thermogenesis.

Preoptic warm-sensitive neurons also synapse with shiver-promoting dorsomedial hypothalamus neurons. Warm-sensitive MPO neurons are activated by glutaminergic interneurons of the MnPO. These MPO warm-sensitive neurons supress CVC sympathetic premotor neurons in the rostral ventromedial medulla and intermediolateral nucleus (IML), in which CVC sympathetic tone is modulated by serotonin and glutamate.

2.1.4.2. Hyperthermia

The body's main defence against hyperthermia is heat loss via evaporation from the skin and respiratory passages, thus transferring heat from the body to the environment**.** The human body has three types of sweat gland, eccrine, apo-eccrine and apocrine. Eccrine glands are particularly densely populated in the forehead, palms, soles and axillae. Hypothalamic efferents descend via the lateral reticular formation and tegmentum of the pons to the intermediolateral column of the spinal cord where cholinergic neurons synapse with

paravertebral sympathetic ganglia. Post-ganglionic sympathetic cholinergic sudomotor axons then effect eccrine glands (Morrison and Nakamura, 2011). Sudomotor innervation of eccrine glands can be represented dermatonally;

- ⇒ T1-T4 sympathetic sudomotor neurons innervate the face
- ⇒ T2-T9 sympathetic sudomotor neurons innervate the upper limbs
- ⇒ T4-T12 sympathetic sudomotor neurons innervate the trunk
- ⇒ T10-L2 sympathetic sudomotor neurons innervate the lower limbs (Kirshblum et al., 2014, Nicotra et al., 2006).

These cholinergic sympathetic sudomotor neurons innervate 2-4 million eccrine glands that secrete a hypotonic saline solution during heat stress. Sweat evaporation cools the surrounding skin, which then cools the local cutaneous blood flow. Body temperature can also be regulated via skin blood flow (see 2.1.3.2. Cutaneous blood flow).

2.1.4.3 Hypothermia

Vasoconstriction during cold stress conserves heat and lessens peripheral blood flow. Hypothermia is defined as a core temperature of ≤35°C. The neural pathways modulating cold stress thermoregulations are better described than heat stress responses. Sympathetic preganglionic neurons are activated by the caudal portion of the raphe pallidus via descending neural pathways (Nagashima et al., 2000) (McAllen, 2007). Cold responsive neurons in the caudal portion of the raphe pallidus and dorsomedial nucleus of the hypothalamus that initiate cold-defence behaviours are inhibited by hypothalamic warm sensitive neurons. Glutamatergic cool-sensitive neurons of the external lateral subnucleus of the lateral parabrachial nucleus (LPBel) synapse with GABAergic interneurons in the MnPO area to inhibit warm-sensitive neurons of the MPO subnucleus and mediate cutaneous vasoconstriction, shivering and BAT. Preoptic warm-sensitive neurons also synapse with shiver-promoting dorsomedial hypothalamic neurons which, via shivering premotor neurons in the rostral raphe pallidus and ventral horn, provide efferents to skeletal muscle α and γ motor neurons to invoke shivering (see Figure 10). Cutaneous vasoconstriction sympathetic tone is modulated by NA and NPY (both post-ganglionic), serotonin and glutamate.

Figure 10. Thermoregulatory pathways. From Morrison and Nakamura (2011)

2.2. Autonomic neuroanatomy

Central autonomic networks within the spinal cord, brainstem and hypothalamus mediate cardiovascular and thermoregulatory autonomic outflows (see figures 11a and 11b)

(Benarroch, 1993). The ventromedial prefrontal cortex (vmPFC) is involved with PNS and antisympathetic activity (Gianaros et al., 2004; Matthews et al., 2004) and supragenual areas of the mid and anterior cingulate are associated with SNS activity. Haemodynamic changes are global autonomic responses requiring input from the cortex, limbic forebrain and midbrain (Saper, 2002) (Morrison, 2001). Magnetic resonance imaging (MRI) and functional MRI (fMRI) report activity within the dorsal anterior cingulate cortex (Critchley et al., 2003) and insula cortex (Critchley et al., 2000a, Critchley et al., 2000b) reflects engagement of sympathetic activity coupled to mental and physical behaviours (see figure 11b). Increased activity in the medial prefrontal cortex (mPFC), anterior and posterior insula and ventroposterior thalamus occurs during respiration, isometric hand-grip exercise and the valsalva manoeuvre (King et al., 1999), a clinical assessment of autonomic integrity in which the subject breathes against a closed glottis (Mathias et al., 2013).

Activity in the anterior cingulate cortex (Acc), insula, medial temporal lobe (MTL), ventral PFC (vPFC) and mPFC, medial thalamus, cerebellum, midbrain and pons increases during cold pressor and valsalva manoeuvres (Harper et al., 2000). Using positron emission tomography (PET) to assess brain activity during isometric hand-grip exercise and mental arithmetic (both well-validated pressor exercises (Mathias et al., 2013)) in healthy controls, Critchley and colleagues (Critchley et al., 2000a) found increases in BP were positively correlated with right dorsal Acc activity, supporting findings that sympathetic responses are lateralized to the right hemisphere (Oppenheimer et al., 1992) and the left insular cortex is involved in parasympathetic cardiovascular regulation, e.g., acute left insular stroke disrupts the correlation between HR and BP (Oppenheimer et al., 1996).

4a. **4b.**

Figure 11. Left panel (11a) displays the key central autonomic structures related to autonomic function. Right panel (11b) displays amygdala and central nucleus areas involved with emotion-related autonomic and behavioural responses. From Benarroch (1993).

Hypothalamic, pontine and medullary sympathetic and parasympathetic nuclei interact with homeostatic representations to generate physically or behaviourally-induced organ-specific autonomic responses (Saper, 2002). HR changes are predicted by amygdala and dorsal Acc activity (Janig and Habler, 2003) and during threat/stress induction, amygdala function predicts cardiac contractility (Dalton et al., 2005). The amygdala and other limbic structures supply a descending efferent drive to the hypothalamus and brainstem for congruent autonomic responses to emotion-related behaviour (see figure 11b) (Saper, 2002).

The nucleus of the solitary tract (NTS) receives baroreceptor afferents that synapse with the rostral ventrolateral medulla to set efferent pressor tone (see figure 12). Reduced baroreceptor tone has been associated with Acc, amygdala and anterior insula (AI) function, whereas

initiation of baroreflexes increases activity in lateral PFC (lPFC) and posterior insula (Kimmerly et al., 2005).

Figure 12. Spinal (sympathetic) and brainstem (parasympathetic) visceral sensory pathways to the thalamus and cortex. NTS = nucleus of the solitary tract. Adapted from Saper (2002)

2.3. Dysautonomia

Autonomic disease and dysfunction (dysautonomia) can be classified as either fixed or intermittent (Mathias and Bannister, 2013). Fixed ANS disorders cause autonomic failure (AF) as the lesion is fixed and usually irreversible, as in spinal cord injury (SCI) or pure autonomic failure (PAF). The lesion may also be progressive, as in Parkinson's disease with AF or multiple system atrophy (MSA). AF is characterised by a postural fall in BP which is defined as orthostatic hypotension (OH) when the fall is > 20 mmHg systolic BP (SBP) or > 10mmHg diastolic BP (DBP). Fixed ANS disorders commonly present in patients of >40 years, whereas intermittent ANS disorders can present in all ages.

Intermittent dysautonomia is a temporary dysregulation of normative autonomic function attributable to a specific factor, such as orthostatic intolerance (OI) or thermoregulatory dysfunction. Thermoregulatory dysautonomia may occur due to a systemic (malignancy, shock), metabolic (diabetes mellitus, menopause) or febrile illness (infection), as well as neurological disorders (stroke, Parkinsons disease) and can be focal or generalised in nature. Cardiovascular intermittent dysautonomia relates to orthostatic intolerance (OI), though factors such as food digestion, dehydration and exercise can also exacerbate symptoms. Sudomotor and cardiovascular intermittent dysautonomia often present in adolescence/early adulthood and with strong positive family histories (Kaufmann et al., 2003, Iodice et al., 2010).

2.3.1. Postural tachycardia syndrome

Postural tachycardia syndrome (PoTS) is the most common form of OI, with prevalence accounting for at least 170 cases per 100,000 individuals in the general population (Schondorf et al., 1999). PoTS is characterised by an excessive HR increase of +30 bpm or HR >120 bpm without OH within 10 mins of orthostasis or head up tilt (HUT) (Freeman et al., 2011a). PoTS has only relatively recently (1993) been clearly described (Schondorf and Low, 1993) and as understanding has increased, other factors, such as prolonged standing, heat or eating can provoke symptoms and presentation (Mathias et al., 2012).

PoTS can be broadly divided into hyperadrenergic or neuropathic phenotypes (see Table 1) (Benarroch, 2012), however, dysfunction of the noradrenaline transporter gene promoter region (Esler et al., 2006), infection (Schondorf and Low, 1993), deconditioning (Parsaik et al., 2012), hypovolemia and/or poor orthostatic cerebral autoregulation (Ocon et al., 2009b) have also been implicated in PoTS pathophysiology.

PoTS patients may also present with pre-syncope, syncope, dizziness, palpations, headache, fatigue, bladder and gastrointestinal (GI) symptoms and around 70% also have the heritable rheumatological condition, Ehlers-Danlos Syndrome iii/joint hypermobility type (Mathias et al., 2012), which also leads to vascular abnormalities that exacerbate orthostatic-related symptoms (Benarroch, 2012, Mathias et al., 2012).

Mechanism of PoTS subtype	Markers	Examples
Neuropathic PoTS: Impaired sympathetically mediated vasoconstriction in the lower limbs	Impaired distal sweating, blunted late phase ii in Valsalva maneuver, low supine BP, reduced NA spillover in leg veins, reduced cardiac meta-iodobenzylguanidine uptake, High leg blood flow	Restricted post-viral or autoimmune neuropathies
Hyperadrenergic PoTS: exaggerated cardiac sympathoexcitatory responses	Standing plasma NA $\geq$600 pg/mL, fluctuating BP or hypertension during HUT	Anxiety, Pheochromocytoma, Mast cell activation disorders, voltage-gated potassium channel autoimmunity
Volume dysregulation	Elevated plasma angiotensin II, Impairment of renin-angiotensin-aldosterone system, impaired renal control of fluid secretion	Conditions associated with hypovolemia
Physical deconditioning	$\dot{V}_{O2max}$ $\leq$85% on exercise testing, reduced left ventricular mass	Prolonged bed rest, Chronic fatigue syndrome

Table 1 Overview of PoTS phenotypes, adapted from Benarroch (2012).

2.3.2. Autonomic (neurally) mediated syncope

Although intrinsically autoregulated (see 2.1.3.1. Cerebral perfusion & autoregulation), neurovascular coupling allows for potential breakdown in cerebral perfusion. Orthostasis should normally provoke an intricate integration of central and peripheral autonomic reflexes and feedback mechanisms to ensure cerebral perfusion, which is dependent on systemic vascular resistance, cardiac output, arterial pressure, local metabolic control and cerebrovascular resistance. Transient loss of consciousness (TLoC) can be induced by a variety of physiological phenomena that lead to either inadequate cerebral perfusion pressure or abnormally high cerebral vascular resistance (see Table 2). Autonomic (neurally) mediated

syncope (AMS) is a group of syncopal (fainting) phenotypes that are caused by the breakdown of autonomic reflexes. The three forms of AMS are;

I. Carotid sinus hypersensitivity (CSH)
II. Situational syncope (SS)
III. Vasovagal syncope (VVS)

VVS is caused by vasodilatation and/or bradycardia and predominantly occurs in females under 40 years, as opposed to CSH typically occurs in those >50 years of age due to exaggerated baroreceptor activation (Humm and Mathias, 2010). The lifetime incidence of syncope is approximately 39% (Lipsitz et al., 1985, Ganzeboom et al., 2006) and accounts for 3-5% of emergency room admissions (Kapoor et al., 1995, Linzer et al., 1991, Linzer et al., 1994). 70% of patients with recurrent syncope suffer impairment of daily activities, 39% have to change occupation, 64% are unable to drive and 6% suffer fractures (Linzer et al., 1991, Linzer et al., 1994). UK ambulance services respond to between 300,000–400,000 emergency calls for falls and syncopal episodes annually, with up to 50% being taken to hospital (Close et al., 2002, Marks et al., 2002). Once admitted, the diagnostic yield of standard investigations such as electroencephalography (EEG) and brain imaging in syncope, particularly in non-convulsive blackouts, can be less than 5% (Eagle and Black, 1983, Kapoor et al., 1983). In addition to paramedic costs, the average cost of admittance for a patient who has fallen/fainted is approximately £2000–£3000 (Scuffham et al., 2003). If the patient has no cardiac structural abnormalities, electrophysiological and electrocardiogram (ECG) can have a very low yield (Hess et al., 1982, Krahn et al., 1999) in defining the cause of the fall, moreover, due to the episodic nature of attacks, only 2-4% of ECG investigations obtain relevant data

VVS typically first presents in late adolescence/early adulthood, whereas syncope in the elderly is predominately cardiogenic or due to OH (Vaddadi et al., 2007). VVS constitutes around 40% of syncopal events, making it the most common cause of syncope (Fenton et al., 2000). VVS is a paroxysmal malfunction of baroreflexes and the autonomic instability of a vasovagal episode, wherein sympathoexcitation is a prodromal phenomenon that precedes parasympathetoexciation (vasodilatation, reduced cardiac output) has long been reported (Medow et al., 2008, Barcroft and Edholm, 1945).

<table>
<tr><th>Low arterial blood pressure</th><th>Increased resistance to cerebral blood flow</th><th>Other causes of cerebral dysfunction</th></tr>
<tr><td>Low cardiac output</td><td>Cerebral vasoconstriction</td><td>Epilepsy may be confused with simple faints</td></tr>
<tr><td>Inadequate venous return due to excessive venous pooling or low blood volume</td><td>Low Paco2, due to hyperventilation</td><td>Metabolic and endocrine disorders—hypoglycaemia, Addison's disease, hypopituitarism</td></tr>
<tr><td>Cardiac causes - tachyarrhythmias, bradyarrhythmias, valvular disease, bradycardia</td><td>Cerebral vasospasm</td><td rowspan="8">Electrolyte disorders—may be associated with hypovolaemia or predispose to cardiac arrhythmias</td></tr>
<tr><td>Low total peripheral vascular resistance</td><td rowspan="7">Vascular disease—either extracranial of intracranial areteries.</td></tr>
<tr><td>Vasovagal attacks</td></tr>
<tr><td>Widespread cutaneous vasodilatation in thermal stress</td></tr>
<tr><td>Reflex causes — vasovagal attacks, 'carotid sinus syndrome', visceral pain reflexes (may cause vasodilatation or vasoconstriction), decreased stimulation of visceral stretch receptors (e.g. voiding distended bladder)</td></tr>
<tr><td>Vasodilator drugs</td></tr>
<tr><td>Autonomic neuropathies</td></tr>
</table>

Table 2 Classification and causes of syncope. Hainsworth and Claydon, 2012.

2.3.2.1. Updating 'psychogenic pseudosyncope'

Despite the wealth of laboratory and ambulatory equipment available, the cause of 10-26% of syncope cases remains unexplainable (Brignole et al., 2005, Krahn et al., 1995, Krahn et al., 1998) and psychiatric illness is more prevalent in these patients with unexplained syncope, particularly if syncopal episodes are recurrent and/or include multiple somatic symptomology (Kapoor et al., 1995). Directed treatment focused on psychiatric symptoms can result in syncope remission in up to 90% of these cases (Linzer et al., 1990).

'Psychogenic pseudosyncope' (PSS) is the occurrence of apparent syncope (unresponsiveness and loss of postural tone) during normal physiological indices that would not result in cerebral hypoperfusion, as measured by HR, BP, ECG, electroencephalogram (EEG) or transcranial Doppler. PSS would appear to be a form of conversion disorder but there is currently a paucity of literature on PSS (van Dijk and Wieling, 2013) and direct observation of pseudosyncope in a clinical setting is rare (Luzza et al., 2004). Moreover, symptoms of OI, particularly pre-syncope, are commonly reported in functional somatic disorders (Kroenke and Rosmalen, 2006). In comparison to other types of syncope, PPS patients often report a greater number of prodromal symptoms, such as chest pains, palpitations, paraesthesia, dyspnea, dizziness (Luzza et al., 2004), however, during a PSS episode, the vast majority of patients close

their eyes and resist eyelid opening (Tannemaat et al., 2013). PSS patients' periods of apparent unconscious are also significantly longer than syncope patients and occur with greater frequency.

Conversion or medically unexplainable symptoms during autonomic testing remains under-researched and inadequately understood. One may also question the clarity, objectivity and accuracy of the term 'psychogenic pseudosyncope' due to the fact that actual episodes of VVS can be psychogenic, such as the site of blood, frustration or humiliation. Some have proposed that diagnoses of this nature can be 'a disguise for ignorance and a fertile source of clinical error' (Slater, 1965). Syncope of unknown aetiology significantly impairs the patient's quality of life (QoL) (Raj et al., 2014) and contributes to ~£18 billion per annum spent treating and supporting patients with somatization disorders (Bermingham et al., 2010). Trimble (Trimble, 1982) proposes the use of the term 'functional' in such cases as, in its original usage, 'functional' referred to aberrant function of the nervous system, the cause of which was under investigation. Therefore, the term 'functional syncope' (FS) will be used in this thesis, rather than the less objective, inaccurate and repetitive term of psychogenic pseudosyncope.

FS appears to be a conversion disorder yet it is often reported or described with little attempt to try and unpick the psychophysiological mechanisms that may be involved in its presentation. Other functional disorders, such as fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome have been reported in PoTS (the most common form of OI), therefore, **specific aim # 1 of this thesis will;**

- **(iv) review the historical case notes of FS patients to ascertain whether FS is a typical conversion disorder**
- **(v) investigate any underlying autonomic or dysautonomic contributions to FS,**
- **(vi) describe the presentation and incidence of FS during autonomic testing**

2.3.3. Essential hyperhidrosis

Essential hyperhidrosis (EH) is diagnosed when an individual's excreted sweat exceeds that required to normalise body temperature and causes significant functional impairment. The aetiology of EH remains unknown but the condition is defined by excessive local or generalised sweating, typically on the palms of the hands, soles of feet and axillary. The prevalence of the condition has been estimated to be 2-3% (Lai et al., 2014, Moraites et al., 2014). Eccrine glands are primarily implicated in EH, with the exception of axillary EH, which appears to have a more diffuse pathophysiology (Lonsdale-Eccles et al., 2003, Bovell et al., 2001). Once a secondary cause of hyperhidrosis has been eliminated (see Table 3), sudomotor activity can be examined with moisture-sensitive indicator dyes during a thermoregulatory sweat test (Low and Fealey, 2013). EH can be provoked by everyday factors, such as mild exertion or food ingestion.

GENERALISED	CAUSES OF HYPERHIDROSIS
Environment	Heat, humidity, exercise
Febrile disease, systemic disease	Acute and chronic infections, malignancy, cardiovascular disorders, shock and syncope, respiratory failure, intense pain, alcohol, drug withdrawal
Metabolic	Thyrotoxicosis, diabetes mellitus, hypoglycaemia, gout, pheochromocytoma, hyperpituitarism, acromegaly, carcinoid tumor, menopause
Neurologic	Riley-Day syndrome, hypothalamic lesions, Parkinson´s disease
Drugs	Propranolol, physostigmine, pilocarpine, tricyclic antidepressants, venlafaxine
FOCAL	CAUSES OF HYPERHIDROSIS
Extrinsic	Heat, olfactory
Gustatory	Citric acid, coffee, chocolate, peanut butter, spicy food
Neurological	Central or peripheral nervous system lesions causing localized anhidrosis can cause compensatory sweating in other areas (stroke, spinal cord lesion, neuropathy, Ross Syndrome), Frey Syndrome (gustatory sweating); eccrine nevus, social anxiety disorder
Idiopathic	Primary or essential hyperhidrosis

Table 3. Examples of causes of secondary and essential hyperhidrosis. Adapted from Naumann, 2012.

2.4. Postural tachycardia syndrome, vasovagal syncope & essential hyperhidrosis: autonomic endophenotypes of anxiety

Although psychiatric patients may report symptoms akin to intermittent dysautonomia, e.g., sweating, faintness or palpitations, autonomic diagnostic criteria are rarely met (Ruchinskas et al., 2002, Lkhagvasuren et al., 2011). However, comorbid psychological symptoms are often reported in AMS, EH and PoTS (Giada et al., 2005, Gracie et al., 2006, Ruchinskas, 2007, D'Antono et al., 2009, Raj et al., 2009, Vazquez et al., 2011, Rios-Martinez et al., 2009), with recent evidence suggesting these co-morbid psychological factors may be, to some extent, resultant rather than causative of autonomic dysfunction in PoTS (Khurana, 2006, Masuki et al., 2007, Raj et al., 2009).

2.4.1. Palpations, dizziness, tremulousness: the postural tachycardia syndrome endophenotype of anxiety

In the United Kingdom, approximately 70% of PoTS patients meet the diagnostic criteria for the heritable rheumatological condition Ehlers-Danlos Syndrome III/Joint Hypermobility Type (Mathias et al., 2012) which has been associated with anxiety disorders (60%–68% prevalence), particularly panic disorder (Bulbena et al., 2004, Eccles et al., 2011, Eccles et al., 2012). Like

PoTS, comorbid EDSiii/JHT and anxiety is significantly more common in young females (Martin-Santos et al., 1998). Investigations of functional disability in PoTS have found day-to-day limitations closely related to catastrophising thoughts, which also mediate anxiety and somatic hypervigilance (Benrud-Larson et al., 2003), another common anxiety trait in PoTS (Raj et al., 2009, Masuki et al., 2007, Raj, 2006). Although PoTS and panic disorder may share psychological (e.g., tremulousness, health anxiety, impaired concentration) and physiological (e.g., palpitations, tachycardia, chest pain, dyspnea) symptomatology and can co-exist (Esler et al., 2004), a differentiating factor is that PoTS can be provoked by physiological challenges alone (Masuki et al., 2007).

Umeda and colleagues used simultaneous fMRI and physiological recording during emotional stimuli showing that, regardless of emotional valence, PoTS patients produced exaggerated supine cardiac responses to visual emotional stimuli in comparison to healthy controls. Activation of the ventromedial PFC, which has an 'anti-sympathetic' role (see Autonomic neuroanatomy), and the right dorsolateral PFC was significantly reduced in PoTS patients during stimulus presentation across all valences. Functional connectivity between PoTS patients' dorsolateral PFCs, orbital PFCs and basal ganglia were positively correlated with the magnitude of emotional supine cardiac response and state anxiety (Umeda et al., 2009). These data may help elucidate the interrelationship of autonomic and neurobiological pathophysiology that drives the diffuse secondary psychological symptoms reported in PoTS and the potential perturbation of autonomic-sensitive neuroanatomy by the syndrome.

In addition to affective symptoms, cognitive function can be impaired in PoTS (Anderson et al., 2014, Raj et al., 2009), e.g., patients' short term memory (Anderson et al., 2014) and attentional and recall abilities are significantly poorer than controls and PoTS patients score significantly higher on attention deficit hyperactivity disorder indexes (Raj et al., 2009). Inattention has been found to decrease with illness duration, likely due to adaptive or treatment responses. Furthermore, hyperactive traits were absent in childhood, suggestive of a causal role in these cognitive symptoms that often present in PoTS. Masuki and colleagues' (Masuki et al., 2007) disproved PoTS as being psychogenic by comparing orthostatic and psychological stress responses in PoTS patients and healthy controls. It may be noteworthy that catastrophic cognitions of visceral feedback are more commonly applied to cardiac signals in anxiety disorders (Willem Van der Does et al., 2000, Domschke et al., 2010).

It may be relevant that poor quality sleep, daytime sleepiness and fatigue are also common in PoTS (Bagai et al., 2011). In PoTS patients with comorbid chronic fatigue syndrome (CFS), working memory, accuracy and information processing are impaired during orthostasis, yet the cause of this 'brain fog' that is commonly reported by many PoTS patients, remains elusive,

despite investigations into cerebral blood velocity, sleep quality or neurotransmitter function (Ocon, 2013, Ross et al., 2013). In a related study, PoTS patients performed worse in tests of current verbal and non-verbal IQ intellectual functioning and in measures of focused attention and short term memory. Cognitive data was influenced by years of education and underlying levels of anxiety and depression (Anderson et al., 2014).

2.4.2. Dizziness, nausea, dissociation: the vasovagal syncope endophenotype of anxiety

The occurrence of the vasovagal reflex (sympathetic inhibition and vagal activation) during haemorrhagic shock, such as blood donation or physical injury, causes bradycardia and decreases myocardial oxygen consumption which prevents exsanguination during major bleeding. A phenomenon comparable to the sham death or tonic immobility seen in many invertebrates when caught by a predator (Alboni et al., 2008, Diehl, 2005). In a study of 66 VVS patients, Cohen et al (Cohen et al., 2000a) found that anxiety scores were positively correlated with positive (symptomatic hypotension and/or bradycardia) HUT. Anxiety has also been associated with greater syncope burden (Lerma et al., 2013). Though emotional stress may increase BP and HR, vascular resistance is not typically influenced by psychological factors, however, in an episode of emotionally-induced VVS, BP, HR and peripheral resistance fall profoundly (Mosqueda-Garcia et al., 2000).

Abnormally high levels of depression, anxiety and blood/injury phobia are common in VVS (Graham, 1961, McGrady et al., 2001, Luborsky et al., 1973, Karaca et al., 2007), with syncopal episodes often proceeding anticipation of real or fantasised physical harm in a social context, where fight/flight was perceived as unacceptable, i.e., "…*when an individual experiences fear he must deny*" (Engel, 1962). Depression, anxiety, frustration and helplessness have been identified as VVS antecedents (Luborsky et al., 1973) and psychosocial threats, such as humiliation and mortification, to which the fainter feels they cannot escape can also provoke vasovagal episodes (Sledge, 1978).

Psychiatry, neurology and cardiology research groups have found psychiatric conditions are over-represented in patients with VVS, particularly anxiety, depression and somatization disorders (Giada et al., 2005). Leftheriotis (Leftheriotis et al., 2008) and co-workers surveyed 67 patients with 'minor psychiatric disorder' for VVS. 58% had a vasovagal episode during HUT and 45% had a history of syncope. VVS patients who do not respond to treatment are more anxious and depressed than VVS treatment responders, report more negative thoughts regarding threats to physical harm or death, as well as higher levels of avoidance/protection coping and rumination (Gracie et al., 2006).

Imaging studies have provided evidence of reduced medulla and midbrain grey matter volume in VVS. Moreover, left caudate nucleus volumes were negatively correlated with cardiac vagal tone (as measured by HF-HRV), syncopal episodes and anxiety (see Figure 13), suggesting that VVS predisposition relates to differences in brainstem neuroanatomy that regulate baroreflex BP control and cardiovascular homeostasis (Beacher et al., 2009).

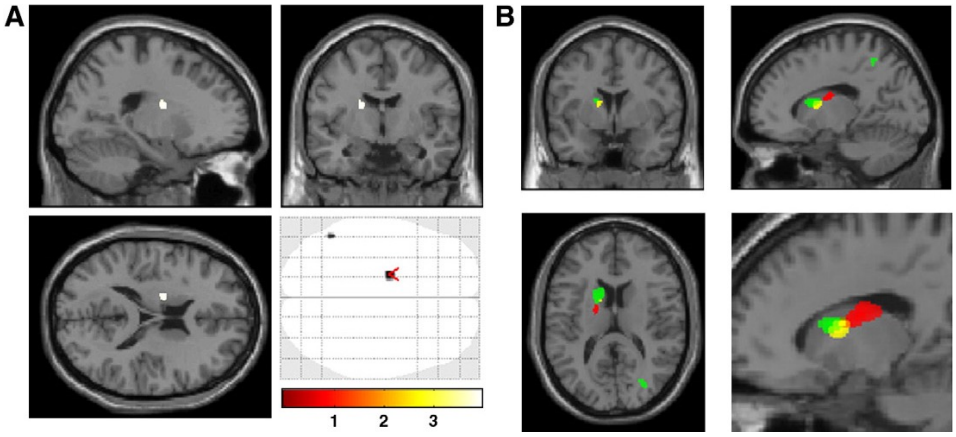


Figure 13. Figure 5. (A) Caudate regions showing significant negative correlations between regional gray matter volumes and anxiety levels, within VVS participants. (B) Within VVS participants, left caudate regions showing significant negative correlations between regional gray matter volumes and anxiety levels (red), fainting frequency (yellow) and HF-HRV (green). From Beacher et al., (2009)

Anticipatory processing has a perceptual role in the assessment of a sensory stimulus by coordinating a series of preparatory physiological adjustments that allow the subject to respond and potentially interact with the stimulus (Van Boxtel and Böcker, 2004). Studies have shown that when faced with a threat stimulus, the decision to avoid the threat stimulus follows an increase in SBP which does not occur when the subject is powerless to avoid the noxious stimulus (Manuck et al., 1978) (Light and Obrist, 1980). A recent study using Stimulus Preceding Negativity (SPN) during emotional stressors in AMS patients has provided a central measure of reduced emotional variation, anticipation and regulation in this cohort (Buodo et al., 2012).

2.4.3. Sweating, clamminess & flushing: the essential hyperhidrosis endophenotype of anxiety

EH remains a neglected area of study. Although the aetiology of the condition remains uncertain, patients commonly report anxiety (Karaca et al., 2007), though it remains unclear whether anxiety is a prodromal symptom of EH or *vice versa* (Noppen et al., 1997, Ruchinskas, 2007). Explanations of EH as simple basal sympathetic hyperactivity are complicated by most patients' accompanying affective distress and HRV findings of increased parasympathetic cardiac activity (HF-HRV) (Birner et al., 2000, Kaya et al., 2005). In a study by De Marinis and co-workers (Kaya et al., 2005), 34% of EH patients also had 'OH', furthermore, this sub-group had

greater total body sweat rates and larger orthostatic BP and HR changes than the remaining EH patients and normal controls. However, in consideration of the subjects' age range (28 ± 6 years); these were more likely to be vasovagal episodes rather than autonomic failure-induced hypotensive episodes.

In a survey of 'treatment-seeking' patients referred to a dermatology clinic, patients receiving a diagnosis of EH were typically younger (mean age 34 years), unmarried, employed, more educated, and received a higher annual salary than non-EH patients. Moreover, hyperhidrotics were also more greatly disabled by their symptoms, had poorer QoL as well as having higher levels of social anxiety (Lessa Lda et al., 2014). Interestingly, a recent survey found the greatest levels of anxiety in moderate rather than severe cases of axillary and craniofacial hyperhidrosis cases to be the most anxious (Braganca et al., 2014). Surgical interventions for EH typically involve thoracic sympathectomy, which often causes compensatory sweating yet still apparently improves psychosocial distress (Ramos et al., 2006). Such convoluted findings make delineating emotional and sudomotor factors in EH challenging.

In studies examining emotion in autonomic failure (AF) patients, i.e., endophenotypes of fixed or progressive autonomic hypoarousal, complex higher order emotional responses, such as empathy are diminished (Chauhan et al., 2008, Heims et al., 2006b), indicating the emotional impairment of insufficient reciprocal autonomic arousal. Therefore, **specific aim # 2 of this thesis will**

(iv) **thoroughly and systematically investigate cognitive-affective symptoms in EH, AMS and PoTS to**

(v) **decipher if these psychological symptoms are related to dysautonomia symptoms that functionally overlap with physical manifestations of anxiety and panic**

(vi) **or are trait-like or trauma-related affective phenomena independent of dysautonomia**.

2.5. Brain, body & emotion: the autonomic common thread

Facial expressions have been used to define cross-cultural 'basic emotions', such as disgust, happiness, sadness, fear, surprise and anger (Ekman, 1993). Cross-species studies suggest that basic emotions most likely have a phylogenetic basis, as even basic life forms display defined aggressive behaviours (Aaltonen et al., 2013) and many mammals exhibit facial expressions of disgust (Berridge and Robinson, 2003) (see figure 14a and 14b).

A B

Figure 14. Top: dog and cat defence behaviours. From Darwin (1872). (A) Bottom left panel: (right) Male drosophila raises it wings as a display of aggression. (A) Bottom right panel: decapitated female drosophila provokes the males to attack each other. From Chen et al (2002). (B) Top: cross-species (infant homo sapien, infant orang-utan, rat) facial expressions associated with palatable tastents and (bottom right) unpalatable tastents. From Berridge and Robinson (2003).

To study emotion, it has been necessary to define emotions in terms of arousal and valence. Theories of emotion connect affect with motor, neurobiological and autonomic responses to define a spectrum and time course (used to define emotions from moods) of phenomena initiated by the valence and arousal of a stimulus, which can be internal or located in the environment (LeDoux, 1992, McTeague et al., 2012).

From a psychological construction perspective, emotions are influenced by afferent signals evoked by the stimulus that are represented within the CNS. These representations interact with perceptions of the surroundings and previous emotional experience during emotion formation. This 'top-down' perspective has evidenced much heterogeneity of emotion (Barrett, 2006), which is explained by classifying emotions as cognitive categories comprised of a spectrum of unique 'instances' that reflect the relevant psychosocial factors of a given situation (Clore and Ortony, 2013). The psychological constructionist perspective posits that physiological afferent feedback only becomes relevant when caused by or related to a defined situation.

'Dual process' theories have attributed cognition with a corrective role on emotion in adults. Emotional processing and decision-making are now not only seen as interrelated but complimentary (Bechara and Damasio, 2005). The Acc and anterior insula are involved in the processing of visceral afferent feedback (see figure 5), as well as the mediation of responses to somatosensory and sensory information (Medford and Critchley, 2010). The ANS provides a key role in cognitive-affective processes as central processing of autonomic feedback influences behaviour in order to both avoid punishment and maximize reward, as evidenced by autonomic arousal reflecting behavioural learning (Bechara et al., 1997b, Damasio et al., 1991, Critchley et al., 2001a, Coricelli et al., 2005).

2.5.1. Insights from affective neuroscience

Functional neuroimaging has seen a sea change away from functional localization of brain structures to viewing brain function in terms of networks and regional interactions that are defined as much by their connections as local functional architecture. Key emotional neuroanatomy are the insula, Acc, orbitofrontal cortex and amygdala (LeDoux, 1992) (see

figure 15). Brain imaging has allowed the definition of four emotional neural substrates; fear, panic, seeking and rage (Panksepp, 2010), that have been utilised to develop therapeutic applications (Harrison and Critchley, 2007).

The orbital and ventromedial PFC (vmPFC) are vital social and higher function centres. The medial PFC (mPFC) is known to mediate and assess emotions (Damasio, 1994) and, together with the amygdala and Acc, are important centres in emotional processing as well as autonomic reactivity (LeDoux, 1995, Devinsky et al., 1995), underlining how affect and autonomic function are coupled. Vulnerabilities to anxiety disorders has been linked to Acc morphology (Mayberg, 2003, Pujol et al., 2002) and depression susceptibility with vmPFC morphology (Mayberg, 2003). Both the insula and cingulofrontal areas are important for emotional perception (Critchley et al., 2001b, Katkin et al., 2001).

Figure 15. Fundamental neuroanatomical emotional centres: insula (purple), orbitofrontal cortex (red), anterior cingulate cortex (yellow) and amygdala (orange). Adapted from LeDoux, 2005.

2.5.1.1. Emotion & the autonomic nervous system

The interaction and contribution of brain, body and environment in emotion was aptly demonstrated by Schachter and Singer (Schachter and Singer, 1962) in 1962. Participants were injected with adrenaline or saline before entering a room inhabited by actors portraying angry or happy behaviour. The recipients of the adrenaline infusion reported feeling happier or angrier in parallel with the emotion portrayed by the study confederates, whereas recipients of the saline infusion experienced no significant change in affect. Interpretation of environmental factors determined the emotional valence that was experienced but autonomic arousal (via sympathomimetic) heightened emotion.

Regardless of whether a stimulus evokes a defensive or appetitive response, the two primary reflexes of increased sensory processing and preparation for mobilisation remain the same (Lang and Davis, 2006) across valances. This overlap, along with methodological inconsistencies (e.g., experimental protocols, knowledge of the ANS, length of time responses were monitored), may explain the lack of validated emotion-specific autonomic signatures to date (Lang, 1994, Kreibig, 2010). For example, Ekman and colleagues (Ekman et al., 1983) trained subjects to facially express various emotions whilst simultaneously trying to subjectively experience the corresponding emotion. Autonomic (skin temperature and heart rate) recording during testing found that;

⇒ ANGER = High heart rate + high skin temperature

⇒ SADNESS, FEAR = High heart rate + low skin temperature

⇒ DISGUST, HAPPINESS, SURPRISE = low heart rate

Rainville and co-workers (Rainville et al., 2006) recorded heart rate, cardiac vagal tone (HF-HRV) and respiration during emotion provocation, concluding that;

⇒ ANGER = Increased heart rate

⇒ FEAR = Increased heart rate + decreased HF-HRV + coupled respiration changes

⇒ HAPPINESS = Increased heart rate + decreased HF-HRV + no respiration changes

⇒ SADNESS = Increased heart rate + decreased HF-HRV + increased respiration variability

Much of this research was influenced by the James-Lange theory, which proposes that physiological responses differentiate emotion from non-emotion (Lange and James, 1922) and that certain emotions are attached to the central interpretation (interoception) of bodily states, which are primarily defined by varying patterns of autonomic activity. The James-Lange theory provided the foundation for modern 'peripheral' theories of emotion, such as Antonio Damasio's '*Somatic Marker Hypothesis*' (Damasio, 1999), which emphasises how homeostatic requirements motivate and shape behaviour, for example, individuals are more mindful of palatable sensory signals when hungry. This view was supported by Damasio's findings that lesions to brain centres that represent the internal visceral state impair social and emotional behaviour and can result in 'acquired sociopathy' (Damasio et al., 1990).

Such theories of brain-body integration posit that the sensitivity of the brain to bodily responses governs the intensity of emotional experience (Paulus, 2013). This is supported by neuroimaging findings that somatovisceral information enters the CNS via brainstem nuclei from the spinal cord, is translated to the insula, amygdala and somatosensory cortex before reaching the PFC (Critchley et al., 2004). During this synaptic transmission, the original afferent autonomic and somatic information is integrated with other subjective information to inform the interpretive response (Paulus and Stein, 2006, Suzuki et al., 2013).

2.5.1.2. Trauma & sympathoexcitation

During emotional or physical trauma, SNA increases due to psychogenic or allostatic demand. If the defence response does not re-establish homeostasis, the subject becomes over-exposed to the perceived threat, or a stimulus becomes associated with trauma, then disorders of emotion may develop, which establish a new homeostatic baseline (Cohen et al., 1998)

and/or acute maladaptive responses to real or, in extreme cases, imagined stimulus exposure (Bale, 2006, de Kloet et al., 2005). This dysregulation causes intolerance to physiological and/or emotional stressors, predisposing to dysfunctional behaviours, such as self-harm, self-mutilation or substance abuse, which are seen as attempts to regulate a dysfunctional ANS (Ogden et al., 2006) that has become sensitised to markers of the original trauma (Van der Kolk, 1996).

Post-traumatic stress disorder (PTSD) alters autonomic thresholds so that autonomic mediation of bodily systems, such as cardiovascular, sleep (Germain et al., 2008) or respiratory control, are sympathetically-dominated (Blechert et al., 2007, Buckley and Kaloupek, 2001). PTSD subjects report greater distress to unpredictable and uncontrollable anxiety-related somatic symptoms in comparison to individuals with panic disorder (Pfaltz et al., 2010). PTSD also effects noradrenergic function, as evidenced by supressed growth hormone (GH) responses to intravenous clonidine challenge (though BP was not measured) (Morris et al., 2004). Clonidine is a peripheral a2-agonist, therefore, these findings result from desensitization of post-synaptic a2-receptors in PTSD subjects.

2.5.1.3. Dissociation & sympathetic inhibition

Despite marked anxiety, distress and functional impairment, dissociation and dissociative disorders tend to downregulate sympathetic activity, unlike most anxiety disorders. Depersonalization disorder (DPD) is a dissociative disorder defined by derealization (one's surroundings feel unreal), emotional numbing, feelings of disembodiment and memory recall deficits relating to the personalization but not retrieval of memory (Lee et al., 2012). DPD is a defensive, emotionally-disengaging response that is implemented to accommodate threat deemed as beyond ones' control (Lee et al., 2012). It has a lifetime prevalence of 74% for mild episodes and 1%-2% for chronic DPD (Sierra and David, 2011).

Skin conductance responses (SCRs) are both more quickly manifested and yet abnormally weakened in DPD during aversive stimuli exposure (Sierra et al., 2002), indicating hypervigilant attentional appraisal and rapid suppression of psychogenic autonomic arousal. NA levels have also been found to be negatively correlated with DPD severity (Simeon et al., 2003). Models of DPD predict hypervigilance of environmental and emotional stimuli and the engagement of an emotionally dampening mechanism during aversion, evidenced by reduced skin conductance responses (SCRs) to disagreeable images compared to both healthy controls and anxiety disorder patients, despite depersonalized subjects being equally as anxious as anxiety participants (Sierra et al., 2002). Inverse correlations between SCRs and dorsal PFC responses (Lemche et al., 2008, Lemche et al., 2007) indicate a central correlate for the blunted autonomic arousal and brain-body dysregulation in DPD.

Peritraumatic dissociation shares some symptoms with depersonalization - emotional numbing, derealisation, self-observation, and dysmorphia - and occurs at a time of extreme inescapable threat (Mooren and van Minnen, 2014). In a survey of peritraumatic dissociation in 85 females who had recently (2 months) been the victim of sexual assault, those who had experienced high levels of peritraumatic dissociation recorded reduced post-traumatic sympathetic (SCRs and HR) arousal during trauma interviews, yet also perceived their attack as more life-threatening (Griffin et al., 1997).

2.5.1.4. Interoception in emotion, cognition & homeostasis

'Interoception' is the term given to the processing of afferent visceral nerve activity, which informs autonomic mediation of homeostasis and contributes to emotion, behaviour and cognition at varying levels of consciousness (see figure 16), from baroreceptors modulating cardiac responses to fluctuations in BP to maintain cerebral perfusion, to discarding an item of clothing as an act of behavioural thermoregulation. An individual's interoceptive accuracy (IA) moderates the degree to which somatic events are linked to cognitive-affective processes (Damasio, 1999, Gray et al., 2012) and individuals with greater IA experience emotions more deeply, particularly anxiety (Schandry, 1981). Conversely, depressed individuals have impaired interoception (Pollatos et al., 2009, Dunn et al., 2010).

Interoception of sensory signals is therefore a fundamental process of central and visceral homeostatic and allostatic integration, as evidenced by the recent finding that interoceptor (arterial baroreceptors) activity influences cognitive-affective processes on a preconscious level (Garfinkel et al., 2014) or that the sight or smell of food causes the release of insulin (Teff, 2011). Interoceptive signalling moderates the degree to which subjective awareness of physical events within one's body are linked to emotional and cognitive processes (Dunn et al., 2010, James, 1894, Damasio, 1999, Gray et al., 2012), meaning that interoception not only binds the body and the self (Seth, 2013) but mediaties onself to others via affective empathy, cognitive empathy and shared emotion (Tajadura-Jimenez and Tsakiris, 2014, Grynberg and Pollatos, 2015).

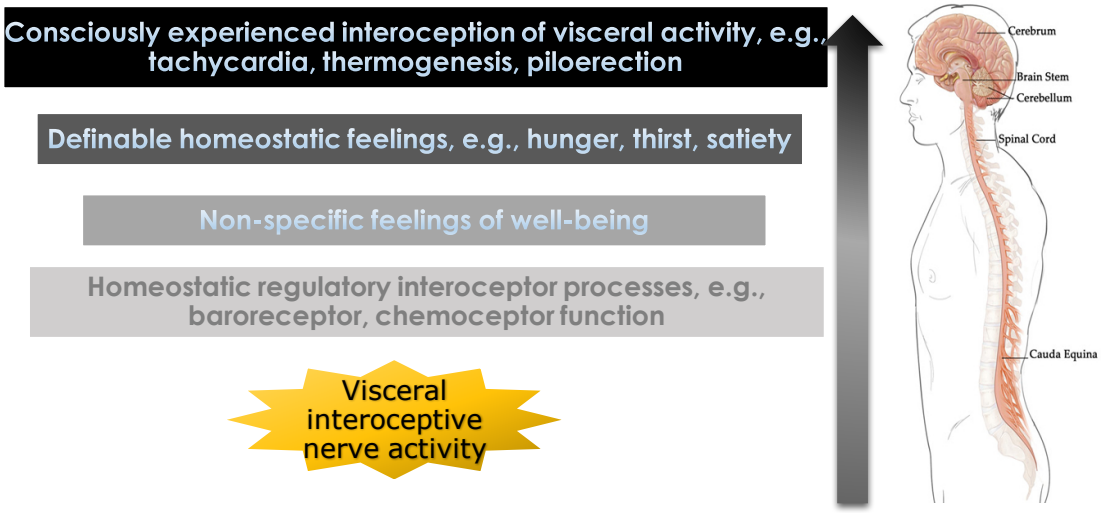


Figure 16. Varying levels of interoception.

It has been proposed that predictions of experienced versus expected interoceptive error signals of bodily events can be a 'bottom up' source of anxiety (Paulus and Stein, 2006). Therefore, if one were to feel dizzy, tachycardic or too hot or sweaty whilst being aware that the situation did not require these aberrant allostatic adaptions, the interoceptive processing of these error signals would create anxiety at the discordant bodily states. This hypothesis is supported by evidence that the insula detect discrepancies in predictions of one's physical state rather than actual changes in physical state (Gray et al., 2007), and that these error code predictions then influence behaviour and mood.

The anterior insula, dorsal Acc and VMPFC are vital for the integrative processing of interoceptive information. The Acc shares some functionality with the amygdala, such as attentional mechanisms, genesis of motivated behaviour and pain appraisal, assigning both structures vital roles in autonomic and emotional reactivity (LeDoux, 1992). Using fMRI, Critchley and co-workers (Critchley et al., 2004) found that activation of the insula cortex, particularly the right, highly correlated with interoceptive awareness and accuracy in healthy controls (n=17). The right insula was found to depict internal bodily state that could be consciously accessed and its activity was positively correlated with anxiety and interoceptive awareness. Moreover, anterior and mid insula cortices, Acc and somatomotor cortex were functionally associated with shifting one's attention to interoceptive events. The role of the right insula in second-order conscious homeostatic representations has been further evidenced using false physiological feedback of HR during fMRI by Gray and colleagues (Gray et al., 2007), who examined emotional appraisal of neutral faces during baseline and isometric handgrip exercise. False feedback of increased HR during emotional stimuli caused appraisal levels of emotional intensity/salience to increase.

In hypochondriasis, anxiety disorders and somatisation disorders, patients report somatic hypervigilance and somatosensory amplification (Barsky, 1992, Rief et al., 1998, Ludewig et al., 2005, Anderson and Hope, 2009), indicating anxiety shifts attention to interoceptive events. The only interoception study to date in dysautonomia concerned 11 PoTS patients and 10 controls (Khurana, 2014). PoTS patients were not any better or worse at counting their heartbeats at supine rest, during head up tilt, drug (Atropine) induced vagal blockade or the Valsalva manoeuvre than controls, but were more able to describe varying types of palpitations during testing (Khurana, 2014), leading the author to conclude that palpitations were independent of tachycardia in PoTS patients' subjective experience of cardiothoracic symptoms. Therefore, to investigate the potential influences of intermittent cardiovascular (PoTS, AMS) and sudomotor (EH) autonomic overactivity on brain-body integration processes, such as interoception, **specific aim # 3 of this thesis will;**

- **assess somatic hypervigilance (anxiety attributable to fear and worry of bodily symptoms that are common in EH, AMS and PoTS) in AMS, EH and PoTS in comparison to controls.**
- **assess empathy (an emotion influenced by interoception (Grynberg and Pollatos, 2015) that predicts autonomic arousal during emotional stimulation (Bogdanov et al., 2013) in AMS, EH and PoTS in comparison to controls to examine the potential influence of 'bottom-up' somatic perturbation on higher order affect.**
- **define the subjective measure of interoceptive sensibility, objective measure of interoceptive accuracy and metacognitive measure of interoceptive awareness in AMS, EH and PoTS in comparison to healthy controls.**
- **assess HRV to examine autonomic variability and how this relates to brain-body integration in AMS, EH and PoTS in comparison to healthy controls from the perspective of 'neurovisceral phenotypes', which emphasises the importance of autonomic variability in emotion regulation.**

These areas will be sequentially and systematically examined to attempt to construct a framework of neurovisceral architecture and how this may inform emotion and behaviour through homeostatic drives, in an attempt to elucidate the comorbid psychological symptoms that commonly present in EH, AMS and PoTS.

2.5.1.5. The shared somatic markers of intermittent dysautonomia & phylogenetic defence responses

The ANS is the primary mediator of efferent and afferent nerve traffic between the brain and the periphery and provides a potential framework to explore the associations between autonomic activity and affective disorders (Thayer et al., 1996, Thayer et al., 2000). It also leads one to consider what happens to cognitive-affective processes in conditions of exaggerated autonomic responsivity (Eccles et al., 2015).

Phylogenetic defence responses have evolved to protect from physical harm, e.g., eye blink to air puff or limb shock withdrawal (Darwin, 1872/1998). These innate defence responses, particularly fight/flight, share many autonomic characteristics with intermittent forms of dysautonomia. In the 1920's Ivan Pavlov (Pavlov, 1927b) and Walter Cannon (Cannon, 1929) defined a number of somatomotor and autonomic responses to noxious or threatening stimuli that rely on sympathoexcitation and share many autonomic manifestation with PoTS, EH and VVS (in fact, it has been argued that VVS is a phylogenetic relic for the (further) prevention of injury and blood loss);

- **Freezing/hypervigilance** – All movement except oculomotor and respiratory is suspended (Blanchar and Blanchar, 1969). This response makes it more difficult to localise prey for movement-dependent predators.
- **Fight or flight** – a heightened defence response to threat. The SNS enables physiological responses to escape or repel the heightened danger, including:
    - Increased heart rate (PoTS)
    - Bladder relaxation (VVS)
    - Face flushing (EH)
    - Xerostomia (PoTS)
    - Shaking (PoTS, VVS)
    - Sudomotor activation (EH)
- **Tonic immobility** (TI) – has been well-documented in animals as 'sham death' and is an end-stage strategy (Monassi et al., 1999). In humans, TI typically occurs during sexual assault and is often preceded by peritraumatic fear and perceived inescapability (Bovin et al., 2008).

During heightened threat, information is processed and integrated with contextual information from the hippocampus, before being conveyed to the amygdala. If one's well-being is threatened, processing of both the insula and amygdala are sensitive to changes in autonomic activity (Critchley et al., 2002). The locus coeruleus (LC), located on the floor of the fourth ventricle of the pons, is important for sensory processing, as well as attention and arousal states, implicating it in the defence response process (Abercrombie and Jacobs, 1987). The LC has diffuse projections that regulate NA tone (Aston-Jones and Cohen, 2005) and, along with sympathetic nuclei in the medulla and pons, comprise the reticular activating system (RAS), which modulates intracortial synchronization of processes, such as, the startle response, sleep and BP (Bhaskaran and Freed, 1988, Aston-Jones, 1991). Hypervigilance is also facilitated by the LC filtering out unimportant information, leading to a centrally-driven increase in SNA, HPA axis stimulation (via corticotrophin-releasing hormone [CRH] release of adrenocorticotrophic releasing hormone [ACTH]) and immune system mobilization. The SNS is activated by the hypothalamic lateral nucleus (autonomic pathways) and the parabrachial nucleus (endocrine pathways) (see figure 17).

Figure 17. Schematic of main neuroanatomy of the fight/flight/freeze response. From Gorman et al, 2000

The LC facilities behavioural arousal by NA release and activation of the PAG invokes defensive behaviours, including fight/flight and movement cessation. In cats, caudal stimulation of the dorsolateral PAG (dlPAG) and lateral PAG (lPAG) invoke flight behaviours, whereas rostral activation of the dlPAG and lPAG provokes fight and aggressive responses, such as confrontation. Venrolateral PAG (vlPAG) stimulation induces passivity and down-regulation of HR and BP (Porges, 2003).

2.5.1.6. The orienting response – is it compromised by orthostatic intolerance?

Despite the inconsistencies in defining emotion-specific autonomic signatures (Hodgson and Rachman, 1974, Rachman and Hodgson, 1974), a reliable and robust early response to a novel stimulus, especially unpleasant, is cardiac deceleration (Fanselow, 1994). This response is centrally mediated by the 'defence system', particularly the amygdala (Hermans et al., 2013) and peripherally mediated by the vagus nerve (Mathias, 1976, May et al., 1989). Cardiac deceleration is a peripheral component of the 'orienting response' (OR), which is a series of involuntary sensory, motor and autonomic adjustments (see figure 18) that occur in response to an emotionally salient stimulus. These adjustments of sympathetic and parasympathetic activity ensure optimal perception of the stimulus including inhibition of conditioned and unconditioned reflexes (Pavlov, 1953, Hedger et al., 2015) to *'increase analyser sensitivity'* (Sokolov, 1963a). The OR is the first response provoked by any novel stimulus and its magnitude depends on the evocative potential of the stimulus.

The OR is differentiated from the cardiac defence response (CDR) by the cardiac deceleration during the OR to a moderate or novel stimulus facilitates attention and perception of the stimulus. In contrast, the defining cardiac acceleration during the CDR to an intense or aversive stimulus reduces attention and perception to protection against the stimulus (Pavlov, 1927a, Sokolov, 1963b, Fernandez and Vila, 1989). It is widely accepted from psychophysiological research that the OR is therefore the opposite of the CDR. The issue of stimulus has received empirical support (Turpin, 1986), however, there is no formal definition or criteria on the level of stimulus intensity that differentiates ORs from CDRs, neither have any studies investigated the effect of intensity in different sensory modalities.

Originally believed to be a unitary reflex (Sokolov, 1963a), subsequent studies have evidenced that the electroencephalogram (EEG) and respiratory components of the OR represent novelty, peripheral vasoconstriction ORs reflect stimulus intensity and cardiac deceleration indicates stimulus detection (Barry, 2009). Moreover, the degree of cardiac deceleration

predicts subsequent memory performance (Buchanan et al., 2006). Greater ORs are proposed to represent greater emotional significance of the stimulus and greater interoceptive accuracy (IA) is associated with increased subjective emotional experience, therefore, it is possible that a relationship may exist between IA and ORs and could provide an insight into holistic brain-body integration. However, this has not been investigated.

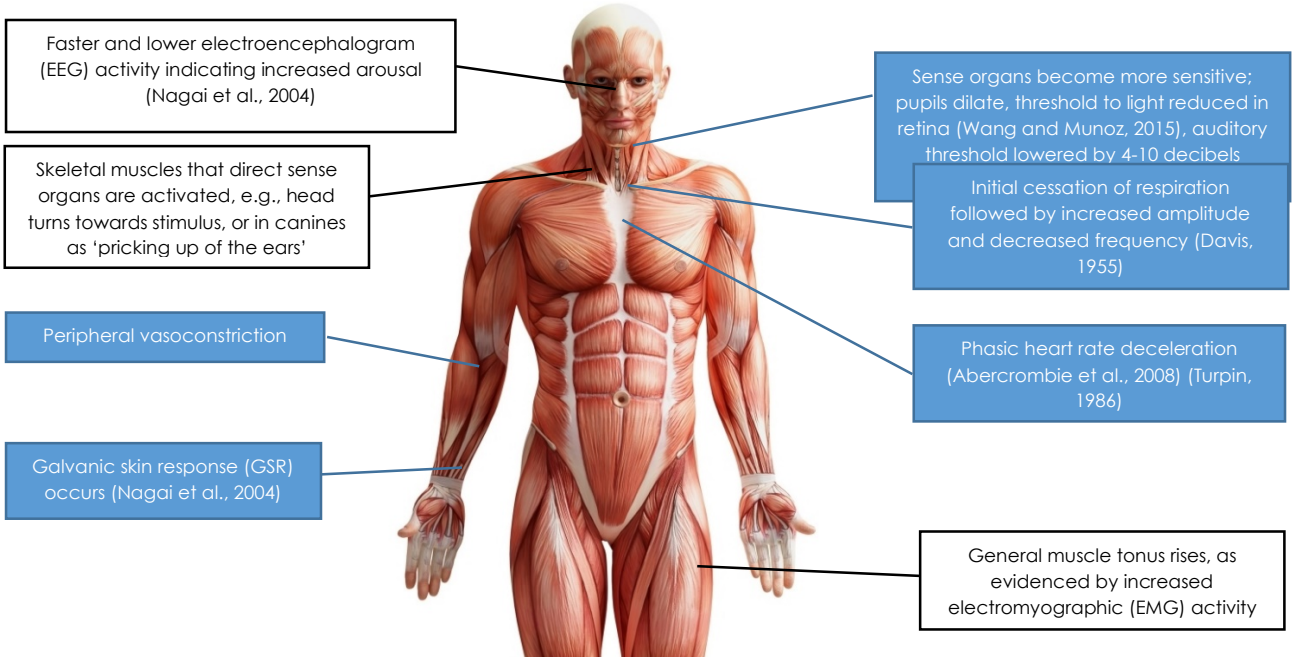


Figure 18. Central and visceral correlates of the orienting response (OR). Blue = autonomically mediated OR components.

The non-muscular visceral components of the OR are autonomically mediated but there have been no investigations into whether autonomic disease or dysfunction effects ORs or related processes. This is worthy of investigation because the functional and organ-specific autonomic patterns that maintain homeostasis are permanently compromised in autonomic failure (AF) (e.g., spinal cord injury (SCI), pure autonomic failure (PAF)) and intermittently compromised in conditions of OI, such as PoTS and AMS. In addition, many of these patients report comorbid affective, functional and cognitive symptoms not attributable to autonomic pathophysiology or neuropathophysiology (Heims et al., 2006a, Guaraldi et al., 2014, Ross et al., 2013, Ocon et al., 2009b, Stewart et al., 2012) (see Postural tachycardia syndrome, vasovagal syncope & essential hyperhidrosis: autonomic endophenotypes of anxiety). From a clinical autonomic perspective, some unanswered questions remain, such as, (i) how do ORs compare at supine rest and during orthostasis, (ii) and between healthy controls and patients with compromised baroreflex function, particularly as PoTS and AMS have an over-representation of comorbid cognitive-affective symptoms? (iii) Would investigating the possible relationship between IA and ORs provide an insight into brain-body integration or these patients' common comorbid psychological symptoms, as greater ORs are proposed to represent greater emotional significance of the stimulus and greater IA is associated with increased emotional experience?

Therefore, specific aim # 4 of this thesis will investigate;

(i) the effects of orthostatic stress on ORs in PoTS and AMS in comparison to controls to examine the influence (if any) of dysautonomia-related dysregulated ORs

(ii) explore any interactions between ORs and IA in controls and OI.

2.6. Specific aims

Specific aim # 1 of this thesis will;

I. review the historical casenote of FS patients to ascertain whether FS is a typical conversion disorder
II. investigate any underlying autonomic or dysautonomic contributions to FS,
III. describe the presentation and incidence of FS during autonomic testing

Specific aim # 2 of this thesis will

I. thoroughly and systematically investigate cognitive-affective symptoms in EH, AMS and PoTS to
II. decipher if these psychological symptoms are related to dysautonomia symptoms that functionally overlap with physical manifestations of anxiety and panic
III. or are trait-like or trauma-related affective phenomena independent of dysautonomia.

Specific aim # 3 of this thesis will;

I. assess somatic hypervigilance (anxiety attributable to fear and worry of bodily symptoms that are common in EH, AMS and PoTS) in AMS, EH and PoTS in comparison to controls.
II. assess empathy (an emotion influenced by interoception (Grynberg and Pollatos, 2015) that predicts autonomic arousal during emotional stimulation (Bogdanov et al., 2013) in AMS, EH and PoTS in comparison to controls to examine the potential influence of 'bottom-up' somatic perturbation on higher order affect.
III. define the subjective measure of interoceptive sensibility, objective measure of interoceptive accuracy and metacognitive measure of interoceptive awareness in AMS, EH and PoTS in comparison to healthy controls.
IV. assess HRV to examine autonomic variability and how this relates to brain-body integration in AMS, EH and PoTS in comparison to healthy controls from the perspective of 'neurovisceral phenotypes', which emphasises the importance of autonomic variability in emotion regulation.

Specific aim # 4 of this thesis will investigate;

I. the effects of orthostatic stress on ORs in PoTS and AMS in comparison to controls to examine the influence (if any) of dysautonomia-related dysregulated ORs

II. explore any interactions between ORs and IA in controls and OI.

Chapter 3. General Methods

3. Introduction

For the purposes of this PhD, it was necessary to use a battery of clinical and experimental methodologies. All experimental procedures received local ethical approval (NRES Committee London - Harrow, University College London Healthcare Trust Research and Design Office, Imperial AHSC Joint Research Compliance Office). The study was conducted in compliance with the Helsinki declaration (1968).

3.1. Participants

Clinical and healthy control participants were recruited from the Autonomic Units at St Mary's Hospital and The National Hospital for Neurology and Neurosurgery (NHNN) at Queen Square, London and included the following patient cohorts: Postural Tachycardia Syndrome (PoTS), essential hyperhidrosis (EH) and vasovagal syncope (VVS). Healthy control participants were recruited from the general population. Patients must have received a positive diagnosis from the London Autonomic Units and were recruited by mail from a database of patients at both London Autonomic Units. Diagnosis of hyperhidrosis (Benson et al., 2013, Cohen et al., 2007) was made after thermoregulatory sweat test (Low and Fealey, 2013) and of orthostatic intolerance (OI) (Freeman et al., 2011b) after cardiovascular autonomic function tests (see Clinical autonomic investigations) by consultant autonomic neurologists (CJM or VI). A detailed history was obtained in all cases, with an emphasis on information to help explain the cause of syncope, including potential symptom exacerbation in relation to orthostasis, postprandial hypotension or tachycardia and whether syncope was associated with blood-injury phobia and/or emotional provocation. Information on familial syncope and the relation to neck movement was sought, particularly in elderly patients.

Using established protocols, including, head up tilt (HUT), prolonged head up tilt (pHUT), supine exercise testing and liquid meal challenge, central and peripheral stimuli (Valsalva manoeuvre, pressor responses to mental arithmetic, isometric exercise, and cutaneous cold application) were used in the assessment of autonomic function, including, sympathetic and parasympathetic nerve function (Mathias et al., 2013, Mathias and Bannister, 2013). Parasympathetic cardiac function was tested using respiratory sinus arrhythmia (RSA) responses to deep breathing, hyperventilation and the Valsalva manoeuvre and pressor exercises investigated vasomotor integrity (Mathias et al., 2013). In those with suspected blood-injury phobia relating to VVS, suitable observations and precautions were made during venepuncture on HUT and pHUT (45 min maximum). In patients >50 years in whom autonomic

failure (AF) was excluded, carotid sinus massage (CSM) was performed to exclude carotid sinus hypersensitivity (CSH) during supine baseline and HUT, unless contraindicated due to carotid artery disease. A symptomatic fall in systolic blood pressure (SBP) of 20 mmHg and/or diastolic blood pressure (DBP) of at least 10 mm Hg within 3 min of standing, and/or with HR below 40 beats per min (BPM) was regarded as abnormal (Mathias et al., 2013).

Healthy controls were required to not have any previous or current autonomic disorders, cardiovascular disease or psychiatric conditions. Fully informed written and verbal and ethically approved consent was obtained from all clinical and control participants.

3.2. Clinical autonomic investigations

Participants were asked to discontinue any medications which could alter their autonomic function for 24 hours before participation and to also abstain from nicotine and caffeine consumption on the day of testing.

3.2.1. Head up tilt (HUT)

A variety of non-invasive tests can be used to investigate autonomic cardiovascular function. HUT is used to diagnose various forms of dysautonomia. In healthy subjects, the initial blood pressure fall induced by HUT should recover within 60 seconds because when decreased venous return to the heart causes reduced stroke volume and cardiac output, arterial baroreceptors and cardiopulmonary mechanoreceptors then signal autonomic brain centres to increases sympathetic nerve activity (SNA), raising HR and causing vasoconstriction of the blood vessels in various vascular beds to compensate for postural and gravitational demands (Imholz et al., 1990). In normal subjects where the baroreflex is intact, HUT of 45-90° should not provoke a prolonged fall in BP. HUT has proven an invaluable and relatively simple investigative tool(Mathias et al., 2013). Following a 10 minute unstimulated supine baseline period of recording, the tilt table is electrically-operated and raised to 60° for a period of 10 minutes (Mathias et al., 2013). HUT was terminated if syncopal, pre-syncopal or other OI-related symptoms were recorded or reported by the participant.

3.2.2. Pressor exercises

Pressor manoeuvres, including isometric (hand-grip) exercise, cutaneous cold application, deep breathing and mental arithmetic provide an index of SNA and induce autonomic cardiovascular changes, particularly BP, which is regulated via the SNS. Pressor stimuli have been well-validated and correlate with HUT (RK Khurana, 1996). Isometric and cutaneous cold

pressor stimuli raise BP via activation of sympathetic efferent nerve pathways and provide the most responsive data in comparison to mental arithmetic or other pressor tests. Peripheral receptors are activated but in both cutaneous cold or isometric exercise tests there is an important central command (isometric) or nociceptive (cold) role, which is more pronounced in isometric exercise study leading to a greater increase SNA in this test compared to the cold pressor.

Pressor exercises were carried out in the supine position, so that orthostatic demand does not confound the pressor responses. Isometric exercise involved the participant using their right hand to partially inflate a sphygmomanometer cuff to sub-maximal pressure, i.e., one third of a previously obtained maximal voluntary contraction. The sub-maximal pressure was then maintained for 3 mins. A minimum of 4 mins baseline was then carried out to allow autonomic activity to return to baseline levels. The cold pressor uses a col compress to be applied to the right hand for 90 seconds. A minimum of 4 mins baseline was then carried out to allow autonomic activity to return to baseline levels.

3.2.3. Heart rate variability (HRV)

Much cardiac tissue has intrinsic pacemaker properties and the ANS regulates the myocardium's contractile and electrical output via vagal (parasympathetic) and sympathetic outflows (Spyer, 1994). Pacemaker depolarisation is increased by activation of the SNS and parasympathetic vagal flow promotes the cardiac pacemaker cells to hyperpolarise and slow depolarisation speed (Spyer, 1994). Autonomic mediation of localized ion channel function is vital in depolarisation of all cardiac pacemaker cells.

In normal populations, there is an increase in HR during inspiration and a decrease in HR during expiration, known as respiratory sinus arrhythmia (RSA), which is a measure of the functional endpoint of cardioinhibitory vagal fibres emanating from the nucleus ambiguus in the brainstem (Neff et al., 2003). Heart rate variability (HRV) records the beat-to-beat variations of HR and the intervals between QRS complexes (RR intervals) of sinus depolarisations (Stein et al., 1994). HRV describes sympathetic and vagal influence on the sinus node using non-invasive electrocardiographic markers. In a healthy individual with an unlesioned heart and intact ANS, continuous sinus cycles reflect a balanced and integrated sympthovagal state (van Ravenswaaij-Arts et al., 1993).

The high frequency (HF) band of HRV is a measure of vagal efferent activity and is comparable to RSA. LF heart rate variability (HRV) was, until recently, believed to depict sympathetic

cardiac influences (Malliani et al., 1991) however, LF-HRV as a purely sympathetic measure has been called into question (Goldstein et al., 2011, Parati et al., 2006) as research has shown that endogenous fluctuations in LF-HRV provide information about sympathetic regulation of BP, such as vasomotor tone and baroreceptor activity. Moreover, recent studies have positively correlated LF-HRV and baroreceptor sensitivity (Goldstein et al., 2011, Moak et al., 2007) as well as reduced LF-HRV and baroreflex-cardiovagal failure (Rahman et al., 2011). Therefore, LF-HRV may well provide information about sympathetic mechanisms but perhaps not cardiac sympathetic nerve activity specifically but rather of baroreflex function and dysfunction. In addition, very low frequency (VLF) can also be assessed, but VLF's role is less clearly defied than that of LF and HF. Exercise-induced increases in LF-HRV has been linked with metabolic activity in insular, cingulate and somatomotor regions (Critchley et al., 2003) and HF-HRV with the basal ganglia and anterior temporal lobe (Matthews et al., 2004, Lane et al., 2009). Emotion-induced changes in HRV are associated with the insula, PAG and caudate nucleus (Lane et al., 2009).

The application of spectral analytical techniques to short or long-term neurocardiovascular changes is now widely utilized as a measure of cardiovagal activity (see figure 19). Power spectral analysis can be performed using parametric or nonparametric methodologies:

- ⇒ The Fast Fourier transformation (FFT) nonparametric method is typified by discrete peaks of the frequency bands. FFT is a simple and quickly performed equation.
- ⇒ The Autoregressive model (Ori et al., 1992) results in a continuous spectrum of events. It is more complex than the FFT model and must be suitable to the experimental model.

Figure 19. Depiction of LF and HF activity at supine rest (left panel) and at 90° HUT in a healthy subject (right panel). During HUT, the LF component predominates over HF due to the additional sympathetic load provoked by orthostatic load. From Task Force, 1996.

For these studies, FFT was the model of spectral analysis used to examine the data of the supine unstimulated baseline and 60° baseline HUT and 60° HUT with psychological stimuli. The RR intervals of each participant were transformed into bands with different spectral frequencies. The results can be transferred into Hertz (Hz) by dividing the mean RR interval length. In this experiment, this calculation was performed by the PowerLabs ECG and accompanying Labchart software post hoc. Spectral analysis of HRV was used as the main frequency-domain measure. In addition to the continuous recording of BP and HR reactions to the pressor responses, regular BP recordings were taken at 5 min intervals using an armcuff and Dinamap Pro Series as an additional measure of BP.

3.3. Psychological & psychophysiological methods

3.3.1. The Schandry Task - a measure of cardiac interoception

Heartbeats have a distinct cycle and rhythmicity allowing them to be easily measured, moreover, cardiac interoception is positively correlated with the interoception of other autonomically mediated organs (Whitehead and Drescher, 1980). The Schandry mental tracking task is a way of measuring cardioception, wherein the subject is asked to count individual heartbeats within a brief undisclosed window of time, between 21-45 seconds (Schandry, 1981).

With the relatively recent interest in conscious interoception, important methodological issues have developed with its measurement, interpretation and inconsistent and interchangeable use of terms such as, 'interoceptive accuracy', 'interoceptive awareness', 'interoceptive sensitivity' or simply 'interoception'. To address these issues, Garfinkel and colleagues (Garfinkel and Critchley, 2013, Garfinkel et al., 2015) recently stratified '*interoceptive awareness*' as a metacognitive measure of the degree to which objective interoceptive accuracy (as measured by a heartbeat tracking tasks, for example) relates to subjective sensibility in one's performance in the interoceptive task, i.e., if someone has good interoceptive awareness, the level of their interoceptive accuracy will match their sensibility in their accuracy.

Interoceptive accuracy scores will be yielded by counting the R waves in the event-marked ECG traces and averaging the following equation over the 3 tracking tasks of each stage of the protocol (supine baseline, HG, CP, HUT) and for global scores for the entirety of the experiment: $1 - (|n\text{beats}_{real} - n\text{beats}_{reported}|) / ((n\text{beatsreal}+n\text{beats}_{reported})/2)$.

Measures of interoceptive awareness will be taken from the participants' subjective appraisals (interoceptive sensitivity) of their heartbeat tracking task performance (interoceptive accuracy) during the experimental protocol. Interoceptive awareness scores will be extracted by obtaining the *r* value of interoceptive accuracy and interoceptive sensibility.

3.3.2. The orienting response (OR)

The orienting response (OR) is a collection of transient physiological and behavioural adjustments, typified by increased parasympathetic tone, such as bradycardia or reduced SCRs elicited by the conscious occurrence of a motivationally or emotionally salient stimulus.

This "investigatory reaction" to a novel stimulus was first described by Pavlov in his animal studies as a behavioural adjustment of a being's faculties and resources to a novel cue (Pavlov, 1927b). It is proposed that the physiological downregulation facilitates cognitive processing and appropriate behavioural response (Turpin, 1986). The skin conductance response (SCR) does not differentiate between ORs and CDRs (Sokolov, 1963b) and was therefore not included for the purposes of this thesis.

3.3.3. The International Affective Picture System (IAPS)

The International Affective Picture System (IAPS) is a database of images of varying quantified valences (categorised into neutral, pleasant and unpleasant), dominance ratings and arousal scores. Originally developed by the National Institute of Mental Health, the IAPS were validated in a cohort of 100 America college students (50% female). The IAPS has been extensively and reliably used as a robust investigative tool in emotional paradigms in clinical and non-clinical cohorts (Lang PJ, 2005, Jasson et al., 1997) and is one of the most well-validated psychological tools available. The IAPS has been used in research on mental disorders such as schizophrenia, major depression, anxiety or psychopathic personality traits.

3.3.4. Self-report questionnaires

For the purposes of better understanding the prevalence and source of any significant co-morbid psychological symptoms amongst VVS, EH and PoTS patients, a battery of well-validated questionnaires was used to survey patients and controls. These questionnaires were generally completed on the day of testing and were broadly divided into self-report measures looking at affective items only and those looking at affective factors in relation to somatic parameters. See appendix for copies of the questionnaires.

⇒ **Anxiety sensitivity index (ASI);** An 18 item questionnaire designed to assess apprehension of anxiety-related sensations based on beliefs about their harmful consequences (Reiss et al., 1986). Response options range from 0 = 'not at all like me' to 4 = 'extremely like me'.'

⇒ **Balanced Emotional Empathy Scale (BEES):** Is a 30 item questionnaire designed to record the subject's vicarious experience of another's emotional experiences (Mehrabian, 1996). Response options range from 0 = 'not at all like me' to 4 = 'extremely like me'. Response options range from -4 = 'very strong disagreement' to +4 = 'very strong agreement'.

⇒ **Beck Depression Inventory (BDI):** A 21 item multiple-choice questionnaire designed to assess the severity of depression (Beck et al., 2001). Response options range from 0 = e.g., 'I do not feel I am worthless' to 3 = e.g., 'I feel utterly worthless'.

⇒ **Body vigilance scale (BVS):** Is an 18 item questionnaire designed to measure the subject's tendency to selectively attend to physiological changes (Schmidt et al., 1997). Response options range from 0 = 'not at all like me' to 10 = 'extremely like me'.

⇒ **Cardiac anxiety scale (CAS):** An 18 item questionnaire designed to assess '*cardiophobia*', i.e., the interpretation of cardiac symptoms, sensations and related behaviours (Eifert, 1992). Response options range from 1 = 'never' to 5 = 'always'.

⇒ **Childhood traumatic events scale (CTES):** Is a 13 item questionnaire designed to assess traumatic events during adulthood and childhood. Responses options range from 1 = not at all traumatic to 7 = 'extremely traumatic' (Pennebaker and Susman, 1988).

⇒ **The Self-consciousness Scale (SCS-R)** (revised): Is a 23 item questionnaire designed to assess private and public self-consciousness and social anxiety (Scheier and Carver, 1985). Response options range from 0 = 'not at all like me' to 4 = 'a lot like me'.

⇒ **State Anxiety Inventory (SAI):** A 20 item questionnaire designed to assess anxiety at the time of filing out the questionnaire (Spielberger, 1983). The questionnaire is taken from the state-trait anxiety inventory (STAI) which also includes a set of 20 questions examining trait anxiety, which was not included in the current study for the sake of time and that the SAI section provided a more current measure in relation to autonomic symptoms. The SAI includes a number of negatively scored items to negate confounding self-reporting issues. Response options range from 0 = 'not at all like' to 4 = 'very much so'.

3.5. 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.

Chapter 4. Functional syncope: conversion disorder & aberrant response to orthostatic intolerance

4.1. Introduction

The cause of 10-26% of syncope cases remains unknown and psychiatric illness is more prevalent in these patients, particularly if episodes are recurrent or include somatic symptomology (Brignole et al., 2005, Krahn et al., 1995, Krahn et al., 1998, Mathias et al., 2001). 'Psychogenic pseudosyncope' is the behavioural occurrence of apparent syncope (unresponsiveness and loss of postural tone) during physiological indices that would not result in cerebral hypoperfusion, as measured by beat-to-beat HR, BP, ECG, EEG and/or cerebral blood flow. In this chapter, I present the largest cohort so far. I evaluate the characteristics of this cohort in relation to dysautonomia, anxiety and functional neurological disorders.

One may argue against the clarity, objectivity and accuracy of the term 'psychogenic pseudosyncope' due to actual episodes of VVS being caused by psychogenic factors, such as the site of blood, frustration or humiliation. Therefore, the term 'functional syncope' (FS) will be used in place of the less objective, inaccurate and repetitive term 'psychogenic pseudosyncope'. FS was chosen to be preferable to other options (see table 4), as it allows for the fact that some patients may also have autonomic disorders, such as autonomic (neurally) mediated syncope (AMS) or the postural tachycardia syndrome (PoTS), in which case a term such as '*non-autonomic mediated syncope*', which mirrors AMS, negates an autonomic component and may be confusing for clinician and patient.

FS appears to be a conversion disorder yet there is a paucity of FS literature (van Dijk and Wieling, 2013) and direct observation in a clinical setting is rare (Luzza et al., 2004). Moreover, FS is often reported or described with little attempt to try and unpick the psychophysiological mechanisms that may be involved in its presentation, such as the diminished interoception in patients with OI reported in chapter 6 of this thesis, which may be one potential factor linking symptomatic autonomic dysfunction with FS. Other functional disorders, such as fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome have been reported in PoTS (the most common form of OI), therefore, this chapter will

I. review the historical casenotes of FS patients to ascertain whether FS is a typical conversion disorder
II. investigate any underlying autonomic or dysautonomic contributions to FS,
III. describe the presentation and incidence of FS during autonomic testing

Table 4. Possible alternatives and rationale to the currently used 'psychogenic pseudosyncope'.

Term and abbreviation	Advantages	Disadvantages
Behavioural syncope (BS)	✓ Discounts an organic cause ✓ More accurate than 'functional'	× Not currently used × Risk of stigmatizing or alienating patient
Functional syncope (FS)	✓ Can be aligned with Functional Neurological Symptoms (FMS) and Functional Movement Disorder (FMD)	× Not currently used × Unnecessarily broad as in most cases, a neurological cause has been discounted and an autonomic cause has been fully discounted after autonomic testing
Non-autonomic (neurally) mediated syncope (NAMS)	✓ Comparable to currently used 'autonomic (neurally) mediated syncope' ✓ Discounts an autonomic cause ✓ Allows for subsequent neurological investigations if required ✓ Low risk of stigmatizing or alienating patient	× Not currently used × Long × negates an autonomic component × may be confusing for clinician and patient
Non-autonomic syncope (NAS)	✓ Discounts an autonomic cause ✓ Allows for subsequent neurological investigations if required ✓ Low risk of stigmatizing or alienating patient	× Not currently used
Psychogenic pseudosyncope (PSS)	✓ Broad ✓ Currently in use	× Repetitive × Risk of stigmatizing or alienating patient
Syncope of unknown aetiology (SoUA)	✓ Broad	× Not currently used × Long × Provides no clinical insight

4.2. Methods

The medical records of all consecutive patients referred over a 7 year period for suspected syncope or pre-syncope to two London-based national referral centres for cardiovascular dysautonomia were reviewed. FS was defined as unresponsiveness and loss of postural tone during normal ECG, HR and BP activity that would not induce a syncopal episode. Demographic and clinical characteristics of this population are described.

4.2.1. Procedure

A detailed history was obtained in all cases, with an emphasis on information to help explain the cause of syncope, including potential symptom exacerbation in relation to orthostasis, postprandial hypotension or tachycardia and whether syncope was associated with blood-injury phobia and/or emotional provocation. Information on familial syncope and the relation to neck movement was sought, particularly in elderly patients.

Using established protocols, including, HUT, prolonged head up tilt testing (pHUT), supine exercise testing and liquid meal challenge, central and peripheral stimuli (Valsalva manoeuvre, pressor responses to mental arithmetic, isometric exercise, and cutaneous cold application) were used in the assessment of autonomic function, including, sympathetic and parasympathetic nerve function (Mathias et al., 2013, Mathias and Bannister, 2013). Parasympathetic cardiac function was tested using respiratory sinus arrhythmia (RSA) responses to deep breathing, hyperventilation and the Valsalva manoeuvre and pressor exercises investigated vasomotor integrity (Mathias et al., 2013) (see Clinical autonomic investigations). In those with suspected blood-injury phobia relating to VVS, suitable observations and precautions were made during venepuncture on HUT and pHUT (45 min maximum). In patients >50 years in whom autonomic failure (AF) was excluded, carotid sinus massage (CSM) was performed to exclude carotid sinus hypersensitivity (CSH) during supine baseline and HUT, unless contraindicated due to carotid artery disease. A symptomatic fall in systolic blood pressure (SBP) of 30 mmHg or below or a BP fall of over 50 mmHg without symptoms, and/or with HR below 40 beats per min (BPM) was regarded as abnormal (Mathias et al., 2013). FS was defined as apparent syncopal behaviour (unresponsiveness, loss of postural tone) during normative cardiovascular autonomic indices that would not cause cerebral hypoperfusion and subsequent TLoC.

4.2.2 Instrumentation

HR and ECG were continually monitored online (PowerLab 16/30/ECG (Bioamp) (AD Instruments, Oxford, United Kingdom) and analysed online (Labchart 7). BP was continually recorded using digital photplethysmography (Finometer, Smart Medical, Gloucestershire, United Kingdom) and acute BP and HR measures were taken using automated sphygmomanometry (Dinamap Pro400V2, GE Healthcare, Buckinghamshire, United Kingdom). Videotelemetry used in some patients in whom FS diagnoses were suspected.

4.3. Results

68 patients (63 female) provided a positive diagnosis of FS (mean age: 37.5 $\pm$ 15.1 yr) during clinical autonomic testing. After initial analysis, it became clear that the incidence of FS had to be divided into three patient groups;

i. FS group (n=29, 42.7%) experienced episodes of FS during testing.
ii. FS/PoTS group (n=30, 44.1%) experienced episodes of FS during testing but also met the diagnostic criteria for the postural tachycardia syndrome (PoTS) during HUT, pHUT or stand.
iii. FS/AMS group (n=9, 13.2%) experienced episodes of FS and actual autonomic mediated syncope (AMS) during HUT, pHUT or standing.

4.3.1. Historical Profiles

The FS group reported the most prodromal symptoms. The FS group was predominantly female (n=26, 90%) and had a mean age of 40 ± 15.1 years. Loss of consciousness (n=10, 34.5%), dizziness (n=10, 34.5%), and palpitations (n=8, 27.6%) where the primary historical symptoms previously reported in relation to their referral. 13.8% (n=4) reported injury during these episodes and 13.8% (n=4) also had a cardiac arrhythmia. 24.1% (n=7) reported gastrointestinal (GI) symptoms related to diarrhoea or constipation, 13.8% (n=4) reported bladder urgency or incontinence during previous syncope and 17.2% (n=5) had experienced motor abnormalities, such as tremor or myoclonus before, during or after syncope. 17.2% had experienced visual disturbances during syncopal episodes and 31.1% were currently receiving treatment for psychiatric symptoms (n=9); 27.6% (n=8) for depression, 6.9% (n=2) for anxiety and 3.5% (n=1) for posttraumatic stress disorder (PTSD) (see table 5).

Current medications for the FS subgroup included, 13 x psychotropic, 6 x analgesic, , 4 x antihistamine, 4 x antispasmodic, 2 x anti-hypertensive, 2 x thyroid hormone, 2 x anti-inflammatory, 2 x beta blocker, 2 x proton pump inhibitors, 1 x antifibrinolytic, 1 x laxative , 17 x other non-prescription.

The FS/PoTS group was 100% (n=30) female with a mean age of 27.7 ± 11.6 yr. Just over half (n=16, 53.3%) had a pre-existing diagnosis or presented with sigs of ehlers-danlos syndrome III or joint hypermobility syndrome EDSIII/JHS (Beighton et al., 1998), a predisposing rheumatological trait for PoTS (Mathias et al., 2012). Historically, 26.7% (n=8) reported previous complete TLoC and 23.3% (n=7) experienced constipation or diarrhoea. 16.7% (n=5) were currently receiving treatment for an affective disorder and 3.3% (n=1) for anorexia nervosa (see table 5).

Current medications for the FS/PoTS subgroup included 11 x vasopressor/antihypotensive agent, 8 x asthma/bronchospasm medication, 5 x psychotropic, 4 x antispasmodic, 3 x OCP, 3 x analgesic, 2 x anticonvulsant drug, 2 x anticonvulsant drug, 1 x antiviral, 1 x sinoatrial node inhibitor, anti-inflammatory, 1 x antihistamine, 1 x insulin, 1 x diuretic.

The small (n=9) FS/AMS group was predominantly female (n=7, 77.8%), had a mean age of 40.4 ± 18.3 years and 66.7% (n=6) had a pre-existing diagnosis of EDSIII/JHS. 66.7% (n=6) also reported dizziness during previous syncopal episodes. TLoC and nausea (both 44.4%, n=4) were

this groups primary syncope-related symptoms. 44.4% (n=4) also reported experiencing functional motor symptoms during these historic syncopal episodes (see table 5).

On the day of testing, current medications for the FS/AMS subgroup included, 3 x analgesics, 2 x vasopressor/antihypotensive agent, 2 x antiepileptic, 2 x asthma/bronchospasm medication, 1 x anti-hypotenisve, 1 x proton pump inhibitor, 1 x anti-inflammatory, 2 x asthma/bronchospasm, 1 x antihistamine.

4.3.2. Clinical profiles

Prolonged head up tilt (pHUT) (73.1%) and head up tilt (HUT) (50%) proved the most effective tests of provoking FS. During orthostatic challenge, 4/29 (13.8%) pooled in the periphery on HUT and 1/7 (14.3%) during pHUT. 2 (6.9%) had FS episodes during hyperventilation, 2 (6.9%) during Valsalva manoeuvre, 2 (6.9%) during stand, 14 (48.3%) during HUT. 7/29 (24.1%) FS patients underwent pHUT, of whom, 7/7 (100%) experienced FS during pHUT. 3 (10%) FS episodes occurred whilst the patients was in the department but not attached to any monitoring equipment (see figure 20). During FS episodes, aside from unresponsiveness and loss of postural tone (defining symptoms of FS) functional motor symptoms (n=10, 33.3%) and eyelid fluttering/rolling (n=10, 34.5%) were the main comorbid FS symptoms observed (see figure 21). The main reported symptoms pre-or-post FS episodes were dizziness (n=6, 20.7%) and thermoregulatory symptoms, such as hot flush or clammy hands (n=6, 20.7%) (see figure 22).

During orthostatic challenge, 7/30 (23.33%) FS/PoTS patients were observed to pool in the periphery on HUT and 10/17 (58.8%) during pHUT. 3 (10%) patients had FS episodes during hyperventilation, 1 (3.3%) during Valsalva manoeuvre, 6 (20%) during stand, 15 (50%) during HUT. 17/29 FS/PoTS patients underwent pHUT (56.7%), of whom, 10/17 (58.8%) experienced FS during pHUT. 3 (10%) FS episodes occurred whilst in the department but not attached to any monitoring equipment. The main FS symptoms observed were functional motor symptoms (n=10, 33.3%) (see figure 13). The main reported symptoms pre-or-post FS were dizziness (n=10, 30%) and thermoregulatory symptoms (n=6, 20.7%) (see figure 22).

During orthostatic challenge, 2/9 (22.2%) FS/AMS patients were observed to pool in the periphery on HUT and 2/4 (50%) during pHUT. 1 (11.1%) had an FS episode during hyperventilation, 1 (11.1%) during isometric exercise, 1 (11.1%) during stand, 3 (33.3%) during HUT. 4 underwent pHUT (44.4%), of whom, 1 (25%) experienced FS during pHUT. 2 (22.2%) FS episodes occurred whilst in the department but not attached to any monitoring equipment. During FS episodes, the main symptoms observed were eyelid fluttering/eye rolling (n=4, 44.4%)

and functional motor symptoms (n=3, 33.3%) (see figure 21). The main reported symptom pre-or-post FS episode nausea (n=2, 22%) (see figure 22).

Table 5. Historical data of patients who experienced an episode of functional syncope during autonomic testing. Subjects were broadly divided into three groups, those who were found to have undiagnosed PoTS ('FS/PoTS'), those who were found to experienced functional syncope episodes and actual episodes of autonomic-mediated syncope (FS/AMS) and those who only presented episodes of functional syncope during testing ('FS').

	History				***Syncope-related***					***Gastrointestinal***		***Bladder-related***		***Functional neurological symptoms***		
Group	**Gender (%female)**	**Age**	**EDSIII/ JHS**	**Psychiatric history**	**Dizziness**	**LoC**	**Injury**	**Arrhythmia**	**Palpitations**	**Nausea**	**Constipation /diarrhoea**	**Urgency**	**Incontinent**	**Motor**	**Paraesthesia**	**Visual disturbances**
FS n=29	90%	40.3	31%	31.%	34.5%	34.5%	13.8%	13.8%	27.6%	13.8%	24.1%	13.8%	13.8%	17.2%	3.5%	17.2%
FS/PoTS n=30	100%	27.7	53.3%	6.7%	13.3%	26.7%	13.3%	10.0%	6.7%	13.3%	23.3%	10.0%	3.3%	16.7%	3.33	3.3%
FS/AMS n=9	78%	40.4	66.7%	0.00	77.8%	44.4%	33.3%	22.2%	11.1%	44.4%	0.00%	0.00%	0.00%	44.4%	11.1%	22.2%

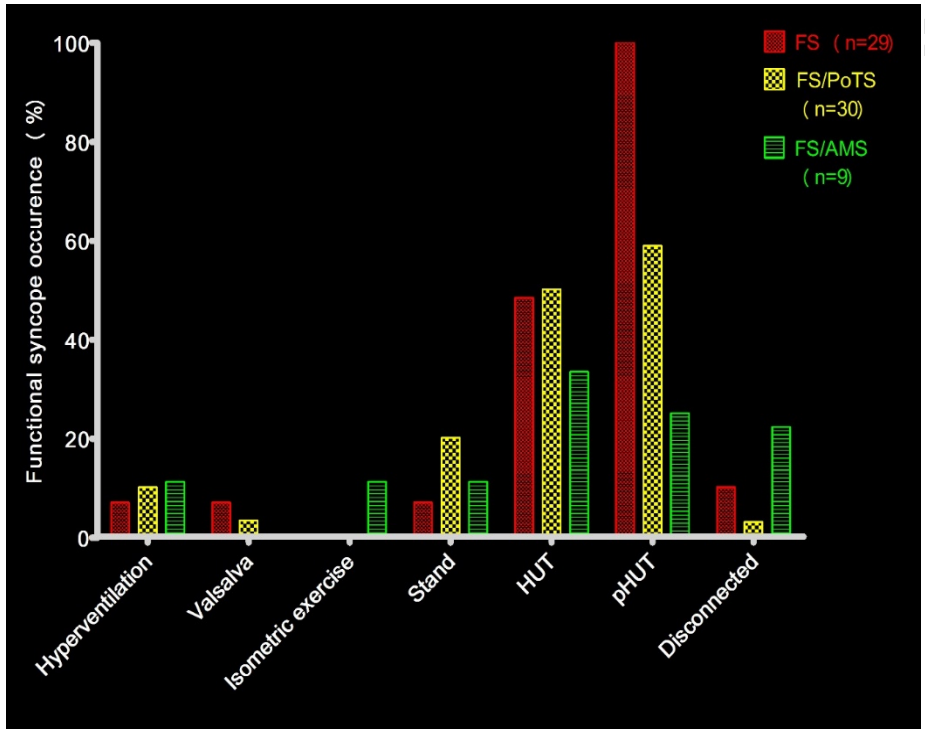


Figure 20. Incidence of functional syncopal episodes during testing. FS/PoTS = functional syncope patients postural tachycardia syndrome; FS = functional syncope only; FS/AMS = functional syncope patients with auto mediated syncope

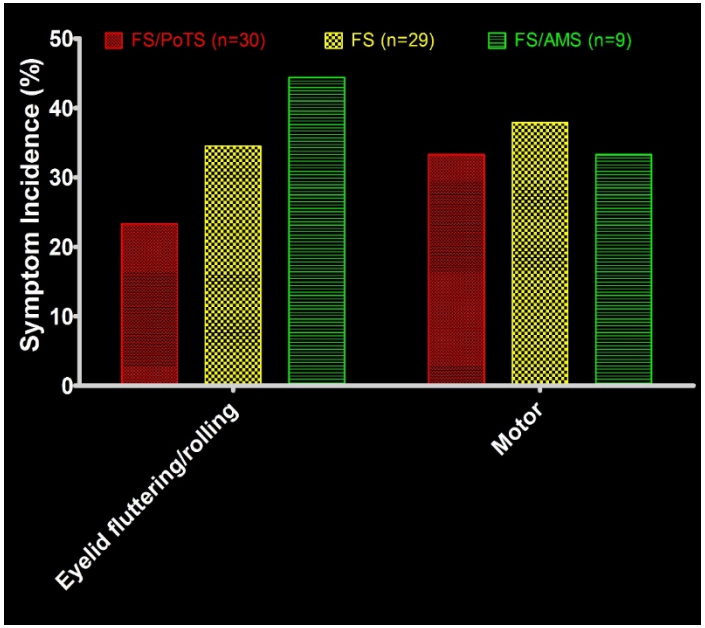


Figure 21. Observed symptoms during functional syncope episodes

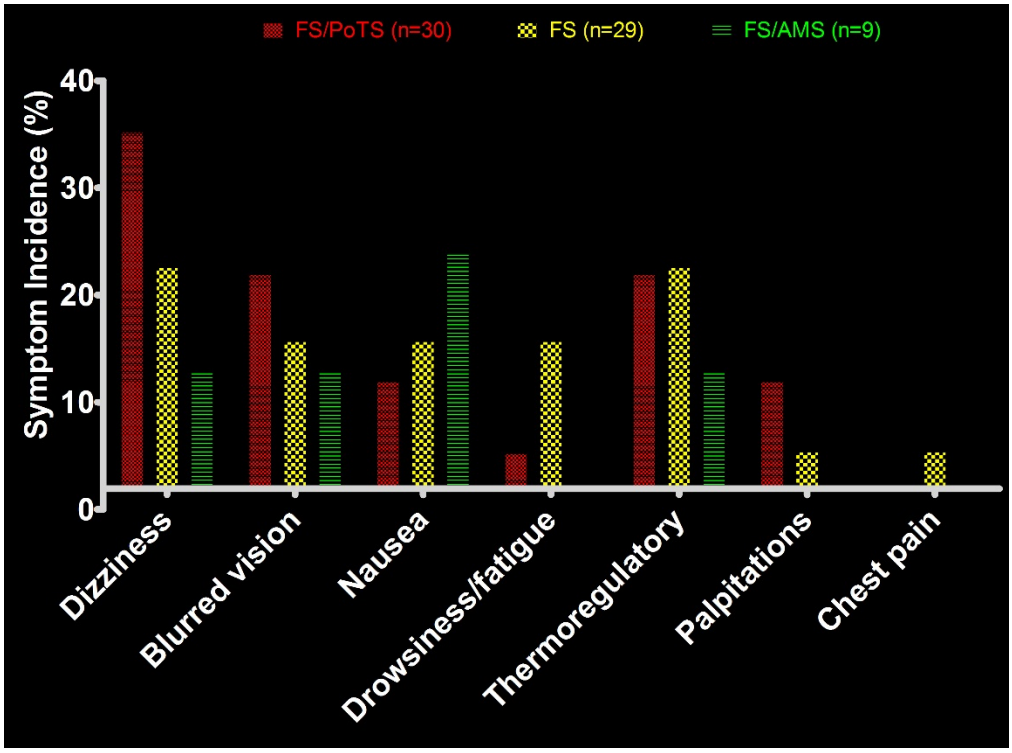


Figure 22. Symptoms reported by the patient pre/post functional syncope episode.

4.3.3. Cardiovascular autonomic data

At supine baseline the mean HR of the FS group was 71.7 ± 11.7 beats per minute (BPM). The FS/PoTS mean supine baseline HR was 79.1 ± 12.6 BPM and the mean HR of the FS/AMS group at supine baseline was 61.2 ± 7.9 BPM (see figure 23). During episodes of FS, the mean HR of the FS group was 84.9 + 17.4 BPM, the mean HR of the FS/PoTS group was 129.33 ± 30.3 and the mean HR of FS/AMS patients during episodes of FS was 76.80 ± 34.1.

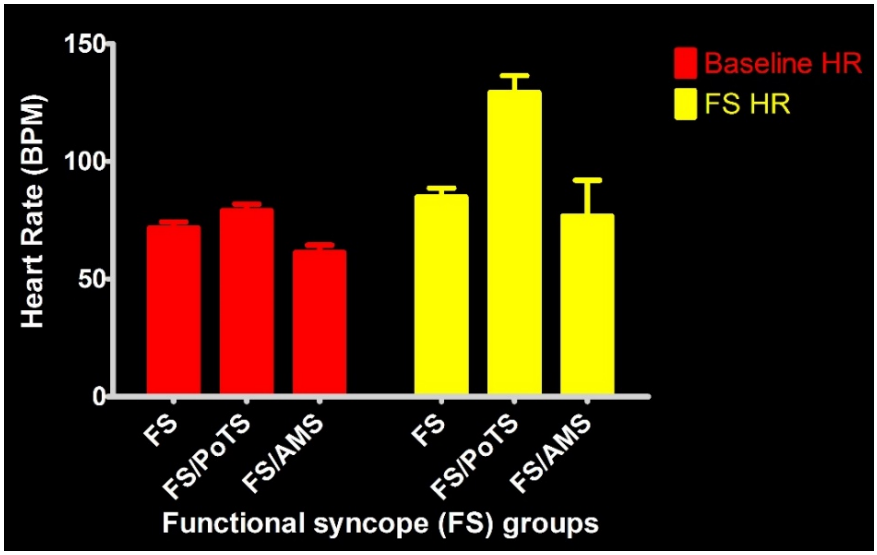


Figure 23. Group heart rate (BPM) during baseline and functional syncope episode. FS = functional syncope group, FS/PoTS = comorbid functional syncope and postural tachycardia syndrome group, FS/AMS = comorbid functional syncope and autonomic mediated syncope group. Error bars = standard deviation

During supine baseline, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the FS group was 119.1 ± 15.2 mmHg and 68.9 ± 8.7 mmHg respectively. The FS/PoTS group's mean SBP and DBP at baseline was 119.2 ± 13.6 mmHg and 68.5 ± 11.3 mmHg respectively. The mean SBP and DBP of the FS/AMS group at supine baseline was 111.5 ± 9.4 mmHg and 65.5 ± 3.9 mmHg respectively (see figure 24). During episodes of FS, the BP profile of the FS group was 130.9 ± 24.6 (mmHg) SBP and 73.1 ± 11.9 (mmHg) DBP. FS/PoTS mean BP during FS was 133 ± 21.7 (mmHg) SBP and 75.6 (mmHg) DBP and FS/AMS patients' mean SBP during episodes of FS was 66.2 ± 20.1 (mmHg) and DBP was 35.2 ± 17.3 mmHg.

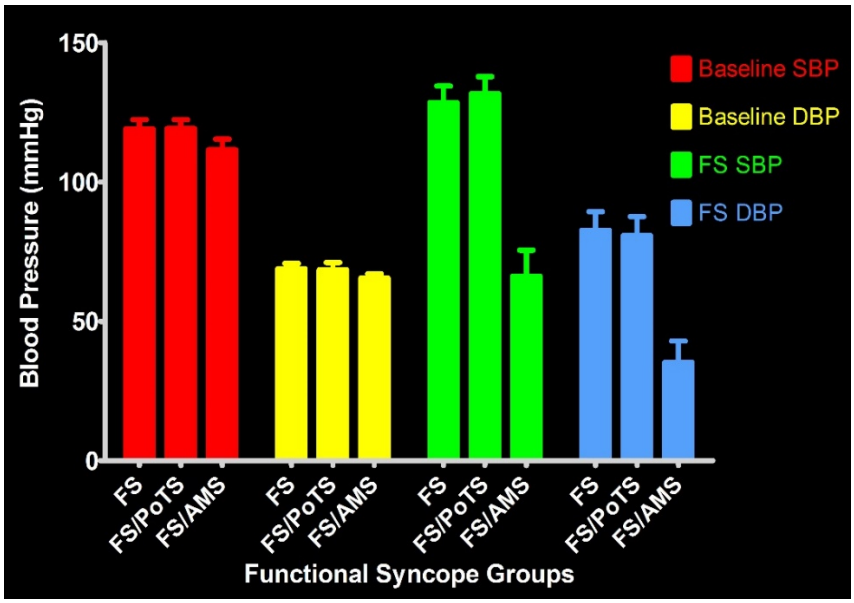


Figure 24. Group systolic blood pressure (SBP) and diastolic blood pressure (DBP) during baseline and functional syncope episode. FS = functional syncope group, FS/PoTS = comorbid functional syncope and postural tachycardia syndrome group, FS/AMS = comorbid functional syncope and autonomic mediated syncope group. Error bars = standard deviation

4.4. Discussion

This study investigated the poorly understood phenomena of FS in a cohort of 68 patients referred for suspected syncope or pre-syncope who experienced episodes of FS during testing. FS was defined as syncopal behaviour (unresponsiveness, loss of postural tone) during normative cardiovascular autonomic indices that would not induce cerebral hypoperfusion and subsequent TLoC.

pHUT (73.1%) and HUT (50%) proved the most effective tests in inducing FS. 30 (44.1%) FS patients (mean age: 28 ± 12), all female, met the PoTS diagnostic criteria, over half of whom (53.3%) also presented with JHS/EDSIII. 9 FS patients experienced actual episodes of AMS

(mean age 40.4 ± 18.3) during autonomic testing. Of the 29 remaining FS patients (mean age 40.3 ± 15.1), 31% were currently receiving psychiatric treatment, compared with 6.7% in the FS/PoTS subgroup and none in the FS/AMS subgroup. Prior to autonomic assessment, the FS subgroup appeared to be the most symptomatic, reporting the most prodromal symptoms and episodes of TLoC.

During autonomic testing, eyelid fluttering/eye rolling (FS/PoTS=23.3%, FS=34.48%, FS/AMS=44.4%) and functional motor symptoms were the most common accompanying behaviours of FS in addition to unresponsiveness and loss of postural tone. Motor symptoms are common during FS episodes but are under-reported and poorly understood (Tannemaat et al., 2013). 44.4% of the FS/AMS subgroup also reported previous involuntary motor symptoms prior to testing as part of their typical syncope prodrome. Dizziness (FS/PoTS=33%, FS=21%, FS/AMS=11%) and thermoregulatory symptoms (FS/PoTS=20%, FS=21%, FS/AMS=11%) were the most commonly reported symptoms prior to FS.

To date, the 68 FS patients identified in this study is the largest FS sample in the literature (previously n=43 (Tannemaat et al., 2013)). The current findings confirm and extend the indications from previous studies that FS patients were predominantly female, remained unresponsive during FS for significantly longer than a typical syncopal episode and that FS patients' eyes remained closed and resistant to opening. However, either due to the patients being referred to a national tertiary referral centre for autonomic disorders or because of the efficacy of the clinical protocols in unmasking autonomic dysfunction, two other FS groups were also clearly defined who either met the diagnostic criteria for PoTS or experienced an actual syncopal event as well as an FS event during testing. The prevalence of OI and the size of the FS/PoTS subgroup is particularly striking, particularly as PoTS has recently been strongly associated with functional GI disorders (Safder et al., 2009) (Chelimsky et al., 2015), particularly in paediatric patients (Kovacic et al., 2014). The current study indicates that the association between PoTS and functional phenomena is not limited to GI symptoms.

The small number of previous FS studies have consistently found a prevalence of psychiatric morbidity in test subjects (Luzza et al., 2003, Luzza et al., 2004, Benbadis and Chichkova, 2006) as was the case in the FS only subgroup, suggesting that FS was likely to be a manifestation of a conversion disorder rather than of OI (Raj et al., 2014) in the FS group, as only 6.7% FS/PoTS patients and no FS/AMS patients had a current or previous history of psychiatric morbidity. This supports previous findings that the elevated levels of anxiety in PoTS and syncope (Kapoor et al., 1995, Linzer et al., 1991) do not generally reach clinical levels (Raj et al., 2009). PoTS and

panic disorder share psychological (e.g., health anxiety, anxiety sensitivity, impaired concentration) and physiological (e.g., palpitations, tachycardia, chest pain, dyspnea) (Mathias et al., 2012) symptomatology and can co-exist (Esler et al., 2006) but the differentiating factor between the two conditions is that PoTS is provoked by orthostatic stress due to the breakdown of autonomic reflexes rather than anxiety (Khurana, 2006, Masuki et al., 2007). This is clearly illustrated by the current data, in which HUT, pHUT and standing provoked more episodes of FS than hyperventilation in the FS/PoTS group, which is a useful clinical exercise for increasing sympathetic nerve activity (SNA) but is also a reliable interoceptive threat in anxiety sensitive individuals and healthy controls (Melzig et al., 2011), is a more anxiogenic exercise than orthostatic challenges (Arch and Craske, 2010) and induces panic attack symptoms, such as anxiety, derealisation and paraesthesia (Funayama et al., 2013). This is further evidence that the tachycardia in PoTS patients during orthostatic challenge is related to a breakdown of autonomic reflexes and not psychogenic (Masuki et al., 2007).

Although there is a dearth of neuroimaging research on OI, recently, Umeda and colleagues (fMRI) have positively associated neuroticism scores in PoTS patients with enhanced left cerebellum and periaqueductal grey (PAG) activity during processing of emotional visual stimuli (Umeda et al., 2009). The PAG is a key area in defence behaviours, such as tonic immobility, as well as cardiovascular and respiratory function (Monassi et al., 1999, Dampney et al., 2013), so it may be possible that FS in the FS/PoTS group was due to an exaggerated phylogenetic defence response exacerbated by the over-representation of neuroticism in PoTS patients.

FS and non-epileptic seizurenon-epileptic seizures share many commonalities (Benbadis and Chichkova, 2006) and it is noteworthy that basal autonomic hypervigilance and positively biased processing during social threat have been found in non-epileptic seizure patients (Bakvis et al., 2009), leading to the proposition of non-epileptic seizure as a dissociative response to physical or emotional threat (Bakvis et al., 2010). This sounds remarkably similar to, but should not be confused with, descriptions of the psychosocial stressors that can cause VVS. Although there is a lack of psychophysiological studies on AMS, Buodo and colleagues evidenced attenuated electrodermal Stimulus Processing Negativity (SPN) during anticipation of unpleasant images in VVS patients (Buodo et al., 2012), suggestive of a lack of emotional adaption and anticipation.

A recent study of 22 female non-epileptic seizure patients recorded significantly lower sensory gating (p50) and disturbed attention processing regardless of episode frequency or disease

duration, potentially leading to aberrant perception of stressful events that cognitively overload the individual's capacity to cope and providing a neurological predisposition to be overwhelmed by stressors (Almis et al., 2013). This reaction may equally be provoked by interoceptive threat, such as symptomatic OI and further impacted by the impaired interoceptive accuracy found in PoTS and AMS patients in chapter 6 of this thesis. Impaired interoceptive accuracy may also help explain why the FS/PoTS patients were referred for syncope or pre-syncope rather than tachycardia or palpations. Further evidence of diminished interoception can be found in the fact that prodromal palpations (n=2, 6.7%) and pre/post FS palpitations (n=2, 6.7%) and prodromal chest pain (n=1, 3.33%), and pre/post FS chest pain (0%) both typical PoTS-related symptoms, were not commonly reported by the FS/PoTS subgroup, restating the body vigilance survey findings in chapter 5 of this thesis and further emphasising the possibility of a brain-body disconnection in these patients.

From a simple classical conditioning perspective, the cardiovascular data during episodes of FS in the two OI groups raises the possibility that FS has become a learned response to OI symptoms in FS/PoTS and FS/AMS patients, who may have subconsciously learned that assuming the supine position alleviated OI-related symptoms. Both OI groups would appear to be symptomatic during episodes of FS, with FS/PoTS patients mean HR being 129.3 $\pm$ 30.3 BPM (baseline FS/PoTS HR: 79.1 $\pm$ 12.6 BPM) and the FS/AMS BP profile being that of a vasodepressor episode during FS: 66.2 $\pm$ 20.1 SBP, 35.2 $\pm$ 17.3 DBP, compared to baseline: 111.5 $\pm$ 9.4 SBP and 65.5 $\pm$ 3.9 DBP, though this also raises the question of why the cluster of FS and eyelid fluttering/rolling and functional motor symptoms become part of the pre-syncopal symptom cluster in the FS/AMS group. The answer may lie in the prevalence of JHS/EDSIII in the FS/AMS group and that JHS/EDSIII is also associated functional disorders (Nijs et al., 2006, Kovacic et al., 2014, Acasuso-Diaz and Collantes-Estevez, 1998). The higher order interoceptive deficits described in chapter 6 of this thesis may also play a contributing role to this aberrant response to OI in both cohorts.

Predictive coding models have been applied to schizophrenic patients to explain their reduced sense of agency, a symptom also shared with FS patients during an episode of FS. These models provide a cognitive, sensory and affective matrix to explain the common symptoms in schizophrenia as resulting from inaccurate sensory predictions and interpretations of actions (Blakemore et al., 2000) (Voss et al., 2010). Originally applied to computational and theoretical models, predictive coding uses Bayesian probability theory to calculate the strength of a given hypothesis on previous probability and related data (Clark, 2013). Seth and Critchley recently extended this predictive coding model to human interoceptive processing (Seth and Critchley, 2013). In predictive coding models of the brain, error code predictions are

constantly produced to process the afferent sensory inputs. The scale of any discrepancies in these predictions, known as a prediction error (variation between the brain's prediction and the actual incoming afferent signal) must be kept to a minimum to maintain homeostasis and minimize miscalculations (Clark, 2013, Friston and Frith, 2015). This theoretical framework depicts the brain as a hierarchical structure, in which one level receives afferent input from the previous level (Felleman and Van Essen, 1991), with defined neuronal populations acting as prediction units and prediction error units. Prior beliefs and expectations provide top-down contributions to error predictions, as do bottom-up sensory and visceral inputs to minimise the size of prediction errors and maximise the evidence for its predictions.

Seth and Critchley recently extended this predictive coding model to human interoceptive processing (Seth and Critchley, 2013), describing a model in which central interoceptive predictions supress autonomic homeostatic signals and somatic responses to visceral sensory signals. Friston's 'free energy principle' theory (Friston, 2010), also known as 'active inference', proposes that should a prediction error become too large, thereby disrupting neural homeostasis, it can (i) be modified by retrogradley propagating the signal to the previous brain level that assimilated the signal, (ii) engage allostatic measures to meet the original prediction error or (iii) alter how the brain attends to the incoming afferent signal (Mesulam, 1998). In chapter 6 of this thesis, I propose this third predication error modification as a potential explanation for OI patients constantly underestimating their heartbeats. Here, I am proposing that the second prediction error modification strategy of engaging the motor system to meet the noisy incoming autonomic afferent feedback of tachycardia or pre-syncope may account for FS episodes generally occurring during symptomatic OI in FS/PoTS and FS/AMS patients. This strategy may have been chosen over modifying how afferent feedback was attended to because the experimental protocol described in chapter 6 was far less rigorous and arduous than the clinical protocols used in autonomic function tests (AFTs), which are designed to unmask any forms of dysautonomia. In fact, as soon as a patient reported any symptoms or their beat-to-beat data showed any OI trends during the interoception study, testing was halted.

Individuals who somatise are more vigilant of bodily sensations, with prior beliefs (a key Bayesian factor) about illness and disease playing a significant role (Kirmayer and Robbins, 1996) in the somatised presentation of their illness symptoms which are the product of an underlying psychiatric rather than organic pathology. This could potentially explain why the primary symptoms of syncope – unresponsiveness, loss of postural tone – were also distilled with the seizure-like symptoms of eyelid fluttering/rolling and clonic, myoclonic and other motor symptoms that do not typically occur in vasovagal syncope in all three FS groups during their

functional episodes. In chapter 5 of this thesis, PoTS and AMS patients were found to score highly in scales of body vigilance. In the AMS cohort, this body vigilance related to symptoms of pre-syncope and syncope, but the PoTS group reported a far wider spectrum of symptoms, as was the case in this study, as PoTS patients reported far more pre-and-post FS symptoms (see figure 3). This somatic attribution style of vigilance and sensitivity to physical sensations may also explain why more PoTS patients encountered episodes of FS than AMS patients.

Patients with functional tremor have been found to misattribute the agency of voluntary movement so that they judge both the intent to move and the act of moving as occurring simultaneously in an aberrant attribution style (Edwards et al., 2011). It could be argued that it is even easier to adopt this attribution style if the individual was also tachycardic or pre-syncopal at the time, especially OI pre-diagnosis. The interoception data in chapter 6 indicates a higher order deficit when AMS and PoTS patients' conscious cardiac interoceptive accuracy but the current data is also suggestive of a subconscious or pre-conscious disruption of brain-body integration driven by episodes of OI.

Functional or conversion disorders are associated with psychiatric morbidity or malingering, so the fact that so few FS/PoTS and FS/AMS had a history of an psychiatric disorder and were found to have a diagnosable form of OI is reassuring as, presumably, the various clinical care pathways may well have filtered out patients with pronounced mental health needs to more appropriate care providers. However, only the FS group had a higher prevalence of psychiatric morbidity, suggesting that delineating organic and psychiatric disorders can be problematic without appropriate allied clinical and psychiatric assessments. As with seizures and non-epileptic seizurenon-epileptic seizures (Andrade et al., 2006), OI and FS can co-exist (Mathias et al., 2000), making diagnostic protocols that can distinguish psychogenic autonomic arousal from OI essential in elucidating the often opaque presentation of FS.

4.4.1. Summary of main findings:

This study aimed to investigate the genesis and presentation of the poorly understood and under-reported phenomenon of functional syncope, concluding that;

- FS appears to be a conversion symptom in the FS group
- FS appears to be an aberrant response to undiagnosed PoTS and AMS in the FS/PoTS and FS/AMS groups.

4.4.2. Conclusions

This study defined three groups of FS patients; the first experienced episodes of FS during autonomic testing, aged ~40 with a previous or current history of psychiatric morbidity. The second group on autonomic investigation had confirmed PoTS, was aged ~27, tended to have joint hypermobility/EDSIII and typically experienced FS whilst tachycardic on HUT or pHUT. The third group who were also found to have AMS was the smallest in number (n=9), aged ~40, tended to have joint hypermobility/EDSIII and typically experienced FS during pre-syncopal episodes whilst on HUT or pHUT. HUT and especially pHUT proved to be the most likely test to produce FS. In the FS only group, FS was likely to be a conversion symptom of an underlining psychiatric pathology due to the normal BP and HR data during FS and the overrepresentation of psychiatric illness in this group. The presence of the FS/PoTS group suggests that previous studies linking PoTS with functional GI disorders may also apply to a broader spectrum of functional disorders, though the prevalence of JHS/EDSIII may be a confounding factor (Acasuso-Diaz and Collantes-Estevez, 1998, Kovacic et al., 2014). JHS/EDSIII was also common in the FS/AMS group, indicating it may be a predisposing factor for all forms of OI, not just PoTS (Mathias et al., 2012). In light of the impaired interoception in PoTS and AMS reported in chapters 6 and 7 of this thesis, predictive processing models may offer an alternative to understanding FS, as the engagement of motor systems to reduce interoceptive prediction errors of previously undiagnosed OI during HUT could account for FS episodes generally occurring during symptomatic OI in FS/PoTS and FS/AMS patients in the current study, substantiated by the finding that FS/PoTS patients were referred for syncope not PoTS-related symptoms. This study also emphasises the efficacy of robust clinical autonomic protocols in delineating any underling autonomic pathology in functional disorders, of which, it may well play a contributing role.

Chapter 5. Comorbid cognitive-affective symptoms due to autonomic (neurally) mediated syncope, essential hyperhidrosis & the postural tachycardia syndrome

5. Introduction

The interaction of autonomic and psychological symptoms in AMS, EH and PoTS is a neglected area of research, however, one study has found that the functional disability in PoTS is closely correlated with catastrophising thoughts, which also mediate anxiety and somatic hypervigilance (Benrud-Larson et al., 2003), another common anxiety-based PoTS trait (Raj et al., 2009, Masuki et al., 2007, Raj, 2006). This is the only study to-date to investigate the association between emotional factors and autonomic symptoms in PoTS, rather than reporting global self-report items as a secondary outcome of symptomatic impairment. Given the prevalence of EH, PoTS and AMS, the common presentation of OI symptoms in primary care settings, as well as in 'functional' medically unexplained symptoms, there may be a proportion of individuals with an intermittent autonomic disorder who are misdiagnosed as having a mainly psychological basis to their autonomic symptoms, including malingering. This could be further complicated by the prevalence of sub-clinical affective symptoms in OI and EH. Therefore, **specific aim # 2 of this thesis will thoroughly and systematically investigate cognitive-affective symptoms in EH, AMS and PoTS to decipher if these psychological symptoms are related to dysautonomia symptoms that functionally overlap with physical manifestations of anxiety and panic or are trait-like phenomena independent of dysautonomia.**

5.1. Methods

5.1.1. Participants

Ninety-two individuals completed the battery of self-report questionnaires aimed at elucidating the prevalence and potential cause of any affective morbidity in intermittent dysautonomia (n=71) patients in comparison to 22 healthy controls (11 females, mean age 35 $\pm$ 8.02). Patient questionnaire data were grouped by clinical cohort of 30 x PoTS patients (26 female, mean age 35 $\pm$ 10.70) 20 x EH patients (mean age 41.87 $\pm$ 11.65) and 22 x AMS patients (16 female, mean age 38.50 $\pm$ 13.43). All patients had established diagnoses from and were

under the care of the London Autonomic Units at St Mary's Hospital and the National Hospital for Neurology and Neurosurgery (NHNN) from March 2012 to December 2014. Patients were asked in clinic, pre/post testing or sent a questionnaire in the mail to participate in the survey.

5.1.2. Self-report questionnaires

The battery of questionnaires was selected with the main purposes of (i) describing the prevalence and severity of co-morbid psychological symptoms in PoTS, AMS and EH, and (ii) to examine if these symptoms, if present, were pre-existing trait-like phenomena or perpetuated in some way by organic symptoms related to autonomic dysfunction.

5.2. Results

5.2.1. Beck Depression Inventory (BDI)

PoTS (p=.000) and EH patients (p=.008) had significantly higher BDI scores than controls (see figure 25). The 21 items of the BDI can be divided into 15 x affective depressive symptoms, 2 x cognitive depressive symptoms and 4 x somatic depressive symptoms. AMS, EH and PoTS groups scored significantly higher than controls on both the cognitive depressive symptom items of '*indecisiveness* (PoTS [p=.000], AMS [p=.003], EH [p=.001]) and '*concentration difficulty*' (PoTS [p=.000], AMS [p=.008], EH [p=.005]). EH, AMS and PoTS patients also scored higher on the somatic depressive item of '*changes in sleep pattern*' (PoTS [p=.008], AMS [p=.020], EH [p=.002]). PoTS and EH patients in general scored higher on BDI items than AMS patients. PoTS patients scored than controls all somatic depressive items.

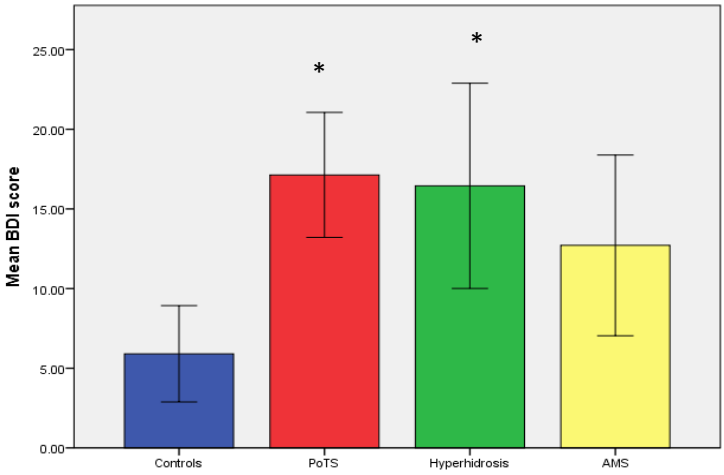


Figure 25. Global Beck Depression Inventory (BDI) scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

5.2.2. Anxiety sensitivity index (ASI)

PoTS patients were found to be significantly more sensitive to anxiety than controls (see figure 26). 'It scares me when I feel faint' was the one item of the ASI that all 3 clinical cohorts were found to score more highly on than healthy controls (PoTS *p*=.034), AMS (*P*=.022), EH (*p*=.047). PoTS and EH patients were more sensitive to;

⇒ It scares me when I feel "shaky" (trembling): PoTS (*p*=.007), EH (*p*=.030)

⇒ When I cannot keep my mind on a task, I worry that I might be going crazy: PoTS (*p*=.003), EH (*p*=.050)

⇒ When I am nervous, I worry that I might be mentally ill: PoTS (*p*=.006), EH (*p*=.043)

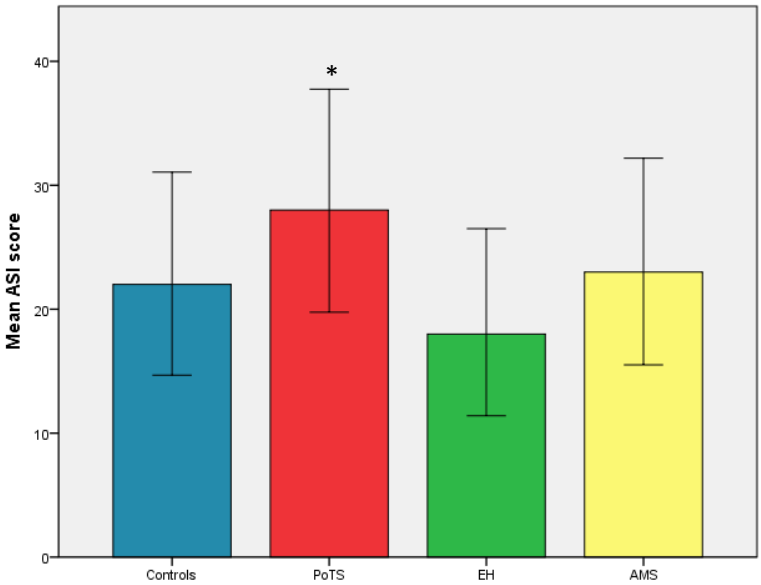


Figure 26. Mean Anxiety Sensitivity Scores for scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis (EH) and autonomic-mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

PoTS patients were more anxiety sensitive to the ASI items of 'When I cannot keep my mind on a task, I worry that I might be going crazy' (*p*=.050), 'It scares me when I feel faint' (*p*=.034), 'When I am nervous, I worry that I might be mentally ill' (*p*=.008).

5.2.3. Body vigilance scale (BVS)

AMS patients reported being more sensitive to changes in their body (*p*=.043) and paid close attention to bodily sensations (*p*=.015). It is noteworthy that the cardiothoracic items of '*palpitations*' (*p*=.176) and '*chest pain'* (*p*=.225) were not significantly higher in PoTS patients. However, this group was found to dedicate the most attention to specific BVS items and the EH cohort the least. AMS and EH patients were found to invest significantly more time scanning their bodies for symptoms (EH, *p*=.022, AMS, *p*=.045) and EH patients were found to be hypervigilant only in relation to thermoregulatory items ('*sweaty/clammy hands'* [EH, *p*=.000; PoTS, *p*=.014, AMS, *p*=.021) and '*hot flash*' [EH, *p*=.003; PoTS, *p*=.025) (see figure 27).

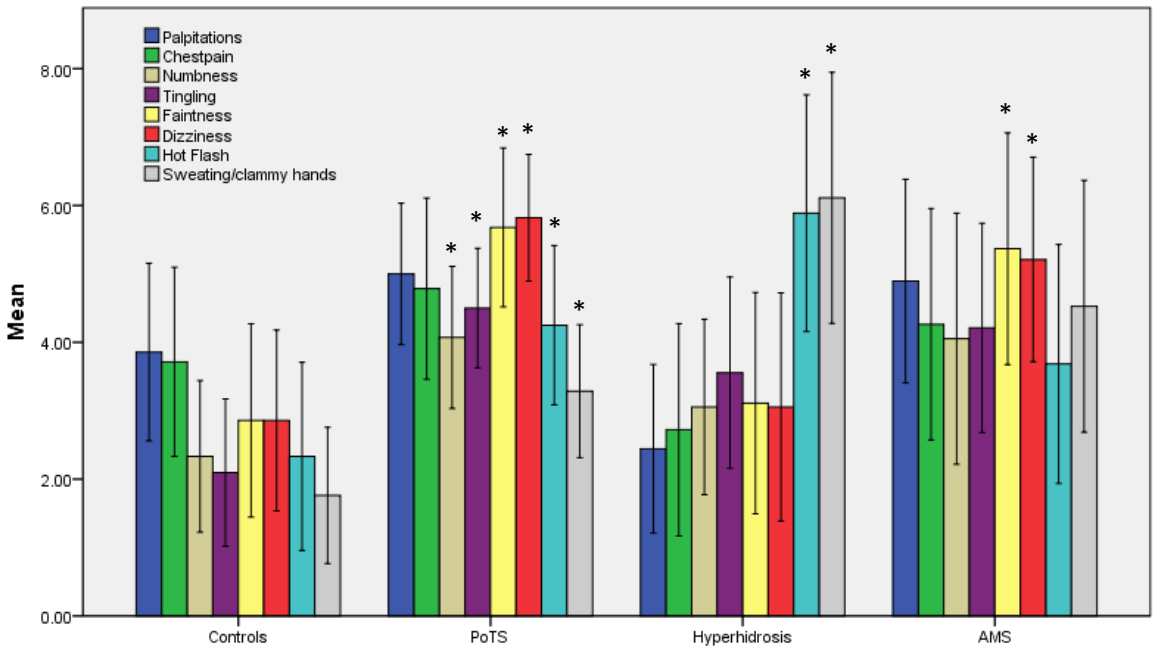


Figure 27. Body Vigilance Scale mean item scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic-mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

5.2.4. Cardiac anxiety scale (CAS)

Predictably, PoTS patients had greater mean and specific cardiac-related anxiety compared to controls and EH and AMS patients (see figure 28). The PoTS group also claimed to have greater interoceptive sensibility, such as '*My racing heart wakes me up at night*' (PoTS, *p*=000) and '*I can feel my heart in my chest*' (PoTS, *p*=.001). PoTS patients also reported that they had significant (PoTS, *p*=.007) impairment in concentration. The CAS items that were increased in the EH group related to avoiding increased physical exertion and/sudomotor activation ('*I avoid activities that make me sweat*' [EH, *p*=.000], '*I avoid physical exertion*' [EH, *p*=.002, PoTS, *p*=.001]. There were no significant global or individual findings in the AMS group.

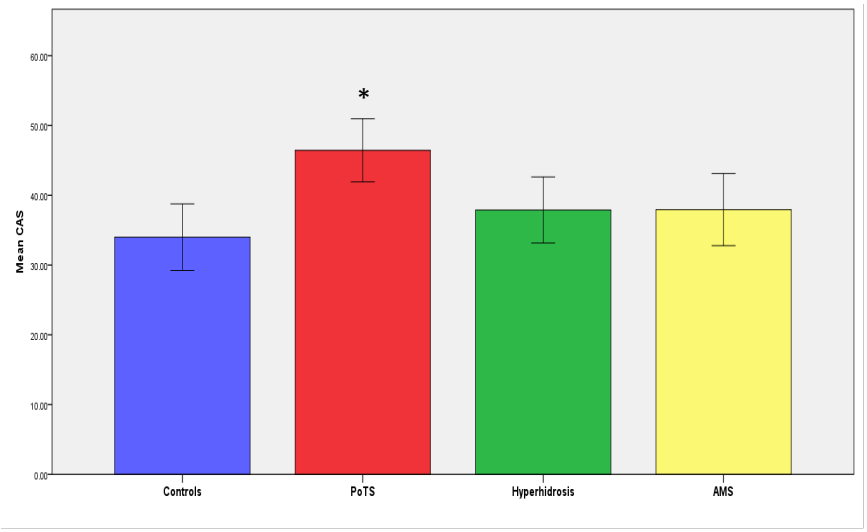


Figure 28. Cardiac Anxiety Scale (CAS) mean scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic-mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

5.2.5. State anxiety inventory (SAI)

PoTS patients had significantly greater (*p*=.020) overall state anxiety (see figure 29). In terms of individual items on the SAI, the only other significant finding was that of PoTS patients feeling more confused than healthy controls (*p*=.027).

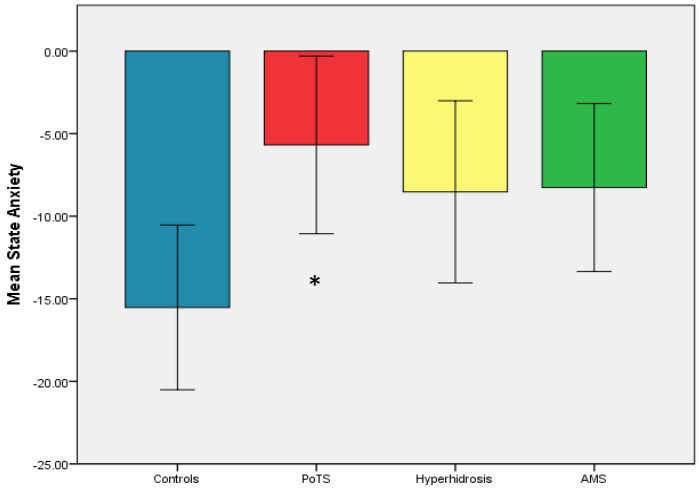


Figure 29. Mean state anxiety scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic-mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

5.2.6. The Self-consciousness Scale (SCS-R) (revised)

There were no significant differences in overall SCS-R scoring (see figure 22). AMS patients did not differ from healthy controls on any of the individual SCS-R items, however, PoTS and EH patients were found to be more sensitive to noticing changes in their mood (PoTS, *p*=.021; EH, *p*=.013) and EH patients were also more concerned with how they presented themselves (*p*=.022).

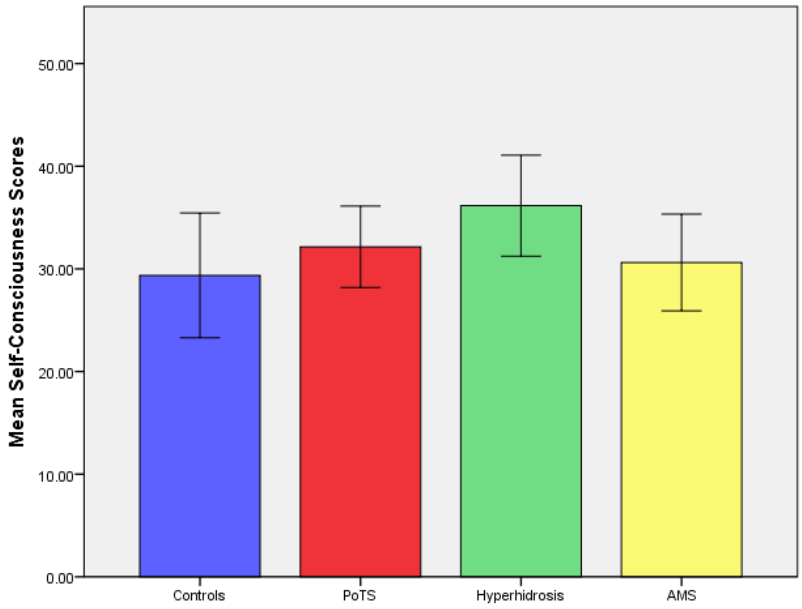


Figure 30. Mean Self-Consciousness Scale scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic-mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

5.2.7. Childhood Traumatic Events Scale (CTES)

There were no significant group differences in either childhood or adult physical, sexual or emotional trauma between AMS (*p*=.232), PoTS (*p*=.685) and EH (*p*=.413) patients in comparison to controls (see figure 31). Nor were there any significant differences in the subjective severity of how traumatic any childhood (AMS, *p*=.0.83; PoTS, *p*=.0.525; EH, *p*=.0.55) or adult events (AMS, *p*=.0.70; PoTS, *p*=.0.74; EH, *p*=.0.79) were felt to be by the participants.

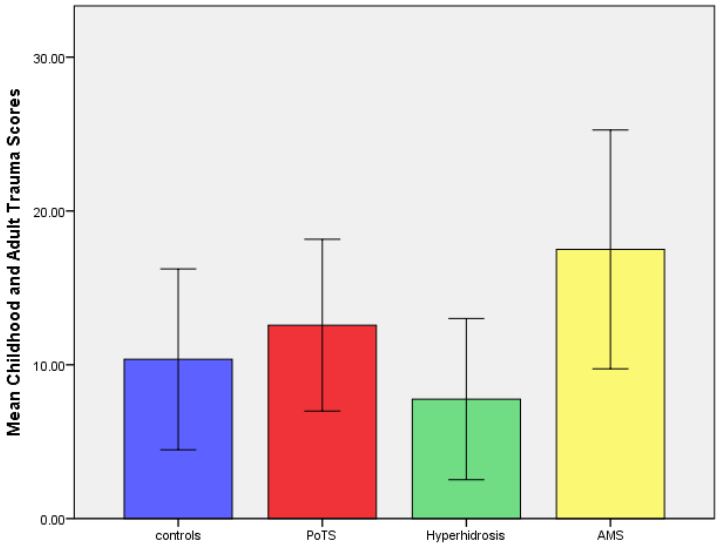


Figure 31. Mean Childhood Traumatic Event Scale scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic-mediated syncope (AMS) patients in comparison to healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

5.3. Central & visceral symptom associations

In order to better understand the prevalence and presentation of comorbid psychological symptoms in the three autonomic cohorts, correlation analysis was applied to both individual questionnaire items and also questionnaire mean scores. This analysis lead to the correlations between cognitive-affective, visceral and dysautonomic symptoms, establishing the following symptom categories of;

- ⇒ *affective-attentional sensitivity and derealisation,*
- ⇒ *affective-attentional sensitivity,*
- ⇒ *somatic anxiety sensitivity,*
- ⇒ *somatic hypervigilance and attentional deficits*
- ⇒ *somatic sensitivity and derealisation*.

The strongest correlations amongst PoTS patients were those relating to somatic anxiety sensitivity (x12), followed by somatic hypervigilance and attentional deficits (x7) and finally affective-attentional sensitivity and derealisation (x2) (see table 6).

POTS CENTRAL & VISCERAL SYMPTOM ASSOCIATIONS

SOMATIC ANXIETY SENSITIVITY	Total anxiety sensitivity score	Total cardiac anxiety score (r_s = 778, p=.000**)
	When I notice that my heart is beating rapidly, I worry that I might have had a heart attack	I get frightened (r_s = 778, p=.000**)
	Total anxiety sensitivity score	I pay attention to my heart beat (r_s = 751, p=.000**)
	It scares me when I feel "shaky" (trembling)	Total cardiac anxiety score (r_s = 725, p=.000**)
	I am very sensitive to changes in my internal bodily sensations.	Total cardiac anxiety score (r_s = 722, p=.000**)
	I am very sensitive to changes in my internal bodily sensations.	I avoid activates that make my heart beat faster (r_s = 710, p=.000**)
	I am the kind of person who pays close attention to internal bodily sensations.	Total cardiac anxiety score (r_s = 710, p=.000**)
	I am worried	Time spent each day "scanning" your body for sensations (r_s = 673, p=.000**)
	Unusual body sensations scare me	I get frightened (r_s = 664, p=.000**)
	It scares me when I feel "shaky" (trembling)	I get frightened (r_s = 664, p=.000**)
	Time spent each day "scanning" your body for sensations	I pay attention to my heart beat (r_s = 634, p=.000**)
	I am very sensitive to changes in my internal bodily sensations.	I pay attention to my heart beat (r_s = 621, p=.000**)
	I am worried	Time spent each day "scanning" your body for sensations (r_s = 619, p=.000**)
SOMATIC HYPERVIGILANCE & ATTENTIONAL DEFICITS	It scares me when I am unable to keep my mind on a task	I avoid activities that make me sweat (r_s = 710, p=.000**)
	I am very sensitive to changes in my internal bodily sensations.	I have difficulty concentrating on anything else (r_s = 683, p=.000**)
	When I cannot keep my mind on a task, I worry that I might be going crazy	I avoid physical exertion (r_s = 663, p=.000**)
	I am the kind of person who pays close attention to internal bodily sensations.	I have difficulty concentrating on anything else (r_s = 643, p=.000**)
	It scares me when I feel faint	Concentration Difficulty (r_s = 607, p=.000**)
AFFECTIVE-ATTENTIONAL SENSITIVITY & DEREALISATION	I am jittery	Feelings of unreality (r_s = 636, p=.000**)
	I am jittery	Feeling detached from self (r_s = 635, p=.000**)

Table 6. Associations between central and visceral symptoms in postural tachycardia (PoTS) patients

EH subjects' most common categories, in order of prevalence were affective-attentional sensitivity and derealisation (x8), somatic anxiety sensitivity (x7), somatic hypervigilance and attentional deficits (x3) and affective-attentional sensitivity (x2) (see table 7).

EH CENTRAL & VISCERAL SYMPTOM ASSOCIATIONS

AFFECTIVE-ATTENTIONAL SENSITIVITY & DEREALISATION	When I am nervous, I worry that I might be mentally ill	Feeling detached from self (r_s = 803, p=.000**)
	When I am nervous, I worry that I might be mentally ill	Feelings of unreality (r_s = 741, p=.000**)
	When I cannot keep my mind on a task, I worry that I might be going crazy	Feeling detached from self (r_s = 718, p=.000**)
	Total depression score	Feelings of unreality (r_s = 707, p=.000**)
	Total depression score	Feeling detached from self (r_s = 679, p=.001**)
	Total Anxiety Sensitivity score	Feeling detached from self (r_s = 666, p=.004**)
	Concentration Difficulty	Feeling detached from self (r_s = 660, p=.002**)
	Concentration Difficulty	Feelings of unreality (r_s = 654, p=.002)
SOMATIC ANXIETY SENSITIVITY	It scares me when my heart beats rapidly	Total cardiac anxiety score (r_s = 740, p=.006**)
	Total anxiety sensitivity score	I avoid activities that make my heart beat faster (r_s = 727, p=.001**)
	When I notice that my heart is beating rapidly, I worry that I might have had a heart attack	Changes in Sleeping Pattern (r_s = 727, p=.001**)
	It scares me when my heart beats rapidly	I can feel my heart in my chest (r_s = 701, p=.004**)
	I can feel my heart in my chest	Total body vigilance Score (r_s = 665, p=.004**)
	I feel at ease	I am very sensitive to changes in my internal bodily sensations (-.650, p=.003**)
	Total cardiac anxiety score	Total body vigilance score (r_s = 647, p=.003**)
SOMATIC HYPERVIGILANCE & ATTENTIONAL DEFICITS	It scares me when I feel faint.	I have difficulty concentrating on anything else (r_s = 693, p=.002**)
	Total anxiety sensitivity score	Concentration Difficulty (r_s = 686, p=.002**)
	I have difficulty concentrating on anything else	Total body vigilance score (r_s = 646, p=.004**)
AFFECTIVE-ATTENTIONAL SENSITIVITY	It scares me when I am unable to keep my mind on a task,, I worry that I might be going crazy	Concentration Difficulty (r_s = 704, p=.005**)
	When I am nervous, I worry that I might be mentally ill	Concentration Difficulty (r_s = 672, p=.003**)

Table 7. Associations between central and visceral symptoms in essential hyperhidrosis (EH) patients

The strongest symptom associations amongst AMS patients were somatic anxiety, affective-attentional sensitivity and derealisation, somatic sensitivity and derealisation and somatic hypervigilance and attentional deficits (see table 8).

AMS CENTRAL & VISCERAL SYMPTOM ASSOCIATIONS

SOMATIC ANXIETY SENSITIVITY	Unusual body sensations scare me ⟺	I get frightened (r_s = 839, p=.000**)
	Total anxiety sensitivity score ⟺	I get frightened (r_s = 838, p=.000**)
	Unusual body sensations scare me ⟺	I like to be checked out by a doctor (r_s = 803, p=.000**)
	When I notice that my heart is beating rapidly, I worry that I might have had a heart attack ⟺	I get frightened (r_s = 739, p=.000**)
	Total cardiac anxiety score ⟺	Time spent each day "scanning" your body for sensations (r_s = 739, p=.000**)
	It scares me when I feel "shaky" (trembling) ⟺	I get frightened (r_s = 734, p=.000**)
	I get frightened ⟺	Total body vigilance score(r_s = 699, p=.001**)
	Unusual body sensations scare me ⟺	Total cardiac anxiety score (r_s = 695, p=.002**)
AFFECTIVE-ATTENTIONAL SENSITIVITY & DEREALISATION	I feel highly strung ⟺	Feeling detached from self (r_s = 841, p=.000**)
	I feel highly strung ⟺	Feelings of unreality (r_s = 839, p=.000**)
	It scares me when I feel "shaky" (trembling) ⟺	Feelings of unreality (r_s = 672, p=.002**)
	Total anxiety sensitivity score	Feelings of unreality (r_s = 667, p=.002**)
	Concentration Difficulty ⟺	Feeling detached from self (r_s = 663, p=.003**)
	I am jittery ⟺	Feelings of unreality (r_s = 662, p=.003**)
	I get frightened ⟺	Feelings of unreality (r_s = 635, p=.004)
SOMATIC SENSITIVITY & DEREALISATION	Unusual body sensations scare me ⟺	Feelings of unreality (r_s = 690, p=.001**)
	Unusual body sensations scare me ⟺	Feeling detached from self (r_s = 652, p=.002**)
	It scares me when I feel faint ⟺	Feelings of unreality (r_s = 651, p=.003**)
	It scares me when my heart beats rapidly ⟺	Feelings of unreality (r_s = 641, p=.003**)
SOMATIC HYPERVIGILANCE & ATTENTIONAL DEFICITS	I have difficulty concentrating on anything else ⟺	Time spent each day "scanning" your body for sensations (r_s = 637, p=.003**)

Table 8. Associations between central and visceral symptoms in autonomic mediated syncope (AMS) patients

5.4. Discussion

The aim of this study was to examine the genesis of the co-morbid psychological symptoms in AMS, EH and PoTS patients. A battery of validated questionnaires was used to survey patients in comparison to healthy controls. These questionnaires were broadly divided into measures looking at psychological items only and those looking at psychological factors in relation to somatic and dysautonomia factors.

5.4.1. Depressive Symptoms

PoTS and EH patients were significantly more depressed than controls, however, all three clinical cohorts reported greater cognitive depressive symptoms of indecisiveness and concentration difficulty than controls.

There is a lack of literature on cognitive symptoms in patients with AMS and EH, however, a small number of studies have investigated the cause of 'brain fog' in PoTS by examining cerebral perfusion, flow velocity, fatigue and noradrenergic coupling, yet the cause of this ill-defined symptom cluster remains unknown (Ross et al., 2013). Cognitive function is also impaired in fixed dysautonomia, especially during orthostasis, despite no clinical evidence of neurological deficits (Heims et al., 2006a) (Guaraldi et al., 2014) and it remains unclear whether this is due to common pathological processes effecting cognitive or autonomic neuroanatomy from cerebral hypoperfusion or an as yet unknown cause. It may be of relevance that a recent study has concluded that memory formation is poorer at systole in comparison to diastole (Garfinkel et al., 2014) in healthy controls, therefore, the dysfunctional baroreflex in AMS and PoTS may contribute to cognitive symptoms when OI patients are symptomatic.

However, the current data also reports cognitive symptoms in EH patients, who have no OI and no pathological changes in cerebral perfusion, suggesting that these comorbid cognitive symptoms may be centrally mediated due to the differing peripheral cardiovascular (AMS, PoTS) and sudomotor (EH) pathophysiological profiles in the study patient groups. As with the functional syncope patients in chapter 4, Friston's 'free energy principle' (Friston, 2010) may help explain these symptoms as a manifestation of EH or OI producing noisy interoceptive

prediction errors and the brain having to alter how it attends to incoming afferent signals (Mesulam, 1998) (see also chapter 6).

EH remains a neglected area of study, particularly in terms of pathophysiological investigations, so the finding that these patients also report cognitive symptoms lacks a comprehensive backdrop of literature to draw on. Hyperhidrotics also reported changes in sleep pattern, which is of interest as sleep is integrated with thermoregulation (Collins, 2013). Sleep disruption has not previously been reported in EH or AMS but poor quality sleep, daytime sleepiness and fatigue have been reported in PoTS (Bagai et al., 2011). In the current findings, PoTS patients also reported significant fatigue, lack of energy and reduced appetite, which corresponds with previous findings that working memory, accuracy and information processing are impaired during orthostasis in PoTS (Ocon, 2013).

5.4.2. Anxiety sensitivity

PoTS patients were found to have significantly greater global anxiety sensitivity. Anxiety sensitivity to feeling faint was the only ASI item of that all 3 clinical cohorts were found to score significantly higher on than controls. As with cognitive depressive traits, PoTS and EH patients reported symptoms relating to being unable to concentrate, further emphasising the likelihood of a common central dysregulation in intermittent dysautonomia. Ocon and colleagues have found that cerebral autoregulation is impaired during orthostasis in VVS (Ocon et al., 2009a) and PoTS (Stewart et al., 2012, Ocon, 2013). Diminished cerebral and sub-cortical blood flow impairs brain perfusion, likely contributing to the cognitive deficits subjectively experienced as brain fog or mental fatigue in OI, (Stewart et al., 2012), however, this does not explain the reporting of cognitive deficits by EH subjects who experience no fluctuations in cerebral autoregulation. These findings require further investigation into the previously unreported cognitive symptoms in EH and whether this can elucidate a common pathway shared with the attentional symptoms in PoTS and AMS beyond the previously reported neurovascular investigations in OI subjects, which may only partly account for these common comorbid symptoms.

5.4.3. Somatic Hypervigilance

AMS patients were significantly more sensitive to physiological changes in their body, perhaps because pre-syncopal symptoms are somatic markers of an impending and potentially injurious syncopal episode. This may also explain AMS patients paying more attention to such

bodily changes, in order that they know when to adopt contingent behaviour to prevent a faint. The PoTS group were the most preoccupied with specific physiological phenomena, such as numbness, tingling, faintness, dizziness, hot flash and sweaty clammy hands, though interestingly, not palpitations or chest pain, suggestive of diminished interoception. The pre-syncope and neuropathic symptoms the PoTS group were found to be hypervigilant of may be reflective of broader pathophysiological factors in neuropathic and hyperadrenergic PoTS phenotypes. The finding that PoTS patients did not report hypervigilance of palpations and chest pain, though initially counterintuitive, does support the findings of a recent study investigating cardiac interoception in PoTS, which found that the interoception of palpations was separate to that of tachycardia (Khurana, 2014). However, in the current data, palpitations were not self-reported as being prevalent, though it could be argued that this may be due to the questionnaires being completed in a state of rest.

Predictably, EH patients paid significantly more attention to the hyperhidrosis-related BVS items of '*hot flash*' and '*sweaty clammy hands*'. Likewise, the only noteworthy symptoms that significantly preoccupied AMS patients were '*dizziness*' and '*faintness*'. No subjects reported any significant dissociative symptoms from the BVS, therefore we can deduce that the cognitive symptoms reported above were not the result of dissociative fugue or dissociative-memory impairment.

5.4.4. 'Cardiophobia'

Understandably, PoTS had elevated levels of 'cardiophobia', scoring highly on items related to both avoiding physical exertion and the interoception of cardiac symptoms, such as being awoken by increased heart rate or checking their pulse. As with the depression and anxiety sensitivity questionnaires, PoTS patients also reported difficulty in concentrating, though it is of note that neither EH nor AMS subjects scored highly for the cognitive item on this questionnaire. In this instance, EH participants acted as a clinical control group but did score highly in relation to avoiding physical exertion and exercise, presumably as a way of minimizing their excessive sudomotor activity.

Although PoTS patients scored highly on items related to subjective interoception, such as '*My racing heart wakes me up at night*' and '*I can feel my heart in my chest*' the lack of reported cardiothoracic symptoms in the BVS as well as in PoTS patients who also experienced functional syncope in chapter 4, lead one to question the accuracy of this interoception. This

view is supported by the use of interoceptive exercises in chapters 7 and 6, indicating subjective sensitisation rather than interoceptive accuracy in PoTS, AMS and EH.

5.4.5. State anxiety

State anxiety proved to be the least prevalent trait in the surveyed AMS and EH patients. PoTS patients again proved to be the most symptomatic, scoring greater mean state anxiety scores than controls. In line with the prevailing cognitive symptoms experienced by PoTS patients, this cohort also reported a significantly increased prevalence of feeling confused, further underlining the role of cognitive as well as emotional symptoms in the PoTS psychiatric profile, more so than in EH and AMS participants.

5.4.6. Self-consciousness

PoTS and EH patients were found to be more sensitive to noticing changes in their mood and EH patients were also more concerned with how they presented themselves, most likely due to the social stigma that is applied to inappropriately and profusely sweating. However, other items and global self-consciousness scales did not differ significantly between groups, indicating normative levels of social anxiety in the selected control and clinical populations. This leads to the conclusion that the psychological symptoms experienced by AMS, EH and PoTS patients are not due to neurotic traits but rather derived from the physiological and homeostatic dysregulation caused by their intermittent autonomic disorder, as evidenced by anxiety being firmly aligned with somatic events, visceral sensations, attentional deficits and the vigilance and anxious apprehension of these phenomena.

5.4.7. Trauma

There were no significant between groups differences in the incidence of subjective severity of adult or childhood trauma, indicating that the autonomic dysregulation in the EH, AMS and PoTS cohorts was not related to trauma but symptomatic of an organic clinical condition, as per their diagnoses.

5.4.8. Central & visceral symptom associations

Somatic anxiety sensitivity was particularly common in both OI groups. As already stated, there is some literature on the ill-defined 'brain fog' in PoTS but the current data indicates that these cognitive symptoms may also be common not just in other forms of OI, such as AMS, but also in EH, indicating that these symptoms may relate to the central integration of (aberrant) afferent autonomic signalling. This anxiety sensitivity to cognitive and autonomic aberrations that are defining symptoms of OI may also elucidate the prevalence of functional symptoms in PoTS and AMS patients during autonomic testing in see chapter 4 of this thesis.

Although not an initially pervasive symptom, derealisation (one's surroundings feel unreal) was found to be highly positively correlated with affective-attentional sensitivity, particularly in the EH and AMS groups. Derealisation is typically a transient symptom (Medford, 2014) unless associated with the symptom cluster of hypoemotionality and feelings of disembodiment that define depersonalisation disorder (DPD) (Sierra et al., 2005, Baker et al., 2003). DPD is a defensive, emotionally-disengaging response that is subconsciously implemented to accommodate threat deemed as beyond ones' control (Lee et al., 2012), sharing some parallels with the vasovagal response.

DPD symptoms overlap with corticolimbic disconnections (Mayer-Gross, 1935), supporting the hypothesis that emotional formation has become out-of-step with the neural processes required for emotion formation in depersonalised subjects. Inverse correlations between skin conductance responses and dorsal prefrontal cortex responses (Lemche et al., 2008, Lemche et al., 2007) indicate a central correlate for the autonomic dysregulation during emotional stress in DPD (Owens et al., 2015). It could be argued that the present autonomic patient data represents a comparable but less severe dysregulation of brain-body integration, manifesting in the association between sub-clinical derealisation and sensitisation/hypervigilance of anxiety, depression and attentional deficits in EH, AMS and PoTS. Moreover, it is noteworthy that derealisation was predominantly associated with sensitivity to anxiety, depression and attentional deficits rather than visceral symptoms, as DPD patients often report the additional anxiety caused by the awareness (sensitivity) of their affective and cognitive (particularly memory) DPD symptoms. Taken together with the functional syncope data in chapter 4, sensitivity to visceral symptoms appears to be associated with functional symptoms, whereas sensitivity to central symptoms is associated with derealisation, as there is no evasive behaviour other than dissociation or distraction (perhaps contributing to attentional deficits) that will alleviate the distress caused by the sensitivity and awareness of these affective and attentional symptoms.

The strongest correlations amongst all intermittent dysautonomia patient groups related to anxiety sensitivity to visceral sympathetic arousal and attentional deficits, lending further support to the conclusion that the common comorbid cognitive-affective symptoms in EH, AMS and PoTS are not trait-like neurotic symptoms but consequential rather than causative of intermittent dysautonomia.

5.4.9. Summary of key findings

This study was designed to profile comorbid cognitive-affective symptoms in disorders of autonomic over-reactivity, concluding that;

- Cognitive-affective symptoms in EH, PoTS and AMS appear to be more aligned with vigilance and apprehension of physical symptoms rather than be neurotic or trauma-related phenomena.
- Cognitive symptoms are also present in AMS and EH, not only PoTS.

5.4.10. Conclusion

Trauma was not a likely mediator of the pervasive cognitive-affective symptoms reported by intermittent dysautonomia patients. PoTS patients in particular have pronounced anxiety, attentional difficulties and fixation on somatic symptom-related phenomena. Somatic and cognitive symptoms predominated as the source of distress in all patients groups, rather than anxiety being a neurotic trait-like phenomena, e.g., self-consciousness or social anxiety. Cognitive symptoms were also present in EH, demonstrating that these higher order symptoms may relate to the central integration of (aberrant) afferent autonomic signalling. Derealisation was positively correlated with affective-attentional sensitivity, particularly in the EH and AMS groups, further indicating a central dysregulation of brain-body integration. This may help explain why visceral symptoms appear to be associated with functional symptoms, whereas sensitivity to cognitive-affective symptoms is associated with dissociation. Together, these data indicate how brain and body are coupled by the ANS, how this link can be decoupled by intermittent dysautonomia and that the prevalent psychological symptoms in these conditions are consequential rather than causative of intermittent dysautonomia.

Chapter 6. Brain-body integration in disorders of intermittent cardiovascular & sudomotor overactivity

6. Introduction

Afferent signalling of visceral nerve activity, known as '*interoception*', is required for autonomic mediation of homeostasis and contributes to emotion and behaviour at varying levels of consciousness (see figure 32) (Critchley et al., 2004), from baroreceptors modulating cardiac responses to fluctuations in BP to maintain cerebral perfusion, to discarding an item of clothing as an act of behavioural thermoregulation.

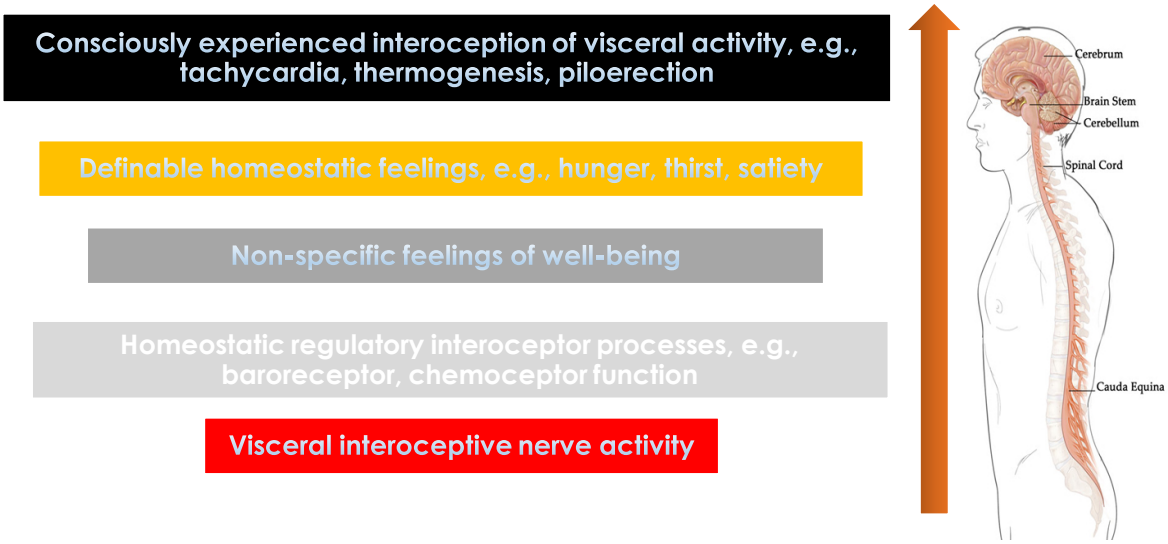


Figure 32. Varying levels of interoception.

Interoceptor (arterial baroreceptors) activity influences cognitive-affective processes on a preconscious level (Garfinkel et al., 2014) and sensory signals also influence endocrine function, e.g., the sight or smell of food causes insulin release (Teff, 2011). Empathy is an emotion influenced by interoception (Grynberg and Pollatos, 2015), as autonomic arousal to emotional stimulation predicts empathy levels (Bogdanov et al., 2013). Interoception and empathy allow us to build cognitive interpersonal models and predict outcomes of our own and others' behaviour. It has been proposed that predictions of experienced versus expected interoceptive error signals of bodily events can be a 'bottom up' source of anxiety (Paulus and Stein, 2006). Therefore, if one were to feel dizzy, tachycardic or too hot or sweaty whilst being aware that the situation did not require these aberrant allostatic adaptions, the interoceptive processing of these error signals would create anxiety at the discordant bodily states, as

defined by aberrant autonomic activity. However, the amount of anxiety caused by any discrepancies would depend on how interoceptively sensitive one is.

Heart rate variability (HRV) has been used as a surrogate marker of central sympathetic and parasympathetic dominance on visceral autonomic processes (Task Force, 1996). It has been proposed that the reduced vagal tone, as measured by high frequency HRV (HF-HRV), in affective disorders serves to disinhibit sympathoexcitation, causing sympathetic dominance of somatic and psychological processes. Increased cardiac reactivity, attentional threat bias (Mathews, 1990) and somatic hypervigilance (Verkuil et al., 2007) in anxious patients has been taken as further support of a persistent state of increased autonomic and psychological arousal in anxiety and depression. This psychophysiological coupling via the ANS of body and brain causes an excitatory feedback loop that perpetuates trait sympathoexcitation and anxiogenesis, hence interoception's contributory role to anxiety disorders (Dunn et al., 2010) via somatic hypervigilance (Clark, 1986).

These findings lead one to consider what happens to cognitive-affective processes in conditions of exaggerated autonomic responsivity (Eccles et al., 2015), particularly if these autonomic conditions have a prevalence of comorbid affective morbidity, such is the case in PoTS (Raj et al., 2009), AMS (Cohen et al., 2000b) and EH (Karaca et al., 2007). With the relatively recent interest in conscious interoception, important methodological issues have developed with its measurement, interpretation and inconsistent and interchangeable use of terms such as, 'interoceptive accuracy', 'interoceptive awareness', 'interoceptive sensitivity' or simply 'interoception'. To address these issues, Garfinkel and colleagues (Garfinkel and Critchley, 2013, Garfinkel et al., 2015) recently stratified '*interoceptive awareness*' as a metacognitive measure of the degree to which objective interoceptive accuracy (as measured by a heartbeat tracking tasks, for example) relates to subjective sensibility in one's performance in the interoceptive task, i.e., if someone has good interoceptive awareness, the level of their interoceptive accuracy (IA) will match their sensibility in their accuracy. Therefore, to investigate the potential influences of clinical disorders of intermittent cardiovascular (PoTS, AMS) and sudomotor (EH) autonomic overactivity on brain-body integration processes, such as interoception, **specific aim # 3 of this thesis** will;

I. assess somatic hypervigilance (anxiety attributable to fear and worry of bodily symptoms that are common in EH, AMS and PoTS) in AMS, EH and PoTS in comparison to controls.
II. assess empathy (an emotion influenced by interoception (Grynberg and Pollatos, 2015) that predicts autonomic arousal during emotional stimulation (Bogdanov et al., 2013) in AMS, EH and PoTS in comparison to controls to examine the potential influence of 'bottom-up' somatic perturbation on higher order affect.

III. define the subjective measure of interoceptive sensibility, objective measure of interoceptive accuracy and metacognitive measure of interoceptive awareness in AMS, EH and PoTS in comparison to healthy controls.

IV. assess HRV to examine autonomic variability and how this relates to brain-body integration in AMS, EH and PoTS in comparison to healthy controls from the perspective of 'neurovisceral phenotypes', which emphasises the importance of autonomic variability in emotion regulation.

These areas will be sequentially and systematically examined to attempt to construct a framework of neurovisceral architecture and how this may inform emotion and behaviour through homeostatic drives, in an attempt to elucidate the comorbid psychological symptoms that commonly present in EH, AMS and PoTS.

6.1. Methods

6.1.1. Participants

All experimental procedures were ethically approved by University College London Healthcare Trust Research and Design Office. The study was conducted in compliance with the Helsinki declaration (Bahit et al., 2013). 23 x healthy controls (13 females, mean age 35 $\pm$ 7.56 years) and 21 x PoTS patients (19 female, mean age 36 $\pm$ 10.84 years), 17 x EH patients (5 female, mean age 46 $\pm$ 13.26) and 16 x AMS patients (13 female, mean age 37 $\pm$ 13.00) were tested. Autonomic diagnoses were received from 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. Autonomic testing was carried at the Autonomic Unit, National Hospital for Neurology and Neurosurgery or Autonomic and Neurovascular Medicine Unit, St Mary's Hospital, national referral centres for cardiovascular and sudomotor dysautonomia.

6.1.2. Self-report measures

To record the prevalence of empathy and somatic hypervigilance, the following questionnaires were completed by the participants prior to testing. Mehrabian's Balanced Emotional Empathy Scale (BEES) records the subject's vicarious experience of another's emotional experiences. (Mehrabian, 1996).

The Body vigilance scale (BVS) examines the tendency to selectively attend to physiological changes in one's body (Schmidt et al., 1997).

6.1.3. Interoception protocol

Ambient temperature of the treatment room was maintained at 21°c throughout testing for all participants and hear rate (HR) and heart rate variability (HRV) were recorded using the PowerLab 16/30/ECG (Bioamp) (AD Instruments, Oxford, United Kingdom) and analysed using the Labchart 7 software package for the three experiments. Blood pressure (BP) was continually recorded using Finometer (Smart Medical, Gloucestershire, United Kingdom) and intermittent BP and HR measures were taken using Dinamap Pro400V2 (GE Healthcare, Buckinghamshire, United Kingdom).

6.1.3.1. Supine baseline interoception phase

Participants lay in the supine position for 10 mins to establish a baseline recording of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate variability (HRV) and heart rate (HR) before carrying out the heartbeat tracking task (Schandry, 1981) during the 3rd, 6th and 9th minutes of supine baseline, the participant was asked to carry out a heartbeat tracking task involving the individual being asked to silently count each individual heartbeat from when the experimenter said "start" to when he said "stop". Participants were instructed to manually take or touch their pulse and to declare that they couldn't feel their pulse pressing against any clothing or apparatus. This task was repeated two more time. Randomised epochs of the supine baseline mental tracking task were 25, 35 or 45 seconds. The choice of epoch was taken from previous studies using the mental tracking task that have identified the optimum task windows (Dunn et al., 2010, Pollatos et al., 2009). Immediately after each heartbeat tracking task once the number of counted heartbeats had been relayed to the researcher, the subject was asked to rate their confidence in the accuracy of their heartbeat counting on an analogue scale of 1 ('not confident at all/guessing') to 10 ('extremely confident/counted every beat'). This provided a rating of interoceptive sensibility.

6.1.3.2. Supine pressor interoception phase

Pressor exercises were carried out in the supine position, so that orthostatic demand does not confound the pressor responses. Pressor maneuverers are reliable and robust clinical

assessment of vasomotor integrity (RK Khurana, 1996, Mathias et al., 2013, Mathias, 2003). During isometric handgrip exercise (HG), the participants were requested to sustain a handgrip at 1/3 of maximum voluntary contraction pressure for 3 mins using a gauge directly in front of them. At 30, 88 and 144 seconds the participants performed the heartbeat tracking task. Randomised epochs of the HG mental tracking task were 21, 26, 36 seconds. After each task was performed, the subject was also required to give a confidence rating between 1 ('not confident at all/guessing') to 10 ('extremely confident/counted every beat') to provide a measure of interoceptive sensibility.

After the isometric exercise had been completed, a second baseline of a minimum of 3 mins elapsed allowing autonomic activity to return to baseline levels before the cutaneous cold pressor (CP) exercise was carried out. The subjects' right hand was placed in an icepack chilled to 4°C for a minimum of 90 seconds, tolerance permitting. At 3 seconds, 40 seconds and 54 seconds the participants performed the heartbeat tracking task. Interoceptive sensibility measures were taken for each task.

6.1.3.3. Head up tilt interoception phase

Cardiovascular autonomic activity was then allowed to return to baseline levels (minimum of 3 mins) before 10 mins 60° head-up tilt (HUT). In healthy subjects, the initial BP fall induced by HUT should recover within 60 seconds because when decreased venous return to the heart causes reduced stroke volume and cardiac output, arterial baroreceptors and cardiopulmonary mechanoreceptors then signal autonomic brain centres to increases SNA, raising HR and causing vasoconstriction of the blood vessels in various vascular beds to compensate for postural and gravitational demands At 3 minutes, 6 minutes and 9 minutes the participants performed the heartbeat tracking task. Randomised epochs of the heartbeat mental tracking task were 25, 35, 45 seconds. Interoceptive sensibility measures were taken for each task.

Interoceptive performance was analysed post-hoc by examining task and global interoceptive accuracy, interoceptive sensibility and interoceptive awareness. Interoceptive accuracy scores were yielded by counting the R waves in the event-marked ECG traces and averaging the following equation over the 3 tracking tasks of each stage of the protocol (supine baseline, HG, CP, HUT) and for global scores for the entirety of the experiment: $1 - (|n\text{beats}_{real} - n\text{beats}_{reported}|) / ((n\text{beats}real + n\text{beats}_{reported})/2)$.

Measures of global interoceptive awareness were taken from the participants' subjective appraisals (interoceptive sensitivity) of their heartbeat tracking task performance (interoceptive accuracy) during the experimental protocol. Interoceptive awareness scores were extracted by obtaining the *r* value of interoceptive accuracy and interoceptive sensibility.

6.1.4. Heart rate variability (HRV)

The high frequency (HF) band of heart rate variability (HRV) is a measure of vagal efferent activity and is comparable to RSA. Low frequency (LF) heart rate variability (HRV) was, until recently, believed to depict sympathetic cardiac influences (Malliani et al., 1991) however, LF power as a purely sympathetic measure has been called into question (Goldstein et al., 2011, Parati et al., 2006) as research has shown that endogenous fluctuations in LF power provide information about sympathetic regulation of BP, such as vasomotor tone and baroreceptor activity. Moreover, recent studies have positively correlated LF power and baroreceptor sensitivity (Goldstein et al., 2011, Moak et al., 2007) as well as reduced LF power and baroreflex-cardiovagal failure (Rahman et al., 2011). Therefore, LF power may well provide information about sympathetic mechanisms but perhaps not cardiac sympathetic nerve activity specifically but rather of baroreflex function and dysfunction. HRV was assessed post hoc for the baseline, pressor and HUT sections of the current study.

6.2. Results

6.2.1. Body vigilance scale (BVS)

The AMS patients reported being more sensitive to changes (p=.043) in their body and paid close attention to bodily sensations (p=.015). Interestingly, the cardiothoracic items of 'palpitations' (p=.176) and 'chest pain' (p=.225) were not significantly higher in PoTS patients who were found to dedicate the most attention to specific BVS items, and the EH cohort the least. AMS and EH patients were found to invest significantly more time scanning their bodies for symptoms (EH, p=.022, AMS, p=.045) and EH patients were found to be significantly more hypervigilant only in relation to thermoregulatory items ('sweaty/clammy hands' [EH, p=.000; PoTS, p=.014, AMS, p=.021) and 'hot flash' [EH, p=.003; PoTS, p=.025) (see figure 33).

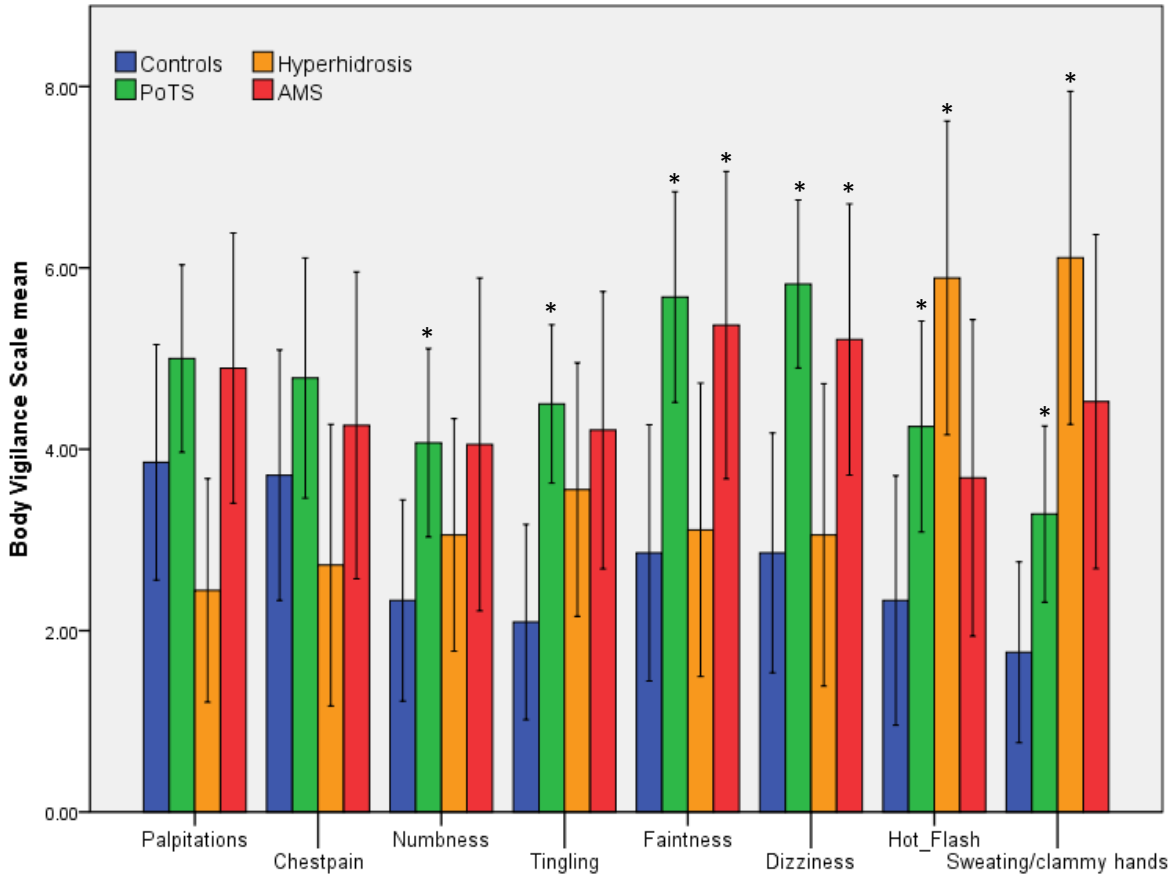


Figure 33. Body Vigilance Scale mean item scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic (neurally) mediated syncope (AMS) patients Vs healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

6.2.2. Empathy scores

There were no differences in overall empathy scores between the control and clinical groups. However, relative to controls, PoTS patients scored higher on the following BEES items, 'I can almost feel the pain of elderly people who are weak and must struggle to move about,' (*p*=.009), 'It really hurts me to watch someone who is suffering from a terminal illness.' (*p*=.039), and 'I would not watch an execution.' (*p*=.025). PoTS patients scored lower on the following BEES items, 'The unhappiness or distress of a stranger are (sic) not especially moving for me.' (*p*=.034), 'Helpless old people don't have much of an emotional effect on me.' (*p*=.030) and 'I am rarely moved to tears while reading a book or watching a movie.' (*p*=.048) (see figure 3).

AMS patients scored significantly higher on the BEES item, 'It upsets me to see someone being mistreated.' (*p*=.036) relative to controls.

Although the EH group produced the highest mean BEES score (EH: 16.3 ± 14.1 (*p*=.283, Controls: 11.3 ± 6.8, PoTS: 7.9 ± 15.1 (*p*=.217, AMS: 9.2 ± 15.4 (*p*=.894), they did not score significantly higher on any individual item (see figure 34).

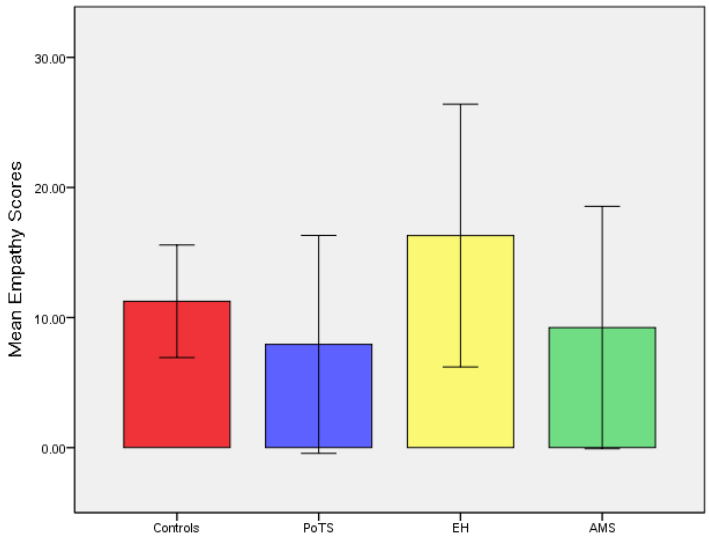


Figure 34. Balanced Emotional Empathy Scale mean global scores for postural tachycardia syndrome (PoTS), essential hyperhidrosis and autonomic-mediated syncope (AMS) patients Vs healthy controls. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

6.2.3. Interoceptive measures

6.2.3.1. Interoceptive accuracy (IA)

OI and EH patients consistently underestimated their heartbeats during testing. PoTS patients interoceptive accuracy was poorer during isometric exercise (*p*=.024) and cold pressor (*p*=.025) in comparison to healthy controls (see figure 35). EH patients interoceptive accuracy was poorer during baseline (*p*=.009), isometric exercise (*p*=.002) and HUT (*p*=.001) relative to controls. AMS patients interoceptive accuracy was also poorer during baseline (*p*=.049), isometric exercise (*p*=.033) and HUT (*p*=.048).

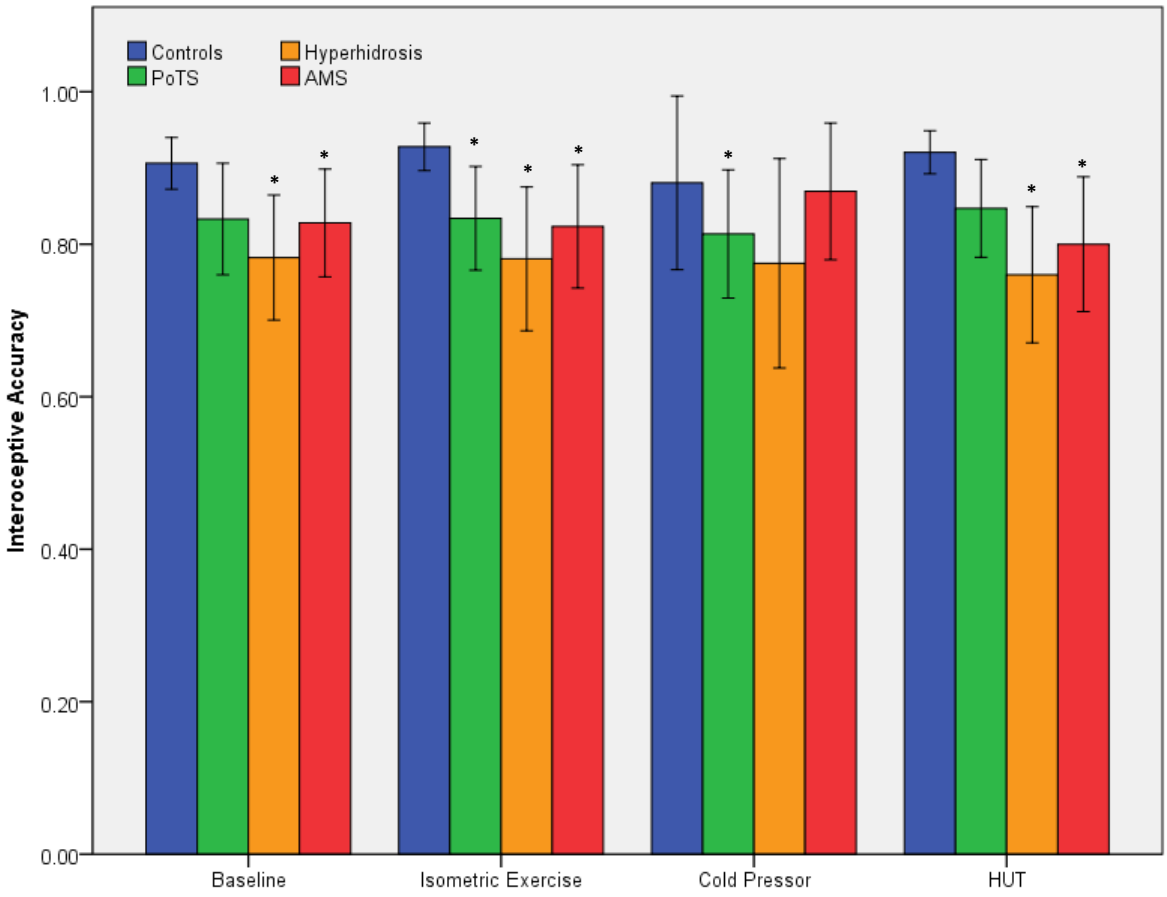


Figure 35. Interoceptive accuracy during supine baseline, isometric exercise, cold pressor and head up tilt (HUT). PoTS = postural tachycardia syndrome; EH = essential hyperhidrosis, AMS = autonomic (neurally) mediated syncope. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

6.2.3.2. Interoceptive sensibility

There were no between group differences in interoceptive sensibility at any stage of the protocol (see table 9).

Table 9. Group interoceptive sensibility scores at various stages of the protocol

	Supine Baseline	Isometric Exercise	Cold Pressor	Head-up Tilt
Controls	5.0 ± 4.5	4.0 ± 4.5	5.0 ± 2.3	3.7 ± 7.8
Postural Tachycardia Syndrome	5.2 ± 1.8	5.2 ± 1.8	4.5 ± 2.1	5.1 ± 1.7
Essential Hyperhidrosis	3.8 ± 2.4	3.6 ± 2.1	4.1 ± 2.4	4.2 ± 1.9
Autonomically Mediated Syncope	4.2 ± 2.1	3.9 ± 1.9	3.7 ± 1.7	3.9 ± 2.3

6.2.3.3 Interoceptive awareness

There were no between group differences in metacognitive interoceptive awareness (see table 10).

Table 10. Group interoceptive awareness scores.

Group	Interoceptive Awareness
Controls	.29 ± .37
Postural Tachycardia Syndrome	.22 ± .53
Essential Hyperhidrosis	-.05 ± .54
Autonomically Mediated Syncope	.22 ± .42

6.2.4. Emotion and interoception correlations

6.2.4.1. Somatic vigilance & interoception

In the healthy control group, baseline interoceptive accuracy was negatively correlated with the amount of time spent scanning their body for sensations (r_s= -.466, n= 19, *p*=.044), the attention paid to the sensations of 'tingling' (r_s= -.479, n= 19, *p*=.038), 'numbness' (r_s= -.558, n= 19, *p*=.013) and 'faintness' (r_s= -.456, n= 19, *p*=.050), 'choking' (r_s= -.460, n= 19, *p*=.048), 'nausea' (r_s= -.620, n= 19, *p*=.005), 'stomach upset' (r_s= -.503, n= 19, *p*=.028), sweaty and clammy hands' (r_s= -.506, n= 19, *p*=.027) and the total Body Vigilance Scale scores (r_s= -.459, n= 19, *p*=.048) (see table 3). Isometric exercise interoceptive accuracy was negatively correlated with the amount of attention paid to 'chest pain' (r_s= -.500, n= 19, *p*=.029) and HUT interoceptive accuracy was negatively correlated with the amount of attention paid to 'tingling' (r_s= -.500, n= 19, *p*=.035), 'stomach upset' (r_s= -.498, n= 19, *p*=.035) and 'faintness' (r_s= -.531, n= 19, *p*=.023). Both isometric and HUT interoceptive accuracy were negatively related to the amount of attention paid to 'vision changes' (isometric; r_s= -.559, n= 19, *p*=.013; HUT: r_s= -.490, n= 19, *p*=.039) and 'dizziness' (isometric; r_s= -.489, n= 19, *p*=.034; HUT: r_s= -.551, n= 19, *p*=.018) (see table 11).

There was a positive relationship between cold pressor interoceptive accuracy and the amount of attention PoTS patients paid to 'shortness of breath' (r_s= .616, n= 21, *p*=.003), 'dizziness' (r_s= .616, n= 21, *p*=.003), 'choking' (r_s= .607, n= 21, *p*=.004) and total Body Vigilance Scale scores (r_s= .453, n= 21, *p*=.039) (see table 11).

In AMS subject, the amount of time invested in scanning their bodies for symptoms was negatively correlated with supine baseline interoceptive accuracy and (r_s= -.564, n= 16, *p*=.023) and cold pressor interoceptive accuracy (r_s= -.642, n= 15, *p*=.010) (see table 11).

6.2.4.2. Empathy & interoception

In the control group, there was a significant negative relationship between baseline interoceptive accuracy and the BEES item 'It is difficult for me to experience strongly the feelings of characters in a book or movie,' (r_s= -.582, n= 15, *p*=.044) (see table 11).

In the PoTS cohort, there were significant negative relationships between baseline interoceptive accuracy and 'I cannot feel much sorrow for those who are responsible for their own misery' (r_s= -.526, n= 15, *p*=.044), 'I don't get overly involved with friends' problems,' (r_s= -.572, n= 15, *p*=.026), and 'The unhappiness or distress of a stranger is not especially moving for me', (r_s= -.587, n= 15, *p*=.021). A significant positive relationship between 'I am moved deeply when I observe strangers who are struggling to survive' and baseline interoceptive accuracy (r_s= .605, n= 15, *p*=.017) was also found (see table 11).

EH cold pressor interoceptive accuracy and the BEES item 'The unhappiness or distress of a stranger are not especially moving for me' was negatively correlated (r_s= -.747, n= 10, *p*=.013), whereas cold pressor interoceptive accuracy and 'Another's happiness can be very uplifting for me', were positively correlated (r_s= .651, n= 10, *p*=.042) (see table 11).

There were no correlations between BEES and interoceptive measures in the AMS group.

	Supine Baseline Interoceptive Accuracy	Isometric Exercise Interoceptive Accuracy	Cold Pressor Interoceptive Accuracy	HUT Interoceptive Accuracy
Controls	-Time scanning - Numbness - Tingling - Faintness - Choking - Nausea - Stomach upset - Sweaty clammy hands - Total Body Vigilance Scale score	- Chest pain - Vision changes - Dizziness		- Tingling - Faintness - Stomach upset - Vision changes - Dizziness
	- It is difficult for me to experience strongly the feelings of characters in a book or movie			
PoTS	- I cannot feel much sorrow for those who are responsible for their own misery + I am moved deeply when I observe strangers who are struggling to survive - I don't get overly involved with friends' problems - The unhappiness or distress of a stranger is not especially moving for me.		+ Choking + Dizziness + Shortness of breath. + Total body vigilance scores	
EH			+ Another's happiness can be very uplifting for me - The unhappiness or distress of a stranger is not especially moving for me.	
AMS	-Time scanning		-Time scanning	

Table 11. Body vigilance and empathy correlations with interoceptive accuracy. PoTS = postural tachycardia syndrome; EH = essential hyperhidrosis, AMS = autonomic (neurally) mediated syncope.

6.3. Heart rate variability profiles

During the interoception protocol, PoTS patients LF power (*p*=.045), indicating sympathetic (via baroreflex function) and vagal activity, and HF power (*p*=.030), indicating parasympathetic (vagal) nerve function, were significantly reduced during HUT (see table 12). EH patients LF power (*p*=.042) and HF power (*p*=.046) were also reduced during HUT. AMS patients produced a reduction in LF power (*p*=.013) only during HUT.

Table 12. Heart rate variability profiles during testing. PoTS = postural tachycardia syndrome; EH = essential hyperhidrosis, AMS = autonomic (neurally) mediated syncope. Error bars = +/- standard deviation, * = statistically significant (*p*=.05)

	Supine baseline	Isometric exercise	Cold pressor	HUT
Controls	LF: 4274.74 ± 5111.70 HF: 2480.12 ± 1935.96 LF/HF: 1.69 ± 0.81	LF: 1550.03 ± 1423.20 HF: 1509.11 ± 2205.23 LF/HF: 4.08 ± 11.07	LF: 4164.89 ± 7052.03 HF: 2446.63 ± 3766.44 LF/HF: 2.29 ± 1.89	LF: 3049.96 ± 2337.62 HF: 1409.27 ± 1186.36 LF/HF: 3.07 ± 2.63
PoTS	LF: 6982.36 ± 10403.18 HF: 4338.44 ± 1935.96 LF/HF: 1.90 ± 1.16	LF: 2792.79 ± 6763.06 HF: 1662.65 ± 2963.18 LF/HF: 1.61 ±1.05	LF: 6020.67 ± 10678.52 HF: 3855.06 ± 6793.70 LF/HF: 2.33 1.75	LF: 1410.46 ± 1211.28* HF: 887.93 ± 3256.28* LF/HF: 4.19 ± 3.75
EH	LF: 3109.65 3919.12 HF: 1957.20 ± 2158.35 LF/HF: 1.70 1.15	LF: 2981.8378 ± 9073.36863 HF: 1743.6891 ± 3802.59247 LF/HF: 2.39 ± 1.84	LF: 1757.55 ± 2153.61 HF: 3181.58 ± 5658.50 LF/HF: 2.42 ± 2.49	LF: 1778.78 ± 2004.13* HF: 984.40 ± 1433.92* LF/HF: 3.78 ± 3.13
AMS	LF: 4688.10 ± 7116.17 HF: 3749.40 ± 6775.03 LF/HF: 1.72 ± .91	LF: 960.00 ± 880.14 HF: 1044.78 ± 1276.50 LF/HF: 2.38 ± 2.52	LF: 7167.07 ± 13818.53 HF: 4141.47 ± 7754.45 LF/HF: 2.68 ± 2.53	LF: 1554.77 ± 1309.08* HF: 1599.70 ± 2167.32 LF/HF: 2.87 ± 3.77

6.3.1. Heart rate variability, interoception & emotion

The heartbeat tracking task measures cardiac interoception yet, despite neuroimaging studies that have identified the neural correlates of conscious interoception (Critchley et al., 2004), the peripheral mechanism for conscious cardiac interoception remains less well-defined (Cameron, 2009). Therefore, the relationship between sympathetic and parasympathetic activity and balance and how these variables relate to subjective, objective and metacognitive interoceptive measures may clarify the visceral and psychological pathways of interoception its influence on homeostatic and high order functions, which, in turn, may improve understanding of the comorbid psychological symptoms in PoTS, EH and AMS.

In the control group, baseline interoceptive sensibility was positively related to baseline LF power (r_s= .816, n= 18, *p*=.000) and HF power (r_s= .676, n= 18, *p*=.002). Isometric exercise

interoceptive sensibility was positively related to isometric exercise LF power (r_s= .523, n= 17, *p*=.031) and HF power (r_s= .573, n= 17, *p*=.016). Cold pressor interoceptive accuracy was positively correlated with cold pressor HF power (r_s= .504, n= 17, *p*=.039*). Total body vigilance scale (BVS) scores were positively correlated (r_s= .474, n= 19, *p*=.040*) with supine baseline LF/HF ratio (see table 13).

In the PoTS cohort, cold pressor interoceptive sensibility and cold pressor LF/HF ratio were negatively related (r_s= -.727, n= 9, *p*=.027). HUT interoceptive accuracy was negatively related to HUT HF power (r_s= -.457, n= 9, *p*=.043). Interoceptive awareness was positively correlated with cold pressor LF power (r_s = .689, n= 11, *p*=.019) and HF power (r_s = .648, n= 11, *p*=.031). Total body vigilance scale (BVS) scores were negatively correlated with HUT LF power (r_s = -.510, n= 20, *p*=.022) and HF power (r_s = -.519, n= 20, *p*=.019) (see table 13).

In the EH group, supine baseline interoceptive sensibility was positively correlated with baseline LF power (r_s= .580, n= 13, *p*=.038) and HUT interoceptive sensibility was negatively correlated to HUT LF power (r_s= -.635, n= 13, *p*=.020) and HF power (r_s= -.566, n= 13, *p*=.044) (see table 13).

In the AMS group of subjects, HUT interoceptive accuracy was negatively related to HUT HF power (r_s= -.658, n= 13, *p*=.015). Isometric exercise interoceptive sensibility was positively related to isometric exercise LF power (r_s= .556, n= 13, *p*=.049). Interoceptive awareness was positively correlated with baseline LF/HF (r_s= .738, n= 12, *p*=.006) and HF power during isometric exercise (r_s= .635, n= 11, *p*=.036) (see table 13).

Table 13. Body vigilance and empathy, interoceptive and heart rate variability (HRV) correlations. PoTS = postural tachycardia syndrome; EH = essential hyperhidrosis, AMS = autonomic (neurally) mediated syncope.

	Supine Baseline HRV	Isometric Exercise HRV	Cold Pressor HRV	HUT HRV
Controls	+Interoceptive sensibility/LF-HRV +Interoceptive sensibility/HF-HRV +Total body vigilance/LF/HF	+Interoceptive sensibility/LF-HRV +Interoceptive sensibility/HF-HRV	+Interoceptive accuracy/HF-HRV	
PoTS			-Interoceptive sensibility/LF/HF +Interoceptive awareness/LF-HRV +Interoceptive awareness/HF-HRV	-Interoceptive accuracy/HF-HRV -total body vigilance/LF-HRV -total body vigilance/HF-HRV
EH	+Interoceptive sensibility/LF-HRV		-Interoceptive accuracy/LF-HRV	-Interoceptive sensibility/LF-HRV -Interoceptive sensibility/HF-HRV
AMS	+Interoceptive awareness/HF-HRV	+Interoceptive awareness/HF-HRV		-Interoceptive accuracy/HF-HRV

6.4. Discussion

This study examined brain-body integrative processes in patients with clinical disorders that cause intermittent but recurrent overactivity of the autonomic nervous system (ANS). This was undertaken by firstly examining vigilance of autonomic symptoms and empathy – an emotion highly related to interoception - in EH, AMS and PoTS patients in comparison to controls. Next, interoceptive accuracy, sensibility and awareness were examined in patients in comparison to controls and how these factors interacted with vigilance of physical events and empathy were analysed. Finally, heart rate variability (HRV) was studied, particularly high frequency HRV (HF-HRV) which is a measure of vagal (parasympathetic) tone. These objectives were established because (i) of the contribution the ANS makes to emotion - particularly somatic anxiety and empathy, (ii) the prevalence of anxiety in postural tachycardia syndrome (PoTS) (Benrud-Larson et al., 2003), essential hyperhidrosis (EH) (Karaca et al., 2007) and autonomic mediated syncope (AMS) and (iii) because of previous research that has proposed reduced HRV in anxious subjects as perpetuating sympathoexcitation and anxiogenesis. These investigations were designed to identify the contributing factors of the overrepresentation of anxiety symptoms in PoTS, AMS and EH from the perspective of brain-body integration via the ANS.

6.4.1. Body vigilance findings

The PoTS group were found to have higher global BVS scores and the AMS groups spent more time scanning their body for symptoms. Specific physical symptoms that were increased in the AMS (faintness, dizziness, sweaty/clammy hands) and EH (sweaty/clammy hands, hot flash) groups were directly symptom-related, whereas the symptoms PoTS patients spent more time scanning for than controls were related to pre-syncope (dizziness, faintness, sweaty/clammy hands) and neuropathic (tingling, numbness) symptoms, though curiously not the cardio-thoracic items of palpitations and chest pain.

The fact that AMS patients reported being significantly more sensitive and paid more attention to changes in their body can be viewed from a homeostatic perspective, in consideration that these symptoms can often be a somatic marker of an imminent syncopal episode, therefore warning for the need of contingent behaviour to avoid trauma.

The pre-syncope and neuropathic symptoms the PoTS group were hypervigilant of may be reflective of the broader pathophysiological factors in neuropathic and hyperadrenergic PoTS phenotypes. The finding that PoTS patients did not report hypervigilance of palpations and

chest pain, though initially counterintuitive, does support the findings of the only other study to investigate cardiac interoception in PoTS, which found that the interoception of palpations was separate to that of tachycardia (Khurana, 2014). However, in the current data, palpitations were not self-reported as being prevalent either. The current data reinforce this conclusion as the non-cardiothoracic BVS symptoms that related to orthostatic intolerance (OI) were reported to be the subject of somatic hypervigilance by the PoTS group.

Overall, global somatic hypervigilance was higher in PoTS and its reporting in EH and AMS patients related directly to their conditions. Although AMS patients were reported to be more vigilant and sensitive to changes in their body, this may be justifiable to a certain extent due to the syncope-related trauma they may suffer if these symptoms become too pronounced and a syncopal episode occurs.

6.4.2 Empathy findings

There were no group differences in global empathy scores. PoTS patients scored more highly on 5 questionnaire items, three of which related to physical frailty and infirmity. The role of autonomic arousal in empathy has been established, which is why it was of interest to ask patients with autonomic overactivity to complete the Balanced Emotional Empathy Scale (BEES). However, the questionnaires were undoubtedly completed in a restful state and the current data may have differed if autonomic symptoms had been provoked during empathy reporting.

6.4.3 Interoception findings

Subjects with anxious 'Type A' personalities have been found to consistently overestimate their heartbeats (Essau and Jamieson, 1987), yet interoceptive accuracy was diminished in the patients groups despite their increased somatic anxiety, with EH, PoTS and AMS patients consistently underestimating their heartbeats. These findings compliment the questionnaire survey data in chapter 5 of this thesis, in that the anxiety-related phenomena in autonomic patients is not typical of anxiety only patients but rather appears to be mostly defined by visceral factors. However, there were no between-group differences in interoceptive sensibility or interoceptive awareness. PoTS interoceptive accuracy was significantly diminished during isometric exercise and cold pressor and AMS and EH interoceptive accuracy was significantly diminished at supine baseline, isometric exercise and HUT.

As PoTS patients' heart rate (HR) increased and OI was provoked on HUT, it is noteworthy that neither their interoceptive accuracy nor sensibility increased. One peripheral explanation of this could be that conscious cardiac interoception may involve mechanoreceptors in more than one location, not only those located in the heart.

EH and AMS interoceptive accuracy was significantly diminished during supine baseline, isometric exercise and HUT, yet PoTS interoceptive accuracy was significantly diminished during both pressor exercises only. In EH, the autonomic disorder is thermoregulatory and predominantly causes sudomotor overactivity, whereas AMS and PoTS are forms of OI and therefore predominantly involve intermittent breakdown of baroreflex arcs and cardiovascular autonomic dysfunction. Yet all three clinical autonomic cohorts consistently underestimated their heartbeats and EH and AMS in particular had identical profiles. This points towards the involvement of a common central dysregulation causing these interoceptive findings, as both sudomotor and cardiovascular forms of autonomic dysfunction have comparable interoceptive deficits.

Despite a lack of neuroimaging studies into OI, Umeda et al., (Umeda et al., 2015) recently evidenced left insula volume reductions in 11 PoTS patients that correlated with affective symptoms. Reduced right insula volumes in 32 AMS patients have recently been correlated with BP falls on HUT (Kim et al., 2014). This implication of the insula (interoceptive, nociceptive and autonomic centre) in OI 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), as evidenced by increased anterior and posterior insula activity during isometric exercise and Valsalva manoeuvre (King et al., 1999) (Harper et al., 2000). Activation of the insula cortex, particularly the right, correlates with interoceptive accuracy and anxiety in healthy controls (Critchley et al., 2004). The right insula depicts internal bodily state that can be consciously accessed. Sympathetic responses are lateralized to the right hemisphere (Oppenheimer et al., 1992) and the left insular cortex is involved in parasympathetic cardiovascular regulation, e.g., acute left insular stroke disrupts the correlation between HR and BP (Oppenheimer et al., 1996).

As with orthostatic intolerance (OI), there is a lack of brain imaging literature on EH. However, in healthy controls, a relationship between arousal-induced sympathetic skin responses (SSRs) and activation of the right anterior insula exists as well as the right orbitofrontal cortex and right anterior insula, confirming right hemisphere sympathetic lateralization (Critchley et al., 2000b).

If we consider interoception from a Bayesian (maximization of expected utility) perspective, active inference refers to neural representations based on previous experience (Clark, 2013, Friston and Frith, 2015) and may help explain why the three dysautonomia patient groups consistently underestimated their heartbeats. Moreover, the mechanisms of how interoceptive error code predications of expected versus received bodily events are generated within in the lamination gradients of corticocortical pathways (Barbas and Rempel-Clower, 1997) also offers a possible framework for the cognitive-affective symptoms in the EH and OI patients. Active inference accounts propose that should a prediction error (variation between the brain's prediction and the actual incoming afferent signal) become too large and thereby disrupt the maintenance of homeostatic processes, the prediction can be modified by retrogradley propagating the signal back, by engaging allostatic measures to more closely meet the original incoming afferent signal or by altering how the brain regards the incoming afferent signal (Mesulam, 1998). This third predication error modification may explain why the EH and OI patients underestimated their heartbeats at rest and during autonomic arousal and, in the case of AMS and PoTS patients, symptom provocation.

Cardiac interoception may have been underestimated by the clinical cohorts due to cognitive control networks (Seeley et al., 2007) altering the weight of various afferent inputs. This may also explain why PoTS patients did not report palpations and chest pain as symptoms of somatic hypervigilance. This demand on cognitive control networks may also contribute to the previously reported cognitive difficulties in PoTS (Raj et al., 2009, Ross et al., 2013, Ocon, 2013) and help clarify why EH, AMS and PoTS patients reported significant symptoms of indecisiveness and difficulty in concentrating in the previous chapter (5) of this thesis. Autonomic arousal is integrated with decision-making, as reflected by activation of the 'Default Mode Network', particularly the dorsal anterior cingulate cortex during risk assessment and HR increases during anticipation of the outcome and also outcome feedback of gambling (Coricelli et al., 2005).

These neuroimaging studies tested healthy controls to discover the influence of ANS activity on the brain during decision-making, but we can speculate on what may happen during decision-making in patients with EH, AMS and PoTS, especially when symptomatic. Autonomic reactivity indicates the behavioural salience of an object, this reactivity is generated via interoceptive signals that are received via the spinal cord, the lamina I spinothalamocortical pathway in particular, are gated by the brainstem and ultimately integrated with cognitive-affective process in the right anterior insula (Critchley et al., 2004). Damasio and colleagues have reported how behaviour is influenced by this interoceptive feedback to maximise reward and avoid punishment (Damasio et al., 1991, Bechara et al., 1997a). Therefore, it is reasonable to assume that if this interoceptive feedback of increased autonomic activity is too noisy or causes large prediction errors requiring alterations in how the brain attends to interoceptive

signals that inform behavioural learning, then cognitive and attentional difficulties will occur, at least during dysautonomic symptom provocation. This study and that in the previous chapter (5), suggests these deficits may occur at rest also, perhaps due to the conditioning of brain-body integrative processes over time.

Sudomotor and cardiovascular autonomic disorders appear to have comparable deficits in interoceptive accuracy but not interoceptive sensibility or awareness. Recent neuroimaging studies in OI and psychophysiological studies of the neural correlates of SSRs suggest that these interoceptive deficits may, at least in part, be mediated by the central autonomic network, particularly the insula. However, functional neuroimaging studies of the central autonomic network in AMS, PoTS and EH are required.

6.4.4 Emotional & interoceptive integration

Somatic vigilance was used in the current study as an emotional variable of interoception and anxiety of ANS activity. Empathy is an interoceptively influenced emotion. To test the relationship between somatic vigilance, empathy, the ANS and interoception using clinical autonomic techniques, it was intended that further insight into brain-body integration could be gained in healthy controls and also to explore any potential effects of neurovisceral disruption by intermittent ANS dysfunction, in this case, cardiovascular (PoTS, AMS) and sudomotor (EH).

In healthy controls, interoception appeared to be working correctly as the more interoceptively accurate controls were at rest (supine baseline) and during autonomic arousal (isometric exercise and HUT), the less time they reported spending scanning their body for symptoms of sympathoexcitation, indicating interoception's modulatory homeostatic role. This pattern of association was reversed in the PoTS cohort. The more interoceptively accurate PoTS subjects were during cold pressor, the more time they reported investing in scanning their bodies in general and for PoTS-related symptoms, suggesting that interoception appears to be anxiogenic rather than homeostatic in this cohort.

The BVS survey data alone found that cardiothoracic symptoms were not the target of somatic hypervigilance in PoTS, yet the symptoms associated with interoceptive accuracy in PoTS were not only primary symptoms of PoTS (dizziness, shortness of breath, choking), but the relationship of hypervigilance of these symptoms with interoceptive accuracy was positively related, again suggesting that interoception may be involved in somatic anxiety rather than homeostasis in PoTS. Conversely, in controls, global and individual items of somatic vigilance were negatively

correlated with interoceptive accuracy, suggesting that interoceptive accuracy was not somatically anxiogenic, yet in the PoTS cohort, cold pressor interoceptive accuracy and global and PoTS-related somatic hypervigilance were positively related. This could be interpreted as a breakdown of neurovisceral integration in PoTS subjects, where interoceptive accuracy appears to be more aligned with somatic anxiogenesis rather than homeostasis, as is the case in controls.

In the other group of OI participants included in the study, AMS interoceptive accuracy was negatively correlated with the amount of time spent scanning one's body for symptoms, a profile comparable to controls and normative neurovisceral integration in that accurate interoception is not anxiogenic. There were no correlations between the body vigilance scale (BVS) and interoceptive measures in the hyperhidrotic cohort.

In healthy controls, poor interoceptive accuracy was associated with reduced empathy but only in a single questionnaire item, not in global Balanced Emotional Empathy Scale (BEES) scores. PoTS and EH items and interoceptive accuracy appear to be correlated as previous research in healthy controls (Fukushima et al., 2011) would predict, i.e., better interoceptive accuracy is negatively related to reduced empathy. In autonomic disorders, empathy is normal, body vigilance and it's interaction with interoception is not.

6.4.5 Heart rate variability, emotional & interoceptive integration

Amongst controls, baseline and isometric exercise interoceptive sensibility were positively related to greater HRV in high and low frequency bands, suggesting subjective interoception parameters are related to greater parasympathetic and baroreflex activity, seemingly reflecting normative brain-body integration, i.e., greater confidence in the awareness of one's homeostatic state positively correlated with cardiovascular autonomic adaptability. Controls' total body vigilance scores were also positively correlated with sympathetic dominance of the LF/HF ratio at baseline, further supporting previous research findings that sympathoexcitation perpetuates anxious mood and cognitive states, as demonstrated by Pollatos and co-workers (Pollatos et al., 2007), who found that subjects with high reactivity during isometric exercise had greater interoceptive accuracy and trait anxiety.

The positive association between controls' interoceptive accuracy and parasympathetic activity during the thermoregulatory and nociceptive stressor of the cold pressor test supports the view that thermoregulation and nociception could be considered as part of the interoception system that maintains homeostasis rather than 'exteroceptive' senses. This is

sustained by the association between interoceptive accuracy and autonomic adaptions during cold pressor and the recent findings that thermoception and nociception interact as part of interoceptive homeostasis during heat and cold stress (Alfonsi et al., 2015).

No relationships were identified between HRV on HUT and interoceptive measures in controls. This is unsurprising in consideration that interoceptive accuracy is both higher in anxious individuals (Pollatos et al., 2009, Dunn et al., 2010) and also at supine rest in controls (Cameron, 2009) when minimal allostatic demand cannot confound viscerosensory perception. Together, these findings in the control group provide further evidence that increased basal sympathetic outflow is positively related to interoceptive accuracy and sub-clinical somatic anxiety, that subjective (interoceptive sensibility) and objective (interoceptive accuracy) measures of interoception may relate to autonomic cardiovascular flexibility and that interoception is a homeostatic regulator of multimodal afferent feedback.

In PoTS participants, LF reduced during HUT when tachycardia was provoked, lending further evidence to the view that LF power is not just a measure of cardiac sympathetic nerve activity (Goldstein et al., 2011). Positive correlations were found between cold pressor HRV and interoceptive awareness. Interoceptive sensibility was negatively correlated with cold pressor LF/HF ratio, i.e., subjective interoceptive confidence correlated to parasympathetic dominance of the LF/HF ratio which may relate to reduced activation of cardiac, thoracic or cutaneous mechanoreceptors sensing of cardiac activity. This finding was complimented by the negative correlation between interoceptive accuracy and HUT HF power, i.e., objective interoceptive accuracy decreased with parasympathetic tone during provocation of orthostatic intolerance (OI).

Previous research has found cardiovascular arousal increases interoception (Schandry et al., 1993), yet the opposite appears be true of OI and EH patients on tilt.

As with controls at rest, the EH group's subjective measure of interoceptive sensibility positively related to baseline HRV. EH interoceptive accuracy negatively related to cold pressor sympathetic and parasympathetic HRV, also complimenting the cold pressor data in controls. As with the PoTS cohort, EH global body vigilance scales were negatively correlated with HUT LF and HF HRV power. Subjective interoceptive sensibility was also negatively correlated with HUT HRV, a similar pattern of aberrant bran-body interaction as the PoTS group.

The AMS group's LF power reduced during HUT, in line with previous research also finding reduced LF power on HUT in comparison to baseline in AMS patients (Prinz-Zaiss et al., 1995, Shim et al., 2014). Similar to control baseline measures, AMS interoceptive measures were positively related to HRV, particularly parasympathetic HRV, at rest and during isometric exercise. As with the other OI cohort (PoTS), AMS interoceptive accuracy on tilt was negatively related to HUT HF-HRV, reiterating the argument that symptom provocation on tilt may impair interoception in OI.

LF power was reduced in all three patient groups and HF power was also reduced in EH and PoTS subjects during HUT. Previous research using HRV to investigate neurovisceral integration would argue that this would be reflected in a predisposition for physical sympathoexcitation and anxiogenic thought processes in these groups. In the instance of EH, AMS and PoTS, the sympathetic and parasympathetic overexcitation in EH, PoTS and AMS is due to primary dysautonomia, however, the positive correlation between controls' body vigilance scale (BVS) scores and sympathetic dominance of the LF/HF ratio at baseline provides further evidence of disrupted neurovisceral integration in dysautonomia.

In the current BVS data, the chapter 5 questionnaire surveys and previous research, EH (Karaca et al., 2007), PoTS (Benrud-Larson et al., 2003) and AMS (McGrady et al., 2001) patients have been found to be significantly more anxious than controls. In chapter 5 and the current study this anxiety is mostly attributable to somatic anxiety, hypervigilance and interoception of dysautonomic symptoms that are similar to physical manifestations of acute anxiety and panic. Anxious individuals, e.g., Type A, have increased interoceptive accuracy and also overestimate their heart rate but in this study of patients with primary autonomic disorders of intermittent over-activation, although patients were more (somatically) anxious, they also significantly underestimated their heartbeats, this may be attributable to changes to afferent pathways at rest in EH and AMS and also during autonomic arousal in EH, AMS and PoTS.

The negative correlations of interoceptive measures and HUT HRV could be interpreted as a further breakdown of brain-body integration, particularly as there were no HUT HRV correlations with affective or interoceptive parameters in the control group. Metacognitive measures provide insights into high-order executive processes (Thompson and Thompson, 1998). The diverging findings of negative correlations between HUT HRV and subjective (EH) and objective (AMS, PoTS) interoception findings in comparison to the positive correlations between supine baseline and pressor HRV and metacognitive interoceptive measures in PoTS and AMS patients may relate to previous evidence of higher order cognitive differences in OI patients (Raj et al., 2009, Ross et al., 2013), and may elucidate why OI patients reported significant (PoTS (p=.000), AMS (p=.008), EH (p=.005)) attentional difficulties in the chapter 5

survey data. The fact that EH patients cognitive and interoceptive measures are also attenuated points towards a common pathophysiological pathway(s) in sudomotor and cardiovascular autonomic disorders, perhaps accounting for the common presentation of anxiety in all three patient groups. Moreover, it may also provide some support to how, in patients with intermittent autonomic disorders, metacognitive higher order and cognitive processes have become associated with visceral activity via a dysfunctional autonomic nervous system.

6.4.6. Summary of key findings

This study investigated interoception in EH, AMS and PoTS in comparison to healthy controls. It also was designed to examine the potential interrelationship between emotion, interoception and autonomic variability, concluding that;

- Interoception was reduced in all three patient groups, potentially due to a common central dysregulation of interoception
- Interoception appears to be anxiogenic rather than homeostatic in EH, AMS and PoTS.

6.4.6 Conclusions

Autonomic patients consistently underestimated their cardiac activity, even during autonomic arousal, despite having increased levels of somatic anxiety. Diminished interoception may be due to a common central dysregulation, such as interoceptive error code predictions, as both sudomotor and cardiovascular forms of autonomic dysfunction had comparable interoceptive accuracy deficits. Recent neuroimaging studies in OI also suggest that these interoceptive deficits may, at least in part, be mediated by the insula. From a peripheral perspective, the PoTS interoceptive accuracy data suggests conscious cardiac interoception could involve non-cardiac mechanoreceptors. In PoTS, AMS and EH, interoception appears to be anxiogenic, as opposed to its homeostatic role in controls. Interoception of excessive autonomic activity that should inform behavioural learning causes large prediction errors requiring alterations in how interoceptive signals are attended to, potentially contributing to the cognitive and attentional difficulties reported in chapter 5. Should this be true, it would provide further evidence for Stein and Paulus' (Paulus and Stein, 2006) interoceptive view of anxiety and Antonio Damasio's 'somatic marker hypothesis' (Damasio, 1999) that discrepancies and aberrations in interoceptive expectations are somatic sources of anxiety and disrupt cognition. This may be a possible therapeutic pathway for psychological symptoms in autonomic disorders and potentially of therapeutic use in panic disorder.

Chapter 7. Supine & orthostatic orienting responses & cardiac interoception in orthostatic intolerance

7. Introduction

Despite the inconsistencies in defining emotion-specific autonomic signatures (Hodgson and Rachman, 1974, Rachman and Hodgson, 1974, Kreibig, 2010), a reliable and robust early response to a novel stimulus, especially unpleasant, is cardiac deceleration (Fanselow, 1994). Cardiac deceleration is a peripheral component of the 'orienting response' (OR), which is a series of involuntary sensory, motor and autonomic adjustments (see figure 36) that occur in response to an emotionally salient stimulus to '*increase analyser sensitivity*' (Sokolov, 1963a).

The OR is differentiated from the cardiac defence response (CDR) by the cardiac deceleration during the OR to a moderate or novel stimulus facilitating attention and perception of the stimulus. In contrast, the defining cardiac acceleration during the CDR to an intense or aversive stimulus reduces attention and perception to protection against the stimulus (Pavlov, 1927a, Sokolov, 1963b, Fernandez and Vila, 1989). It is widely accepted form psychophysiological research that the OR is therefore the opposite of the CDR. The issue of stimulus intensity has received empirical support (Turpin, 1986), however, there is no formal definition or criteria on the level of stimulus intensity that differentiates ORs from CDRs, neither have any studies investigated the effect of intensity in different sensory modalities.

Originally believed to be a unitary reflex (Sokolov, 1963a), subsequent studies have evidenced that the electroencephalogram (EEG) and respiratory components of the OR represent novelty, peripheral vasoconstriction ORs reflect stimulus intensity and cardiac deceleration indicates stimulus detection (Barry, 2009). Greater ORs are proposed to represent greater emotional significance of the stimulus and greater interoceptive accuracy (IA) is associated with increased emotional experience (see Interoception in emotion, cognition & homeostasis), therefore, it is possible that a relationship may exist between IA and ORs and could provide an insight into holistic brain-body integration. However, this has not yet been investigated.

The non-muscular visceral components of the OR are autonomically mediated but there have been no investigations into whether dysautonomia affects ORs or subsequent emotion formation and behaviour. This is worthy of investigation because the functional and organ-specific autonomic patterns that maintain homeostasis are intermittently compromised in orthostatic intolerance (OI). In addition, many of these patients report comorbid affective,

psychological symptoms (see Palpations, dizziness, tremulousness: the postural tachycardia syndrome endophenotype of anxiety and Dizziness, nausea, dissociation: the vasovagal syncope endophenotype of anxiety) (Heims et al., 2006a, Guaraldi et al., 2014, Ross et al., 2013, Ocon et al., 2009b, Stewart et al., 2012).

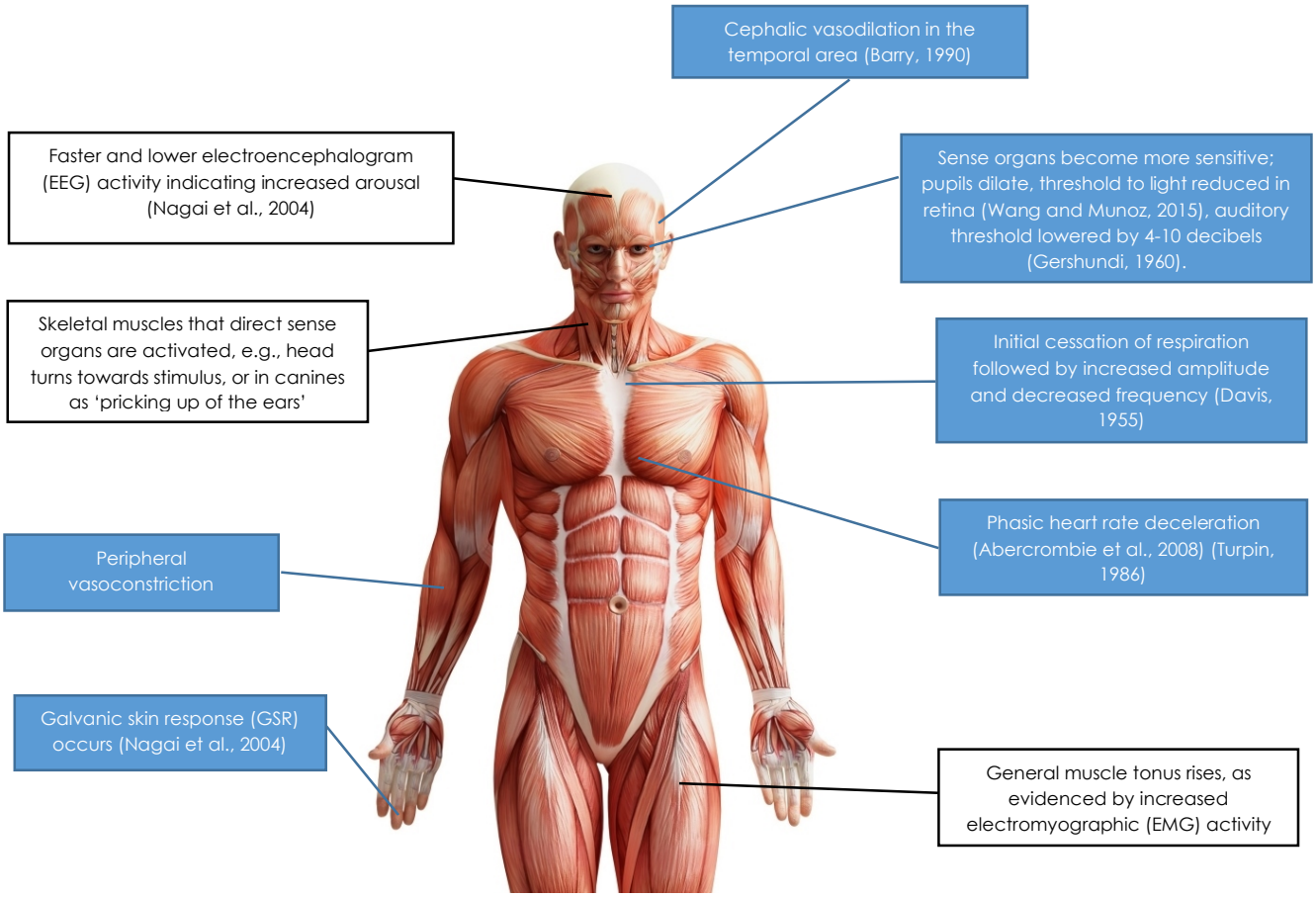


Figure 36. Central and visceral correlates of the orienting response (OR). Blue = autonomically mediated OR components.

From a clinical perspective, some unanswered questions remain, such as; (i) how do ORs compare at supine rest and during orthostasis between healthy controls and in patients with compromised baroreflex function, particularly as the two main forms of OI, PoTS and AMS (Freeman et al., 2011b) have an over-representation of comorbid cognitive-affective symptoms, such as anxiety (Raj et al., 2009, Cohen et al., 2000a) depression (Lee et al., 2013) and ill-defined 'brain fog' (Ocon et al., 2009b, Ross et al., 2013, Ocon et al., 2009a) (see also chapter 5 of this thesis)? (ii) Would investigating the possible relationship between IA and ORs provide an insight into brain-body integration or of these patients' common comorbid psychological symptoms, as greater ORs are proposed to represent greater emotional significance of the stimulus and greater IA is associated with increased emotional experience? Therefore, **Specific aim # 4 of this thesis will investigate**;

(i) the effects of orthostatic stress on ORs in PoTS and AMS in comparison to controls to examine the influence (if any) of dysautonomia-related dysregulated ORs

(ii) explore any interactions between ORs and IA in controls and OI.

7.1. Methods

7.1.1. Participants

Healthy control participants (20; 10 females, mean age 36 ± 8 years), PoTS patients (20; 18 females, mean age 38 ± 13 years) and AMS patients (16; 14 females, mean age 39 ± 12 years) were recruited for the study. Autonomic diagnoses were received from 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 and verbal informed consent was provided by all participants prior to participation. Autonomic testing was carried at the Autonomic Unit, National Hospital for Neurology and Neurosurgery or Autonomic and Neurovascular Medicine Unit, St Mary's Hospital; both national referral centres for cardiovascular and sudomotor dysautonomia.

Ambient temperature of the laboratory was maintained at 21°C throughout testing for all participants and heart rate (HR) and heart rate variability (HRV) were continuously recorded online (PowerLab 16/30; ECG Bioamp, AD Instruments, Oxford, United Kingdom) and analysed offline (Labchart 7 software). Blood pressure (BP) was continually recorded using digital photoplethysmography (Finometer, Smart Medical, Gloucestershire, United Kingdom) and intermittent BP and HR were also recorded (Dinamap Pro400V2, GE Healthcare, Buckinghamshire, United Kingdom). Visual emotional stimuli were synchronised with beat-to-beat data using the Superlabs Stim Tracker (Cedrus Corporation, USA).

7.1.2. Experimental procedures

7.1.3. Orienting responses (OR)

After an 10-15 mins supine baseline, participants were requested to look at a screen 1 metre from their head and informed that they were about to be shown a series of images and that during all images that they should keep their eyes fixed on the screen but not say anything. Cardiac and peripheral vascular ORs were recorded and analysed post hoc. Participants were then presented with one of two randomly selected sets of images taken from the International Affective Picture System (IAPS). Image set 1 consisted of 12 neutral images, 13 unpleasant images and 13 pleasant images (mean valence 5.07 ± 1.4, mean arousal 4.38 ±

2.2, dominance 1 mean 5.35 ± 2.1, dominance 2 mean 4.60 ± 2.1) that were presented in a pseudorandom order. Image set 2 consisted of 12 neutral images, 14 unpleasant images and 12 pleasant images (mean valence 5.07 ± 1.4, mean arousal 4.38 ± 2.2, dominance 1 mean 5.6 ± 2.1, dominance 2 mean 5.2 ± 2.1). Whichever of the two image sets was randomly selected to be presented in the supine position, the remaining set of images was presented during HUT so as to avoid OR habituation. Each image was presented for 10 seconds.

Emotion formation to each image was recorded using a visual analogue scale (VAS) presented after each image, requesting: "*Please rate out loud the image you just saw using a number between 1 – 10; 1 being unpleasant, 5 being neutral and 10 being pleasant.*'"

Following another 5-10 mins second supine, participants then underwent a 3-5 mins 60° baseline head up tilt (HUT) before being presented with the remaining second set of images. ORs and emotion formation were recorded and analysed identically to the supine phase of the protocol.

7.1.4. Interoceptive accuracy (IA)

After the OR section of the protocol, participants rested while supine for 10 mins before the protocol started. After 3, 6 and 9mins, participants were asked to carry out a heartbeat tracking task (Schandry, 1981) involving silently counting their own individual heartbeats during the three epochs (Schandry, 1981). Participants were instructed to not manually take or touch their pulse and to declare that they couldn't feel their pulse pressing against any clothing or apparatus. Randomised epochs of the supine phase of the heartbeat mental tracking task were either 25, 35 or 45 seconds, elected to the optimum task windows from previous studies (Pollatos et al., 2009).

Next, during isometric handgrip exercise (HG), the participants were requested to sustain a handgrip at 1/3 of maximum voluntary contraction for 3 mins using a gauge directly in front of them. At 30 seconds, 88 seconds and 144 seconds the participants performed the heartbeat tracking task. Randomised epochs of the HG mental tracking task were 21, 26, 36 seconds.

Cutaneous cold pressor (CP) task was carried out. The subjects' right hand was placed in an icepack chilled to 4°C for a minimum of 90 seconds, tolerance permitting. At 3 seconds, 40 seconds and 54 seconds the participants performed the heartbeat tracking task.

Cardiovascular autonomic activity was then allowed to return to baseline levels (minimum of 3 mins) before a 10 mins 60° head-up tilt (HUT) was conducted. At 3, 6 and 9 minutes the participants performed the heartbeat tracking task. Randomised epochs of the heartbeat mental tracking task were 25, 35, 45 seconds.

Interoceptive accuracy scores were yielded post hoc by counting the R waves in each task epoch and averaging the following equation over the 3 tracking tasks of each stage of the protocol (supine baseline, HG, CP, HUT):

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

7.2. Results

7.2.1. Supine and HUT baseline data

Supine and HUT baseline data is shown in table 14. There were no between-group differences amongst healthy controls and OI patients.

Table 14.Supine baseline and head up tilt (HUT) autonomic indices in healthy controls, postural tachycardia syndrome (PoTS) patients and autonomically mediated syncope (AMS) patients. HR = heart rate, BPM = beat per minute, SBP = systolic blood pressure, DBP = diastolic blood pressure

	Supine HR (BPM)	Supine SBP (mmHg)	Supine DBP (mmHg)	HUT HR (BPM)	HUT SBP (mmHg)	HUT DBP (mmHg)
Controls	72 ± 11.9	127.7 + 29.1	68.7 + 20.5	80.7 + 10.1	131.8 + 21	75.3 + 14.1
PoTS	73.3 + 11.2	127.7 + 15.3	67.3 + 8.6	94.7 + 14.1*	126 + 28.6	67.1 + 13.3
AMS	71.1 + 12.1	136.3 + 43.8	60.9 + 22.4	71.5 + 12.7	138.3 + 42	61.8 + 21.7

7.2.2. Supine & HUT orienting responses to emotionally neutral stimuli

7.2.2.1. Within group findings

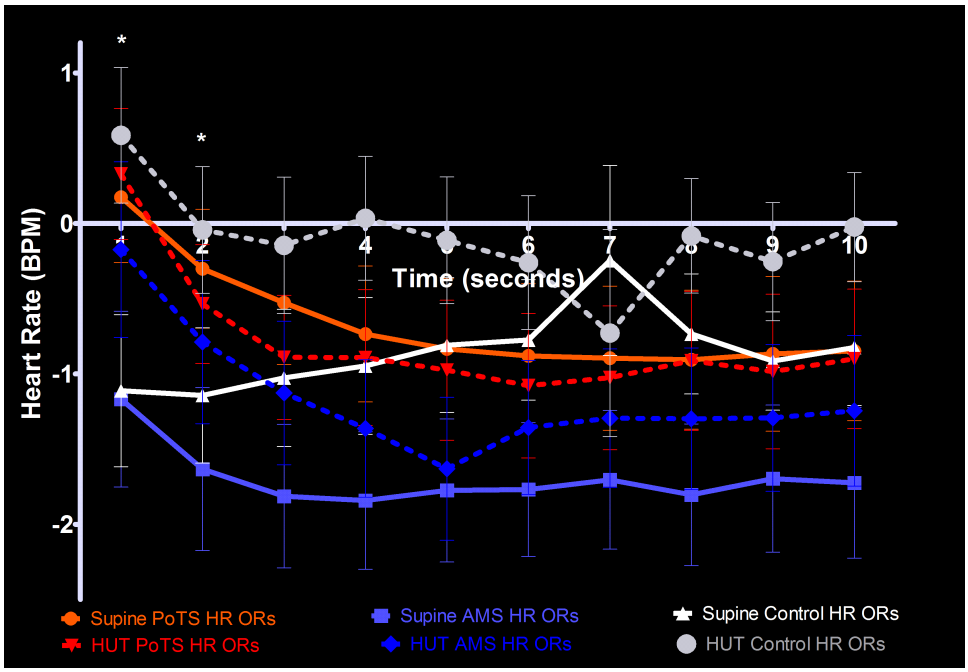
Healthy controls produced larger supine cardiac ORs (i.e., greater cardiac deceleration) at 1s (p=.010) and 2s (p=.042) in comparison to HUT presentation of neutral images. There were no other significant within group differences in control or OI cohorts (see figure 37).

7.2.2.2. Between group findings

During the presentation of supine and HUT neutral images, there were no differences in autonomic indices or appraisal of neutral images in AMS patients in comparison to healthy controls.

There were no between-group differences amongst healthy controls and PoTS patients during supine neutral image presentation, however, during HUT neutral image presentation, the PoTS group produced a significantly higher HR (*p*=.002-.047) for the entire 10s epoch of neutral image presentation.

Figure 37. Cardiac orienting responses to neutral images whilst supine and during head up tilt (HUT, dotted lines). Postural tachycardia syndrome (PoTS) patients and autonomic (neurally) mediated syncope (AMS) patients.



7.2.2.3. Supine & HUT responses to emotionally pleasant stimuli

7.2.2.4. Within group findings

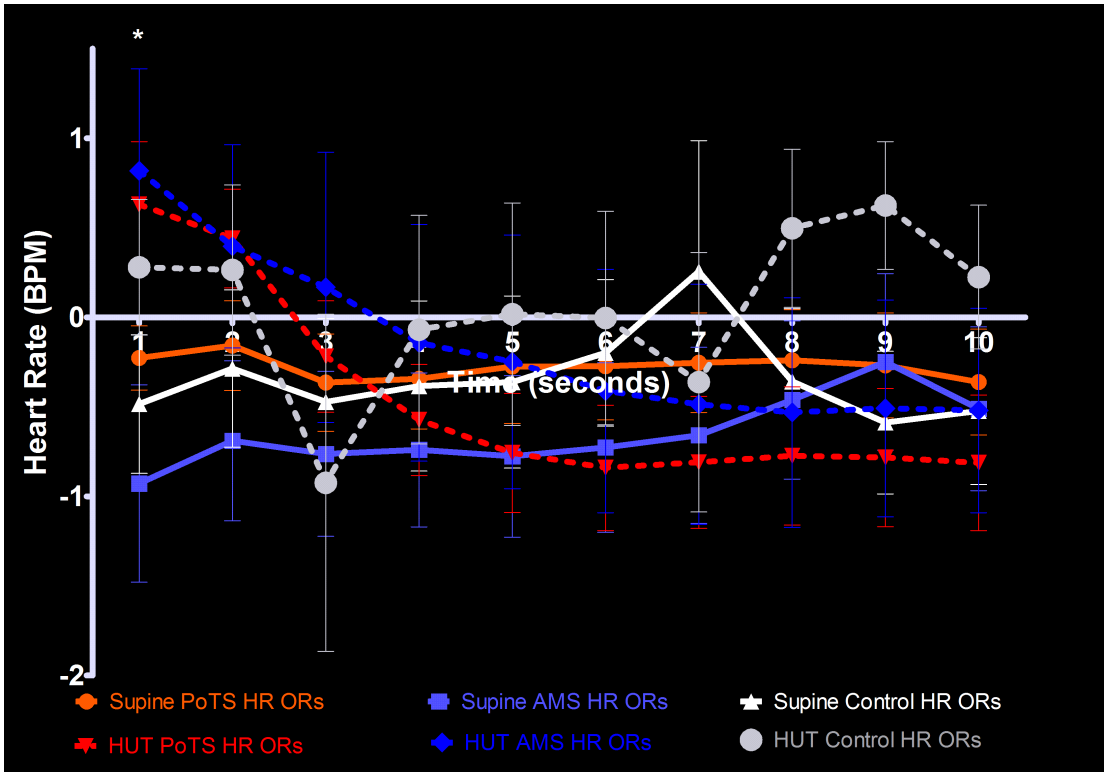
In comparison to their viewing of pleasant images in the supine position, AMS participants produced an attenuated (*p*=.010) (i.e., reduced HR deceleration) cardiac OR at 1s during HUT viewing of pleasant images (see figure 30). There were no other within-group differences in the three cohorts.

7.2.2.5. Between group findings

During the presentation of supine and HUT pleasant images, there were no differences in autonomic indices or appraisal of pleasant images in AMS patients in comparison to healthy controls.

During tilted presentation of pleasant images, the PoTS group had a significantly higher HR for the entire 10s of stimuli exposure (*p*=.001-.008).

Figure 38. Cardiac orienting responses to pleasant images whilst supine and during head up tilt (HUT, dotted lines). Postural tachycardia syndrome (PoTS) patients and autonomic (neurally) mediated syncope (AMS) patients.



7.2.2.6. Supine & HUT responses to emotionally unpleasant stimuli

7.2.2.7. Within group findings

There were no within group differences in the two OI patient groups, however, control subjects' DBP ORs at 1s (*p*=.040), 4s (*p*=.032), 7s (*p*=.046), 8s (*p*=.019), 9s (*p*=.009), 10s (*p*=.008) were diminished in comparison to supine viewing (see figure 39). Controls also produced an attenuated (i.e., reduced HR deceleration) cardiac OR at 1s (*p*=0.14) and 2s (*p*=.020) during HUT viewing of unpleasant images (see figure 40).

Figure 39. Diastolic blood pressure (DBP) orienting responses to unpleasant images whilst supine and during head up tilt (HUT, dotted lines). Postural tachycardia syndrome (PoTS) patients and autonomic (neurally) mediated syncope (AMS) patients.

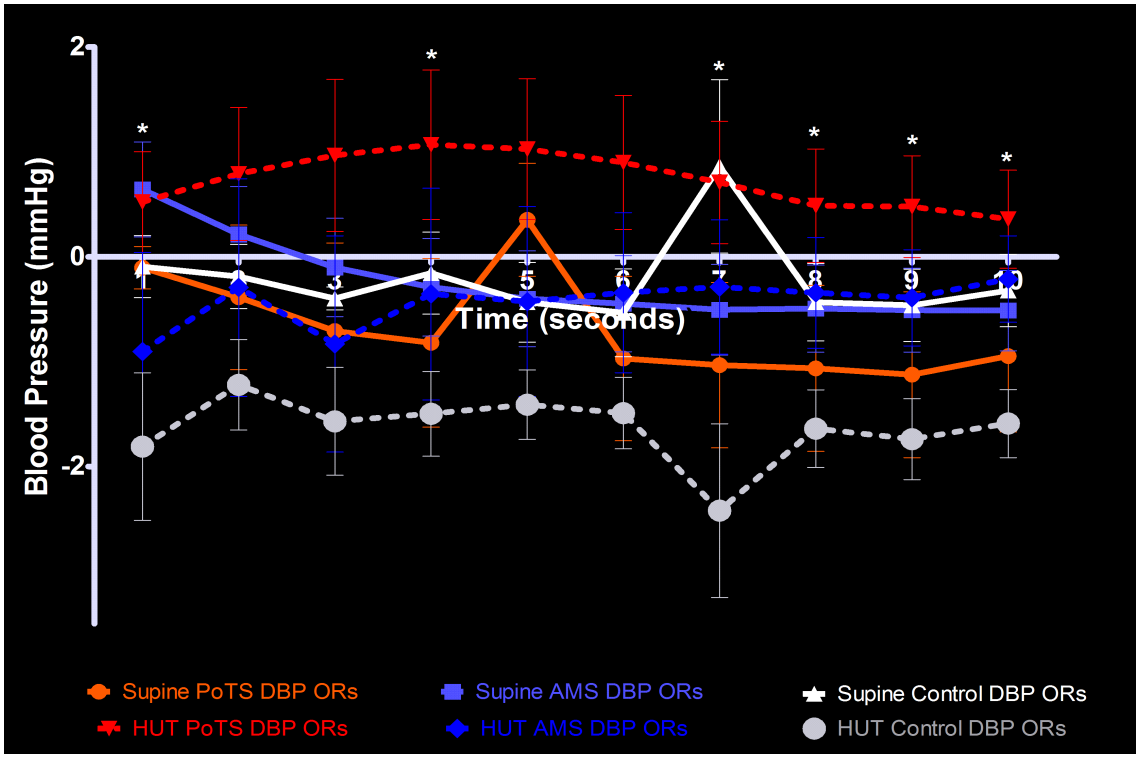
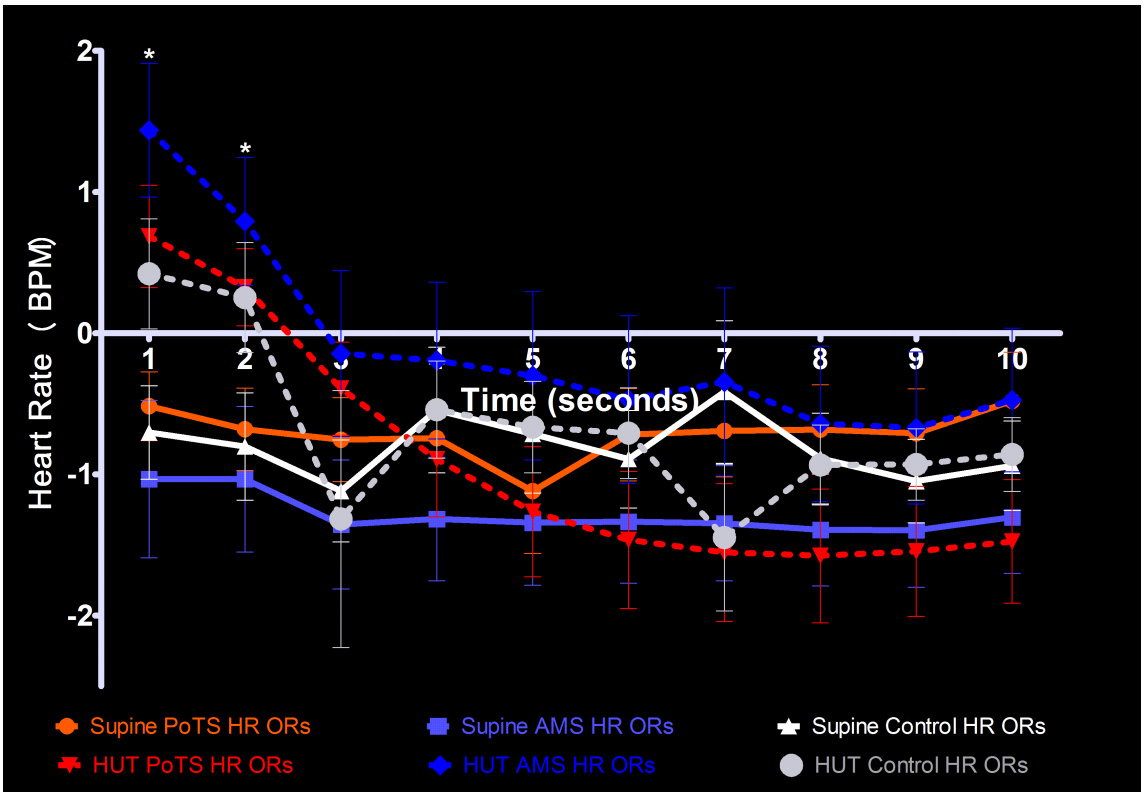
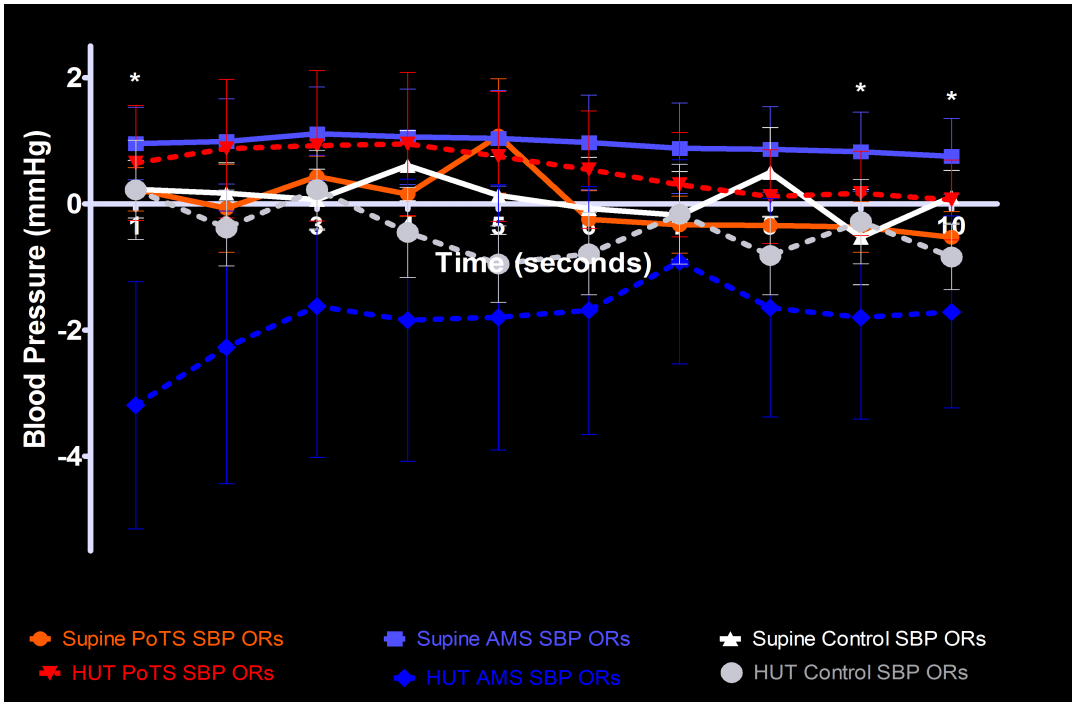


Figure 40. Cardiac orienting responses to unpleasant images whilst supine and during head up tilt (HUT, dotted lines). Postural tachycardia syndrome (PoTS) patients and autonomic (neurally) mediated syncope (AMS) patients.



PoTS patients also produced a weakened cardiac OR at 1s of tilted unpleasant image viewing in comparison to their group's cardiac OR at 1s (p=.013) of supine unpleasant image viewing (see figure 41).

Figure 41. Systolic blood pressure (SBP) orienting responses to unpleasant images whilst supine and during head up tilt (HUT, dotted lines). Postural tachycardia syndrome (PoTS) patients and autonomic (neurally) mediated syncope (AMS) patients.



AMS patients produced a diminished cardiac OR at 1s (p=.007) and 2s (p=.025) of HUT viewing of unpleasant images in comparison to supine (see figure 31). SBP ORs during HUT viewing of unpleasant images in the AMS group were significantly diminished (i.e., fall rather than rise in SBP) at 1s (p=.034), 9s (p=.048) and 10s (p=.049) in comparison to supine (see figure 33).

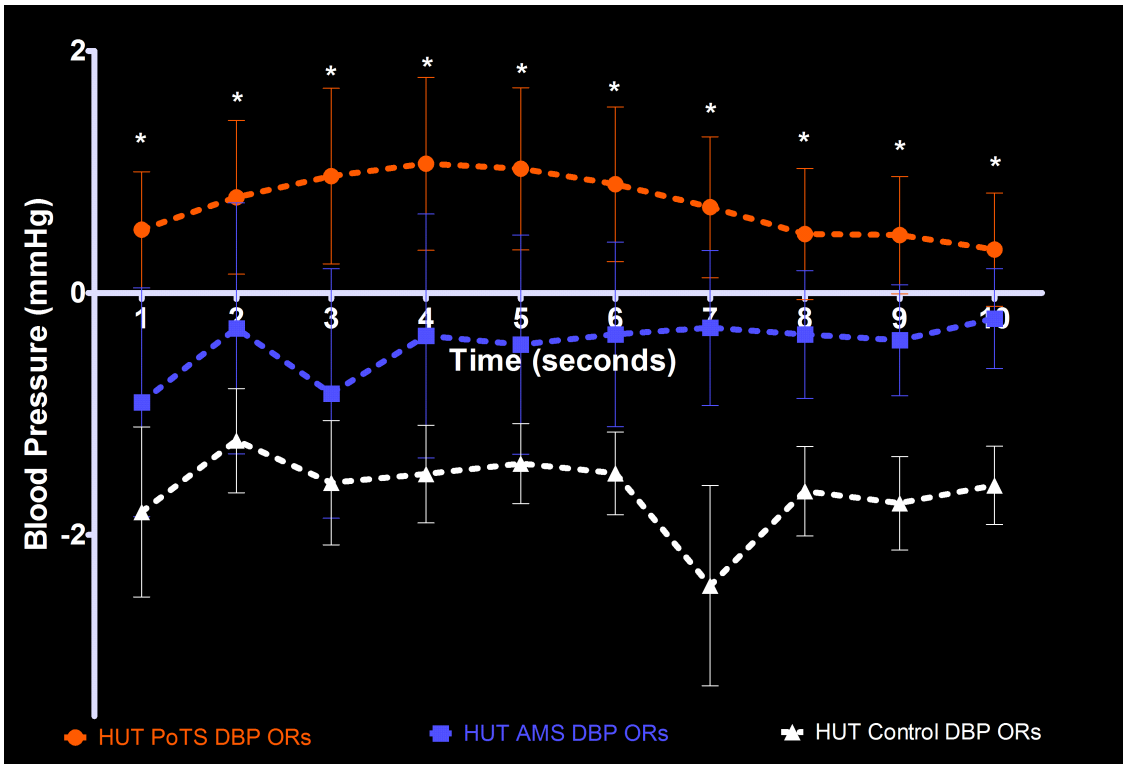
7.2.2.8. Between group findings

During supine presentation of unpleasant images, there were no between-group differences amongst healthy controls and the OI cohorts, including subjective appraisal of the emotional stimuli. During tilted viewing of unpleasant images, the PoTS group had a significantly higher HR for the entire 10s epoch of neutral image presentation (p=.002-.014).

In comparison to healthy controls, PoTS patients produced exaggerated (i.e., greater increase in DBP) DBP ORs to unpleasant images on tilt for 1s (p=.039), 2s (p=.003), 3s (p=.002), 4s (p=.003), 5s (p=.004), 6s (p=.004), 7s (p=.005), 8s (p=.006), 9s (p=.006) and 10s (p=.007) (see figure 34).

During viewing of unpleasant images on tilt, the AMS group also produced exaggerated DBP ORs in comparison to healthy controls during 4s (p=.008), 5s (p=.020), 6s (p=.014), 7s (p=.004), 8s (p=.009), 9s (p=.011), 10s (p=.003) (see figure 42).

Figure 42. DBP orienting responses to unpleasant images during head up tilt (HUT, dotted lines). Postural tachycardia syndrome (PoTS) patients and autonomic (neurally) mediated syncope (AMS) patients.

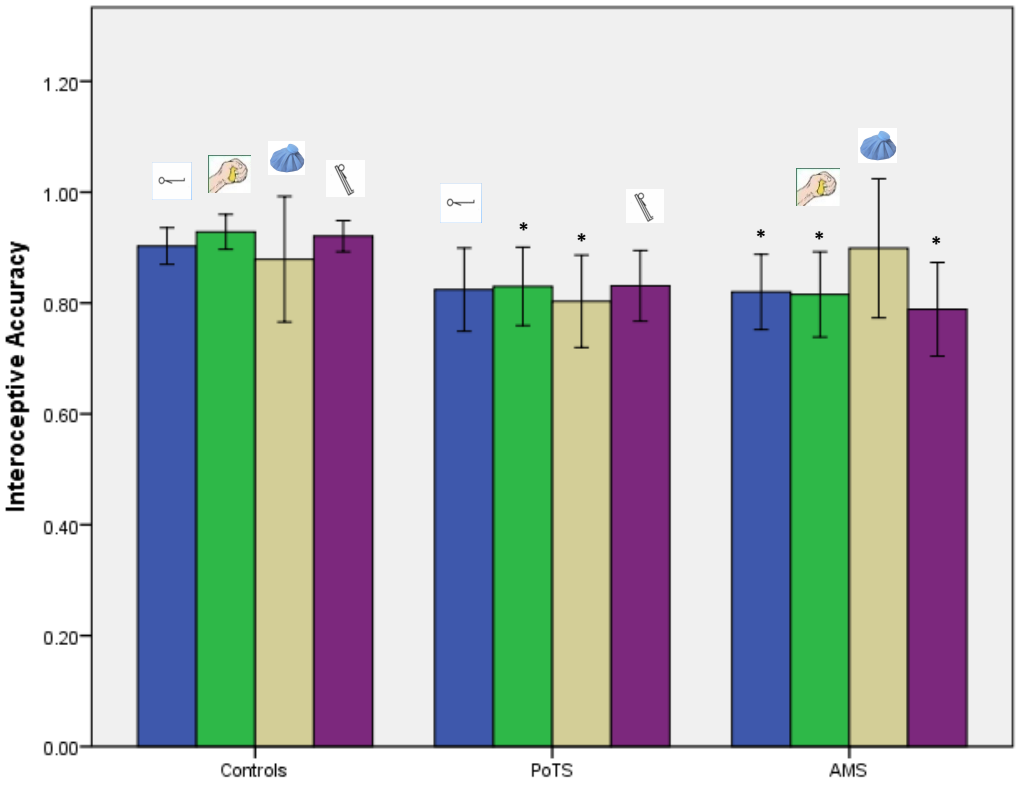


7.2.2.9. Interoceptive accuracy (IA)

PoTS patients' interoceptive accuracy (IA) was significantly poorer during isometric exercise (p=.043) and cold pressor testing (p=.025) than healthy controls (see figure 35).

AMS patients' IA was significantly poorer during baseline (p=.028), isometric exercise (p=.010) and HUT (p=.015) (see figure 43).

Figure 43. Interoceptive accuracy during supine baseline, isometric exercise, cold pressor and head up tilt (HUT). PoTS = postural tachycardia syndrome; AMS = autonomic mediated syncope.



7.2.2.10. Interoceptive correlations with neutral orienting data

Healthy controls' emotional assessment of neutral images on HUT was negatively correlated with IA on HUT (r_s= -.566, n= 16, *p*=.022).

PoTS patients' DBP during 2-10 seconds (r_s= .623 - .631) of neutral images on HUT was positively correlated with their IA on HUT.

In the AMS cohort, neutral image ratings viewed whilst supine were negatively correlated (r_s= -.745, n= 13, *p*=.003) with isometric exercise IA (see table 15). Ratings of neutral images during HUT were negatively correlated with cold pressor IA (r_s= -.645, n= 13, *p*=.029). For the entire 10s epoch of supine neutral image presentation, SBP (r_s= .875 -.883) and DBP (r_s= .774 - .879) was positively correlated to cold pressor IA.

Table 15. Correlations between autonomic indices during supine and HUT viewing of neutral images and interoceptive accuracy (IA) during supine baseline and clinical autonomic manoeuvres (isometric exercise, cold pressor, head up tilt [HUT]).

Neutral	Baseline IA	Isometric IA	Cold Pressor IA	HUT IA
Controls				-HUT neutral image rating
PoTS				+2-10s HUT DBP
AMS		-Supine neutral image ratings	+1-10s supine SBP +1-10s supine DBP -HUT neutral image ratings	

7.2.2.11. Interoceptive correlations with pleasant orienting data

Controls' ratings whilst supine of pleasant images were negatively correlated to isometric exercise IA (r_s= -.534, n= 17, *p*=.027) (see table 16). During the entire 10 second epoch of tilted viewing of pleasant images, controls' SBP (r_s= .496 - .563) was positively correlated with baseline IA (see table 16).

PoTS patients' DBP (r_s= .581 - .615) during pleasant images on tilt was positively correlated with HUT IA for the 10s duration of pleasant image presentation (see table 16).

During 1-10 seconds of supine viewing of pleasant images, AMS patients' SBP (r_s= .871 - .876) and DBP (r_s= .764 - .784) was positively correlated with cold pressor IA (see table 16).

Table 16. Correlations between autonomic indices during supine and HUT viewing of pleasant images and interoceptive accuracy (IA) during supine baseline and clinical autonomic manoeuvres (isometric exercise, cold pressor, head up tilt [HUT]).

Pleasant	Baseline IA	Isometric IA	Cold Pressor IA	HUT IA
Controls	+1-10s supine SBP	-Supine pleasant image ratings		
PoTS				+1-10s supine DBP
AMS			+1-10s supine SBP +1-10s supine DBP	

7.2.2.12. Interoceptive correlations with unpleasant orienting data

Healthy controls' SBP during HUT viewing of unpleasant images was positively related ($r_{s=}$ .468 - .633) to isometric exercise IA for the entire 10 seconds of image exposure (see table 17).

During 2-10 seconds of supine viewing of unpleasant images, PoTS cardiac ORs were negatively correlated with baseline IA ($r_{s=}$ -.553 - -.858), isometric exercise IA ($r_{s=}$ .581 - .615) and HUT IA ($r_{s=}$ .533 - .689) (see table 17).

During 2-10 seconds of HUT viewing of unpleasant images, PoTS DBP was also positively correlated with baseline ($r_{s=}$ .578 - .598), isometric exercise ($r_{s=}$ .579 - .595) and HUT IA ($r_{s=}$ .643 - .655). SBP for the entire 10 second duration of unpleasant image exposure was positively correlated ($r_{s=}$ .597 - .629) with isometric exercise IA.

Cold pressor IA was positively correlated with AMS SBP ($r_{s=}$ .736 - .751) and DBP ($r_{s=}$ .608 - .712) during the 10 second entirety of unpleasant image exposure in the supine position (see table 7). AMS cold pressor IA was negatively correlated with SBP ($r_{s=}$ -.665 - -.796) and DBP ($r_{s=}$ -.634 - -.784) ORs to unpleasant images on tilt for the entire 10 second epoch.

Table 17. Correlations between supine and HUT autonomic indices during exposure to unpleasant images and interoceptive accuracy (IA) during baseline and clinical autonomic manoeuvres.

Unpleasant	Baseline IA	Isometric IA	Cold Pressor IA	HUT IA
Controls		+1-10s HUT SBP		
PoTS	-2-10s supine cardiac ORs	-2-10s supine cardiac ORs		-2-10s supine cardiac ORs
	+2-10s HUT SBP	+1-10s HUT SBP		+2-10s HUT SBP
	+2-10s HUT DBP	+2-10s HUT DBP		+2-10s HUT DBP
AMS			+1-10s supine SBP	
			+1-10s supine DBP	
			-1-10s HUT SBP ORs	
			-1-10s HUT DBP ORs	

7.3. Discussion

This study aimed to investigate (i) the effects of orthostatic stress on ORs in PoTS and AMS in comparison to controls and (ii) to explore any interactions between ORs and IA due to the

magnitude of ORs representing the emotional significance of a stimulus and greater IA being associated with increased emotional experience, particularly anxiety – a common comorbid affective symptom in AMS and PoTS. These questions were addressed from the perspective that homeostatic processes (IA) and/or innate assimilative reflexes (ORs) may be susceptible to disruption by symptomatic OI and help elucidate the cause of the common comorbid affective and cognitive symptoms in OI.

7.2.3. Orienting response findings

Control cardiac ORs on tilt during 1s and 2s of neutral image presentation were weaker compared to 1s and 2s of supine presentation. The cardiac deceleration component of the OR indicates stimulus detection (Barry, 1977) (Barry, 2009), indicating an attenuation or delay in stimulus detection on HUT. However, physiologically, the engagement of the baroreflex during HUT may contribute to the initial attenuation of cardiac ORs on HUT in controls rather than being a psychogenically or stimulus derived finding. As supine ORs have not been compared with HUT ORs before, it is difficult to confidently identify the cause of this difference in early phase HUT ORs in comparison to supine ORs, however, the fact that emotional assessment of the stimuli did not differ between HUT and supine viewing, makes a physiological cause a possibility but may also indicate that other levels (e.g., subcortical, cortical, preconscious, conscious) of emotional integration compensated for this initial perturbation.

As with controls' HUT cardiac ORs to neutral images, there was a similar diminishing of cardiac ORs to pleasant images in the AMS group at 1s and 2s of stimulus exposure on HUT, yet the finding that unpleasant images also caused an attenuation of early cardiac ORs in all three groups during 1s (controls, AMS, PoTS) and 2s (controls, AMS) provides support for a stimulus/valence-related aspect to this finding rather than a physiological cause. This is substantiated by the attenuated early (1s) and late phase (9s, 10s) HUT SBP ORs (in comparison to supine) to unpleasant HUT images in the AMS group. It may also be possible that any downstream emotional effects of this early OR finding require a more sensitive instrument than the VAS used in this study.

An alternative explanation may be found in recent studies examining embodied cognition and posture. Although supine subjects have been found to experience less negative emotion compared to standing (Harmon-Jones and Peterson, 2009), standing and HUT differ in that HUT negates the use of peripheral muscular pumps to aid venous return, thus offering a more thorough insight into the subject's vasomotor integrity in various vascular beds by reclining the patient backwards away from the stimulus to 60-90°. This reclining withdrawal-oriented posture may account for the early stage attenuation in HUT ORs as it has been found to reduce cortical

responses (Price and Harmon-Jones, 2011) and eye blink reflex to emotional stimuli in comparison to approached-oriented (forward leaning) posture. The authors concluded that the blunting of central and peripheral responses to negatively valenced stimuli is attributable to the reclining posture being associated with reduced stimulus-approach motivation. Therefore, the initial attenuation of cardiac HUT ORs in the current data may be representative of delayed stimulus engagement in relation to withdrawal-motivated posture on tilt.

In the AMS group, the reduced SBP ORs to unpleasant images on HUT are noteworthy, as increased SBP has been linked with coping demands and behaviour. Studies have shown that when faced with a threat stimulus, the decision to avoid the threat stimulus follows an increase in SBP which does not occur when the subject is powerless to avoid the noxious stimulus (Manuck et al., 1978) (Light and Obrist, 1980). Therefore, the current findings in the AMS cohort may represent a constitutional disposition to not engage in defence responses, such as fight or flight, supporting comparisons between the vasovagal reflex and tonic immobility (sham death) seen in many invertebrates when caught by a predator (Alboni et al., 2008, Diehl, 2005). A recent study using Stimulus Preceding Negativity (SPN) during emotional stressors in AMS patients has provided a central measure of reduced emotional variation, anticipation and regulation in these patients (Buodo et al., 2012). It is unfortunate that this study was only performed in the seated position, as repeating the protocol during orthostasis may have provided even greater insights into the elusive pathophysiology of AMS. Together these findings suggest an innate difference in AMS patients assimilation of unpleasant, aversive or noxious stimuli, arguably manifesting in their common blood injury phobia (Graham, 1961).

The peripheral vasoconstriction OR is a neglected measure, meaning that there are currently no differential roles allocated to the SBP and DBP ORs but I believe the current data highlights the need for a more in-depth examination of the potential different meanings of SBP ORs and DBP ORs. AMS and PoTS patients produced greater DBP ORs to unpleasant images on HUT compared to controls. The peripheral vasoconstriction OR represents stimulus intensity, therefore, the unpleasant images during HUT either had greater intensity for OI patients, OI patients were less effected by the HUT-related withdrawal posture, or differences in β_2-adrenoreceptor or vasomotor function related to OI pathophysiological influenced orthostatic vasoconstriction. One could argue against the former, as image ratings did not differ between groups or within groups when comparing supine and HUT image ratings, however, the fact that this finding was specific to unpleasant images only indicates a psychological basis. There may be an argument for the VAS not directly requesting the subjects to relay image intensity, however, the fact that the VAS was a sliding scale, infers valence intensity, i.e., the higher the number towards 10, the more pleasant the image and the lower the number towards 1, the more unpleasant the image. The VAS was also sensitive enough to define a negative correlation in the control group between isometric exercise IA and supine ratings of pleasant

image (i.e., the greater the IA, the lower their ratings of supine pleasant images), and also HUT IA and supine ratings of neutral images (i.e., the greater the IA, the lower their ratings of supine neutral images).

One of the aims of this study was to investigate the effects of orthostatic stress on ORs in PoTS and AMS in comparison to controls. HUT blunted initial OR activity, particularly during tilted viewing of unpleasant images, which also produced exaggerated DBP ORs in both OI groups, suggesting these images possessed greater intensity for the clinical cohorts and indicating that OI symptom provocation may contribute to negative affect, at least at an unconscious level. This potential for OI to exacerbate negative affect may help explain the prevalence of somatic anxiety in chapters 5 and 6. Though ORs were most disrupted by simultaneous HUT and unpleasant image presentation, it may be necessary to compare standing with HUT stimulus exposure or integrate auditory stimuli in light of recent posture-related research (Harmon-Jones and Peterson, 2009, Price and Harmon-Jones, 2011).

7.2.4. Interoception findings

OI patients consistently underestimated their heartbeats during testing. PoTS patients' interoceptive accuracy was significantly poorer during isometric exercise and cold pressor in comparison to healthy controls and AMS patients' interoceptive accuracy was significantly poorer during baseline, isometric exercise and HUT. Curiously, AMS IA during cold pressor was higher than the PoTS and healthy control groups, though not significantly so. The cold pressor manoeuvre causes vasoconstriction, making it a useful exercise to test autonomic integrity but it also has a strong nociceptive component. Nociception, and the apprehension of nociception, are common causes of AMS (van Lieshout et al., 1991, Humm and Mathias, 2010) and this sensitivity may relate to the cold pressor findings and the pervasive anxious apprehension of pain in AMS (McGrady et al., 2001, Graham, 1961).

Interoception of visceral feedback is required for autonomic mediation of homeostasis, even on a physiological level, with baroreceptors and chemoreceptors serving as 'interoceptors', yet AMS and PoTS are conditions defined by the intermittent breakdown of these homeostatic mechanisms. It could be proposed from the current data that the breakdown of interoceptive homeostatic reflexes is also apparent at a conscious level of IA in OI subjects (see also chapter 6).

7.2.5. Interoceptive & orienting response correlation findings

Supine and HUT BP data (ORs and mean data) was more strongly related to IA than cardiac data in the AMS and PoTS subjects, lending further support (see also chapter 6) to mechanoreceptors in the great vessels, for example, the aortic arch, having primary cardiac interoceptive roles in OI, possibly accounting for their reduced cardiac IA in comparison to controls. This is further supported by PoTS DBP during HUT and neutral images being positively related to HUT IA and DBP during pleasant images being positively related to HUT IA. In contrast, in controls supine SBP during pleasant images positively related to baseline IA and HUT SBP during unpleasant images positively related to isometric IA. SBP indicates stroke volume, aortic compliance and left ventricular ejection velocity, whereas DBP indicates peripheral resistance of blood flow from arterioles to capillaries (Dampney et al., 2002), therefore peripheral vasomotor afferent signalling appears to be more closely related to cardiac IA than cardiac nerve activity in PoTS, whereas, controls cardiac IA in controls was more strongly related to systolic cardiac activity. This may explain the recent finding that the interoception of palpations in PoTS was separate to that of tachycardia (Khurana, 2014), as well as indicating differences in the central integration of afferent feedback in OI, as in chapter 6 where interoception was found to be anxiogenic rather than homeostatic in nature dysautonomia.

During supine unpleasant image exposure, PoTS cardiac ORs negatively correlated with baseline, isometric exercise and HUT IA., i.e., greater cardiac deceleration to unpleasant images representing stimulus detection correlated with increased IA, substantiating the role of ORs and IA in emotion formation in this cohort. PoTS SBP and DBP during supine unpleasant images positively correlated with HUT IA, when orthostatic tachycardia would have been provoked, again indicating a dominant role of vasomotor or baroreceptor over cardiac afferent feedback in cardiac IA in PoTS.

The areas implicated in this potential disruption of interoceptive feedback may relate to the recent study of 32 AMS patients (mean age 24) that evidenced reduced right insula volumes. These reductions were related to greater falls in SBP and DBP (Kim et al., 2014) during HUT. In animal studies, decreases in BP correlate with decreased right insula activity in anaesthetised cats (Henderson et al., 2004) and in humans, right insula activity co-varies with increases in HR and BP during task engagement (Critchley et al., 2000a). Cardiac IA has been found to decrease after right insula resection of a neoplastic lesion (Ronchi et al., 2015) and right hemisphere infarction involving the insula causes pervasive cardiovascular autonomic dysregulation in comparison to left hemisphere infarction involving the insula (Meyer et al., 2004). Moreover, The role of the right insula in second-order conscious homeostatic representations has been further evidenced using false physiological feedback of HR during functional magnetic resonance imaging (fMRI) by Gray and colleagues (Gray et al., 2007), who examined emotional appraisal of neutral faces during baseline and isometric handgrip

exercise. False feedback of increased HR during emotional stimuli caused appraisal levels of emotional intensity/salience to increase. Using fMRI, Critchley and co-workers (Critchley et al., 2004) found that activation of the insula cortex, particularly the right, highly correlated with interoceptive awareness and accuracy in healthy controls. The authors concluded that the right insula depicts internal bodily state that can be consciously accessed and insula activity was positively correlated with anxiety and interoceptive awareness. The anterior and mid insula cortices, Acc and somatomotor cortex were functionally associated with shifting one's attention to interoceptive events.

As with AMS, there is a dearth of brain imaging studies in PoTS, however, one recent study evidenced reduced left insula grey matter volumes in 11 PoTS patients (mean age 32) (Umeda et al., 2015). These reductions were negatively correlated with depression and anxiety scores. The reduced insula volumes in this study and that of Kim et al in AMS patients are unlikely to result from age-related neurodegeneration due to the age of the subjects, implicating the insula in both AMS and PoTS neuropathophysiology. The insula are also involved in pressor tone and initiation of the baroreflex (Kimmerly et al., 2005), which fails during orthostasis in AMS and PoTS. Along with the dorsal Acc, insula activity reflects the engagement of sympathetic activity coupled to mental and physical behaviours (Critchley et al., 2000a, Critchley et al., 2000b) and the role of the insula as part of the central autonomic network (CAN) (Benarroch, 1993) is further evidenced by increased anterior and posterior insula activity during isometric exercise and the Valsalva manoeuvre (King et al., 1999) (Harper et al., 2000). Together, these recent investigations into the neuropathophysiology of AMS and PoTS may provide a useful starting point for defining the central mechanisms that may be implicated in the current IA and OR findings.

The second aim of this study was to investigate any interactions between ORs and IA in order to better understand the genesis and presentation of psychological symptoms in OI. From the AMS data, one could hypothesise that the strong relationship between cold pressor IA, which was more accurate than PoTS and controls, and HUT ORs during emotional stimuli provide further support for an innate difference in AMS patients' brain-body integration of emotionally challenging stimuli, particularly during simultaneous autonomic and affective stress. It could be argued that this is manifested in the common blood-injury phobia in AMS.

Human cognitive models of anxiety propose that anxiety is perpetuated by somatic hypervigilance (Wilhelm and Roth, 2001), biased ORs to perceived threat (Bar-Haim et al., 2007) and attentional deficits (Eysenck et al., 2007). Somatic hypervigilance and attentional deficits are also common symptoms reported by AMS and PoTS patients (see chapters 5 and 6 of this thesis) who also appear to have exaggerated peripheral vasoconstrictor ORs to

simultaneous orthostatic and emotional challenges. However, PoTS and AMS differ from typical anxious cohorts, in that anxiety symptoms are predominantly defined by somatic and dysautonomic factors. As attentional habits that are weighted towards threat (Mathews, 1990) and somatic hypervigilance (Verkuil et al., 2007) cause a cycle of anxiety, these aspects could be perpetuated by a having a condition that excessively increases autonomic activity, such as PoTS or AMS, particularly as the current data indicate, for the first time, how brain-body orienting and homeostatic processes susceptible to dysregulation by dysautonomia appear to be related this these patients, indicative of a 'bottom-up' model of emotion formation.

The pathophysiology of VVS is still not yet fully understood (Meyer et al., 2004), the neuropathophysiology even less so, therefore the implication of structural differences in the insula of VVS patients may contribute to both the cardiovascular autonomic, interoceptive and cognitive-affective symptoms in these patients. The current IA data suggests that AMS and PoTS patients have difficulty either consciously accessing accurate interoceptive representations perhaps due to dysautonomia-related error code size (Seth and Critchley, 2013) or that the internal state is improperly represented, potentially due to differences in brain-body integration, in comparison to controls, as reflected by the IA being highly correlated with ORs in OI and reports of structural differences in key interoceptive centres (insula) in AMS.

7.2.6. Summary of key findings

This study examined supine and HUT ORs in EH, AMS and PoTS in comparison to healthy controls, concluding that;

- HUT induced an attenuation or delay in initial stimulus detection on HUT.
- Unpleasant images on HUT appeared to have greater intensity for AMS and PoTS patients according to their peripheral vasoconstrictor ORs, though this was not reflected in the valence VAS ratings, potentially due to the categorical differences between valence and intensity

7.2.7. Conclusions

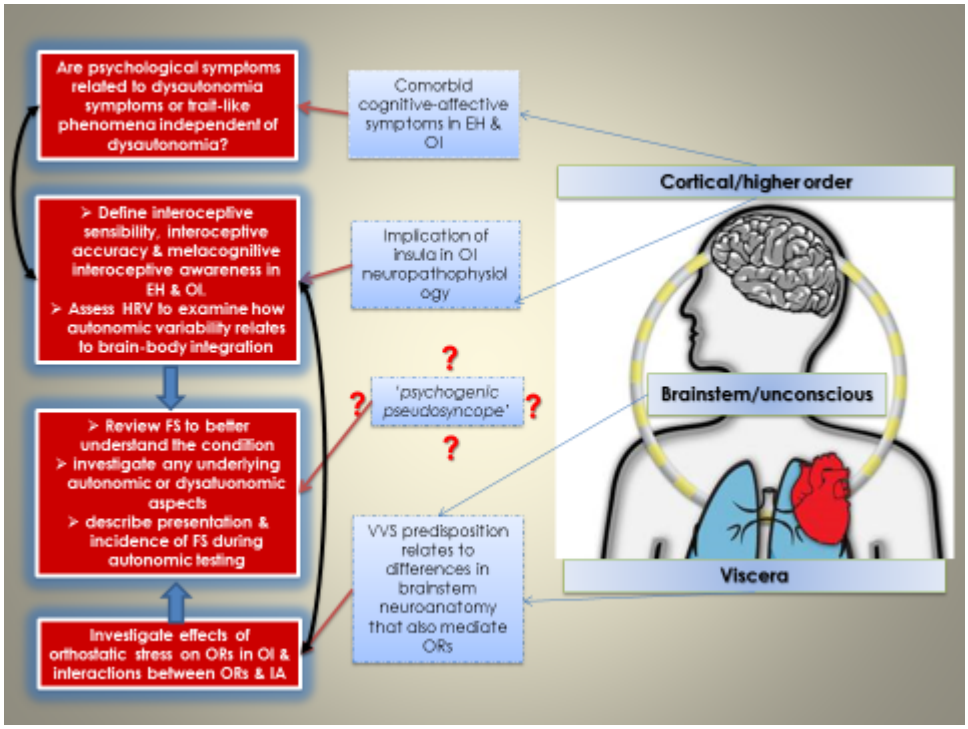
These findings indicate greater stimulus detection is related to visceral sensitivity in PoTS and supports the argument for a reduced repertoire of defence responses in AMS, as evident by this cohort's reduced α_1 and α_2-adrenoceptor vasoconstrictive responses to unpleasant images during HUT and lack of association between IA and OR data in controls. The implication of the insula in the neuropathophysiology of OI may have profound downstream effects on

cardiovascular autonomic, emotional and interoceptive function and further study is warranted.

Chapter 8. Synthesis of findings

This thesis was structured to examine the genesis and presentation of psychological symptoms that commonly present in AMS, EH and PoTS by utilising physiological and psychological tests that recruited varying levels of cerebral engagement (see figure 44) (Critchley et al., 2002). It has been proposed that the reduced vagal tone in affective disorders disinhibits sympathoexcitation, causing sympathetic dominance of central and peripheral processes. This autonomically mediated feedback loop perpetuates trait sympathoexcitation and anxiogenesis, likely explaining interoception's contributory role to anxiety disorders via somatic hypervigilance. Excessive but intermittent sympathoexcitation is also a primary symptom in the pathophysiology of AMS, EH and PoTS, forms of dysautonomia in which subclinical anxiety and somatic hypervigilance are prevalent.

Figure 44. Rational for experiments



8.1. Subnormal interoception in PoTS predisposes to functional symptoms

The findings in chapter 4 indicate that functional syncope is a conversion disorder in the functional syncope (FS) only group and an aberrant response to orthostatic intolerance (OI) in the FS/PoTS and FS/AMS groups, as these patients were OI symptomatic during FS. A neurological predisposition to be overwhelmed by stressors has been described in non-epileptic seizure (Almis et al., 2013) and this reaction could potentially be provoked by the interoceptive threat of symptomatic OI and further impacted by the impaired interoceptive

accuracy found in PoTS and AMS in chapters 6 and 7 of this thesis. This is supported by the fact that FS/PoTS patients were referred for syncope or pre-syncope rather than cardiothoracic symptoms and, likewise, during testing, FS/PoTS patients rarely reported cardiothoracic symptoms. It may also be relevance that JHS/EDSIII - a rheumatological marker for PoTS - is also associated functional disorders (Nijs et al., 2006, Kovacic et al., 2014, Acasuso-Diaz and Collantes-Estevez, 1998).

The prediction error modification strategy of motor engagement to meet the noisy incoming autonomic afferent feedback of tachycardia or pre-syncope may account for FS episodes generally occurring during symptomatic OI in FS/PoTS and FS/AMS. Individuals who somatise are more vigilant of bodily sensations (a common PoTS and AMS trait, see chapter 5), with prior illness beliefs (a key Bayesian factor) playing a significant role (Kirmayer and Robbins, 1996), potentially explaining the primary symptoms of syncope – unresponsiveness, loss of postural tone – being synthesised with the seizure-like symptoms of eyelid fluttering/rolling and clonic, myoclonic and other motor symptoms in FS. In chapters 4, 5 and 6, PoTS patients consistently reported a far wider spectrum of symptoms than AMS and EH and this somatic attribution style may explain why more PoTS patients encountered FS.

Patients with functional tremor have been found to misattribute the agency of voluntary movement so that they judge both the intent to move and the act of moving as occurring simultaneously in an aberrant attribution style (Edwards et al., 2011). It could be argued that it is even easier to adopt this maladaptive attribution style if the individual is also tachycardic or pre-syncopal at the time, especially pre-diagnosis of OI when these autonomic symptoms could act as a somatic marker of unknown illness. Chapter 6 indicates a higher order deficit in OI and EH patients' conscious cardiac interoceptive accuracy but the prevalence of FS in PoTS is suggestive of a subconscious or pre-conscious disruption of brain-body integration driven by episodes of OI.

In light of the impaired interoception in PoTS and AMS, predictive processing models may offer an alternative to understanding FS as the engagement of motor systems to reduce interoceptive prediction errors of symptomatic OI, substantiated by the finding that FS/PoTS patients were referred for syncope not PoTS-related symptoms and reported mainly neuropathic rather than cardiothoracic symptoms pre and post FS.

8.2. Anxiety sensitivity to autonomic & cognitive aberrations due to intermittent dysautonomia

Trauma was not a mediator of the pervasive cognitive-affective symptoms reported by intermittent dysautonomia patients and all three clinical cohorts reported greater cognitive depressive symptoms of indecisiveness and concentration difficulty than controls. Anxiety-related phenomena in autonomic patients is not typical of clinical anxiety disorder patients but is rather defined by visceral factors. The fact that AMS patients reported being significantly more sensitive and paid more attention to changes in their body can be viewed from a homeostatic perspective, in that these symptoms can be a somatic marker of an imminent syncopal episode. PoTS patients in particular reported pronounced anxiety, attentional difficulties and somatic hypervigilant symptoms.

Rather than anxiety being a neurotic trait-like phenomena, such as self-consciousness or social anxiety, somatic and cognitive symptoms predominated as the source of distress in all patients groups, demonstrating that these higher order symptoms may relate to the central integration of (aberrant) afferent autonomic signalling. Some insight into this potential central mediation may be garnered from the recent neuroimaging findings that reduced left insula grey matter volumes in PoTS (Umeda et al., 2015) have been negatively correlated with depression and anxiety scores, and that reduced right insula volumes in AMS are correlated with BP falls during HUT (Kim et al., 2014).

Although PoTS patients reported themselves as having accurate subjective interoception via self-report measures, their lack of reported cardiothoracic symptoms in chapters 4 and 5, and the interoceptive findings in chapters 6 and 7, is more representative of subjective sensitisation rather than interoceptive accuracy, which was actually found to be diminished in all patient groups.

The lack of state anxiety, social anxiety or self-consciousness indicates that the common psychological symptoms experienced by AMS, EH and PoTS patients are derived from the physiological and homeostatic dysregulation caused by their intermittent autonomic disorder, as evidenced by anxiety being firmly aligned with somatic events, visceral sensations, attentional deficits and the vigilance and anxious apprehension of these phenomena. This is substantiated by the strongest correlations amongst all intermittent dysautonomia patient groups relating to anxiety sensitivity to visceral sympathetic arousal and attentional deficits.

This anxiety sensitivity to cognitive and autonomic symptoms that are defining symptoms of OI may also elucidate the prevalence of FS in OI patients during autonomic testing in chapter 4.

Sensitivity to visceral symptoms appears to be associated with functional symptoms, whereas sensitivity to central symptoms is associated with derealisation, presumably as there is no evasive behaviour other than dissociation or distraction (perhaps contributing to attentional deficits) that alleviates the distress caused by the sensitivity and awareness of these affective and attentional symptoms. This may also explain the incidence of FS during symptom provocation in undiagnosed OI patients with subnormal interoception (as evidenced in chapters 6 and 7). These findings indicate how the prevalent psychological symptoms in EH and OI are caused by rather than causative of intermittent dysautonomia.

8.3. Interoception is anxiogenic in intermittent dysautonomia: interoceptive prediction error strategies as a potential explanation for attentional symptoms

Despite increased somatic anxiety, EH, PoTS and AMS patients consistently underestimated their cardiac activity and EH and AMS groups had identical interoceptive profiles, providing further support for the involvement of a common (central) integrative dysregulation of visceral sensory information. This is supported by PoTS patients' symptoms being provoked on HUT, yet neither their interoceptive accuracy nor interoceptive sensibility improving. In addition, AMS and EH subjects' interoceptive accuracy significantly worsened on HUT, implicating non-cardiac mechanoreceptors in OI and EH cardiac interoception and further evidencing differences between high order processing of visceral nerve activity between the autonomic cohorts and controls.

The implication of the insula in OI neuropathophysiology may contribute to perturbed interoception in AMS and PoTS, as the right insula depicts internal bodily state that can be consciously accessed and the left insula is involved in parasympathetic cardiovascular regulation (Oppenheimer et al., 1996). Alternatively or additionally, the underestimated cardiac interoception may be due to cognitive control networks (Seeley et al., 2007) altering the interoceptive weight of afferent inputs from the periphery, also explaining PoTS patients under-reporting of cardiothoracic symptoms in chapters 4 and 5. This demand on cognitive control networks may also contribute to the attentional symptoms reported in chapters 5 and 6. Behaviour is influenced by interoception to maximise reward and avoid punishment (Damasio et al., 1991, Bechara et al., 1997a) and it follows that if interoceptive feedback of increased autonomic activity is too dysregulating, i.e., causes large prediction errors requiring alterations in how the brain attends to interoceptive signals that inform behavioural learning, then cognitive and attentional difficulties will occur, at least during symptom provocation. However, the current data suggests these deficits may also occur at rest, perhaps due to the conditioning of brain-body integrative processes over time.

In healthy controls, interoception appeared to be serving its homeostatic purpose, as the more interoceptively accurate controls were, the less time they scanned their body for symptoms of sympathoexcitation. This was reversed in PoTS, further suggesting that interoception appears to be anxiogenic rather than homeostatic in this cohort. The Body Vigilance Scale survey data alone found that cardiothoracic symptoms were not the target of somatic hypervigilance in PoTS, yet the symptoms associated with interoceptive accuracy in PoTS were not only primary symptoms of PoTS (dizziness, shortness of breath, choking), but the relationship of hypervigilance of these symptoms to interoceptive accuracy was positively related, again suggesting that interoception is driving somatic anxiety in PoTS.

Further evidence for this breakdown in the central processing of visceral activity can also be found in the fact that cardiovascular arousal increases interoception (Schandry et al., 1993), yet the opposite was true of AMS, EH and PoTS patients. This may also substantiate the implementation of strategies to accommodate large interoceptive predication errors in these cohorts. Together, these findings indicate that discrepancies and aberrations in interoceptive expectations are somatic sources of anxiety and disrupt cognition, supporting current 'peripheral' theories of emotion. This may also offer a possible therapeutic pathway for psychological symptoms in OI and EH.

8.4. Orienting & visceral sensory processes are dysregulated by dysautonomia

Tilted viewing of unpleasant images produced exaggerated DBP ORs in both OI groups, suggesting these images possessed greater intensity and that OI symptom provocation may contribute to negative affect, at least at an unconscious level. This potential for OI to exacerbate negative affect may help explain the prevalence of somatic anxiety in chapters 5 and 6. The lack of association between interoceptive accuracy and systolic blood pressure (stroke volume, aortic compliance and left ventricular ejection velocity) in favour of correlations between interoceptive accuracy and diastolic blood pressure (peripheral resistance of blood flow from arterioles to capillaries) in PoTS, in addition to AMS and PoTS supine and HUT blood pressure data (ORs and mean) being more strongly related to interoception than cardiac data, further implicates vasomotor afferent signalling of mechanoreceptors rather than cardiac nerve activity in OI cardiac interoception, conceivably accounting for these patients reduced cardiac interoceptive accuracy and also the recent finding that the interoception of palpations in PoTS is separable to tachycardia (Khurana, 2014). Conversely, healthy controls' cardiac interoceptive accuracy was strongly aligned to systolic activity, restating differences in the way visceral activity is centrally processed between patients and healthy controls, as in chapter 6 where interoception was found to be anxiogenic rather than homeostatic in nature in OI. Barry's 'preliminary process

theory' states that the peripheral vasoconstriction OR is an index of stimulus intensity (Barry, 2009), however, it is important to note that PoTS and AMS valance ratings on the VAS to unpleasant images on HUT did not differ from that of controls. The IAPS database provides valence ratings for each image but during pilot study data collection, asking patients with OI to provide both valence and intensity ratings proved difficult and often meant the clinical participants needed significantly longer between images than controls to provide both measures. In hindsight, it may have been preferable to focus on intensity rather than valence ratings with the VAS, as the intention that the degree of valence on the sliding VAS would provide a proxy measure of intensity was not found.

PoTS greater cardiac deceleration to unpleasant images representing stimulus detection correlated with increased interoceptive accuracy, which substantiates the integrative roles of ORs and IA in this cohort and supports the concept of visceral sensitisation in this cohort. Moreover, greater stimulus detection (cardiac declaration) was related to visceral sensitivity in PoTS. Chapter 7 provided further evidence for a reduced repertoire of defence responses in AMS, indicating that these patients' common blood injury phobia may be a manifestation of innate differences in the assimilation of aversive stimuli.

Anxiety is perpetuated by somatic hypervigilance (Wilhelm and Roth, 2001), biased ORs to perceived threat (Bar-Haim et al., 2007) and attentional deficits (Eysenck et al., 2007). Somatic hypervigilance and attentional deficits are also common symptoms reported by EH, AMS and PoTS patients but differing from clinical anxiety cohorts in that anxiety symptoms were predominantly defined by somatic and cognitive factors. Attentional habits that are weighted towards threat (Mathews, 1990) and somatic hypervigilance (Verkuil et al., 2007) cause a cycle of anxiety and could be perpetuated by a condition that excessively increases autonomic activity, particularly as the data in chapters 6 and 7 indicate how psychophysiological processes, such as orienting and interoception are dysregulated by dysautonomia, as supported by the lack of correlations between interoception and ORs in controls.

8.5. Impact & future research

The functional and psychosomatic findings in chapter 4, the somatic and cognitive anxiety sensitivity and depression in chapter 5, the aberrant affective and visceral integration in chapter 6 and the disruption of innate phylogenetic assimilative reflexes and homeostatic mediation in chapter 7 not only evidences the psychological impact of intermittent dysautonomia but also provides a potential treatment pathway for these symptoms. Further research is required on how treatment of dysautonomia interacts with these comorbid psychological symptoms, the neuropathophysiology of OI and EH at rest and during symptom

provocation and how these findings relate to autonomic and psychological symptoms to improve treatment and diagnosis of intermittent dysautonomia, and also how the autonomic nervous system couples brain and body to drive cognitive-affective processes in health and disease.

Due to a number of constraints, the experiments undertaken in this thesis had some limitations. In chapter 4 examining FS, retrospective analysis, which dated back over a number of years, was limited to patient files and clinical data gathered by a number of varying clinicians, almost all of whom, would have had no interest in collecting data related to investigating FS. I would like to rectify this and build on the data I have collected so far carrying out a prospective study looking at a broader spectrum of functional neurological symptoms, including FS, during autonomic testing and if the presentation of these symptoms is influenced by the diagnosis and treatment of autonomic symptoms. I was only able to hypothesise about the possible reasons for FS occurring in PoTS and AMS patients, therefore it would also be useful to ask these patients to participate in the interoceptive exercises from chapter 6, to better understand how they interpret being symptomatic during HUT and pHUT.

For a questionnaire survey, chapter 5 was underpowered (22 x healthy controls, 30 x PoTS patients, 20 x EH patients, 22 x AMS patients) and I will continue to collect data from OI and EH patients to ensure the findings are publishable. I also would like to investigate further the prevalence of the subtle dissociative symptoms correlation analysis revealed in EH patients. Psychological investigations are typically limited to anxiety in EH, however, a 2013 study (Ak et al., 2013) found alexithymia to be increased in EH. In light of this and the chapter 5 data, I think dissociative symptoms in EH warrants further study from a psychodermatological perspective (Poot et al., 2007), considering the role of the skin in emotional expression and selfhood (Koblenzer, 1983).

I found that most PoTS, EH and AMS patients experience attentional problems. However, despite a small number of studies in PoTS investigating cerebral perfusion and noradrenergic coupling, the cause of this brain fog remains unknown in PoTS and is under-researched in AMS and EH (Ross et al., 2013). Cognitive function is also impaired in fixed ANS disorders, especially during orthostasis, despite no evidence of neurological deficits (Guaraldi et al., 2014, Heims et al., 2006a) and it is unclear whether this is due to common pathological processes effecting cognitive or autonomic neuroanatomy, from cerebral hypoperfusion, or an unknown cause. The baroreflex modulates cardiac responses to BP fluctuations and is intermittently compromised in AMS and PoTS and permanently compromised in AF. A recent study evidenced memory formation in healthy controls is poorer at systole compared to diastole (Garfinkel et al., 2014), therefore, I would like to investigate the potential role of the baroreflex

(and its central regulation) (Gianaros et al., 2012) in the expression of brain fog in intermittent and fixed ANS disorders, combining simultaneous functional neuroimaging, psychophysiological challenge and peripheral stimulation in comparison to healthy controls, to gain insight into the interaction of central and peripheral pathologies.

Considering the interoceptive findings in chapters 6 and 7, I proposed that OI cardiac interoception may involve mechanoreceptors in more than one location, not only those located in the heart. Unfortunately, due to the Finometer using a finger cuff to collect beat-to-beat BP data, it was not possible to collect any BP data during these studies which wold of been particularly relevant. As with chapter 5, the number of participants was low (23 x healthy controls, 21 x PoTS patients, 17 x EH patients, i6 x AMS patients) due to various constraints. I also propose the possibility of a centrally mediated dysregulation of brain-body integration causing the interoceptive findings, therefore, repeating these exercises during functional brain imaging may present some significant insights into possible neurobiological mechanisms that contribute to the common psychological symptoms in AMS, EH and PoTS.

Due to the prevalence of blood-injury phobia in VVS (Humm and Mathias, 2010), the potential for pain to induce vasovagal episodes and the pain sensitivity in PoTS (Mathias et al., 2012), I would like to investigate in the future whether neuroimaging can elucidate interoception and nociception symptoms in OI, particularly in light of the recent implications of the insula (interoceptive, nociceptive and autonomic centre) in OI neuropathophysiology (Umeda et al., 2015) (Kim et al., 2014). Additionally, subjective experience of pain is inversely correlated with BP (Delgado et al., 2014) and baroreceptor activity influences pain sensitivity (Gray et al., 2010), yet this has not been investigated in AMS and PoTS, where the baroreflex is intermittently compromised and patients have low BP profiles. Therefore, I believe conducting a large scale imaging survey of potential structural abnormalities and combining simultaneous functional neuroimaging, low level pain fibre stimulation and interoception testing may be of value.

In chapter 7, VAS data for neutral, pleasant and unpleasant valences was presented in mean form. I suspect matching each VAS image rating to each OR may have the potential to offer further findings into the effect of OI on HUT ORs. Unfortunately, due to time constraints, the reanalysed data could not be presented in this thesis. The inclusion of aversive sound stimuli may also be useful in examining ORs and CDRs to different sensory signals as well as utilising emotion regulation paradigms to progress the current.

In distilling and synthesising the various findings of this thesis, I feel it is reasonable to conclude that subnormal interoception in PoTS predisposes to functional symptoms, the affective

symptoms many OI and EH patients report are primarily related to somatic factors rather than being trait-like phenomena, anxiety sensitivity to autonomic and cognitive aberrations in OI and EH is due to intermittent dysautonomia, interoception is anxiogenic in intermittent dysautonomia and orienting & visceral sensory processes are dysregulated by dysautonomia. I feel that these findings may provide a worthwhile contribution to the psychophysiology of dysautonomia.

Appendix A: The Body Vigilance Questionnaire

Schmidt, Lerew, & Trakowski (1997)

In this section, we are interested in learning how sensitive you are to internal bodily sensations such as heart palpitations or dizziness. Please fill it out according to how you have felt for the **past week**.

1. I am the kind of person who pays close attention to internal bodily sensations.

0 1 2 3 4 5 6 7 8 9 10

Not at all like me **Moderately like me** **Extremely like me**

2. I am very sensitive to changes in my internal bodily sensations.

0 1 2 3 4 5 6 7 8 9 10

Not at all like me **Moderately like me** **Extremely like me**

3. On average, how much time do you spend each day "scanning" your body for sensations (eg., sweating, heart palpitations, dizziness)?

0 1 2 3 4 5 6 7 8 9 10

No time **Half of the time** **All of the time**

4. Rate how much attention you pay to each of the following sensations using the scale below. Write the appropriate number on the line next to each item.

0 1 2 3 4 5 6 7 8 9 10

None **Slight** **Moderate** **Substantial** **Extreme**

1. Heart palpitations _____
2. Chest pain/discomfort _____
3. Numbness _____
4. Tingling _____
5. Shortness of breath/smothering _____
6. Faintness _____
7. Vision changes _____
8. Feelings of unreality _____
9. Feeling detached from self _____
10. Dizziness _____
11. Hot Flash _____
12. Sweating/clammy hands _____
13. Stomach Upset _____
14. Nausea _____
15. Choking/throat closing _____

Appendix B: Beck Depression Inventory

Name		Date	

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1.Sadness	6.Punishment Feelings
0 I do not feel sad 1 I feel sad much of the time 2 I am sad all the time 3 I am so sad or unhappy that I can't stand it	0 I don't feel I am being punished 1 I feel like I may be punished 2 I expect to be punished 3 I feel I am being punished
2.Pessimism	**7.Self-Dislike**
0 I am not discouraged about my future 1 I feel more discouraged about my future than I used to be 2 I do not expect things to work out for me 3 I feel my future is hopeless and will only get worse	0 I feel the same about myself as ever 1 I have lost confidence in myself 2 I am disappointed in myself 3 I dislike myself
3.Past Failure	**8.Self-Criticalness**
0 I do not feel like a failure 1 I have failed more than I should have 2 As I look back, I see a lot of failures 3 I feel I am a total failure as a person	0 I don't criticise or blame myself more than usual 1 I am more critical of myself than I used to be 2I criticise myself for all of my faults 3 I blame myself for everything bad that happens
4.Loss of Pleasure	**9. Suicidal Thoughts or Wishes**
0 I get as much pleasure as I ever did from the things I enjoy 1 I don't enjoy things as much as I used to 2 I get very little pleasure from the things I used to enjoy 3 I can't get any pleasure from the things I used to enjoy	0 I don't have any thoughts of killing myself 1 I have thoughts of killing myself, but I would not carry them out 2 I would like to kill myself 3 I would kill myself if I had the chance
5.Guilty Feelings	**10. Crying**
0 I don't feel particularly guilty 1 I feel guilty over many things I have done or should have done 2 I feel quite guilty most of the time 3 I feel guilty all of the time	0 I don't cry any more than I used to 1 I cry more than I used to 2 I cry over every little thing 3 I feel like crying, but I can't
11. Agitation	**17. Irritability**
0 I am no more restless or wound up than usual 1 I feel more restless or wound up than usual 2 I am so restless or agitated that it's hard to stay still 3 I am so restless or agitated that I have to keep moving or doing something	0 I am no more irritable than usual 1 I am more irritable than usual 2 I am much more irritable than usual 3 I am irritable all the time
12. Loss of Interest	**18. Changes in Appetite**
0 I have not lost interest in other people or activities 1 I am less interested in other people or things than before 2 I have lost most of my interest in other people or things 3 It's hard to get interested in anything	0 I have not experienced any change in my appetite 1a My appetite is somewhat less than usual 1b My appetite is somewhat greater than usual 2a My appetite is much less than before 2b My appetite is much greater than usual 3a I have no appetite at all 3b I crave food all the time
13. Indecisiveness	**19. Concentration Difficulty**
0 I make decisions about as well as ever	0 I can concentrate as well as ever

1 I find it more difficult to make decisions than usual 2 I have much greater difficulty in making decisions than I used to 3 I have trouble making any decisions	1 I can't concentrate as well as usual 2 It's hard to keep my mind on anything for very long 3 I find I can't concentrate on anything
14. Worthlessness	20. Tiredness or Fatigue
0 I do not feel I am worthless 1 I don't consider myself as a worthwhile and useful as I used to 2 I feel more worthless as compared to other people 3 I feel utterly worthless	0 I am no more tired or fatigued than usual 1 I get more tired or fatigued more easily than usual 2 I am too tired or fatigued to do a lot of the things I used to do 3 I am too tired or fatigued to do most of the things I used to do
15. Loss of Energy	21. Loss of Interest in Sex
0 I have as much energy as ever 1 I have less energy than I used to have 2 I don't have enough energy to do very much 3 I don't have enough energy to do anything	0 I have not noticed any recent change in my interest in sex 1 I am less interested in sex than I used to be 2 I am much less interested in sex now 3 I have lost interest in sex completely
16. Changes in Sleeping Pattern	
0 I have not experienced any change in my sleeping pattern 1a I sleep somewhat more than usual 1b I sleep somewhat less than usual 2a I sleep a lot more than usual 2b I sleep a lot less than usual 3a I sleep most of the day 3b I wake up 1-2 hours early and can't get back to sleep	Subtotal Page 1 Subtotal Page 2 Total Score

Appendix C: Cardiac Anxiety Scale

Please rate each item by circling the answer (number) that best applies to you:

	Never	Rarely	Sometimes	Often	Always
1. I pay attention to my heart beat	1	2	3	4	5
2. I avoid physical exertion	1	2	3	4	5
3. My racing heart wakes me up at night	1	2	3	4	5
4. Chest pain/discomfort wakes me up at night	1	2	3	4	5
5. I take it easy as much as possible	1	2	3	4	5
6. I check my pulse	1	2	3	4	5
7. I avoid exercise or other physical work	1	2	3	4	5
8. I can feel my heart in my chest	1	2	3	4	5
9. I avoid activities that make my heart beat faster	1	2	3	4	5
10. If tests come out normal, I still worry about my heart	1	2	3	4	5
11. I feel safe being around a hospital, physician or other medical facility	1	2	3	4	5
12. I avoid activities that make me sweat	1	2	3	4	5
13. I worry that doctors do not believe my symptoms are real	1	2	3	4	5
When I have chest discomfort or when my heart is beating fast:	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
14. I worry that I may have a heart attack	1	2	3	4	5
15. I have difficulty concentrating on anything else	1	2	3	4	5
16. I get frightened	1	2	3	4	5
17. I like to be checked out by a doctor	1	2	3	4	5
18. I tell my family or friends	1	2	3	4	5

Appendix D: Anxiety Sensitivity Index

A number of statements that people have used to describe themselves are given below. Read each statement and mark the appropriate number to indicate how you feel right now at this moment. There are no right or wrong answers. Don't spend too much time on one statement but give the answer that best describes your present feelings.	0. Not at all like me	1. Slightly disagree	2. Moderately like me	3. Quite like me	4. Extremely like
1. When I cannot keep my mind on a task, I worry that I might be going crazy	☐	☐	☐	☐	☐
2. It scares me when I feel "shaky" (trembling)	☐	☐	☐	☐	☐
3. It scares me when I feel faint.	☐	☐	☐	☐	☐
4. It scares me when my heart beats rapidly	☐	☐	☐	☐	☐
5. When I notice that my heart is beating rapidly, I worry that I might have had a heart attack	☐	☐	☐	☐	☐
6. It scares me when I become short of breath	☐	☐	☐	☐	☐
7. When my stomach is upset, I worry that I might be seriously ill	☐	☐	☐	☐	☐
8. It scares me when I am unable to keep my mind on a task	☐	☐	☐	☐	☐
9. Unusual body sensations scare me	☐	☐	☐	☐	☐
10. When I am nervous, I worry that I might be mentally ill	☐	☐	☐	☐	☐
11. It scares me when I am nervous	☐	☐	☐	☐	☐

Appendix E: State Anxiety Inventory

A number of statements that people have used to describe themselves are given below. Read each statement and mark the appropriate number to indicate how you feel right now at this moment. There are no right or wrong answers. Don't spend too much time on one statement but give the answer that best describes your present feelings.	1. Not at all	2. Somewhat	3. Moderately so	4. Very much so
1. I feel calm	☐	☐	☐	☐
2. I feel secure	☐	☐	☐	☐
3. I am tense	☐	☐	☐	☐
4. I am regretful	☐	☐	☐	☐
5. I feel at ease	☐	☐	☐	☐
6. I feel upset	☐	☐	☐	☐
7. I am presently worrying over possible misfortunes	☐	☐	☐	☐
8. I feel rested	☐	☐	☐	☐
9. I feel anxious	☐	☐	☐	☐
10. I feel comfortable	☐	☐	☐	☐
11. I feel self-confident	☐	☐	☐	☐
12. I feel nervous	☐	☐	☐	☐
13. I am jittery	☐	☐	☐	☐
14. I feel "highly strung"	☐	☐	☐	☐
15. I am relaxed	☐	☐	☐	☐
16. I feel content	☐	☐	☐	☐
17. I am worried	☐	☐	☐	☐
18. I feel confused	☐	☐	☐	☐
19. I feel steady	☐	☐	☐	☐
20. I feel pleasant	☐	☐	☐	☐

Appendix F: Self-consciousness Scale (revised)

	Not at all like me	A little like me	Somewhat like me	A lot like me
1. I always try to figure myself out	0	1	2	3
2. I'm concerned about my style of doing things	0	1	2	3
3. Generally, I'm not very aware of myself	0	1	2	3
4. It takes me time to overcome my shyness in new situations	0	1	2	3
5. I reflect about myself a lot	0	1	2	3
6. I'm concerned about the way I present myself	0	1	2	3
7. I'm often the subject of my own fantasies	0	1	2	3
8. I have trouble working when someone is watching me	0	1	2	3
9. I never scrutinize myself	0	1	2	3
10. I get embarrassed very easily	0	1	2	3
11. I am self-conscious about the way I look	0	1	2	3
12. I don't find it hard to talk to strangers	0	1	2	3
13. I'm generally attentive to my inner feelings	0	1	2	3
14. I usually worry about making a good impression	0	1	2	3
15. I'm constantly examining my motives	0	1	2	3
16. I feel anxious when I speak in front of a group	0	1	2	3
17. One of the last things I do before I leave home is look in the mirror	0	1	2	3
18. I sometimes have the feeling that I'm off somewhere watching myself	0	1	2	3
19. I'm concerned about what other people think of me	0	1	2	3
20. I'm alert to changes in my mood	0	1	2	3
21. I'm usually aware of my appearance	0	1	2	3
22. I'm aware of how my mind works when I work through a problem	0	1	2	3
23. Large groups make me nervous	0	1	2	3

Appendix G: Balanced Emotional Empathy Scale (BEES):

Please use the following scale to indicate the degree of your agreement or disagreement with each of the statements below. Record your numerical answer to each statement in the space provided preceding the statement. Try to describe yourself accurately and in terms of how you are generally (that is, the average of the way you are in most situations -- not the way you are in specific situations or the way you would hope to be).

+4 = very strong agreement
+3 = strong agreement
+2 = moderate agreement
+1 = slight agreement
0 = neither agreement nor disagreement
-1 = slight disagreement
-2 = moderate disagreement
-3 = strong disagreement
-4 = very strong disagreement

_____ 1. I very much enjoy and feel uplifted by happy endings.
_____ 2. I cannot feel much sorrow for those who are responsible for their own misery.
_____ 3. I am moved deeply when I observe strangers who are struggling to survive.
_____ 4. I hardly ever cry when watching a very sad movie.
_____ 5. I can almost feel the pain of elderly people who are weak and must struggle to move about.
_____ 6. I cannot relate to the crying and sniffling at weddings.
_____ 7. It would be extremely painful for me to have to convey very bad news to another.
_____ 8. I cannot easily empathize with the hopes and aspirations of strangers.
_____ 9. I don't get caught up easily in the emotions generated by a crowd.
_____ 10. Unhappy movie endings haunt me for hours afterward.
_____ 11. It pains me to see young people in wheelchairs.

_____ 12. It is very exciting for me to watch children open presents.
_____ 13. Helpless old people don't have much of an emotional effect on me.
_____ 14. The sadness of a close one easily rubs off on me.
_____ 15. I don't get overly involved with friends' problems.
_____ 16. It is difficult for me to experience strongly the feelings of characters in a book or movie.
_____ 17. It upsets me to see someone being mistreated.
_____ 18. I easily get carried away by the lyrics of love songs.
_____ 19. I am not affected easily by the strong emotions of people around me.
_____ 20. I have difficulty knowing what babies and children feel.
_____ 21. It really hurts me to watch someone who is suffering from a terminal illness.
_____ 22. A crying child does not necessarily get my attention.
_____ 23. Another's happiness can be very uplifting for me.
_____ 24. I have difficulty feeling and reacting to the emotional expressions of foreigners.
_____ 25. I get a strong urge to help when I see someone in distress.
_____ 26. I am rarely moved to tears while reading a book or watching a movie.
_____ 27. I have little sympathy for people who cause their own serious illnesses (e.g., heart disease, diabetes, lung cancer).
_____ 28. I would not watch an execution.
_____ 29. I easily get excited when those around me are lively and happy.
_____ 30. The unhappiness or distress of a stranger are not especially moving for me.

Appendix H: Childhood Traumatic Events Scale

For the following questions, answer each item that is relevant. Be as honest as you can. Each question refers to any event that you may have experienced **prior to the age of 17**.

1. Prior to the age of 17, did you experience a death of a very close friend or family member?_____ If yes, how old were you?_____
If yes, how traumatic was this? (using a 7-point scale, where 1 = not at all traumatic, 4 = somewhat traumatic, 7 = extremely traumatic)_____
If yes, how much did you confide in others about this traumatic experience at the time? (1 = not at all, 7 = a great deal)_____
2. Prior to the age of 17, was there a major upheaval between your parents (such as divorce, separation)?_____ If yes, how old were you?_____
If yes, how traumatic was this? (where 7 = extremely traumatic)_____
If yes, how much did you confide in others? (7 = a great deal)_____
3. Prior to the age of 17, did you have a traumatic sexual experience (raped, molested, etc.)?_____ If yes, how old were you?_____
If yes, how traumatic was this? (7 = extremely traumatic)_____
If yes, how much did you confide in others? (7 = a great deal)_____
4. Prior to the age of 17, were you the victim of violence (child abuse, mugged or assaulted -- other than sexual)?_____ If yes, how old were you?_____
If yes, how traumatic was this? (7 = extremely traumatic)_____
If yes, how much did you confide in others? (7 = a great deal)_____
5. Prior to the age of 17, were you extremely ill or injured?_____ If yes, how old were you?_____
If yes, how traumatic was this? (7 = extremely traumatic)_____
If yes, how much did you confide in others? (7 = a great deal)_____
6. Prior to the age of 17, did you experience any other major upheaval that you think may have
shaped your life or personality significantly?_____ If yes, how old were you?_____
If yes, what was the event?_____
If yes, how traumatic was this? (7 = extremely traumatic)_____
If yes, how much did you confide in others? (7 = a great deal)_____

Appendix I: Recent Traumatic Events Scale

For the following questions, again answer each item that is relevant and again be as honest as you
can. Each question refers to any event that you may have experienced **within the last 3 years**.

1. Within the last 3 years, did you experience a death of a very close friend or family member?

_____
If yes, how traumatic was this? (1 = not at all traumatic, 7 = extremely traumatic)_____
If yes, how much did you confide in others about the experience at the time? (1 = not at all, 7 = a great deal)_____

2. Within the last 3 years, was there a major upheaval between you and your spouse (such as divorce, separation)?_____
If yes, how traumatic was this?_____
If yes, how much did you confide in others?_____

3. Within the last 3 years, did you have a traumatic sexual experience (raped, molested, etc.)?_____
If yes, how traumatic was this?_____
If yes, how much did you confide in others?_____

4. Within the last 3 years, were you the victim of violence (other than sexual)?_____
If yes, how traumatic was this?_____
If yes, how much did you confide in others?_____

5. Within the last 3 years, were you extremely ill or injured?_____
If yes, how traumatic was this?_____
If yes, how much did you confide in others?_____

6. Within the last 3 years, has there been a major change in the kind of work you do (e.g., a new
job, promotion, demotion, lateral transfer)?_____
If yes, how traumatic was this?_____
If yes, how much did you confide in others?_____

7. Within the last 3 years, did you experience any other major upheaval that you think may have
shaped your life or personality significantly?_____
If yes, what was the event?_____
If yes, how traumatic was this?_____
If yes, how much did you confide in others?_____

Appendix J: PATIENT INFORMATION SHEET (i)

Study Title: Interoception of Sympathetic Nerve Activity in Dysautonomia (PhD study)

Investigators: Andrew Owens, Dr Valeria Iodice, Professor Christopher Mathias, Professor Hugo Critchley, Dr David Low

You are invited to participate in the above study, before you decide, it is important for you to understand why the research is being carried out and what is involved. Please take some time to read the following information carefully and feel free to discuss with others if you wish.

Part 1 of this patient information sheet tells you the purpose of the study and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the study

Thank you very much for taking the time to read more about this study.

Part 1. Purpose of the research.

Background of the study:

Theories of emotion suggest that emotions are a result of things we see, hear and feel, such as reactions to bodily sensations caused by things we experience. So, if something that makes our heart rate increase or causes us to sweat, this may well influence our emotions. The autonomic nervous system (ANS) controls a range of bodily responses, such as blood pressure (BP), heart rate (HR) and sweating. The word 'autonomic' is used because ANS function is unconsciously controlled. We are investigating if disorders of the ANS that affect blood pressure, heart rate and sweating, e.g., excessive uncontrollable sweating (hyperhidrosis), Postural Tachycardia Syndrome (PoTS) and fainting (syncope), also influence emotions, as patients may physical states similar to heightened emotions, like;

- a racing heart caused by excitement or stress in PoTS
- light-headedness or feeling overwhelmed during fainting
- feeling hot or clammy in hyperhidrosis

The link between autonomic dysfunction (dysautonomia) of these disorders and any emotional changes that may occur has not been thoroughly investigated, however. For example, does the severity of the autonomic dysfunction dictate the influence on any emotional changes, if any changes are present?

Specific aims of this study:

In this study, emotional and autonomic factors in dysautonomia patients will be compared to participants without dysautonomia.

Why have you been chosen?

You have been chosen because you have a form of dysautonomia.

Do I have to take part?

Taking part in this research study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights at all.

Part 2 – what will happen if you take part

How long will the study last?

All procedures will last ~60 mins in total in 1 visit. The testing will take place at the Autonomic Unit, National Hospital for Neurology and Neurosurgery, London.

Study procedures:

First you will be asked to complete some questionnaires that are designed to assess your experiences and emotions, which should take no more than 20 minutes. You will then be asked to lie down on a bed for ten minutes while cuffs are wrapped around one of your arms and fingers to record your BP and sensors are placed on your chest and ankles to record your HR. Next, you will be asked to squeeze a pad, and then put your hand on something cold, whilst trying to count your own heartbeats for brief periods during these 2 (gripping, cold pack) exercises. You may have previously performed these exercises at our department as they provide a very good insight into your autonomic nervous system.

The bed you are laying on will then be tilted to sixty degrees (head up tilt table test) and you will be asked to try and count along to your own heartbeat (experimental task) again for between 60-120 seconds during the 9 minute period of being tilted with your head up. You may have previously performed a tilt table test at our department as it provides a very good insight into your autonomic nervous system function. The bed will then be lowered back to its normal position, you will be disconnected from the BP and HR monitors and will be free to go home. Please feel free to ask the investigator any questions at the end of testing or after you have left via the contact details provided.

What data will be collected?

The data that will be collected is your BP and HR reactions to the exercises and your questionnaires. All data will be anonymised (e.g., it will not identify you).

What are the possible risks of taking part?

There are a minimal amount of risks to taking part in this study. Should you have any adverse reactions, the Autonomic Unit, as well as the Hospital, have a number of highly-trained experts and emergency paramedics for such situations. There is possible risk of fainting during the upright phase of the tilting. BP and HR will be measured continuously during this test (and all the others) and therefore will be frequently monitored and, if blood pressure does fall to low levels, action can be taken immediately by stopping the test and returning you to the lying down position, when BP will return to normal and you should feel much better almost

immediately. If any new information becomes available during your participation that suggests that it might be in your best interests to withdraw from the study, this decision will be made by the Principal Investigator, your doctor and yourself. In all cases, the reasons will be thoroughly explained to you.

What are the benefits of taking part?

There is no direct benefit to you for taking part, however, it is hoped that the findings from this research will help the understanding and treatment of dysautonomia.

What if something goes wrong?

University College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that University College is at fault. This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator Andrew Owens (andrew.owens.13@ucl.ac.uk, tel: 020 3456 1383 or 020 3448 3413). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the University Joint Research Compliance Office.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. An identification code will be ascribed to each participant and all data collected will be electronically compiled anonymously. Any information about you which leaves the Unit will have your name removed so that you cannot be recognised from it. Procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998. We would like to inform your GP that you are taking part in this research, which you will be free to decide (or not) to provide your consent for us to do so.

What will happen to the results of the research study?

Results will be presented anonymously at scientific conferences and in published research articles, which will typically occur ~6 months after the final participant has completed the study. If you would like, the Chief Investigator can provide you with a copy of the published results. You will not be identified in any report/publication.

Who is organising and funding the research?

This research study is being organised through University College London.

Contact for Further Information

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Appendix K: PATIENT INFORMATION SHEET (ii)

Study Title: Psychological symptoms and dysautonomia: antecedent or succedent complications? (PhD study)

Investigators: Andrew Owens (PhD student), Dr Valeria Iodice, Professor Christopher Mathias, Professor Hugo Critchley, Dr David Low

You are invited to participate in the above study, before you decide, it is important for you to understand why the research is being carried out and what is involved. Please take some time to read the following information carefully and feel free to discuss with others if you wish. This study has been reviewed and approved by the London – Harrow Research Ethics Committee.

Part 1 of this patient information sheet tells you the purpose of the study and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the study

Thank you very much for taking the time to read more about this study.

Part 1. Purpose of the research.

Background of the study:

Theories of emotion suggest that emotions are a result of things we see, hear and feel, such as reactions to bodily sensations caused by things we experience. So, if something that makes our heart rate increase or causes us to sweat, this may well influence our emotions. The autonomic nervous system (ANS) controls a range of bodily responses, such as blood pressure (BP), heart rate (HR) and sweating. The word 'autonomic' is used because ANS function is unconsciously controlled. We are investigating if disorders of the ANS that affect blood pressure, heart rate and sweating, e.g., excessive uncontrollable sweating (hyperhidrosis), Postural Tachycardia Syndrome (PoTS) and fainting (syncope), also influence emotions, as patients may physical states similar to heightened emotions, like;

- a racing heart caused by excitement or stress in PoTS
- light-headedness or feeling overwhelmed during fainting
- feeling hot or clammy in hyperhidrosis

The link between autonomic dysfunction (dysautonomia) of these disorders and any emotional changes that may occur has not been thoroughly investigated, however. For example, does the severity of the autonomic dysfunction dictate the influence on any emotional changes, if any changes are present?

Specific aims of this study:

In this study, the autonomic responses (BP and HR) to physical and psychological stimuli in dysautonomia patients who have difficulty in regulating their sweating and body temperature, heart rate (such as Postural Tachycardia Syndrome) and blood pressure (causing fainting), will be compared to volunteers without any symptoms. Awareness of bodily sensations, such as a racing heart, has been proposed to play an important part in the formation of emotions, such as feeling nervous or excited. This study aims to examine how dysautonomia patients, who have symptoms that can mimic emotional responses, such as sweating, fainting or a racing heart, respond to emotional stimuli, like pictures and music.

Why have you been chosen?

You have been chosen because you have dysautonomia or because you do not have dysautonomia or any other autonomic conditions and your data will be used as 'control data' and used as a normative comparison for the data of the dysautonomia group.

Do I have to take part?

Taking part in this research study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights at all.

Part 2 – what will happen if you take part

How long will the study last?

About an hour. The testing will take place at the Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London.

Study procedures:

This study should take no more than 90 minutes and combines some tests that are part of your routine diagnosis (head up tilt) and visual and audio stimuli that may provoke an emotional response. First you will be asked to complete some questionnaires that are designed to assess your experiences of mood, this should take no more than 15 minutes. You will then be asked to lie down on a bed for ten minutes while a cuff is wrapped around one of your arms and fingers to measure blood pressure and sensors are placed on your collar bones, rib cage and ankles. These sensors are connected to an electrocardiogram (ECG) which records your heart function. You will be shown some pictures and played pieces of music that contain an assortment of pleasant, neutral and unpleasant stimuli and be asked to rate each image and piece of music. The images are shown for around 5 minutes and the music played for around 12 minutes. The bed you are on will then be safely tilted to 60 degrees with your head up and you will be presented with a new set of pictures for around 5 minutes and music for around 12 minutes that contain an assortment of pleasant, neutral and unpleasant stimuli and asked to rate each image and piece of music. The bed will then be lowered back to its normal position and the study will end.

What data will be collected?

All data is anonymised. The other data that is collected is your ratings and BP and HR reactions to the autonomic and emotional stimuli, as well as the questionnaire data.

What are the possible risks of taking part?

Minimal. Should you have any adverse reactions, a team of emergency paramedics operate at the hospital around the clock. The Autonomic Unit also has a number of highly-trained

experts on-hand. There is possible risk of fainting during the upright phase of the tilting procedure. BP and HR will be measured continuously during this test (and all the others) and therefore will be frequently monitored and, if blood pressure does fall to precipitously low levels, action can be taken immediately by stopping the test and returning you to the supine position, when BP will return to normal and you should feel much better almost immediately.

If any new information becomes available during your participation that suggests that it might be in your best interests to withdraw from the study, this decision will be made by the Principal Investigator, your doctor and yourself. In all cases, the reasons will be thoroughly explained to you.

What are the benefits of taking part?

There is no direct benefit to you for taking part, however, it is hoped that the findings from this research will help the understanding and treatment of dysautonomia.

What if something goes wrong?

University College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator Andrew Owens (andrew.owens.13@ucl.ac.uk, tel: 020 3456 1383 or 020 3448 3413). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the University College London Hospitals NHS Foundation Trust, Joint Research Office.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. An identification code will be ascribed to each participant and all data collected will be electronically compiled anonymously. Any information about you which leaves the Unit will have your name removed so that you cannot be recognised from it. Procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998. We would like to inform your GP that you are taking part in this research, which you will be free to decide (or not) to provide your consent for us to do so.

What will happen to the results of the research study?

Results will be presented anonymously at scientific conferences and in published research articles, which will typically occur ~6 months after the final participant has completed the study. If you would like, the Principal Investigator can provide you with a copy of the published results. You will not be identified in any report/publication.

Who is organising and funding the research?

This research study is being organised through University College London.

Contact for Further Information

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References

1968. Code of ethics on human experimentation adapted from the Helsinki Declaration of the World Medical Association. *Am J Orthopsychiatry,* 38**,** 589-90.

AALTONEN, T., AMERIO, S., AMIDEI, D., ANASTASSOV, A., ANNOVI, A., ANTOS, J., APOLLINARI, G., APPEL, J. A., ARISAWA, T., ARTIKOV, A., ASAADI, J., ASHMANSKAS, W., AUERBACH, B., AURISANO, A., AZFAR, F., BADGETT, W., BAE, T., BARBARO-GALTIERI, A., BARNES, V. E., BARNETT, B. A., BARRIA, P., BARTOS, P., BAUCE, M., BEDESCHI, F., BEHARI, S., BELLETTINI, G., BELLINGER, J., BENJAMIN, D., BERETVAS, A., BHATTI, A., BLAND, K. R., BLUMENFELD, B., BOCCI, A., BODEK, A., BORTOLETTO, D., BOUDREAU, J., BOVEIA, A., BRIGLIADORI, L., BROMBERG, C., BRUCKEN, E., BUDAGOV, J., BUDD, H. S., BURKETT, K., BUSETTO, G., BUSSEY, P., BUTTI, P., BUZATU, A., CALAMBA, A., CAMARDA, S., CAMPANELLI, M., CANELLI, F., CARLS, B., CARLSMITH, D., CAROSI, R., CARRILLO, S., CASAL, B., CASARSA, M., CASTRO, A., CATASTINI, P., CAUZ, D., CAVALIERE, V., CAVALLI-SFORZA, M., CERRI, A., CERRITO, L., CHEN, Y. C., CHERTOK, M., CHIARELLI, G., CHLACHIDZE, G., CHO, K., CHOKHELI, D., CLARK, A., CLARKE, C., CONVERY, M. E., CONWAY, J., CORBO, M., CORDELLI, M., COX, C. A., COX, D. J., CREMONESI, M., CRUZ, D., CUEVAS, J., CULBERTSON, R., D'ASCENZO, N., DATTA, M., DE BARBARO, P., DEMORTIER, L., DENINNO, M., D'ERRICO, M., DEVOTO, F., DI CANTO, A., DI RUZZA, B., DITTMANN, J. R., DONATI, S., D'ONOFRIO, M., DORIGO, M., DRIUTTI, A., EBINA, K., EDGAR, R., ELAGIN, A., ERBACHER, R., et al. 2013. Measurement of the differential cross section dsigma/d(costheta(t)) for Top-Quark Pair Production in pp Collisions at sqrt[s] = 1.96 TeV. *Phys Rev Lett,* 111**,** 182002.

ABERCROMBIE, E. D. & JACOBS, B. L. 1987. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and nonstressful stimuli. *J Neurosci,* 7**,** 2837-43.

ABERCROMBIE, H. C., CHAMBERS, A. S., GREISCHAR, L. & MONTICELLI, R. M. 2008. Orienting, emotion, and memory: phasic and tonic variation in heart rate predicts memory for emotional pictures in men. *Neurobiol Learn Mem,* 90**,** 644-50.

ACASUSO-DIAZ, M. & COLLANTES-ESTEVEZ, E. 1998. Joint hypermobility in patients with fibromyalgia syndrome. *Arthritis Care Res,* 11**,** 39-42.

AK, M., DINCER, D., HACIOMEROGLU, B., AKARSU, S., LAPSEKILI, N. & ADA, S. 2013. The evaluation of primary idiopathic focal hyperhidrosis patients in terms of alexithymia. *J Health Psychol,* 18**,** 704-10.

ALBONI, P., ALBONI, M. & BERTORELLE, G. 2008. The origin of vasovagal syncope: to protect the heart or to escape predation? *Clin Auton Res,* 18**,** 170-8.

ALFONSI, P., ADAM, F. & BOUHASSIRA, D. 2015. Thermoregulation and pain perception: Evidence for a homoeostatic (interoceptive) dimension of pain. *Eur J Pain*.

ALMIS, B. H., CUMURCU, B. E., UNAL, S., OZCAN, A. C. & AYTAS, O. 2013. The neuropsychological and neurophysiological profile of women with non-epileptic seizure. *Compr Psychiatry,* 54**,** 649-57.

ANDERSON, E. R. & HOPE, D. A. 2009. The relationship among social phobia, objective and perceived physiological reactivity, and anxiety sensitivity in an adolescent population. *J Anxiety Disord.,* 23**,** 18-26.

ANDERSON, J. W., LAMBERT, E. A., SARI, C. I., DAWOOD, T., ESLER, M. D., VADDADI, G. & LAMBERT, G. W. 2014. Cognitive function, health-related quality of life, and symptoms of depression and anxiety sensitivity are impaired in patients with the postural orthostatic tachycardia syndrome (POTS). *Front Physiol,* 5**,** 230.

ANDRADE, C., SINGH, N. M. & BHAKTA, S. G. 2006. Simultaneous true seizures and non-epileptic seizures. *J Clin Psychiatry,* 67**,** 673.

ARCH, J. J. & CRASKE, M. G. 2010. Laboratory stressors in clinically anxious and non-anxious individuals: the moderating role of mindfulness. *Behav Res Ther,* 48**,** 495-505.

ASTON-JONES, G., CHIANG C, ALEXINSKY T 1991. Discharge of noradrenergic locus coeruleus neurons in behvaing rats and monkeys suggests a role in vigilance. *In:* CD BARNES, O. P. (ed.) *Brogress in Brain Research.* Amsterdam: Elsevier Science Publishers.

ASTON-JONES, G. & COHEN, J. D. 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci,* 28**,** 403-50.

BAGAI, K., SONG, Y., LING, J. F., MALOW, B., BLACK, B. K., BIAGGIONI, I., ROBERTSON, D. & RAJ, S. R. 2011. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J Clin Sleep Med,* 7**,** 204-10.

BAHIT, M. C., LOPES, R. D., CLARE, R. M., NEWBY, L. K., PIEPER, K. S., VAN DE WERF, F., ARMSTRONG, P. W., MAHAFFEY, K. W., HARRINGTON, R. A., DIAZ, R., OHMAN, E. M., WHITE, H. D., JAMES, S. & GRANGER, C. B. 2013. Heart Failure Complicating Non-ST-Segment Elevation Acute Coronary Syndrome: Timing, Predictors, and Clinical Outcomes. *JACC Heart Fail,* 1**,** 223-9.

BAKER, D., HUNTER, E., LAWRENCE, E., MEDFORD, N., PATEL, M., SENIOR, C., SIERRA, M., LAMBERT, M. V., PHILLIPS, M. L. & DAVID, A. S. 2003. Depersonalisation disorder: clinical features of 204 cases. *Br J Psychiatry,* 182**,** 428-33.

BAKVIS, P., ROELOFS, K., KUYK, J., EDELBROEK, P. M., SWINKELS, W. A. & SPINHOVEN, P. 2009. Trauma, stress, and preconscious threat processing in patients with psychogenic nonepileptic seizures. *Epilepsia,* 50**,** 1001-11.

BAKVIS, P., SPINHOVEN, P., PUTMAN, P., ZITMAN, F. G. & ROELOFS, K. 2010. The effect of stress induction on working memory in patients with psychogenic nonepileptic seizures. *Epilepsy Behav,* 19**,** 448-54.

BALE, T. L. 2006. Stress sensitivity and the development of affective disorders. *Horm Behav,* 50**,** 529-33.

BAR-HAIM, Y., LAMY, D., PERGAMIN, L., BAKERMANS-KRANENBURG, M. J. & VAN, I. M. H. 2007. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol Bull,* 133**,** 1-24.

BARBAS, H. & REMPEL-CLOWER, N. 1997. Cortical structure predicts the pattern of corticocortical connections. *Cereb Cortex,* 7**,** 635-46.

BARCROFT, H. & EDHOLM, O. G. 1945. On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting. *J Physiol,* 104**,** 161-75.

BARRETT, L. F. 2006. Are Emotions Natural Kinds? *Perspect Psychol Sci,* 1**,** 28-58.

BARRY, R. J. 1977. The effect of “significance” upon indices of Sokolov's orienting response: A new conceptualisation to replace the OR. . *Physiological Psychology***,** 209–214.

BARRY, R. J. 1990. The orienting response: stimulus factors and response measures. *Pavlov J Biol Sci,* 25**,** 93-9; discussion 99-103.

BARRY, R. J. 2009. Habituation of the orienting reflex and the development of Preliminary Process Theory. *Neurobiol Learn Mem,* 92**,** 235-42.

BARSKY, A. J. 1992. Amplification, somatization, and the somatoform disorders. *Psychosomatics,* 33**,** 28-34.

BEACHER, F. D., GRAY, M. A., MATHIAS, C. J. & CRITCHLEY, H. D. 2009. Vulnerability to simple faints is predicted by regional differences in brain anatomy. *Neuroimage,* 47**,** 937-45.

BECHARA, A. & DAMASIO, A. R. 2005. The somatic marker hypothesis: a neural theory of economic decision. *Games Econ Behav* 336-372.

BECHARA, A., DAMASIO, H., TRANEL, D. & DAMASIO, A. R. 1997a. Deciding advantageously before knowing the advantageous strategy. *Science,* 275**,** 1293-5.

BECHARA, A., DAMASIO, H., TRANEL, D. & DAMASIO, A. R. 1997b. Deciding advantageously before knowing the advantageous strategy. *Science. ,* 275**,** 1293-5.

BECK, A. T., BROWN, G. K., STEER, R. A., KUYKEN, W. & GRISHAM, J. 2001. Psychometric properties of the Beck Self-Esteem Scales. *Behav Res Ther,* 39**,** 115-24.

BEIGHTON, P., DE PAEPE, A., STEINMANN, B., TSIPOURAS, P. & WENSTRUP, R. J. 1998. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet,* 77**,** 31-7.

BENARROCH, E. E. 1993. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc,* 68**,** 988-1001.

BENARROCH, E. E. 2012. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. *Mayo Clin Proc,* 87**,** 1214-25.

BENBADIS, S. R. & CHICHKOVA, R. 2006. Psychogenic pseudosyncope: an underestimated and provable diagnosis. *Epilepsy Behav,* 9**,** 106-10.

BENRUD-LARSON, L. M., SANDRONI, P., HAYTHORNTHWAITE, J. A., RUMMANS, T. A. & LOW, P. A. 2003. Correlates of functional disability in patients with postural tachycardia syndrome: preliminary cross-sectional findings. *Health Psychol,* 22**,** 643-8.

BENSON, R. A., PALIN, R., HOLT, P. J. & LOFTUS, I. M. 2013. Diagnosis and management of hyperhidrosis. *BMJ,* 347**,** f6800.

BENZINGER, T. H. 1969. Heat regulation: homeostasis of central temperature in man. *Physiol Rev,* 49**,** 671-759.

BERMINGHAM, S. L., COHEN, A., HAGUE, J. & PARSONAGE, M. 2010. The cost of somatisation among the working-age population in England for the year 2008-2009. *Ment Health Fam Med,* 7**,** 71-84.

BERRIDGE, K. C. & ROBINSON, T. E. 2003. Parsing reward. *Trends Neurosci,* 26**,** 507-13.

BHASKARAN, D. & FREED, C. R. 1988. Changes in neurotransmitter turnover in locus coeruleus produced by changes in arterial blood pressure. *Brain Res Bull,* 21**,** 191-9.

BIRNER, P., HEINZL, H., SCHINDL, M., PUMPRLA, J. & SCHNIDER, P. 2000. Cardiac autonomic function in patients suffering from primary focal hyperhidrosis. *Eur Neurol,* 44**,** 112-6.

BLAKEMORE, S. J., SMITH, J., STEEL, R., JOHNSTONE, C. E. & FRITH, C. D. 2000. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. *Psychol Med,* 30**,** 1131-9.

BLANCHAR, R. J. & BLANCHAR, D. C. 1969. Crouching as an Index of Fear. *Journal of Comparative and Physiological Psychology,* 67**,** 370-&.

BLECHERT, J., MICHAEL, T., GROSSMAN, P., LAJTMAN, M. & WILHELM, F. H. 2007. Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. *Psychosom Med,* 69**,** 935-43.

BOGDANOV, V. B., BOGDANOVA, O. V., GORLOV, D. S., GORGO, Y. P., DIRCKX, J. J., MAKARCHUK, M. Y., SCHOENEN, J. & CRITCHLEY, H. 2013. Alexithymia and empathy predict changes in autonomic arousal during affective stimulation. *Cogn Behav Neurol,* 26**,** 121-32.

BOVELL, D. L., CLUNES, M. T., ELDER, H. Y., MILSOM, J. & JENKINSON, D. M. 2001. Ultrastructure of the hyperhidrotic eccrine sweat gland. *Br J Dermatol,* 145**,** 298-301.

BOVIN, M. J., JAGER-HYMAN, S., GOLD, S. D., MARX, B. P. & SLOAN, D. M. 2008. Tonic immobility mediates the influence of peritraumatic fear and perceived inescapability on posttraumatic stress symptom severity among sexual assault survivors. *J Trauma Stress,* 21**,** 402-9.

BRAGANCA, G. M., LIMA, S. O., PINTO NETO, A. F., MARQUES, L. M., MELO, E. V. & REIS, F. P. 2014. Evaluation of anxiety and depression prevalence in patients with primary severe hyperhidrosis. *An Bras Dermatol,* 89**,** 230-5.

BRIGNOLE, M., ALBONI, P., BENDITT, D. G., BERGFELDT, L., BLANC, J. J., BLOCH THOMSEN, P. E., GERT VAN DIJK, J., FITZPATRICK, A., HOHNLOSER, S., JANOUSEK, J., KAPOOR, W., ANNE KENNY, R., KULAKOWSKI, P., MASOTTI, G., MOYA, A., RAVIELE, A., SUTTON, R., THEODORAKIS, G., UNGAR, A., WIELING, W. & GROUPO DE TRABAJO SOBRE EL SINCOPE DE LA SOCIEDAD EUROPEA DE, C. 2005. [Guidelines on management (diagnosis and treatment) of syncope. Update 2004. Executive summary]. *Rev Esp Cardiol,* 58**,** 175-93.

BUCHANAN, T. W., ETZEL, J. A., ADOLPHS, R. & TRANEL, D. 2006. The influence of autonomic arousal and semantic relatedness on memory for emotional words. *Int J Psychophysiol,* 61**,** 26-33.

BUCKLEY, T. C. & KALOUPEK, D. G. 2001. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosom Med,* 63**,** 585-94.

BULBENA, A., PAILHEZ, G. & GAGO, J. 2004. "Connective tissue" between panic disorder and dysautonomia. *Am J Med,* 116**,** 783; author reply 783-4.

BUODO, G., SARLO, M., POLI, S., GIADA, F., MADALOSSO, M., ROSSI, C. & PALOMBA, D. 2012. Emotional anticipation rather than processing is altered in patients with vasovagal syncope. *Clin Neurophysiol.,* 123**,** 1319-27.

CAMERON, O. G. 2009. Visceral brain-body information transfer. *Neuroimage,* 47**,** 787-94.

CANNON, W. 1929. *Bodily changes in pain, hunger, fear and rage. An account of researches into the function of emotional excitement,* New York, Appleton Century Crofts.

CHAUHAN, B., MATHIAS, C. J. & CRITCHLEY, H. D. 2008. Autonomic contributions to empathy: evidence from patients with primary autonomic failure. *Auton Neurosci,* 140**,** 96-100.

CHELIMSKY, G., KOVACIC, K., NUGENT, M., MUELLER, A., SIMPSON, P. & CHELIMSKY, T. C. 2015. Comorbid Conditions Do Not Differ in Children and Young Adults with Functional Disorders with or without Postural Tachycardia Syndrome. *J Pediatr*.

CLARK, A. 2013. Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav Brain Sci,* 36**,** 181-204.

CLARK, D. M. 1986. A cognitive approach to panic. *Behav Res Ther,* 24**,** 461-70.

CLORE, G. L. & ORTONY, A. 2013. Psychological Construction in the OCC Model of Emotion. *Emot Rev,* 5**,** 335-343.

CLOSE, J. C., HALTER, M., ELRICK, A., BRAIN, G. & SWIFT, C. G. 2002. Falls in the older population: a pilot study to assess those attended by London ambulance service but not taken to A&E. *Age Ageing,* 31**,** 488-9.

COHEN, H., KOTLER, M., MATAR, M. A., KAPLAN, Z., LOEWENTHAL, U., MIODOWNIK, H. & CASSUTO, Y. 1998. Analysis of heart rate variability in posttraumatic stress disorder patients in response to a trauma-related reminder. *Biol Psychiatry,* 44**,** 1054-9.

COHEN, J. L., COHEN, G., SOLISH, N. & MURRAY, C. A. 2007. Diagnosis, impact, and management of focal hyperhidrosis: treatment review including botulinum toxin therapy. *Facial Plast Surg Clin North Am,* 15**,** 17-30, v-vi.

COHEN, T. J., THAYAPRAN, N., IBRAHIM, B., QUAN, C., QUAN, W. & VON ZUR MUHLEN, F. 2000a. An association between anxiety and neurocardiogenic syncope during head-up tilt table testing. *Pacing Clin Electrophysiol,* 23**,** 837-41.

COHEN, T. J., THAYAPRAN, N., IBRAHIM, B., QUAN, C., QUAN, W. & VON ZUR MUHLEN, F. 2000b. An association between anxiety and neurocardiogenic syncope during head-up tilt table testing. *Pacing Clin Electrophysiol,* 23**,** 837-41.

COLLINS, K. J. 2013. Temperature Regulation and the autonomic nervous system. *In:* MATHIAS CJ., B. R. (ed.) *Autonomic Failure: a textbook of clinical disorders of the autonomic nervous system.* 5th ed. Oxford: Oxford University Press.

COOTE, J. H. 2005. A role for the paraventricular nucleus of the hypothalamus in the autonomic control of heart and kidney. *Exp Physiol,* 90**,** 169-73.

CORICELLI, G., CRITCHLEY, H. D., JOFFILY, M., O'DOHERTY, J. P., SIRIGU, A. & DOLAN, R. J. 2005. Regret and its avoidance: a neuroimaging study of choice behavior. *Nat Neurosci,* 8**,** 1255-62.

CRAIG, A. D., BUSHNELL, M. C., ZHANG, E. T. & BLOMQVIST, A. 1994. A thalamic nucleus specific for pain and temperature sensation. *Nature,* 372**,** 770-3.

CRITCHLEY, H. D., CORFIELD, D. R., CHANDLER, M. P., MATHIAS, C. J. & DOLAN, R. J. 2000a. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol,* 523 Pt 1**,** 259-70.

CRITCHLEY, H. D., ELLIOTT, R., MATHIAS, C. J. & DOLAN, R. J. 2000b. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *J Neurosci,* 20**,** 3033-40.

CRITCHLEY, H. D., MATHIAS, C. J. & DOLAN, R. J. 2001a. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron,* 29**,** 537-45.

CRITCHLEY, H. D., MATHIAS, C. J. & DOLAN, R. J. 2001b. Neuroanatomical basis for first- and second-order representations of bodily states. *Nat Neurosci,* 4**,** 207-12.

CRITCHLEY, H. D., MATHIAS, C. J. & DOLAN, R. J. 2002. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. *Neuron,* 33**,** 653-63.

CRITCHLEY, H. D., MATHIAS, C. J., JOSEPHS, O., O'DOHERTY, J., ZANINI, S., DEWAR, B. K., CIPOLOTTI, L., SHALLICE, T. & DOLAN, R. J. 2003. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain,* 126**,** 2139-52.

CRITCHLEY, H. D., WIENS, S., ROTSHTEIN, P., OHMAN, A. & DOLAN, R. J. 2004. Neural systems supporting interoceptive awareness. *Nat Neurosci,* 7**,** 189-95.

D'ANTONO, B., DUPUIS, G., ST-JEAN, K., LEVESQUE, K., NADEAU, R., GUERRA, P., THIBAULT, B. & KUS, T. 2009. Prospective evaluation of psychological distress and psychiatric morbidity in recurrent vasovagal and unexplained syncope. *J Psychosom Res,* 67**,** 213-22.

DALTON, K. M., KALIN, N. H., GRIST, T. M. & DAVIDSON, R. J. 2005. Neural-cardiac coupling in threat-evoked anxiety. *J Cogn Neurosci,* 17**,** 969-80.

DAMASIO, A. R. 1994. *Descartes' Error: Emotion, Reason, and the Human Brain. ,* New York, GP Putnam's.

DAMASIO, A. R. 1999. *The feeling of What Happens: Body and Emotion in the Making of Consciousness,* New York, Harcourt Brace.

DAMASIO, A. R., TRANEL, D. & DAMASIO, H. 1990. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav Brain Res,* 41**,** 81-94.

DAMASIO, H., KULJIS, R. O., YUH, W., VAN HOESEN, G. W. & EHRHARDT, J. 1991. Magnetic resonance imaging of human intracortical structure in vivo. *Cereb Cortex,* 1**,** 374-9.

DAMPNEY, R. A., COLEMAN, M. J., FONTES, M. A., HIROOKA, Y., HORIUCHI, J., LI, Y. W., POLSON, J. W., POTTS, P. D. & TAGAWA, T. 2002. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin Exp Pharmacol Physiol,* 29**,** 261-8.

DAMPNEY, R. A., FURLONG, T. M., HORIUCHI, J. & IIGAYA, K. 2013. Role of dorsolateral periaqueductal grey in the coordinated regulation of cardiovascular and respiratory function. *Auton Neurosci*.

DARWIN, C. 1872/1998. *The Expression of the Emotions in Man and Animals,* London, New York, Harper & Collins; Oxford University Press. .

DAVIS, R. C., BUCHWALD, A. M., FRANKMANN, R. W. 1955. Autonomic and muscular responses, and their relation to simple stimuli. . *Psychological Monographs: General and Applied. ,* 69**,** 1-71.

DE KLOET, E. R., JOELS, M. & HOLSBOER, F. 2005. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci,* 6**,** 463-75.

DELGADO, L. C., VILA, J. & REYES DEL PASO, G. A. 2014. Proneness to worry is negatively associated with blood pressure and baroreflex sensitivity: further evidence of the blood pressure emotional dampening hypothesis. *Biol Psychol,* 96**,** 20-7.

DEVINSKY, O., MORRELL, M. J. & VOGT, B. A. 1995. Contributions of anterior cingulate cortex to behaviour. *Brain,* 118 (Pt 1)**,** 279-306.

DIEHL, R. R. 2005. Vasovagal syncope and Darwinian fitness. *Clin Auton Res,* 15**,** 126-9.

DIMICCO, J. A. & ZARETSKY, D. V. 2007. The dorsomedial hypothalamus: a new player in thermoregulation. *Am J Physiol Regul Integr Comp Physiol,* 292**,** R47-63.

DOMSCHKE, K., STEVENS, S., PFLEIDERER, B. & GERLACH, A. L. 2010. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. *Clin Psychol Rev,* 30**,** 1-11.

DUNN, B. D., STEFANOVITCH, I., EVANS, D., OLIVER, C., HAWKINS, A. & T., D. 2010. Can you feel the beat? Interoceptive awareness is an interactive function of anxiety- and depression-specific symptom dimensions. *Behav Res Ther. ,* 48**,** 1133-8.

EAGLE, K. A. & BLACK, H. R. 1983. The impact of diagnostic tests in evaluating patients with syncope. *Yale J Biol Med,* 56**,** 1-8.

ECCLES, J., HARRISON, N. & CRITCHLEY, H. 2011. Joint hypermobility syndrome. Psychiatric manifestations. *BMJ,* 342**,** d998.

ECCLES, J. A., BEACHER, F. D., GRAY, M. A., JONES, C. L., MINATI, L., HARRISON, N. A. & CRITCHLEY, H. D. 2012. Brain structure and joint hypermobility: relevance to the expression of psychiatric symptoms. *Br J Psychiatry,* 200**,** 508-9.

ECCLES, J. A., OWENS, A. P., MATHIAS, C. J., UMEDA, S. & CRITCHLEY, H. D. 2015. Neurovisceral phenotypes in the expression of psychiatric symptoms. *Front Neurosci,* 9**,** 4.

EDWARDS, M. J., MORETTO, G., SCHWINGENSCHUH, P., KATSCHNIG, P., BHATIA, K. P. & HAGGARD, P. 2011. Abnormal sense of intention preceding voluntary movement in patients with psychogenic tremor. *Neuropsychologia,* 49**,** 2791-3.

EIFERT, G. H. 1992. Cardiophobia: a paradigmatic behavioural model of heart-focused anxiety and non-anginal chest pain. *Behav Res Ther,* 30**,** 329-45.

EKMAN, P. 1993. Facial expression and emotion. *Am Psychol,* 48**,** 384-92.

EKMAN, P., LEVENSON, R. W. & FRIESEN, W. V. 1983. Autonomic nervous system activity distinguishes among emotions. *Science,* 221**,** 1208-10.

ENGEL, G. L. 1962. Fainting. *In:* THOMAS., C. C. (ed.) *Fainting.* 2nd ed. Springfield, Ill.

ESLER, M., ALVARENGA, M., LAMBERT, G., KAYE, D., HASTINGS, J., JENNINGS, G., MORRIS, M., SCHWARZ, R. & RICHARDS, J. 2004. Cardiac sympathetic nerve biology and brain monoamine turnover in panic disorder. *Ann N Y Acad Sci,* 1018**,** 505-14.

ESLER, M., ALVARENGA, M., PIER, C., RICHARDS, J., EL-OSTA, A., BARTON, D., HAIKERWAL, D., KAYE, D., SCHLAICH, M., GUO, L., JENNINGS, G., SOCRATOUS, F. & LAMBERT, G. 2006. The neuronal noradrenaline transporter, anxiety and cardiovascular disease. *J Psychopharmacol,* 20**,** 60-6.

ESSAU, C. A. & JAMIESON, J. L. 1987. Heart rate perception in the type A personality. *Health Psychol,* 6**,** 43-54.

EYSENCK, M. W., DERAKSHAN, N., SANTOS, R. & CALVO, M. G. 2007. Anxiety and cognitive performance: attentional control theory. *Emotion,* 7**,** 336-53.

FANSELOW, M. S. 1994. Neural organization of the defensive behavior system responsible for fear. *Psychon Bull Rev,* 1**,** 429-38.

FELLEMAN, D. J. & VAN ESSEN, D. C. 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex,* 1**,** 1-47.

FENTON, A. M., HAMMILL, S. C., REA, R. F., LOW, P. A. & SHEN, W. K. 2000. Vasovagal syncope. *Ann Intern Med,* 133**,** 714-25.

FERNANDEZ, M. C. & VILA, J. 1989. Sympathetic-parasympathetic mediation of the cardiac defense response in humans. *Biol Psychol,* 28**,** 123-33.

FLOURIS, A. D. & CHEUNG, S. S. 2009. Human conscious response to thermal input is adjusted to changes in mean body temperature. *Br J Sports Med,* 43**,** 199-203.

FREEMAN, R., WIELING, W., AXELROD, F. B., BENDITT, D. G., BENARROCH, E., BIAGGIONI, I., CHESHIRE, W. P., CHELIMSKY, T., CORTELLI, P., GIBBONS, C. H., GOLDSTEIN, D. S., HAINSWORTH, R., HILZ, M. J., JACOB, G., KAUFMANN, H., JORDAN, J., LIPSITZ, L. A., LEVINE, B. D., LOW, P., A., , MATHIAS, C., RAJ, S. R., ROBERTSON, D., SANDRONI, P., SCHATZ, I., SCHONDORFF, R., STEWART, J. M. & VAN DIJK, J. G. 2011a. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res,* 21**,** 69-72.

FREEMAN, R., WIELING, W., AXELROD, F. B., BENDITT, D. G., BENARROCH, E., BIAGGIONI, I., CHESHIRE, W. P., CHELIMSKY, T., CORTELLI, P., GIBBONS, C. H., GOLDSTEIN, D. S., HAINSWORTH, R., HILZ, M. J., JACOB, G., KAUFMANN, H., JORDAN, J., LIPSITZ, L. A., LEVINE, B. D., LOW, P. A., MATHIAS, C., RAJ, S. R., ROBERTSON, D., SANDRONI, P., SCHATZ, I., SCHONDORFF, R., STEWART, J. M. & VAN DIJK, J. G. 2011b. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res,* 21**,** 69-72.

FRISTON, K. 2010. The free-energy principle: a unified brain theory? *Nat Rev Neurosci,* 11**,** 127-38.

FRISTON, K. J. & FRITH, C. D. 2015. Active inference, communication and hermeneutics. *Cortex*.

FUKUSHIMA, H., TERASAWA, Y. & UMEDA, S. 2011. Association between interoception and empathy: evidence from heartbeat-evoked brain potential. *Int J Psychophysiol,* 79**,** 259-65.

FUNAYAMA, T., FURUKAWA, T. A., NAKANO, Y., NODA, Y., OGAWA, S., WATANABE, N., CHEN, J. & NOGUCHI, Y. 2013. In-situation safety behaviors among patients with panic disorder: descriptive and correlational study. *Psychiatry Clin Neurosci,* 67**,** 332-9.

GANZEBOOM, K. S., MAIRUHU, G., REITSMA, J. B., LINZER, M., WIELING, W. & VAN DIJK, N. 2006. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. *J Cardiovasc Electrophysiol,* 17**,** 1172-6.

GARFINKEL, S. N. & CRITCHLEY, H. D. 2013. Interoception, emotion and brain: new insights link internal physiology to social behaviour. Commentary on:: "Anterior insular cortex mediates bodily sensibility and social anxiety" by Terasawa et al. (2012). *Soc Cogn Affect Neurosci,* 8**,** 231-4.

GARFINKEL, S. N., MINATI, L., GRAY, M. A., SETH, A. K., DOLAN, R. J. & CRITCHLEY, H. D. 2014. Fear from the heart: sensitivity to fear stimuli depends on individual heartbeats. *J Neurosci,* 34**,** 6573-82.

GARFINKEL, S. N., SETH, A. K., BARRETT, A. B., SUZUKI, K. & CRITCHLEY, H. D. 2015. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol Psychol,* 104**,** 65-74.

GERMAIN, A., BUYSSE, D. J. & NOFZINGER, E. 2008. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. *Sleep Med Rev,* 12**,** 185-95.

GERSHUNDI, G. V., KOZHEVNIKOV, V. A., MARUSEVA, A. M., AVAKYAN, R. V., RADIONOVA, E. A., ALTMAN J. A., SOROKO, V. I. 1960. Modifications in electrical responses of the auditory system in different states of higher nervous activity. . *In:* H. H. JASPER, G. D. S. (ed.) *The Moscow Colloquium on Electrophysiology of Higher Nervous Activity. .*

GIADA, F., SILVESTRI, I., ROSSILLO, A., NICOTERA, P. G., MANZILLO, G. F. & RAVIELE, A. 2005. Psychiatric profile, quality of life and risk of syncopal recurrence in patients with tilt-induced vasovagal syncope. *Europace,* 7**,** 465-71.

GOLDSTEIN, D. S., BENTHO, O., PARK, M. Y. & SHARABI, Y. 2011. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. *Exp Physiol,* 96**,** 1255-61.

GRACIE, J., NEWTON, J. L., NORTON, M., BAKER, C. & FREESTON, M. 2006. The role of psychological factors in response to treatment in neurocardiogenic (vasovagal) syncope. *Europace,* 8**,** 636-43.

GRAHAM, D. T. 1961. Prediction of fainting in blood donors. *Circulation,* 23**,** 901-6.

GRAY, M. A., BEACHER, F. D., MINATI, L., NAGAI, Y., KEMP, A. H., HARRISON, N. A. & CRITCHLEY, H. D. 2012. Emotional appraisal is influenced by cardiac afferent information. *Emotion,* 12**,** 180-91.

GRAY, M. A., HARRISON, N. A., WIENS, S. & CRITCHLEY, H. D. 2007. Modulation of emotional appraisal by false physiological feedback during fMRI. *PLoS One,* 2**,** e546.

GRAY, M. A., MINATI, L., PAOLETTI, G. & CRITCHLEY, H. D. 2010. Baroreceptor activation attenuates attentional effects on pain-evoked potentials. *Pain,* 151**,** 853-61.

GRIFFIN, M. G., RESICK, P. A. & MECHANIC, M. B. 1997. Objective assessment of peritraumatic dissociation: psychophysiological indicators. *Am J Psychiatry,* 154**,** 1081-8.

GRYNBERG, D. & POLLATOS, O. 2015. Perceiving one's body shapes empathy. *Physiol Behav,* 140**,** 54-60.

GUARALDI, P., PODA, R., CALANDRA-BUONAURA, G., SOLIERI, L., SAMBATI, L., GALLASSI, R. & CORTELLI, P. 2014. Cognitive function in peripheral autonomic disorders. *PLoS One,* 9**,** e85020.

GUYTON, A. C. 1991. Blood pressure control--special role of the kidneys and body fluids. *Science,* 252**,** 1813-6.

HARMON-JONES, E. & PETERSON, C. K. 2009. Supine body position reduces neural response to anger evocation. *Psychol Sci,* 20**,** 1209-10.

HARPER, R. M., BANDLER, R., SPRIGGS, D. & ALGER, J. R. 2000. Lateralized and widespread brain activation during transient blood pressure elevation revealed by magnetic resonance imaging. *J Comp Neurol,* 417**,** 195-204.

HARRISON, N. A. & CRITCHLEY, H. D. 2007. Affective neuroscience and psychiatry. *Br J Psychiatry,* 191**,** 192-4.

HEDGER, N., ADAMS, W. J. & GARNER, M. 2015. Autonomic arousal and attentional orienting to visual threat are predicted by awareness. *J Exp Psychol Hum Percept Perform,* 41**,** 798-806.

HEIMS, H. C., CRITCHLEY, H. D., MARTIN, N. H., JAGER, H. R., MATHIAS, C. J. & CIPOLOTTI, L. 2006a. Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res,* 16**,** 113-20.

HEIMS, H. C., CRITCHLEY, H. D., MARTIN, N. H., JÄGER, H. R., MATHIAS, C. J. & CIPOLOTTI, L. 2006b. Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res,* 16**,** 113-20.

HENDERSON, L. A., RICHARD, C. A., MACEY, P. M., RUNQUIST, M. L., YU, P. L., GALONS, J. P. & HARPER, R. M. 2004. Functional magnetic resonance signal changes in neural structures to baroreceptor reflex activation. *J Appl Physiol (1985),* 96**,** 693-703.

HERMANS, E. J., HENCKENS, M. J., ROELOFS, K. & FERNANDEZ, G. 2013. Fear bradycardia and activation of the human periaqueductal grey. *Neuroimage,* 66**,** 278-87.

HESS, D. S., MORADY, F. & SCHEINMAN, M. M. 1982. Electrophysiologic testing in the evaluation of patients with syncope of undetermined origin. *Am J Cardiol,* 50**,** 1309-15.

HODGSON, R. & RACHMAN, S. 1974. II. Desynchrony in measures of fear. *Behav Res Ther,* 12**,** 319-26.

HORNYAK, M. E., NAVER, H. K., RYDENHAG, B. & WALLIN, B. G. 1990. Sympathetic activity influences the vascular axon reflex in the skin. *Acta Physiol Scand,* 139**,** 77-84.

HUMM, A. M. & MATHIAS, C. J. 2010. Abnormal cardiovascular responses to carotid sinus massage also occur in vasovagal syncope - implications for diagnosis and treatment. *Eur J Neurol,* 17**,** 1061-7.

IMHOLZ, B. P., DAMBRINK, J. H., KAREMAKER, J. M. & WIELING, W. 1990. Orthostatic circulatory control in the elderly evaluated by non-invasive continuous blood pressure measurement. *Clin Sci (Lond),* 79**,** 73-9.

IODICE, V., LOW, D. A., GRAHAME, R. & MATHIAS, C. J. 2010. Familial Postural Tachycardia Syndrome and Ehlers-Danlos Syndrome Type III: Clinical Description and Autonomic Evaluation. *Congress of the European Federation of Autonomic Societies. May 2010).* Taormina, Italy. .

JAMES, W. 1894. Physical basis of emotion. Psychological Review 1: 516-529, reprinted in 1994. *Psychological Review,* 101**,** 205-210.

JANIG, W. & HABLER, H. J. 2003. Neurophysiological analysis of target-related sympathetic pathways--from animal to human: similarities and differences. *Acta Physiol Scand,* 177**,** 255-74.

JASSON, S., MEDIGUE, C., MAISON-BLANCHE, P., MONTANO, N., MEYER, L., VERMEIREN, C., MANSIER, P., COUMEL, P., MALLIANI, A. & SWYNGHEDAUW, B. 1997. Instant power spectrum analysis of heart rate variability during orthostatic tilt using a time-/frequency-domain method. *Circulation,* 96**,** 3521-6.

KANOSUE, K., SADATO, N., OKADA, T., YODA, T., NAKAI, S., YOSHIDA, K., HOSONO, T., NAGASHIMA, K., YAGISHITA, T., INOUE, O., KOBAYASHI, K. & YONEKURA, Y. 2002. Brain activation during whole body cooling in humans studied with functional magnetic resonance imaging. *Neurosci Lett,* 329**,** 157-60.

KAPOOR, W. N., FORTUNATO, M., HANUSA, B. H. & SCHULBERG, H. C. 1995. Psychiatric illnesses in patients with syncope. *Am J Med,* 99**,** 505-12.

KAPOOR, W. N., KARPF, M., WIEAND, S., PETERSON, J. R. & LEVEY, G. S. 1983. A prospective evaluation and follow-up of patients with syncope. *N Engl J Med,* 309**,** 197-204.

KARACA, S., EMUL, M., KULAC, M., YUKSEL, S., OZBULUT, O., GULER, O. & GECICI, O. 2007. Temperament and character profile in patients with essential hyperhidrosis. *Dermatology,* 214**,** 240-5.

KATKIN, E. S., WIENS, S. & OHMAN, A. 2001. Nonconscious fear conditioning, visceral perception, and the development of gut feelings. *Psychol Sci,* 12**,** 366-70.

KAUFMANN, H., SAADIA, D., POLIN, C., HAGUE, S., SINGLETON, A. & SINGLETON, A. 2003. Primary hyperhidrosis--evidence for autosomal dominant inheritance. *Clin Auton Res,* 13**,** 96-8.

KAYA, D., KARACA, S., BARUTCU, I., ESEN, A. M., KULAC, M. & ESEN, O. 2005. Heart rate variability in patients with essential hyperhidrosis: dynamic influence of sympathetic and parasympathetic maneuvers. *Ann Noninvasive Electrocardiol,* 10**,** 1-6.

KELLOGG, D. L., JR. 2006. In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. *J Appl Physiol (1985),* 100**,** 1709-18.

KHURANA, R. K. 2006. Experimental induction of panic-like symptoms in patients with postural tachycardia syndrome. *Clin Auton Res,* 16**,** 371-7.

KHURANA, R. K. 2014. Visceral sensitization in postural tachycardia syndrome. *Clin Auton Res,* 24**,** 71-6.

KIM, J. B., SUH, S. I., SEO, W. K., KOH, S. B. & KIM, J. H. 2014. Right insular atrophy in neurocardiogenic syncope: a volumetric MRI study. *AJNR Am J Neuroradiol,* 35**,** 113-8.

KIMMERLY, D. S., O'LEARY, D. D., MENON, R. S., GATI, J. S. & SHOEMAKER, J. K. 2005. Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans. *J Physiol,* 569**,** 331-45.

KING, A. B., MENON, R. S., HACHINSKI, V. & CECHETTO, D. F. 1999. Human forebrain activation by visceral stimuli. *J Comp Neurol,* 413**,** 572-82.

KIRMAYER, L. J. & ROBBINS, J. M. 1996. Patients who somatize in primary care: a longitudinal study of cognitive and social characteristics. *Psychol Med,* 26**,** 937-51.

KIRSHBLUM, S. C., BIERING-SORENSEN, F., BETZ, R., BURNS, S., DONOVAN, W., GRAVES, D. E., JOHANSEN, M., JONES, L., MULCAHEY, M. J., RODRIGUEZ, G. M., SCHMIDT-READ, M., STEEVES, J. D., TANSEY, K. & WARING, W. 2014. International Standards for Neurological Classification of Spinal Cord Injury: Cases with classification challenges. *J Spinal Cord Med,* 37**,** 120-7.

KOBLENZER, C. S. 1983. Psychosomatic concepts in dermatology. A dermatologist-psychoanalyst's viewpoint. *Arch Dermatol,* 119**,** 501-12.

KOVACIC, K., CHELIMSKY, T. C., SOOD, M. R., SIMPSON, P., NUGENT, M. & CHELIMSKY, G. 2014. Joint hypermobility: a common association with complex functional gastrointestinal disorders. *J Pediatr,* 165**,** 973-8.

KRAHN, A. D., KLEIN, G. J., NORRIS, C. & YEE, R. 1995. The etiology of syncope in patients with negative tilt table and electrophysiological testing. *Circulation,* 92**,** 1819-24.

KRAHN, A. D., KLEIN, G. J., YEE, R. & MANDA, V. 1999. The high cost of syncope: cost implications of a new insertable loop recorder in the investigation of recurrent syncope. *Am Heart J,* 137**,** 870-7.

KRAHN, A. D., KLEIN, G. J., YEE, R. & NORRIS, C. 1998. Final results from a pilot study with an implantable loop recorder to determine the etiology of syncope in patients with negative noninvasive and invasive testing. *Am J Cardiol,* 82**,** 117-9.

KREIBIG, S. D. 2010. Autonomic nervous system activity in emotion: a review. *Biol Psychol,* 84**,** 394-421.

KROENKE, K. & ROSMALEN, J. G. 2006. Symptoms, syndromes, and the value of psychiatric diagnostics in patients who have functional somatic disorders. *Med Clin North Am,* 90**,** 603-26.

LAI, F. C., TU, Y. R., LI, Y. P., LI, X., LIN, M., CHEN, J. F. & LIN, J. B. 2014. Nation wide epidemiological survey of primary palmar hyperhidrosis in the People's Republic of China. *Clin Auton Res*.

LANE, R. D., MCRAE, K., REIMAN, E. M., CHEN, K., AHERN, G. L. & THAYER, J. F. 2009. Neural correlates of heart rate variability during emotion. *Neuroimage,* 44**,** 213-22.

LANG, P. J. 1994. The varieties of emotional experience: a meditation on James-Lange theory. *Psychol Rev,* 101**,** 211-21.

LANG PJ, B. M., CUTHBERT BN. 2005. International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual.

LANG, P. J. & DAVIS, M. 2006. Emotion, motivation, and the brain: reflex foundations in animal and human research. *Prog Brain Res,* 156**,** 3-29.

LANGE, C. G. & JAMES, W. 1922. *The Emotions* Baltimore, Williams & Wilkins Company.

LASZLO, Z., ROSSLER, A. & HINGHOFER-SZALKAY, H. G. 2001. Cardiovascular and hormonal changes with different angles of head-up tilt in men. *Physiol Res,* 50**,** 71-82.

LEDOUX, J. E. 1992. Brain mechanisms of emotion and emotional learning. *Curr Opin Neurobiol,* 2**,** 191-7.

LEDOUX, J. E. 1995. Emotion: clues from the brain. *Annu Rev Psychol,* 46**,** 209-35.

LEE, S. H., PARK, S. J., BYEON, K., ON, Y. K., YIM, H. R. & KIM, J. S. 2013. Prevalence and clinical factors of anxiety and depression in neurally mediated and unexplained syncope. *Yonsei Med J,* 54**,** 583-9.

LEE, W. E., KWOK, C. H., HUNTER, E. C., RICHARDS, M. & DAVID, A. S. 2012. Prevalence and childhood antecedents of depersonalization syndrome in a UK birth cohort. *Soc Psychiatry Psychiatr Epidemiol,* 47**,** 253-61.

LEFTHERIOTIS, D., MICHOPOULOS, I., FLEVARI, P., DOUZENIS, A., KOBOROZOS, C., KOSTOPOULOU, A., THEODORAKIS, G. N., LYKOURAS, L. & KREMASTINOS, D. T. 2008. Minor psychiatric disorders and syncope: the role of psychopathology in the expression of vasovagal reflex. *Psychother Psychosom,* 77**,** 372-6.

LEMCHE, E., ANILKUMAR, A., GIAMPIETRO, V. P., BRAMMER, M. J., SURGULADZE, S. A., LAWRENCE, N. S., GASSTON, D., CHITNIS, X., WILLIAMS, S. C., SIERRA, M., JORASCHKY, P. & PHILLIPS, M. L. 2008. Cerebral and autonomic responses to emotional facial expressions in depersonalisation disorder. *Br J Psychiatry,* 193**,** 222-8.

LEMCHE, E., SURGULADZE, S. A., GIAMPIETRO, V. P., ANILKUMAR, A., BRAMMER, M. J., SIERRA, M., CHITNIS, X., WILLIAMS, S. C., GASSTON, D., JORASCHKY, P., DAVID, A. S. & PHILLIPS, M. L. 2007. Limbic and prefrontal responses to facial emotion expressions in depersonalization. *Neuroreport,* 18**,** 473-7.

LERMA, A., LERMA, C., MARQUEZ, M. F., CARDENAS, M. & HERMOSILLO, A. G. 2013. Correlation of syncopal burden with anxiety symptoms score in recurrent vasovagal syncope. *Int J Cardiol,* 166**,** 266-7.

LESSA LDA, R., LUZ, F. B., DE REZENDE, R. M., DURAES, S. M., HARRISON, B. J., DE MENEZES, G. B. & FONTENELLE, L. F. 2014. The psychiatric facet of hyperhidrosis: demographics, disability, quality of life, and associated psychopathology. *J Psychiatr Pract,* 20**,** 316-23.

LIGHT, K. C. & OBRIST, P. A. 1980. Cardiovascular response to stress: effects of opportunity to avoid, shock experience, and performance feedback. *Psychophysiology,* 17**,** 243-52.

LINZER, M., FELDER, A., HACKEL, A., PERRY, A. J., VARIA, I., MELVILLE, M. L. & KRISHNAN, K. R. 1990. Psychiatric syncope: a new look at an old disease. *Psychosomatics,* 31**,** 181-8.

LINZER, M., GOLD, D. T., PONTINEN, M., DIVINE, G. W., FELDER, A. & BROOKS, W. B. 1994. Recurrent syncope as a chronic disease: preliminary validation of a disease-specific measure of functional impairment. *J Gen Intern Med,* 9**,** 181-6.

LINZER, M., PONTINEN, M., GOLD, D. T., DIVINE, G. W., FELDER, A. & BROOKS, W. B. 1991. Impairment of physical and psychosocial function in recurrent syncope. *J Clin Epidemiol,* 44**,** 1037-43.

LIPSITZ, L. A., WEI, J. Y. & ROWE, J. W. 1985. Syncope in an elderly, institutionalised population: prevalence, incidence, and associated risk. *Q J Med,* 55**,** 45-54.

LKHAGVASUREN, B., OKA, T., KAWAI, K., TAKII, M., KANEMITSU, Y., TOKUNAGA, S. & KUBO, C. 2011. Prevalence of postural orthostatic tachycardia syndrome in patients with psychiatric disorders. *Psychother Psychosom,* 80**,** 308-9.

LONSDALE-ECCLES, A., LEONARD, N. & LAWRENCE, C. 2003. Axillary hyperhidrosis: eccrine or apocrine? *Clin Exp Dermatol,* 28**,** 2-7.

LOW, P. A. & FEALEY, F. D. 2013. Evaluation of sudomotor function. . *In:* MATHIAS CJ, B. R. (ed.) *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System. .* 5 ed. Oxford, United Kingdom. : Oxford University Press.

LUBORSKY, L., DOCHERTY, J. P. & PENICK, S. 1973. Onset conditions for psychosomatic symptoms: a comparative review of immediate observation with retrospective research. *Psychosom Med,* 35**,** 187-204.

LUDEWIG, S., GEYER, M. A., RAMSEIER, M., VOLLENWEIDER, F. X., RECHSTEINER, E. & CATTAPAN-LUDEWIG, K. 2005. Information-processing deficits and cognitive dysfunction in panic disorder. *J Psychiatry Neurosci,* 30**,** 37-43.

LUZZA, F., DI ROSA, S., PUGLIATTI, P., ANDO, G., CARERJ, S. & RIZZO, F. 2004. Syncope of psychiatric origin. *Clin Auton Res,* 14**,** 26-9.

LUZZA, F., PUGLIATTI, P., DI ROSA, S., CALABRO, D., CARERJ, S. & ORETO, G. 2003. Tilt-induced pseudosyncope. *Int J Clin Pract,* 57**,** 373-5.

MALLIANI, A., PAGANI, M., LOMBARDI, F. & CERUTTI, S. 1991. Cardiovascular neural regulation explored in the frequency domain. *Circulation,* 84**,** 482-92.

MANUCK, S. B., HARVEY, A. H., LECHLEITER, S. L. & NEAL, S. K. 1978. Effects of coping on blood pressure responses to threat of aversive stimulation. *Psychophysiology,* 15**,** 544-9.

MARKS, P. J., DANIEL, T. D., AFOLABI, O., SPIERS, G. & NGUYEN-VAN-TAM, J. S. 2002. Emergency (999) calls to the ambulance service that do not result in the patient being transported to hospital: an epidemiological study. *Emerg Med J,* 19**,** 449-52.

MARTIN-SANTOS, R., BULBENA, A., PORTA, M., GAGO, J., MOLINA, L. & DURO, J. C. 1998. Association between joint hypermobility syndrome and panic disorder. *Am J Psychiatry,* 155**,** 1578-83.

MASUKI, S., EISENACH, J. H., JOHNSON, C. P., DIETZ, N. M., BENRUD-LARSON, L. M., SCHRAGE, W. G., CURRY, T. B., SANDRONI, P., LOW, P. A. & JOYNER, M. J. 2007. Excessive heart rate response to orthostatic stress in postural tachycardia syndrome is not caused by anxiety. *J Appl Physiol,* 102**,** 896-903.

MATHEWS, A. 1990. Why worry? The cognitive function of anxiety. *Behav Res Ther,* 28**,** 455-68.

MATHIAS, C. J. 1976. Bradycardia and cardiac arrest during tracheal suction--mechanisms in tetraplegic patients. *Eur J Intensive Care Med,* 2**,** 147-56.

MATHIAS, C. J. 2003. Autonomic diseases: clinical features and laboratory evaluation. *J Neurol Neurosurg Psychiatry,* 74 Suppl 3**,** iii31-41.

MATHIAS, C. J. & BANNISTER, R. 2013. Introduction and classification of autonomic disorders. *In:* MATHIAS, C. J., BANNISTER, R. (ed.) *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System.* 5th ed. Oxford: Oxford University Press.

MATHIAS, C. J., DEGUCHI, K., BLEASDALE-BARR, K. & SMITH, S. 2000. Familial vasovagal syncope and pseudosyncope: observations in a case with both natural and adopted siblings. *Clin Auton Res,* 10**,** 43-5.

MATHIAS, C. J., DEGUCHI, K. & SCHATZ, I. 2001. Observations on recurrent syncope and presyncope in 641 patients. *Lancet,* 357**,** 348-53.

MATHIAS, C. J., IODICE, V., LOW, D. A. & BANNISTER, R. 2013. Investigation of autonomic disorders. *In:* MATHIAS, C. J., BANNISTER, R. (ed.) *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System* Oxford University Press

MATHIAS, C. J., LOW, D. A., IODICE, V., OWENS, A. P., KIRBIS, M. & GRAHAME, R. 2012. Postural tachycardia syndrome--current experience and concepts. *Nat Rev Neurol,* 8**,** 22-34.

MATTHEWS, S. C., PAULUS, M. P., SIMMONS, A. N., NELESEN, R. A. & DIMSDALE, J. E. 2004. Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. *Neuroimage,* 22**,** 1151-6.

MAY, C. N., DASHWOOD, M. R., WHITEHEAD, C. J. & MATHIAS, C. J. 1989. Differential cardiovascular and respiratory responses to central administration of selective opioid agonists in conscious rabbits: correlation with receptor distribution. *Br J Pharmacol,* 98**,** 903-13.

MAYBERG, H. S. 2003. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull,* 65**,** 193-207.

MAYER-GROSS, W. 1935. On Depersonalization. *British Journal of Medical Psychology,* 15**,** 103-126.

MCALLEN, R. M. 2007. The cold path to BAT. *Am J Physiol Regul Integr Comp Physiol,* 292**,** R124-6.

MCCORD, G. R., CRACOWSKI, J. L. & MINSON, C. T. 2006. Prostanoids contribute to cutaneous active vasodilation in humans. *Am J Physiol Regul Integr Comp Physiol,* 291**,** R596-602.

MCGRADY, A., KERN-BUELL, C., BUSH, E., KHUDER, S. & GRUBB, B. P. 2001. Psychological and physiological factors associated with tilt table testing for neurally mediated syncopal syndromes. *Pacing Clin Electrophysiol,* 24**,** 296-301.

MCTEAGUE, L. M., LANG, P. J., WANGELIN, B. C., LAPLANTE, M. C. & BRADLEY, M. M. 2012. Defensive mobilization in specific phobia: fear specificity, negative affectivity, and diagnostic prominence. *Biol Psychiatry,* 72**,** 8-18.

MEDFORD, N. 2014. Dissociative symptoms and epilepsy. *Epilepsy Behav,* 30**,** 10-3.

MEDFORD, N. & CRITCHLEY, H. D. 2010. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. *Brain Struct Funct,* 214**,** 535-49.

MEDOW, M. S., STEWART, J. M., SANYAL, S., MUMTAZ, A., SICA, D. & FRISHMAN, W. H. 2008. Pathophysiology, diagnosis, and treatment of orthostatic hypotension and vasovagal syncope. *Cardiol Rev,* 16**,** 4-20.

MEHRABIAN, A. 1996. *Manual for the Balanced Emotional Empathy Scale (BEES)*, (Available from Albert Mehrabian, 1130 Alta Mesa Road, Monterey, CA, USA 93940).

MELZIG, C. A., HOLTZ, K., MICHALOWSKI, J. M. & HAMM, A. O. 2011. Interoceptive threat leads to defensive mobilization in highly anxiety sensitive persons. *Psychophysiology,* 48**,** 745-54.

MESULAM, M. M. 1998. From sensation to cognition. *Brain,* 121 (Pt 6)**,** 1013-52.

MEYER, S., STRITTMATTER, M., FISCHER, C., GEORG, T. & SCHMITZ, B. 2004. Lateralization in autonomic dysfunction in ischemic stroke involving the insular cortex. *Neuroreport,* 15**,** 357-61.

MOAK, J. P., GOLDSTEIN, D. S., ELDADAH, B. A., SALEEM, A., HOLMES, C., PECHNIK, S. & SHARABI, Y. 2007. Supine low-frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Heart Rhythm,* 4**,** 1523-9.

MONASSI, C. R., LEITE-PANISSI, C. R. & MENESCAL-DE-OLIVEIRA, L. 1999. Ventrolateral periaqueductal gray matter and the control of tonic immobility. *Brain Res Bull,* 50**,** 201-8.

MOOREN, N. & VAN MINNEN, A. 2014. Feeling psychologically restrained: the effect of social exclusion on tonic immobility. *Eur J Psychotraumatol,* 5.

MORAITES, E., VAUGHN, O. A. & HILL, S. 2014. Incidence and prevalence of hyperhidrosis. *Dermatol Clin,* 32**,** 457-65.

MORRIS, P., HOPWOOD, M., MAGUIRE, K., NORMAN, T. & SCHWEITZER, I. 2004. Blunted growth hormone response to clonidine in post-traumatic stress disorder. *Psychoneuroendocrinology,* 29**,** 269-78.

MORRISON, S. F. 2001. Differential control of sympathetic outflow. *Am J Physiol Regul Integr Comp Physiol,* 281**,** R683-98.

MORRISON, S. F. & NAKAMURA, K. 2011. Central neural pathways for thermoregulation. *Front Biosci (Landmark Ed),* 16**,** 74-104.

MOSQUEDA-GARCIA, R., FURLAN, R., TANK, J. & FERNANDEZ-VIOLANTE, R. 2000. The elusive pathophysiology of neurally mediated syncope. *Circulation,* 102**,** 2898-906.

MUNDEL, T., BUNN, S. J., HOOPER, P. L. & JONES, D. A. 2007. The effects of face cooling during hyperthermic exercise in man: evidence for an integrated thermal, neuroendocrine and behavioural response. *Exp Physiol,* 92**,** 187-95.

NAGAI, Y., CRITCHLEY, H. D., FEATHERSTONE, E., FENWICK, P. B., TRIMBLE, M. R. & DOLAN, R. J. 2004. Brain activity relating to the contingent negative variation: an fMRI investigation. *Neuroimage,* 21**,** 1232-41.

NAGASHIMA, K., NAKAI, S., TANAKA, M. & KANOSUE, K. 2000. Neuronal circuitries involved in thermoregulation. *Auton Neurosci,* 85**,** 18-25.

NAKAMURA, M., YODA, T., CRAWSHAW, L. I., YASUHARA, S., SAITO, Y., KASUGA, M., NAGASHIMA, K. & KANOSUE, K. 2008. Regional differences in temperature sensation and thermal comfort in humans. *J Appl Physiol (1985),* 105**,** 1897-906.

NEFF, R. A., WANG, J., BAXI, S., EVANS, C. & MENDELOWITZ, D. 2003. Respiratory sinus arrhythmia: endogenous activation of nicotinic receptors mediates respiratory modulation of brainstem cardioinhibitory parasympathetic neurons. *Circ Res,* 93**,** 565-72.

NICOTRA, A., ASAHINA, M., YOUNG, T. M. & MATHIAS, C. J. 2006. Heat-provoked skin vasodilatation in innervated and denervated trunk dermatomes in human spinal cord injury. *Spinal Cord,* 44**,** 222-6.

NIJS, J., AERTS, A. & DE MEIRLEIR, K. 2006. Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. *J Manipulative Physiol Ther,* 29**,** 32-9.

NOPPEN, M., SEVENS, C., GERLO, E. & VINCKEN, W. 1997. Plasma catecholamine concentrations in essential hyperhidrosis and effects of thoracoscopic D2-D3 sympathicolysis. *Eur J Clin Invest,* 27**,** 202-5.

OCON, A. J. 2013. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. *Front Physiol,* 4**,** 63.

OCON, A. J., KULESA, J., CLARKE, D., TANEJA, I., MEDOW, M. S. & STEWART, J. M. 2009a. Increased phase synchronization and decreased cerebral autoregulation during fainting in the young. *Am J Physiol Heart Circ Physiol,* 297**,** H2084-95.

OCON, A. J., MEDOW, M. S., TANEJA, I., CLARKE, D. & STEWART, J. M. 2009b. Decreased upright cerebral blood flow and cerebral autoregulation in normocapnic postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol,* 297**,** H664-73.

OGDEN, P., MINTON, K. & PAIN, C. 2006. *Trauma and the body: a sensorimotor approach to psychotherapy.,* New York, Norton.

OPPENHEIMER, S. M., GELB, A., GIRVIN, J. P. & HACHINSKI, V. C. 1992. Cardiovascular effects of human insular cortex stimulation. *Neurology,* 42**,** 1727-32.

OPPENHEIMER, S. M., KEDEM, G. & MARTIN, W. M. 1996. Left-insular cortex lesions perturb cardiac autonomic tone in humans. *Clin Auton Res,* 6**,** 131-40.

ORI, Z., MONIR, G., WEISS, J., SAYHOUNI, X. & SINGER, D. H. 1992. Heart rate variability. Frequency domain analysis. *Cardiol Clin,* 10**,** 499-537.

OWENS, A. P., DAVID, A. S., LOW, D. A., MATHIAS, C. J. & SIERRA-SIEGERT, M. 2015. Abnormal cardiovascular sympathetic and parasympathetic responses to physical and emotional stimuli in depersonalization disorder. *Front Neurosci,* 9**,** 89.

PANKSEPP, J. 2010. Affective neuroscience of the emotional BrainMind: evolutionary perspectives and implications for understanding depression. *Dialogues Clin Neurosci,* 12**,** 533-45.

PARATI, G., MANCIA, G., DI RIENZO, M. & CASTIGLIONI, P. 2006. Point: cardiovascular variability is/is not an index of autonomic control of circulation. *J Appl Physiol (1985),* 101**,** 676-8; discussion 681-2.

PARSAIK, A., ALLISON, T. G., SINGER, W., SLETTEN, D. M., JOYNER, M. J., BENARROCH, E. E., LOW, P. A. & SANDRONI, P. 2012. Deconditioning in patients with orthostatic intolerance. *Neurology,* 79**,** 1435-9.

PAULUS, M. P. 2013. The breathing conundrum-interoceptive sensitivity and anxiety. *Depress Anxiety,* 30**,** 315-20.

PAULUS, M. P. & STEIN, M. B. 2006. An insular view of anxiety. *Biol Psychiatry,* 60**,** 383-7.

PAVLOV, I. 1927a. *Conditioned reflexes,* Oxford, Oxford University Press.

PAVLOV, I. P. 1927b. *Conditioned Reflexes,* Oxford, Oxford University Press.

PAVLOV, I. P. 1953. [Application of the results of our animal experiments to man]. *Dtsch Gesundheitsw,* 8**,** 32-40.

PENNEBAKER, J. W. & SUSMAN, J. R. 1988. Disclosure of traumas and psychosomatic processes. *Soc Sci Med,* 26**,** 327-32.

PFALTZ, M. C., MICHAEL, T., GROSSMAN, P., MARGRAF, J. & WILHELM, F. H. 2010. Instability of physical anxiety symptoms in daily life of patients with panic disorder and patients with posttraumatic stress disorder. *J Anxiety Disord,* 24**,** 792-8.

POLLATOS, O., HERBERT, B. M., KAUFMANN, C., AUER, D. P. & SCHANDRY, R. 2007. Interoceptive awareness, anxiety and cardiovascular reactivity to isometric exercise. *Int J Psychophysiol,* 65**,** 167-73.

POLLATOS, O., TRAUT-MATTAUSCH, E. & SCHANDRY, R. 2009. Differential effects of anxiety and depression on interoceptive accuracy. *Depress Anxiety,* 26**,** 167-73.

POOT, F., SAMPOGNA, F. & ONNIS, L. 2007. Basic knowledge in psychodermatology. *J Eur Acad Dermatol Venereol,* 21**,** 227-34.

PORGES, S. W. 2003. Social engagement and attachment: a phylogenetic perspective. *Ann N Y Acad Sci,* 1008**,** 31-47.

PRICE, T. F. & HARMON-JONES, E. 2011. Approach motivational body postures lean toward left frontal brain activity. *Psychophysiology,* 48**,** 718-22.

PRINZ-ZAISS, M., YEAP, A. N., MOGUILEVSKI, V., TRIGG, L. & MCGRATH, B. P. 1995. Power spectral analysis of heart rate variability during graded head-up tilting in patients with vasodepressor syncope. *Clin Exp Pharmacol Physiol,* 22**,** 472-4.

PUJOL, J., LOPEZ, A., DEUS, J., CARDONER, N., VALLEJO, J., CAPDEVILA, A. & PAUS, T. 2002. Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. *Neuroimage,* 15**,** 847-55.

RACHMAN, S. & HODGSON, R. 1974. I. Synchrony and desynchrony in fear and avoidance. *Behav Res Ther,* 12**,** 311-8.

RAHMAN, F., PECHNIK, S., GROSS, D., SEWELL, L. & GOLDSTEIN, D. S. 2011. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Clin Auton Res,* 21**,** 133-41.

RAINVILLE, P., BECHARA, A., NAQVI, N. & DAMASIO, A. R. 2006. Basic emotions are associated with distinct patterns of cardiorespiratory activity. *Int J Psychophysiol,* 61**,** 5-18.

RAJ, S. R. 2006. The Postural Tachycardia Syndrome (POTS): pathophysiology, diagnosis & management. *Indian Pacing Electrophysiol J,* 6**,** 84-99.

RAJ, V., HAMAN, K. L., RAJ, S. R., BYRNE, D., BLAKELY, R. D., BIAGGIONI, I., ROBERTSON, D. & SHELTON, R. C. 2009. Psychiatric profile and attention deficits in postural tachycardia syndrome. *J Neurol Neurosurg Psychiatry,* 80**,** 339-44.

RAJ, V., ROWE, A. A., FLEISCH, S. B., PARANJAPE, S. Y., ARAIN, A. M. & NICOLSON, S. E. 2014. Psychogenic pseudosyncope: diagnosis and management. *Auton Neurosci,* 184**,** 66-72.

RAMOS, R., MOYA, J., MORERA, R., MASUET, C., PERNA, V., MACIA, I., ESCOBAR, I. & VILLALONGA, R. 2006. An assessment of anxiety in patients with primary hyperhidrosis before and after endoscopic thoracic sympathicolysis. *Eur J Cardiothorac Surg,* 30**,** 228-31.

REISS, S., PETERSON, R. A., GURSKY, D. M. & MCNALLY, R. J. 1986. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther,* 24**,** 1-8.

RIEF, W., HILLER, W. & MARGRAF, J. 1998. Cognitive aspects of hypochondriasis and the somatization syndrome. *J Abnorm Psychol,* 107**,** 587-95.

RIOS-MARTINEZ, B. P., HUITRON-CERVANTES, G., MARQUEZ, M. F., GONZALEZ-HERMOSILLO, J. A., RANGEL-RODRIGUEZ, G. A. & PEDRAZA-MOCTEZUMA, L. G. 2009. [Psychopathology and personality in patients with vasovagal syncope]. *Arch Cardiol Mex,* 79**,** 207-11.

RK KHURANA, A. S. 1996. The value of the isometric hand-grip test--studies in various autonomic disorders. *Clin Auton Res,* 6**,** 211-218.

ROBERTSON, G. L. 2001. Antidiuretic hormone. Normal and disordered function. *Endocrinol Metab Clin North Am,* 30**,** 671-94, vii.

RONCHI, R., BELLO-RUIZ, J., LUKOWSKA, M., HERBELIN, B., CABRILO, I., SCHALLER, K. & BLANKE, O. 2015. Right insular damage decreases heartbeat awareness and alters cardio-visual effects on bodily self-consciousness. *Neuropsychologia,* 70**,** 11-20.

ROSNER, M. J., ROSNER, S. D. & JOHNSON, A. H. 1995. Cerebral perfusion pressure: management protocol and clinical results. *J Neurosurg,* 83**,** 949-62.

ROSS, A. J., MEDOW, M. S., ROWE, P. C. & STEWART, J. M. 2013. What is brain fog? An evaluation of the symptom in postural tachycardia syndrome. *Clin Auton Res,* 23**,** 305-11.

RUCHINSKAS, R. 2007. Hyperhidrosis and anxiety: chicken or egg? *Dermatology,* 214**,** 195-6.

RUCHINSKAS, R. A., NARAYAN, R. K., MEAGHER, R. J. & FURUKAWA, S. 2002. The relationship of psychopathology and hyperhidrosis. *Br J Dermatol,* 147**,** 733-5.

SAFDER, S., CHELIMSKY, T. C., O'RIORDAN, M. A. & CHELIMSKY, G. 2009. Autonomic testing in functional gastrointestinal disorders: implications of reproducible gastrointestinal complaints during tilt table testing. *Gastroenterol Res Pract,* 2009**,** 868496.

SAPER, C. B. 2002. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu Rev Neurosci,* 25**,** 433-69.

SCHACHTER, S. & SINGER, J. E. 1962. Cognitive, social, and physiological determinants of emotional state. *Psychol Rev,* 69**,** 379-99.

SCHANDRY, R. 1981. Heart beat perception and emotional experience. *Psychophysiology,* 18**,** 483-8.

SCHANDRY, R., BESTLER, M. & MONTOYA, P. 1993. On the relation between cardiodynamics and heartbeat perception. *Psychophysiology,* 30**,** 467-74.

SCHEIER, M. F. & CARVER, C. S. 1985. The self-consciousness scale: A revised version for use with general populations. *Journal of Applied Social Psychology,* 15**,** 687-699.

SCHLADER, Z. J., PRANGE, H. D., MICKLEBOROUGH, T. D. & STAGER, J. M. 2009. Characteristics of the control of human thermoregulatory behavior. *Physiol Behav,* 98**,** 557-62.

SCHMIDT, N. B., LEREW, D. R. & TRAKOWSKI, J. H. 1997. Body vigilance in panic disorder: evaluating attention to bodily perturbations. *J Consult Clin Psychol,* 65**,** 214-20.

SCHONDORF, R., BENOIT, J., WEIN, T. & PHANEUF, D. 1999. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst,* 75**,** 192-201.

SCHONDORF, R. & LOW, P. A. 1993. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology,* 43**,** 132-7.

SCUFFHAM, P., CHAPLIN, S. & LEGOOD, R. 2003. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health,* 57**,** 740-4.

SEELEY, W. W., MENON, V., SCHATZBERG, A. F., KELLER, J., GLOVER, G. H., KENNA, H., REISS, A. L. & GREICIUS, M. D. 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci,* 27**,** 2349-56.

SETH, A. K. 2013. Interoceptive inference, emotion, and the embodied self. *Trends Cogn Sci,* 17**,** 565-73.

SETH, A. K. & CRITCHLEY, H. D. 2013. Extending predictive processing to the body: emotion as interoceptive inference. *Behav Brain Sci,* 36**,** 227-8.

SHIM, S. H., PARK, S. Y., MOON, S. N., OH, J. H., LEE, J. Y., KIM, H. H., HAN, J. W. & LEE, S. J. 2014. Baseline heart rate variability in children and adolescents with vasovagal syncope. *Korean J Pediatr,* 57**,** 193-8.

SIERRA, M., BAKER, D., MEDFORD, N. & DAVID, A. S. 2005. Unpacking the depersonalization syndrome: an exploratory factor analysis on the Cambridge Depersonalization Scale. *Psychol Med,* 35**,** 1523-32.

SIERRA, M. & DAVID, A. S. 2011. Depersonalization: a selective impairment of self-awareness. *Conscious Cogn,* 20**,** 99-108.

SIERRA, M., SENIOR, C., DALTON, J., MCDONOUGH, M., BOND, A., PHILLIPS, M. L., O'DWYER, A. M. & DAVID, A. S. 2002. Autonomic response in depersonalization disorder. *Arch Gen Psychiatry,* 59**,** 833-8.

SIMEON, D., KNUTELSKA, M., NELSON, D. & GURALNIK, O. 2003. Feeling unreal: a depersonalization disorder update of 117 cases. *J Clin Psychiatry,* 64**,** 990-7.

SLATER, E. 1965. Diagnosis of "Hysteria". *Br Med J,* 1**,** 1395-9.

SLEDGE, W. H. 1978. Antecedent psychological factors in the onset of vasovagal syncope. *Psychosom Med,* 40**,** 568-79.

SMIT, A. A., HALLIWILL, J. R., LOW, P. A. & WIELING, W. 1999. Pathophysiological basis of orthostatic hypotension in autonomic failure. *J Physiol,* 519 Pt 1**,** 1-10.

SOKOLOV, E. N. 1963a. Higher nervous functions; the orienting reflex. *Annu Rev Physiol,* 25**,** 545-80.

SOKOLOV, E. N. 1963b. *Perception and the conditioned reflex.,* Oxford, Pergamon Press.

SPIELBERGER, C. D., GORSSUCH, R.L., LUSHENE, P.R., VAGG, P.R., JACOBS, G.A 1983. *Manual for the State-Trait Anxiety Inventory.* , Consulting Psychologists Press, Inc.

SPYER, K. M. 1994. Annual review prize lecture. Central nervous mechanisms contributing to cardiovascular control. *J Physiol,* 474**,** 1-19.

STEIN, P. K., BOSNER, M. S., KLEIGER, R. E. & CONGER, B. M. 1994. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J,* 127**,** 1376-81.

STEWART, J. M., MEDOW, M. S., MESSER, Z. R., BAUGHAM, I. L., TERILLI, C. & OCON, A. J. 2012. Postural neurocognitive and neuronal activated cerebral blood flow deficits in young chronic fatigue syndrome patients with postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol,* 302**,** H1185-94.

SUZUKI, K., GARFINKEL, S. N., CRITCHLEY, H. D. & SETH, A. K. 2013. Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia,* 51**,** 2909-17.

TAJADURA-JIMENEZ, A. & TSAKIRIS, M. 2014. Balancing the "inner" and the "outer" self: interoceptive sensitivity modulates self-other boundaries. *J Exp Psychol Gen,* 143**,** 736-44.

TANNEMAAT, M. R., VAN NIEKERK, J., REIJNTJES, R. H., THIJS, R. D., SUTTON, R. & VAN DIJK, J. G. 2013. The semiology of tilt-induced psychogenic pseudosyncope. *Neurology,* 81**,** 752-8.

TATTERSON, A. J., HAHN, A. G., MARTIN, D. T. & FEBBRAIO, M. A. 2000. Effects of heat stress on physiological responses and exercise performance in elite cyclists. *J Sci Med Sport,* 3**,** 186-93.

TEFF, K. L. 2011. How neural mediation of anticipatory and compensatory insulin release helps us tolerate food. *Physiol Behav,* 103**,** 44-50.

THAYER, J. F., FRIEDMAN, B. H. & BORKOVEC, T. D. 1996. Autonomic characteristics of generalized anxiety disorder and worry. *Biol Psychiatry,* 39**,** 255-66.

THAYER, J. F., FRIEDMAN, B. H., BORKOVEC, T. D., JOHNSEN, B. H. & MOLINA, S. 2000. Phasic heart period reactions to cued threat and nonthreat stimuli in generalized anxiety disorder. *Psychophysiology,* 37**,** 361-8.

THOMPSON, L. & THOMPSON, M. 1998. Neurofeedback combined with training in metacognitive strategies: effectiveness in students with ADD. *Appl Psychophysiol Biofeedback,* 23**,** 243-63.

TRIMBLE, M. R. 1982. Functional diseases. *Br Med J (Clin Res Ed),* 285**,** 1768-70.

TUCKER, R., MARLE, T., LAMBERT, E. V. & NOAKES, T. D. 2006. The rate of heat storage mediates an anticipatory reduction in exercise intensity during cycling at a fixed rating of perceived exertion. *J Physiol,* 574**,** 905-15.

TURPIN, G. 1986. Effects of stimulus intensity on autonomic responding: the problem of differentiating orienting and defense reflexes. *Psychophysiology,* 23**,** 1-14.

UMEDA, S., HARRISON, N. A., GRAY, M. A., MATHIAS, C. J. & CRITCHLEY, H. D. 2009. Functional MRI investigations of emotional processing and autonomic responses in patients with autonomic hyperactivity. *Neuroimage,* 47**,** S39-S41.

UMEDA, S., HARRISON, N. A., GRAY, M. A., MATHIAS, C. J. & CRITCHLEY, H. D. 2015. Structural brain abnormalities in postural tachycardia syndrome: A VBM-DARTEL study. *Front Neurosci,* 9**,** 34.

VADDADI, G., LAMBERT, E., CORCORAN, S. J. & ESLER, M. D. 2007. Postural syncope: mechanisms and management. *Med J Aust,* 187**,** 299-304.

VALLBO, A. B., HAGBARTH, K. E. & WALLIN, B. G. 2004. Microneurography: how the technique developed and its role in the investigation of the sympathetic nervous system. *J Appl Physiol (1985),* 96**,** 1262-9.

VAN BOXTEL, G. J. M. & BÖCKER, K. B. E. 2004. Cortical measures of anticipation. *J Psychophysiol* 18**,** 61–76.

VAN DER KOLK, B. A. 1996. *Traumatic Stress: the Effects of Overwhelming Experience on Mind, Body, and Society.,* New York, Guilford Press.

VAN DIJK, J. G. & WIELING, W. 2013. Pathophysiological basis of syncope and neurological conditions that mimic syncope. *Prog Cardiovasc Dis,* 55**,** 345-56.

VAN LIESHOUT, J. J., WIELING, W., KAREMAKER, J. M. & SECHER, N. H. 2003. Syncope, cerebral perfusion, and oxygenation. *J Appl Physiol (1985),* 94**,** 833-48.

VAN RAVENSWAAIJ-ARTS, C. M., KOLLEE, L. A., HOPMAN, J. C., STOELINGA, G. B. & VAN GEIJN, H. P. 1993. Heart rate variability. *Ann Intern Med,* 118**,** 436-47.

VAZQUEZ, L. D., STAPLES, N. L., SEARS, S. F. & KLODELL, C. T. 2011. Psychosocial functioning of patients after endoscopic thoracic sympathectomy. *Eur J Cardiothorac Surg,* 39**,** 1018-21.

VERHAGEN, J. V., KADOHISA, M. & ROLLS, E. T. 2004. Primate insular/opercular taste cortex: neuronal representations of the viscosity, fat texture, grittiness, temperature, and taste of foods. *J Neurophysiol,* 92**,** 1685-99.

VERKUIL, B., BROSSCHOT, J. F. & THAYER, J. F. 2007. A sensitive body or a sensitive mind? Associations among somatic sensitization, cognitive sensitization, health worry, and subjective health complaints. *J Psychosom Res,* 63**,** 673-81.

VOSS, M., MOORE, J., HAUSER, M., GALLINAT, J., HEINZ, A. & HAGGARD, P. 2010. Altered awareness of action in schizophrenia: a specific deficit in predicting action consequences. *Brain,* 133**,** 3104-12.

WANG, C. A. & MUNOZ, D. P. 2015. A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. *Curr Opin Neurobiol,* 33**,** 134-140.

WHITEHEAD, W. E. & DRESCHER, V. M. 1980. Perception of gastric contractions and self-control of gastric motility. *Psychophysiology,* 17**,** 552-8.

WILHELM, F. H. & ROTH, W. T. 2001. The somatic symptom paradox in DSM-IV anxiety disorders: suggestions for a clinical focus in psychophysiology. *Biol Psychol,* 57**,** 105-40.

WILLEM VAN DER DOES, A. J., ANTONY, M. M., EHLERS, A. & BARSKY, A. J. 2000. Heartbeat perception in panic disorder: a reanalysis. *Behav Res Ther,* 38**,** 47-62.