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Autonomic hyper-vigilance in post-infective fatigue syndrome

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ABSTRACT

This study examined whether post-infective fatigue syndrome (PIFS) is associated with a disturbance in bidirectional autonomic signalling resulting in heightened perception of symptoms and sensations from the body in conjunction with autonomic hyper-reactivity to perceived challenges. We studied 23 patients with PIFS and 25 healthy matched control subjects. A heartbeat discrimination task and a pressure pain threshold test were used to assess interoceptive sensitivity. Cardiac response was assessed over a 4-min Stroop task. PIFS was associated with higher accuracy in heartbeat discrimination and a lower pressure pain threshold. Increased interoceptive sensitivity correlated strongly with current symptoms and potentiated differences in the cardiac response to the Stroop task, which in PIFS was characterized by insensitivity to task difficulty and lack of habituation. Our results provide the first evidence of heightened interoceptive sensitivity in PIFS. Together with the distinct pattern in cardiac responsivity these findings present a picture of physiological hyper-vigilance and response inflexibility.

1. Introduction

Despite intensive research efforts, the pathophysiology of the enigmatic clinical disorder, chronic fatigue syndrome (CFS) remains obscure and curative therapies are not available. The substantial heterogeneity in cross-sectional samples of patients fulfilling the diagnostic criteria for CFS has been identified as an important contributor to the inconclusive and inconsistent research findings (Wilson et al., 2001; Sullivan et al., 2002; Vollmer-Conna et al., 2006). In response to this conundrum, some groups have shifted their research focus to post-infective fatigue as a model for CFS. Prospective cohort studies have empirically verified the existence of a post-infective fatigue syndrome (PIFS) consistent with CFS, triggered by infection with Epstein-Barr virus (EBV), Ross River virus (RRV, epidemic polyarthritis), or *Coxiella burnetii* (the causative agent of Q fever) (White et al., 1998; Buchwald et al., 2000; Candy et al., 2003; Hickie et al., 2006; Katz et al., 2009). At 6 months post-infection, PIFS cases constitute a subset of the broader CFS group. Like all patients with CFS, they fulfill international diagnostic criteria (Fukuda et al., 1994); however patients with PIFS are distinct in that their CFS follows directly upon a documented acute infective illness. Thus PIFS constitutes a valid disease model for CFS, which permits examination of pathophysiological hypothesis in a well-defined, homogeneous patient group.

Previous research examining autonomic dysfunction in CFS has provided inconsistent support for functional disturbances in autonomic cardiac regulation associated with orthostatic challenges (e.g. Rowe and Calkins, 1998; Rowe et al., 2001; Poole et al., 2000; Winkler et al., 2004; Jones et al., 2005; Wyller et al., 2008). Additionally, there is some evidence suggesting sympathetic hyper-arousal [increased resting heart rate (HR) and reduced HR variability] that persists even during sleep (Vollmer-Conna et al., 2006; Boneva et al., 2007). The precise nature and extent of autonomic system dysregulation in CFS are still unclear.

A fresh perspective of the role of the autonomic nervous system in health and disease was provided by the delineation of an interoceptive pathway within the afferent nervous system (Craig, 2002). Converging evidence from functional anatomy and neuroimaging studies (Craig, 2002, 2003; Critchley et al., 2004; Harrison et al., 2009) has established that fibres of the lamina I spinothalamocortical system merge with vagus nerve afferents to convey signals from essentially all physiological systems and microenvironments (including inflammatory, metabolic, hormonal) to autonomic and homeostatic centres, and then to higher limbic and cortical regions (including the anterior cingulate cortex, the insular and orbitofrontal cortex). This sequential cortical processing

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endows the brain with conscious awareness of the physiological condition of the entire body, termed interoception. In response to perceived homeostatic imbalances the brain adjusts emotions, motivated behaviours and descending autonomic responses in order to maintain body integrity (Craig, 2002).

These new insights into interoception and its neural substrates have redefined our understanding of modalities such as pain, which was conventionally thought of as 'exteroceptive', somatosensory and distinct from visceral sensations that were labeled 'interoceptive'. This categorisation however neglects the inherent emotional and motivational qualities that pain shares with all feelings from the body (Rainville et al., 1997; Craig, 2003). A series of novel findings (Craig, 2002, 2003) suggested that in humans, pain may be best understood as part of an integrated homeostatic network providing both a distinct sense of the physiological condition of the body (i.e. interoception) and a specific behavioural motivation.

Although the potential pathophysiological importance of a functional disturbance in the afferent homeostatic system providing the brain with dynamic representations of the state of the body is widely acknowledged (Craig, 2002; Thayer and Brosschot, 2005; Vollmer-Conna et al., 2008; Thayer, 2009; Harrison et al., 2009), this possibility has not been explored in CFS. Interoceptive sensitivity can be assessed experimentally by recording awareness of ongoing physiological activity (e.g. heartbeat, pressure) and has been linked to more intense emotional processing and increased autonomic reactivity to stressors (Pollatos et al., 2007; Wiens et al., 2000; Barrett et al., 2004).

In this study, we examine the hypothesis that following exposure to a significant physiological stressor (e.g. an acute infective illness) PIFS/CFS is associated with sensitization in neurovisceral regulatory circuits, resulting in abnormally heightened perception of symptoms and sensations from the body (physiological hyper-vigilance) in conjunction with autonomic hyper-reactivity to perceived challenges.

2. Methods

2.1. Participants

Twenty-three patients with PIFS (16 females, 7 males; mean age 40 years, range 21–63) were recruited through the Dubbo Infection Outcomes Study (Western New South Wales, Australia) our ongoing cohort study of subjects followed from the onset of documented acute infection due to EBV; *C. burnetii*, or RRV until complete recovery; or from a tertiary referral assessment clinic at a public teaching hospital in Sydney (A. Lloyd, infectious diseases physician). To participate in the study, patients' current symptom profiles had to fulfill international diagnostic criteria for CFS (Fukuda et al., 1994).

As previously detailed (Hickie et al., 2006) at 6 months post-infection all our patients undergo a medical interview and examination by a physician (Andrew Lloyd) and laboratory investigation to exclude alternative medical explanations for ongoing symptoms, such as hypothyroidism or primary sleep disorder. A psychiatrist also assesses them to ensure that no exclusionary psychiatric diagnosis is evident and to allocate comorbid diagnoses according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). Where appropriate, a diagnosis of CFS is made by consensus.

Chronic fatigue followed directly from a documented acute infectious illness in 20 subjects (RRV: $n = 9$; EBV: $n = 7$; *C. burnetii*: $n = 4$). In three patients viral infection was documented in the medical history of the patient however, the precise microorganism was not serologically established.

Twenty-five healthy control subjects matched for age, sex, body mass index (BMI), and activity levels (16 females, 9 males; mean age 42 years, range 22–63) were recruited from community volunteers.

Exclusion criteria were pregnancy, uncorrected visual impairment (including colour blindness), significant hearing impairment; primary sleep disorder (obstructive sleep apnoea or narcolepsy); endocrine (untreated diabetes, uncontrolled thyroid disease) or neurological (uncontrolled epilepsy, stroke, dementia, autonomic neuropathy) co-morbidities; uncontrolled/untreated cardiovascular disease (hypertension, heart failure) or pacemaker; active autoimmune disease (e.g. SLE, Sjogren's syndrome, rheumatoid arthritis); major depressive disorder, psychotic or substance abuse disorders. In addition, medications known to affect autonomic functioning including beta blockers, benzodiazepines, corticosteroids (e.g. prednisone, cortisone acetate, fludrocortisone), other centrally active drugs (e.g. methylphenidate, dexamphetamine) were exclusionary.

Written informed consent was obtained from all subjects prior to participation in the study. The relevant institutional review boards approved the study protocol.

2.2. Procedure

All testing was carried out in a light- and temperature-controlled clinic room at the University of New South Wales, Sydney, and at the pathology clinic rooms linked to the Dubbo Infection Outcomes Study. Participants were asked to abstain from caffeine, alcohol and exercise for 12 h prior to testing. After baseline heart rate recording, the order of tests was counterbalanced to control for possible order or carry-over effects on performance, including fatigue and learning.

2.3. Self-report questionnaires

Subjects completed self-report questionnaires to provide relevant demographic, medical history and general health information, and to assess physical symptoms, psychological variables; and functional impairment. Specifically, the 34 item Somatic and Psychological Health Report (SPHERE; Hickie et al., 2001) was used to assess a wide range of physical and psychological symptoms. An empirically derived subscale that records somatic symptoms (the SOMA) identified the key clinical features of prolonged fatigue states. The Kessler 10 measured current psychological distress (K10; Kessler et al., 2002). The Brief Disability Questionnaire (BDQ; von Korff et al., 1996) was used to assess functional impairment, and 'days out of role' quantified the days over the past months the respondent was unable to carry out usual daily activities fully.

Dimensions of personality, in particular negative affectivity/neuroticism and social inhibition have been associated with an individuals' response to stressors and an increased risk of psychiatric and medical conditions. We used the type D or 'Distressed' personality scale (DS14; Denollet, 2005), which permits efficient assessment of negative affectivity (an enduring tendency to experience negative emotions) and trait social inhibition (the tendency to feel inhibited, tense, and insecure when with others).

2.4. Measures of interoceptive awareness

2.4.1. Heartbeat discrimination task

A pulse oximeter (Nonin9600, Proact Medical Systems, Australia) was used to monitor HR (beats per min, bpm) without visual feedback to the subject, with the onset of each pulse waveform triggering a tone which was presented to the subject via headphones. This task was based on the Method of Constant Stimuli originally described by Brener et al. (1993) and used here as later modified by Critchley et al. (2004). Forty trials were played, each involving delivery of a set of 10 tones, which were either "synchronous" to the individual's heartbeat or delayed by 500 ms. Subjects attended to their own heartbeat and indicated, at the end of each trial, whether the feedback was synchronous (YES) or delayed (NO). These trials, heralded by the appearance of the word HEART on the screen, were interleaved with forty trials of an exteroceptive control task, signaled by the word NOTE. During NOTE trials, the subject was required to attend to the quality of the feedback notes. One note of a lower pitch (785 Hz) than the other nine notes (800 Hz) was included in half of the trials at a random position in the sequence. At the end of each NOTE trial the subjects had to indicate whether all notes were the same (YES) or not (NO). Thus, subjects were required to shift their attention appropriately to their heartbeat timing during the interoceptive HEART task, and to note quality during the NOTE trials. Prior to testing, each subject was given instructions and a short practice session to familiarize with the basic task demands.

"HEART" and "NOTE" scores were calculated by dividing the number of hits by the total number of trials. The HEART score was used as a measure of interoceptive accuracy. In our study, the NOTE score served to ascertain that the subjects' performance is not affected by attention deficits.

2.4.2. Pain sensitivity test

A Pain Test Algometer with a 1 cm^2 flat rubber tip (Force Ten FDX Force Gage, Wagner Instruments Greenwich, CT) was used to quantify subjects' pressure pain threshold—the minimum amount of pressure that triggers pain. This simple, non-invasive test was carried out by the same, trained and experienced operator following a standard protocol (Chesterton et al., 2007). All subjects were given standard instructions and practice trials prior to testing. During testing, the subject's hand was placed behind a visual barrier to avoid any bias introduced by visual cues. Two sites on each hand were tested: the muscle belly of the first dorsal interosseus muscle, and the middle phalanx of the middle digit.

Previous studies have shown that "neutral" regions, such as the thumb accurately reflect overall pressure pain sensitivity even in individuals where pain sensitivity is part of the clinical presentation such as in fibromyalgia sufferers (Petzke et al., 2001). Pressure was applied manually using the algometer at a constantly escalating rate. Subjects were asked to say 'yes' as soon as the sensation of pressure changed to one of pain. As soon as subjects said 'yes' the pressure was stopped and the value (in kgF) recorded. Each site was tested three times in a counterbalanced manner, and the average of the three values was used to reflect pain sensitivity at that site. The pressure pain threshold for each subject was indicated by the grand mean across all sites. To avoid habituation or sensitization at the level