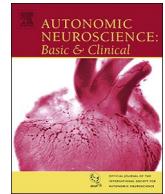




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Emotional orienting during interoceptive threat in orthostatic intolerance: Dysautonomic contributions to psychological symptomatology in the postural tachycardia syndrome and vasovagal syncope

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ABSTRACT

Cognitive and emotional processes are influenced by interoception (homeostatic somatic feedback), particularly when physiological arousal is unexpected and discrepancies between predicted and experienced interoceptive signals may engender anxiety. Due to the vulnerability for comorbid psychological symptoms in forms of orthostatic intolerance (OI), this study investigated psychophysiological contributions to emotional symptomatology in 20 healthy control participants (13 females, mean age 36 ± 8 years), 20 postural tachycardia syndrome (PoTS) patients (18 females, mean age 38 ± 13 years) and 20 vasovagal syncope (VVS) patients (15 females, mean age 39 ± 12 years). We investigated indices of emotional orienting responses (OR) to randomly presented neutral, pleasant and unpleasant images in the supine position and during the induced interoceptive threat of symptom provocation of head-up tilt (HUT). PoTS and VVS patients produced greater indices of emotional responsivity to unpleasant images and, to a lesser degree, pleasant images, during interoceptive threat. Our findings are consistent with biased deployment of response-focused emotion regulation (ER) while patients are symptomatic, providing a mechanistic underpinning of how pathological autonomic overexcitation predisposes to anxiogenic traits in PoTS and VVS patients. This hypothesis may improve our understanding of why orthostasis exacerbates cognitive symptoms despite apparently normal cerebral autoregulation, and offer novel therapeutic targets for behavioural interventions aimed at reducing comorbid cognitive-affective symptoms in PoTS and VVS.

1. Introduction

Cognitive and emotional processes are influenced by interoception (homeostatic somatic feedback) (Damasio, 1999; Gray et al., 2012; Lange and James, 1922), particularly when physiological arousal is abnormal and discrepancies between predicted and experienced interoceptive signals may engender anxiety (Garfinkel et al., 2016; Paulus and Stein, 2006; Owens et al., 2018a). Baroreceptor pathways directly relay cardiovascular interoceptive information to brainstem centres, where normative baroreflex function is subject to modulation by ‘top-down’ brain activity by descending forebrain (e.g. prefrontal cortex) and hypothalamic signalling on medullary centres, including the

nucleus of the solitary tract (Skinner, 1988). Dysfunction of the baroreflex causes orthostatic intolerance (OI) and syncope due to cerebral hypoperfusion. Two common clinical forms of OI are the postural tachycardia syndrome (PoTS) (prevalence of >170 cases per 100,000 in the general population (Schondorf et al., 1999)) and vasovagal syncope (VVS) (accounting for 40% of faints (Vaddadi et al., 2007)).

PoTS is defined by an excessive orthostatic HR increase, of >30 beats per minute (BPM) or a HR of >120 BPM, without orthostatic hypotension (fall of >20 mm Hg systolic BP (SBP) or >10 mm Hg diastolic BP (DBP) (Freeman et al., 2011) within 10 min of orthostasis or head-up tilt (HUT). Symptoms include dizziness and palpitations when upright; some have orthostatic headache, fatigue, bladder and

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gastrointestinal (GI) symptoms (Mathias et al., 2012). Take out functional impairment as not a symptom (Thieben et al., 2007). Infection (Schondorf and Low, 1993), deconditioning (Parsaik et al., 2012) and hypovolemia have also been implicated in PoTS pathophysiology and can worsen symptoms. Some divide PoTS into hyperadrenergic or neuropathic phenotypes (Benarroch, 2012).

The lifetime incidence of syncope is approximately 39% (Sledge, 1978; Owens et al., 2017b) and accounts for 3–5% of emergency room admissions (Critchley and Garfinkel, 2013; Eccles et al., 2015; Benrud-Larson et al., 2003). There are various conditions that cause syncope, including cardiac causes. Neurally mediated syncope (NMS) is probably the most prevalent, as reported in certain age groups, such as teenagers and the young. It comprises situation, vasovagal (VVS) and carotid sinus hypersensitivity. Of the different causes of NMS the most common is VVS, which is characterised by a paroxysmal malfunction of baroreflex function and autonomic instability during which aberrant sympathoexcitation (e.g. palpitations, sudomotor activation) often precedes sympathetic withdrawal causing profound vasodilatation, a fall in BP, as well as vagal/parasympathetic excitation with a fall in HR and cardiac output, resulting in syncope (Medow et al., 2008; Barcroft and Edholm, 1945). In many patients, perceived physical and psychosocial stressors may also induce VVS (Sledge, 1978).

Consistent with the perturbed integration of central and autonomic nervous system (ANS) function (Owens et al., 2017b; Critchley and Garfinkel, 2013), psychological symptoms are overrepresented in PoTS and VVS (Eccles et al., 2015). In PoTS, the profile of cognitive-affective symptoms includes anxiety, attentional deficits, impaired working memory, somatic hypervigilance and subjective ‘brain-fog’ (Benrud-Larson et al., 2003; Raj et al., 2009; Masuki et al., 2007; Raj, 2006; Bagai et al., 2011). Cognitive symptoms are typically exacerbated by orthostasis and autonomic symptom provocation (Anderson et al., 2014) but despite investigations into cerebral blood flow, sleep behaviour and neurotransmitter function, the cause of this brain-fog remains elusive in PoTS patients (Ocon, 2013; Ross et al., 2013). In VVS, depression, anxiety and blood-injection-injury phobia are common (Graham, 1961; McGrady et al., 2001; Luborsky et al., 1973; Karaca et al., 2007). Moreover, heightened anxiety levels increase the risk of VVS during HUT (Cohen et al., 2000) and can determine frequency and severity of syncopal episodes (Lerma et al., 2013). During induced emotional stress, VVS patients also evidence reduced anticipation and regulation of emotional states (Buodo et al., 2012) and patients with psychiatric disorders, such as psychogenic fever, report symptoms similar to VVS and PoTS, such as light-headedness and fatigue (Lkhagvasuren et al., 2013).

In a recent study (Owens et al., 2017a) by our group, we found most cognitive-affective symptoms in PoTS and VVS patients are typically subclinical, without strong causative links to personality (neurosis, trait anxiety) or traumatic experience. Instead, symptoms appeared better explained by ‘interoceptive’ anxiety of physical sensations and dysautonomic symptoms. This was further supported by observed deficits in interoceptive accuracy and anxiogenic interpretation of interoceptive signals by PoTS and VVS patients during head-up tilt (HUT).

The orienting response (OR) encompasses a series of involuntary sensory, motor, parasympathetic and sympathetic adjustments that occur in response to the presentation of a salient stimulus. When the stimulus is emotive, especially unpleasant, the OR is more robust (Fanselow, 1994). Evoked cardiac deceleration (ECR1) is the earliest component of the OR, and is centrally mediated by ‘defence’ circuitry, including the amygdala (Hermans et al., 2013), and peripherally mediated by the vagus nerve. The OR facilitates perception of the stimulus, including inhibition of conditioned and unconditioned reflexes (Pavlov, 1953) to ‘increase analyser sensitivity’ (Sokolov, 1963). Despite autonomic orchestration of the visceral non-muscular components of the OR, there have been no investigations into whether dysautonomia affects ORs or related psychological processes, for example, if the OR inhibits conditioned and unconditioned reflexes, does this include

dysautonomic symptom provocation? This is relevance to conditions such as PoTS and VVS in which autonomic overexcitation is expressed with a prevalence of comorbid psychological symptoms. If interoception is at the core of psychological symptomatology in PoTS and VVS, the generation of emotional ORs may be exaggerated by orthostatic challenge, where the interoceptive threat of OI symptom provocation would amplify ‘bottom-up’ stress.

The current study extends description of the link between OI, interoception and psychological symptoms by examining emotional ORs in PoTS and VVS in comparison to healthy controls. We predicted interoceptive threat/symptom provocation would exacerbate low-order emotional responsivity during HUT in PoTS and VVS patients.

2. Materials and methods

2.1. Participants

All experimental procedures received national and institutional ethical approval (NRES Committee London - Harrow, University College London Healthcare Trust Research and Design Office, Imperial College London AHSC Joint Research Compliance Office). Twenty healthy control participants (13 females, mean age 36 ± 8 years), twenty PoTS patients (18 females, mean age 38 ± 13 years) and twenty VVS patients (15 females, mean age 39 ± 12 years) gave full informed consent to participate in the study. The predominance of females in this study's patients groups is due to PoTS being more common in women (female:male ratio, 4.5:1) (Mathias et al., 2012; Benarroch, 2012). Patients with any current psychiatric comorbidities requiring treatment were not included in the current study.

2.2. Supine and head-up tilt baseline protocol

Participants were instructed to withdraw any medication and/or abstain from any stimulants that may affect autonomic function on the day of testing, such as beta-adrenergic blockers, vasodilators, nicotine and caffeine. Normative heart rate (HR) and blood pressure (BP) data was collected from participants over 10 min supine baseline and 10 min HUT baseline periods using PowerLab 16/30, AD Instruments, Oxford, United Kingdom. BP was continually recorded using digital photoplethysmography (Finometer, FMS, NL).

2.3. Orienting response protocol

Originally believed to be a unitary reflex (Sokolov, 1963), Barry's development of the ‘Preliminary Process Theory’ redefined the OR (Barry, 2009). The early evoked cardiac response of HR deceleration (ECR1) of the OR indicates stimulus detection (Barry, 1977, 2009), with the degree of cardiac deceleration predicting subsequent memory performance (Buchanan et al., 2006). ECR1 is differentiated from the cardiac defence response (CDR) by the defining cardiac acceleration during the CDR to an intense or aversive stimulus, which reduces attention and perception to protect against the stimulus (Fernandez and Vila, 1989). It is widely accepted that the OR is therefore the opposite of the CDR. The PVC component of the OR provides an index of stimulus strength, as it shows substantial linear effects of intensity with no decrement in response with stimulus repetition (Barry, 2009). This study therefore focused on both the ECR1 and PVC components of the OR as (i) neither have habituation effects, (ii) both provide indices of attentional and emotional mechanisms and (iii) are the most likely components of the OR to be compromised by autonomic cardiovascular pathophysiology in PoTS and VVS. PVC was extracted from the beat-to-beat measures of diastolic blood pressure from continuous digital photoplethysmography. In line with previous guidelines, ORs were analysed for 6 s post-stimulus presentation and followed by an Inter Trial Interval (ITI) of 10 s (Graham, 1978). The last 1 s of the ITI prior to stimulus presentation acted as baseline and change scores for each 1 s of

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