EXPLORING THE EFFECTS OF PERSONALITY ON CENTRAL AND AUTONOMIC EMOTION-PAIN RESPONSES

A thesis submitted to the University of Manchester for the degree of Ph.D. in the faculty of Medical and Human Sciences

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ABSTRACT THE UNIVERSITY OF MANCHESTER

ABSTRACT OF THESIS submitted by Peter Paine for the degree of PhD and entitled "Exploring the effects of personality on central and autonomic emotion-pain responses" February 2008

Background Unexplained medical symptoms are a major challenge for modern health care, with high costs and patient/physician dissatisfaction. Pain, the archetypal symptom, can appear in excess or in absence of observed disease activity. Pain and emotion are constructs which overlap, interact, and share biological bases within central (CNS) and autonomic (ANS) nervous systems. Personality traits are related constructs to pain and emotion, which include negative affect (neuroticism) and social introversion. Personality traits and emotional state impact pain sensitivity and vulnerability for chronic pain and emotion disorders. The relationships of ANS and central pain responses to emotional state and traits are poorly understood.

Aim To explore relationships between autonomic and central pain responses, emotional state and traits.

Methods All studies employed healthy volunteers in whom personality traits and emotional state were assessed. ***Study 1*** measured ANS responses to distal oesophageal pain. ***Study 2*** compared ANS responses to oesophageal intubation, distal and proximal oesophageal pain and also nail-bed pain. Improved psychophysics and an expanded repertoire of superior time resolution ANS measures were used. ***Studies 3&4*** combined distal oesophageal pain with emotional face perception. Blood oxygen level dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) responses were analysed. Top-down effects of negative (fearful) emotional faces on the perceived intensity of oesophageal pain were explored in study three. Bottom-up effects of oesophageal pain on the perceived intensity of positive (happy) facial emotion were explored in study four.

Results ***Study 1***: Two clusters of ANS response to oesophageal pain were found: (i) a "neurotic-introvert" profile with lower oesophageal balloon volumes, high resting sympathetic (SNS)/low parasympathetic (PNS) activity and a blunted SNS/ increased PNS "passive-active/freeze" defence response. (ii) an "emotionally stable-extrovert", profile with converse balloon, resting and an "active/fight-flight" defence response profile. ***Study 2***: Novel SNS/PNS co-activation responses were found for pain at all sites compared with classic reciprocal changes to intubation. Personality relations of distal balloon pain to PNS changes were confirmed. ***Study 3***: Fearful faces induced oesophageal hyperalgesia. ***Study 4***: Oesophageal pain induced "dyshedonia" (a reduction in the perception of happy faces intensity) that was greater for neurotic-introverts. **Studies 3&4:** Differential BOLD fMRI activation was found for neurotic-introverts in a distributed network of structures implicated in pain-emotion processing.

Conclusions (i) Neurotic-introverts had different ANS and central responses to pain and emotion than emotionally-stable extroverts. (ii) Somatic and visceral pain both induced SNS/PNS co-activation but only "true" visceral pain had significant differential PNS pain responses according to personality type. (iii) Emotion and pain perception exhibited bi-directional influences. These findings extend our understanding of shared neurobiological bases for emotion, pain and personality. The relevance of these psychophysiological phenotypes for vulnerability and treatment response in clinical pain and emotion symptoms warrants further exploration.

Declaration

Dr Jessin Kishor helped conduct some of the experimental work in chapter four of this thesis and also some of the subsequent data handling. She has included this as part of her M.Sc. thesis submitted to the University of London, 2007.

Copyright

Signed

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All that is good in this thesis I am sure is in large part thanks to this fantastic group of people – I take full responsibility for the rest!

The author

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List of Abbreviations

AER – anterior executive region

ACC – anterior cingulate cortex

ANS – autonomic nervous system

ASI – Anxiety Sensitivity Index

BIS-BAS – Behavioural Inhibition System – Behavioural Activation System

CAN – central autonomic network

CEP – cortical evoked potential

CNS – central nervous system

CSI – Cardiac Sympathetic Index

CVC – Cardiac Vagal Control

CVC_{NA} – Cardiac Vagal Control – Nucleus Ambiguus component

CVT – Cardiac Vagal Tone

DMX – Dorsal Motor Nucleus of Vagus

E-I – Extroversion-Introversion personality dimension

FFFS – Fight-Freeze-Flight System

fMRI – functional magnetic resonance imaging

HPA – hypothalamic pituitary axis

HR – heart rate

HRV – Heart Rate Variability

NA – Nucleus Ambiguus

N-S – Neuroticism-Emotional Stability personality dimension

NTS – Nucleus of Solitary Tract

OFC – orbito-frontal cortex

PAG – peri-aqueductal gray matter

PFC – prefrontal cortex

PNS – parasympathetic nervous system

R-R – interval between 2 consecutive R waves in the ECG

RSA – Respiratory Sinus Arrhythmia

RVLM – rostral ventrolateral medulla

SAM – sympatho-adrenal medullary

SCR – Skin Conductance Response

SNS – sympathetic nervous system

STAI-ST – Spielberger trait anxiety index – State/trait

VNS – vagal nerve stimulator

VLPAG – ventrolateral peri-aqueductal gray

Chapter 1 Introduction

1.1 Opening remarks

Core themes in historical context

The core themes explored in my thesis are the inter-relationships between personality, emotional state and physiology – in particular the physiology of autonomic (ANS) and central neural (CNS) responses to pain. The recognition and description of these inter-relationships has a long established history.

Early Semitic and Greek literature show that the body in general and viscera in particular have been considered from antiquity to be core components of normal emotional life [e.g. in ancient Hebrew "rehem-rahamim" means viscera *or* passion and in Greek "splanchnizomai-splanchnon" means bowels *or* compassion (Vine et al. 1985)].

The "visceralist" view of emotional life, centred on the "solar plexus", was a dominant medical model from Hippocrates until relatively recently (Williams 2007) and still echoes in the popular vernacular (e.g. "butterflies in my stomach", "gutted"). The role of the brain in emotions by contrast has been a more recent accretion (Dror 2001; Williams 2007).

The putative pathophysiological role of extreme emotions/passions or "stress" in bodily ills also has a long attested history. Furthermore, the existence of individual constitutional differences and vulnerabilities has been attested to as far back as the time of Galen in the 2nd Century BC (Eysenck 1967).

Convergence of opportunities

Despite the long history of mind/body studies a number of factors have converged to encourage a fresh scientific exploration of visceral psychophysiological processes:

1) An epidemic of functional syndromes which consume massive healthcare resources. This is combined with a relative failure of pharmaceutical and academic industry investment to produce effective diagnostic or therapeutic interventions using a grouped clinical trials approach.

2) New conceptual heuristic frameworks: a) a "homeostatic processing network" has suggested a clearer neurobiological basis for the sensory or felt aspects of interactions between pain and emotion (Mayer et al. 2006). b) "Polyvagal theory" has highlighted motor outputs of the brainstem vagal complex in pain/emotion responses as a key psychophysiological hub (Porges 2007).

3) Methodological developments: a) In autonomic neuroscience, "beat-to-beat" (Little et al. 1999) and "breath-to-breath" (Porges 1985) selective cardiac vagal measures and beat-to-beat non-invasive blood pressure measures have been developed. b) In functional neuroimaging, greater field strengths have improved spatial resolution of brain activation and event-related paradigms have enabled non-invasive measurement of central responses (Kwong et al. 1992).

A cautionary note

Although addressing undoubtedly important, fundamental and interesting scientific questions - new constructs and new methodologies alone do not guarantee scientific solubility. There may be inherent epistemic insurmountables dividing mind and body (Uttal 2001).

1.2 An explanation of the "alternative thesis format"

Permission to prepare this thesis manuscript in "alternative thesis format" has been granted by the University of Manchester.

This allows part or the entire thesis to be presented in a format prepared for publication and therefore some repetition between papers and a longer thesis length. Since constraints on space arise in publication format, the University of Manchester require that further breadth and depth of detail regarding background, methodology and discussion are presented in separate chapters (chapters 1, 2 and 7 respectively).

I have drafted experimental chapters 3-6 for submission to peer-reviewed journals. Title pages have not been included (i.e. list of co-authors, correspondence for address etc). University guidelines require that references for each paper are merged at the end of the thesis rather than given at the end of each paper separately.

1.3 The clinical problem: syndromes of medically unexplained symptoms in gastroenterology

The core themes in my thesis, i.e. the inter-relationships between personality, emotional state and ANS/CNS pain physiology, arose in response to a perceived hiatus in medically unexplained gastroenterological symptoms. What is currently known suggests that personality, emotional state and ANS/CNS physiology are all important players in these, but how they interact is less well characterised.

1.3.1 An epidemic of medically unexplained symptoms and functional syndromes

Kroenke and Mangelsdorff reviewed 1000 internal medical patients in the USA over a 3 year period and found that for 10 common new symptoms the largest proportion remained "unexplained" [see figure 1.1](Kroenke and Mangelsdorff 1989).

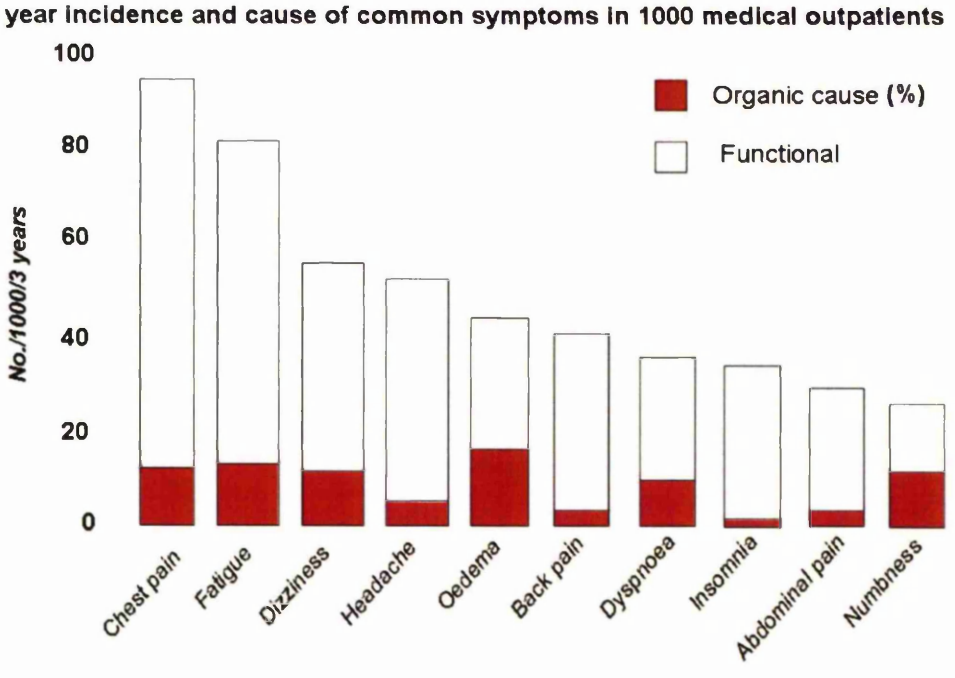

Figure 1.1 Adapted from Kroenke and Mangelsdorff 1989

A UK study found over 40% of patients in secondary care cardiology, gastroenterology and neurology clinics were unexplained or functional (Hamilton et al. 1996). Resultant unmet patient expectation results in reduced patient satisfaction (Jackson and Kroenke 2001) and difficulty in the doctor-patient relationship (Hahn

2001), impaired health related quality of life, and increased health care and loss of productivity costs (Creed et al. 2001).

Which symptoms and at what threshold individuals consult physicians may be culturally determined and not necessarily rooted in pathophysiology (Levy et al. 2001). This is also true however, of which symptoms physicians consider legitimate (Aronowitz 2001).

The study of symptoms has largely given way to the study of "functional syndromes" which are varying combinations of symptoms (Sharpe and Carson 2001). This has facilitated the "ownership" of particular symptom clusters (syndromes) by medical sub-specialties for further research, but potentially masked the considerable overlap between them and inhibited exploration of common mechanisms (Wessely et al. 1999; Aaron and Buchwald 2001; Sharpe and Carson 2001). "Lumpers and splitters" are divided over this issue (Wessely and White 2004).

1.3.2 Functional Gut Disorders and the biopsychosocial model

Within gastroenterology, several gut-focused symptom clusters have been designated as syndromes within a "biopsychosocial" framework (Drossman 1998; Drossman 2006).

By "covering all the bases" there has been a proliferation of aetiological possibilities, whilst hopes of unifying and integrative common mechanisms have rescinded. This aetiological amplification is exacerbated further by sub-divisions of functional syndromes by organ, e.g. oesophagus – non-cardiac chest pain; stomach – functional dyspepsia and post-prandial distress syndrome.

The heterogeneity of these clinical groups is reflected in poor responses to specific treatments. By contrast a pointer to over-arching similarities is the high placebo response rates of functional syndromes compared to overt inflammatory disease (Patel et al. 2005; Dorn et al. 2007; Su et al. 2007).

1.3.3 Functional disturbance of the nervous system: are medically unexplained symptoms "all in the mind" or "all in the brain"?

According to Michael Sharpe, professor of "symptoms research", what is called for is a "paradigm shift" in research and clinical practice which places a "functional disturbance of the nervous system" at the heart of unexplained medical symptoms (Sharpe and Carson 2001).

By his own admission "functional neural disturbance" is not a new idea, being postulated by Charcot, Willis and Beard. In the intervening century an increasingly dualistic biomedical model has however differentiated the physical from the psychological (Drossman 1998) and the idea of purely "psychological" illness was birthed by figures such as Sydenham, Babinski, Janet and Freud (Sharpe and Carson 2001). This gradually acquired a pejorative sense in which the symptoms were "all in the mind"- a diagnosis with a very low "number needed to offend" (Stone et al. 2002). The conception of functional neural disturbances allows a less pejorative "all in the brain" approach which may facilitate more biologically based research.

Although in terms of novelty the notion of a functional neural disturbance is not new and therefore in this sense is a "paradigm retreat" rather than a "shift", nonetheless there have been several developments since the time of Charcot which allow for a more sophisticated approach (Clauw 1995). In particular the discovery of genes, neurotransmitters and functional imaging; a deepened understanding of the basic science of nociceptors, the autonomic, neuroendocrine and central nervous systems; and epidemiological evidence for modulation by psychiatric illness and the neurodevelopmental effects of abuse have all converged to make this a timely opportunity to revisit the notion of functional neural disturbance.

1.3.4 Pain, central sensitisation, inhibition and personality

A related construct to "functional neural disturbance" is "visceral hypersensitivity", based on mechanisms of peripheral or spinal/central "sensitisation" (Sarkar et al. 2001; Sarkar et al. 2003; Sarkar et al. 2004; Willert et al. 2004). This explanation has largely displaced that of visceral motor disturbances in functional GI research (Mayer et al. 1996). Marked individual variability for pain thresholds exist so that although visceral hypersensitivity is exhibited at a group level it has little clinical utility as a discriminatory biomarker. It may in fact be only a subset of medically unexplained symptoms that are due to the narrowly defined peripheral or spinal dorsal horn mechanism of sensitisation. The broader concept of generalised neural/psychological sensitisation may have more wide-spread relevance (Clauw 1995; Eriksen and Ursin 2002; Wilhelmsen 2002; Wessely and White 2004).

Changing concepts of hierarchical neural control have begun to emphasise inhibitory and disinhibitory mechanisms over sensitisation as a possible root of functional neural disturbance (Thayer and Friedman 2002). Moreover, individual

differences in inhibitory and activating neural systems have recently been suggested as a basis of fundamental personality differences and may have greater promise for the development of discriminatory biomarkers (Gray 1970; Gray and McNaughton 2000; McNaughton and Corr 2004).

Summary of section 1.3

Medically unexplained syndromes, including functional gastrointestinal symptoms, are common and problematic. Functional "sensitisation" of the brain/mind is a commonly employed explanatory framework.

1.4 The biological basis of personality

In this section I will review the core theme of personality, starting with its theoretical basis, then a summary of evidence for its biological basis and finally its relationship to clinical pain and evidence from brain imaging studies of its central neural instantiation.

1.4.1 The theoretical basis of personality

Personality constructs have not been built from the "bottom-up" based on behavioural physiology but rather, starting "top-down" with a-priori constructs, theoretical and then experimental biological correlations have accrued with remarkable success.

Galen is first credited with a systematic attempt at categorising "types" of people using Hippocrates biological theories of circulating "humors" [figure 1.2] (Eysenck 1967). Personality research has since developed a broad complex of divergent concepts, levels of analysis and experimental approach (Revelle 1995).

The "lexical approach" to personality taxonomy has been dominant in the preceding century. This is essentially compiling and categorising lists of colloquial adjectives for personality to arrive at core groupings (John and Srivastava 1999). Hans Eysenck attempted to increase scientific rigor in the process by use of factor-analysis techniques and descriptors from clinical samples (Corr 2004). Regardless of methodology, there has been a surprising amount of consistency in defining two dimensions of personality in particular with variations on 3 other dimensions.

The two consistent dimensions are neuroticism-emotional stability and introversion-extroversion. Debate continues however as to whether dimensions or categories are more appropriate (Claridge and Davis 2001; Robinson 2001).

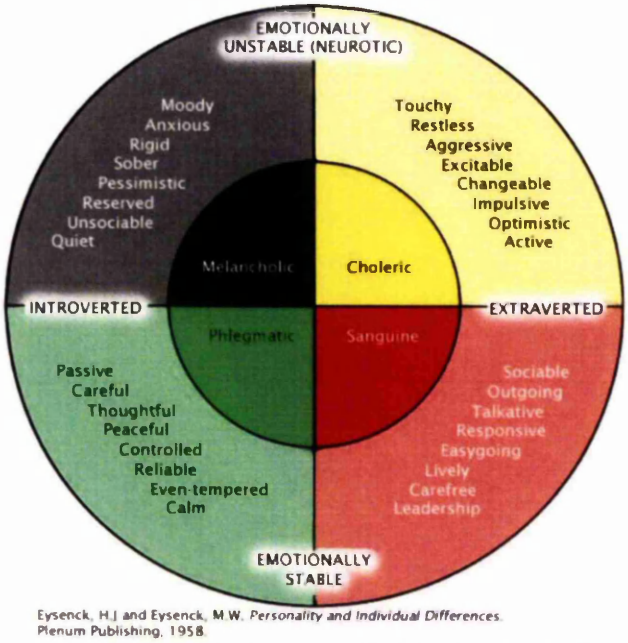

Figure 1.2 Galen's temperamental categories are displayed here at the core of Eysenck's superimposed dimensions of personality. Adapted from (Eysenck 1967)

1.4.2 The biological basis of personality

Eysenck held that neuroticism and extroversion dimensions fulfilled criteria for a biological basis of personality including: (i) psychometric properties of replicability and reliability (ii) evidence of heritability (iii) theoretical backing leading to objective laboratory verification (iv) social relevance (i.e. they correlate with social parameters) (Eysenck 1957; 1963; Eysenck 1967; Eysenck 1977).

The "5 factor model" of personality has since become influential, which also includes neuroticism-stability and extroversion-introversion. These are also lexically based dimensions (John and Srivastava 1999) but it is claimed that they are 5 biologically based basic tendencies with further elaborated, biologically instantiated, "characteristic adaptations" on top which are culturally conditioned phenomena (McCrae et al. 2000).

McCrae and Costa set out an impressive array of evidence for a biological basis for personality/temperament, i.e. that they are "endogenous/constitutional dispositions that follow intrinsic paths of development essentially independent of environmental influences". They list 5 strands of evidence - 1) studies of heritability 2)

evidence of limited parental influence 3) structural invariance a) across cultures (Benet-Martinez and John 1998) b) across species (Gosling and John 1999; Gosling 2001; Vazire and Gosling 2003) 4) temporal stability 5) trans-cultural "intrinsic maturation" (McCrae et al. 2000).

Sensory Sensitivity and Emotionality

Having arrayed a considerable amount of evidence that the "Big Two" personality dimensions have strong credentials for biological underpinnings, the question naturally arises – what might they be? The two leading contenders seem to be "sensitivity" (sensory sensitivity) on the one hand – linked more strongly to introversion-extroversion and "reactivity" (emotional reactivity or emotionality) on the other linked more strongly to neuroticism.

Eysenck originally conceived of the neurobiological basis of introversion as a balance between inhibition/excitation where inhibition approximated to stimulus satiation / habituation / boredom. He proposed that introverts were slow to inhibit in order to protect themselves from over excitation (Eysenck 1957).

Eysenck revised his neurobiological theories in 1967 in terms of arousal. He based neuroticism on "emotional dependent visceral brain + ANS activation" and extroversion on "sensory/psychological stimulation dependent cortical arousability" independent of ANS/emotions, possibly via the reticular activating system. He claimed "for something like 90% of our lives cortical arousal is dependent on mild sensory stimulation rather than on emotional activation" introverts were then said to *avoid* high levels of arousal (Eysenck 1967).

A personality sub-trait related to introversion has been elaborated called "sensory processing sensitivity" – not for sense organs per se but occurring as sensory information is transmitted to or processed in the brain. Aron and Aron summarise evidence that introverts have lower auditory, pain, electrocutaneous and visual threshold sensitivity and greater vigilance (Aron and Aron 1997). Kagan suggested that inhibited children's response to novelty reflected a greater sensitivity that could arise from 3 potential individual differences 1) reactivity of the amygdala 2) degree of visceral feedback to limbic sites 3) preparedness to detect subtle differences (Kagan 1994). Reminiscent of Jung's recognition of "innate sensitiveness", Aron identified this as characteristic of twenty percent of humans (Aron 2004). Jung suggested that it predisposes some individuals to be particularly

affected by negative childhood experiences, so that later, when under pressure to adapt to some challenge, they retreat into infantile fantasies based on those experiences and become "neurotic". Jung observed, given the same degree of stress in childhood as non-sensitive individuals, sensitive persons will develop more depression, anxiety, and shyness. Without undue stress, they evidence no more - or even less - of these difficulties than the non-sensitive, being unusually aware of supportive as well as negative cues from caregivers (Aron 2004). Sensation Seeking is another more widely used related personality sub-trait linked to introversion (Stelmack 2004).

Emotional or affective "reactivity" in emotions research has provided a bridge between cognitive constructs and differences in biological reactivity in regard to temperament which assesses the interoceptive awareness of individuals to emotional states (Calkins 1994; Zvolensky et al. 2001). Similarly, the concept of "emotional intelligence" (EI) takes the concept of awareness of individual emotional activity and ability to regulate emotion to the next level of awareness of the emotions of others and ability to negotiate these effectively (Goleman 1995; Engelberg and Lennart 2004). Impaired EI has been linked to another concept of "alexithymia" which is a construct of impoverished emotional awareness and misattribution of bodily sensation (Lane et al. 1997; Parker 2001).

"Sensitivity" and "reactivity" are possible neurobiological markers of individual difference but neither is a perfect fit for neuroticism and extroversion.

Gray-McNaughton reformulation

Whilst not a truly "bottom-up" reconstruction, Jeffrey Gray's reformulation of Eysenck's personality dimensions has probably been the most influential explicit attempt at a neurobiologically based model. He proposed a behavioural inhibition system (BIS) and a behavioural activation system (BAS). In order to fit the personality structures better to these putative biological systems he rotated Eysenck's dimensions through 30 degrees (Gray 1970). In a subsequent recent revision the BIS system was further subdivided to include a flight-freeze-fight system (FFFS) (Gray and McNaughton 2000) [figure 1.3].

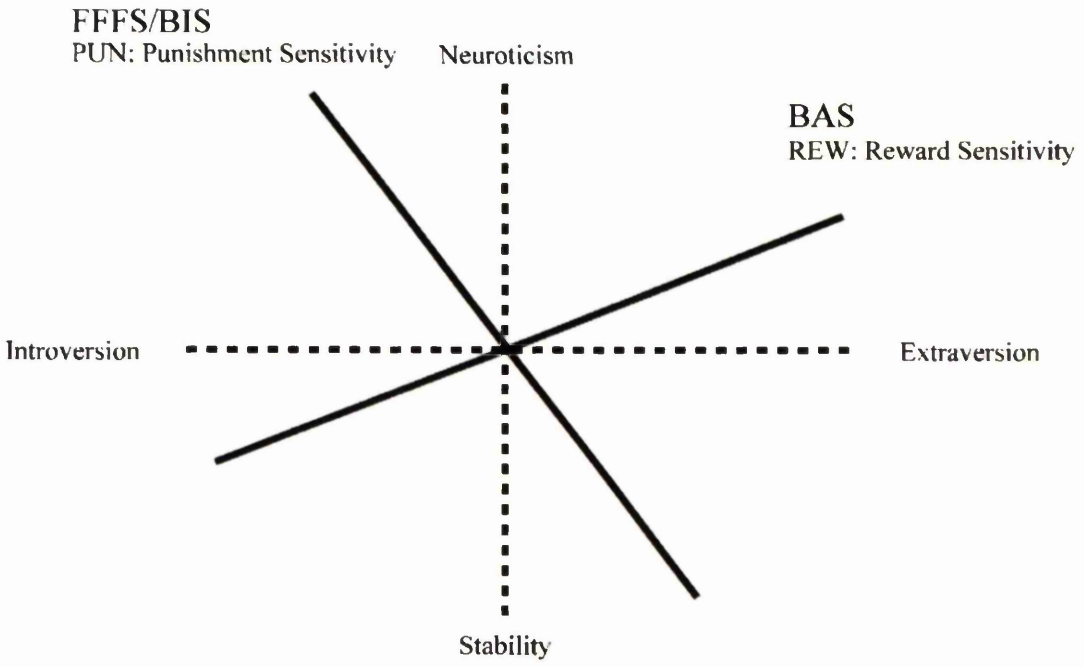

Figure 1.3 Position in factor space of the fundamental FFFS/BIS (PUN, punishment sensitivity) and BAS (REW, reward sensitivity) (unbroken lines) and the emergent surface expressions of these sensitivities, viz. Extraversion (E) and Neuroticism (N) (broken lines). In the revised theory, a clear distinction exists between fear (FFFS) and anxiety (BIS), and separate personality factors may relate to these systems; however, these two systems can be considered to reflect a common dimension of punishment sensitivity (Corr 2004).

This model is of particular interest for the purposes of my thesis since it is the clearest integration of central inhibitory control systems on the one hand [which may relate to a prefrontal-HRV axis (Thayer and Friedman 2002)] and sub-cortically controlled patterned ANS defence responses and behaviours on the other.

Personality and clinical pain

Neuroticism and related constructs have been linked to increased symptom reporting and medically unexplained symptoms for example chest pain in the absence of coronary artery disease (Costa 1987; Costa and McCrae 1987; 1987; Netter and Hennig 1998; Kolk et al. 2003; Okpa et al. 2003; Williams et al. 2004; Zautra et al. 2004; Raselli and Broderick 2007).

Pain catastrophizing and pain-related fear mediated the relationship between neuroticism and vigilance to pain in another study. Furthermore, vigilance to pain was found to be associated with heightened pain severity. Finally, it was found that

neuroticism moderated the relationship between pain severity and catastrophic thinking about pain. The authors felt that their results strongly support the idea that vigilance to pain is dependent upon catastrophic thinking and pain-related fear. Neuroticism the authors suggested is best conceived of as a vulnerability factor; it lowers the threshold at which pain is perceived as threatening, and at which catastrophic thoughts about pain emerge (Goubert et al. 2004).

Positive relationships were found in chronic pain patients between neuroticism, the use of passive coping strategies, and the intensity of pain. On the other hand, extraversion was positively related to the use of active coping strategies and negatively related to the perceived intensity of pain (Ramirez-Maestre et al. 2004).

Results in a study of myofascial pain indicated that the personality traits of neither extraversion nor neuroticism affect sensory mechanisms of nociceptive processing but appear to exert their influence by means of cognitive processes related to the ways in which people constitute the meanings and implications of pain (Harkins et al. 1989).

Bodily pain was independently associated with depression. Neuroticism moderated the associations between pain and both depressive symptom severity and major depression, albeit not independent of overall medical burden; the relationships were stronger in subjects with lower neuroticism scores (Calabrese et al. 2006).

1.4.3 Human brain imaging studies in personality

Canli has reviewed studies using functional magnetic resonance imaging which have shown that individual differences in participants' Extroversion (E) and Neuroticism (N) scores are correlated with individual differences in brain activation in specific brain regions that are engaged during cognitive-affective tasks. Imaging studies using genotyped participants have begun to address the molecular mechanisms that may underlie these individual differences (Canli 2004).

Individual differences in both tonic activation and phasic reactivity in the pre-frontal/amygdala circuit were found to play an important role in governing different aspects of anxiety. Affective chronometry, or the time course of emotional responding, was identified as a key attribute of individual differences in propensity for anxiety that is regulated by this circuitry (Davidson 2000; 2002).

Behaviourally Inhibited (BI) adolescents, relative to Behaviourally Non-inhibited (BN) adolescents, showed exaggerated amygdala response during subjective fear

ratings and deactivation during passive viewing, across different emotion faces. In addition, the BI group showed an abnormally high amygdala response to a task condition marked by novelty and uncertainty (Perez-Edgar et al. 2007).

Positive correlations emerged between extraversion and perfusion in the basal ganglia, thalamus, inferior frontal gyrus and cerebellum and between novelty seeking and perfusion in the cerebellum, cuneus and thalamus in another study (O'Gorman et al. 2006).

Kumari et al observed that, as predicted by Eysenck's model, the higher the E score, the greater the change in fMRI signal from rest to the 3-back condition in the dorsolateral prefrontal cortex and anterior cingulate. In addition, E scores were negatively associated with resting fMRI signals in the thalamus and Broca's area extending to Wernicke's area, supporting the hypothesized (negative) relationship between E and resting arousal (Kumari et al. 2004).

Neuroticism correlated positively with amygdala and subgenual AC activation during trials of high emotional conflict, compared with trials of low emotional conflict. The subscale of neuroticism that reflected the anxious form of neuroticism explained a greater proportion of variance within the observed clusters than the subscale of neuroticism that reflected the depressive form of neuroticism (Haas et al. 2007).

Yucel et al employed a multi-modal neuroimaging approach combined with a task designed to specifically activate the human dorsal anterior cingulate cortex and statistical path analysis to demonstrate clear roles for intelligence, personality and concentrations of neuronal N-acetylaspartate in determining dACC activation. These influences were comparable in magnitude to those associated with the experience of conflict (Yucel et al. 2007).

Using neuroanatomic measures of the cerebral cortex and amygdala, Wright observed that the thickness of specific prefrontal cortex regions correlates with measures of extraversion and neuroticism. In contrast, no such correlations were observed for the volume of the amygdala (Wright et al. 2006).

Anxiety-prone subjects had significantly greater bilateral amygdala and insula activation to emotional faces than did the anxiety-normative comparison subjects. Higher scores on several measures assessing anxiety proneness (e.g., neuroticism, trait anxiety, and anxiety sensitivity) were associated with greater activation of the amygdala (predominantly left-sided) and the anterior insula (bilateral) (Stein et al. 2007).

In response to an oddball task, neuroticism was associated with increased dorsal anterior cingulate cortex (dACC) reactivity, whereas extraversion and self-consciousness were associated with lateral and medial frontoparietal networks respectively. Interoceptive accuracy, an outcome associated with neuroticism, was better accounted for by dACC reactivity than by self-reported neuroticism, suggesting that neural reactivities may provide a more direct measure of personality than self-reports do (Eisenberger et al. 2005).

Significant negative correlations were found between neuroticism and regional cerebral glucose metabolism (rCMRglu) in the insular cortex and positive correlations between extraversion and rCMRglu in the orbitofrontal cortex (Deckersbach et al. 2006).

Hariri et al found neuroticism was linked to serotonin transporter protein polymorphisms (SERTP) and amygdala activity (Hariri et al. 2002). Similarly, Pezawas et al found that SERTP polymorphisms impacted human amygdala-ACC interactions which inversely predicted 30% of variation in temperamental anxiety (Pezawas et al. 2005).

Adults who had been categorized in the second year of life as inhibited, compared with those previously categorized as uninhibited, showed greater functional MRI signal response within the amygdala to novel versus familiar faces (Schwartz et al. 2003).

ANS studies in personality will be reviewed later in section 1.8 after an explanation of ANS neurophysiology and its relationship to personality has been provided.

Summary of section 1.4

(i) Personality constructs, whilst primarily based on lexical descriptors show evidence for significant biological contributions (ii) Extroversion-Introversion and Neuroticism-Stability are major personality dimensions. Sensory sensitivity/emotional reactivity and behavioural inhibition/activation systems have been put forward as underlying neurobiological substrates (iii) Evidence links neuroticism in particular to a wide variety of negative physical, mental and functional health outcomes. (iv) Human brain imaging studies of personality were reviewed and ANS studies will be reviewed in section 1.8.

1.5 The biological basis of emotion

In this section I will review the second core theme of emotions – in particular "affect" (its sensory/felt aspect) with related interoception and secondly "motivation" with related motor systems. Pain will be discussed as a "homeostatic emotion" and brain imaging data will be presented for the central neural instantiation of emotion and pain.

Emotions defined

Definitions of emotion abound but most include a felt/sensory "affect" component and motor "motivational" components. Emotions are usually arranged along the dimensions of hedonic valence (approach/avoid) and arousal (Rolls 2000).

1.5.1 Affect: homeostasis, interoception and emotions

Homeostasis as an organising principle

Homeostasis involves three fundamental processes: 1) detecting the inner needs of the organism (interoception) 2) detecting external environmental sources of supply or threat to those inner needs (exteroception) and 3) moving towards or away from the external source appropriately (Cameron 2002; Craig 2002; 2003). In simpler organisms these basic mechanisms are sub-served by chemical or chemico-humeral means. The next phylogenetic stage employs the immune system and ultimately an increasingly elaborate and sophisticated neural system (Porges 2001).

In the simplest organisms movement consists of reflex tropisms and therefore relatively simple apparatus are required for interoception and exteroception. As complexity increases more sophisticated amounts of appraisal occur in interoception and exteroception and more executive control is exerted over movement and so consequently the sensory, motor and motivational apparatus become more complex. Finally, as individual survival is more dependent on survival within the group, the neuro-endocrine and immune systems become increasingly geared towards ***social homeostatic*** requirements (Porges 2001). In humans where social homeostatic requirements have developed to the point where they can even override more basic physiological homeostatic function, the behavioural concomitants are less clear. The notions of engagement or disengagement may be more helpful than approach-avoidance in this context where the response may be an affective-motivational one and not behaviourally overt (Porges 2003).

Phylogenetic studies of comparative functional anatomy reveal that there are basic homeostatic mechanisms shared by all vertebrates but which increase in complexity and reach their zenith in man. As the complexity of these mechanisms increases it becomes less intuitive that their basic function is survival of the individual through homeostasis. This is especially so when considering emotion, attention, learning, social behaviour and consciousness, which can seem far removed from simple homeostatic physiological processes such as digestion, and yet are ultimately rooted in them (Morris and Dolan 2001).

Interoception & visceral sensation

Cameron concluded in his Presidential address in Psychosomatic Medicine by saying that "understanding the physical basis of psychosomatic processes, including the so-called mind-body problem, will require a detailed understanding of the ***"psychobiology of interoception"*** (Cameron 2001). Generally, interoception is taken to include perceptual signals arising from the body itself and especially from the viscera as opposed to exteroception which refers to perceptual signals arising from the external environment.

There are several good recent sources for overviews on the subject of interoception including the recent textbooks - "visceral sensory neuroscience" (Cameron 2002) and "visceral perception – understanding internal cognition" (Adam 1998) which outline much of the work already done in this field building on earlier work such as "Psychophysiology of the GI tract" (Holzl and Whitehead 1983). The subject of interoception is also covered well in chapter 18 of "the handbook of Psychophysiology" (Cacioppo et al. 2000). In addition there have been several reviews (Aziz and Thompson 1998; Cameron 2001; Craig 2002; Ray and Slobounov 2002; Saper 2002; Saper et al. 2002; Craig 2003; Critchley 2005; Wiens 2005; Pollatos et al. 2007). Visceral perception is mostly taken in these works to cover perception arising from internal organs although the majority of the ground covered is split between cardiovascular and gastrointestinal systems.

There remains some contention as to definitions of perception vs. detection; over what else should be considered to be interoception vs. exteroception and where the borders of these are drawn up (Pennebaker and Hoover 1984). A recent more radical approach incorporates almost all bodily sensation under the rubric "interoception" (including proprioception, fine/affective touch and nociception –

leaving only "crude touch", sight, smell, hearing and taste as exteroceptive) and argues for shared functional neural networks (Craig 2002; 2003).

Pain as a homeostatic emotion

Concepts of what constitutes pain and its processing in the brain have substantially broadened with elaborations of a "pain neuromatrix". This includes sensory-discriminative dimensions concerned with site and intensity of pain; cognitive-evaluative dimensions concerned with attention to and anticipation of pain and affective-motivational dimensions concerned with affective evaluation of pain (Melzack and Casey 1968; Melzack and Katz 1999; Schnitzler and Ploner 2000) [figure 1.4].

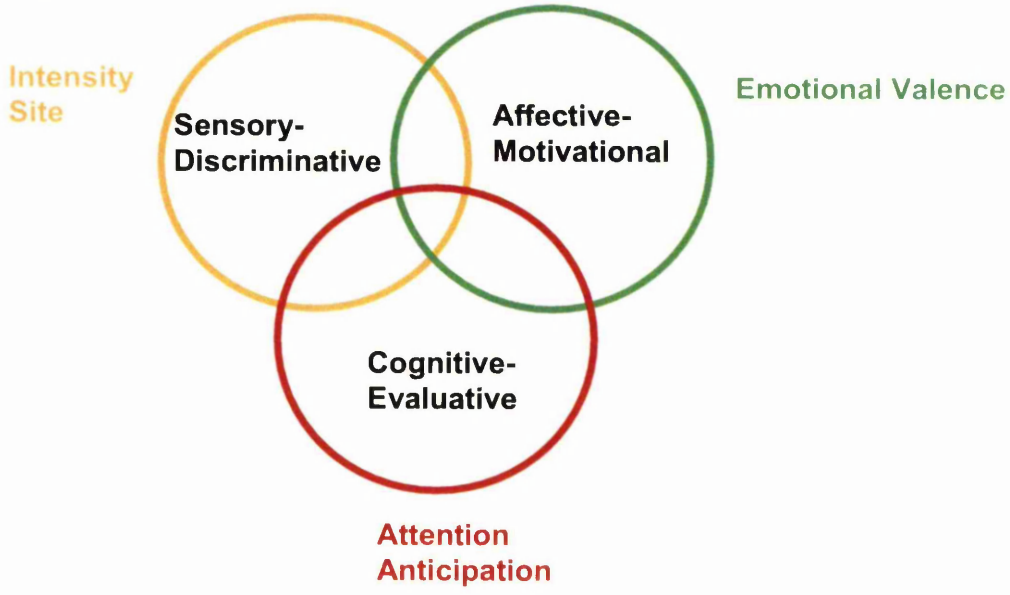

Figure 1.4 the pain neuromatrix (Melzack and Casey 1968; Melzack and Katz 1999).

Neuroanatomically, these dimensions are related to lateral "sensory" and medial "emotional" pain systems. The "medial" neuroanatomic cortical pain system is thought to mediate the sensory discriminative aspects of pain whilst a "lateral" cortical pain system to sub-serve affective/attentional components (Bowsher 1957; Albe-Fessard et al. 1985) [figure 1.5].

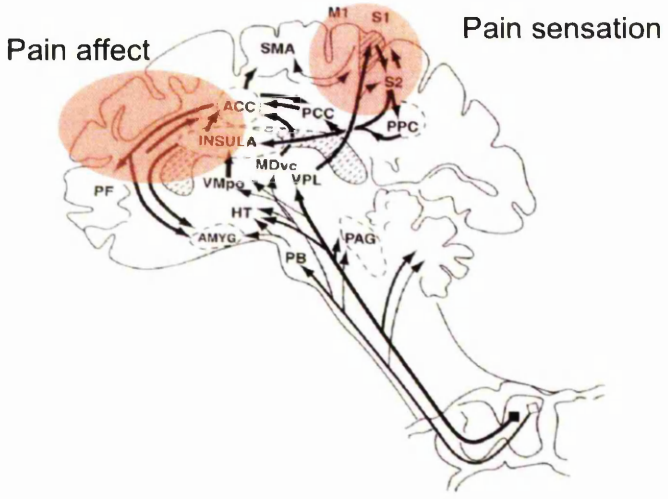

Figure1.5 medial and lateral pain pathways adapted from (Price 2000).

A more fundamental reclassification of pain has recently been proposed as an interoceptive rather than exteroceptive process (Craig 2002; 2003) forming part of a "homeostatic afferent processing network" (Mayer et al. 2006). Within this conceptual framework, pain is considered to be one of many "homeostatic emotions", sharing common neural substrates at the level of the central nervous system (Craig 2003). Certainly it no longer seems tenable to treat emotion and pain as sharply demarcated phenomena. This has considerable heuristic value when considering the commonly observed clinical overlap between pain and emotional states (Mayer et al. 2006). This model itself may ultimately be refined further by incorporation of a dynamic systems approach (Thayer and Friedman 2002).

1.5.2 Motivation: emotion "moves us"

The "emotional motor system" includes the central autonomic network (CAN), the autonomic nervous system, the sympathoadrenal medullary system, the hypothalamopituitary and psychoneuroimmune axes, facial expressions, vocalisations and the skeletomotor system (Berry and Pennebaker 1993; Hughes et al. 1994; Holstege et al. 1996; Mayer et al. 2001; Butler et al. 2003; Ekman 2003; 2003; Bhatia and Tandon 2005).

Whereas traditionally emphasis has been placed on "activation systems", in humans behavioural engagement and disengagement may primarily be mediated by *inhibition*. Peripherally this is achieved by the inhibitory vagal control of cardiovascular responses, both tonically and in phasic changes. Centrally this is achieved by tonic

inhibitory effects of GABA, which "may be linked by a network of neural structures that guide the organism from one state of relative stability to another" (Thayer and Friedman 2002). There are numerous strands of evidence for the connection between these peripheral and central inhibitory mechanisms (DiMicco 1987; Adinoff et al. 1992; Ferini-Strambi et al. 1995; Berntson et al. 1996; Agelink et al. 2002).

Charles Darwin first highlighted that facial expression is unique to mammals and especially in primates plays a primary role in both the expression and perception of emotion (Ekman 2003; 2003). For this reason both the perception and expression of facial representations of emotion have successfully been employed in emotions research.

1.5.3 Human brain imaging studies in emotion, interoception and pain

ANS studies in emotion, interoception and pain will be reviewed in section 1.8 following an explanation of ANS neurophysiology.

Emotion studies

An early PET study of emotions found that pleasant and unpleasant emotions were each distinguished from neutral emotion conditions by significantly increased cerebral blood flow in the medial prefrontal cortex, thalamus, hypothalamus and midbrain. Unpleasant was distinguished from neutral or pleasant emotion by activation of the bilateral occipito-temporal cortex and cerebellum, and left parahippocampal gyrus, hippocampus and amygdala. Pleasant was distinguished from neutral but not unpleasant emotion by activation of the head of the left caudate nucleus (Lane et al. 1997). In another PET study, self-generated emotions activated somatosensory cortices and the upper brainstem nuclei (Damasio et al. 2000).

The anterior cingulate cortex (ACC) was more active during social exclusion than during inclusion and correlated positively with self-reported distress. Right ventral prefrontal cortex (RVPFC) was active during exclusion and correlated negatively with self-reported distress. ACC changes mediated the RVPFC-distress correlation, suggesting that RVPFC regulates the distress of social exclusion by disrupting ACC activity (Eisenberger et al. 2003).

While expecting unpleasant stimuli, a "cognitive control" group showed higher activity in left medial and dorsolateral prefrontal cortex areas but reduced activity in the left extended amygdala, pulvinar/lateral geniculate nucleus and fusiform gyrus.

Cognitive control during the "unknown" expectation was associated with reduced amygdala activity as well and further with reduced insula and thalamic activity. The amygdala activations associated with cognitive control correlated negatively with the reappraisal scores of an emotion regulation questionnaire. The results indicate that cognitive control of particularly unpleasant emotions is associated with elevated prefrontal cortex activity that may serve to attenuate emotion processing in for instance amygdala, and, notably, in perception related brain areas (Herwig et al. 2007).

Increasing negative and positive emotion engaged primarily left-lateralized prefrontal regions, whereas decreasing emotion activated bilateral prefrontal regions. Different activations unique to increasing versus decreasing emotion were observed for positive and negative stimuli: unique increase-related activations were observed only for positive stimuli, whereas unique decrease-related activations were observed only for negative stimuli. Regulation also modulated activity in the amygdala. Regulation effects on amygdala activity were larger for positive than for negative stimuli (Kim and Hamann 2007).

In an fMRI study performed by Hope GI sciences and Institute of Psychiatry, a significant effect was found of negative emotional context on neural processing of non-painful oesophageal stimuli in the dorsal ACC; high intensity of negative emotional context during oesophageal stimulation significantly activated dACC and anterior insula and increased subjective ratings of anxiety, discomfort and emotional intensity and significantly there was a positive correlation between psychophysical ratings and neural activity (Phillips et al. 2003).

Interoception

ACC activation was found to be related to levels of emotional perception (Lane et al. 1998). Human perception of heartbeat timing (an interoceptive task) appeared to be mediated by right (non-dominant) anterior insula cortex, and the activity and size of this region was directly correlated with individuals' subjective awareness of inner body feelings and emotionality (Craig 2004; Critchley et al. 2004).

Critchley produced complementary evidence using functional brain imaging to implicate the anterior cingulate cortex in the intentional modulation of bodily arousal and a central matrix of cortical, subcortical and brainstem autonomic centres activated during biofeedback relaxation, as well as regions that mediate visual and

somatesthetic representations and executive control. Anterior cingulate, amygdala, and insula activity was modulated by task manipulations that increased demand on processing interoceptive representations, while variation in anterior insula activity reflected an interaction between accuracy and sensitivity of feedback. Critchley suggested that these findings identified neural substrates that support integration of perceptual processing, interoception, and intentional modulation of bodily states of arousal (Critchley et al. 2001; 2002). In peripheral autonomic failure patients, evidence of the neuro-anatomical basis for first and second order representations of bodily states was determined (Critchley et al. 2001).

Interoceptive accuracy, an outcome associated with neuroticism, was better accounted for by dACC reactivity than by self-reported neuroticism, suggesting that neural reactivities may provide a more direct measure of personality than self-reports do (Eisenberger et al. 2005).

Chae et al reviewed functional imaging studies of implanted vagal nerve stimulators and found that VNS causes immediate and longer-term changes in brain regions including the thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla (Chae et al. 2003). Similarly, there are functional imaging studies in spinal cord injured women of vaginal-cervical self stimulation to orgasm, presumably entirely vagally afferent mediated (Komisaruk 2005).

Dolan has recently reviewed imaging studies of OFC-amygdala interactions for emotion (Dolan 2007). Whalen et al found that the dorsal amygdale activity was significantly greater to fear versus anger. Significant BOLD signal changes in the ventral amygdala were observed in contrasts of fear versus neutral expressions and, in a more spatially circumscribed region, to anger versus neutral expressions (Whalen et al. 2001).

Face perception and amygdala activation

Ishai et al found that face perception was mediated by a distributed network of structures. These included the inferior occipital gyrus, fusiform gyrus, superior temporal sulcus, hippocampus, amygdala, inferior frontal gyrus, and orbitofrontal cortex. Although bilateral activation was found in all regions, the response in the right hemisphere was stronger (Ishai et al. 2005).

Davis and Whalen reviewed imaging studies of the amygdala in normal human subjects and patient groups [figure 1.6, faces panel 1A] (Davis and Whalen 2001).

Table 3 Neuroimaging studies assessing amygdala response in normal human subjects (I–III) and patient groups (IV)

I. Learned and/or innate (unmanipulated) stimuli	Reference
A. FACES	
1. Increases	
a. Fear faces	
(1) Fear *vs* neutral	213–216
(2) Fear *vs* happy faces	214,217
(3) Fear faces *vs* fixation	217,218
b. Other facial expressions	
(1) Happy *vs* neutral faces	213
(2) Sad *vs* anger faces	219
(3) Fear and anger *vs* neutral faces	220
(4) Anger and happy *vs* neutral faces (amyg/hippo junction)	221
c. Other facial characteristics	
(1) Unfamiliar *vs* familiar neutral faces	222
(2) Eye contact *vs* variable eye contact in neutral faces	223
2. Decreases	
a. Happy faces	
(1) Happy *vs* neutral faces	214
(2) Happy faces *vs* fixation	217
3. Null findings	
a. Fear faces	
(1) No activation to fear *vs* neutral faces	224
b. Anger faces	
(1) No activation to anger *vs* neutral faces	219,224
(2) No activation to anger *vs* sad faces	219
c. Other facial expressions	
(1) No activation to happy *vs* neutral faces	216
(2) No activation to disgust *vs* neutral faces	215,224
(3) No activation to sad *vs* neutral	216,219
B. COMPLEX VISUAL STIMULI	
1. Aversive *vs* neutral pictures	225,226,266
2. Aversive *vs* neutral films	227
3. Aversive *vs* pleasant pictures	228
4. Neutral films (habituated over time)	229
C. MEMORY	
1. Correlation with recall of aversive films	230
2. Correlation with recall of aversive pictures	231
3. Correlation with recall of positive pictures	231
4. Correlation with retrieval of positive and negative *vs* neutral items	232
D. ODOR	
1. Aversive *vs* neutral odors	233
E. TASTE	
1. Aversive *vs* neutral tastes	234
F. WORDS	
1. Increase	
a. Threatening *vs* neutral words (nonrepeating)	235
2. Null Finding	
a. No activation to negative *vs* neutral words (repeating)	236

I. Learned and/or innate (unmanipulated) stimuli	Refere
G. PROSODY	
1. Increase	
a. Fearful *vs* neutral voices (amyg/hippo junction)	216
2. Decrease	
a. Fearful *vs* sad, happy and neutral voices	237
H. COGNITIVE PARADIGMS	
1. Unsolvable anagrams *vs* rest	238
I. BIOLOGICAL MOTION	
1. Biological motion pattern *vs* random	239
II. Aversively conditioned (manipulated) stimuli	
A. Correlation with CS+ (snake film) predicting shock *vs* CS–	240
B. CS+ (shape) predicting shock *vs* CS–	241
C. CS+ (neutral face) partially predicting aversive noise *vs* CS–	242
D. CS+ (masked angry face) predicting aversive noise *vs* CS–	243
E. CS (tone) partially predicting aversive noise *vs* CS–	244
F. Instructed CS+ (color) predicting shock *vs* CS–	245
III. State inductions/pharmacological manipulations	
A. INCREASES	
1. Sad state (w/sad face) *vs* neutral state	246–248
2. Happy state (w/happy face) *vs* neutral state	247
3. Procaine injection *vs* saline	249,250
B. DECREASES	
1. acupuncture *vs* rest	251
2. meditation *vs* rest	252
3. pain *vs* warm	253,254
IV. Psychiatric patients	
A. PTSD	
1. Script-driven imagery of combat scenes	255
2. Imagery of combat scenes	256
2. Combat sounds *vs* white noise	257
3. Fear *vs* happy faces (masked)	258
4. Cognitive paradigm (comorbid drug abuse)	259
B. DEPRESSION	
1. Resting blood flow	260
2. Correlation with negative affect	261
C. SOCIAL PHOBIA	
1. Neutral faces *vs* fixation	262
2. CS+ (face) predicting negative odor *vs* CS–	263

Figure 1.6 table summarizing human imaging studies of amygdala reactivity up to 2001 (Davis and Whalen 2001).

On the afferent limb, automatic and intentional brain responses have been recorded to facial expressions (Winston et al. 2002), and to "the acquired moral status of faces" (Singer et al. 2004). There are dissociable responses evident to different valence facial expressions of emotion such as fear and sadness (Blair et al. 1999). The human amygdala responds in particular to facial expressions of fear or anger

(Morris et al. 1998; Whalen et al. 2001) but it may simply be playing a neuromodulatory role in processing emotional facial expressions (Morris et al. 1998). Discriminating emotional faces without primary visual cortices involves the right amygdala (Pegna et al. 2004) but stronger amygdala activation occurs to affective faces than affective scenes indicating that this is a specific pathway for affective facial processing (Hariri et al. 2002). Amygdala responses to facial expressions have been found to vary in children and adults (Thomas et al. 2001) and to vary according to SERTP genotype (Hariri et al. 2002).

Kim observed activation of the amygdala during imagination of emotional facial affect versus imagining neutral facial affects. In addition, they observed activation of several areas of the brain, including the dorsolateral prefrontal cortex, ventral premotor cortex, superior temporal sulcus, parahippocampal gyrus, lingual gyrus, and the midbrain. Their results suggest that the areas of the brain known to be involved in the actual perception of affective facial expressions are also implicated in the imagery of affective facial expressions (Kim et al. 2007).

Sustained responses to pain and angry faces were found in the superior temporal sulcus (STS). Stronger transient activation was also observed to male expression of pain (Vs neutral and anger) in high-order visual areas (STS and fusiform face area) and in emotion-related areas including the amygdala, perigenual anterior cingulate cortex (ACC), and SI. Male pain compared to anger expression also activated the ventromedial prefrontal cortex, SII/posterior insula and anterior insula. It was hypothesised that the implicit processing of male pain expression triggers an emotional reaction characterized by a threat-related response. Unexpectedly, several areas responsive to male expression, including the amygdala, perigenual ACC, and somatosensory areas, showed a decrease in activation to female pain faces (vs. neutral). This sharp contrast in the response to male and female faces suggested to the authors potential differences in the socio-functional role of pain expression in males and females (Simon et al. 2006).

Pain studies

A review and meta-analysis has recently been performed of functional imaging of brain responses to pain (Peyron et al. 2000).

Multiple imaging studies have explored diverse aspects of pain including the role that pain plays in "social homeostatic situations" (Eisenberger et al. 2003;

Panksepp 2003; Singer et al. 2004); as have interactions between emotion, attention, novelty, anxiety and pain (Arntz et al. 1994; Dowman 2001; Bantick et al. 2002; Lenz and Treede 2002; Villemure and Bushnell 2002; Keogh et al. 2003) hypnotically induced vs. imagined pain (Derbyshire et al. 2004); and the interaction between and compared to emotional responses (Ness and Gebhart 1988). Anatomical cortical-brainstem connectivities in pain have been explored with diffusion tensor imaging (Hadjipavlou et al. 2006). Placebo analgesia was related to decreased brain activity in "pain-sensitive brain regions", including the thalamus, insula, and anterior cingulate cortex, and was associated with increased activity during anticipation of pain in the prefrontal cortex (Wager et al. 2004).

Recent studies using an individualised approach to central neural processing of pain ranked individuals according to sensitivity to a painful (somatic) stimulus and assessed their central neural pain responses. Primary differences between high and low sensitivity individuals resided in greater ACC and PFC activation in the higher sensitivity group but identical levels of thalamic activation suggesting a greater central neural reactivity to pain rather than differences in afferent barrage [figure 1.7](Coghill and Eisenach 2003; Coghill et al. 2003; Koyama et al. 2005).

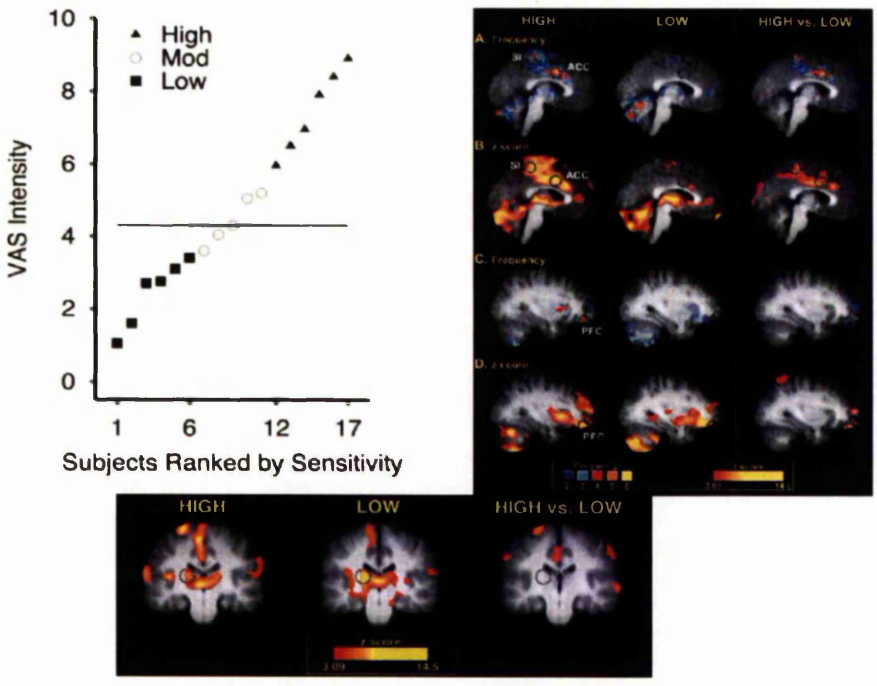

Figure 1.7 greater central neural but not thalamic reactivity to pain in high pain sensitivity subjects (Coghill et al. 2003).

Psychophysical differences were found between superficial and deep somatic pain [figure 1.8] and also signal differences were found in regions implicated in emotion (perigenual cingulate cortex), stimulus localization and intensity (somatosensory cortex) and motor control (motor cortex, cingulate motor area). Furthermore, most fMRI signal changes matched perceived changes in pain intensity (Henderson et al. 2006).

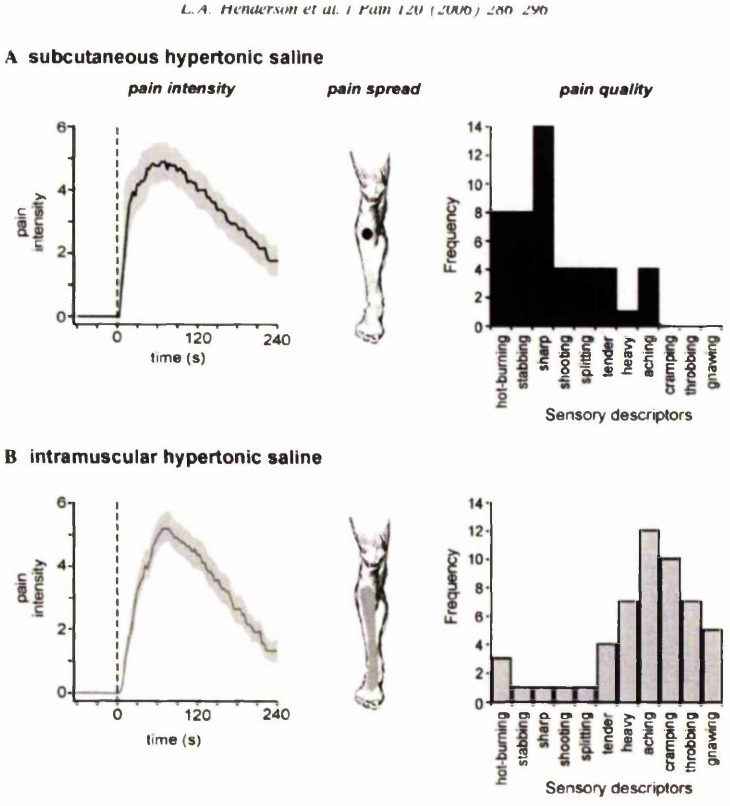

Figure 1.8 psychophysical differences between superficial and deep somatic pain (Henderson et al. 2006).

Summary of section 1.5

(i) The sensory aspect of emotion (affect), which includes pain, may be underpinned by a homeostatic afferent processing network (ii) The motor aspect of emotion (motivational) relates to several output systems of which the ANS in general and an inhibitory pre-frontal cortex/vagal axis in particular may be core components. (iii) Human brain imaging studies in pain, emotion and interoception were reviewed. ANS studies will be reviewed in section 1.8.

1.6 Visceral sensation and visceral pain

This section supplements and extends the overview of pain as a homeostatic emotion in section 1.5.1 by focussing on visceral pain.

1.6.1 Visceral sensory afferents

Most knowledge of visceral sensory and pain afferents is from animal work (Berthoud et al. 2004). In humans no easy ways exist of directly accessing peripheral afferent function independently of central afferent processing or verbal report (Aziz et al. 2000; Hobson et al. 2000; Saper 2002; Bielefeldt et al. 2005). Other objective measures, such as ANS responses, are indirect consequences of pain. Most visceral sensory traffic is subliminal (Adam 1998; Cameron 2002), i.e. does not reach conscious level. Liminal sensory stimuli from the viscera include the "call to stool" and flatus, swallowing, hunger and satiety signals, nausea, emotion and pain. The molecular, peripheral and central neural machinery for visceral sensory trafficking are increasingly well characterised (Aziz and Thompson 1998; Berthoud et al. 2004). Figure 1.9 gives an overview of anatomical structures involved in visceral sensation.

TABLE 1. Anatomical Structures and Pathways Involved in Visceral Sensation, From the Periphery to the Cortex

Periphery
Visceral sensory pathways
Receptors—pain, physiological, specialized (chemo-, osmo-, and thermo-receptors)
Fibers—sympathetic, parasympathetic
Enteric nervous system
Spinal cord
Sympathetic, some parasympathetic (from pelvic nerves)
Via laminae I, V, VII, and VIII
Brainstem
Tracts
Major—spinothalamic, spinoreticular, spinomesencephalic
Others—spinocervical, spinohypothalamic
Nuclei
Nucleus of the solitary tract—entry point of some parasympathetic fibers (eg, vagus nerve)
Parabrachial nucleus
Adrenergic, especially A6 (also known as the locus coeruleus)
Central gray
From brainstem to cortex
Thalamus
Hypothalamus
Cerebellum
"Limbic system"
Amygdala
Cortex
Somatosensory—SI, SII
Cingulate—anterior, medial
Frontal—medial orbitofrontal, lateral
Insula

Figure 1.9 Overview of structures involved in visceral sensation. From (Cameron 2001).

1.6.2 Visceral Pain: Psychophysics and central neural pathways

A fundamental psychophysical distinction exists between painful and liminal but non-painful sensation (Cervero and Laird 1996). Melzack and Wall described the pain gating theory which has stood the test of time with modification (Sufka and Price 2002) which is centered on the dorsal horn of the spinal cord. Changes at the dorsal horn level are believed to underlie processes of allodynia (painful sensation from previously non-painful stimuli) and hyperalgesia (more painful sensation from previously painful sensation). There is also descending modulation of pain at the brain stem level both facilitatory and inhibitory (Suzuki et al. 2004). Psychophysiological factors chiefly come into play at levels above the brain stem.

The psychophysics of visceral pain together with its underlying neurobiology is summarized in figure 1.10 (Cervero and Laird 1999). Psychophysical differences have been found between visceral and somatic pain which are grounded in the neurobiological properties outlined in the table (Strigo et al. 2002; Strigo et al. 2003; Strigo et al. 2005).

Sensory characteristics of visceral pain and related mechanism

Psychophysics	Neurobiology
Not evoked from all viscera	Not all viscera are innervated by "sensory" receptors
Not linked to injury	Functional properties of visceral "sensory" afferents
Referred to body wall	Viscerosomatic convergence in central pain pathways
Diffuse and poorly localised	Few "sensory" visceral afferents. Extensive divergence in central nervous system
Intense motor and autonomic reactions	Mainly a warning system, with a substantial capacity for amplification

Figure 1.10 neurobiological accounts for psychophysical properties of visceral pain, from (Cervero and Laird 1999).

The major ascending and descending neuroanatomic pathways mediating visceral pain are summarized in figures 1.11 & 1.12 (Drossman 2004). Painful afferent visceral and somatic traffic primarily ascend in spinal pathways via lamina 1 and 5 of the spinal cord to the thalamus whereas most non-painful visceral sensory information is transmitted via the vagus nerve to the NTS.

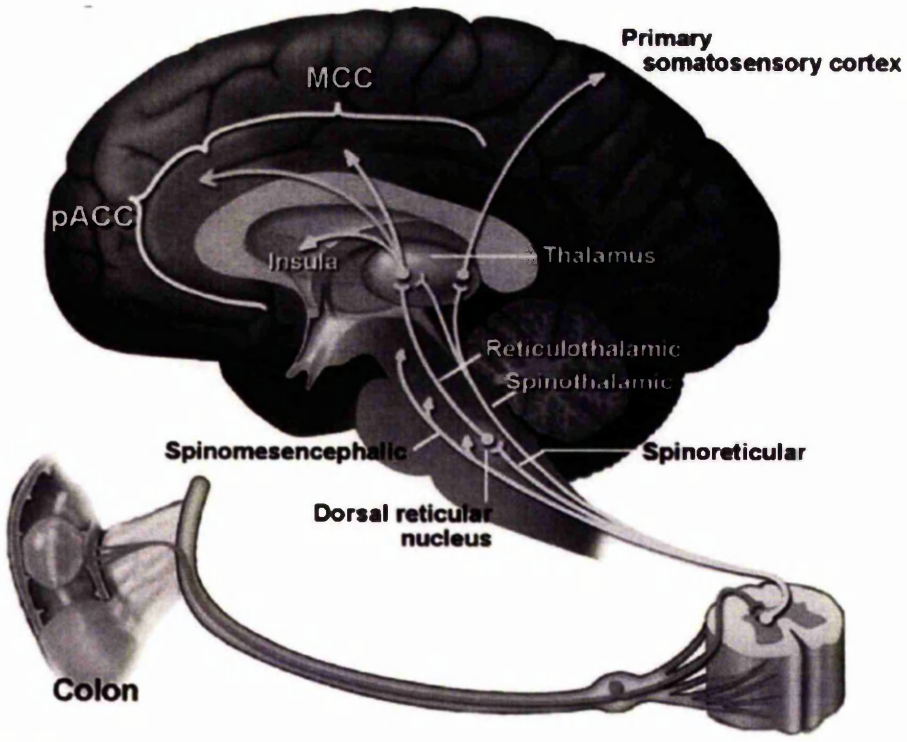

Figure 1.11 Ascending visceral pain pathways from (Drossman 2004)

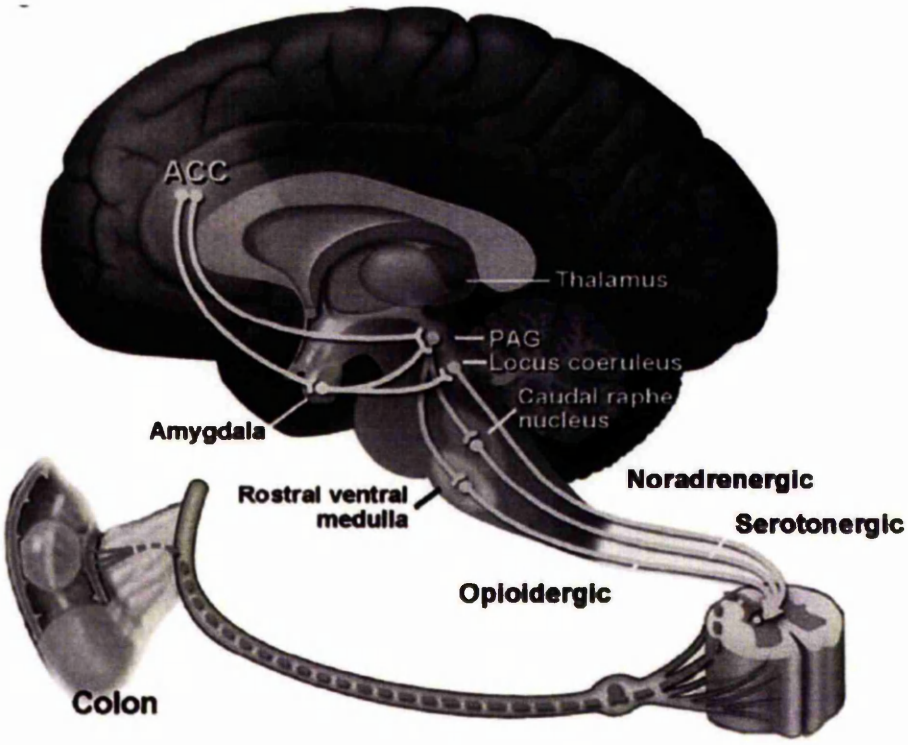

Figure 1.12 Descending visceral pain pathways from (Drossman 2004)

1.6.3 Human brain imaging studies in visceral pain

ANS studies will be reviewed in section 1.8 after an explanation of ANS neurophysiology has been given.

Recent reviews have summarized imaging findings in normal GI sensation (Hobson and Aziz 2003; 2006; Mayer et al. 2006).

Many imaging studies have been performed to explore normal brain processes involved in visceral perception, whether liminal or subliminal and its modulation by attention, conditioning and emotional context (Kern et al. 1998; Aziz et al. 2000; Aziz et al. 2000; Hobday et al. 2000; Hobson et al. 2000; Hobday et al. 2001; Cameron and Minoshima 2002; Hobday et al. 2002; Kern and Shaker 2002; Strigo et al. 2002; Gregory et al. 2003; Hobson and Aziz 2003; Phillips et al. 2003; Strigo et al. 2003; Critchley et al. 2004; Hobson and Aziz 2004; Dunckley et al. 2005; Dunckley et al. 2005; Hobson et al. 2005; Strigo et al. 2005; Yaguez et al. 2005; Dunckley et al. 2007). Several studies have also looked at the role of visceral perception in particular in emotions and cognitive processes such as learning (Ferguson and Katkin 1996; Schulkin et al. 2003).

Visceral pain has been contrasted with pain arising from superficial skin structures (Strigo et al. 2002; Strigo et al. 2003).

Functional GI disorders and brain imaging

Mayer et al have recently reviewed imaging studies in functional gut disorders (Mayer et al. 2006) and they have also been critiqued by Hobson (Hobson and Aziz 2003; 2004; 2006).

"Visceral hypersensitivity" is a hallmark feature in IBS patients who show an abnormal pattern of ACC activation during pain perception which is an interesting parallel to ACC activation relative to increasing pain perception in healthy subjects (Silverman et al. 1997; Coghill et al. 2003; Verne et al. 2003); hemispheric preference, as well as cognitive style of information processing served as indicators of covert changes in brain functions in adult IBS patients (Fent et al. 1999); and abnormal cerebral processing of oesophageal stimuli was found in patients with non-cardiac chest pain (NCCP) (Hollerbach et al. 2000; Hobson et al. 2006).

Drossman et al found that alterations of brain activity were associated with resolution of emotional distress and pain in a case of severe IBS (Drossman et al. 2003).

A recent longitudinal study in IBS found that there were significant decreases in amygdala, dACC, dorsal brainstem activation over a 12 month period during the anticipation for pain although pain-related activations and symptoms were stable (Naliboff et al. 2006). Rectal pain induced significant activation of the perigenual ACC, right insula, and right prefrontal cortex. Amitriptylline was associated with reduced pain related cerebral activations in the perigenual ACC and the left posterior parietal cortex, but only during stress (Morgan et al. 2005).

1.7 A hierarchical central network for response organisation and selection

Motor aspects of pain and emotion are both grounded in cortical and sub-cortical defence systems. Differences in dispositional response characteristics of these systems may underlie some aspects of personality; therefore these are reviewed in more detail in this section.

Thayer and Lane (Thayer and Lane 2000) recently reviewed convergent literature from that (i) exploring the central control of the autonomic nervous system, labelled the "Central Autonomic Network" (CAN) (Benarroch 1993; 1997); (ii) that involved in *"assessing the motivational content of internal and external stimuli and regulating context-dependent behaviours"* labeled the Anterior Executive Region (AER) or "rostral limbic system" (Devinsky et al. 1995); and (iii) the so-called "emotion circuit" (Damasio 1998) [see figure 1.13].

Structures and functions associated with the CAN, the rostral limbic system, and the 'emotion circuit'[a]

Circuit, source and function	IC	AC	PF	Amy	PG	Other areas
CAN (Benarroch, 1997)						
Cardiovascular control	X	X	X	X	X	NTS, NA
AER (Devinsky et al., 1995)						
Motivated and context-dependent behavior	X	X	X	X	X	Ventral striatum
Damasio (1998)						
Affect	X	X	X	X	X	BG

[a] Key: insular cortex (IC), anterior cingulate (AC), prefrontal cortex (PF), amygdala (Amy), periaquaductal gray (PG), nucleus of the solitary tract (NTS), nucleus ambiguus (NA), basal ganglia (BG).

Figure 1.13: convergent evidence for one functional network (Thayer and Lane 2000).

Thayer and Lane concluded that *"the CAN, the AER and its projections, the 'emotion circuit' and related systems are* ***one and the same functional network*** *identified by different researchers from differing orientations. This network of CNS*

structures is associated with the processes of response organisation and selection and serves to modulate psychophysiological resources in attention and emotion" (Thayer and Lane 2000).

These are similar to conclusions reached by others that tie "executive, social and motivated behaviours" to these same frontal-subcortical circuits (Masterman and Cummings 1997; Hagemann et al. 2003; Craig 2005). They are also structures which were consistently activated during studies of visceral pain highlighted in the previous section.

1.7.1 Behavioural defence systems and the sub-cortical network

Hierarchical organisation

The CNS is hierarchically organized and it appears that the inhibitory PFC is at the apex of this hierarchy (Thayer and Friedman 2002). Insula cortex and anterior cingulate may be the next hierarchical level down as homeostatic sensory and motor cortices respectively (Mayer et al. 2006). At the next level are sub-cortical structures: hypothalamus, septo-hippocampal systems, amygdala and peri-aqueductal gray. These are hierarchically followed by the thalamus, nucleus of solitary tract and nucleus ambiguus/dorsal motor vagal nuclei and rostral ventrolateral medulla as sensory and motor brainstem ANS nuclei respectively. The final hierarchical level comprises peripheral neural afferent and efferent components of the ANS [see figures 1.22 and 7.1]. Roles of the insula and ACC have recently been well delineated in the neuroenterology literature (Mayer et al. 2006) so I will review in the next section the sub-cortical and brainstem components more closely.

"Re-Cannonisation" of defence: freezing and inhibition

It is notable in Saper's review of central autonomic control that parasympathetic (PNS) and sympathetic nervous systems (SNS) get "equal billing" for sensory aspects (Saper 2002). However when it comes to efferent (motor) autonomic pattern generation, he deals almost exclusively with SNS/sympathoadrenal medullary and hypothalamic pituitary axes with barely a mention of the PNS. This is reflective of a general tenet of emotion theory and research which has *arousal* as a core component i.e. SNS activation in origin (Barrett et al. 2004). This emphasis on the SNS to the marked neglect of PNS reflects the original work by Cannon and Bard which concentrated on the – at that time more

measurable - SNS components of the "fight/flight" response. Cardiovascular responses were chiefly attributed to SNS activity whilst the PNS contribution was considered to be mainly reduced activity. It may be however that in the "fight-flight", response the PNS withdrawal is of at least equal importance to the SNS activation.

It has emerged that there is far more than a simple reciprocal relationship between SNS and PNS in defence responses. The defence response repertoire is broader than fight-flight and also includes a spectrum of freeze responses and fainting, in all of which the PNS plays a major role (Bracha 2004; Bracha et al. 2004; Bracha et al. 2005; Bracha 2006). It is timely to undertake a "re-Cannonisation" of defence responses. The PNS also appears to have a more fundamental role than the SNS in positive affect, bonding, relaxation and recuperation (Porges 1998).

The ANS concomitants of defence responses are better characterised in animals than in humans. Janig has summarised the animal research findings (predominantly cat and rat) of parasympathetic and sympathetic cardiomotor and other selective sympathetic effects during various behaviours [figure 1.14] (Janig 2006).

				Defense Reaction					
Organ	Pathway	Diving response	Exercise	Confrontation	Flight	Quiescence	Tonic immobility	Vigilance	Freezing reaction
Heart	SCM	↓↓	↑↑ (tonic)	↑↑	↑↑	∅/↓?	↓↓	?	?
	PCM	↑↑↑	↓↓ (initial)	↓↓	↓↓	↑↑	↑↑↑	↑↑	↑
Skeletal	MVC	↑↑↑	↑	↑	↑	↑	↓↓	↑↑	↑
Muscle	MVD**	∅	∅	↑↑?	↑↑	∅	↑?/∅	∅	∅
Skin	CVC (av a.)	↓↓	↑↑	↑↑*	↑↑	↑?	↓↓	?	?
	CVC (nutrit.)	↑↑↑	↑↑	↑↑	↑↑	↑?	↓↓	?	?
Kidney	VVC	↑↑↑	↑↑	↑↑	↑↑	↑?	↓↓	↑↑	↑?
GIT	VVC	↑↑↑	↑↑	↑↑	↑↑	↑?	↓↓	↑↑	?
Art. BP		∅	↑	↑	↑	↓↓	↓↓↓	↑↑	∅
Card. Output		↓↓↓	↑↑	↑↑	↑↑	↓↓	↓↓	↓	↓
Respiration		↓↓↓	↑↑	↑/∅	↑↑	↓	↓↓↓	↓	↓

Notes:
These patterns of activity can be quickly recruited by the forebrain or reflexly by activating afferents. Not included are non-cardiovascular changes occurring during these behavioral reactions/responses. Modified from Folkow (2000).
CVC, cutaneous vasoconstrictor neurons (to arteriovenous anastomoses [av a.]; nutritional [nutrit.] vessels); MVC, muscle vasoconstrictor neurons; MVD, muscle vasodilator neurons; GIT, gastrointestinal tract; PCM/SCM, parasympathetic/sympathetic cardiomotor neurons; VVC, visceral vasoconstrictor neurons; ↑, ↑↑, ↑↑↑/↓, ↓↓, ↓↓↓, increase/decrease of activity (or of cardiovascular and respiratory parameters); ∅, relatively unchanged; ?, effect unknown; Art. BP, mean arterial blood pressure. Modified from Folkow (2000), Bandler et al. (2000a) and Keay and Bandler (2004).
*Extracranial vasodilation in facial skin;
**Probably only present in some species (see Subchapter 4.2).

Figure 1.14: patterns of activity in PNS and SNS pathways during different behavioural reactions organised in the upper brain stem and hypothalamus (rats & cats from (Janig 2006).

As can be seen from the above figure there are various defensive responses where surges in parasympathetic cardiomotor (PCM) activity are seen (diving, quiescence, tonic immobility, vigilance and freezing reactions). Even in animals the ANS patterns for these other defence behaviours are not well characterised as can be seen from the "gaps" in the table, particularly on the correlations between PNS and SNS effects. In fact even the classification of these various kinds of "freezing" response is not yet sufficiently clarified in animals and even less clearly in humans.

Peri-aqueductal gray matter (PAG)

An extremely well characterised part of the brainstem control of defence responses, primarily in rats and cats by Bandler and Keay, is the peri-aqueductal gray (PAG) (Bernard and Bandler 1998; Henderson et al. 1998; Bandler et al. 2000; Bandler et al. 2000; Clement et al. 2000; Floyd et al. 2000; Keay et al. 2000; Keay and Bandler 2001; Keay et al. 2001; Keay and Bandler 2002). It has been found that direct stimulation of different parts of the PAG gives rise to predictable patterns of behavioural and autonomic defence response [figure 1.15].

In particular, it was found that the rostral (i.e. face forward) parts of the lateral and dorsolateral PAG give rise to "confrontational" defence responses (fight) whereas the caudal (hindmost) portions of the lateral and dorsolateral PAG give rise to flight responses. Finally the ventrolateral PAG gives rise to quiescent (freezing) responses including fainting/playing dead. All these areas additionally give rise to analgesic effects.

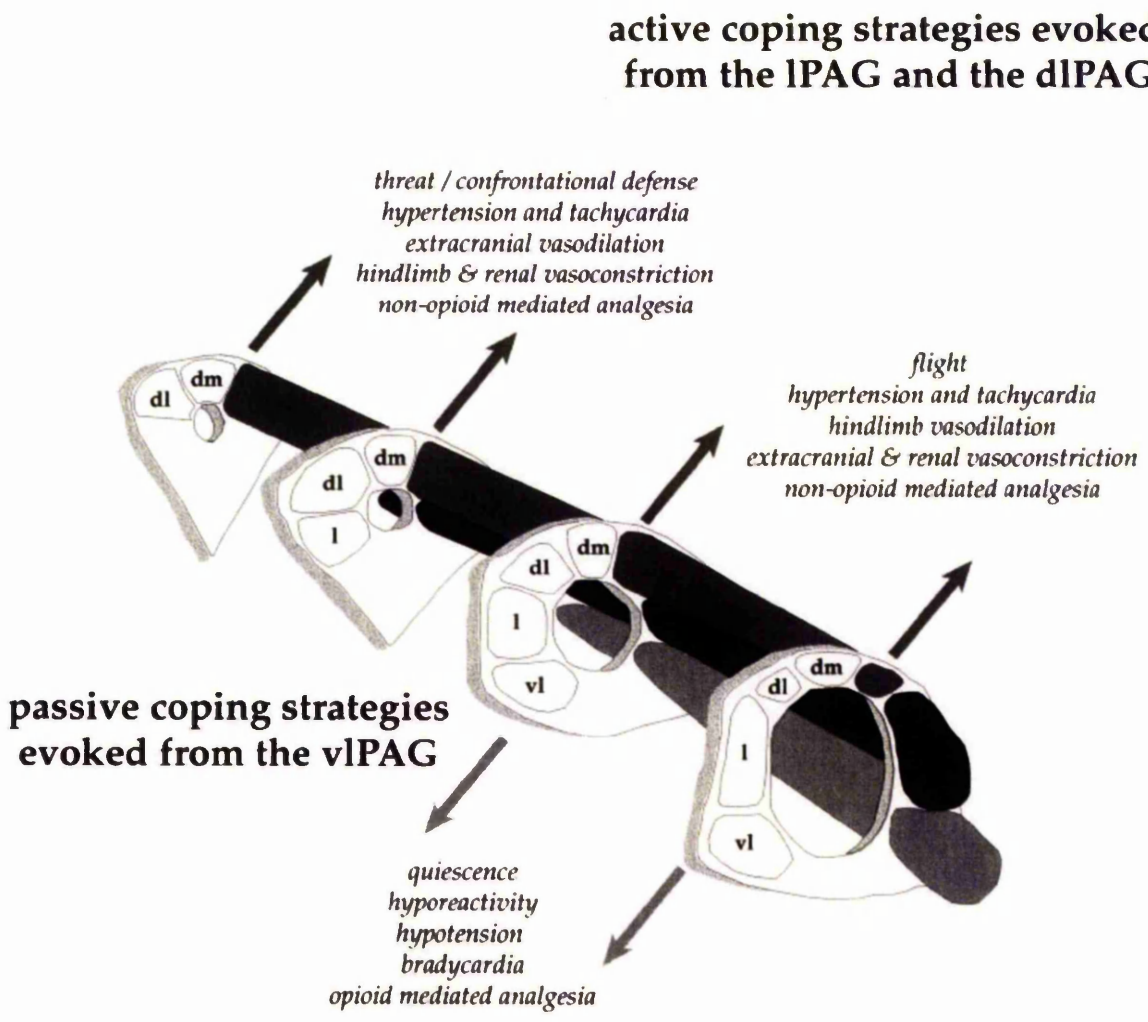

Figure 1.15 dorsomedial, dorsolateral, lateral and ventrolateral neuronal columns within (from left to right) the rostral peri-aqueductal gray (PAG), the intermediate PAG (two sections) and the caudal PAG. Injections of excitatory amino acids (EAA) within the dorsolateral (dlPAG)/lateral (lPAG; dark shadings) vs. ventrolateral (vlPAG; light shading) columns evoke fundamentally opposite, active vs. passive emotional coping strategies. EAA injections made within the rostral portions of dlPAG and lPAG columns evoke a confrontational defensive reaction, tachycardia, and hypertension (associated with decreased blood flow to limbs and viscera and increased blood flow to extra cranial vascular beds). EAA injections made within the caudal portions of the dlPAG and lPAG evoke flight, tachycardia and hypertension (associated with decreased blood flow to visceral and extra cranial vascular beds and increased blood flow to limbs). In contrast, EAA injections made within the vlPAG evoke cessation of all spontaneous activity (quiescence), a decreased responsiveness to the environment (hyporeactivity), hypotension and bradycardia. A non opioid-mediated vs. an opioid-mediated analgesia is evoked from the dlPAG/lPAG vs. vlPAG (Bandler et al. 2000).

Furthermore, Bandler and Keay have established that visceral and deep somatic stimulation activates the ventrolateral PAG through relays from the NTS [figure 1.16] and therefore these stimuli are more likely to initiate the parasympathetic

predominant quiescent responses. Spinal (somatic) afferents, particularly superficial afferents also activate the lateral PAG (Bandler et al. 2000).

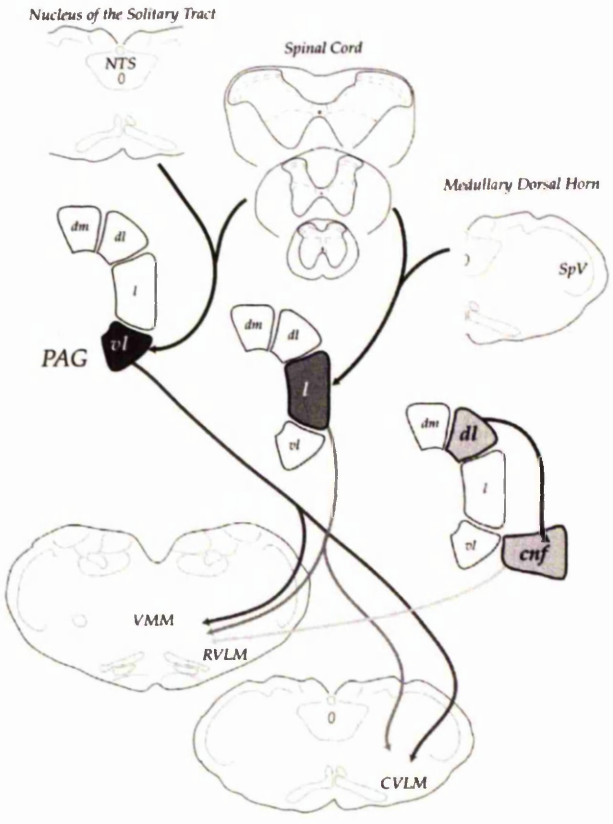

Figure 1.16 somatic and visceral afferents to different peri-aqueductal gray (PAG) neuronal columns (top half of figure), and medullary projections arising from different PAG neuronal columns (bottom half of figure). The ventrolateral (VL) column of the PAG receives afferents from the spinal cord and the nucleus of the solitary tract (NTS), and projects to both the rostral and caudal ventromedial (VMM) and ventrolateral (VLM) medulla. The lateral column of the PAG receives afferents from spinal cord and the spinal trigeminal nucleus (SpV/medullary dorsal horn) and projects to both the rostral and caudal ventromedial and ventrolateral medulla. The dorsolateral column of the PAG (dlPAG) has no significant somatic or visceral inputs arising from spinal cord, spinal trigeminal nucleus or NTS. The dlPAG does not project directly to the medulla, but can influence the rostral ventromedial and ventrolateral medulla via a projection to the cuneiform nucleus (cnf) (Bandler et al. 2000).

Important complementary work on the PAG and conditioned fear responses in rats by Walker and Carrive has shown how rather than simply *either* fight-flight (lPAG) *or* "flaccid" freeze responses, the inhibitory output of the VLPAG may be "blended" with those of the defence arousal system to produce tonic freeze/immobility responses [figure1.17 middle panel shows blending of patterned responses] (Walker and Carrive 2003)

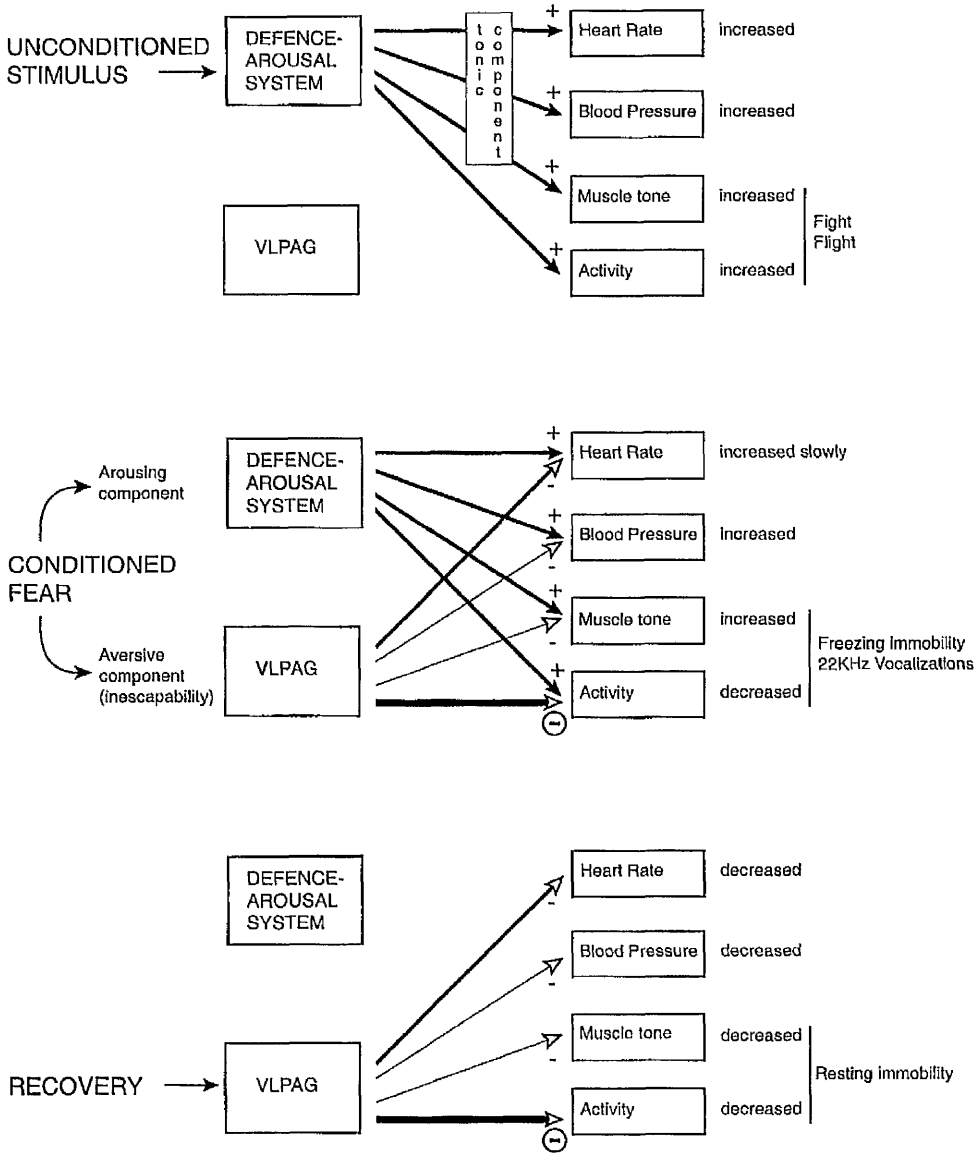

Figure 1.17 the role of the ventrolateral peri-aqueductal gray (VLPAG) during conditioned fear and recovery. The upper panel shows the defence-arousal system and its final output. The middle panel shows how the VLPAG modifies the output of the defence-arousal system to produce the conditioned fear response. The lower panel shows the VLPAG final output alone and how it contributes to the recovery response (Walker and Carrive 2003).

Hypothalamus – escapable and inescapable pain

In parallel to the work on the PAG, Bridget Lumb from Bristol has been exploring the role of hypothalamic inputs to the PAG (Lumb and Lovick 1993; Lumb 2002; 2004). As seen from figure 1.18, her work suggests that which brain-stem system is activated is not dependent on the site of stimulus but rather the characteristic of the stimulus. In particular *inescapable* pain, despite arising from

cutaneous structures, could elicit both VL-PAG and "depressor" anterior hypothalamic responses.

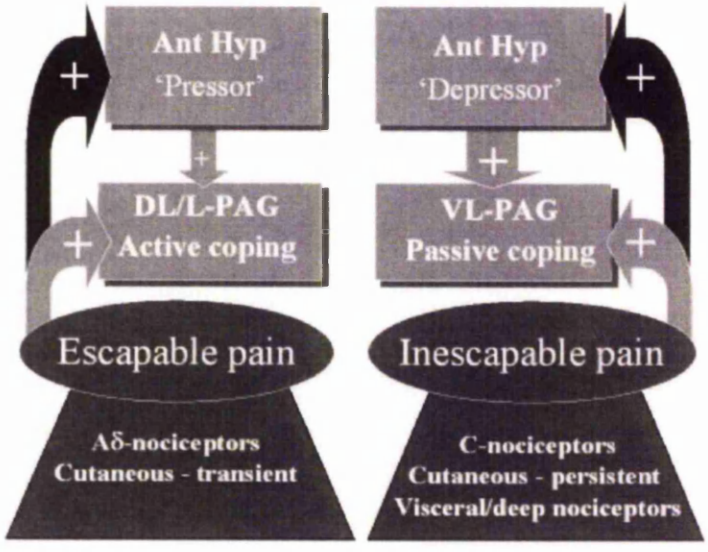

Figure 1.18 brainstem and midbrain effects of escapable and inescapable pain (Lumb 2004).

Amygdala

As part of the central components of the functional neural network identified by Thayer and Lane, the amygdala in particular appears to play an important role as a mediator between cortical, sub-cortical and peripheral components of the homeostatic functional neural network.

A greater elaboration of amygdala connections with the cerebral cortex was seen in primates (Price 2003). These connections and their behavioural and ANS concomitants in the human are summarised in figure 1.19 (Davis and Whalen 2001).

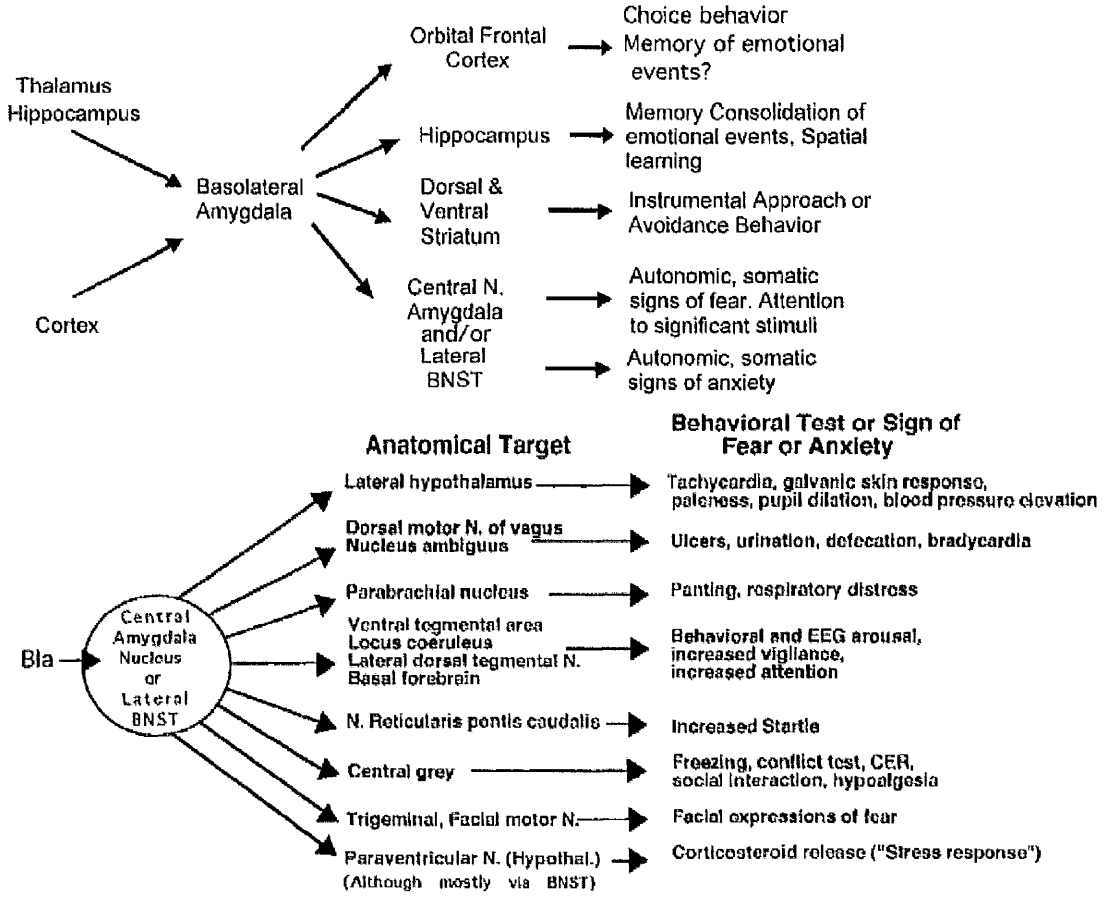

Figure 1.19 amygdala connectivity Bla = basolateral amygdala BNST = basal nucleus of stria terminalis, adapted from (Davis and Whalen 2001).

1.7.2 Defence systems and personality

In the neurobiologically revised version of personality by Gray and McNaughton (Gray 1970; Gray and McNaughton 2000; Corr 2004; McNaughton and Corr 2004; Corr 2005; Corr and Perkins 2006) [section 1.4], individual differences in defence response systems have been explicitly incorporated. This is therefore a particularly important model for this thesis in tying together "surface traits" of neuroticism and extroversion, with individual differences in underlying behavioural activation, inhibition and defence systems and also the "emotional" valence dimensions of reward and punishment [figure 1.20]. They additionally relate the model to conditioning, arousal and attention (not shown). In this model the behavioural inhibition system has a superior position in the hierarchy of influencing decision making and conflict detection.

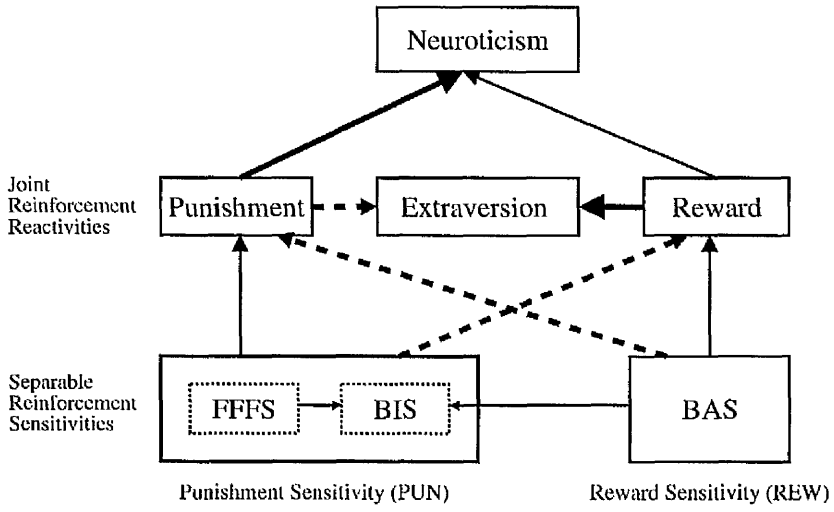

Figure 1.20 hypothesized relationship between (a) FFFS/BIS (punishment sensitivity; PUN) and BAS (reward sensitivity; REW); (b) their joint effects on reactions to punishment and reward; and (c) their relations to Extraversion (E) and Neuroticism (N). E is shown as the balance of punishment (PUN) and reward (REW) reactivities; N reflects their combined strengths. Inputs from the FFFS/BIS and BAS are excitatory (unbroken line) and inhibitory (broken line)—their respective influences are dependent on experimental factors (see text). The strength of inputs to E and N reflects the 308 rotation of PUN/REW and E/N: relatively strong (thick line) and weak (thin line) relations. The input from Punishment reactivity to E is inhibitory (i.e. it reduces E), the input from Reward reactivity is excitatory (i.e. it increases E). The BIS is activated by simultaneous activation of the FFFS and the BAS, and its activation increases punishment sensitivity. It is hypothesized that the joint effects of PUN and REW gives rise to the surface expression of E and N: PUN and REW represent the underlying biology; E and N represent their joint influences at the level of integrated behaviour. BIS = behavioural inhibition system. FFFS = Fight Flight Freeze System; BAS = behavioural activation system; E = extroversion; N = Neuroticism, REW = reward (Corr 2004).

Furthermore, different behavioural and autonomic responses relate to "defensive distance" and in particular whether a threat is avoidable or unavoidable. Clearly this has some symmetry with the Lumb escapable/inescapable pain dichotomy but is likely to have a greater cognitive-evaluative appraisal element to it compared with presumably more reflexive pain responses [figure 1.21].

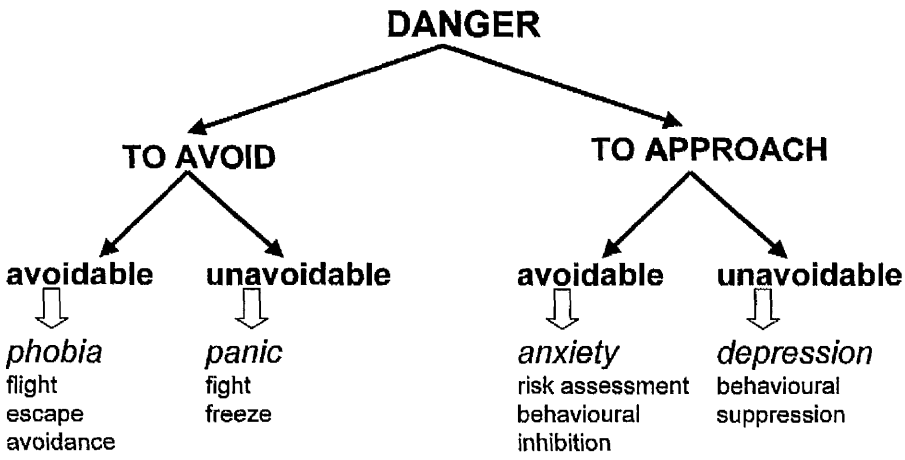

Figure 1.21 Categories of emotion and defensive response derived from defensive direction (avoid or approach the danger) and avoidability of the threat, from (McNaughton and Corr 2004).

The Gray-McNaughton model lastly relates the two dimensions of defence response (approach/avoid) and defensive distance (avoidable/unavoidable) to the hierarchical defence response system [figure 1.22]. Of note a role for the brainstem autonomic nuclei in this model has not yet been elaborated. The two defence dimensions of avoid and approach were divided into a number of hierarchical levels. These are ordered with respect to neural level (and cytoarchitectonic complexity) and to also to functional level. Each level is associated with specific classes of behaviour and so symptom and syndrome. It is proposed that syndromes are associated with phasic hyper-reactivity of a structure and symptoms with tonic/basal high activity. It is suggested that given the interconnections within the system (and effects of e.g. conditioning) symptoms will not be a good guide to syndromes (McNaughton and Corr 2004).

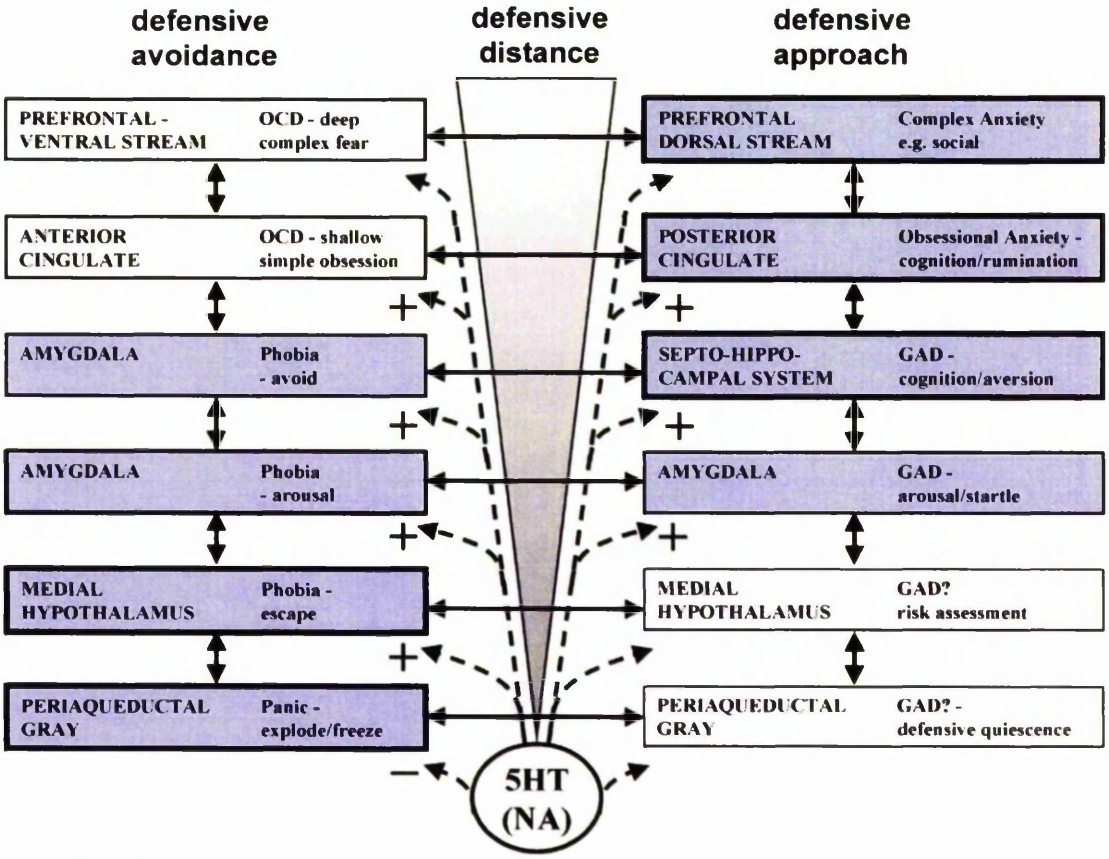

Figure 1.22 The two dimensional defense system. On either side are defensive avoidance and defensive approach respectively (a categorical dimension) (McNaughton and Corr 2004).

Summary of section 1.7

(i) Defensive behaviour is controlled by a hierarchically organised cortical, subcortical and brainstem network of structures involved in emotion and ANS control (ii) A greater appreciation of blends of freeze as well as fight/flight defence behaviours has arisen in which the role of inhibitory pre-frontal cortex/parasympathetic circuits has been emphasised. (iii) Sub-cortical structures, especially peri-aqueductal gray, hypothalamus and amygdala have discrete sub-nuclei capable of eliciting broad ranges of ANS responses and defence behaviours along the basic approach/avoid dimensions (iv) A personality model based on Gray's reformulation explicitly incorporates defence responses within a hierarchy of CNS structures but doesn't elaborate on brainstem ANS components.

1.8 Autonomic Brainstem Neurophysiology

In this section brainstem ANS control is reviewed with evidence presented for complex models of ANS function including co-activation of PNS/SNS; an elaboration of Polyvagal theory with respect to cardiac vagal control and thereafter a review of differentiated SNS activity. Human studies are reviewed which link ANS activity to pain, emotion and personality.

1.8.1 ANS: Basic overview, peripheral and central components

The anatomical and functional structure of the peripheral efferent ANS and its functional targets are outlined in figure 1.23 and the enteric nervous system (ENS) is summarised in figure 1.24 and are reviewed by Janig (Janig 2006).

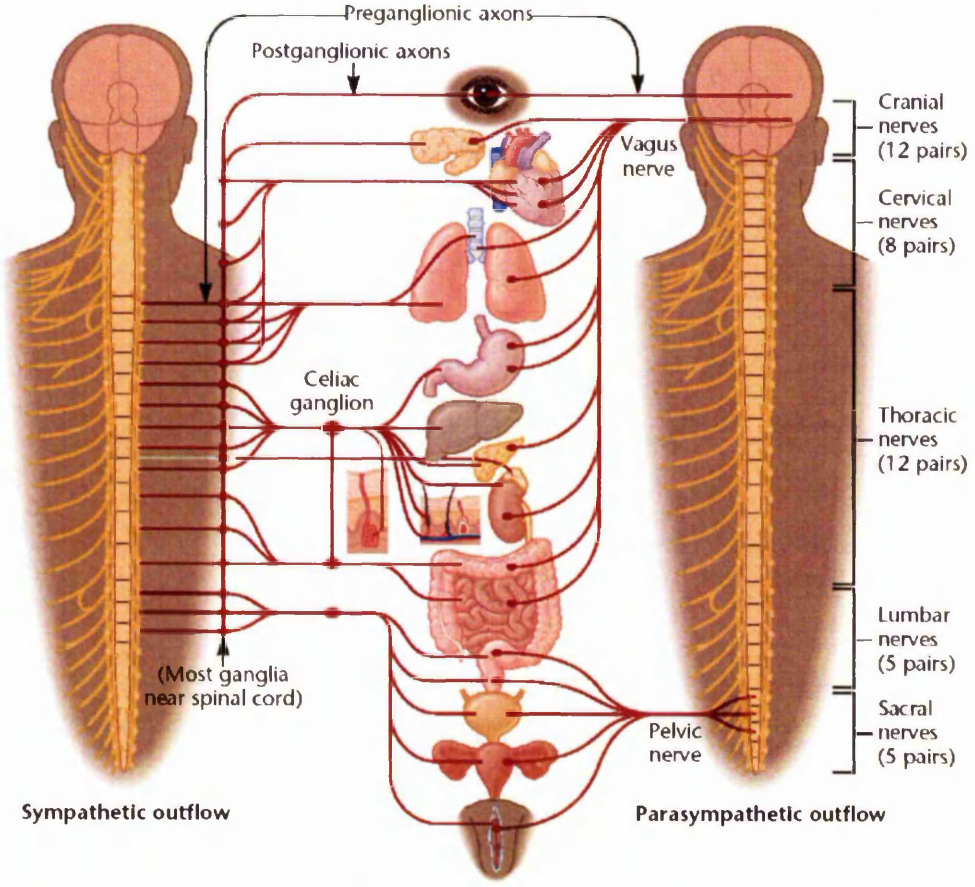

Figure 1.23 peripheral structures of the ANS and its functional targets

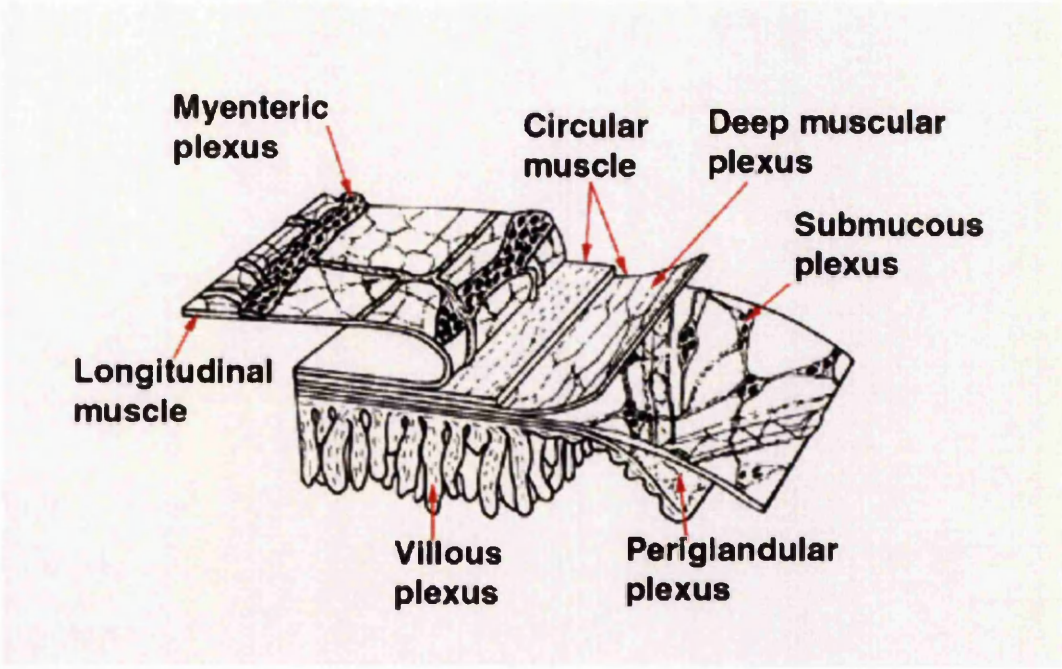

Figure 1.24 enteric nervous plexi of the ENS

1.8.2 Models of ANS function: Reciprocity vs. autonomic space

*"The autonomic nervous system as a whole may be viewed as a **dissipative structure** progressively assembled in the course of evolution, plastically and rhythmically interfaced between forebrain, internal and external environments, to regulate energy, matter and information exchanges" (Recordati 2003)*

The preceding quote emphasises the ANS as a key player in the homeostatic functional neural network. The traditional view of the ANS has been a purely effector model of simple reciprocal antagonism between sympathetic and parasympathetic branches (Schachter and Singer 1962; Cannon 1987; Berntson et al. 1991). These models have tended to denigrate firstly the afferent and secondly integrative components of the ANS (Freire-Maia and Azevedo 1990). Moreover it has led to experimental approaches which downgraded the peripheral ANS role in emotion regulation through a particular emphasis on sympathetic responses in fight or flight with a perceived lack of flexibility of ANS responses.

More recent approaches emphasise "dynamic systems", outlining the interactive function of components of the ANS, proposing that *"the multiple modes of autonomic control do not lie along a single continuum extending from parasympathetic to sympathetic dominance but rather distribute within a 2-dimensional space"*. This concept of "autonomic space" becomes more complicated

as levels are included of reactive lability as a function of the direction of movement (mode of control) within autonomic space (Berntson et al. 1991).

These ideas are picked up and incorporated into Thayer and Friedman's notion of "autonomic balance" (Friedman and Thayer 1998; 1998), autonomic flexibility (Friedman 2007) and the dynamic systems approach (Thayer and Friedman 2002)

1.8.3 Co-activation of SNS and PNS in pain and the Nucleus Tractus Solitarius (NTS)

Experimental confirmation of non-reciprocal, co-active possibilities of ANS activation have come from Boscan and Paton in their studies of autonomic control during pain in rats (Boscan et al. 2002; Pickering et al. 2003; Paton et al. 2005; Paton et al. 2006). They were surprised to find that noxious stimulation of the forelimb in rats evoked burst discharges in inferior cardiac & lumbar sympathetic nerves simultaneously with the cardiac vagal branch. The cardiac vagal branch activity was surprising since it was accompanied by a tachy rather than bradycardia. This suggested that both sympathetic and parasympathetic outflows to the heart can be coactivated during nociception. Furthermore, Boscan & Paton proposed a paradoxically active role for the parasympathetic nervous system in mediating the tachycardia during nociception. The mechanisms involved in mediating a vagal tachycardia are not known. Possibilities suggested include: (i) activation of chromaffin and/or small intensely fluorescent (SIF) cells in the cardiac ganglia; (ii) a possible direct effect of acetylcholine on cardiac activity; and (iii) release of cardio-acceleratory neuropeptides from vagal nerve endings (Boscan et al. 2002). They posit that most of the integration between nociceptive and baroreflex afferents with sympathetic and cardiac vagal motoneurones is co-coordinated by the NTS [figure 1.25](Pickering et al. 2003)

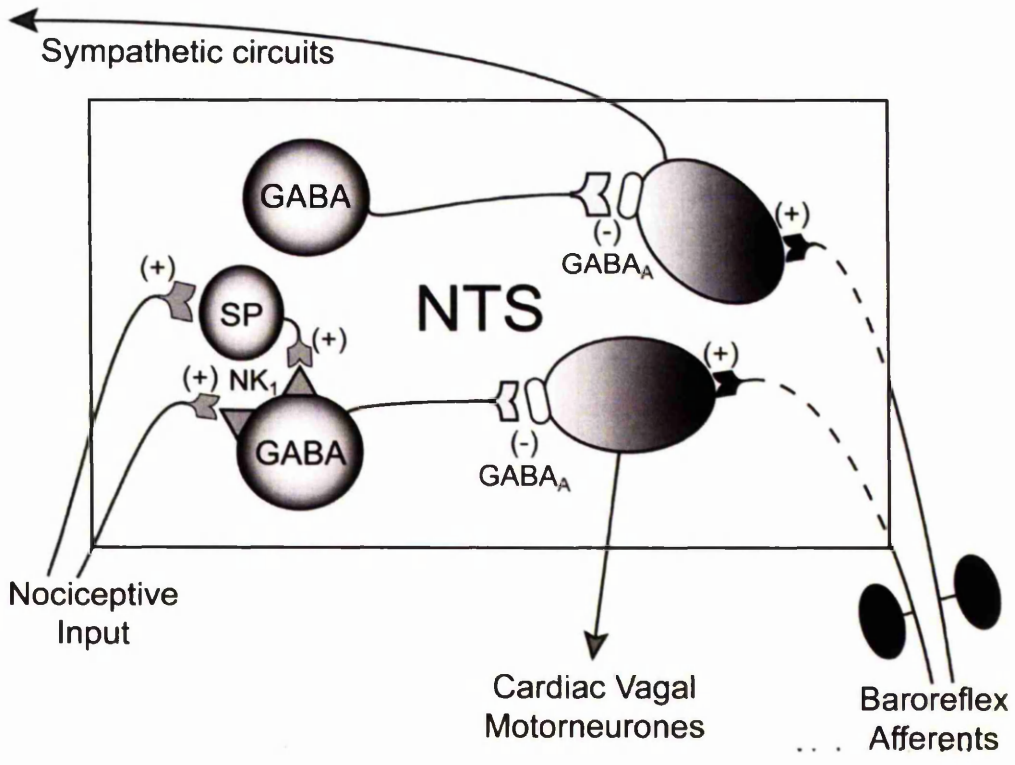

Figure 1.25 Nucleus Tractus Solitarius (NTS) integration of nociceptive and baroreflex afferent input with sympathetic and cardiac vagal motoneurone output (Pickering et al. 2003).

1.8.4 Polyvagal theory & Brainstem CVC regulation

"for spontaneously stable states to occur, slowing of the metabolic rate, withdrawal of the sympathetic drive and reinforcement of the vagal tone to the heart and circulation are required, thus confirming that the parasympathetic division of the autonomic nervous system is the main controller of homeostasis" (Recordati 2003; Recordati and Bellini 2004).

A recent special issue of biological psychology (Chambers and Allen 2007) has been devoted to "the Polyvagal theory" of Stephen Porges and cardiac vagal control measurement (Allen et al. 2007). In this issue it was outlined that Polyvagal theory has been linked in turn to the Central Autonomic Network, to dynamic systems/chaos theory and to the McNaughton-Gray personality model (Beauchaine 2001; Berntson et al. 2007; Chambers and Allen 2007; Friedman 2007).

Polyvagal theory provides evidence for the hierarchical and phylogenetic development of the cardiac vagal complex which facilitates increasingly complex behavioural repertoires (Porges 1995; 2001; 2003; 2003; 2007; 2007). The vagus is primarily a sensory nerve which wanders (as its name suggests) over vast tracts of

the body to innervate the viscera. The destination sensory nucleus in the brainstem is the nucleus of the solitary tract (NTS). The vagus has two brainstem motor nuclei [figure 1.26]. The nucleus ambiguus (NA) gives rise to myelinated fast-effector neurones which innervate the heart, larynx and upper gut, whilst the dorsal motor vagal nucleus (DMX) gives rise to unmyelinated slow effector neurones innervating the heart and lower gut. The DMX output results in a profound bradycardia, akin to an "emergency stop" in driving, which occurs in immobilisation behaviours such as death feigning and passive avoidance and is considered to be a very primitive defence response (Porges 2001). By contrast the NA output (CVC_{NA}) allows for subtler beat-to-beat heart rate modulation: – increased CVC_{NA} causes milder slowing of the heart rate which may be involved in behavioural inhibition and bonding whilst withdrawal of CVC_{NA} reduces the external constraint on intrinsic sino-atrial node (SA) automaticity and therefore a faster heart-rate ensues to facilitate behavioural activation.

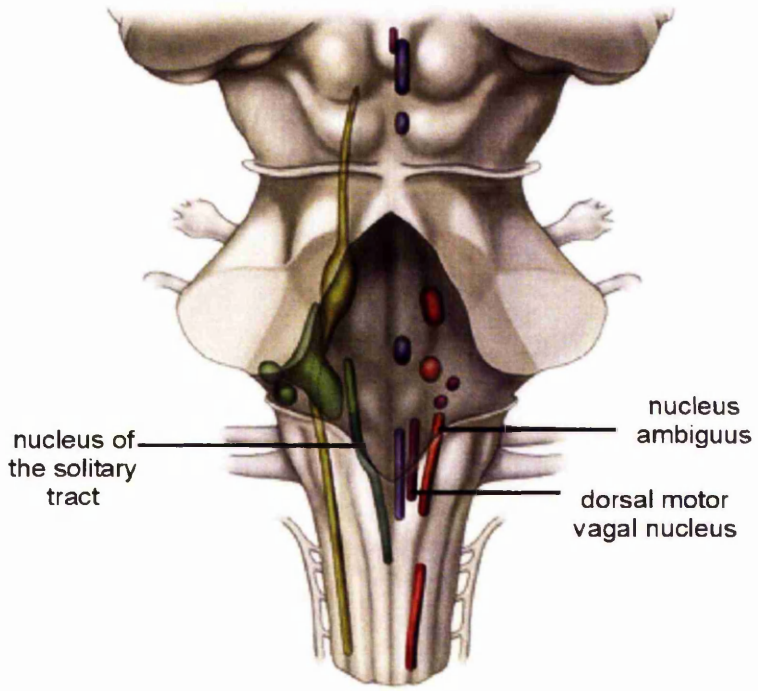

Figure 1.26 Brainstem ANS nuclei involved in Cardiac Vagal Control (adapted from internet image).

A primary *physiological* function of beat-to-beat CVC_{NA} appears to be heart rate control for blood pressure regulation and orthostatic tolerance. The mean blood pressure from each consecutive heart beat is sensed by arterial baroreceptors that evoke a NTS mediated vago-vagal reflex, adjusting CVC_{NA} rate control for the

following heart beat. Heart rate determines cardiac output and, together with systemic vascular resistance, the resultant blood pressure [figure 1.27](Janig 2006).

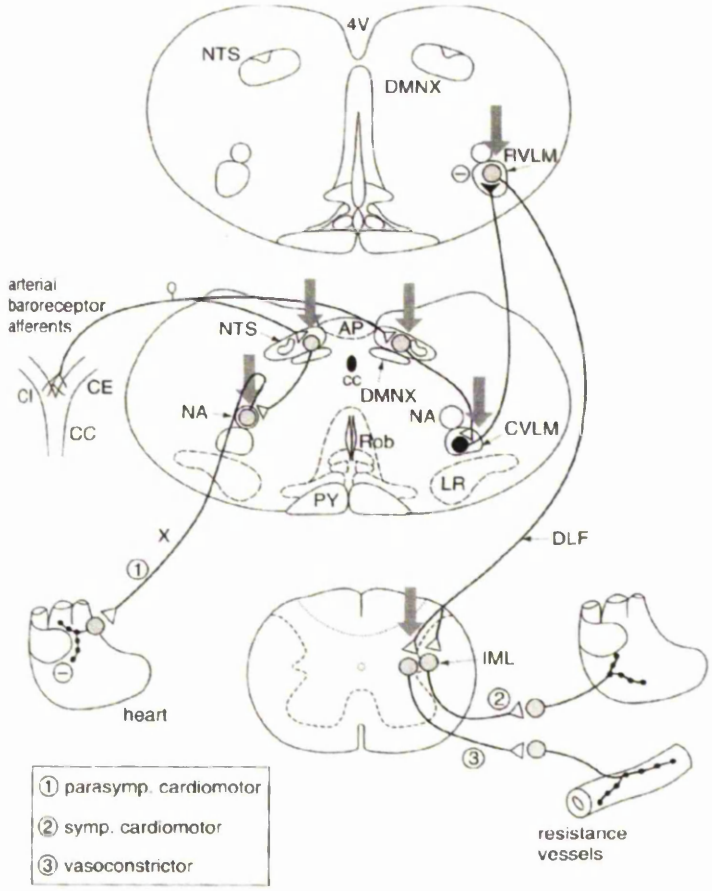

Figure 1.27 Arterial baroreceptor reflexes. Note in particular the left lower third showing the baroreceptor-NTS-NA-SA node parasympathetic cardiomotor reflex, from (Janig 2006) p401.

Further vago-vagal reflexes evoked by direct inputs to the NA from pulmonary stretch receptors during lung inflation, arterial chemoreceptors and respiratory neurones result in "breath-to-breath" CVC_{NA} modulation. This gives rise to respiratory sinus arrhythmia (RSA) which is the basis for the vast majority of CVC_{NA} measures (Allen et al. 2007).

Given the primary role of "beat-to-beat" and "breath-to-breath" CVC_{NA} modulation in blood pressure control and cardio-respiratory integration it is unsurprising that abnormal CVC_{NA} has been found in cardiovascular disease, chronic obstructive airways disease, diabetes and with increasing age and reducing fitness (Masi et al. 2007; Thayer and Lane 2007).

However, there are also NTS mediated and direct inputs allowing for modulation of CVC_{NA} from the amygdala in emotional responses; the peri-aqueductal gray matter in defence responses; the hypothalamus in other aspects of homeostatic function; and facial and laryngeal receptors in communication [figure 1.28] (Julu 2001; Porges 2007). It should be unsurprising therefore that CVC_{NA} abnormalities have also been seen in unstable infant temperaments, in individual differences in neonatal pain reactivity, in reactivity of central emotional circuits and in chronic pain and affective disorders (Chambers and Allen 2002; 2007; Rottenberg 2007). It is thus apparent that CVC_{NA} is a central psychophysiological hub for which heart rate variability (HRV) measures permit a non-invasive window on this mind-body interface.

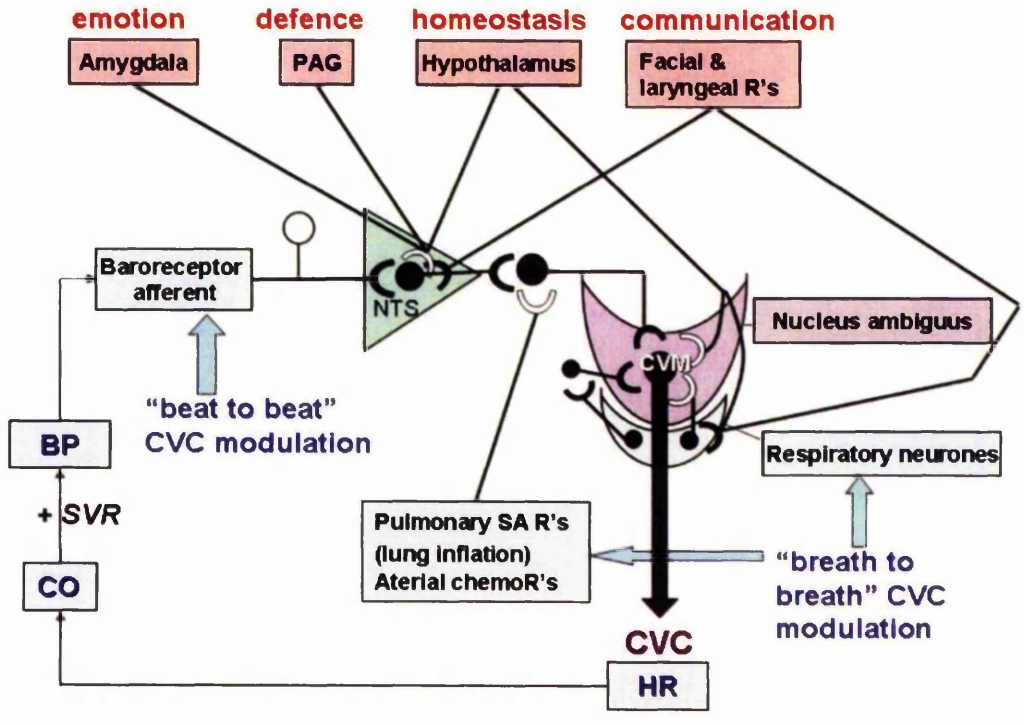

Figure 1.28 showing the "functional" neuroanatomy of Cardiac Vagal Control. PAG = peri-aqueductal gray matter; NTS = nucleus of solitary tract; CVM = cardiac vagal motor neurones; HR = heart rate; CVC = cardiac vagal control; BP = blood pressure; SVR = systemic vascular resistance; CO = cardiac output, adapted from (Julu 2001).

Polyvagal Theory has been linked to many processes already touched on: homeostasis in newborns (Groome et al. 1999); a sub-conscious system for detecting threats and safety (Porges 2004); the emotion system (Porges 1997) and its regulation (Porges et al. 1994); attentional and memory mechanisms (Suess et al.

1994; Hansen et al. 2003); social behaviour (Porges 2001; 2003) including social engagement and attachment (Porges 2003); mother-child interactions (Doussard-Roosevelt et al. 2003) and affiliative emotions (Porges 1998)

Additionally Porges has experimentally found evidence for vagal tone differences as a reflection of individual differences in infant temperament (Huffman et al. 1998) and pathologically as both a marker of stress vulnerability (Porges 1992) (Porges 1995) and also related to behavioural and visceral features associated with autism (Porges 2004).

1.8.5 Differentiated SNS activity

In a similar way to which the parasympathetic system should be considered a "Polyvagal" system, with the facility for differential activity, so too it is increasingly recognised that the SNS is capable of nuanced responses (Janig and Habler 2003). In particular differentiated function is seen in cardiomotor, vasomotor and sudomotor dimensions of the SNS. Cardiomotor and vasomotor reflexes as part of the baroreflex are shown in figure 1.28. Brainstem SNS activity exhibits a close relationship with changes in the mean arterial pressure (Sun and Guyenet 1986).

Sympathetic cholinergic sudomotor function induces change in skin resistance to electrical conduction. SCR is a somato-sympathetic reflex with a spinal, a bulbar and a suprabulbar component, although the precise pathways in humans are not fully defined. Efferent sweat fibers originate in the hypothalamic preoptic sweat center, and then descend through the ipsilateral brainstem and medulla to synapse with the intermediolateral column neurons. Unmyelinated postganglionic sympathetic class C fibers arising from the sympathetic ganglia reach the sweat glands, providing them with cholinergic innervation (Vetrugno et al. 2003).

Two types of sweating occur: "thermoregulatory sweating" over the whole body in response to changes in the environment, and "emotional sweating" which is confined to the palms, axillae and soles of feet. The two have different and independent rhythmicity due to seperate central drives. At the cortical level, the Anterior Cingulate Cortex (ACC) is prominently implicated in the control of emotional sweating. Ventral ACC receives visceral sensory inputs from the Nucleus Tractus Solitarius (NTS), dorsal and median raphe nuclei and Parabrachial nucleus (PBN) and directs outputs to the brainstem visceral control areas (NTS, Doral motor nucleus

of vagus, Nucleus Ambiguus) and to the sympathetic preganglionic neurons in the intermediolateral cell column (Vetrugno et al. 2003).

1.8.6 ANS studies

ANS and emotion

A number of studies have related differences in ANS activity to emotional processes. Rainville et al found that distinct patterns of peripheral cardiorespiratory and SCR physiological activity were associated with different emotions (Rainville et al. 2006). Furthermore, voluntary facial action can generate emotion-specific autonomic nervous system activity (Levenson et al. 1990). Diurnal variations occurred in skin conductance response (SCR) which related to changes in emotional experience (Hot et al. 2005). Lee et al used a neural network to recognize human emotions from heart rate variability (HRV) and SCR with 80% accuracy (Lee et al. 2005).

Reduced parasympathetic ANS activity as measured by HRV is predictive of the development of negative mood after deprivation of usual exercise activities (Weinstein et al. 2007).

Individual differences in parasympathetic cardiac control measured at rest in human adults were able to discriminate cardiac response patterns during viewing of emotional films (Palomba et al. 2000; Buss et al. 2004) and there were further individual differences in defence and orienting associated ANS patterns to unpleasant pictures (Sanchez-Navarro et al. 2006). HR and respiratory sinus arrhythmia (RSA) changes in 24 month olds during emotion-eliciting tasks were associated with negative affect (Buss et al. 2005).

For adults - individuals who were high in vagal tone were unlikely to experience high levels of negative emotional arousal in response to stressors, but this relation held only for moderate- to high-intensity stressors (Fabes and Eisenberg 1997). Hypnotic susceptibility and mood state were linked to cardiovascular reactivity and vagal tone in female adults whilst hypnotic state itself was associated with some particular autonomic changes (Harris et al. 1993; DeBenedittis et al. 1994; Hippel et al. 2001; Sobrinho et al. 2003; Derbyshire et al. 2004).

On the afferent side, emotion processing style was related to interoceptive sensitivity – in this case to a heart beat detection method (Barrett et al. 2004).

ANS and emotion disorders

Vagal tone abnormalities (especially low vagal tone) have been linked to numerous conditions including autism (Ming et al. 2004; Porges 2004) and stereotyped behaviour (MacLean et al. 1989) ; depression (Lehofer et al. 1997; Rottenberg et al. 2003; Rottenberg 2007) including seasonal affective disorder (Austen and Wilson 2001), bereavement (O'Connor et al. 2005) and premenstrual dysphoric disorder (Landen et al. 2004) which improve with treatment (Chambers and Allen 2002); anxiety (Friedman and Thayer 1998); dissociation (Scaer 2001); disturbed sensory processing in children (Schaaf et al. 2003); panic disorder (Asmundson and Stein 1994; 1994; Friedman and Thayer 1998; McCraty et al. 2001); emotional dysregulation (Woolley et al. 2004) and behavioural problems (Cole et al. 1996); schizophrenia (Malaspina et al. 1997); PTSD (Sack et al. 2004); chronic fatigue syndrome (Sisto et al. 1995; Stewart 2000); fibromyalgia (Pagani and Lucini 1999); cardiovascular disease via impaired anger inhibition (Brosschot and Thayer 1998); and borderline personality disorder (Austin et al. 2007).

ANS and personality

Researchers have provided much evidence for relationships between ANS activity and personality; however the diversity of personality and ANS measures used makes it difficult to draw overarching conclusions. Some studies however failed to find links (Lang et al. 1993) and one study even suggested that dissociations between ANS and verbal reports during stress may be a stable trait itself (Schwerdtfeger et al. 2006).

"Tonic" or resting HRV has been explored as a measure of an individual trait: short recordings of HRV (5 minutes) in a non-laboratory setting are stable within individuals over short periods (Kleiger et al. 1991) but also over months and are therefore characteristic of an individual. They are also influenced by sex and age. The stability and reliability of HRV suggests it can be informative in population based measures (Sinnreich et al. 1998).

In another prospective longitudinal study comparing continuity, stability and concordance, cardiac vagal tone was measured at 2 months and 5 years in mothers and their children. This was both at rest (baseline) and during an "environmental task" (Bornstein and Suess 2000). Infants with high vagal tone at 40 weeks of age always had positive developmental outcome at both eight and 12 months of age on the

mental scale of the Bayley Scales of Mental Development (Fox and Porges 1985). Vagal tone was associated with attention span and placidity (as a measure of temperament) in 12 week old infants (Huffman et al. 1998). Baseline cardiac vagal tone and task related vagal-suppression was related to temperament in another study in young children (Calkins 1997). Vagal tone was related to negative emotional expressiveness in girls but otherwise there was no great association between autonomic and behavioural measures (Quas et al. 2000). Person-oriented analysis indicated that children characterized by both high level of approach and high level of withdrawal tended to exhibit lower resting vagal tone, higher initial cortisol, and minimal cortisol and vagal change (Blair et al. 2004).

In normal adults, at least in males, there was a link between heart rate variability measures and coping style (Ramaekers et al. 1998). Poorer modulation for vagal tone was associated with greater social anxiety, while lower vagal tone across recording periods was associated with greater defensiveness and lower behavioral activation sensitivity (Movius and Allen 2005). Neuroticism was negatively correlated to baroreflex sensitivity (BRS) and HRV. Neuroticism was not correlated to inter-beat-interval. For BRS, this phenotypical relation was entirely determined by shared genetic influences. For HRV, the genetic contribution to the phenotypical correlation was not significant, but the proportions of explained covariance showed a trend for more genetic than environmental influences on the phenotypical relationship (Riese et al. 2007).

"Phasic" changes in HRV measures have also been assessed: either "event related" changes to stimuli or a "block design" where there is a continuous performance task. Typically a phasic response would last less than 30 sec and show a latency from the eliciting event of <10 sec (Jennings et al. 1981). Response to a challenge is operationalised as suppression of vagal tone which is also a stable trait of an individual (Calkins and Keane 2004). Although most individuals have highly reproducible HRV measures some have marked variability (Hohnloser et al. 1992). Neonatal stress reactivity to a heel-prick was related to vagal tone and cortisol release and predicted emotional temperament at 6 months (Gunnar et al. 1995). Infants with difficulties in decreasing vagal tone during a social/attention task at 9 months of age had significantly more behavioral problems at 3 years of age (Porges et al. 1996). When examining groups based on degrees of reactivity and regulation, Stifter found infants who responded negatively to frustration but who also displayed

more regulatory behavior to have higher vagal tone (Stifter and Jain 1996). Cardiovascular and HPA indices during a threat stimulus were able to differentiate overly fearful children from their normally reactive counterparts (Buss et al. 2004).

Psychological individual differences were associated with physiological (vagal tone) differences in young adults during an exam (Spangler 1997). Behavioural activation system (BAS) sensitivity was related to HR reactivity and parasympathetic withdrawal during the tasks, but was unrelated to baseline levels. Behavioural inhibition system (BIS) sensitivity was unrelated to both reactivity and baseline levels of all measures (Heponiemi et al. 2004). Higher levels of social desirability were associated with a decrease in SCR's to masked threat pictures (relative to neutral), whereas elevated levels of trait anxiety were associated with an increase in SCR's. This latter effect, however, was mainly seen among participants who simultaneously scored low on social desirability (Najstrom and Jansson 2006).

ANS and pain

Several recent reviews have explicitly explored the neuroanatomical basis for interactions between pain and the ANS both in acute and chronic pain (Benarroch 2001; Cortelli and Pierangeli 2003; Benarroch 2006). They show that the process of nociception interacts with the ANS at levels of the periphery, spinal cord, brainstem, and forebrain. Spinal and visceral afferents provide converging information to spinothalamic neurons in the dorsal horn and to neurons of the NTS and parabrachial nuclei. These structures project to areas involved in reflexive, homeostatic, and behavioral control of autonomic outflow, endocrine function, and nociception. These include monoaminergic cell groups of the medulla and pons, peri-aqueductal gray, hypothalamus, amygdala, insular cortex, and anterior cingulate gyrus.

Specific experimental findings include that in newborns during pain, cardiac PNS measures correlate with individual differences in pain responses (Porter et al. 1988; Morison et al. 2001; Arditi et al. 2006) and were also affected by heel lancing (Lindh et al. 1999). A response to an acute noxious stimulus produced an increase in respiratory-related sympathetic heart rate (HR) control and a significant decrease in respiratory-related parasympathetic control at both 4 and 8 months old (Oberlander et al. 1999). Conversely, early pain exposure at very low gestational age may alter the long term autonomic response (Grunau et al. 2001). At 18-months of age, 35% of the variability in infant pain behavior was predicted by maternal sensitivity and infant

vagal tone level (Sweet et al. 1999). Campbell found relationships between HRV, blood pressure (BP) and pain sensitivity above 8 years old (Campbell et al. 2003).

In adults there has been a consistent pattern emerging of greater SNS reactivity, resting higher blood pressure and relative hypoalgesia (France 1999; Campbell et al. 2006) which may be influenced by race (Mechlin et al. 2005). Nordin found that nail bed pressure evoked a generalized muscle sympathetic nerve activity increase (Nordin and Fagius 1995)

In adults, distraction altered autonomic activity and inhibited pain (Terkelsen et al. 2004). Ness found that low intensity vagal nerve stimulation lowered thermal pain threshold (Ness et al. 2000).

Pain related emotions modulated experimental pain perception and cardiac responses in a recent study (Rainville et al. 2005). Rhudy found conversely that viewing emotional pictures could modulate ANS reaction to noxious stimuli (Rhudy et al. 2007).

Placebo analgesia was associated with SNS cardiac changes in another study (Pollo et al. 2003). Conversely, pain changed heart rate responses during the Valsalva manouevre (Drummond 2003). Musically induced arousal affected ANS responses and pain perception in females (Kenntner-Mabiala et al. 2007). Vowles found that CO2 induced anxiety potentiated ANS and perceptual pain responses (Vowles et al. 2006).

ANS Psychophysiological endophenotypes

The concept of genetic psychophysiology (De Geus and Boomsma 2001; de Geus 2002) has tended to concentrate on peripheral mechanisms as with most of psychophysiology. Out of this field has emerged the "endophenotype" concept which denotes a simpler component of a more complex phenotype (e.g. ANS activity or amygdala activation as a subcomponent of emotion) which is therefore closer to the site of action of the genes and therefore likely to have less complex polygenic influences (Gottesman and Gould 2003).

Examples of this approach are that Singh et al found 13-23% of HRV variance was genetic (Singh et al. 2001); a putative major gene explained 28%-34% of the adjusted inter-individual variability of heart rate variability in the "Kibbutzim family study" (Sinnreich et al. 1998; Sinnreich et al. 1999); and 84% of the relationship between RSA, HR and exercise behaviour (16-29% RSA alone) was found to be of

genetic origin in twin studies (De Geus et al. 2003). Heritability of ambulatory heart rate variability was found to be 35-48% in a further study and RSA between 28-43% in another (Snieder et al. 1997; Kupper et al. 2004). Allelic variation in the serotonin transporter gene-linked polymorphic region (5-HTTLPR/SERTP) is highly correlated with greater cardiovascular reactivity in young adult male and female twins (McCaffery et al. 2003).

ANS psychophysiological phenotypes and clinical pain

Janig reviewed relationships between pain and autonomic phenomena in headache and other pain conditions (Janig 2003).

Diatchenko found that three major haplotypes of the B2 adrenoceptor defined psychological profile, blood pressure and the risk for development of a common musculoskeletal pain disorder (Diatchenko et al. 2006) A review of relationships between individual differences in autonomic reactivity and pain perception and response identified an inverse relationship between pain sensitivity and sympathetic reactivity. Phasic hypertension induced by a stressor was found to attenuate pain sensitivity but a lack of inhibitory effects on pain perception was found in individuals with a hypo reactive sympathetic system leading to hypothesised "hypofunctional stress systems" in fibromyalgia (Okifuji and Turk 2002).

Patients with fibromyalgia have an overall enhancement of cardiovascular sympathetic activity while recumbent. Lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity characterize their autonomic profile during tilt test (Furlan et al. 2005).

Fibromyalgia (FMS) patients showed significantly higher stress ratings and self-reported stress responses than healthy controls. Baseline EMG levels were significantly lower, and baseline HR was significantly elevated in FMS. During both stress tasks, HR reactivity was significantly lower, and skin conductance reactivity was significantly higher in the FMS group (Thieme et al. 2006).

The same group found that a fibromyalgia patient sample demonstrated lower baseline EMG levels compared to healthy controls (HC). In contrast, the patients displayed elevated HR and SCL during stress tasks. A cluster analysis identified four psychophysiological response patterns: 63.3% of HC's showed increased muscle tension and stable cardiovascular responses; 34.8% of FMS patients showed a pattern of increased sympathetic vasomotor reactivity with stable sudomotor and

reduced muscular response; 12.2% of FMS patients showed a pattern of increased sympathetic sudomotor reactivity connected with increased sympathetic vasomotor response and reduced muscular response; and, in contrast, 46.7% of FMS patients showed a pattern of parasympathetic vasomotor reactivity and reduced sudomotor as well as muscular response (Thieme and Turk 2006).

A more recent psychophysiological study in fibromyalgia patients found two subgroups based on the autonomic lability among FSS patients, which were independent of the type of symptoms and diagnostic category (Kanbara et al. 2007)

Fibromyalgia patients scored high on neuroticism, anxiety, depression and general distress, however only a minor part of variance in pain was explained by psychological factors alone. High pain score was associated with high neuroticism, low baseline cortisol level and small drop in systolic blood pressure after buspirone challenge test. This model explained 41.5% of total pain in fibromyalgia patients (Malt et al. 2002).

As well as possible clinical discriminators, ANS changes were also related to improvement in clinical pain. Patients with fibromyalgia were taught to breathe at their "resonant frequency" using HRV feedback. This resulted in increases in HRV and blood pressure variability and also reductions in pain and depression (Hassett et al. 2006). Improvement in chronic pain has also been indexed to HRV changes (Storella et al. 1999).

HRV has been linked clinically to cardiovascular disease (Vingerhoets et al. 1996; Singh et al. 1999; Thayer and Lane 2007); diseases of aging; obesity, diabetes and hypertension (Masi et al. 2007); hyperthyroidism (Cacciatori et al. 1996; Burggraaf et al. 2001). Vagal tone has also been used in biofeedback to treat asthma (Lehrer et al. 1992); and noted to improve during relaxation exercises (Stancak et al. 1991).

Gastrointestinal ANS

The text book "psychophysiology of the GI tract" explores each subsection of the GI tract and reviews evidence for both normal psychophysiological mechanisms in healthy subjects and also evidence for abnormal psychophysiological mechanisms in operation (Holzl and Whitehead 1983). This book is now 20 years old and there has been no further comprehensive review of the subsequent data from a

psychophysiological perspective although there has been a recent review on the psychophysiology of nausea (Stern 2002).

Further evidence for the functional sub-specialisation of the vagus is found in that there are differentiated RSA (respiratory sinus arrhythmia) & EGG (electrogastrogram) effects during emotional responses because the Dorsal motor vagal complex is controlling gastric tone but the nucleus ambiguus is determining RSA (Muth et al. 1998; Muth et al. 1999; Baldaro et al. 2001; Ferreira et al. 2002; Monroe et al. 2004). Vianna and Tranel found that gastric myoelectrical activity could be used as an index of emotional arousal (Vianna and Tranel 2006). Vagal afferent stimulation with (i) implanted vagal nerve stimulators and (ii) electrical stimulation of the oesophagus by catheter increased vagal efferent activity (Fallen et al. 2001). Iovinio conversely found that the SNS modulated perception and reflexes to gut distension (Iovino et al. 1995).

Functional gut disorders and ANS

"Under certain conditions, altered autonomic balance (including low vagal tone and increased sympathetic activity) may alter visceral perception. Autonomic dysfunction may also represent the physiological pathway accounting for many of the extraintestinal symptoms seen in irritable bowel syndrome patients and some of the frequent gastrointestinal complaints reported by patients with disorders such as chronic fatigue and fibromyalgia." (Tougas 1999)

Irritable bowel syndrome (IBS) - As might be expected in such a heterogenous group as "irritable bowel syndrome" conflicting results have been found experimentally in linking IBS to ANS abnormalities: low vagal tone has been found in females with IBS with patterns of sympathovagal balance altering between subgroups of IBS (Heitkemper et al. 1998; Burr et al. 2000; Heitkemper et al. 2001); however high sympathetic predominant activity with normal vagal HRV was found in another IBS study (Karling et al. 1998); whilst abnormal HRV (vagal) with normal skin conductance responses was found in yet another (Lee et al. 1998).

Reduced sympathetic influence on the heart period was found in response to orthostatic stress and diminished parasympathetic modulation during deep breathing in IBS (Adeyemi et al. 1999). The IBS constipation subgroup was associated with a cholinergic abnormality and the diarrhea-predominant subgroup with an adrenergic abnormality (Aggarwal et al. 1994). Autonomic functioning during REM sleep may be

a useful biological marker to identify IBS patient subgroups as evidenced by variations in sympathovagal balance (Thompson et al. 2002).

Attenuated cardiac vagal tone and relative sympathetic excess during stimulated conditions was seen in another IBS study (Waring et al. 2004). Despite higher basal urine catecholamine levels, cardiovascular reactivity to a cognitive challenge in a laboratory setting was not elevated in women with diagnosed IBS (Levine et al. 1997). Acute stress altered gut-specific efferent autonomic innervation (laser-doppler flowmetry) in both controls and patients with IBS, although normalization was delayed in IBS (Murray et al. 2004). IBS patients have altered autonomic responsiveness to a visceral stressor, with increased sympathetic and decreased parasympathetic activity. These differences are predominantly seen in males (Tillisch et al. 2005). Reduced baseline activity as well as responsiveness of the parasympathetic system could play a role in the pathogenesis of IBS (van Orshoven et al. 2006).

For comparable pain perception, IBS subject demonstrated different autonomic nervous system responses to pain, which supports the view of autonomic dysregulation in IBS (Tousignant-Laflamme et al. 2006). The presence of a viscerosensory-cardiovascular reflex in healthy individuals and in IBS patients was demonstrated to rectal distension. The authors suggest that increased BRS in IBS patients at baseline may either be a training-effect (frequent challenging of the reflex) or reflects altered viscerosensory processing at the nucleus tractus solitarii (van der Veek et al. 2005).

Functional Dyspepsia (FD) is another complex symptom cluster in which vagal tone has been studied and found to be low (Hausken et al. 1993; Hveem et al. 1998; Kamath et al. 2000; Hjelland et al. 2002). Low vagal activity was postulated as the mediating mechanism for the relationship between personality factors and gastric symptoms in functional dyspepsia in another study (Haug et al. 1994). Low vagal tone was further linked to antral dysmotility in functional dyspepsia (Hausken et al. 1993; Hausken et al. 1997); in another study however differences were not evident between patients with functional dyspepsia and healthy individuals compared to the wide gastric antrum and low vagal tone found in patients with diabetes mellitus type 1 (Undeland et al. 1996).

The diminished PP response after insulin hypoglycaemia indicates disturbed efferent vagal function in a subgroup of patients with functional dyspepsia. The data

also suggest that the intact vagal nerve may exert an antinociceptive visceral effect (Holtmann et al. 1998).

Upper GI other: In non-cardiac chest pain low vagal tone was found (Kamath et al. 2000) but increased vagal activity during acid infusion (Tougas et al. 2001); however low vagal tone has been found in GERD with concomitant high SNS activity (Chen and Orr 2004); lastly vagal tone was not affected in another study of oesophageal acid infusion (Zollei et al. 2003). It was postulated that H. pylori infection may affect ANS activity (HRV) and via this way also contribute to gastro-oesophageal and cardiovascular pathology (Budzynski et al. 2004).

During endoscopic procedures vagal withdrawal was noted during ERCP (although possibly drug related) (Christensen et al. 2000; Christensen et al. 2002); whilst colonoscopy increased SNS activity (Petelenz et al. 2004). Autonomic nervous function in patients with peptic ulcer studied by spectral analysis of heart rate variability revealed differences in circadian HF/LF spectra (Nada et al. 2001). The results of the ONDAN study in bulimia nervosa subjects suggest that cyclic increases in vagal activity drive the urge to binge-eat and vomit (Faris et al. 2006). Low vagal tone was found in glossodynia (Koji 2003)

Children - normal vagal tone was found in children with chronic abdominal pain (Olafsdottir et al. 2001) and normal vagal tone was found in infants with colic (Kirjavainen et al. 2001). Pediatric patients with chronic upper gastrointestinal symptoms may have underlying orthostatic intolerance. In patients with upper gastrointestinal symptoms and orthostatic intolerance, treatment of orthostatic intolerance may result in resolution of gastrointestinal symptoms (Sullivan et al. 2005). Others have also found ANS abnormalities in children with GI symptoms (Chelimsky and Chelimsky 2001; 2003; Chelimsky and Chelimsky 2007). Familial rectal pain (recently renamed) is a rare familial autonomic disorder as a cause of paroxysmal attacks in the newborn baby (Bednarek et al. 2005).

Combined ANS-imaging studies

There have been relatively few studies which have combined ANS and brain imaging measures. This is partly due to technical difficulties e.g. non-ferromagnetic equipment required in Magnetic Resonance scanners, partly due to miss-matches in time course between ANS and brain-imaging measures (generally seconds vs. milliseconds respectively) and lastly a lack of appreciation that the one has much

relevance to the other (ANS measures largely considered "peripheral"). Nonetheless some studies have attempted to bridge this gap.

Physiological ANS-CNS studies include that responses to hypoglycaemia have been found to correlate with mPFC activity (Teves et al. 2004). Skin conductance response co-varies with activity in ventromedial prefrontal cortex (Critchley et al. 2000; Nagai et al. 2004). Choline transporter (CHT1) variation is related to differences in a distributed corticolimbic circuitry mediating behavioral and physiologic arousal (Neumann et al. 2006). A study using lower body negative pressure in humans found activation of the insula, anterior cingulate cortex and amygdala in central autonomic cardiovascular control involved specifically with baroreflex-mediated autonomic cardiovascular function in conscious humans (Kimmerly et al. 2005).

Personality ANS-CNS studies include that Electroencephalogram (EEG) and vagal tone are related at baseline and during a social task to shy temperament (Schmidt et al. 1999).

Emotion ANS-CNS studies include a functional MRI study of Infants that linked vagal tone to affective faces processing (Weinberg and Tronick 1996). Hemispheric lateralisation was observed for parasympathetic control (vagal tone) during emotional films in normals (Wittling et al. 1998). Orienting heart rate acceleration to emotional face stimuli was modulated as a function of the emotion depicted. The magnitude of evoked heart rate increase, both across the stimulus set and within each emotion category, was predicted by level of activity within a matrix of interconnected brain regions, including amygdala, insula, anterior cingulate, and brainstem (Critchley et al. 2005). Results suggest that the medial orbitofrontal cortex plays a pivotal role in top-down regulation of peripheral physiological responses accompanying emotional experiences (Ohira et al. 2006).

Pain ANS-CNS studies include that of brainstem and hypothalamic responses during pain (Petrovic et al. 2004). Spinal Cord Injury (SCI) patients showed a relative enhancement during a conditioned electric shock task of activity within dorsal anterior cingulate, peri-aqueductal grey matter (PAG) and superior temporal gyrus. Conversely, SCI patients showed relative attenuation of activity in subgenual cingulate, ventromedial prefrontal and posterior cingulate cortices to threat of painful arm stimulation (Nicotra et al. 2006). MR signal change in the amygdala and the prefrontal and insula cortices predicts cardiac contractility to the threat of shock.

Participants with greater MR signal change in these regions show increased cardiac contractility to the threat versus safety condition (Dalton et al. 2005).

Other cognitive ANS-CNS studies include that regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working memory tasks (Critchley et al. 2000; Gianaros et al. 2004) and anterior cingulate cortex activity is proportional to cardiac activity during cognitive tasks (Critchley et al. 2003). ACC activity was related to pupil diameter changes during performance errors (Critchley et al. 2005). Hypnotisability has been concurrently related to ANS and EEG changes (De Pascalis et al. 1999; De Pascalis et al. 2001). Another study measured changes in cardiac response simultaneously with electroencephalography during mental stress (Gray et al. 2007).

Summary of section 1.8

(i) Inflexible reciprocal activation models of the ANS have given way to more complex dynamic systems models emphasising afferent, integrative and nuanced flexibly patterned components (ii) Evidence exists for PNS and SNS co-activation in pain (iii) Polyvagal theory emphasises fundamental roles for nuanced aspects of PNS activity in diverse behaviours in addition to primary physiological roles (iv) Similarly evidence exists for nuanced SNS activity in various behaviours (v) ANS activity in healthy humans is related to emotional state, pain and temperament although evidence for pain and temperament has been explored more in paediatric populations. Evidence is presented for genetic ANS endophenotypes particularly for heart rate variability. (vi) In clinical studies patient populations tend to show low resting vagal tone, high SNS activity and poor recovery to a stressor.

1.9 Rationale and strategy

The clinical problem motivating the research conducted in this thesis is that of unexplained gastrointestinal symptoms and in particular visceral pain. Existing approaches have failed to produce effective diagnostic and therapeutic tools in part because the reductionist model generally employed does not reflect the underlying psychobiological complexity.

The research context and previously conducted studies which have been reviewed in this chapter have informed my program of research and suggested that experimental approaches attempting an account of pain should incorporate measures

of 1) personality traits 2) emotional state 3) central and autonomic nervous system responses 4) psychophysical measures of stimulus input and subjective experience 5) comparisons between visceral and somatic pain.

This could be characterised as a psychophysiological approach. A definition of psychophysiology has lacked universal consensus although it involves the "mapping of relationships between and mechanisms underlying psychological and physiological events" emphasising multiple levels of analysis but with an integrated approach relating the function of the entire organism to its environment (Cacioppo et al. 2000). A psychophysiological approach then is one which attempts to ground cognitive processes and constructs in physiology, or at least to measure their physiological correlates. Such an approach discerns individual differences at the psychological level to be at least in part derived from differences in their generative (neuro)-physiological mechanisms (Davidson 1999; Cacioppo et al. 2000). In addition to these defining features, psychophysiological studies are "based on assumptions that human perception, thought, emotion & action are embodied phenomena and that physical responses can shed light on these" (Cacioppo et al. 2000).

The strategy of the research therefore was to aim at a "pluralistic account" of individual differences in pain perception and response (Matthews 2004). Employing the measures outlined in 1-5 should enable identification experimentally of a) response endophenotypes and b) pain-emotion mechanisms which permit bridging of the mind-body gap. Subsequently these can be used in exploration of the genetic and pharmacological influences and clinical relevance to pain and other medically unexplained/refractory symptoms.

Relations of experimental findings to background

The experimental findings in my thesis have been built on the foundation of the background conceptual and experimental work which has been reviewed in this chapter. My findings broadly confirm and extend knowledge in these areas, particularly in demonstrating the salience of animal findings for human psychophysiology.

In chapter 3, two psychophysiological endophenotypic groups for ANS responses to oesophageal balloon distension evoked pain are demonstrated. These are similar to the different repertoires of defence response elicited by subcortical structure stimulation in animals, outlined in section 1.7. These differential response patterns have been postulated to relate to different personality types. I experimentally

confirmed this since two ANS phenotypes were related to neuroticism and extroversion dimensions of personality. My data adds to that already known by providing a bridge of evidence that what is known about ANS defence responses and personality from animal literature also can be found in humans. A relationship was also found between personality, defence repertoire pattern and tolerated balloon volume as a marker of hypersensitivity.

In chapter 4, the data found in animals and presented in section 1.8 demonstrating coactivation of SNS and PNS to somatic pain was for the first time confirmed in humans and was also similar for oesophageal balloon distension evoked pain. Further relationships were found between personality and ANS response profiles in terms of slope function.

In chapters 5&6 the close conceptual relationships between emotion, pain and personality outlined in sections 1.4 and 1.5 were confirmed and also previous imaging data reviewed in sections 1.4, 1.5 and 1.6 were confirmed and extended. Firstly a reciprocal relationship between emotion and pain was demonstrated and secondly a distributed network of cortical and subcortical brain structures was shown to be differentially activated during the reciprocal interactions of pain and emotion. These two findings were both influenced by personality.

Chapter 2 Methodology

2.1 Stimulation techniques

2.1.1 Pain stimuli

Oesophageal Pain

Painful stimulation of the oesophagus can be produced by electrical, thermal or mechanical means.

In pilot work I found that electrical stimulation in the oesophagus, especially proximal, produced artefact spikes on the electrocardiogram (ECG). This rendered electrical stimulation less useful for studying cardiac based ANS pain responses, since excessive subsequent artefact editing was required. Furthermore, changes in mucosal contact meant that pain intolerance threshold was not always reached from one stimulus to the next. Pain intolerance threshold is the level at which subjects can no longer tolerate pain and ask for the stimulus to be stopped. Hence this is most accurately described as a pain "intolerance" threshold, i.e. that at which they become intolerant of pain, rather than a pain "tolerance" threshold, i.e. the last level at which they can still tolerate it.

Little experimental work has been done to date using thermal oesophageal pain. My pilot experience with somatic thermal pain was discouraging in that the psychophysics were complex and within the operational safety limits habituation occurred quickly (see fuller discussion of thermal somatic stimulation in the next section).

I therefore elected to use mechanical stimulation of the oesophagus to elicit pain. Pilot work with mechanical stimulation of the oesophagus (balloon distension) showed that this did not cause stimulation artefacts on the ECG; that pain intolerance threshold could be reliably reached and that habituation was easily overcome within safety limits by balloon volume increments. The details of the oesophageal balloon construction are given in the methods section of chapter 3. An example of one of the balloons is shown in figure 2.1. Two different methods of balloon inflation were employed – mechanical pump and manual.

For the brain imaging studies (chapters 5&6) the balloon was inflated with a mechanical pump (medical physics, Hope Hospital) for which the duration time of the

inflation could be changed between either 100 or 250ms according to pain intolerance threshold of the subject. Subjects with higher pain thresholds required longer inflation durations as well as higher pressures. The pressure in the balloon was driven by compressed air with the mechanical pump inflation technique and could be increased in 2 Psi (pounds/square inch) increments. Habituation occurred (i.e. a progressive reduction in the perceived intensity of pain for identical stimuli) with the mechanical pump inflation technique, because it was not possible to compensate for habituation by quickly and accurately increasing pressures between stimuli due to the pumps design. Stimulus pairs (i.e. emotional faces plus balloon distension/non-distension: see chapters 5&6) were randomised across the imaging studies to avoid systematic bias effects on subject ratings of emotional stimuli due to habituation. Balloon volumes were not obtainable with the pump-inflation technique.

The second method of manual inflation using a syringe and 3-way tap [see figure 2.2] was employed in the ANS studies (chapters 3&4). This manual inflation technique avoided habituation by permitting increase of the balloon volume for each stimulus as necessary. Balloon pressures were not obtained with the manual inflation technique so the measure used to indicate stimulus input intensity was balloon inflation volume (mls). The manual inflation technique could not be used for the imaging studies since the randomisation of stimuli and the greater precision of timing of stimulus onset with acquisition of brain activity required a programmed and automated stimulus delivery which was only achieved with the mechanical pump.

Balloon volumes and nail-bed pressures were recorded for each stimulus. It is likely that these parameters are influenced in large part by the biomechanical properties of the tissues themselves as well as those of the balloon material. Hence subjects with a wider diameter and more compliant oesophagus would require larger balloon volumes to reach pain tolerance. Nonetheless differences in measures of balloon volume and nail-bed and balloon pressure may offer some rough approximation of pain sensitivity.

In pilot work, pain-related ANS responses were similar between mechanical pump-driven balloon inflations and manual balloon inflation at pain intolerance thresholds.

Limitations of balloon distension included balloon leakage when 40ml or more of air was introduced (with the manual technique) or when pressures exceeded 30 Psi for 250ms (for the mechanical pump technique) tested ex-vivo. In a few high pain

tolerance subjects, when these levels were reached with the balloon in the distal oesophagus, subsequent volumes extracted on balloon deflation were reduced indicating balloon leakage. This was confirmed after removal of the balloon in these subjects by observing air leakage under water with balloon inflation. In these subjects this meant further pain responses from the distal oesophagus could not be obtained. In effect this limitation also acted as a safety feature since balloons leaked before tissue damage was likely to occur in the oesophagus.

Traction caused by secondary peristalsis on the balloon within the oesophagus induced gagging or coughing occasionally. Balloons additionally sometimes moved with swallowing so that stimuli may not have occurred in exactly the same place. ANS data were viewed and rejected online if contaminated by gagging, coughing or swallowing. For the imaging studies, several stimuli were given before commencing the study to ensure that coughing or gagging was not induced. Furthermore, the image analysis software had inbuilt motion correction procedures to correct for small changes in head position should they be induced by the balloon inflation (see methods sections of chapters 5&6 for further details of motion correction). Finally, the disposable balloon catheters were not fitted with manometric pressure sensors so placement in the oesophagus was based on measurement from the nose/mouth and the knowledge of average oesophageal lengths in adults. It was therefore not possible to be absolutely sure of relations of the balloon to the LOS.

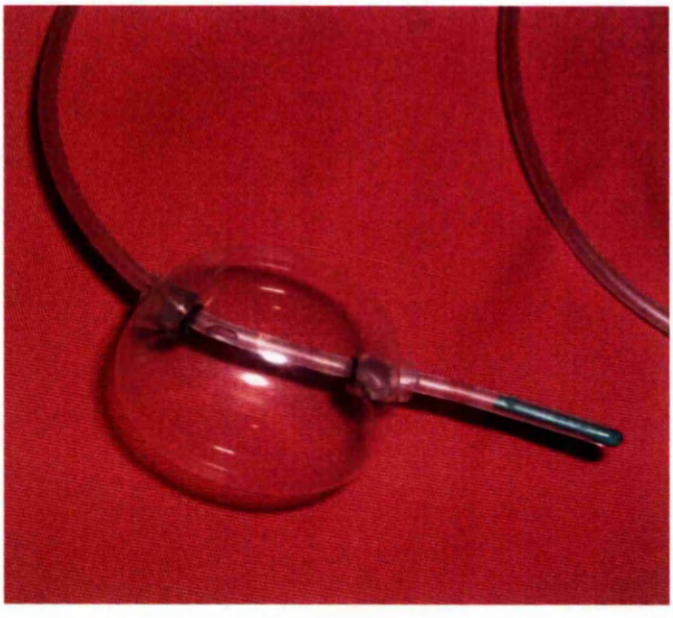

Figure 2.1; example of a balloon used to evoke painful distension of the oesophagus shown here inflated.

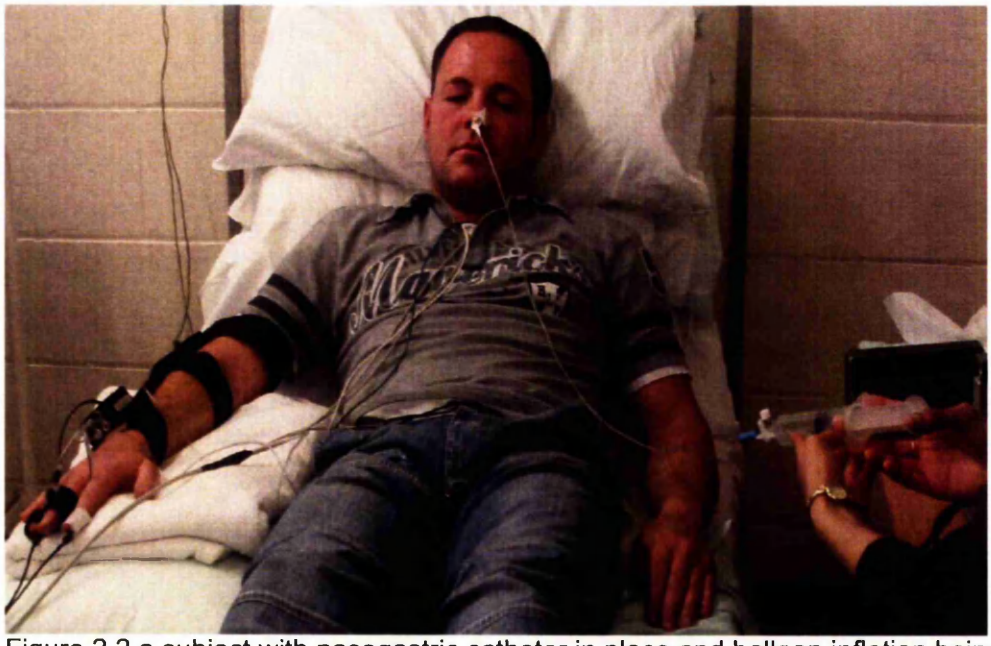

Figure 2.2 a subject with nasogastric catheter in place and balloon inflation being performed manually by means of a syringe and 3-way tap. ECG leads can be seen emerging from the subject's shirt. Digital blood pressure monitor and finger electrodes were attached for skin conductance recordings on the subject's right hand.

Somatic Pain

Somatic pain can be induced by thermal, mechanical and electrical stimuli, with or without the use of sensitising agents (e.g. capsaicin). Much of the direct comparative work between visceral and somatic pain in humans has used thermal cutaneous pain (Strigo et al. 2002; Strigo et al. 2003; Dunckley et al. 2005; Strigo et al. 2005). However in animal studies paw pinch has been a popular model (Pickering et al. 2003).

In pilot work using the Medocs thermal stimulator (TSA-2, Medocs advanced medical systems, Israel), the only commercial MR compatible thermal stimulator available at the time, I found the psychophysical properties of thermal pain unsatisfactory. In particular, it had a safety limit of 50 degrees centigrade and because rapid habituation occurred, pain intolerance thresholds were not reached in many subjects after only a few stimuli. Moreover, the psychophysical properties of thermal sensation were unpredictable in that following initial burning pain, a subsequent stimulus might be perceived as numbness or even sometimes as a cold stimulus. Having made further enquiries from somatic pain researchers it became clear that similar problems existed for laser thermal induced pain if the same skin site was used repeatedly.

With Hope Hospital's medical physics department I developed a manually-operated spring loaded device with attached strain-gauge extension (Mecmesin, UK). A blunt ended probe both delivered and measured focal nail bed pressure (Newton's) [see figure 2.3]. In bench-testing this delivered a reproducibly painful stimulus so nail-bed pressure increments were able to maintain pain intolerance threshold. Furthermore, time characteristics of the stimulus were similar to those of balloon distension, i.e. a slow rise time followed by a rapid offset. Finally comparisons between two mechanical stimuli (nail bed pressure vs. oesophageal balloon distension) have greater face-validity than mechanical vs. thermal or electrical.

A potential limitation of the nail bed pain stimulus was possible characterisation as deep rather than superficial cutaneous pain theoretically minimising differences to visceral pain. Recent theoretical developments highlight overlap of all pain modalities however and previously reported differences to thermal cutaneous pain may be exaggerated due to inadequate pain induction with a thermal stimulus.

In one subject, with small fingers, their thumb was used to achieve sufficient nail-bed pressure since the spring loaded device reached maximum downward pressure before full nail-bed contact was made. Additionally, the equipment was not MR compatible and therefore could not be used in the scanner.

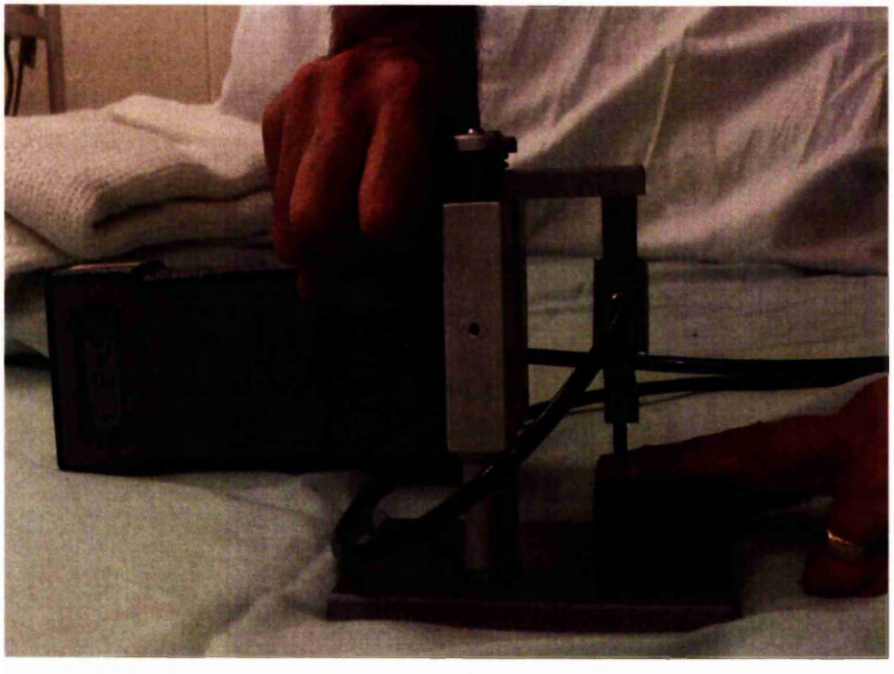

Figure 2.3 a spring loaded nail-bed pressure device with probe pressing on nail-bed. The strain gauge can be seen displaying a pressure of 24.96N which was sufficient in some individuals to reach pain intolerance.

2.1.2 Emotional stimuli

For the studies in chapters 5 and 6, I employed a standardised series of faces depicting facial expressions of varying emotional valence which were developed by Paul Ekman (Ekman and Friesen 1975). For the study in chapter 5 faces depicting the emotional expression of fear and for the study in chapter 6 faces depicting a happy emotional expression were used. Neutral facial expressions were used as the control expression in both studies [figure2.4]. These faces do not overtly affect the subjects rating of their own mood but have nonetheless been shown in functional brain imaging studies to reproducibly activate areas in the brain known to be involved in emotional processes and facial recognition such as amygdala and fusiform gyrus (see section 1.5.3). It could be argued that these faces are not truly emotional stimuli since they do not induce subjective change in subjects' mood. In previous work it has been proposed that the faces have effects on emotional processing and emotional brain networks by providing an emotional priming *context* rather than by a direct effect on mood. Evidence suggests that for primates including humans, facial emotional expressions are powerful social emotional primers (Ekman 2003); also see 1.5.3).

In order to adequately power the imaging studies it was necessary to present 30 of each stimulus-pair combination (emotional/neutral face +/- oesophageal stimulation, see chapters 5&6). Ekman produced only 12 facial identities and so to reduce possible habituation to the facial stimuli, collaboration with the Institute of Psychiatry (IOP) in London was established to produce 8 more facial identities with happy, fearful and neutral expressions to supplement the Ekman faces. These were then FACS coded (Facial Action Coding System (Ekman et al. 2002) by Dr Irwin Lemche at the IOP to ensure they met the same FACS standards as the original Ekman pictures.

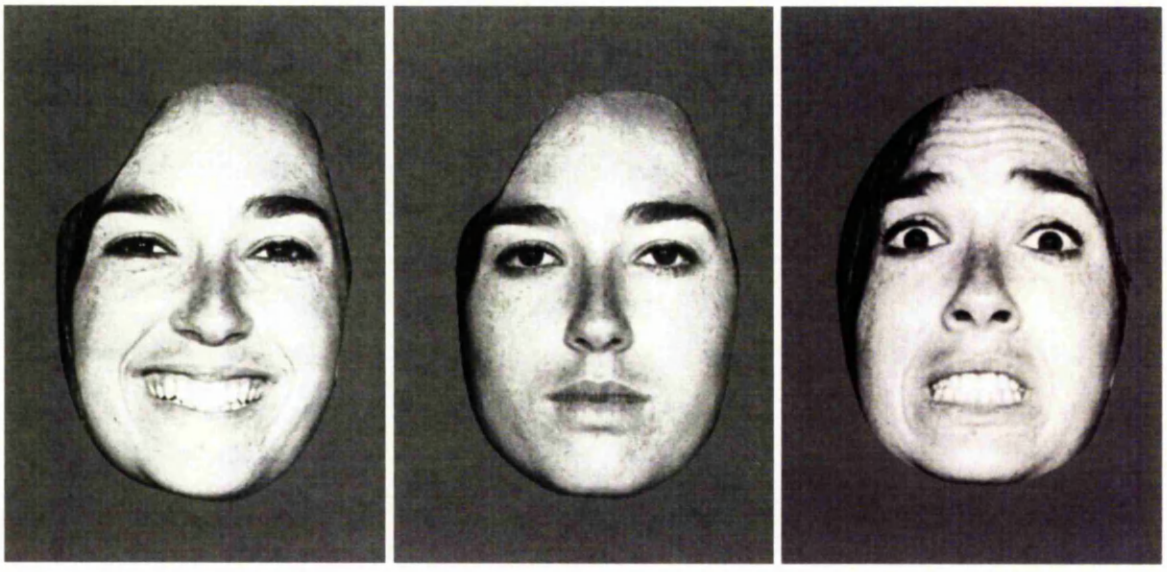

Figure 2.4 One Ekman identity displaying: left panel - happy expression; middle panel - neutral expression; right panel - fearful expression.

2.2 Psychometrics

Verbal report scales

For studies in chapters 3&4 it was not possible for subjects to complete visual analogue scales (VAS) scores of perception of each stimulus. This was firstly because arm movements caused upper limb muscle activity giving rise to ECG artifacts. Secondly, in the study in chapter 4 the right hand was occupied by being attached to blood pressure cuffs and skin conductance electrodes whilst the fingers of the left hand were used for nail-bed stimulation. Verbal report scales were therefore employed for these studies. The anchors were the same as for the visual analogue scales (see next section) but in addition to asking about the pain intensity for each stimulus subjects were also asked to rate it for pain unpleasantness. No artifacts were observed in the ANS recordings when giving verbal responses. At all other times during recording, silence was maintained to minimise distractions and potential for artifacts.

Visual analogue scales

For brain imaging studies in chapters 5&6, on-line visual analogue scales (VAS) were used to record subjects' intensity perceptions for pain, their anxiety levels and that of the intensity of emotional facial expression displayed. The details of the anchors for the VAS are given in the methods section of chapters 5&6 respectively. While in the scanner, subjects practised the use of the VAS before the study started.

Subjects had on average only 6 seconds to respond to the VAS question and they were given several practice stimuli to ensure it was clear that they understood the questions and were responding appropriately. The short time-response window meant it was not possible to obtain responses for both intensity and unpleasantness of pain so only intensity was obtained. The psychometric properties of VAS scores can be improved by altering the weighting at anchors of the scales and also by individualising them (Treutwein 1995; Dionne et al. 2005). These strategies however were not feasible given the time constraints on the subjects' responses.

2.3 Selective parasympathetic measures

The physiological significance and optimal methodology of Heart Rate Variability (HRV) measures, which are the primary selective non-invasive parasympathetic measures available, is a subject of ongoing controversy. Indeed, a recent special issue of biological psychology was entirely devoted to the issue of the measurement and meaning of what was dubbed "cardiac vagal control" (CVC), as derived from HRV (Allen et al. 2007; Chambers and Allen 2007).

Given this methodological and interpretive controversy in this section I will review: (section 2.3.1) the recent development of HRV measures, the range of measures available and the physiological interpretations ascribed to HRV measures (section 2.3.2) an account of the standards for recordings which have been set by international expert consensus, together with an account of methodological pitfalls. I will then focus on the two main CVC methods I have used (section 2.3.3) MXedit (section 2.3.4) Neuroscope.

2.3.1 Heart rate variability (HRV) measures

The beat to beat variation in the heart's inter-beat interval (heart rate variability HRV) can be summarized using simple statistics such as the SDNN (standard deviation of normal-to-normal RR intervals); AAD (average absolute difference of successive RR intervals); rMSSD (root mean square of successive differences in RR intervals) (Hamilton et al. 2004) and coefficient of variation (Jennings et al. 1981). However these do not allow the separation of sympathetic and parasympathetic contributions.

Differentiating activity of extrinsic parasympathetic cardiac control and sympathetic can be achieved from HRV by using several more complex statistical tools including spectral analysis, moving polynomial filters (e.g. MXedit section 2.3.3), Lorenz plots (e.g. section 2.4.1) (Toichi et al. 1997) or phase demodulation (e.g. Neuroscope section 2.3.4) (Little et al. 1999; Hamilton et al. 2004). The most validated and commonly used to date have been spectral analysis and the polynomial filter (Litvack et al. 1995). HRV measures have been employed in multiple applications including a) behavioural studies of stress, attention, learning and cognitive effort; b) physiological studies of exercise, diurnal rhythms and central autonomic control and c) clinical studies of infants at risk, attentional dysfunctions, and cardiovascular disease (Berntson et al. 1993).

Spectral analysis and RSA

Computationally efficient spectral analysis techniques were first used in 1971 to assess "different rhythmicities hidden in RR interval time series" (Malliani 2001) or the "deterministic chaos" of heart rhythm control (Lefebvre et al. 1993). In 1981 it was first used as a quantitative probe of beat-to-beat cardiovascular control (Akselrod et al. 1981) and this has become the predominant model of exploring HRV to date, although its dependence on "complicated mathematical processes that vary among investigations" have reduced its popularity somewhat (Toichi et al. 1997). Several frequencies of rhythm within the RR interval time series have been identified: [see figure 2.5].

1. Ultra-low frequencies (<0.003 Hz) reflecting circadian rhythms
2. Very low frequency (0.003-0.05 Hz) possibly related to thermoregulatory cycles or plasma rennin activity fluctuations
3. mid-low frequency (0.05-0.15 Hz) – these have been suggested to reflect mainly sympathetic outflow (Malliani et al. 1994) but most investigators believe they are of mixed sympathetic and vagal origin (Berntson et al. 1997).
4. High frequency (0.15-0.4 Hz in healthy adult humans at rest) this is the most conspicuous band and is at the respiratory frequency. This frequency band has become synonymous with respiratory sinus arrhythmia (RSA) (Berntson et al. 1997).

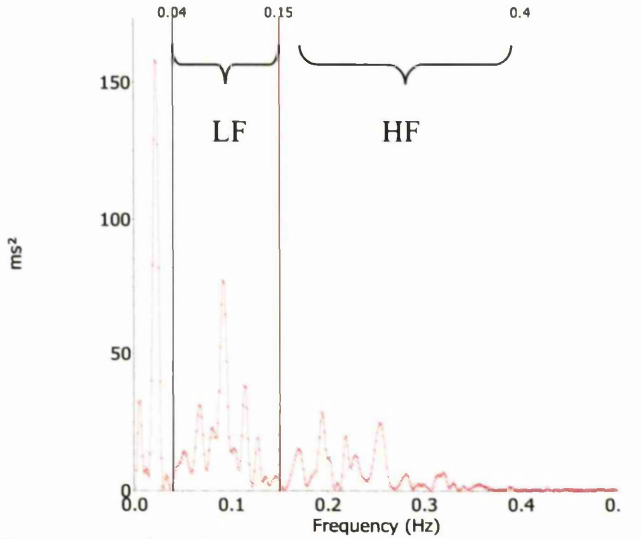

Figure 2.5 an example of a spectral analysis spectrogram derived from digitized ECG, personal data taken from Powerlab. LF = low frequency HF = high frequency.

Unlike the low frequency band it is claimed that there is "practically no debate" that the high frequency band is a vagal-cardiac nerve index (Malliani 2001). Some dissent to this position is mainly in terms of refinement rather than refutation (Grossman and Kollai 1993; Hedman et al. 1995; Sleight et al. 1995; Swenne et al. 1996; Yambe et al. 1999; Taylor et al. 2001; Malpas 2002; Hayano and Yasuma 2003; Pyetan and Akselrod 2003; Grossman et al. 2004; Pyetan and Akselrod 2004). One caveat is that RSA represents parasympathetic cardiac control chiefly when respiratory rate falls within "normal" limits and so should ideally be measured concurrently (Berntson et al. 1997). Within normal limits however it appears unnecessary and for most purposes actually undesirable to control respiratory rate (Denver et al. 2007). Denver et al present data and arguments to support that respiratory rate should not be controlled by paced breathing when CVC is measured, since it artificially elevates CVC, whereas it is not confounded by respiratory rate at spontaneous breathing frequencies (Denver et al. 2007; Porges 2007).

Sympathovagal balance and HF/LF ratios

In the pain and neuroenterology literature, low frequency and LF/HF ratios have been used as measures of sympathetic tone and sympathovagal balance respectively in humans. Since there is good reason to believe these measures do not reflect these physiological properties it is necessary to specifically address them here.

Eckberg (Eckberg 1997) and more recently Porges (Porges 2007) provide a detailed critique of the fallacy of using LF as a measure of sympathetic activity and the LF/HF ratio as a measure of sympathovagal balance. Indeed it is likely that there is a greater parasympathetic influence in the LF than there is sympathetic since it can be blocked by atropine. Indeed it is possible that whilst HF reflects cardiac vagal control arising from the nucleus ambiguus, the LF may reflect dorsal motor vagal nucleus cardiac control (Porges 2007).

The other shortcoming of the HF/LF ratio is that it assumes reciprocal relations between SNS and PNS in cardiac regulation whereas there is good evidence, including that arising from my own PhD thesis (chapter 4) that this is not the case (Berntson et al. 1991; Thayer and Friedman 2002). Nonetheless it is a measure that continues to be used, particularly in GI science circles, and its validity remains questionable.

2.3.2 Standards

Standards and guidelines have been developed for use of HRV in cardiology (1996) which were elaborated and extended for research applications in psychophysiology (Berntson et al. 1997).

The society for psychophysiological research committee report recommended that a minimum of 1 minute recording for high frequency and 2 minutes for low frequency bands be employed and that 5 minutes in most cases was sufficient to establish a baseline and indeed longer epochs themselves become undesirable (Berntson et al. 1997). A recent study has suggested however that as little as 10 seconds of HRV data using simple statistics was a reliable predictor of longer measurements of vagal tone (Hamilton et al. 2004). *"Most of the time and frequency domain analyses in use provide an accurate and common measure of cardiac vagal tone at rest"* (Hayano et al. 1991).

2.3.3 MXedit

Of the extant HRV measures the V-hat technique (Porges 1985) is *"widely used and generates reliable and physiologically sound findings in clinical and non-clinical studies of adult humans"* (Brownley et al. 2000)

Additionally the V-hat technique or "moving polynomial filter" has the advantage of pre-existing sex and age normal values for humans (Byrne et al. 1996).

As outlined in section 1.8.4, this measure has also been used in psychophysiology studies concerned with responses to noxious stimuli. It does not carry an assumption of signal "stationarity" as per spectral analysis which may give a theoretical statistical advantage, but in practice under most conditions they correlate highly.

Given the plethora of experience with the VHAT technique I elected to use it via MXedit software (Porges 1985; Porges 1986), although our laboratory was also equipped to perform spectral analysis using the Powerlab equipment and software. I trained in the use of MXedit by correspondence course and completed an assessment on editing and analysis of 20 pieces of test data. This was reviewed by John Denver (associate Professor with Prof Steve Porges, Chicago) who determined that I had achieved satisfactory levels of accuracy.

The MXedit procedure for RSA quantification involves the following: (adapted from (Austin et al. 2007), [see also fig 2.6] :

1) The R-R series is converted to time-based data by resampling at successive 500-ms intervals.

2) A 21-point moving cubic polynomial filter was stepped through the time-sampled series to produce a smoothed template series.

3) The template series was then subtracted from the original series to produce a residual time series.

4) The residual time series was then processed by a digital bandpass filter with 25 coefficients to extract the variance in the frequency band of .12–.40 Hz (i.e., the frequency of spontaneous breathing for adults).

5) The bandpassed variance was transformed to its natural logarithm and used to quantify RSA.

This procedure truncates the original R-R series by approximately 12-15 seconds at either end and then derives the high frequency (0.12-0.4 Hz) component by application of a moving polynomial filter (Porges-Bohrer). The output is called the "band variance" or the natural log of respiratory sinus arrhythmia (lnRSA). The units are ln (ms^2) where ln = natural log. Normal data for band variance has been published (Byrne et al. 1996).

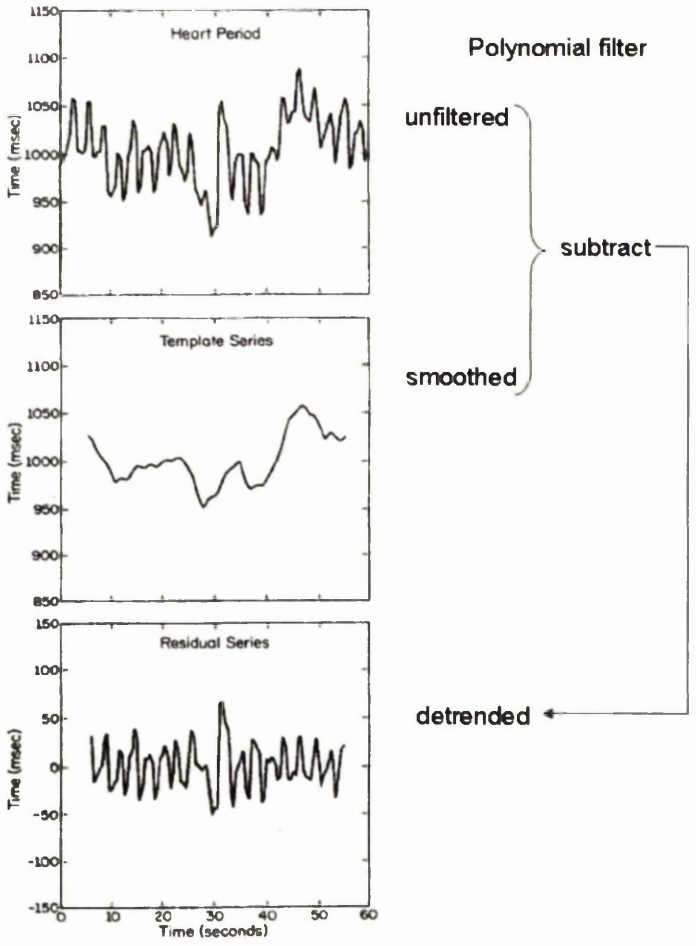

Figure 2.6 Pictorial representation of steps performed by the MXedit program.

2.3.4 Limitations of "breath to breath" RSA techniques

The main limitations of RSA techniques are its temporal resolution (>1 min) and its susceptibility to confounds outside of spontaneous breathing frequencies. Since spontaneous breathing frequencies lie between .12-.4 Hz this measure lacks face validity for shorter time periods where it is unlikely that RSA is the modulating factor in CVC as well as being statistically invalid by international standards.

2.3.5 "Beat-to-beat" measures: Neuroscope

Cardiac Vagal Tone

In my first experimental study (chapter 3), I had access only to the MXedit software and Powerlab equipment to study CVC changes in 1 minute blocks as outlined in chapter 3. It became clear however from observing tachograms of pain responses [figure 2.10 panel A] that most of the cardiovascular response to pain occurred in the first 30 seconds post-stimulus and onset within the first few seconds. From the literature I identified one technique for measuring CVC which claimed to do this on a "beat-to-beat" basis - the "Neuroscope". This uses a new method of measuring CVC and is unique to this system. Given the novelty and potential advantages of beat-to-beat measures over the shorter time period of pain responses I will outline the physiological basis and methodology used in the Neuroscope system for CVC measurement.

As has been shown in section 1.8.4, the primary determinant of beat-to-beat HRV is CVC modulated by the baroreflex. Eckberg thoroughly investigated the relationships between R-R intervals (or P-P as he called them) and blood pressure and discovered that the amount of baroreceptor driven CVC modulation could be determined from a knowledge of the "phase shifts" or "pulse synchronised fast alterations" in R-R intervals (Eckberg 1976) [figure 2.7].

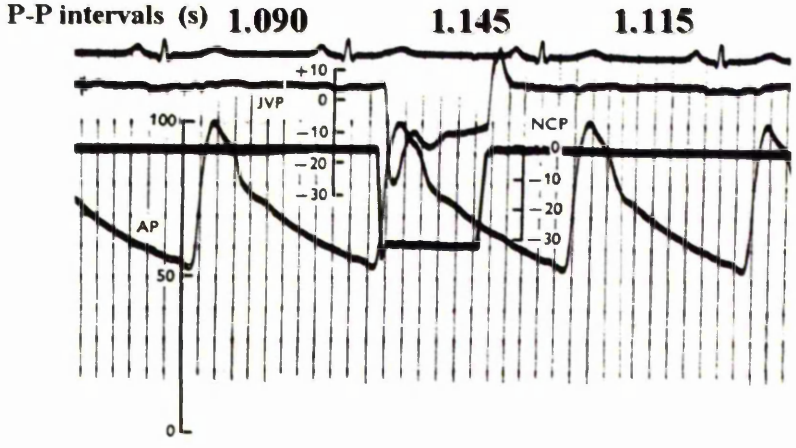

Figure 2.7 the pulse synchronized fast alterations in P-P (R-R) intervals are caused by baroreceptors and mediated through vagal tone (Eckberg 1976). JVP = jugular venous pressure NCP = neck chamber pressure AP = arterial pressure.

Julu et al have applied this physiological principle to the non-invasive beat-to-beat measurement of CVC firstly in dogs (Little et al. 1999) and subsequently validated it in humans and have since used it in clinical settings (Julu 1992; 2001; Julu et al. 2003). Pharmacological validation was performed in humans using atropinisation. By titrating the dose of atropine to diminution of CVC a "linear vagal scale" (LVS) was produced (Julu 1992) [figure 2.8]. Neuroscope has labelled this output "CVT" i.e. cardiac vagal tone. It has recently been suggested that the generic term for all measures of parasympathetic efferent cardiac influence should be called cardiac vagal control (CVC) (Chambers and Allen 2007) but I will use the Neuroscope terminology for this CVC measure when it is used to distinguish it from others such as that of MXedit.

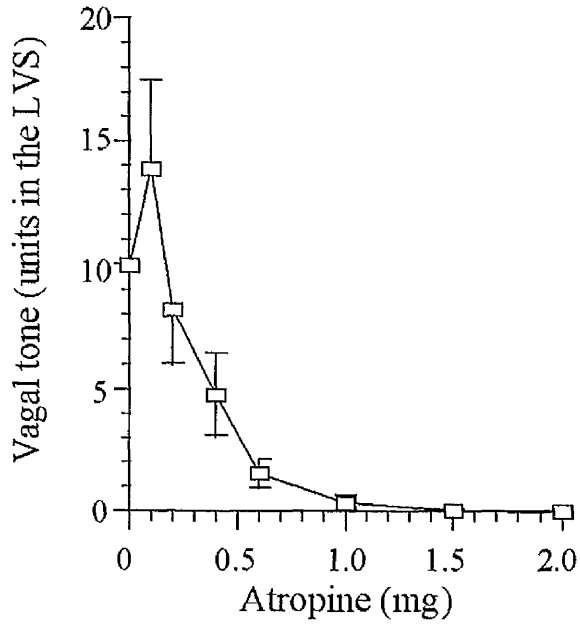

Figure 2.8 atropinisation and Linear vagal scale of beat-to-beat CVC measure

Cardiac sensitivity to baroreflex

The hardware and software for measuring CVT, namely voltage controlled oscillators to detect phase shifts in R-R intervals (Little et al. 1999), were built into a commercially available biosignals acquisition system, Neuroscope (Medifit Instruments Ltd, London, UK). This also incorporates digital artery beat-to-beat blood pressure from the "Portapress" system (Finapress Medical Systems, Copenhagen). From this, the Neuroscope uses the raw analogue Portapress waveform to calculate the arithmetic mean (as opposed to the MAP used clinically as diastolic + 1/3 systolic pressures). The arithmetic MAP is the mean of all pressures DP-SP-DP1 [see figure

2.9]. It integrates R-R series with the blood pressure to calculate the change in pulse interval per unit change in systolic pressures on a 10sec moving average, using the formula: (RR2-RR1)/(SP2-SP1) ms mmHg-1 [figure2.9]. This is called the Cardiac Sensitivity to the Baroreflex and is a putative measure of afferent vagal sensitivity.

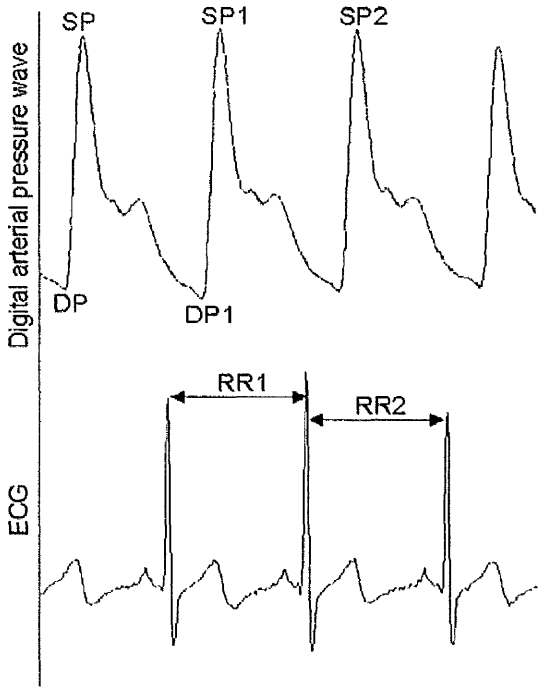

Figure 2.9 MAP =arithmetic mean of all pressures DP-SP-DP1; CSB = change in pulse interval per unit change in systolic pressures (10sec moving average (RR2-RR1)/ (SP2-SP1) ms mmHg-1) (Julu et al. 2003).

Pilot data

On obtaining the neuroscope equipment it was possible to observe beat-to-beat changes post-stimulus in CVT and CSB [figure 2.10 panels B&C]. Neuroscope also allowed consecutive responses for individuals to be overlaid. Figure 2.10 panel D shows 10 consecutive CVT responses to balloon distension in a subject who reproducibly increased CVT to oesophageal pain. In figure 2.10 panel E a subject's data is shown from pilot work with 10 averaged responses to pump-driven painful oesophageal inflations (100-250ms) and syringe inflated painful oesophageal inflations repeated on two occasions. This subject had high resting CVT and a reproducible CVT withdrawal to oesophageal pain. In figure 2.10 panel F a different subject is shown under the same conditions as for panel E, but this subject had quite

a different but equally reproducible pattern of responses to oesophageal pain with a low baseline CVT and an increase in CVT to pain.

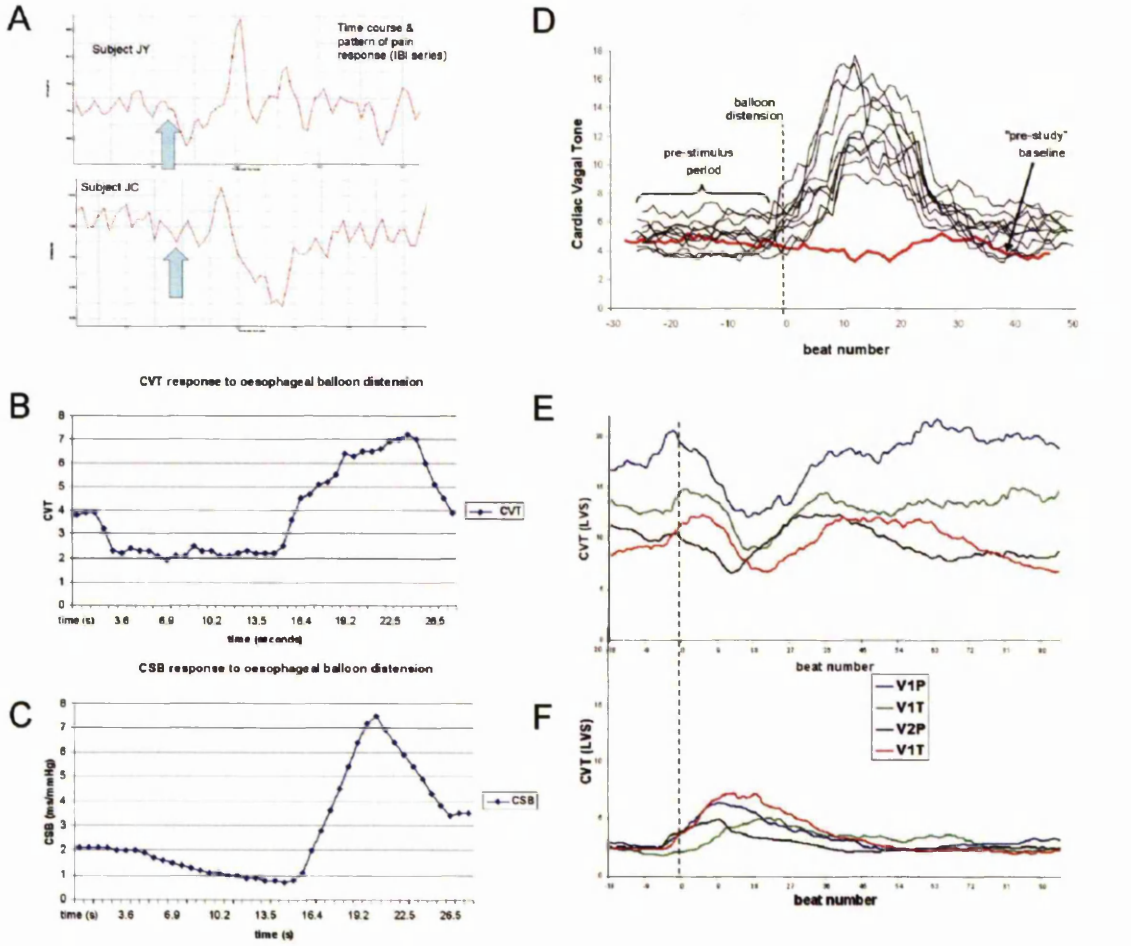

Figure 2.10 **A**: tachograms of cardiac interbeat interval response to pain in 2 subjects. Arrows mark onset of oesophageal balloon distension. **B**: Neuroscope beat-to-beat cardiac vagal tone (CVT) which is a measure of cardiac vagal control (CVC). This is shown following oesophageal balloon distension in 1 subject. **C**: Cardiac Sensitivity to the Baroreflex in one subject measured following oesophageal balloon distension with Neuroscope. **D**: 10 consecutive beat-to-beat CVT responses to oesophageal pain in one subject overlaid with baseline CVT shown in red. **E&F** Average of 10 consecutive CVC responses to oesophageal pain in 2 subjects: subject E has high baseline CVT and CVT withdrawal in response to oesophageal pain. Subject F has low baseline CVT and increases CVT to pain. V1P (blue) = visit 1 phasic balloon stimulation. V1T (green) = visit 1 tonic balloon stimulation. V2P = visit 2 phasic balloon stimulation. V2T = visit 2 tonic balloon stimulation.

Future possible developments

As alluded to in the section dealing with sympathovagal balance, there is evidence that it may be possible to dissect the nucleus ambiguus and dorsal motor nucleus brainstem cardiac vagal motoneurone complex influences from HF and LF HRV respectively (Porges 2007). Certainly there is scope for the application of more sophisticated chaos theory driven mathematical algorithms to HRV (Zhong et al.

2004; Hoyer et al. 2007) facilitated by a dynamic systems perspective (Thayer and Friedman 2002).

2.4 Selective sympathetic measures

It has been shown that the sympathetic nervous system cannot be assumed to act in a unitary manner, and indeed there is evidence that various sympathetic subsystems can produce nuanced patterned responses (section 1.8.5). The chief sympathetic sub-divisions measured in my studies are cardiomotor, vasomotor and sudomotor.

2.4.1 Cardiomotor

As outlined above, in the paragraph on sympathovagal balance, the popularly used LF HRV measure is not a valid index of SNS tone. A more promising measure which I have used in my studies (chapters 3&4) is the recently validated but as yet not widely disseminated Cardiac Sympathetic Index (CSI) (Toichi et al. 1997). The CSI is based on the "Lorenz plot" [figure 2.11]. In the Lorenz plot, R-R fluctuations are plotted into an ellipsoid figure where the length of the transverse axis "T" reflects beat-to-beat variation in the tachogram, while the longitudinal axis "L" reflects the tachogram fluctuations' overall amplitude. The CSI is the L/T ratio and is sensitive to sympathetic blockade. This pharmacological validation in humans held up for segments of data 100 R-R intervals long (i.e. just over 1 minute segments). Hence the currently validated time resolution of the CSI is 1 minute but its underlying physiological basis is unclear at present although it is not affected by atropine whereas it is by sympathetic blockade (Toichi et al. 1997). It therefore appears to be primarily a sympathetic cardiomotor measure.

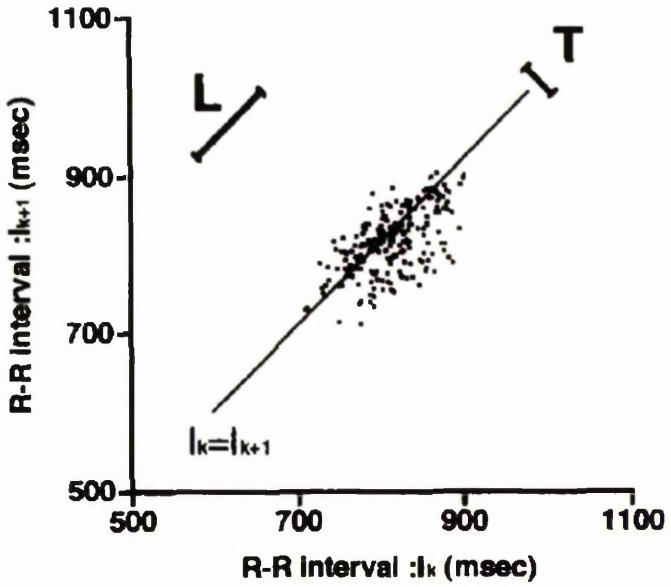

Figure 2.11 Lorenz plot: the transverse axis, T, reflects beat-to-beat variation in the tachogram, while the longitudinal axis, L, reflects the overall amplitude of the fluctuation in the tachogram (Toichi et al. 1997).

2.4.2 Vasomotor

Mean arterial pressure (MAP) pain responses were recorded in studies in chapters 3&4. The MAP has been shown to correlate with invasively recorded sympathetic activity assessed by microneurography (Janig and Habler 2003). It should be emphasised however that this is continuously *measured,* i.e. arithmetic MAP, and not the *calculated* proxy i.e. diastolic + 1/3 systolic-diastolic. The "Portapress" records non-invasive digital arterial waveforms using a photo-plethysmographic cuff. These have been validated against invasive arterial pressure in humans and found to correspond well under normal conditions. The recordings are susceptible to poor peripheral circulation and poor cuff size or position placements.

The analogue beat-to-beat Portapress waveform was transferred to the Neuroscope system where it was digitised. Neuroscope then measured the arithmetic MAP as the mean of all pressures DP-SP-DP1 [see figure 2.9].

It is not possible to be sure that dips in MAP seen after pain (chapter 4) are due to genuine drops in systemic MAP or simply due to digital artery spasm reducing signal.

2.4.3 Sudomotor (SCR)

Skin conductance response (SCR) measurement has been used for more than 100 years and is a measure of selective central sympathetic control over sweat gland activity. It is easy to acquire and can be characteristic of individuals: "stabiles" who habituate quickly and "labiles" who have lots of spontaneous SCR activity and slower habituation (Cacioppo et al. 2000).There are two main methods of SCR acquisition, firstly to measure spontaneous impedance changes across digits (usually called GSR or Galvanic Skin Response) or secondly to pass a small constant current across the digit and record impedance changes to this current crossing the digit (usually called the SCR skin conductance response) – the latter is felt to be more reliable. A commercially available SCR acquisition system – the Powerlab system (AD instruments) was used which employs the constant current approach and measures changes in impedance in micro Siemens (uS)

Care must be taken when preparing skin for the SCR measurements since astringent wipes, such as alcohol, can interfere with response characteristics. I simply wiped fingers with warm water beforehand.

SCR can be acquired from many sites including distal limbs and groin areas but digits were the most convenient. In the study in chapter 4 the right hand was used since this was already being used for finger cuff recordings for blood pressure and the left hand for nail bed stimulation. No SCR artifacts were seen from concomitant use of the blood pressure cuff and equipment.

A number of parameters of the SCR response can be measured including latency and amplitude of response, rise time, mean and slope as well as the number of spontaneous SCR events [figure 2.12]. It became clear in pilot work that measures of latency and amplitude were both laborious and open to subjective decisions as to where departure from baseline occurred and which peak to use for amplitude in multiphasic responses. I therefore opted to use the simpler measure of mean SCR for the study in chapter 4.

SCR responses are non-specific and can be initiated by inspiratory gasps or coughs or by any novel stimulus. It was essential therefore to avoid disturbances during the study which might give rise to non-pain stimulus related SCR changes. This was achieved by performing the studies in a quiet, sound proofed and locked laboratory; by keeping conversation to a minimum other than when giving instructions or eliciting responses; by keeping the recording digits still and rested on a cushion

and under constant observation for movement related artifacts; and by rejection of stimuli contaminated by coughing, sneezing or gasps.

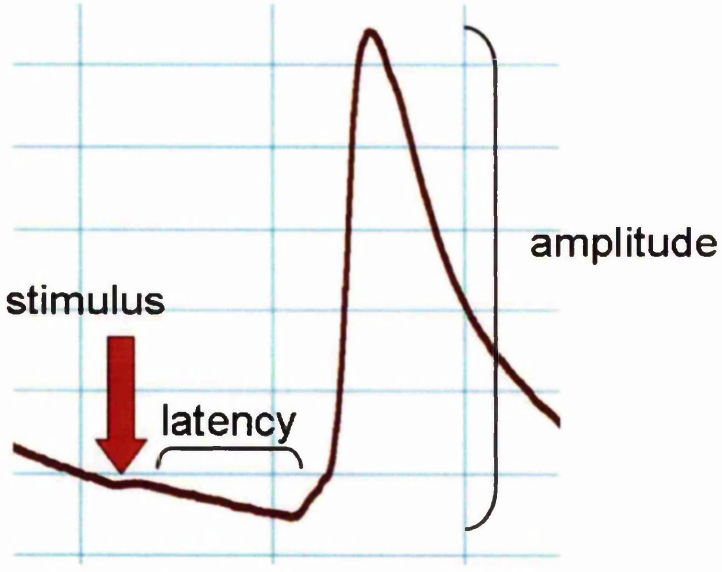

Figure 2.12 SCR response, pilot data

2.5 Functional brain imaging

A general critique of the role of imaging in functional localisation in cognitive neuroscience and the subtraction analysis technique is given in section 7.3.5. Detailed accounts of the data registration techniques, artefact detection and resolution and further BOLD analysis techniques are given in experimental chapters 5&6 methods sections.

2.5.1 Overview (MEG, fMRI, PET, EEG CEP)

A number of non-invasive brain imaging techniques are currently available for measuring different types of brain physiological activity non-invasively in humans and each has its own strengths and weaknesses which I will briefly outline here. On balance for the purposes of my studies, functional magnetic resonance imaging (fMRI) was the best option, particularly since my main interest was in sub-cortical structures involved in ANS responses and implicated in personality differences, in particular the amygdala.

Brain electrical activity is recorded by Cortical Evoked Potentials (CEP) and electroencephalography (EEG) whereas electromagnetic activity is recorded by magnetoencephalography (MEG). Positron emission tomography (PET) records metabolic activity in the brain indirectly through the use of radiolabelled isotopes

injected peripherally in the blood which cross the blood-brain barrier. Functional Magnetic Resonance Imaging measures the change in endogenous brain contrast due to the relative amounts of oxy and deoxyhaemoglobin - the "BOLD effect".

Recently, combinations of these techniques have been used such as fMRI and EEG and MEG/EEG concurrently. The most expensive, unwieldy and hazardous of these techniques is PET whilst the simplest is CEP. CEP however gives very limited information spatially of the anatomic sources of brain activity, although its time resolution is excellent. EEG has similar time resolution but superior spatial resolution to CEP whilst MEG has still better spatial resolution but both remain limited currently to surface cortical sources. The spatial resolution of fMRI is better than both EEG and MEG and is not limited to cortical structures but its time resolution is in the order of seconds rather than milliseconds. Hence different techniques and combinations of techniques have advantages for different experimental conditions.

2.5.2 Functional magnetic resonance imaging (fMRI)

fMRI is based on the blood oxygen level dependent or "BOLD effect". In brief, this works on the principle that in a changing external magnetic field produced by the scanners magnet, in the case of my studies a 3 Tesla magnet, molecules within the brain can be magnetised in turn and induced to oscillate or "precess" and then relax. Haemoglobin is the red blood cell borne iron pigment containing protein that dissociably transports oxygen and carbon dioxide in the blood stream to and from cells as substrate and by-product respectively of mitochondrial based respiration. More metabolically active tissues will net consume oxygen and produce carbon-dioxide, however in the brain this induces dilatation of local blood vessels and a net influx of more oxygenated/less deoxygenated blood – hence paradoxically the oxy/deoxy haemoglobin ratio is higher in metabolically active brain tissues. Oxygenated and deoxygenated haemoglobin precess and relax at slightly different rates which produces an endogenous contrast effect that is affected by the relative proportions of oxy to deoxy haemoglobin. Hence statistical algorithms can be applied which quantify the BOLD effect and extrapolate to brain areas more metabolically active than others at a given time.

2.5.3 Methodological limitations of fMRI

fMRI is limited by the equipment that can be used safely (must be non-ferromagnetic or strongly bolted down) or meaningfully (the magnet can interfere with concurrent biosignals).

The scanner is a noisy and claustrophobic atmosphere which some subjects can find quite distracting or unpleasant. To circumvent this problem, subjects were recruited that had either participated in fMRI studies previously or had an advance visit to lie in the scanner to familiarise themselves. In addition, subjects with pacemakers or implanted ferromagnetic metal were excluded from the study.

2.6 Psychological trait measures

In chapter 3, several psychological trait measures were used whereas chapters 4, 5 and 6 focused on personality traits. This was because personality traits appeared to have the most biological salience and the other measures, such as anxiety are measures of negative emotionality which appear in factor analysis to be related to neuroticism anyway.

Big Five Inventory (BFI)

The 44 item BFI (John et al. 1991; Benet-Martinez and John 1998; John and Srivastava 1999; McConochie 2007) was developed to allow efficient and flexible assessment of the 5 main personality dimensions (Extroversion, Neuroticism, Agreeableness, Openness, Conscientiousness) when there is no need for more differentiated measurement of individual personality facets. It takes only a few minutes to complete. It is freely available in the public domain.

It was developed by Oliver P. John and consists of 44 brief personality descriptors to which the test-taker responds with degree of agreement or disagreement on a 5-point Likert scale. It has been normed on several hundred thousand adult Americans by Sam Gosling and J Potter (Gosling and Potter 2007). Differences between ethnic groups are generally insignificant. Slight variations occur by age from scale to scale.

In analysis only the neuroticism and extroversion subscales were used since these were the ones identified theoretically to be most likely linked to pain and emotion processing. These were used in all 4 studies. The BFI is included in the appendix of the thesis.

Sensory processing

Dunn's "model of sensory processing" incorporates self reported individual differences in putative "nervous system thresholds for acting" in combination with the persons propensity for responding to those thresholds - their "responding strategy". High thresholds are linked to habituation and low thresholds to sensitisation (Dunn 2001) [figure 2.13]. This cognitive construct has features in common with "sensation seeking", "sensory defensiveness" and sensory processing style models and measures (Kinnealey et al. 1995; Aron and Aron 1997; Jerome and Liss 2004; Stelmack 2004). The four "anchor point" factor structures which are derived from this model show significant trait stability over time and considerable convergence with established temperament and personality literature (Dunn 2001). In addition the four distinct sensory processing factor structures show distinct patterns of amplitude and habituation responses in skin conductance measures (Brown et al. 2001).

This was used only in chapter 3. The Sensory processing style questionnaire is included in the appendices at the end of the thesis.

	Responding/Self-Regulation Strategies	
Thresholds/Reactivity	Passive	Active
High	Low Registration	Sensory Seeking
Low	Sensory Sensitivity	Sensory Avoiding

Figure 2.13: Dunn's model of sensory processing

Anxiety Sensitivity Index (ASI)

Another self-report cognitive construct which attempts to bridge the psychological-biological divide is the "anxiety sensitivity index" (Reiss et al. 1986). This is largely based on interoceptive acuity and beliefs and in particular has been used to predict psychophysical and physiological responses to a CO2 challenge

(Zvolensky et al. 2001). This was only used in chapter 3. The ASI questionnaire is provided in the appendix.

Spielberger state and trait anxiety index (STAI-ST)

The Spielberger State and Trait Anxiety questionnaire is a very widely used self-report questionnaire. As may be expected the state questionnaire asks how anxious the subject feels at the present moment whereas the trait questionnaire enquires about longer term feelings of anxiety (Spielberger 1983). Some authorities suggest that trait anxiety and neuroticism are virtually synonymous and interchangeable. I found this to be true in the first ANS study (chapter 3) although there seemed to be additional explanatory power for neuroticism. Separate trait anxiety measures were therefore dropped from the further studies. The STAI-ST questionnaires are provided in the appendix.

Limitations of self-report questionnaires

Self-report questionnaires have been criticized as relatively blunt instruments open to a number of problems. Two of the most well documented limitations are "social desirability" and recall bias. Social desirability is a problem particularly for measurements of trait anxiety when subjects high in social desirability will over-report anxiety (Weinberger et al. 1979). Structured interviews and completion of questionnaires by third party acquaintances of the subjects or use of the "Weinberger adjustment inventory" can improve the accuracy of these but also add to the logistical complexity of a study.

Given the well documented success of personality self-report measures in particular in both cognitive neuroscience and psychophysiological studies the theoretical limitations on their use appeared and proved to be acceptable. A generic critique of psychological construct measurement is given in chapter 7.

Chapter 3 Personality differences affect autonomic responses to visceral pain

Prologue to chapter 3

This first study in my thesis introduces four primary themes: 1) visceral pain 2) autonomic responses 3) individual differences in pain perception and response 4) the influences of personality and its biological substrate. In chapter 4 these foundations are built on in a comparison of visceral and somatic pain. In chapters 5&6 central concomitants of visceral pain as modulated by personality are considered and additionally the relationships between personality, pain and emotion are addressed.

3.1 Abstract

Background Brainstem autonomic nuclei integrate bodily interoceptive inputs, including pain, with descending sub-cortical and cortical modulation. They also in turn produce homeostatic and defence outputs to the body. In the "Polyvagal" framework, brainstem Cardiac Vagal Control (CVC) in particular is a major psychophysiological hub for affiliative and defensive behaviour. Heart Rate Variability measures provide non-invasive windows during pain and emotion onto this mind-body interface. **Aim** to determine if endophenotypic psychophysiological profiles exist for visceral pain in adults. **Methods** 19 healthy subjects had electrocardiogram (ECG) and skin conductance responses (SCR) recorded at rest and to 10 painful oesophageal balloon distensions. A moving polynomial filter was applied to the ECG inter-beat interval series to determine CVC originating from the nucleus ambiguus (CVC_{NA}). Heart rate and the "Cardiac Sympathetic index" (CSI) were also determined. Psychological state and trait measures including neuroticism and extroversion scores were assessed. **Results** Cluster analysis identified two psychophysiological groups: Group 1: (n=11) at baseline demonstrated lower baseline CVC_{NA} ($p=0.0001$) but higher HR ($p=0.02$) and CSI ($p=0.015$). They were intolerant of pain at lower balloon volumes ($p=0.04$) and pain induced a trend towards increased CVC_{NA} ($p=0.1$) but an attenuated HR response ($p=0.01$). Group 2 (n=8) demonstrated the converse psychophysiological baseline and pain responses. Neuroticism scores were higher ($p=0.0004$) and extroversion lower ($p = 0.01$) for group 1 in comparison to group 2. **Conclusions** This study provides evidence for two distinct psychophysiological response profiles to visceral pain which are influenced by personality. These may

reflect the psychobiological basis of active and passive defence repertoires and also be possible vulnerability factors for pain and emotion disorders. The prevalence and clinical relevance of these endophenotypic psychophysiological profiles for visceral pain warrant further exploration.

3.2 Background

Pain is a complex psychophysiological phenomenon comprising sensory-discriminative, affective-motivational and cognitive-evaluative dimensions together with behavioural and physiological responses (Melzack and Casey 1968; Melzack and Katz 1999). Pain is also a common clinical problem that is often medically unexplained. Chronic visceral pain conditions, such as irritable bowel syndrome, are frequently co-morbid with affective disorders such as anxiety and depression (Drossman et al. 1999; Bair et al. 2003).

Recently pain has been redefined as a "homeostatic emotion" which overlaps and interacts with a range of emotions as diverse as satiety and fear (Craig 2003). "Homeostatic emotions" share psychological, anatomical and physiological features including cortical and sub-cortical substrates. Cortical structures especially implicated are the so-called "interoceptive" insula cortex and the "homeostatic motor" anterior cingulate cortex (Mayer et al. 2006). A common effector for homeostatic emotions is the "emotional motor system" which includes the central autonomic network, autonomic nervous system, and the neuro-endocrine-immune systems (Holstege et al. 1996; Mayer et al. 2001).

Group differences in pain sensitivity exist between healthy and clinical chronic pain populations, however wide inter-individual differences make this behavioural measure diagnostically insensitive and non-specific for individual patients (Hobson et al. 2006). There is therefore a pressing need for improved biomarkers and a better mechanistic understanding of differences in pain perception and response. These could then be applied in both healthy subject studies and as clinical discriminators in patients.

Functional brain imaging has provided insights into cortical pain processing and individual differences, however spatial and temporal resolution is limited and the functional significance of brain activation is unclear (Derbyshire 2000; Peyron et al. 2000; Hobson and Aziz 2004). Furthermore, functional imaging is poorly

characterised at brainstem level where sensory and autonomic output nuclei are crucially involved in the integration of incoming interoceptive bodily signals, including pain, with sub-cortical and cortical descending modulatory responses, and in turn with homeostatic and defence motor outputs to the body (Benarroch 1993; 1997; 2001; 2006). Selective, non-invasive, event time-locked and functionally relevant indirect observation of specific brainstem autonomic nuclei activity is possible via measurement of their autonomic outputs. For example heart rate variability measures, inherent in the electrocardiogram, can provide selective information about the brainstem nucleus ambiguus (NA) outflow involved in cardiac vagal control (CVC_{NA}) (Porges 2007).

Traditionally, research exploring defence responses, including for pain, has emphasised the "fight-flight" pattern with its associated behavioural activation, sensitisation and sympathetic nervous system (SNS) reactivity (Bracha 2004; Bracha et al. 2004). There is a growing appreciation however of the hierarchical superiority of inhibitory control over behavioural activation systems such as the SNS. This includes inhibition or conversely disinhibition especially from pre-frontal cortices, together with parasympathetic nervous system activity in a variety of "freeze" defence responses and also in affiliative behaviour (Bandler et al. 2000; Bandler et al. 2000; Gray and McNaughton 2000; Paton et al. 2000; Lumb 2002; Thayer and Friedman 2002; Corr 2004; Lumb 2004; Paton et al. 2005; Paton et al. 2006; Porges 2007; 2007). Indeed such a rich repertoire of overlapping behaviours are associated with this limb of the system that nomenclature for defence alone is somewhat confusing and includes freeze, vigilance, quiescence, cautious-approach, tonic-immobility, fright, faint, and passive coping.

"Polyvagal" theory is a teleological-adaptive framework which provides evidence for the hierarchical and phylogenetic development of the brainstem cardiac vagal complex. This progressive elaboration of brainstem cardiac vagal control is implicated in the facilitation of increasingly complex behavioural repertoires (Porges 2007; 2007). The vagus is primarily a sensory nerve which wanders, as its name suggests, over vast tracts of the body to innervate the viscera. The destination sensory nucleus in the brainstem is the nucleus of the solitary tract (NTS). The vagus also has two brainstem motor nuclei. The nucleus ambiguus (NA) gives rise to myelinated fast-effector neurones which innervate the heart, larynx and upper gut, whilst the dorsal motor vagal nucleus (DMX) gives rise to unmyelinated slow effector

neurones innervating the heart and lower gut. The DMX output results in a profound bradycardia, akin to an "emergency stop" in driving. This occurs in immobilisation behaviours such as death feigning and passive avoidance and is considered from a teleological-adaptive perspective to be a very primitive defence response (Porges 2001). In contrast the NA output (CVC_{NA}) allows for more subtle beat-to-beat heart rate modulation. Increased CVC_{NA} causes more modest slowing of the heart rate than does the DMX and may be involved in behavioural inhibition and bonding. Withdrawal of CVC_{NA} reduces the external constraint on intrinsic sino-atrial node (SA) automaticity and therefore a faster heart-rate ensues to facilitate behavioural activation.

The primary physiological function of CVC_{NA} appears to be the "beat-to-beat" control of heart rate to achieve blood pressure regulation and orthostatic tolerance. The mean blood pressure from each consecutive heart beat is sensed by arterial baroreceptors that evoke a NTS mediated vago-vagal reflex. This reflex adjusts CVC_{NA} control for the following heart beat and thereby the inter-beat interval and heart rate. Heart rate in turn is a primary determinant of cardiac output and, together with systemic vascular resistance, the resultant blood pressure (Janig 2006).

Further vago-vagal reflexes evoked by direct inputs to the NA from pulmonary stretch receptors during lung inflation, arterial chemoreceptors and respiratory neurones result in "breath-to-breath" CVC_{NA} modulation. This gives rise to respiratory sinus arrhythmia (RSA) which is the basis for the vast majority of CVC_{NA} measures (Allen et al. 2007).

Given the primary role of "beat-to-beat" and "breath-to-breath" CVC_{NA} modulation in blood pressure control and cardio-respiratory integration, it is unsurprising that abnormal CVC_{NA} has been found in cardiovascular disease, chronic obstructive airways disease, diabetes and with increasing age and reducing fitness (Masi et al. 2007; Thayer and Lane 2007).

However, there are also direct or NTS mediated inputs allowing for modulation of CVC_{NA} from 1) the amygdala in emotional responses; 2) the peri-aqueductal gray matter in defence responses; 3) the hypothalamus in other aspects of homeostatic function; and 4) facial and laryngeal receptors in communication (Julu 2001; Porges 2007). In addition therefore to the "organic disease" relations of CVC_{NA} already mentioned it is also unsurprising that CVC_{NA} abnormalities have been observed in unstable infant temperaments, in individual differences in neonatal pain reactivity, in

emotional reactivity and in chronic pain and affective disorders (Chambers and Allen 2002; 2007; Rottenberg 2007).

It is thus apparent that CVC_{NA} is a psychophysiological hub for which heart rate variability (HRV) measures permit non-invasive windows onto the mind-body interface (Chambers and Allen 2007).

Personality traits are dimensions of individual difference for which several lines of evidence point towards a biological basis (Eysenck 1967). In particular personality is heritable; subject to limited parental influence; similar in structure across cultures and even species; it is broadly temporally stable but also changes trans-culturally with age (McCrae et al. 2000).

Two of the most studied and pervasive dimensions of personality are extroversion-introversion and neuroticism-emotional stability. Neuroticism is a measure of negative emotionality (Eysenck 1967) that correlates negatively with HRV through pleiotropic genetic effects (Riese et al. 2007). HRV itself has been linked to genetic polymorphisms in the choline transporter (CHT-1 R) together with "limbic" reactivity (Neumann et al. 2006) which in turn has been separately linked to neuroticism via genetic differences in the serotonin transporter protein (SERT-P) system (Hariri et al. 2002). Personality differences have also been found in pain sensitivity and coping both in experimental and clinical settings (Costa 1987; Costa and McCrae 1987; 1987; Aron and Aron 1997; Okpa et al. 2003; Goubert et al. 2004; Ramirez-Maestre et al. 2004; Zautra et al. 2004; Calabrese et al. 2006; Raselli and Broderick 2007).

Since the perception of pain can be interpreted differently among individuals, personality traits and HRV represent promising inter-related biomarkers for differences in pain perception and response. The aim of this study was to explore whether endophenotypic psychophysiological profiles exist for pain in adults by determining the effect of personality on brainstem autonomic output response profiles to visceral pain.

3.3 Methods

3.3.1 Subjects

19 healthy volunteers participated (8 male ages 22-54). Ethics approval for the study was given by Central Manchester Local Research Ethics Committee (ref 07/Q1407/3). Full informed consent was obtained. Subjects were recruited by advertisement and were reimbursed for their time and trouble. Subjects were informed of exclusion criteria by information sheet. These included a history of current or chronic gastrointestinal, neurological or psychiatric medical problems or taking any medication affecting GI, pain or neuropsychological function by use of information. Absence of exclusion criteria was confirmed by brief informal verbal questioning.

3.3.2 Psychological traits and state

Subjects completed the Big Five Inventory, a 44 item personality questionnaire based on the five main personality dimensions of neuroticism, extroversion, agreeableness, openness and conscientiousness (John et al. 1991; Benet-Martinez and John 1998; John and Srivastava 1999). Only the subscales of neuroticism and extroversion were used in the subsequent analysis since there is broad consensus regarding these 2 dimensions in most personality schemata, and they have established links with chronic pain, emotion and GI conditions and therefore potentially more psychophysiological relevance (Eysenck 1967; Ormel et al. 2004; Yousfi et al. 2004). State and trait anxiety were also assessed using the Spielberger state-trait anxiety scores, and anxiety and sensory sensitivity scores (Spielberger 1983; Reiss et al. 1986; Dunn 2001). Trait anxiety is the likely dominant sub-factor of Neuroticism (Stelmack 2004); anxiety sensitivity focuses on the bodily sensations of anxiety whereas sensory sensitivity focuses on trait sensitivity to everyday sensations.

3.3.3 Painful oesophageal balloon distension

Oesophageal balloons were assembled from 3 cm lengths of thin silicone tubing (Medasil UK) tied and glued 0.5cm at each end over perforations 2cm from the end of a commercially available nasogastric tube (Pennine Healthcare Ltd, 2.7 mm, 120cms) thus creating a 2cm diameter balloon. The tube was swallowed either per-orally or trans-nasally according to subject preference and the balloon was positioned 30cm ab orus (mid/lower oesophagus). No local anaesthetic was used for the

intubation but passage was eased through the nasopharynx with a water-based lubricant jelly (KY jelly, Johnson & Johnson). The balloon was inflated manually by syringe at a rate of 2 ml/sec until the subject indicated that pain intolerance threshold had been reached. Subjects were instructed that this should be the level beyond first pain sensation at which they could not tolerate further increase. Hence this is most accurately described as a pain "intolerance" threshold, i.e. that at which they become intolerant of pain, rather than a pain "tolerance" threshold, i.e. the last level at which they can still tolerate it. This level was equivalent to a rating of 7 on a Visual Analogue Scale (VAS) ranging from 0 (no sensation) to 10 (extreme pain). The balloon was manually deflated immediately when pain intolerance threshold was indicated.

3.3.4 Autonomic measures

Electrocardiographic (ECG) measures

Skin was firstly prepared by light excoriation to reduce impedance and improve signal (Nuprep, DO Weaver & Co, USA) in areas for standard 3 lead ECG placement (right and left sub-clavicular fossae and cardiac apex). ECG electrodes (Cleartrace, Conmed Corporation, New York) were placed with a small quantity of conducting gel (Spectra 360 electrode Gel, Parker Laboratories USA). ECG was acquired at a rate of 2 kHz using a commercial biosignals acquisition system (Powerlab, AD instruments)

Heart rate

R waves are the first upwards deflection from the electrical baseline on the ECG which represents ventricular depolarisation as part of the QRS complex. The QRS complex is preceded by the p wave which represents atrial depolarisation and followed by the T wave which represents ventricular repolarisation. The in-built Powerlab HRV analysis software applied an R-wave detection algorithm to the ECG offline. This allowed recognition, detection and correction on-screen of misidentified R wave peaks (e.g. due to peaked T-waves when R/T height differentiation is poor; electrical noise or missed R waves due to chest wall movement perturbing ECG baseline). In this way, all R wave misidentifications were detected and corrected. The R-R interval series (the series of time intervals between successive R waves on the ECG in milliseconds) and thereafter the heart rate were subsequently derived using the Powerlab software.

The continuously acquired ECG was divided into 1 minute epochs for further analysis. These epochs comprised a 20 second pre-stimulus period and a 40 second

post-stimulus period, the inter-stimulus interval being 1 minute duration. 1 minute epochs were selected as being the minimum duration of ECG recording necessary to acquire statistically reliable measures of cardiac vagal control (CVC) using respiratory sinus arrhythmia (RSA) based techniques as defined by international standards (1996; Berntson et al. 1997)

Cardiac Vagal Control from Nucleus Ambiguus (CVC_{NA})

The 1 minute epoch R-R series were processed using MXedit DOS based software which produces an RSA based "breath-to-breath" measure of CVC (Porges 1985; Porges 1986). The details of the MXedit procedure used were (adapted from (Austin et al. 2007): 1) the R-R series was converted to time-based data by resampling at successive 500-ms intervals; 2) a 21-point moving cubic polynomial filter was stepped through the time-sampled series to produce a smoothed template series; 3) the template series was then subtracted from the original series to produce a residual time series; 4) the residual time series was then processed by a digital bandpass filter with 25 coefficients to extract the variance in the frequency band of .12–.40 Hz (i.e., the frequency of spontaneous breathing for adults); and 5) the bandpassed variance was transformed to its natural logarithm and used to quantify RSA.

This procedure truncates the original R-R series by approximately 12-15 seconds at either end and then derives the high frequency (0.12-0.4 Hz) component by application of a moving polynomial filter (Porges-Bohrer). This however differs from spectral analysis by not assuming stationarity. The output is called the "band variance" or the natural log of respiratory sinus arrhythmia (lnRSA). Normal data for band variance has been published (Byrne et al. 1996) and it has been used in multiple studies and is a well validated measure of CVC_{NA} (Brownley et al. 2000). The units are ln (ms^2).

Cardiac Sympathetic Index (CSI)

This is a putative measure of the sympathetic influence on the heart rate (Toichi et al. 1997). It was obtained by importing the R-R series into the "CMet" program (Allen et al. 2007). CSI has been validated in humans as a sympathetic cardiometric in pharmacological blockade studies. It is essentially a ratio of R-R intervals and therefore has no units.

Other CVC measures used in reproducibility study

The study was repeated in six subjects in whom 4 additional measures of CVC were obtained. These were 3 from the CMet program: MSD (mean absolute successive IBI difference) which is a simple time-domain measure of HRV but reflects CVC, the Toichi Cardiac Vagal Index (CVI) (Toichi et al. 1997) and logRSA which uses a digital rather than polynomial filter in a similar way to MXedit (Allen et al. 2007). The fourth measure, called the Neuroscope CVT was somewhat unique amongst CVC measures in that it is based on baroreceptor reflex physiology and detects phase-shifts in the R-R series on a beat-to-beat basis (Julu 1992; Little et al. 1999).

Protocol

All studies were performed in a sound and temperature controlled room. The temperature of the room was adjusted to subject comfort levels at the outset. Subjects completed a Spielberger state anxiety questionnaire at the start of the study and were then seated comfortably in a chair which was reclined to approximately 45 degrees with their head supported. The ECG electrodes were attached and a 3 minute recording obtained of resting autonomic activity. Subsequently the middle minute of this resting period was used as the baseline comparator measure.

Subjects then swallowed the oesophageal balloon catheter as above and a further 10 minutes was allowed for rest. Autonomic responses were then continuously recorded for 10 painful oesophageal balloon distensions, each with an inter-stimulus interval of 1 minute. Onset of balloon stimuli were digitally marked on the Powerlab system and separate notes of time were recorded by a second experimenter.

3.3.5 Statistical analysis

The autonomic data was normally distributed and so comparison of means for baseline and pain conditions for the group and also for the sub-groups identified by cluster analysis was performed using the 2 tailed paired student t-test for autonomic measures and Mann-Whitney U tests for the psychological scores. T-tests and correlation analysis were performed using Stats-Direct software.

Hierarchical cluster analysis was performed to determine the best-fit cluster solution and then k-wise cluster analysis was performed to identify the subgroups and determine the means of the parameters. Input functions for the cluster analysis were baseline CVC, CVC in pain, neuroticism, extroversion and cardiac sympathetic index.

3.4 Results

3.4.1 Pain tolerance thresholds

There were no adverse events during the procedures and no subjects withdrew during the study.

Subjects indicated that pain intolerance threshold was reached on each occasion. Consistent with the phenomenon of habituation (whether nociceptive or due to oesophageal accommodation changes or changes in balloon wall properties) the balloon volume required to achieve pain tolerance threshold increased from first to 10th distension - mean first balloon distension volume 23.5ml ± 1.2; mean tenth balloon distension volume 27.7ml ± 1.3 (2 sided paired t test p 0.004).

3.4.2 Autonomic measures

Group HR and CSI, but not CVC_{NA}, increased during pain

Heart rate and Cardiac Sympathetic Index (CSI) increased during pain compared with baseline [figure 3.1 panels B&C and table 3.1]. CVC_{NA} did not change during pain compared with baseline [figure 3.1 panel A and table 3.1].

Autonomic measure	Baseline	Pain	Significance level
Heart rate (bpm)	69.95 ± 2.44	72.73 ± 2.31	p = 0.03
CSI	2.01 ± 0.17	3.02 ± 0.2	p < 0.0001
CVC_{NA} ln (ms^2)	6.6 ± 0.32	6.6 ± 0.28	p= 0.9

Table 3.1 Group mean ± standard error of mean autonomic measures at rest (baseline) and during pain. Statistical comparisons were performed using 2 sided paired t-tests.

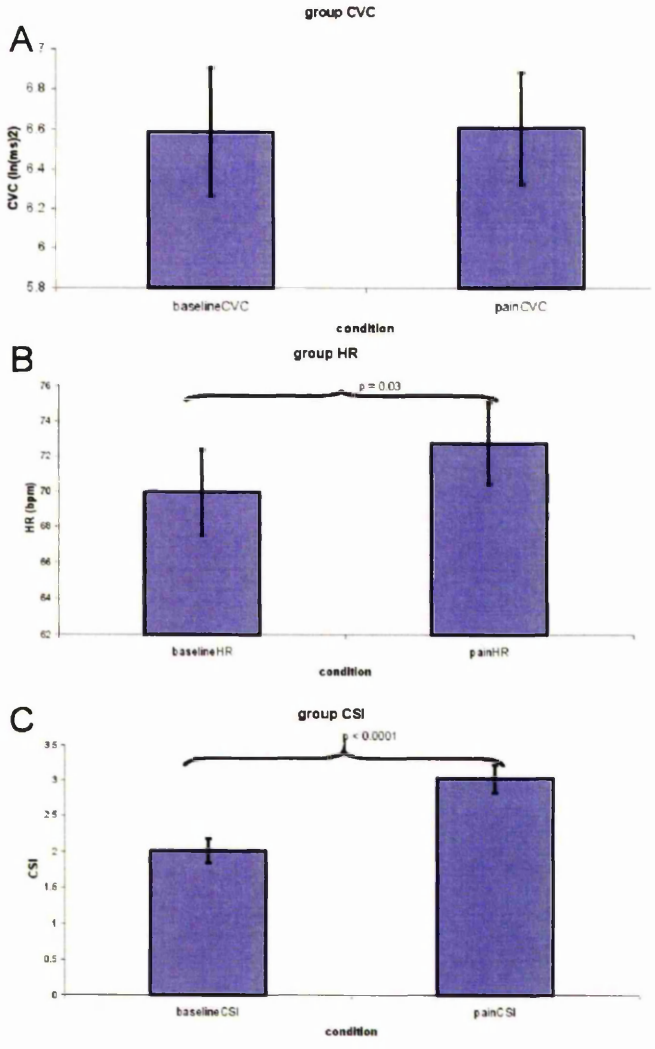

Figure 3.1 – Group mean baseline and pain autonomic recordings **A:** Cardiac Vagal Control did not show an overall change during pain at the group level (p=0.9, 2 sided paired t-test) **B**: Heart rate increased during pain compared to baseline (p=0.03, 2 sided paired t-test) **C:** Cardiac Sympathetic Index increased during pain compared to baseline (p<0.0001, 2 sided paired t-test). Error bars shown are SEM.

Individual differences in CVC_{NA} responses to pain

Approximately half the subjects increased their CVC_{NA} during pain and half reduced their CVC_{NA} during pain when expressed subject by subject as percentage change from baseline [figure 3.2 panel A].

This study was repeated in 6 subjects (4 who initially increased CVC_{NA} to oesophageal pain and 2 who withdrew CVC_{NA}) using 4 additional measures of CVC. Although not quantitatively identical, CVC changed in the same direction for all retested subjects and for all CVC measures as on the first occasion [figure 3.2 panel B]

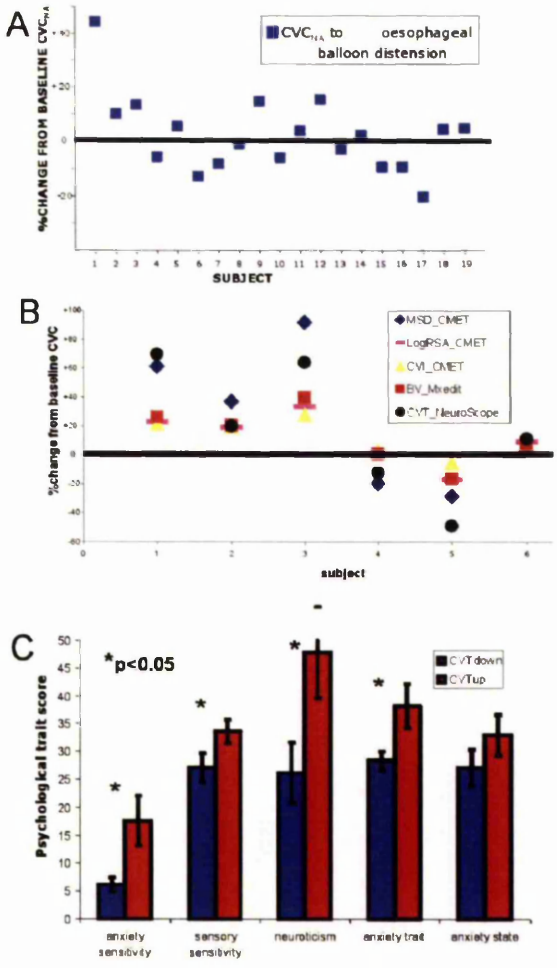

Figure 3.2: **A**. Individual differences in percentage change from baseline of CVC_{NA} to oesophageal balloon distension. The solid black line indicates baseline level. This shows that half the subjects increased whereas the other half decreased CVC_{NA} relative to baseline during pain **B.** Repeat study in 6 subjects with 4 additional measures of CVC. Solid black line again indicates baseline level. 3 of the CVC measures were from the CMet program (MSD, logRSA and Cardiac Vagal Index (CVI)) a further measure called CVT (cardiac vagal tone) from "Neuroscope" and the original MXedit measure of CVC used for the first visit. Subject 1-6 here equate to subjects 1-4, 10, 12 respectively from first study [figure 2 panel A]. CVC_{NA} responses to pain were qualitatively the same for these subjects in both the first and repeat study. **C.** Psychological trait differences were seen between those subjects who increased CVC_{NA} (n=10, greater levels of anxiety sensitivity, sensory sensitivity, neuroticism and trait anxiety, all $p < 0.05$) versus those who reduced CVC to oesophageal pain (n=9). Error bars are SEM.

3.4.3 Psychological trait and state measures relationship to CVC_{NA} change in pain

Neuroticism, sensory sensitivity and anxiety trait scores were higher for subjects who increased CVC_{NA} (n=10) to oesophageal pain than those who reduced CVC_{NA} (n=9) to oesophageal pain [table 3.2 and figure 3.2 panel C]. Anxiety state was not significantly different between the two groups [figure 3.2 panel C].

Measure	Increased CVC_{NA}	Decreased CVC_{NA}	Significance level
Neuroticism	2.9 ± 0.3	2.05 ± 0.2	p=0.035
Sensory sensitivity	33.6 ± 2.1	27.1 ± 2.6	p=0.027
Anxiety trait	38.2 ± 3.9	28.3 ± 1.7	p=0.028

Table 3.2 sub-group mean ± SEM psychological trait scores according to pain related CVC_{NA} response. Statistical comparisons were performed using Mann-Whitney U test. Numbers shown are mean ± SEM.

3.4.4 Correlation analysis

Personality correlations

Neuroticism and extroversion were negatively correlated (r -0.47, p=0.042). In addition neuroticism correlated positively with sensory sensitivity (r 0.5, p = 0.028) anxiety trait (r 0.75, p = 0.0002) and anxiety sensitivity (r 0.62, p =0.004) confirming the strong relationship between measures of anxiety and neuroticism. Neuroticism correlated negatively with baseline CVC_{NA} i.e. the higher the neuroticism score the lower the baseline CVC_{NA} [figure 3.3 panel A].

Extroversion correlated positively with change in heart rate during pain i.e. more extrovert subjects had brisker heart rate increases during pain [figure 3.3 panel D]. Extroversion also correlated positively with balloon volume. In other words more introvert individuals reported pain tolerance at lower balloon volumes than more extrovert individuals [figure 3.3 panel E].

Other physiological correlations with CVC_{NA}

Baseline CVC_{NA} correlated negatively with absolute change in CVC_{NA} during pain in other words those with lower baseline CVC_{NA} tended to increase their CVC_{NA} during pain whereas those with higher baseline CVC_{NA} tended to withdraw CVC_{NA} during pain [figure 3.3 panel B].

Change in CVC_{NA} during pain correlated negatively with change in heart rate during pain that is to say subjects who increased their CVC_{NA} during pain tended to have a blunted heart rate response in pain or even a reduction in heart rate [figure 3.3C].

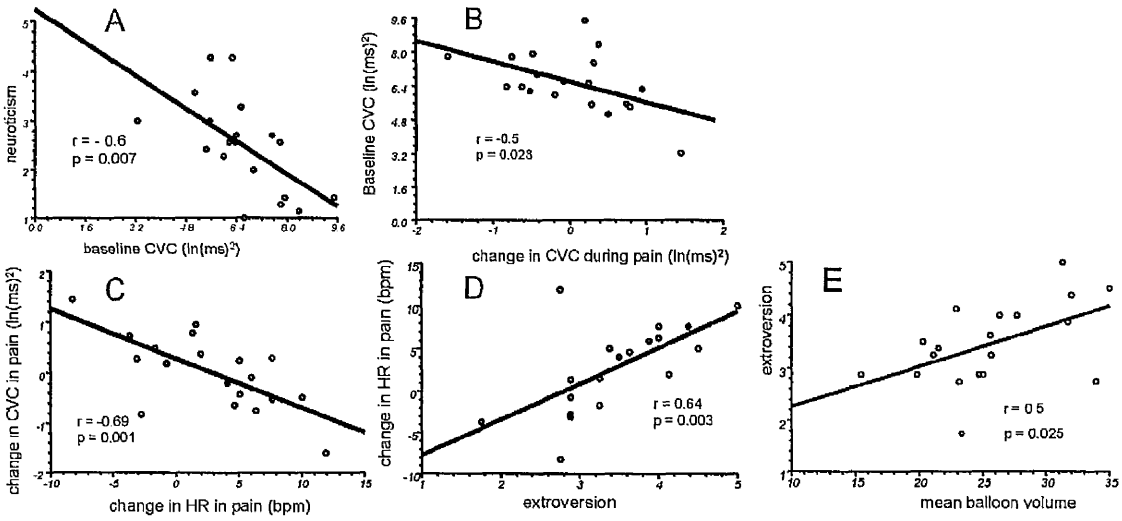

Figure 3.3 Correlations observed between psychological and physiological parameters. **A.** Neuroticism correlated negatively with baseline CVC_{NA} i.e. more neurotic individuals had lower baseline CVC_{NA} **B.** Baseline CVC_{NA} correlated negatively with absolute change in CVC_{NA} during pain i.e. subjects with low baseline CVC_{NA} tended to increase CVC_{NA} during pain whereas those with high baseline CVC_{NA} tended to reduce it during pain. **C.** Change in CVC_{NA} during pain correlated negatively with change in heart rate during pain i.e. subjects who increased CVC_{NA} during pain tended to have a smaller increase or even a decrease in HR during pain. **D.** Extroversion correlated positively with change in heart rate during pain i.e. more extrovert subjects tended to have a greater increase in HR during pain. **E.** Extroversion correlated with mean balloon volume i.e. more extrovert subjects tolerated larger balloon volumes whereas more introvert subjects tolerated lower balloon volumes at pain intolerance levels.

3.4.5 Cluster analysis

A hierarchical cluster analysis was performed for the whole group (n=19) to determine the optimal cluster size solution. Input parameters were CVC and CSI baseline, CVC in pain, neuroticism and extroversion scores. Cluster options solution freedom was given for 2- 4 clusters. The optimal cluster size was 2 clusters, indicated by the largest jump on the dendrogram between the three and two cluster solution [figure 3.4 black arrow].

K-wise cluster analysis was subsequently performed for the 2 group solution with the same input parameters which placed 11 subjects in one cluster (group 1) and 8 subjects in a second cluster (group 2), thus allowing for the further comparison of means between the two groups.

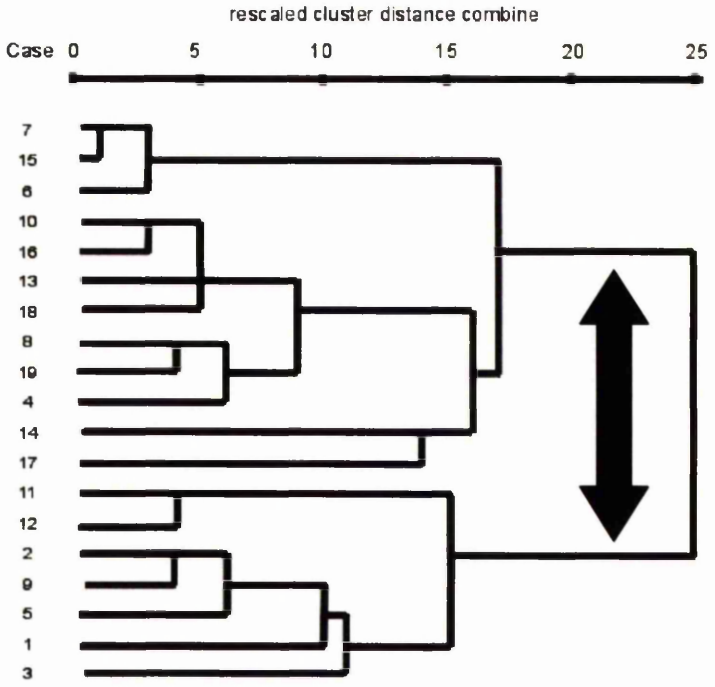

Figure 3.4 dendrogram from hierarchical cluster analysis showing the 2 cluster solution is preferred (black arrow)

Measure	Group1	Group 2	Significance level
Baseline CVC_{NA}	5.69 ± 0.28	7.81 ± 0.31	p = 0.0001
Baseline HR	74.77bpm ± 2.97	63.32bpm ± 2.86	p = 0.02
Baseline CSI	2.34 ± 0.2	1.55 ± 0.13	p = 0.015
Balloon volumes	23.57mls ± 1.46	28.38mls ± 1.64	p = 0.045
Pain delta CVC_{NA}	+0.26 ± 0.2	-0.3 ± 0.2	p = 0.1
Pain delta HR	0.42 ± 1.4	6 ± 1.4	p = 0.016
Neuroticism	3 IQR 1	1.43 IQR 1.25	p = 0.0004
Extroversion	3.25 IQR 0.62	4.07 IQR 1.34	p = 0.016

Table 3.3 Comparisons between the mean ± SEM of the 2 sub-groups identified by cluster analysis for a number of physiological parameters. For personality median and inter-quartial range are shown. Comparisons were performed using 2 sided unpaired t-tests.

The group means of the psychological trait and physiological parameters were compared with 2 sided unpaired t-tests for these 2 groups [table 3.3]. Group1 (n = 11) compared with group 2 (n=8) at baseline demonstrated lower baseline CVC_{NA} [figure 3.5 panel A] but higher HR [figure 3.5 panel B] and CSI [figure 3.5 panel C]. During pain, group1 became intolerant at lower balloon volumes [figure 3.5 panel G] an

increase in CVC_{NA} [figure 3.5 panel D] but an attenuated HR response [figure 3.5 panel E]. They had higher neuroticism [figure 3.5 panel F] and lower extroversion [figure 3.5 panel F].

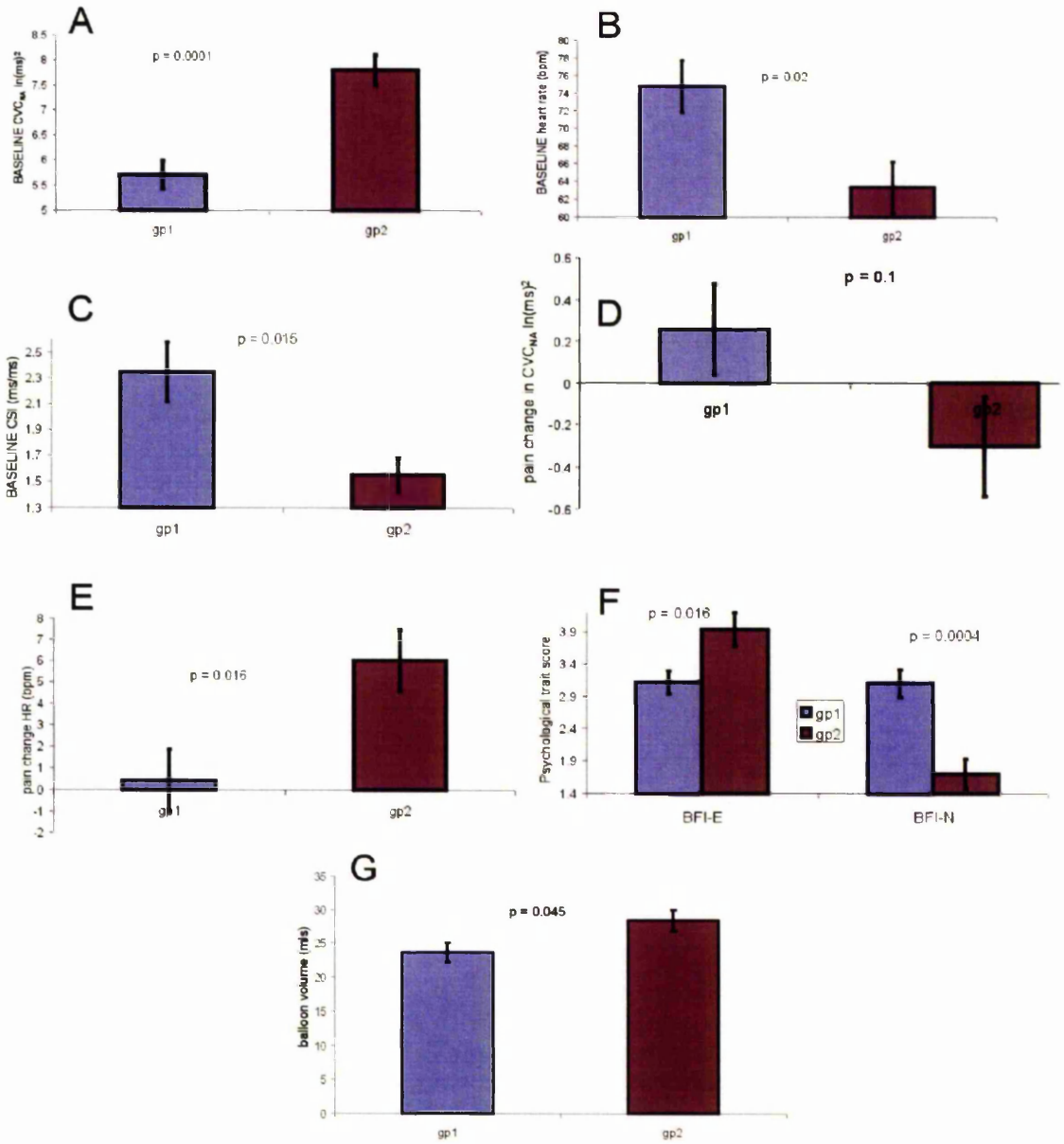

Figure 3.5: comparison of means between 2 subgroups identified in K-wise cluster analysis **A.** Baseline CVC_{NA} was lower in group 1 (p=0.0001) **B.** baseline heart rate was higher in group 1 (p=0.02) **C.** baseline CSI was higher in group 1 (p=0.015) **D.** change in CVC_{NA} during pain was an increase relative to baseline for group 1 and a decrease for group 2 (p=0.1) **E.** change in heart rate during pain was reduced for group 1 (p=0.016) **F.** neuroticism scores (Big Five inventory, BFI-N) were higher (p=0.0004) and extroversion scores (Big Five Inventory, BFI-E) were lower (p=0.016) in group 1. **G.** Balloon volumes at which pain was no longer tolerated were lower in group 1. Error bars are standard error of the mean.

3.5 Discussion

For the first time I have demonstrated two different endophenotypic psychophysiological profiles for visceral pain: firstly, group 1 demonstrated a "neurotic-introvert" profile characterised by low resting CVC_{NA}, high resting heart rate and cardiac sympathetic index, an increase in CVC_{NA} during pain but a blunted heart rate response. In other words this profile was characterised by a sympathetic predominant resting state with a paucity of parasympathetic tone at rest but a predominantly parasympathetic defence response. Conversely, the second "extrovert-emotionally stable" profile in group 2 was characterised by high resting CVC_{NA}, low resting heart rate and CSI, a withdrawal of CVC_{NA} during pain with a brisker heart rate response. This profile could therefore be characterised as having a parasympathetic predominant resting state and a predominantly sympathetic defence response.

Similar patterned physiological defence responses to these have been seen in differentially anxious rodents and birds (Cohen et al. 2003; Frank et al. 2006; Keller et al. 2006; Valance et al. 2007). The parasympathetic predominant response pattern to pain seen in group 1 has been characterised as a "passive-coping" or "tonic-immobilisation" type response whereas the response pattern observed in group 2 as a "fight-flight" or "active-coping" response (Bandler et al. 2000; Bandler et al. 2000; Walker and Carrive 2003).

The possible characterisation of the psychophysiological changes to visceral pain observed in this study falls between dichotomous patterned responses and a spectrum of response. The cluster analysis results favour that the response patterns be characterised as categorical/dichotomous (i.e. 2 "binary" groups) whereas the correlation analysis results favour that they be characterised as a spectrum. In a similar way debate has ranged as to whether independent personality *dimensions* (e.g. neuroticism-emotional stability and extroversion-introversion) or temperamental *categories* (neurotic-introvert vs. emotionally stable-extrovert) are more appropriate psychobiologically (Claridge and Davis 2001; Robinson 2001).

Studies in mammals suggest that dichotomous defence responses can be elicited from the peri-aqueductal gray (PAG) matter. In particular the ventrolateral PAG (VLPAG) receives inputs from the nucleus of the solitary tract and from the spinal dorsal horn. Stimulation in this area elicits ANS responses similar to those seen in group 1: a reduced SNS response (which includes hypotension in animals

when measured) and increased PNS response with blunted HR response or bradycardia (Bandler et al. 2000; Walker and Carrive 2003). Lesions in the VLPAG prevent freezing defence behaviour and it has been characterised as responsible for passive coping (Bandler et al. 2000).

Conversely, lesions in the dorsolateral/lateral PAG block fight-flight responses whereas stimulation elicits tachycardia, SNS activation and PNS withdrawal i.e. a pattern similar to group 2. The dorsolateral PAG can be triggered by higher centres and does not receive input from NTS or spinal cord. The lateral PAG receives input from the dorsal horn but is usually activated by superficial cutaneous pain rather than visceral (Bandler et al. 2000). All three areas of the PAG can evoke analgesia by different mechanisms (Bandler et al. 2000). Other recent work has suggested that a blending can occur between inhibitory VLPAG outputs and "defence arousal systems" to moderate SNS activation in order to produce a tonic-freeze rather than "floppy-freeze" response and also possibly allowing for a spectrum of defence responses (Walker and Carrive 2003).

There is evidence that the parasympathetic nervous system has an anti-nociceptive role (Multon and Schoenen 2005) and also low CVC is related to *chronic* pain conditions and affective disorders (Storella et al. 1999; Rottenberg 2007). Conversely, SNS reactivity has been related to absolute pain thresholds and sensitivities. In particular, during acute pain brisker SNS responses are associated with higher pain thresholds/better pain tolerance. In a study of experimentally induced rectal pain in humans, blunted SNS responses to pain were associated with greater pain report (Elsenbruch et al. 2007). Furthermore a recent study showed that greater pain sensitivity was found in more neurotic individuals with a blunted SNS response although PNS was not measured (Malt et al. 2002). Baseline BP and BP reactivity which are linked to SNS activity affect pain thresholds (France 1999; Campbell et al. 2006).

In my study the extroversion-introversion personality dimension related more directly to SNS reactivity whereas the neuroticism-emotional stability personality dimension related more directly to PNS reactivity. Links between extroversion and higher pain thresholds are well established and it is possible therefore that this is mediated in part through brisk SNS responses whereas neuroticism which is linked more to limbic reactivity is associated with deficiencies in the PNS, which is under

some influence from choline transporter and serotenergic genetic polymorphisms (Hariri et al. 2002; Neumann et al. 2006).

The role seen for CVC in this study, linked to broader personality traits, is consistent with the growing appreciation of CVC and pre-frontal inhibitory circuits in defence responses (Thayer and Friedman 2002; Porges 2007). In particular a recent reformulation of personality structures by Gray is based on hierarchically controlled behavioural inhibition and activation systems (BIS/BAS). The BIS/BAS incorporate fight-flight-freeze defence responses which, it is claimed, are closer to the underlying biological basis of personality than the tangentially related "surface traits" of neuroticism and extroversion (Gray and McNaughton 2000; Corr 2004). Better psychophysiological "fit" for visceral pain might be obtained therefore by incorporating BIS/BAS or possibly narrower personality trait measures such as sensation seeking/sensory sensitivity that may relate more closely to pain processing (Aron and Aron 1997; Stelmack 2004). It may be naive however to expect absolute or simple "isomorphic" mapping of personality constructs and neurobiology (Matthews 2004). Nonetheless, in this study, personality variables do appear to have explanatory power for the variance seen in subgroup pain ANS responses and sensitivities.

The patterns of CVC response were stable in the six subjects it was possible to re-study on a separate occasion. The degree of stability of these patterns of response would benefit from further larger studies on multiple occasions under similar conditions. The effect of sex and age on these response patterns also requires systematic exploration.

It is interesting to speculate on the potential clinical relevance of these endophenotypic psychophysiological response profiles. It is known that high scoring neurotics are overrepresented in functional medical syndromes including IBS and fibromyalgia (Gwee et al. 1999; Tanum and Malt 2000; 2001). These are overlapping syndromes of pain, emotion and autonomic disturbances such as changes in bowel habit. Furthermore it is known that pre-morbid neuroticism score is strongly predictive of the development of post-infectious IBS (Gwee et al. 1999). If a surge in $CVC_{NA,}$ as seen during pain with the neurotic profile, was matched by a general parasympathetic increase a subject might experience diarrhoea since parasympathetic activity is promotile for the colon (Janig 2006).

In conclusion, this study has found for the first time supportive evidence of the concept of psychophysiological endophenotypes in health for visceral pain with

personality type as a major contributory factor. Future work should be aimed at establishing their prevalence, stability, genetic contributions and clinical relevance.

Chapter 4 Pain evoked parasympathetic changes are ubiquitously coactive with sympathetics, but correlate with personality only for viscera.

Prologue to chapter 4

This study builds on the methodological and empirical foundations of chapter 3 in order to improve its design. In particular the following were incorporated: 1) assessment of pain intensity and unpleasantness were obtained for each stimulus. 2) An expanded repertoire of sympathetic (SNS) measures were used to cover the 3 major dimensions of SNS activity simultaneously – sudomotor, vasomotor and cardiomotor. 3) The range of parasympathetic measures was expanded to include baroreceptor reflex mediated cardiac vagal tone (CVT) and cardiac sensitivity to the baroreflex. 4) There was improved beat-to-beat time resolution of ANS measures to allow analysis of the time course of ANS responses and their links with behavioural measures over smaller time frames. 5) Comparison of visceral pain with somatic pain was performed. In pilot work for this comparison the use of a heat probe as a somatic pain comparator was explored (Medocs, Israel). The psychophysical properties of this were such however that pain intolerance threshold could not consistently be reached in many individuals and the sensation changed rapidly from heat to cold or numbness. In conjunction with the medical physics department at Hope Hospital a new device was developed to deliver nail bed pressure pain which in pilot work reproducibly produced pain-intolerance thresholds.

4.1 Abstract

Background The autonomic nervous system (ANS) is a hierarchically controlled, bi-directional, body-brain interface which integrates afferent bodily inputs and central motor outputs for homeostatic-emotional processes. Personality traits are known to affect the pain experience together with its central and ANS responses. Visceral and somatic pain exhibit different psychophysical properties and central responses but their contrasting relations with ANS responses and personality are poorly characterised. The aim of this study was therefore to compare and contrast the

relationships of visceral and somatic pain to brainstem autonomic control and personality whilst matching for pain intensity and unpleasantness.

Methods 18 healthy subjects (16 female, mean age 34 years) underwent continuous autonomic output recordings at rest and during pain. These included heart rate (HR) cardiac vagal tone (CVT), cardiac sensitivity to the baroreflex (CSB), skin conductance response (SCR), cardiac sympathetic index (CSI) and mean blood pressure (MBP). Visceral pain was induced to pain intolerance level at proximal and distal oesophageal sites by means of balloon distension (PB=proximal balloon, DB = distal balloon). Somatic pain was induced to pain intolerance level by nail-bed pressure (NBP). Eight consecutive pain stimuli were delivered at each site and intensity and unpleasantness ratings for each were obtained. Big Five Inventory personality profiles were completed at the start of the study.

Results 1. Oesophageal intubation caused a classic "fight-flight" ANS response pattern when compared to the pre-intubation period (all $p<0.05$): an elevated HR with sympathetic (CSI, SCR) activation, reciprocal parasympathetic (CVT) withdrawal, and a vasopressor (MBP) response 2. The novel observation was made of an elevated HR accompanied by co-activation of parasympathetic and sympathetic systems with vasodepression for visceral and somatic pain when compared to the pre-stimulus period (all $p<0.05$). 3. Correlations were seen between personality traits and the slope of pain related CVT changes for distal oesophageal balloon distension (neuroticism r 0.8, $p <0.05$; extroversion r -0.5, $p <0.05$). More neurotic-introvert subjects had a greater positive pain related CVT slope change whilst emotionally stable-extrovert subjects had a more negative pain related CVT slope change.

Conclusions 1. Visceral and (deep) somatic pain ANS responses were qualitatively similar. 2. A co-active parasympathetic and sympathetic mediated pain-evoked heart-rate increase is a novel finding in humans which has recently been described in animals. This is in contrast to the classic "fight-flight" patterned ANS response evoked by oesophageal intubation. 3. Pain related parasympathetic changes correlate with personality for visceral but not somatic pain. These 3 findings suggest that nuanced rather than simple reciprocal patterns occur for ANS defence responses to noxious stimuli. Furthermore, visceral pain evoked parasympathetic changes relate to personality type, the clinical relevance of which warrants further exploration.

4.2 Background

Pain originating from the viscera, whether intrinsic or extrinsic, has different psychophysical and neurophysiological properties than pain arising from the limbs or trunk (so-called "somatic-pain") (Cervero and Laird 1999; Strigo et al. 2002; Strigo et al. 2003; Strigo et al. 2005). In particular, visceral pain is characterised as more diffuse/less well localised; as exhibiting "referral" to other structures - including somatic/surface structures; and as generally more unpleasant for any given intensity than somatic pain (Cervero and Laird 1999). Further distinctions are made between superficial and deep somatic pain (Henderson et al. 2006).

The diffuse nature of visceral pain when compared to the limbs and trunk is explained by a low density of innervation from nociceptive Aδ and C-fibres (Cervero and Laird 1996). Viscero-visceral and viscero-somatic convergence at the level of the dorsal-horn of the spinal cord accounts for the referral experienced with visceral pain (Cervero and Laird 1996). Functional brain imaging studies have suggested differences between somatic and visceral pain in "limbic cortex" activation underlying the greater unpleasantness of visceral pain (Strigo et al. 2003; Strigo et al. 2005). Recently however, when unpleasantness was controlled for, some of these differences were less evident (Dunckley et al. 2005).

Chronic somatic pain, such as found in the fibromyalgia syndrome and in pain from metastatic cancer, tends to be of a deeper rather than superficial somatic origin. Whilst most experimental human studies have focussed on differences between acute superficial cutaneous thermal pain and visceral pain it may be more relevant clinically to understand those between deep somatic and visceral pain. A recent brain imaging study found significant differences between superficial and deep somatic pain in the brain areas activated (Henderson et al. 2006). Current "homeostatic emotion" models of pain however would tend to minimise neuroanatomical differences between all types of pain (Craig 2003). Clinically it is common to observe overlaps in symptoms between chronic somatic and visceral pain states and both are strongly associated with affective disturbance (Wessely et al. 1999; Sharpe and Carson 2001; Wessely and White 2004).

The oesophagus is a readily accessible part of the viscera which has frequently been studied for experimentally induced acute pain and also central pain sensitisation in humans with brain imaging and electrophysiology (Aziz and

Thompson 1998; Aziz et al. 2000; Gregory et al. 2003; Hobson and Aziz 2003; Phillips et al. 2003; Dunckley et al. 2005; Dunckley et al. 2005; Hobson et al. 2005; Yaguez et al. 2005; Dunckley et al. 2007). The proximal third of the oesophagus consists of striated muscle and has a greater degree of extrinsic innervation than the "true visceral" smooth muscle distal two thirds (Aziz and Thompson 1998). The proximal oesophagus may therefore exhibit intermediate properties between visceral and somatic structures in response to pain.

The autonomic nervous system is a core part of the "emotional motor system" (Holstege et al. 1996; Mayer et al. 2001) and is a hierarchically controlled, bi-directional, body-brain interface that integrates afferent bodily inputs and central motor outputs for homeostatic-emotional processes. This is particularly so for the viscera which receive extrinsic afferent and efferent autonomic innervation, in addition to their own intrinsic myenteric plexi - the enteric nervous system - known as the third division of the ANS (Berthoud et al. 2004; Janig 2006).

It is now possible to study selective components of the ANS non-invasively and with increasingly improved time-resolution. Hitherto it has not been possible to study the time-course of pain evoked changes in cardiac vagal control (CVC) non-invasively in humans. Older techniques which analyse respiratory frequency modulation of CVC are statistically limited to longer time windows, usually in excess of 1 minute (Berntson et al. 1997). CVC due to baroreceptor modulation however can now be measured on a beat-to-beat basis (Julu 1992; Little et al. 1999).

Animal studies suggest that differences in visceral and somatic ANS pain response are mediated largely via defence systems in which the roles of hypothalamus and peri-aqueductal gray (PAG) are best characterised. In particular, differential activation of either the ventrolateral or lateral PAG, in response to pain from deep/visceral or superficial structures respectively, produces varied ANS defence response patterns and behaviours in animals (freeze vs. fight-flight respectively) (Bandler et al. 2000). The relevance of these animal findings for humans is unknown.

Traditionally research into defence responses, i.e. behavioural and physiological effects of noxious or threatening contexts including pain, has emphasised the roles of sensitisation, behavioural activation and sympathetic nervous system (SNS) responses, i.e. the "fight-flight" response. Appreciation has grown more recently for hierarchical superiority of inhibitory/disinhibitory processes,

especially those of the pre-frontal cortex and parasympathetic nervous system (PNS) (Thayer and Friedman 2002). The enumeration of descriptive terms for defence responses associated with the inhibitory/disinhibitory system - e.g. freeze/vigilance/quiescence, cautious/defensive/exploratory-approach, tonic-immobility, fright, faint - may be reflective of a greater range and flexibility of response inherent in this system (Bracha 2004; Bracha et al. 2004; Corr 2004).

Increasingly sophisticated psychophysiological frameworks place the inhibitory-PNS axis centre-stage. The "Polyvagal perspective" (Porges 2007) distinguishes between 1) primitive dorsal motor vagal nucleus cardiac output, giving rise to profound bradycardia (the classic "voodoo-death" freezing response) found in most vertebrates and 2) a chiefly mammalian elaboration of brainstem nucleus ambiguus (NA) cardiac vagal control (CVC). This NA elaboration allowing increased CVC control is postulated to facilitate wider repertoires of defensive and affiliative behavioural flexibility (Porges 2007; 2007) and may relate CVC to more sophisticated cognitive and emotional processes including personality differences (Riese et al. 2007).

Temperamental differences in animals affect behavioural and ANS responses to pain and threat but this is poorly characterised in humans (Cohen et al. 2003; Frank et al. 2006; Keller et al. 2006; Valance et al. 2007). An influential model of personality is based on behavioural activation and inhibition with a central role for defence response systems (Gray and McNaughton 2000; McNaughton and Corr 2004). Personality differences in man are known to affect pain sensitivity and neurophysiological responses to various stressors and are under some genetic influence (Stelmack 2004; Riese et al. 2007).

The current study for the first time attempts to explore the time course of selective autonomic responses to pain evoked from distal oesophagus (true viscera); nail-bed (true "deep" somatic) and proximal oesophagus (possibly viscero-somatic intermediate) and relate them to personality trait variables.

4.3 Methods

4.3.1 Subjects

Healthy volunteers took part in this study. Ethics approval was obtained from Central Manchester Local Research Ethics committee (ref 07/Q1407/3). Fully informed consent was obtained. Subjects with a history of current or chronic gastrointestinal, neurological or psychiatric medical problems or taking medication affecting GI, pain or neuropsychological function were excluded.

4.3.2 Physiological techniques

Painful Oesophageal balloon distension

Oesophageal balloons were assembled from 3 cm lengths of thin silicone tubing (Medasil UK) which were tied and glued, 0.5cm at each end, over perforations that were 2cm from the tip of a commercially available nasogastric tube (Pennine Healthcare Ltd, 2.7 mm, 120cms). This created a 2cm diameter balloon. The nasogastric tube was swallowed either per-orally or trans-nasally according to subject preference and the balloon was positioned 34cm ab orus/ 36cm ab nares for distal oesophagus and 22cm ab orus/ 24cm ab nares for proximal oesophagus. No local anaesthetic was used for the intubation but passage was eased through the nasopharynx with a water-based lubricant jelly (KY jelly, Johnson & Johnson).

The balloon was inflated manually using a syringe at a rate of 2 ml/sec until the subject indicated that pain intolerance threshold had been reached. Subjects were instructed that this should be the level beyond first pain sensation at which they could not tolerate any further increase. Hence this is most accurately described as a pain "intolerance" threshold, i.e. that at which they become intolerant of pain, rather than a pain "tolerance" threshold, i.e. the last level at which they can still tolerate it. The balloon was manually deflated immediately when pain intolerance threshold was reached as indicated. The subjects were then asked to rate the pain they had just felt on a verbal scale of 1-10 for both intensity and unpleasantness, 10 being most intense/unpleasant pain and 1 being no sensation/not unpleasant. A verbal rather than visual analogue scale was chosen to minimize movement artifacts on autonomic measurement recordings and also because both hands were employed during the study with either nail-bed stimulation or autonomic recordings.

Painful nail-bed stimulation

The extension probe of a strain-gauge (Mecmesin, UK) was mounted onto a spring-loaded, manually operated device (Medical Physics Department, Hope hospital). The extension probe incorporated a blunt ended thin rod that was applied to the nail-bed of the subjects left middle finger using the spring-loaded device. As per oesophageal balloon distension, the nail-bed pressure was increased until subjects indicated that pain intolerance threshold had been reached. The pressure was then immediately released. The subjects subsequently rated intensity and unpleasantness using the same verbal scale anchors as for oesophageal pain.

4.3.3 Psychological traits

Subjects completed the Big Five Inventory questionnaire (John et al. 1991; Benet-Martinez and John 1998; John and Srivastava 1999), a 44 item personality questionnaire based on the five main personality dimensions of neuroticism, extroversion, agreeableness, openness and conscientiousness. Only the subscales of neuroticism and extroversion were used in the subsequent analysis.

4.3.4 Autonomic measures

Electrocardiographic

Skin was firstly prepared by light excoriation to reduce impedance and improve signal (Nuprep, DO Weaver & Co, USA) in areas for standard 3 lead ECG placement (right and left sub-clavicular and cardiac apex). ECG electrodes (Cleartrace, Conmed Corporation, New York) were placed with a small quantity of conducting gel (Spectra 360 electrode Gel, Parker Laboratories USA). ECG was acquired at a rate of >3 kHz using a commercially available biosignals acquisition system (Neuroscope, Medifit, UK).

R waves are the first upwards deflection above the electrical baseline on the ECG as part of the QRS complex which represents ventricular depolarisation. The QRS complex is preceded by the p wave, which represents atrial depolarisation, and is then followed by the T wave, which represents ventricular repolarisation. The Neuroscope has an inbuilt R wave detection algorithm, which features accuracy to the nearest millisecond, from which the interbeat (R-R) interval and heart rate is derived.

The Neuroscope also has in-built "voltage controlled oscillators" which detect positive phase shifts in the beat-to-beat R-R interval, a process called "phase shift demodulation". This phase shift technique is based uniquely amongst non-invasive measures of cardiac vagal control (CVC) on "beat-to-beat" baroreceptor reflex physiology (Eckberg 1976; Julu 1992; Little et al. 1999; Julu et al. 2003; Janig 2006). Most traditional CVC measures are based on "breath-to-breath" respiratory modulation, i.e. respiratory sinus arrhythmia (RSA)(Allen et al. 2007). The baroreceptor reflex technique therefore has better face-validity for smaller/beat-to-beat time windows in the study of CVC than do RSA measures. The phase-shift technique has been validated for humans using pharmacological blockade (Julu 1992) and is measured in standardised units on a Linear Vagal Scale (LVS). The Neuroscope refers to this measure of CVC as cardiac vagal tone (CVT).

The edited R-R series was exported into another PC DOS based program called CMET (Allen et al. 2007). This produces a cardiometric called the Toichi Cardiac Sympathetic Index (CSI). This has been validated in humans as a sympathetic cardiometric in pharmacological blockade studies (Toichi et al. 1997). It is essentially a ratio of R-R intervals and therefore has no units.

Skin conductance

This was obtained using commercially available equipment (Powerlab, AD instruments, UK). Skin on the distal digit finger pulps of right index and ring fingers was lightly wiped with water and then dried. Skin conductance electrodes were then attached to these and the skin impedance level (uS, micro Siemens) was zeroed for that subject. The mean skin-impedance level was subsequently extracted off-line.

Blood pressure

Digit arterial blood pressure was obtained using a commercial technique whereby a photoplethysmographic cuff was attached to the distal interphalangeal portion of the right middle finger (Portapress, Finapress Medical Systems, Copenhagen). The analogue waveform generated was exported to the Neuroscope which then directly measured beat-to-beat mean blood pressure. The mean blood pressure under some experimental conditions indexes sympathetic tone (Sun and Guyenet 1986), however blood pressure is broadly under mixed SNS and PNS control as is heart rate.

Cardiac-Sensitivity to the Baroreflex (CSB)

The neuroscope incorporates the beat-to-beat R-R and mean blood pressure into an algorithm on a 10 second cycle which calculates cardiac-sensitivity to the baroreflex (Julu et al. 2003). This is the change in blood pressure for each change in R-R interval (mmHg/ms). The CSB is a putatively indirect measure of parasympathetic afferent sensitivity.

Summary of autonomic measures

This battery of autonomic measures therefore covers mixed (heart rate); efferent cardiac parasympathetic (CVT); afferent parasympathetic activity (CSB) and also 3 major divisions of the efferent sympathetic system - cardiomotor (CSI), sudomotor (SCR) and vasomotor (MBP).

4.3.5 Protocol

Subjects attended for a single visit lasting 3 hours. On arrival they completed consent, and then height, weight and age were obtained. They then completed the Big-Five personality inventory.

They were reclined comfortably at 45 degrees on a bed in a quiet and temperature controlled laboratory. The ANS recording equipment was attached and a 3 minute pre-intubation baseline recording was taken at rest. Subjects were then intubated as described above. ANS recordings were acquired continuously for 6 minutes post-intubation. In counter-balanced randomised order, subjects then received eight stimulations of either distal balloon or nail-bed stimulations with an inter-stimulus interval of 3 minutes. This was then followed after a brief break by runs of eight stimuli each from the other two sites in turn. If stimuli or responses were contaminated by coughing, sneezing, swallowing or other artefacts they were rejected and subsequently repeated.

4.3.6 Analysis

All ANS measures were initially compared using 90 second time windows. Data from the first 90 seconds (early phase) and last 90 seconds (late phase) of the six minute post-intubation ANS recordings were extracted for comparison. For all measures except the SCR and CSI it was subsequently possible to compare 10 second peri-stimulus time windows for CVT, CSB, MBP and HR. Comparisons were

made with 2 sided paired t-tests using Stats-Direct software. Correlation analysis was performed using Pearson's correlations in SPSS software.

To capture the dynamic information available from stimulus to stimulus change in pain-related CVT responses, these were also transformed into a slope statistical summary measure (Excel, Microsoft). The slope measured was that of the linear regression line through data points in known_y's and known_x's. In this case, x was time (minutes) between stimuli and y was the absolute pain related change in 10 second peri-stimulus CVT for the eight consecutive stimuli. The change measured was from the 10 seconds immediately pre-stimulus to the 10-20 second period post-stimulus at which maximum change occurred. The slope was then the vertical difference divided by the horizontal distance between any two points on the line, which was the rate of change along the regression line.

4.4 Results

4.4.1 Subject characteristics

18 subjects were studied (2 male) with a mean age (± SEM) of 35.4 (± 2.7).

In 2 subjects no distal oesophageal balloon responses were obtained because pain intolerance threshold could not be reached at the limit of balloon distension (40mls).

In 1 further subject technical delays resulted in insufficient time to obtain proximal balloon responses. These subjects were excluded where necessary from comparisons between sites and in correlations. When comparisons or correlations are based on fewer than the full group of 18 subjects this is made explicit in the results section by giving the number of subjects incorporated into the analysis.

Therefore, whereas 18 subjects underwent nail bed stimulation only 15 subjects underwent stimulation at all 3 sites. 17 subjects could be compared for both nail bed stimulation and proximal balloon distension; 16 subjects for nail bed stimulation and distal balloon distension; and 15 subjects for proximal and distal balloon distension.

4.4.2 Personality characteristics

The personality characteristics for the group were a mean extroversion score (± SEM) of 3.54 (± 0.19) and neuroticism score of 2.73 (± 0.22).

Neuroticism and extroversion scores were negatively correlated for the group ($r = -0.67$, 2 sided $p = 0.0024$).

4.4.3 ANS responses to intubation

Intubation caused a sustained elevation in heart rate [figure 4.1 panel A, left hand 3 bars]. In the early phase (first 90 seconds) post-intubation this was associated with both sympathetic activation [figure 4.1 panels C; D & E left hand 1st red bar] and parasympathetic withdrawal [figure 4.1 panel B, left hand 1st red bar] and a reduction in parasympathetic afferent sensitivity [figure 4.1 panel F, left hand 1st red bar].

In the late phase post-intubation (last 90 seconds of the 6 minute post-intubation recording period) sympathetic indices [figure 4.1 panels C&D 2nd red bars left hand side], with the exception of MBP [figure 4.1 panel E 2nd red bar left hand side], returned to baseline levels. This pattern was also seen for the vagal afferent sensitivity measure, CSB [figure 4.1 panel F 2nd red bar left hand side]. A post-intubation sustained elevation in heart rate was associated with a sustained cardiac parasympathetic withdrawal [figure 4.1 panels A&B 2nd red bar left hand side]. The detailed findings and significance levels are shown in table 4.1.

Measure	Baseline	Early PI	Late PI	B v EPI	EPI v LPI	B v LPI
Heart rate	70.49 ± 2.19	77.63 ± 2.75	73.63 ± 2.12	p 0.0003	p 0.0056	p 0.001
CVT	7.91 ± 0.75	6.32 ± 0.83	6.30 ± 0.71	p 0.06	p 0.94	p 0.025
CSB	7.16 ± 0.67	5.4 ± 0.7	6.31 ± 0.98	p 0.029	p 0.16	p 0.34
CSI	1.96 ± 0.14	2.62 ± 0.20	2.29 ± 0.13	p 0.0032	p 0.053	p 0.07
MBP	91.69 ± 2.47	98.18 ± 2.89	96.10 ± 2.34	p 0.0001	p 0.09	p 0.002
SCR	3.03 ± 0.76	7.83 ± 0.77	3.56 ± 0.87	p <0.0001	p <0.0001	p 0.4

Table 4.1 ANS responses to intubation compared with baseline. Statistical tests are 2 sided paired t-tests. Numbers are mean and SEM. EPI = early post-intubation; LPI = late post-intubation; B = baseline. CVT = cardiac vagal tone; CSB = cardiac sensitivity to baroreflex; CSI = cardiac sympathetic index; MBP = mean blood pressure; SCR = skin conductance response.

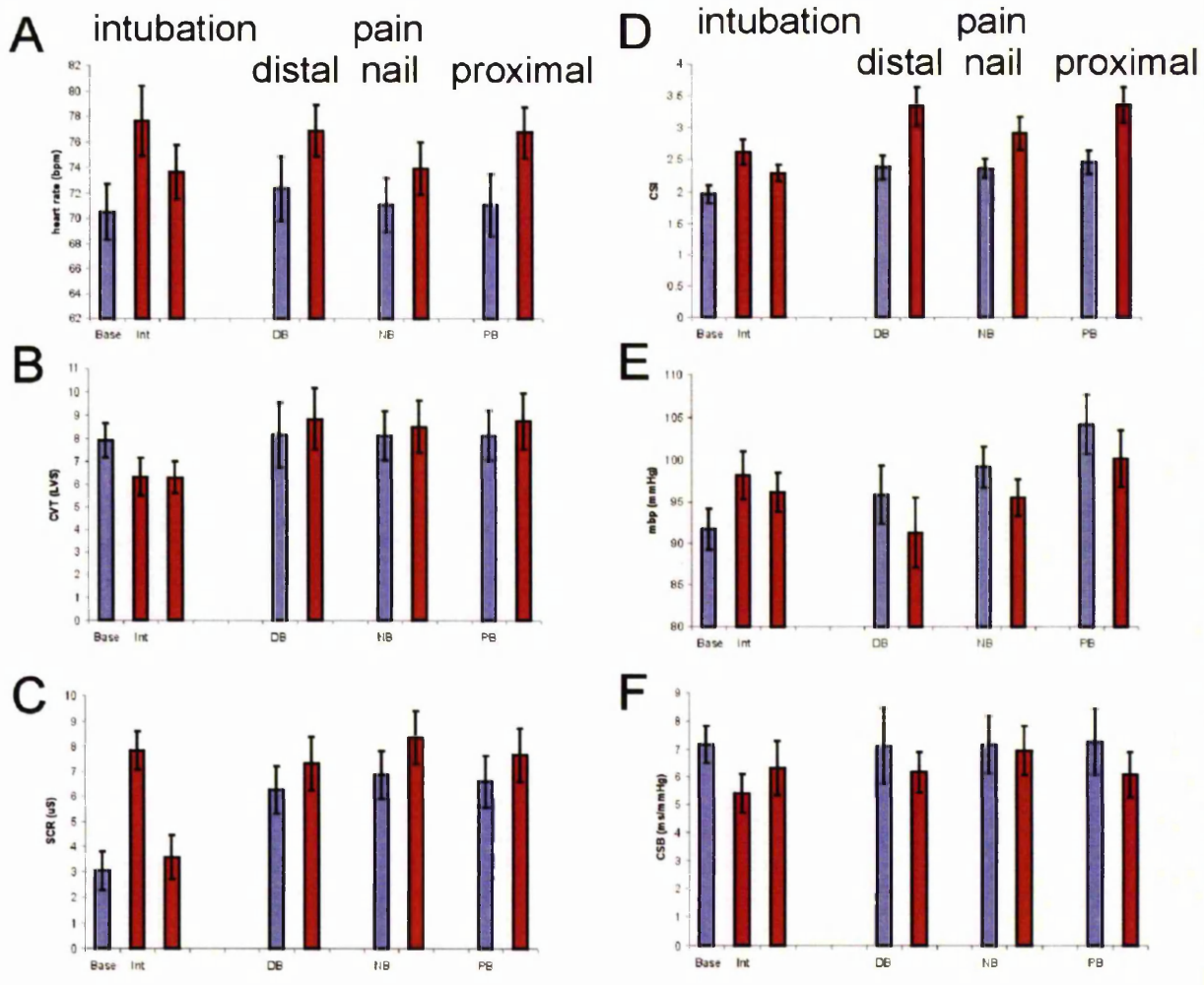

Figure 4.1: left hand side first 3 bars in each panel: ANS changes post-intubation (red bars) relative to baseline (blue bar); right hand side: ANS changes post-pain (red bars) relative to pre-pain (blue bars). **A** heart rate (HR) **B** Cardiac Vagal Tone (CVT) **C** Skin conductance (SCR) **D** Cardiac Sympathetic Index (CSI) **E** Mean Blood Pressure (MBP) **F** Cardiac sensitivity to baroreflex (CSB). All data shown are 90 second epochs apart from pain changes for HR, MBP and CSB. Error bars are SEM. Base = pre-intubation baseline, Int = post-intubation, DB = distal balloon, NB = nail bed pressure, PB = proximal balloon.

4.4.4 Pain responses

1. Psychophysical response characteristics

Behavioural responses

The pain intensity and pain unpleasantness ratings for each of the sites are shown in table 4.2. The sites did not differ with respect to pain intensity but proximal balloon pain was rated as more unpleasant than nail bed pressure in 17 subjects who underwent both (PB 8.2 ± 0.16 vs. NBP 7.68 ± 0.25, 2 tailed paired t-test p = 0.04).

Site	Subject number	Intensity	Unpleasantness
Nail bed	18	8.06 ± 0.17	7.77 ± 0.25
Proximal balloon	17	8.07 ± 0.14	8.17 ± 0.16
Distal balloon	16	7.85 ± 0.19	7.95 ± 0.19

Table 4.2 psychophysical characteristics of pain at different sites

Balloon volumes and nail-bed pressures

Distal balloon volumes at pain intolerance threshold were 24.03 ± 1.09 mls. Proximal balloon volumes were 19.77 ± 1.35 mls. In 15 subjects who had both proximal and distal balloon distension the proximal balloon volumes were significantly lower than the distal (PB 19.1 ± 1.4; DB 23.5 ± 0.99; 2 tailed paired t-test $p = 0.0002$, $n=15$). DB and PB volumes were positively correlated suggesting that subjects had similar pain intolerances at both sites relative to other individuals ($p = 0.0004$, $r = 0.79$).

Nail bed pressures at pain intolerance threshold were 40.51 ± 2.98 N. Nail bed pressures were not correlated with balloon volumes.

2. ANS pain responses

All ANS measures had changes in the post-stimulation period compared to the pre-stimulation period. These changes were maximal in the first minute post-stimulus with recovery occurring in the second minute post-stimulus. In particular maximal change occurred in the 10-20 second period post-stimulus (for measures where this time resolution was available). An exception to this was proximal balloon pain where the biggest decrease of MBP was in the 20-30 second post stimulus epoch.

In summary, a pain-related heart rate increase occurred in response to stimulation at all 3 sites. This was associated with sudomotor and cardiomotor sympathetic increases but vasodepression. Intriguingly the pain-related HR increase was also associated with CVT increases. Reductions occurred (significant only for proximal balloon) in CSB. There were some quantitative differences between the sites but qualitatively the patterned ANS responses were the same at all 3 sites. The details were as follows [see table 4.3 and figure 4.1 right hand side]

HR

There were significant increases at all 3 sites in the second 10s epoch post-stimulus compared to the immediate pre-stimulus 10s epoch. The HR increase was

significantly greater for proximal balloon than for nail bed pressure in the 17 subjects who had both (PB +5.7bpm ± 1.3; NB + 3.03bpm ± 0.7; p = 0.036). [Figure 4.1 panel A].

SNS

SCR

There was a significant increase in SCR in the 30 seconds post-stimulus compared with the 30 seconds pre-stimulus at all 3 sites. [Figure 4.1 panel C].

The increase in SCR was greater for nail bed pressure than for distal balloon distension in 16 subjects who had both (NB +2.6uS ± 0.4; DB 1.7 ± 0.4 p = 0.0028). SCR was also greater for nail bed than for proximal balloon distension in 17 subjects who had both (NB 2.8uS ± 0.4; PB 1.7uS ± 0.3 p = 0.012).

MBP

There was a significant drop in MBP at all 3 sites post stimulus. This was maximal in the second 10s epoch post-stimulus for distal balloon and nail bed but in the third 10s epoch for proximal balloon. [Figure 4.2 panel E].

There were no significant differences between the 3 sites for the maximal drop in blood pressure.

CSI

There was a significant increase in CSI in the 90 seconds post-stimulus compared with the 90 seconds pre-stimulus at all 3 sites [figure 4.1 panel D] but there were no significant differences between the sites.

PNS

CVT

For distal balloon and nail bed there was a significant increase in CVT in the 90 seconds post-stimulus compared with pre-stimulus CVT [figure 4.1 panel B]. There was an increase in CVT for proximal balloon which was just short of significance. The maximal increase of CVT for all 3 sites was seen during the second 10s epoch post stimulus although the inter-individual variability of the changes in this time-frame was such that these did not reach significance levels at the group level.

The change in CVT was significantly greater for distal balloon than for nail bed in the 10 second time-frame for 16 subjects who had both (DB mean change + 1.37 ± 0.7; NB mean change – 0.06 ± 0.5 , p = 0.02).

CSB

There were pain-related decreases in CSB at all 3 sites but these did not reach significance levels except for proximal balloon distension [figure 4.1 panel F]. Maximal change occurred in the 10 second period post-stimulus. There were no significant differences between the sites.

ANS measure	Site	Pre-stim	Post-stim	Significance
HR (bpm)	NB	71.02 ± 2.1	73.9 ± 2.05	p 0.0008
	PB	71.04 ± 2.4	76.7 ± 2.01	p 0.0005
	DB	72.3 ± 2.5	76.9 ± 2.01	p 0.0097
SCR (uS)	NB	6.86 ± 0.97	8.35 ± 1.05	p <0.0001
	PB	6.59 ± 1.04	7.65 ± 1.07	p <0.0001
	DB	6.25 ± 0.96	7.32 ± 1.08	p 0.0002
MBP (mmHg)	NB	99.1 ± 2.5	95.5 ± 2.2	p < 0.0001
	PB	104.2 ± 3.5	100.1 ± 3.4	p 0.0036
	DB	95.8 ± 3.5	91.3 ± 4.3	p 0.0025
CSI	NB	2.36 ± 0.15	2.91 ± 0.26	p 0.006
	PB	2.46 ± 0.18	3.36 ± 0.28	p 0.0004
	DB	2.38 ± 0.19	3.33 ± 0.31	p 0.001
CVT (LVS)	NB	8.11 ± 1.06	8.5 ± 1.12	p 0.03
	PB	8.12 ± 1.08	8.73 ± 1.22	p 0.06
	DB	8.15 ± 1.4	8.84 ± 1.32	p 0.015
CSB	NB	7.2 ± 1.04	6.9 ± 0.9	p 0.7
	PB	7.3 ± 1.2	6.1 ± 0.8	p 0.03
	DB	7.1 ± 1.4	6.17 ± 0.7	p 0.2

Table 4.3 ANS measures pre and post-stimulus for nail bed pressure (NB); proximal balloon distension (PB) and distal balloon (DB). Significance tests were performed using 2 sided paired student t-tests.

4.4.5 Relationships of personality to ANS responses

In a previous study (chapter 3) a relationship was found between pain related CVT change to distal balloon distension and personality. This was explored further for all 3 sites of stimulation using the slope statistical summary measure for pain related peri-stimulus CVT change.

Neuroticism was positively correlated with the slope of pain-related CVT change post distal balloon distension. In other words, subjects with a higher

neuroticism score tended to have a more positive change in CVT with consecutive stimuli whereas those with lower neuroticism scores tended to have a more negative change in CVT with consecutive stimuli [Table 4.4, figure 4.2A]. Extroversion conversely had a negative correlation with the slope of CVT pain-related change for distal balloon [Table 4.4, figure 4.2B].

There were no significant correlations for CVT and personality at the other two sites of painful stimulation [Table 4.4].

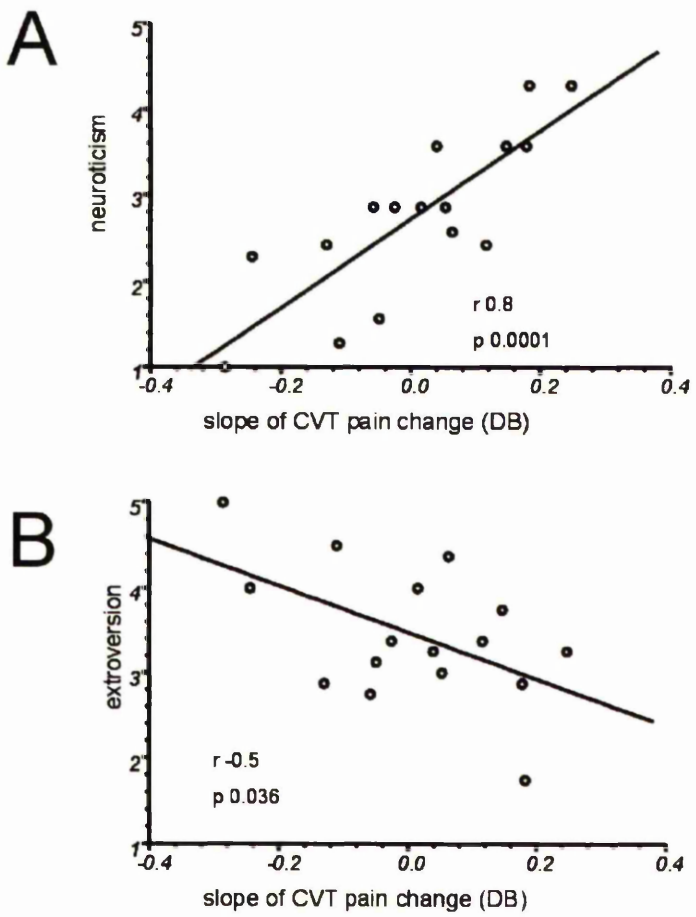

Figure 4.2 relationships of distal balloon (DB) distension pain related changes in CVT to **A.** neuroticism and **B.** extroversion.

Site	Personality	Subject Number	r value	p value
Distal Balloon	Neuroticism	16	0.8	0.0001*
	Extroversion	16	-0.5	0.036*
Proximal Balloon	Neuroticism	17	0.45	0.07
	Extroversion	17	-0.13	0.6
Nail Bed	Neuroticism	18	-0.26	0.3
	Extroversion	18	0.26	0.3

Table 4.4 Correlations of the slope of CVT pain related changes with personality for the 3 sites of stimulation.

4.5 Discussion

This is the first study, to my knowledge, to make a comparative exploration in humans of visceral and somatic pain with regards to (i) psychophysical responses (ii) the time-course over narrow time windows of a) non-invasive and b) selective ANS responses and (iii) to attempt to relate these to personality.

The most striking finding was a pain-related heart-rate elevation that was associated with *co-activation* of the sympathetic (SNS) and parasympathetic nervous system (PNS) but vaso*depression*. This occurred at all 3 sites of painful stimulation. This was in marked contrast to the patterned ANS response to intubation in which the elevated HR was associated with SNS activation, but sustained PNS withdrawal and a vaso*pressor* response.

The ANS patterned response for intubation was what might in part be expected in a typical "fight-flight" stress/defence response. It is striking to note however that, less typically for classic fight/flight, the PNS withdrawal significantly outlasted the SNS activation. This prolonged PNS withdrawal could represent cardiac "disinhibition" (Thayer and Friedman 2002) as the main determinant of the sustained post-intubation HR elevation since SNS activity had returned to near pre-intubation levels in the late post-intubation phase.

Roles for neural control of patterned ANS response defences have variously been assigned to a hierarchical network including prefrontal and cingulate cortices, amygdala, the septo-hippocampal system, medial hypothalamus and peri-aqueductal gray (PAG). Individual functional differences in this network have also been

postulated to underlie differences in temperament (McNaughton and Corr 2004). The best characterised of these defence/pain systems for mediating patterned ANS responses to facilitate certain types of behaviour however are that of the medial hypothalamus (Lumb 2004) and PAG (Bandler et al. 2000). These studies were performed in rats and cats using a top-down lesion/stimulation strategy.

The ventrolateral PAG receives visceral sensory input via the nucleus of the solitary tract (NTS) and also receives pain inputs from the spinal dorsal horn. Only spinal inputs appear to innervate the lateral PAG however. Dorsolateral PAG may in contrast be entirely innervated from higher CNS structures (Bandler et al. 2000). Dorsolateral and lateral PAG stimulation produce a classic fight-flight ANS response, whilst lesions in this area prevent fight-flight behaviour in animals. This is associated with a characteristic ANS response similar to that for intubation, and so it is possible that the intubation patterned ANS response was mediated via the dorsolateral or lateral PAG. The sustained nature of PNS withdrawal may additionally point towards higher e.g. pre-frontal influences via the dorsolateral PAG rather than simply reflex spinal effects on the lateral PAG. Conversely, the ventrolateral PAG (VLPAG) produces a freeze response characterised by hypotension, and bradycardia with marked PNS increased activity and SNS withdrawal.

The pain-related ANS responses in this study did not fit neatly into these dichotomous fight-flight or freeze ANS response patterns but had some features of both albeit more towards the ventrolateral PAG pattern (such as vasodepression). PNS and SNS co-activation may be a characteristic of a different type of freeze behaviour sometimes called "effroi"/"fright", tonic-immobility or hypervigilance (Bracha 2004; Bracha et al. 2004). In this behaviour SNS activation is initially constrained by PNS activation, but prepared if subsequently necessary for SNS activation to be disinhibited from PNS activity for fight/flight behaviours. Recent work by Carrive and Walker has suggested that the VLPAG outputs can be "blended" with defence arousal system outputs to produce just this kind of pattern i.e. neither fight-flight nor "flaccid-freeze" but a more "tonic-freeze" pattern (Walker and Carrive 2003).

Paton et al have used a predominantly bottom-up approach in a working rat heart-brainstem preparation to study ANS responses to pain and their brainstem origins. They were also intrigued to find a pain-related heart rate elevation associated with co-activation of cardiac vagal and SNS. They have since characterised this further using pharmacological blockade studies and found that on occasion the PNS

activity served to constrain the tachycardia but at others paradoxically facilitated it (Paton et al. 2005; Paton et al. 2006).

Clearly, the ways in which PNS and SNS may interact as part of flexible adaptive responding is more varied than simple reciprocal activity (Berntson et al. 1991). My study may be the first to report patterned PNS/SNS co-activation plus tachycardia and vasodepression for pain in humans.

I found little evidence for any considerable distinction between visceral and somatic pain in psychophysical or ANS responses at the group level. Yet despite similar intensity levels, proximal balloon distensions were more unpleasant than nail-bed pain which may account for some of their quantitative differences in ANS responses. It is possible that the lack of major differences in qualitative ANS response patterns, such as might be expected from the lateral/ventrolateral PAG studies, may be because nail-bed pressure represents "deep" somatic as opposed to superficial somatic pain (such as heat). Recent evidence suggests that any such distinctions may be untenable in an integrated "homeostatic afferent processing network" (Craig 2003).

Another novel feature of this study was dissection of the time course of the selective ANS responding to pain. Maximal change occurred in the second 10 second epoch after the commencement of the pain stimulus. The stimuli themselves however took several seconds each to perform; they may not therefore be directly comparable to punctate millisecond stimuli on the one hand or more tonic stimuli on the other. The time-course of pain responses confirms that it is physiologically more meaningful to study ANS change on a beat-to-beat time scale rather than 1 minute blocks as has been the case for non-invasive PNS studies using traditional RSA based measures in humans.

The other main finding was a relationship between personality and pain-related CVT changes for the distal oesophagus. In particular, more neurotic individuals exhibited increases in CVT change with subsequent painful stimuli whereas the more emotionally stable individuals had reduced or more negative CVT changes with subsequent stimuli.

This current finding builds on those from a previous study (chapter 3) which explored relationships between a Respiratory Sinus Arrhythmia (RSA) based measure of cardiac vagal control (CVC) and distal oesophageal balloon distension evoked pain. The previous study found 2 psychophysiological profile clusters for distal

balloon pain – one was that of neurotic-introverts who had an increase in RSA to pain whereas stable-extroverts had a decrease in RSA.

The current study was not however a simple reproduction of the previous findings. Firstly the proportion of those who increased versus decreased RSA to pain was almost equal in the first study whereas in the current study most subjects increased their CVT to pain. Secondly, the time frame and physiological basis of CVT and RSA CVC measures were different - 1 minute blocks of respiratory modulated CVC (RSA) in the first study versus 10 second blocks of baroreceptor modulated CVC (CVT) in the current study. Thirdly, the previous study findings were based on pain-related changes relative to pre-study baseline RSA levels rather than pre-stimulus levels in the current study. Finally, the current study explored the slope of stimulus to stimulus CVT pain related changes rather than simply the mean of all stimulus CVT pain changes in the previous study.

The current study adds to those of the previous study, firstly by a broad confirmation of a relationship between pain related changes in CVC and neuroticism and extroversion dimensions of personality. Furthermore, it suggests that even when there are not clear dichotomous changes in CVC to pain within a group of subjects, personality differences can be identified by using dynamic statistical summary measures such as the slope which take into account stimulus by stimulus alterations in CVC change. Once again these broadly confirm the direction of findings from the previous study that more neurotic-introvert individuals have a tendency towards increasingly positive changes in CVC with subsequent pain stimuli. Lastly, the current study shows that the relationship between CVC pain related changes is evident for the "true visceral" distal oesophagus but not for deep somatic nail-bed pain or "intermediate" proximal oesophagus.

In conclusion, I provide evidence of novel pain-related sympathetic and parasympathetic co-activation with vasodepression which was similar for visceral and somatic pain. Furthermore I found a relationship between personality and pain related changes in cardiac vagal tone. These findings may have relevance for the clinical overlap in somatic and visceral pain conditions and also for understanding individual differences in pain response.

Chapter 5 An fMRI study of the effect of personality on the brain activation during negative emotional context induced visceral hyperalgesia

Prologue to chapter 5

This and the following study in chapter 6 both explore the effects of personality on brain activity during visceral pain. They thus complement the preceding studies of the effects of personality on autonomic responses to visceral pain in chapters 3&4. They however build further on the ANS studies by exploring the interaction between emotion and visceral pain explicitly. They also enabled assessment of activity in key central autonomic control structures such as the amygdala, the insula and the anterior cingulate cortex.

The imaging studies were piloted with ANS measures, however the prolonged inter-stimulus interval necessary for ANS responses meant it was not possible to repeat paired emotion-pain stimuli in large numbers. Non-significant trends were seen for the behavioural interactions between emotion and pain in the pilot work which were confirmed in the subsequent imaging studies. Attempts were made to obtain skin conductance and cardiac vagal control measures in the scanner simultaneously with brain activity, however numerous technical problems with filtering and operation of the equipment in the MR environment prevented this. Technical problems also prevented a direct comparison between visceral and somatic thermal pain.

5.1 Abstract

Brain activity which may underlie the overlapping and interacting constructs of pain, emotion, interoception and personality is poorly understood. I have explored these processes using functional magnetic resonance imaging in healthy female subjects by combining painful balloon distension of the oesophagus with faces expressing different emotional intensities. I found that a negative emotional context caused an increase in the perceived intensity of painful oesophageal balloon distension (hyperalgesia) compared to a neutral context. This was associated with greater brain activity in brainstem, insula, and anterior cingulate, medial frontal and post-central areas. Personality differences correlated with additional thalamic, amygdala and hippocampal activations that weren't apparent at the group level.

These findings may represent neurobiological substrates for individual vulnerabilities to chronic hyperalgesic states and could be explored as biomarkers for diagnostic and therapeutic stratification.

5.3 Background

It is a common clinical observation that chronic functional pain conditions, such as the irritable bowel syndrome and fibromyalgia, share considerable affective co-morbidity including anxiety and depression (Wessely et al. 1999; Sharpe and Carson 2001; Wessely and White 2004). Furthermore it has been shown that negative affective states and personality traits are associated with the development of chronic abdominal pain and bowel dysfunction following an episode of gastroenteritis (Gwee et al. 1999).

This link between negative emotion and unpleasant bodily sensations has also been found experimentally. Using functional magnetic resonance imaging (fMRI) our laboratory has previously demonstrated that non-painful oesophageal sensation is experienced as more unpleasant during a negative emotional context in comparison to a neutral emotional context. Furthermore, there was a positive correlation between the intensity of the negative emotional context and the degree of insula and anterior cingulate cortex activity observed (Phillips et al. 2003).

A recent fundamental reclassification of pain as a "homeostatic emotion" helps to make sense of these convergent clinical and experimental findings (Craig 2003). In this framework, pain is part of a comprehensive "homeostatic afferent processing network" responsible for "interoception", i.e. the sense of the physiological condition of the body (Craig 2002; 2003; 2004; Mayer et al. 2006). Whilst most interoceptive processes are pre-cognitive, for example involving vago-vagal reflexes, many including pain reach consciousness and influence mood and behaviour, possibly even forming the basic substrate of consciousness itself (Damasio 1994; 1999). This suggests that pain and emotion are not sharply demarcated or polarised phenomena in which "hard-wired"/peripheral-to-central nociceptive neuro-transmission contrasts with emotional elaboration that is "soft-ware"/mind-based as in traditional Cartesian models.

Somato-sensory cortex may play a role in localisation and intensity encoding for pain, as per traditional schemata of medial and lateral pain systems (Melzack and Casey 1968; Melzack and Katz 1999; Schnitzler and Ploner 2000). However for pain as a homeostatic emotion the neuroanatomical emphasis is shifted to the insula cortex which seems particularly important as an interoceptive-sensory cortex whilst in turn the anterior cingulate cortex (ACC) appears to sub-serve homeostatic motor functions (Mayer et al. 2006). These may represent neuro-anatomical substrates for bi-directional influences between homeostatic emotions as varied and diverse as hunger, fear and pain.

The personality dimension of neuroticism acts as a general clinical risk factor for functional syndromes among other conditions (Claridge and Davis 2001; Ormel et al. 2004; Yousfi et al. 2004). In particular, neuroticism increases risk for developing post-operative pain (Bisgaard et al. 2001); is associated with chronic painful conditions including post-infective irritable bowel syndrome in both adults and children (Gwee et al. 1999; Tanum and Malt 2001; Weber et al. 2001; Malt et al. 2002; Boyd et al. 2005; Pallegama et al. 2005) and neuroticism also affects response to analgesics (Wasan et al. 2005) and anti-depressants in pain (Tanum and Malt 2000). More neurotic individuals generally exhibit lower pain thresholds and greater affective responses to pain (Goubert et al. 2004; Ramirez-Maestre et al. 2004; Raselli and Broderick 2007). Links have also been found between neuroticism and both the cortical processing (Pauli et al. 1999; Vossen et al. 2006) and physiological reactivity to pain (Netter and Hennig 1998; Vlaeyen et al. 1999; Evers et al. 2001). Finally neuroticism has been found to affect pain beliefs and coping (Asghari and Nicholas 2006).

The core brain areas in the homeostatic processing network (insula and ACC) as well as the amygdala have repeatedly been implicated in separate imaging studies of pain, emotion and personality including neuroticism and related constructs (Canli 2004; Davidson 2004; Kumari et al. 2004; Eisenberger et al. 2005; Deckersbach et al. 2006; O'Gorman et al. 2006; Wright et al. 2006; Haas et al. 2007; Perez-Edgar et al. 2007; Pollatos et al. 2007; Stein et al. 2007; Yucel et al. 2007).

The amygdala, which is thought to be a major structure involved in emotion, differentially activates according to serotonin transporter polymorphisms which affect emotional function and are also linked to neuroticism (Lesch et al. 1996; Hariri et al. 2002; Sen et al. 2004). This suggests that pain, emotion, interoception and

personality not only overlap as constructs, but that some aspects of personality may also arise from shared neural substrates and genetic influences.

Extroversion/social-introversion is another core personality dimension which shares with neuroticism/emotional-stability the greatest degree of consensus. A relationship between introversion to lower sensory and pain thresholds is well established and probably more robust than the relationship with neuroticism (Barnes 1975; Stelmack 2004). Furthermore, extroverts inhibit overt expressions of suffering less than do introverts (Harkins et al. 1989).

Despite the emerging evidence to suggest shared central activity underlying pain, emotion, interoception and personality I know of no studies that have attempted to concurrently explore their interactions and brain activity. The aim of my study was therefore to explore the effects of personality on brain activity during an interoceptive stimulus (oesophageal balloon distension) at levels of pain sensation in a negative emotional context.

I demonstrate here (i) that a negative emotional context induces visceral hyperalgesia (ii) I report the brain activation which is associated with this negative emotional context induced visceral hyperalgesia (iii) I show the differential effects of personality on the brain activation for negative emotional context induced hyperalgesia.

5.4 Methods

5.4.1 Participants

14 healthy female volunteers participated in this study (age range 22-54). Subjects were not on any medications and were all experienced volunteers who had previously undergone GI pain studies. To ensure they were not unduly anxious subjects they also had an orienting visit to lie in the scanner if they had not previously participated in imaging studies. Anxiety levels were assessed at 6 minute intervals throughout the study via an online visual analogue scale.

5.4.2 Physiological techniques

Oesophageal balloon distension

Oesophageal balloons were assembled from 3 cm lengths of thin silicone tubing (Medasil UK) tied and glued 0.5cm at each end over perforations 2cm from the end of a commercially available nasogastric tube (Pennine Healthcare Ltd, 2.7 mm, 120cms) thus creating a 2cm diameter balloon. The tube was swallowed per-orally or trans-nasally according to subject preference and the balloon was positioned 30cm ab orus. No local anaesthetic was used for the intubation but passage was eased through the nasopharynx with a water-based lubricant jelly (KY jelly, Johnson & Johnson).The nasogastric tube was attached via a 10 meter length of plastic tubing passed through the scanner waveguide inlet to an inflation pump (medical physics department, Hope Hospital, Salford) which was positioned in the scanner control room.

Oesophageal pain tolerance thresholds were set with the subject reclined in the scanner. The balloon inflation time was set at 250msec and the pressure in the balloon was increased in 2 Psi increments until the subject indicated that the sensation had reached a level of pain at which they could not tolerate any further increases. This pressure of stimulation was repeated twice further to confirm a consistent level of tolerable pain sensation and was then kept at this same level throughout the study.

The pump design did not permit rapid accurate alterations in balloon pressure whilst the scanner was in operation so subjects tended to habituate throughout the study. To avoid systematic bias effects of this habituation on pain-emotion paired stimuli responses, the stimulus pairs were randomised across the study period. The randomised playlist was generated using random number lists generated from http://www.randomizer.org/form.htm.

Emotional faces

Facial expressions were employed from a standardized series (Ekman and Friesen 1975) to provide neutral and fearful emotional contexts. 12 original Ekman identities (6 female, 6 male) were supplemented by eight new facial identities (4

female, 4 male) which were matched for valence and intensity to the Ekman series using the Facial Affective Coding System (Ekman et al. 2002). These faces and the visual analogue scale questions and responses were back projected using a PC driven digital projector onto a specially made screen (Ellie screens, UK).

5.4.3 Psychological trait measures

Subjects completed the Big Five Inventory questionnaire which is a 44 item personality questionnaire based on the five main personality dimensions of neuroticism, extroversion, agreeableness, openness and conscientiousness (John et al. 1991; Benet-Martinez and John 1998; John and Srivastava 1999). Only the subscales of neuroticism and extroversion were used in the subsequent analysis since there is broad consensus regarding these 2 dimensions in most personality schemata and since there is previous imaging work in the literature for comparison.

5.4.4 Stimulus Presentation and behavioural response measures

30 repetitions of each stimulus pair combination (neutral face plus painful stimulation, fearful face plus painful stimulation) were delivered with a 12 second inter-stimulus interval by a randomly generated playlist as above.

Software was written in visual basic on a PC based windows platform (Mr. Chris Andrews, Institute of Psychiatry) to 1) run the playlist; 2) co-ordinate trigger inputs from the MR scanner (a TTL pulse transmitted every 4 dynamics or every 12 seconds) with face presentation and balloon distension; 3) administer the subsequent presentation of Visual analogue scales (VAS) and the recording of VAS responses.

Each stimulus-face presentation lasted 3 seconds with the balloon distension delivered at the onset of the face presentation. Following each stimulus-face presentation the subjects were asked to respond to a question that was displayed on the screen together with a sliding visual analogue scale (VAS) for subject response by means of a button box (Mr. Chris Andrew, Institute of Psychiatry). The VAS scale was anchored at the two extremes by values of 1 and 10.

The cursor representing the subject's response was randomly assigned a different value at the onset of each VAS question in order to avoid systematic biasing

of the subsequent response. There was a delay between the end of the stimulus-face presentation and VAS display which was randomised between 1 and 3.5 seconds to avoid systematic effects on haemodynamic (BOLD) response. The VAS was then displayed for the remainder of the 12 second inter-stimulus interval (ranging between 5.5 to 8 seconds).

After each combined face presentation + painful stimulation, subjects were asked to rate their perceived intensity of the painful stimulus. The anchor value 1 for this question was labeled as "no sensation" and 10 as "extremely painful".

Additionally, every 10 minutes, both at the beginning of the study and throughout their time in the scanner subjects were asked to rate how anxious they were feeling at that moment in time. The value anchor 1 for this question was labeled as indicating "not at all anxious" and value 10 was labelled as "very anxious".

The subjects were allowed to practice responding to the questions before the actual study commenced to ensure they fully understood and were able to perform the task.

Behavioural scores were analysed offline and compared using paired student t-tests in stats-direct statistical software.

5.4.5 fMRI scanning

Gradient echo echoplanar imaging (EPI) data were acquired on a Philips 3T Achieva system (Philips Medical Systems, Eindhoven, NL) at the University of Manchester's Translational Imaging Unit, Manchester, UK. An 8 channel SENSE head coil was used for radio frequency (RF) reception. 300 T_2^*-weighted images depicting blood oxygenation level dependence (BOLD) contrast were acquired during the experiment at each of 36 near-axial contiguous 3.6 mm thick planes (parallel to the inter-commissural (AC-PC) line): TE 35 ms, TR 3 s. The slices had an in-plane resolution of 1.8 x 1.8 x 3.6 mm. Field of view was 230 mm. Sense factor was 2. Head movement was limited by foam padding within the head coil and a restraining band across the forehead.

fMRI Data analysis

The fMRI data were analysed with software developed at the Institute of Psychiatry (XBAM version 3.4), using a nonparametric approach to minimise assumptions (c.f. http://brainmap.it for more information).

Prior to time-series analysis for the detection of experimentally determined activations, image artifacts caused by subject motion during the course of the functional study were minimised using the realignment method described extensively by (Friston et al. 1996). Following co-registration, the images were then smoothed using a Gaussian filter (FWHM 7.2mm) chosen to improve the signal-to-noise ratio over the spatial neighbourhood of each voxel. A modification of the method of Friston *et al* (Morris et al. 1998) has been developed in which BOLD responses are modeled as the weighted sum of the input function convolved with two Poisson functions. A goodness of fit statistic was computed as the ratio of the modeled and residual sums of squares (SSQ ratio). Under randomisation testing the SSQ ratio can be used to replace an F test. The SSQ ratio does not require knowledge of the degrees of freedom in the model or the residuals. Voxel-wise inference was carried out non-parametrically, and individual maps were identified by spatiotemporal randomisation testing (Bullmore et al. 2001). Presentation of neutral faces in the absence of oesophageal balloon distension was used as the baseline condition from which changes in BOLD response were identified in the other nine stimulus conditions. At the group level individual statistical maps were transformed into standard stereotactic space using a two-stage process; for each subject an average image of all functional volumes was made, this was first registered to a structural image obtained for the same subject and subsequently registered to a template in standard space. The same transformation was then applied to the statistic image to map it into standard space.

5.4.6 Comparing conditions within fMRI data

A repeated measures analysis of co-variance (ANCOVA) was used to test for differences in the median residual sum of squares ratio (SSQ ratio) between the two conditions. This was carried out by first computing the average difference in brain activation between conditions over all subjects at each voxel. The data were then randomly reallocated between the two conditions for each subject (i.e. within subjects

but not between subjects) and the average difference between conditions over all subjects recalculated after each permutation. This randomization procedure was repeated fifty times at each voxel and the results of the computations combined over all voxels. The resulting distribution represents the null hypothesis of no net change in response between conditions. The observed data were compared to the null distribution to identify voxels showing significant changes. Three-dimensional clusters of significant voxels (at $p< 0.05$) were identified and their mass (sum of suprathreshold voxel statistics) compared against a null distribution of cluster mass formed from the permuted data. Results were thresholded at a clusterwise value of $p<0.003$, this being the threshold at which less than one false positive cluster would be expected per analysis over the whole search volume.

5.4.7 Behavioural brain activation maps

1. Simple correlation analysis

With the individual personality trait values (neuroticism and extroversion), correlation analysis was performed between the BOLD effect data for each individual and the behavioural data. This proceeds by first choosing the statistical map (fMRI response) corresponding to the particular experimental contrast of interest. The Pearson product moment correlation coefficient is then computed between the personality data for each subject and the fMRI responses at each voxel for each subject, yielding one correlation coefficient, (r) per intracerebral voxel. To determine the significance of these correlation coefficients the appropriate null distribution of r is computed robustly using data permutation. The order of the behavioural data is randomly permuted without replacement (i.e. each data value occurs once but the order is changed) breaking the association between individual behavioural data and their corresponding fMRI responses. The correlation coefficient is then recomputed many times at each voxel and the resulting values of r combined over all voxels to produce a whole brain null distribution of r. The critical value of r for significance at any particular p value can then be obtained from this distribution after simply sorting it by value of r and selecting the appropriate point from the sorted distribution, e.g. the critical value of r for a one-tailed test at p 0.05 would be the value of r in the null distribution chosen such that 95% of all the null values of r lay below that point. Testing can then be extended to cluster level as described previously. The cluster

probability under the null hypothesis can be chosen to set the level of expected type I error clusters at an acceptable level (e.g. < 1 per whole brain).

2. Analysis of differences in correlations

For the ANOVA of fearful faces alone versus fearful faces plus pain, the differences in correlations with neuroticism and extroversion of activations between the two conditions was calculated as follows. At each voxel, the correlation co-efficient was first calculated for activation maps for fearful faces alone and personality trait scores. This was then repeated for activation maps of fearful faces plus pain and personality trait scores. The difference between these two values was then calculated which gives the observed difference. This difference was then tested statistically by permuting the subjects and scores and by repeating the correlation process.

Brodmann area assignment

Brodmann area assignment of Talairach co-ordinates was firstly via the XBAM analysis package which produces Brodmann assignments for the Talairach co-ordinates generated. For all cluster sizes of 10 or above, the co-ordinates were further checked with Talairach Daemon (Lancaster et al. 2000). Where Talairach Daemon and XBAM agreed these Brodmann assignments were accepted. Where there was disagreement the co-ordinates were checked by hand in a Talairach atlas. In the majority of cases the hand checking agreed most closely with the Talairach Daemon Brodmann assignment.

5.5 Results

5.5.1. Negative emotional context induced visceral hyperalgesia

There was an increase in the perception of pain intensity during the viewing of fearful faces compared with neutral faces (mean ± SEM: 6.52 ± 0.31 pain intensity rating during fearful faces vs. 6.18 ± 0.25 pain intensity rating during neutral faces, $p = 0.0048$, 2 tailed paired t test). In other words there was a heightened painful sensation for what was already a painful sensation. This can be described as negative emotional context induced hyperalgesia [Figure 5.1].

The group mean neuroticism score was 2.61± 0.22 and the extroversion score was 3.48± 0.25. There was a significant negative correlation between neuroticism and extroversion ($r = -0.87$, $p < 0.0001$). The groups mean anxiety levels were 2.06 ± 0.34. No correlations were seen between anxiety scores, personality scores and either absolute pain ratings or change in pain ratings.

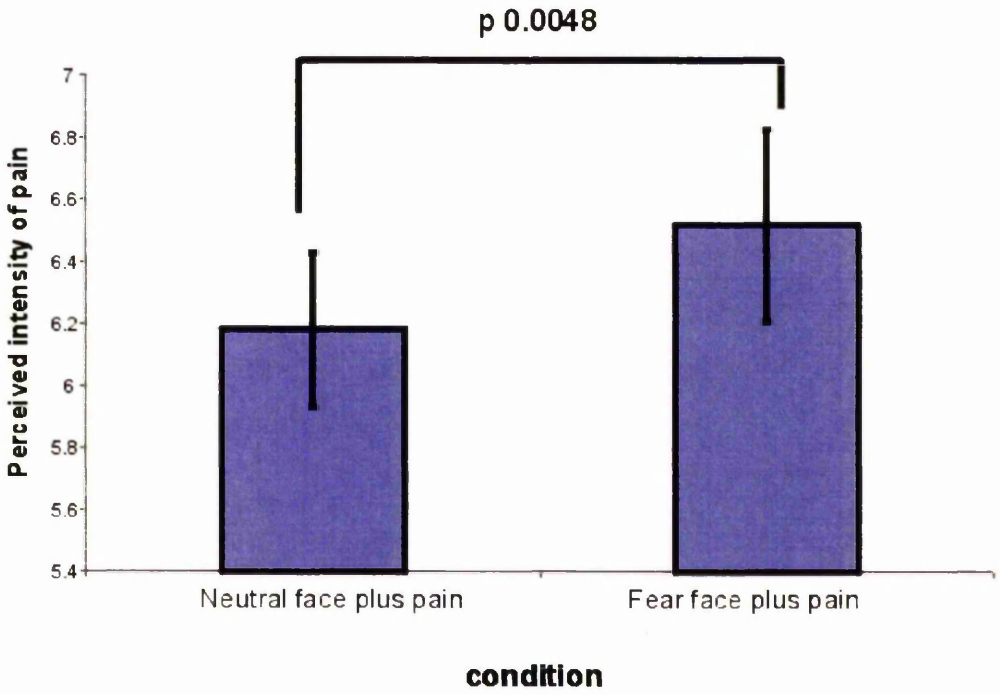

Figure 5.1 Increased perceived pain intensity (mean ± SEM) when oesophageal balloon distension was combined with faces exhibiting fear compared with neutral emotion.

5.5.2. Brain activation seen during emotional context induced hyperalgesia

Fearful faces + pain group brain activations were compared with those for neutral faces + pain. Areas of greater activity were seen during the hyperalgesic fearful face condition in left sided brainstem, insula, medial frontal gyrus, anterior cingulate gyrus and post-central (BA2) gyrus when compared with neutral faces + pain [table 5.1C and figure 5.2]. Brain activity was greater in visual areas for the neutral faces + pain condition than the fearful faces + pain condition [table 5.1D].

Group brain activations are given separately for conditions where subjects viewed neutral faces + pain in table 5.1A and then for subjects viewing fearful faces + pain in table 5.1B.

Analysis type	Cluster size	x,y,z	Side	BA	Location
A Group - Neutral + pain p all < 0.007	21	46,-25,10	R	41	superior temporal
	20	-46,-12,3	L	22	superior temporal
	28	-19,43,16	L	9	medial frontal
	19	-13,46,20	L	9	Superior frontal
	12	-17,46,10	L	10	medial frontal
	24	10,-70,-23	R		cerebellum
B Group - Fear + pain p all <0.004	23	-1,-82,30	L	19	cuneus
	33	1,-14,50	R	6	medial frontal
	11	-1,25,40	L	8	medial frontal
	15	-46,-12,3	L	22	superior temporal
	18	-46,-11,13	L		insula
	21	-7,-55,-23	L		cerebellum
C ANCOVA NEG (fear + pain > neutral + pain) p all < 0.006	13	0,30,33	L	32	Anterior Cingulate
	16	-42,-23,30	L	2	Post-central gyrus
	11	-1,25,40	L	8	medial frontal gyrus
	36	-45,-21,23	L		insula
	18	-4,-43,-33	L		brainstem, pons
	17	-9,-46,-36	L		brainstem, medulla
D ANCOVA POS (neutral + pain > fear + pain) p all < 0.0095	31	26,-46,-10	R	37	parahippocampal gyrus
	34	4,-62,36	R	7	precuneus
	19	-14,-61,36	L	7	precuneus
	71	38,-50,-13	R	37	fusiform gyrus
	17	-49,-34,7	L	22	superior temporal gyrus
	20	13,-64,-36	R		cerebellum

Table 5.1: areas of brain activation seen for the group as a whole **A**. for viewing neutral faces + pain compared with neutral faces alone as baseline **B** for viewing fearful faces + pain compared with neutral faces as baseline **C** ANCOVA of brain areas more active for condition fearful faces + pain than for viewing neutral faces + pain **D** ANCOVA of brain areas more active for condition viewing neutral faces + pain than for fearful faces + pain (BA = Brodmann area; xyz = Talairach co-ordinates L = left, R = right).

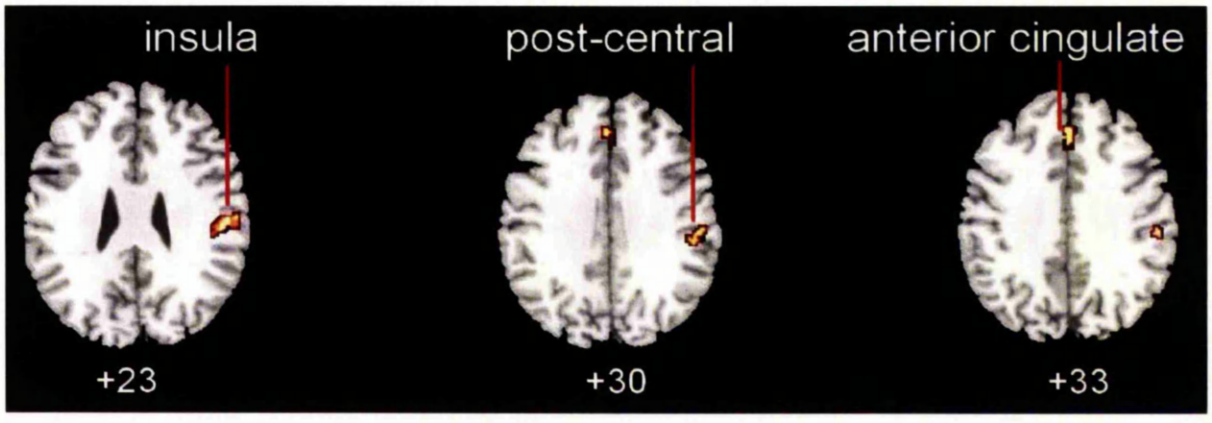

Figure 5.2 Brain activation maps for areas of brain activity greater in fearful faces + pain (hyperalgesia) condition compared with neutral faces + pain

5.5.3. Personality affects brain responses during negative emotional context induced visceral hyperalgesia

The finding of negative emotional context induced visceral hyperalgesia and its concomitant brain activations were not a *directly* measured phenomenon but rather *indirectly inferred* from a comparison of the differences between the two conditions (negative and neutral). Similarly, it was not possible to directly measure effects of personality on the brain responses for negative emotional context induced visceral hyperalgesia. Rather, it was again necessary to use a similar indirect inference based once more on a comparison of the differences between the conditions. The *differences* between personality correlations for the two conditions were analysed. In other words the areas of brain activity were determined that were *more correlated* with personality scores for the first condition (neutral faces + pain) than the second condition (fearful faces + pain) and vice versa. This then was essentially a comparison of means albeit that the means were for strength of correlation (see methods section 5.4.7.2). For this reason the meaning of the results are not immediately intuitive and require some explanation.

Those brain areas for which activity was more correlated to personality with fearful faces + pain vs. neutral faces + pain equate to those areas of increasing brain activity for negative emotional context induced visceral hyperalgesia as personality score increases. These are shown in table 5.2A for neuroticism and table 5.2C for extroversion. Conversely those brain areas for which activity was more correlated to

personality with neutral faces + pain vs. fear faces + pain equate to areas of reducing brain activity for negative emotional context induced hyperalgesia as personality score increases. These are shown in table 5.2B for neuroticism and table 5.2D for extroversion.

I found differences in correlations with personality scores between the two conditions in a widely distributed network of differentially active brain areas. Amygdala, thalamic and hippocampal activations, which weren't observed at the group analysis stage, became evident when correlated with individual differences in personality scores. Given that in my study group the neuroticism and extroversion scores were negatively correlated, some areas of brain activation that correlated more with neuroticism were almost, though not exactly, mirror images of those for extroversion.

In particular, neuroticism scores were more correlated, when viewing neutral faces + pain vs. fearful faces + pain, with activity in brain regions including bilateral amygdala, right posterior cingulate, right precentral and paracentral gyri, left medial frontal gyrus and right thalamus, caudate and putamen [figure 5.2A, table 5.2B]. The inference of this therefore is that for negative emotional context induced visceral hyperalgesia these were areas of reducing brain activity (but not necessarily inactivity) with increasing neuroticism scores. Conversely, some of these areas were more correlated with extroversion scores for fearful faces + pain vs. neutral faces + pain, including right amygdala and paracentral but additionally left hippocampus, insula and right middle frontal [figure 5.2B, table 5.2C]. The inference of this in turn is that for negative emotional context induced visceral hyperalgesia these were areas of increasing brain activity with increasing extroversion.

Neuroticism was also more correlated, for fearful faces + pain vs. neutral faces + pain, with activity in brain regions including left anterior cingulate gyrus [figure 5.2C], right medial frontal gyrus, left putamen and bilateral caudate [table 5.2A]. The inference of this is that for negative emotional context induced visceral hyperalgesia these were areas of increasing brain activity with increasing introversion. Some areas of visual cortex, the left caudate and right midbrain were more correlated with extroversion scores for neutral faces + pain vs. fearful faces + pain [table 5.2D]. The inference of this in turn is that for negative emotional context induced visceral

hyperalgesia these were areas of reducing brain activity (but not necessarily inactivity) with increasing extroversion scores.

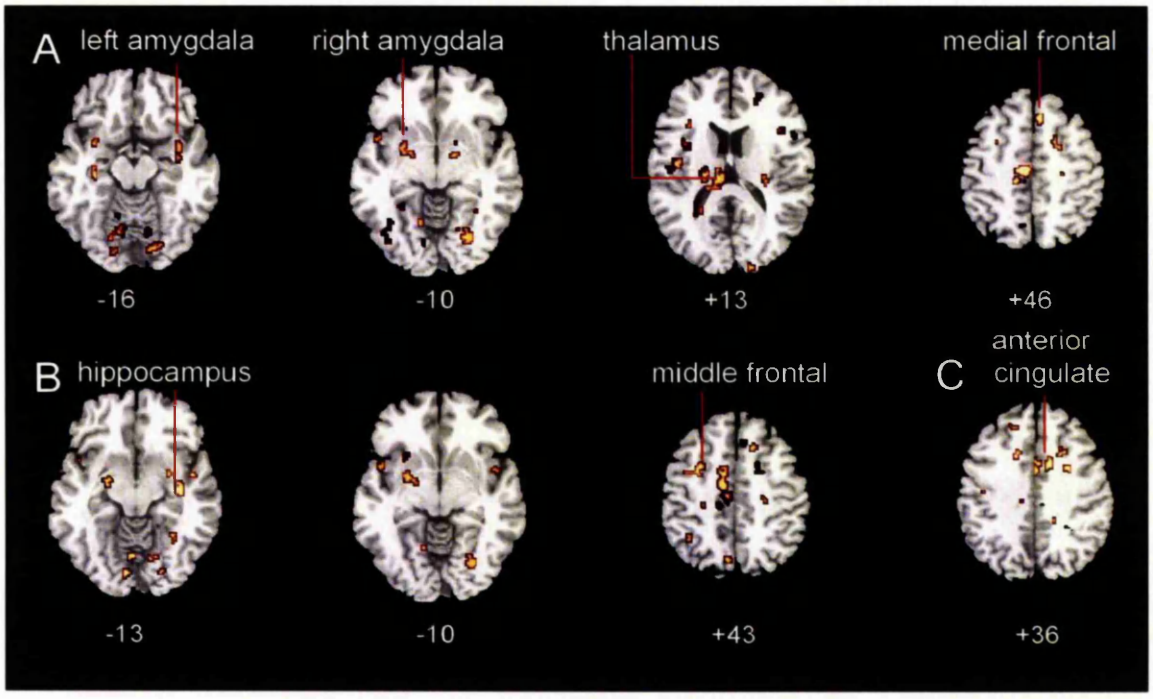

Figure 5.3 Brain activation maps **A:** representative images of activity in areas more correlated to neuroticism when viewing neutral faces + pain compared with fearful faces + pain (i.e. inferentially areas of reducing brain activity (but not necessarily inactivity) as neuroticism increases for negative emotional context induced visceral hyperalgesia) **B:** representative images of activity in areas more correlated to extroversion when viewing fearful faces + pain compared with viewing neutral faces + pain **C:** representative image of activity in areas more correlated to neuroticism when viewing fearful faces + pain compared with neutral faces + pain (i.e. inferentially areas of increasing brain activity as extroversion increases for negative emotional context induced visceral hyperalgesia) (number at base of each brain = z-Talairach co-ordinate level). All activations shown are at significance level $p<0.00002$ and cluster size > 10. See table 3 for other areas of brain activations and Talairach co-ordinates.

A full list of associated areas of activation with personality scores for comparison between neutral faces + pain and fearful faces + pain, together with details of cluster sizes, Talairach co-ordinates and significance levels are given in Table 5.2.

Type of analysis	Size	x,y,z	Side	BA	Location
A ANCOVA: Neuroticism greater correlation with fear plus pain vs. neutral plus pain p all < 0.00002	22	17,-16,-20	R	28	parahippocampal
	13	-9,5,36	L	24	Anterior Cingulate
	19	-7,-41,43	L	31	posterior cingulate
	48	-29,-86,10	L	19	middle occipital
	14	-4,-64,26	L	31	precuneus
	14	22,11,43	R	32	medial frontal
	11	-4,-27,456	L	31	paracentral
	15	-22,4,13	L		putamen
	13	-13,7,20	L		caudate
	12	14,0,13	R		caudate
B ANCOVA: Neuroticism greater correlation with neutral plus pain vs. fear plus pain p all < 0.00002	19	17,-5,-10	R		amygdala
	9	-29,-4,-16	L		amygdala
	10	4,-20,30	R	23	posterior cingulate
	12	13,-77,23	R	18	cuneus
	17	19,-68,33	R	7	precuneus
	13	35,2,33	R	6	precentral
	11	-4,23,46	L	8	medial frontal
	22	6,-20,46	R	31	paracentral
	32	7,-16,13	R		thalamus
	11	7,11,7	R		caudate
	10	29,0,10	R		putamen
	26	23,-62,-26	R		cerebellum
C ANCOVA: Extroversion greater correlation with fear plus pain vs. neutral plus pain p all < 0.00002	15	-27,-18,-13	L		hippocampus
	12	-1,-18,26	L	23	cingulate
	20	1,-41,26	L	31	cingulate
	10	6,-23,30	R		Cingulate Gyrus
	22	9,2,33	R		Cingulate Gyrus
	19	17,-5,-10	R		Amygdala
	16	-19,-71,-10	L	18	lingual gyrus
	29	7,-11,43	R	31	paracentral lobule
	19	23,2,43	R	6	middle frontal gyrus
	11	-32,11,13	L		insula
	13	20,-50,-26	R		cerebellum
D ANCOVA: Extroversion greater correlation with neutral plus pain	22	19,-68,-7	R	19	lingual gyrus
	19	-38,-66,7	L	19	middle occipital gyrus

vs. fear plus pain p all < 0.00002	13	-14,-84,26	L	18	cuneus
	15	-7,-12,46	L	31	paracentral lobule
	17	-16,7,13	L		caudate
	22	1,-11,-7	R		mamillary body

Table 5.2: areas of brain activation **A** more correlated with neuroticism for fearful faces + pain compared to neutral faces + pain (i.e. inferentially areas with increasing brain activity with increasing neuroticism for negative emotional context induced visceral hyperalgesia) **B** more correlated with neuroticism for neutral faces + pain compared to fearful faces + pain (i.e. inferentially areas of reducing brain activity (not necessarily inactivity) with increasing neuroticism for negative emotional context induced visceral hyperalgesia) **C** more correlated with extroversion for fearful faces + pain compared to neutral faces + pain (i.e. inferentially areas with increasing brain activity with increasing extroversion for negative emotional context induced visceral hyperalgesia) **D** more correlated with extroversion for neutral faces + pain compared to fearful faces + pain (i.e. inferentially areas of reducing brain activity (not necessarily inactivity) with increasing extroversion for negative emotional context induced visceral hyperalgesia) (BA = Brodmann area; xyz = Talairach co-ordinates L = left, R = right).

Separate negative and positive correlations of brain activity with neuroticism and extroversion scores for viewing neutral faces + pain and then for fearful faces + pain are given in table 5.3 A-H.

Analysis type	Cluster size	x,y,z	Side	BA	Location
A Negatively correlated with Neuroticism (neutral plus pain) p all < 0.00002	23	33,-16,-10	R		hippocampus
	103	-1,20,20	L	33	Anterior Cingulate
	56	-10,7,33	L	24	Anterior Cingulate
	27	-6,16,40	L	32	Anterior Cingulate
	12	3,-88,0	R	18	lingual
	43	-33,-86,10	L	19	middle occipital
	22	-7,-62,26	L	31	precuneus
	10	-32,-80,-3	L	18	inferior occipital
	62	-36,-57,-13	L	37	fusiform
	18	-30,-55,26	L	22	Superior temporal
	11	-27,-34,0	L		hippocampus
	12	17,30,26	R	32	medial frontal
	10	0,38,30	L	9	medial frontal
	23	-7,-12,46	L	31	paracentral
	14	16,-4,7	R		lentiform nucleus
	23	0,-11,-7	L		mamillary body
B Positively correlated with Neuroticism (neutral plus pain)	46	6,-48,16	R	30	posterior cingulate
	24	-6,-38,20	L	23	posterior cingulate

p all < 0.00002	17	-6,-59,10	L	30	posterior cingulate
	45	3,-2,43	R	24	Anterior Cingulate
	25	17,-12,-10	R	28	parahippocampal
	15	-23,-21,-13	L	35	parahippocampal
	15	20,-84,23	R	18	cuneus
	31	-19,-71,-10	L	18	lingual
	13	45,-23,7	R	13	superior temporal
	11	36,-39,10	R	41	transverse temporal
	16	35,2,33	R	6	precentral
	20	29,12,-13	R	13	inferior frontal
	13	6,-20,46	R	31	paracentral
	35	9,-18,10	R		thalamus
	24	-33,2,7	L		claustrum
C Negatively correlated with Extroversion (neutral plus pain) p all < 0.00002	30	4,-2,43	R	24	Cingulate Gyrus
	14	19,-14,-10	R	28	Parahippocampal Gyrus
	26	3,-23,30	R	23	Cingulate Gyrus
	22	-4,-38,16	L	29	Posterior Cingulate
	14	-19,-73,-10	L	18	Lingual Gyrus
	23	4,48,20	R	9	Medial Frontal Gyrus
	13	27,9,-13	R	47	Inferior Frontal Gyrus
	31	6,-20,46	R	31	Paracentral Lobule
	21	36,-38,13	R	41	Transverse Temporal
	19	-32,11,7	L		Claustrum
D Positively correlated with Extroversion (neutral plus pain) p all < 0.00002	11	23,-45,26	R	31	Posterior Cingulate
	27	-12,23,20	L	32	Anterior Cingulate
	49	-10,5,33	L	24	Anterior Cingulate Gyrus
	46	-1,21,20	L	33	Anterior Cingulate
	31	-9,-73,26	L	18	cuneus
	23	-33,-86,10	L	19	middle occipital gyrus
	13	-17,-68,20	L	31	precuneus
	12	17,-80,10	R	17	cuneus
	11	25,-86,10	R	19	middle occipital gyrus
	13	-43,-51,20	L	39	middle temporal gyrus
	11	-39,-54,13	L	22	superior temporal gyrus
	11	13,2,7	R		lentiform nucleus
	19	0,-11,-7	R		Midbrain, mamillary body
	15	6,-50,-16	R		anterior cerebellum
	12	-3,-34,-13	L		brainstem, midbrain

E negatively correlated with neuroticism (fear plus pain) p all < 0.00002	13	27,-20,-16	R		hippocampus
	18	6,-45,33	R	31	posterior cingulate
	66	-9,-18,36	L	24	Anterior Cingulate
	25	-4,21,16	L	33	Anterior Cingulate
	13	-7,16,30	L	32	Anterior Cingulate
	24	4,-62,30	R	7	precuneus
	10	-10,27,30	L	9	medial frontal
	10	29,-4,16	R		claustrum
	23	-19,-21,13	L		thalamus
	13	-14,5,0	L		lateral globus pallidus
	21	0,-68,-20	R		cerebellum
	13	-3,-52,-40	L		cerebellum
	12	-3,-38,-13	L		midbrain
F positively correlated with neuroticism (fear plus pain) p all < 0.00002	21	9,38,20	R	32	Anterior Cingulate
	20	-7,-54,20	L	31	posterior cingulate
	11	-20,-61,-7	L	19	fusiform
	23	-6,-84,-10	L	18	lingual
	18	-17,-46,46	L	7	precuneus
	65	-30,-29,23	L		insula
	19	12,-2,20	R		caudate
	11	-19,-14,23	L		caudate
	11	-23,-2,13	L		putamen
G Negatively correlated with extroversion (fear plus pain) p all < 0.00002	15	-6,-55,13	L	23	Posterior Cingulate
	18	7,38,20	R	32	Anterior Cingulate
	11	9,-7,46	R	24	Cingulate Gyrus
	16	-4,-88,-10	L	18	Lingual Gyrus
	11	3,-82,30	R	19	Cuneus
H positively correlated with extroversion (fear plus pain) p all < 0.00002	37	-4,-20,36	L	24	Cingulate Gyrus
	14	4,27,36	R	6	medial frontal gyrus
	10	-23,-9,46	L	6	middle frontal
	23	-3,-57,30	L	7	precuneus
	24	-19,-23,13	L		Thalamus
	10	10,-16,16	R		Thalamus
	11	30,16,7	R		Claustrum
	30	-10,-25,-23	L		brainstem
	12	23,-55,-26	R		cerebellum

Table 5.3: areas of brain activation positively and negatively associated with personality scores **A.** viewing neutral faces + pain negatively associated with neuroticism **B** viewing

neutral faces + pain positively associated with neuroticism **C** viewing neutral faces + pain negatively associated with extroversion **D** viewing neutral faces + pain positively associated with extroversion **E** fearful faces + pain negatively associated with neuroticism **F** fearful faces + pain positively associated with neuroticism **G** fearful faces + pain negatively associated with extroversion **H** fearful faces + pain positively associated with extroversion (BA = Brodmann area; xyz = Talairach co-ordinates L = left, R = right.

5.6 Discussion

I have extended previous work by showing that a negative emotional context can induce visceral hyperalgesia. That is to say a previously painful visceral sensation became even more painful. Previously our group showed that a negative emotional context induced visceral allodynia. That is to say a previously non-painful visceral sensation became more uncomfortable/painful. In both studies the negative emotional context was produced by using the same faces depicting emotional expressions of fear.

The visceral hyperalgesic effect appeared to occur in the absence of any subjective mood change since anxiety levels were rated as low. It is therefore possible that fearful faces may change the "cognitive set" for incoming bodily signals compared with neutral faces to one that amplifies afferent pain signal processing, but without changing overt emotional tone. Other possibilities include that the fearful face condition opens the "pain-gate" at the spinothalamic level; or may reduce descending inhibition/ promote descending facilitation at brainstem level.

Certainly there was evidence at the group level for increased activity in the insula and anterior cingulate cortex which could be compatible with increased secondary processing of the afferent pain signal. Secondly there was increased post-central (BA2) activity and increased thalamic activity suggestive that the afferent signal itself had been amplified in its course within the spinothalamic tract. Lastly there was increased brainstem activation within pons and medulla which could be consistent with descending or ascending modulation of the incoming afferent signal but the spatial resolution is insufficient for further information and comment. The central mechanism therefore of the negative emotional context induced visceral hyperalgesia is speculative. Intriguingly the activation appeared left lateralized which goes against some of the current literature suggesting pain lateralization to the right hemisphere (Craig 2005) but this difference may relate to the specific condition of

emotional context induction of hyperalgesia which has not been well documented previously.

In addition to the novel group findings, for the first time I have shown that personality alters the brain activity associated with negative emotional context induced visceral hyperalgesia. I did not however find overt effects of personality on behavioural measures of absolute pain levels or the magnitude of visceral hyperalgesia. In related work however I found that differential brain activation related to personality type was associated with a functional-behavioural difference in the magnitude of visceral pain induced dyshedonia (see chapter 6). This would suggest that the effects of personality on brain responses during negative emotional context induced hyperalgesia may also be behaviourally relevant but this remains to be confirmed.

Furthermore, some of the brain areas correlated with personality differences during emotional context induced visceral hyperalgesia were not apparent at the group level. In particular, differential activation within the amygdala, predominantly on the right side, became apparent when personality was taken into account in analysis. This was more correlated to extroversion in the fearful + pain condition compared to neutral + pain but the converse was true for neuroticism.

The amygdala is a sub-cortical structure that is inter-connected with a widely distributed cortical, sub-cortical and brainstem network involved in emotion/pain/autonomic sensory, motor, integrative and executive function (Thayer and Lane 2000). Personality variables, in particular neuroticism, have been associated with amygdala function, behavioural effects and genotypic differences within the serotenergic system (Hariri et al. 2002). It is known that neuroticism represents a risk factor for hyperalgesic states following inflammation/injury within the gut (Gwee et al. 1999). My findings may be a step towards a neurobiological representation of this.

Although conceived of as independent, uncorrelated and orthogonal dimensions there is often a weak negative correlation between neuroticism and extroversion (Biesanz and West 2004) which converge slightly at the neurotic-introvert ends of the scales. A possible shared basis for overlap between introversion, neuroticism and anxiety may be narrower traits such as "sensation-seeking" or

"sensory-sensitivity" (Aron and Aron 1997; Stelmack 2004). The possible role of "interoceptive sensitivity" such as "anxiety sensitivity" is under-explored (Ferguson and Katkin 1996; Barrett et al. 2004). The biological basis underlying these areas of overlap in "surface traits" have been proposed as behavioural activation and inhibition systems, including the fight-freeze-flight defence systems, in which the amygdala plays a significant role (McNaughton and Corr 2004). There may however be no perfect, "isomorphic" fit between brain structures, phenomenological processes, cognitive states and traits (Matthews 2004).

In conclusion, I have demonstrated for the first time that a negative emotional context induced visceral hyperalgesia, the neural concomitants of which are influenced by personality. The clinical relevance of these findings for vulnerability to post-inflammatory visceral hyperalgesia warrant further exploration.

Chapter 6 "Dyshedonia" induced by visceral pain is modulated by personality: an fMRI study

Prologue to chapter 6

In chapter 5 it has been demonstrated that a negative emotional context induced visceral hyperalgesia and that the central concomitants of this were modulated by personality. These effects of emotional context on pain perception could be described as "top-down" effects. On theoretical grounds of a homeostatic afferent processing network, in which pain is a homeostatic emotion, it is anticipated that modulatory influences of pain and emotion perception would be bi-directional. This study therefore uses similar methodology to explore "bottom-up" effects of visceral pain on the perception of emotional context, its central concomitants and the influence of personality.

6.1 Abstract

Pain, emotion, interoception and personality are overlapping constructs however their interactions and underlying central mechanisms are poorly understood. Using functional magnetic resonance imaging, I have explored these interactions in healthy female subjects using painful balloon distension of the oesophagus combined with happy and neutral depictions of facial emotion expression. I have found that oesophageal pain causes a reduction in the perceived intensity of happy faces. This altered perception for intensity of hedonic context is a novel phenomenon that I have called "dyshedonia". Furthermore I report that the degree of dyshedonia and its associated brain activations are influenced by both neuroticism and extroversion. The brain activations influenced by personality during visceral pain induced dyshedonia occurred in a distributed network of brain foci, including sensory and limbic structures such as the amygdala, insula and anterior cingulate cortex but also the hypothalamus, hippocampus and frontal cortices. These findings may inform both the clinical overlap observed between pain and emotion disorders and also the psychobiological basis for individual vulnerabilities to them.

6.2 Background

Concepts of what constitutes pain and its processing in the brain have broadened substantially with the elaborations of lateral "sensory" and medial "emotional" pain systems (Bowsher 1957; Albe-Fessard et al. 1985) and also with further distinctions between sensory-discriminative, affective-motivational and cognitive-evaluative pain dimensions (Melzack and Casey 1968; Melzack and Katz 1999).

A radical reclassification has redefined pain as an "interoceptive" as opposed to the more traditional "exteroceptive" process (Craig 2002; Saper 2002; Craig 2003) which forms part of a "homeostatic afferent processing network" (Mayer et al. 2006). Within this conceptual framework, pain is considered to be one of many "homeostatic emotions" as seemingly diverse as fear and hunger, but which share common neural substrates at the level of the central nervous system (Craig 2003).

The insula cortex is thought to play a key role in emotion and pain as a "limbic sensory cortex" which sub-serves "interoception", that is to say the "sense of the physiological condition of the body". The dorsal anterior cingulate on the other hand serves as "limbic behavioural motor cortex" giving rise to physiological and behavioural responses (Mayer et al. 2006). It no longer seems tenable therefore to treat emotion and pain as sharply demarcated phenomena.

This framework has considerable heuristic value for understanding the commonly observed clinical overlap between pain and emotional states (Mayer et al. 2006). Clinical observation in the functional gut syndromes has shown that chronic pain and unpleasant gastrointestinal symptoms are associated with negative affect. This includes both anxiety and depression together with its attendant anhedonia – that is to say an inability to derive emotional pleasure from previously enjoyable activities (Blanchard et al. 1990; Loas et al. 1992; Masand et al. 1997; Lydiard 2001; Folks 2004; Lackner et al. 2004). Examples of these syndromes include irritable bowel and non-cardiac chest pain, however similar findings occur also in functional somatic pain syndromes such as fibromyalgia (Wessely et al. 1999; Sharpe and Carson 2001; Wessely and White 2004).

Wide inter-individual differences in pain perception and response occur in healthy as well as clinical populations. These are increasingly recognised as important considerations in imaging studies, indeed highly pain-sensitive healthy

individuals were found to exhibit more pain-induced activation of the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex than less pain-sensitive individuals (Coghill et al. 2003). Important potential sources of these differences include personality traits which are enduring dimensions of inter-individual variance with strong evidence for a neurobiological basis (McCrae et al. 2000).

Neuroticism-emotional stability (Eysenck 1967) is one of the most widely recognised dimensions of personality and is conceived of as a measure of "emotionality", in particular a negative-affect bias. Neuroticism affects pain sensitivity and emotional responses to pain with generally lower pain thresholds and greater affective responses in those with greater neuroticism (Goubert et al. 2004; Ramirez-Maestre et al. 2004; Raselli and Broderick 2007). Links have also been found between neuroticism and the cortical processing of pain (Pauli et al. 1999; Vossen et al. 2006), physiological reactivity to pain (Netter and Hennig 1998; Vlaeyen et al. 1999; Evers et al. 2001) and pain beliefs and coping (Asghari and Nicholas 2006). Clinically, neuroticism is a risk factor for the development of post-operative pain (Bisgaard et al. 2001) and other chronic painful conditions including post-infective irritable bowel syndrome (Gwee et al. 1999; Tanum and Malt 2001; Weber et al. 2001; Malt et al. 2002; Boyd et al. 2005; Pallegama et al. 2005). Neuroticism also augments clinical pain in children (Weber et al. 2001); affects pain response to analgesics (Wasan et al. 2005) and responses to anti-depressants in painful conditions (Tanum and Malt 2000).

Extroversion-social introversion is another core personality dimension which shares with neuroticism-emotional stability the broadest degree of consensus. A relationship between introversion to lower sensory and pain thresholds is well established and probably more robust even than that for neuroticism (Barnes 1975; Stelmack 2004). Extroverts are less inhibited in overt expressions of suffering than introverts (Harkins et al. 1989). There is evidence however that extroversion is not fully independent of neuroticism but has a weak negative correlation such that the introvert and neurotic ends of the scales are convergent (Biesanz and West 2004). A possible shared basis for introversion, neuroticism and anxiety may be "sensitivity" (Aron and Aron 1997) of which the role of "interoceptive sensitivity" such as "anxiety sensitivity" is under-explored (Ferguson and Katkin 1996; Barrett et al. 2004).

The core brain areas in the homeostatic processing network (insula and anterior cingulate) as well as the amygdala have been implicated repeatedly in

separate imaging studies of pain, emotion and personality including neuroticism and related constructs (Canli 2004; Davidson 2004; Kumari et al. 2004; Eisenberger et al. 2005; Deckersbach et al. 2006; O'Gorman et al. 2006; Wright et al. 2006; Haas et al. 2007; Perez-Edgar et al. 2007; Pollatos et al. 2007; Stein et al. 2007; Yucel et al. 2007). The amygdala, which is thought to be a major structure involved in emotion, is known to differentially activate according to serotonin transporter polymorphisms that affect emotional function and are linked with neuroticism (Lesch et al. 1996; Hariri et al. 2002; Sen et al. 2004). This suggests that, not only do pain, emotion interoception and personality overlap as constructs, but that some aspects of personality also arise from the same neural substrates and have shared genetic influences with these.

Using functional magnetic resonance imaging (fMRI) our laboratory has previously demonstrated that non-painful oesophageal sensation is experienced as more unpleasant during a negative emotional context. Furthermore, there was a positive correlation between the intensity of the negative emotional context and the amount of insula and anterior cingulate cortex activity (Phillips et al. 2003). However, it is not known whether the converse is true i.e. if alterations occur in the perceived intensity of emotional context during visceral pain, and what the central correlates of this might be. Such an alteration in hedonic intensity or valence perception might best be described as "dyshedonia". This neologism avoids the connotations of altered mood inherent in "dysthymia" and also the pathological loss of hedonic perception in "anhedonia".

I provide here for the first time, evidence that (i) the perception of intensity of emotional context and its central neural responses are altered by visceral pain and (ii) these are influenced by individual differences in personality.

6.3 Methods

6.3.1 Participants

14 healthy female volunteers participated in this study (age range 22-54). Subjects were not on any medications and were all experienced volunteers who had previously undergone GI pain studies or had an orienting visit during which they had a mock scan while lying in the scanner, to ensure they were not unduly anxious. Anxiety

levels were assessed at 6 minute intervals throughout the study via an online visual analogue scale.

6.3.2 Physiological techniques

Oesophageal balloon distension

Oesophageal balloons were assembled from 3 cm lengths of thin silicone tubing (Medasil UK) tied and glued 0.5cm at each end over perforations 2cm from the end of a commercially available nasogastric tube (Pennine Healthcare Ltd, 2.7 mm, 120cms) to create a 2cm diameter balloon. The tube was swallowed either per-orally or trans-nasally according to subject preference and the balloon was positioned 30cm ab orus. No local anaesthetic was used for the intubation but passage was eased through the nasopharynx with a water-based lubricant jelly (KY jelly, Johnson & Johnson).The nasogastric tube was attached via a 10 meter length of plastic tubing passed through the waveguide inlet to an inflation pump (medical physics department, Hope Hospital, Salford) positioned in the scanner control room. Oesophageal pain tolerance thresholds were set with the subject reclined in the scanner. The balloon inflation time was set at 250msec and the pressure in the balloon was increased in 2 Psi increments until the subject indicated that the sensation had reached a level of pain which they could not tolerate any further increases. This pressure of stimulation was repeated twice further to confirm a consistent level of tolerable painful sensation and was then kept at this same level throughout the study.

It was not possible to alter balloon pressures whilst the scanner was operating so there was a risk that subjects might tend to habituate across the study duration. To avoid systematic bias effects of this habituation on pain-emotion paired stimuli, the stimulus pairs were randomised across the study period.

Emotional faces

Facial expressions were employed from a standardized series (Ekman and Friesen 1975) to provide neutral and happy emotional contexts. 12 original Ekman identities (6 female, 6 male) were supplemented by eight new facial identities (4 female, 4 male) which were matched for valence and intensity to the Ekman series using the Facial Affective Coding System (Ekman et al. 2002). In the imaging study these were

back projected using a PC driven digital projector onto a specially made screen (Ellie screens, UK).

6.3.3 Psychological trait measures

Subjects completed the Big Five Inventory questionnaire which is a 44 item personality questionnaire based on the five main personality dimensions of neuroticism, extroversion, agreeableness, openness and conscientiousness (John et al. 1991; Benet-Martinez and John 1998; John and Srivastava 1999). Only the subscales of neuroticism and extroversion were used in the subsequent analysis since there is broad consensus regarding these 2 dimensions in most personality schemata and since there is previous imaging work in the literature for comparison.

6.3.4 Stimulus Presentation and behavioural response measures

30 repetitions of each stimulus pair combination (neutral face plus painful stimulation, neutral face plus no stimulation, happy face plus painful stimulation and happy face plus no stimulation) were delivered with a 12 second inter-stimulus interval. A randomised playlist was generated using random number lists generated from http://www.randomizer.org/form.htm.

Software to run the playlists and co-ordinate trigger inputs from the MR scanner (a TTL pulse transmitted every 4 dynamics/12 seconds) with face presentation and balloon distension, the subsequent presentation of Visual analogue scales (VAS) and recording of VAS responses were written in visual basic (Mr. Chris Andrews, department of brain imaging institute of Psychiatry) on a PC based windows platform.

Each stimulus-face presentation lasted 3 seconds with the balloon distension delivered at the onset of the face presentation. Following each stimulus-face presentation the subjects were asked to respond to a question which was displayed on the screen together with a sliding visual analogue scale (VAS) for subject response by means of a button box (Mr. Chris Andrew, Centre for Neuroimaging Sciences Institute of Psychiatry). The VAS scale was anchored at the two extremes by values of 1 and 10.

After each face presentation, subjects were asked to rate their perception of the intensity of the emotional expression of the displayed face. They were specifically instructed at the start of the study that this question was not asking how they felt themselves. The anchor value 1 for this question was labeled as "neutral "and 10 as "extremely emotional".

Additionally, every 10 minutes, both at the beginning of the study and throughout their time in the scanner subjects were asked to rate how anxious they were feeling at that moment in time. The value anchor 1 for this question was labelled as indicating "not at all anxious" and value 10 was labelled as "very anxious".

The cursor representing the subject's response was randomly assigned a different value at the onset display of each VAS question in order to avoid systematic biasing of the subsequent response. There was a delay between the end of the stimulus-face presentation and VAS display which was randomised between 1 and 3.5 seconds to avoid systematic effects on haemodynamic (BOLD) response. The VAS was then displayed for the remainder of the 12 second inter-stimulus interval (ranging between 5.5 to 8 seconds).

The subjects were allowed to practice responding to the questions before the actual study commenced to ensure they fully understood and were able to perform the task.

Behavioural scores were analysed offline and compared using paired student t-tests in stats-direct statistical software.

6.3.5 fMRI scanning

Gradient echo echoplanar imaging (EPI) data were acquired on a Philips 3T Achieva system (Philips Medical Systems, Eindhoven, NL) at the University of Manchester's Translational Imaging Unit, Manchester, UK. An 8 channel SENSE head coil was used for radio frequency (RF) reception. 300 T_2^*-weighted images depicting blood oxygenation level dependence (BOLD) contrast were acquired during the experiment at each of 36 near-axial contiguous 3.6 mm thick planes (parallel to the intercommissural (AC-PC) line): TE 35 ms, TR 3 s. The slices had an in-plane resolution of 1.8 x 1.8 x 3.6 mm. Field of view was 230 mm. Head movement was

limited by foam padding within the head coil and a restraining band across the forehead.

6.3.6 fMRI Data analysis

The fMRI data were analysed with software developed at the Institute of Psychiatry (XBAM version 3.4), using a nonparametric approach to minimise assumptions (c.f. http://brainmap.it for more information).

Prior to time-series analysis for the detection of experimentally determined activations, image artifacts caused by subject motion during the course of the functional study were minimised using the realignment method described extensively in (Friston et al. 1996). Following co-registration, the images were then smoothed using a Gaussian filter (FWHM 7.2mm) chosen to improve the signal-to-noise ratio over the spatial neighbourhood of each voxel. A modification of the method of Friston *et al* (Morris et al. 1998) has been developed in which BOLD responses are modeled as the weighted sum of the input function convolved with two Poisson functions. A goodness of fit statistic was computed as the ratio of the modeled and residual sums of squares (SSQ ratio). Under randomisation testing the SSQ ratio can be used to replace an F test. The SSQ ratio does not require knowledge of the degrees of freedom in the model or the residuals. Voxel-wise inference was carried out non-parametrically, and individual maps were identified by spatiotemporal randomisation testing (Bullmore et al. 2001). Presentation of neutral faces in the absence of oesophageal balloon distension was used as the baseline condition from which changes in BOLD response were identified in the other nine stimulus conditions. At the group level individual statistical maps were transformed into standard stereotactic space using a two-stage process; for each subject an average image of all functional volumes was made, this was first registered to a structural image obtained for the same subject and subsequently registered to a template in standard space. The same transformation was then applied to the statistic image to map it into standard space.

6.3.7 Comparing conditions within fMRI data

A repeated measures analysis of co-variance (ANCOVA) was used to test for differences in the median residual sum of squares ratio (SSQ ratio) between the two

conditions. This was carried out by first computing the average difference in brain activation between conditions over all subjects at each voxel. The data were then randomly reallocated between the two conditions for each subject (i.e. within subjects but not between subjects) and the average difference between conditions over all subjects recalculated after each permutation. This randomization procedure was repeated fifty times at each voxel and the results of the computations combined over all voxels. The resulting distribution represents the null hypothesis of no net change in response between conditions. The observed data were compared to the null distribution to identify voxels showing significant changes. Three-dimensional clusters of significant voxels (at $p< 0.05$) were identified and their mass (sum of suprathreshold voxel statistics) compared against a null distribution of cluster mass formed from the permuted data. Results were thresholded at a clusterwise value of $p<0.003$, this being the threshold at which less than one false positive cluster would be expected per analysis over the whole search volume.

6.3.8 Behavioural brain activation maps

1. Simple correlation analysis

With the individual personality trait values (neuroticism and extroversion), correlation analysis was performed between the BOLD effect data for each individual and the behavioural data. This proceeds by first choosing the statistical map (fMRI response) corresponding to the particular experimental contrast of interest. The Pearson product moment correlation coefficient is then computed between the personality data for each subject and the fMRI responses at each voxel for each subject, yielding one correlation coefficient, (r) per intracerebral voxel. To determine the significance of these correlation coefficients the appropriate null distribution of r is computed robustly using data permutation. The order of the behavioural data is randomly permuted without replacement (i.e. each data value occurs once but the order is changed) breaking the association between individual behavioural data and their corresponding fMRI responses. The correlation coefficient is then recomputed many times at each voxel and the resulting values of r combined over all voxels to produce a whole brain null distribution of r. The critical value of r for significance at any particular p value can then be obtained from this distribution after simply sorting it by value of r and selecting the appropriate point from the sorted distribution, e.g. the

critical value of r for a one-tailed test at p 0.05 would be the value of r in the null distribution chosen such that 95% of all the null values of r lay below that point. Testing can then be extended to cluster level as described previously. The cluster probability under the null hypothesis can be chosen to set the level of expected type I error clusters at an acceptable level (e.g. < 1 per whole brain).

2. Analysis of differences in correlations

For the ANOVA of happy faces alone versus happy faces plus pain, the differences in correlations with neuroticism and extroversion of activations between the two conditions was calculated as follows. At each voxel, the correlation co-efficient was first calculated for activation maps for happy faces alone and personality trait scores. This was then repeated for activation maps of happy faces plus pain and personality trait scores. The difference between these two values was then calculated which gives the observed difference. This difference was then tested statistically by permuting the subjects and scores and by repeating the correlation process.

3. Brodmann area assignment

Brodmann area assignment of Talairach co-ordinates was firstly via the XBAM analysis package which produces Brodmann assignments for the Talairach co-ordinates generated. For all cluster sizes of 10 or above, the co-ordinates were double checked with Talairach Daemon (Lancaster et al. 2000). Where Talairach Daemon and XBAM agreed these Brodmann assignments were accepted. Where there was disagreement the co-ordinates were checked by hand in a Talairach atlas. In the majority of cases the hand checking agreed most closely with the Talairach Daemon Brodmann assignment.

6.4 Results

6.4.1. Visceral pain induced dyshedonia

There was a significant group reduction in the perceived emotional intensity of happy facial expressions during pain (mean ± SEM: 7.91 ± 0.24 happy faces alone vs. 7.37 ± 0.18 happy faces plus pain, p = 0.0018, 2 tailed paired t test, [Figure 6.1A]).

As outlined above I have described this altered perception for intensity of hedonic context as "dyshedonia".

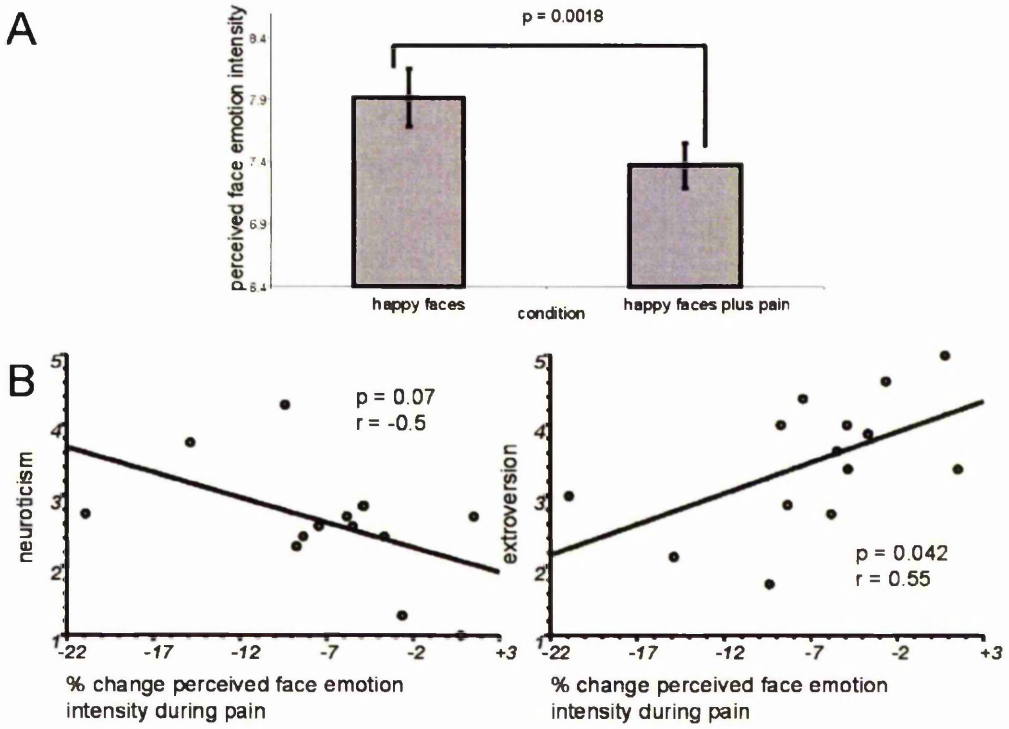

Figure 6.1 Behavioural results **A**. The perceived facial emotion intensity was significantly reduced for happy faces with paired painful stimulation compared to no pain (p = 0.0018). I have called this alteration/reduction in perceived hedonic intensity "dyshedonia". **B** Left panel: Neuroticism showed a trend for correlation with a greater degree of dyshedonia (greater negative percentage change of perceived facial emotion intensity during pain r = -0.5, p = 0.07). Right panel: higher extroversion correlated with a lesser degree of dyshedonia (r=0.55 p = 0.04).

6.4.2. Personality affects the degree of visceral pain induced dyshedonia

The amount and direction of pain-related change in perceived face emotional intensity, that is to say the degree of dyshedonia, varied between individuals in the

group. Two subjects even showed a slight relative increase in pain-related perceived face emotional intensity, against the clear overall group behaviour of a negative change. As possible moderating factors, I explored the relationship between these individual differences in the degree of dyshedonia to personality scores.

There was a positive correlation between extroversion score and negative pain-related changes in face emotion perception ($r=0.55$, $p=0.04$). In other words more introverted individuals had more negative pain-related change in perceived face emotion intensity (greater dyshedonia). Conversely, more extrovert individuals had less negative or slightly positive pain-related change in perceived face emotion intensity (i.e. less dyshedonia) [figure 6.1B, right panel].

There was a negative correlation however between neuroticism scores and negative pain-related changes in perceived face emotion intensity, although this was marginally short of conventional levels of significance ($r = -0.5$, $p = 0.07$). In other words more neurotic individuals had more negative pain-related changes in face emotion perception (greater dyshedonia) whereas more emotionally-stable individuals had less negative or slightly positive pain-related change in perceived face emotion intensity (less dyshedonia) [Figure 6.1B, left panel].

The group mean neuroticism score was 2.61 ± 0.22 and for extroversion was 3.48 ± 0.25. There was a significant negative correlation between neuroticism and extroversion ($r = -0.87$, $p < 0.0001$).

Mean anxiety levels for the group, which were obtained every 10 minutes through the study on a 1-10 Likert scale, were 2.06 ± 0.34. No correlations were observed between anxiety scores, personality scores and face ratings.

6.4.3. Personality affects the brain responses for visceral pain induced dyshedonia

The finding of visceral pain induced dyshedonia and its concomitant brain activations were not a *directly* measured phenomenon but rather *indirectly inferred* from a comparison of the differences between the two conditions (happy faces plus pain and happy faces alone). Similarly, it was not possible to directly

measure effects of personality on the brain responses for visceral pain induced dyshedonia. Rather, it was again necessary to use a similar indirect inference based once more on a comparison of the differences between the conditions. The *differences* between personality correlations for the two conditions were analysed. In other words the areas of brain activity were determined that were *more correlated* with personality scores for the first condition (happy faces + pain) than the second condition (happy faces alone) and vice versa. This then was essentially a comparison of means albeit that the means were for strength of correlation (see methods section 6.3.8.2). For this reason the meaning of the results are not immediately intuitive and require some explanation.

Those brain areas for which activity was more correlated to personality with happy faces plus pain vs. happy faces alone equate to areas of increasing brain activity for visceral pain induced dyshedonia as personality score increases. These are shown in Table 6.1A for neuroticism and table 6.1C for extroversion. Conversely, those brain areas for which activity was more correlated to personality with happy faces alone vs. happy faces plus pain equate to areas of reducing brain activity (but not necessarily inactivity) for visceral pain induced dyshedonia as personality score increases. These are shown in table 6.1B for neuroticism and table 6.1D for extroversion.

I found differences in correlations with personality scores between the two conditions in a widely distributed network of differentially active brain areas. Amygdala activation, which wasn't observed at the group analysis stage, became evident when correlated with individual differences in personality scores. Given that in my group the neuroticism and extroversion scores were strongly negatively correlated, those areas of brain activation that correlated more with neuroticism were almost, though not exactly, mirror images of those for extroversion.

In particular, neuroticism scores were more correlated, when viewing happy faces alone, with activity in brain regions including bilateral amygdala, left hippocampus, right anterior cingulate cortex (BA32) bilateral medial frontal, right claustrum, right hypothalamus and left pons as compared with happy faces plus pain [figure 6.2A, Table 6.1B]. By inference these were areas of reducing brain activity (but not necessarily inactivity) with increasing neuroticism scores for visceral pain induced

dyshedonia. Conversely, most of these areas were more correlated with extroversion scores, when viewing happy faces plus pain, with the exception of the right anterior cingulate, hypothalamus and pons as compared to viewing faces alone [figure 6.2B, Table 6.1C]. By inference these were areas of increasing brain activity with increasing extroversion for visceral pain induced dyshedonia.

Neuroticism was also more correlated, for happy faces plus pain, with activity in brain regions including right hippocampus and left fusiform gyrus as compared to viewing happy faces alone [Table 6.1A]. By inference these were areas of increasing brain activity with increasing neuroticism for visceral pain induced dyshedonia. The right rather than the left fusiform gyrus showed more correlation with extroversion scores for happy faces alone compared to happy faces plus pain [Table 6.1D]. By inference these were areas of reducing brain activity (but not necessarily inactivity) with increasing extroversion scores for visceral pain induced dyshedonia.

Type of analysis	Size	x,y,z	Side	BA	Location
A ANCOVA: Neuroticism greater correlation with happy plus pain vs. happy alone all p<0.00002	21	26,-36,-3	R		hippocampus
	15	-20,-34,-13	L	36	parahippocampal gyrus
	11	-20,-61,-7	L	19	fusiform gyrus
	29	-32,-84,10	L	19	middle occipital gyrus
	19	-27,-68,36	L	7	precuneus
	63	42,-20,7	R	13	superior temporal gyrus
	12	38,-25,13	R	41	transverse temporal gyrus
	12	-27,-7,13	L		putamen
	14	-38,-12,0	L		claustrum
	28	-4,-12,-7	L		mamillary body
	16	-6,-36,-16	L		midbrain
B ANCOVA: neuroticism greater correlation with happy faces alone vs. happy plus pain all p<0.00002	57	-25, -4, -20,	L		amygdala
	9	27, -2, -13,	R		amygdala
	44	-26, -12, -16	L		hippocampus
	39	12, -20, 43,	R	31	posterior cingulate gyrus
	39	-39, -59, 30	L	39	superior temporal gyrus
	37	16, 43, 16,	R	9	medial frontal gyrus
	25	-12, -16, 46	L	6	medial frontal gyrus
	30	39, -2, 33,	R	6	pre-central gyrus
	43	29, -2, 16,	R		claustrum
	23	22, -12, 0,	R		globus pallidus

	10	4, -4, -3,	R		hypothalamus
	20	-10, -34, -23,	L		pons
C ANCOVA: extroversion greater correlation with happy plus pain vs. happy alone all p<0.00002	25	-6,-18,30	L	23	cingulate gyrus
	41	-23,-12,-16	L	28	parahippocampal gyrus
	30	-25,-12,-13	L		hippocampus
	49	-25,-4,-20	L		amygdala
	55	10,-25,40	R	31	cingulate gyrus
	14	20,-50,-3	R	19	parahippocampal gyrus
	16	-22,-79,26	L	31	precuneus
	69	-39,-52,23	L	39	superior temporal gyrus
	32	-12,-16,46	L	6	medial frontal gyrus
	14	-35,-7,33	L	6	pre-central gyrus
	11	16,43,16	R	9	medial frontal gyrus
	35	42,0,33	R	6	pre-central gyrus
	61	29,2,16	R		claustrum
	11	22,-12,0	R		globus pallidus
D ANCOVA: extroversion greater correlation with happy faces alone vs. happy plus pain all p < 0.00002	26	-20,-34,-13	L	36	parahippocampal gyrus
	14	-1,-38,20	L	29	posterior cingulate gyrus
	12	20,-14,-20	R	28	parahippocampal gyrus
	12	-19,-73,33	L	7	cuneus
	14	-17,-84,-7	L	18	lingual gyrus
	18	35,-48,-16	R	37	fusiform gyrus
	15	26,-36,-3	R		hippocampus
	12	48,-27,10	R	41	transverse temporal gyrus
	27	-17,-46,40	L	7	precuneus
	10	-39,23,10	L	13	inferior frontal gyrus
	13	-32,-18,43	L	4	pre-central gyrus
	40	-10,-4,16	L		caudate body
	15	17,7,0	R		putamen
	18	-7,-36,-16	L		midbrain
	18	3,-30,-7	R		midbrain

Table 6.1: areas of brain activation **A** more correlated with neuroticism for happy faces plus pain compared to happy faces alone (i.e. inferentially these were areas of increasing activity with increasing neuroticism for visceral pain induced dyshedonia) **B** more correlated with neuroticism for happy faces alone compared to happy faces plus pain (i.e. inferentially these were areas of reducing activity but not necessarily inactivity with increasing neuroticism for visceral pain induced dyshedonia) **C** more correlated with extroversion for happy faces plus pain compared to happy faces alone (i.e. inferentially areas of increasing activity with increasing extroversion for visceral pain induced dyshedonia) **D** more correlated with extroversion for happy faces alone compared to happy faces plus pain (i.e. inferentially areas

of reducing activity but not necessarily inactivity with increasing extroversion for visceral pain induced dyshedonia) (BA = Brodmann area; xyz = Talairach co-ordinates L = left, R = right).

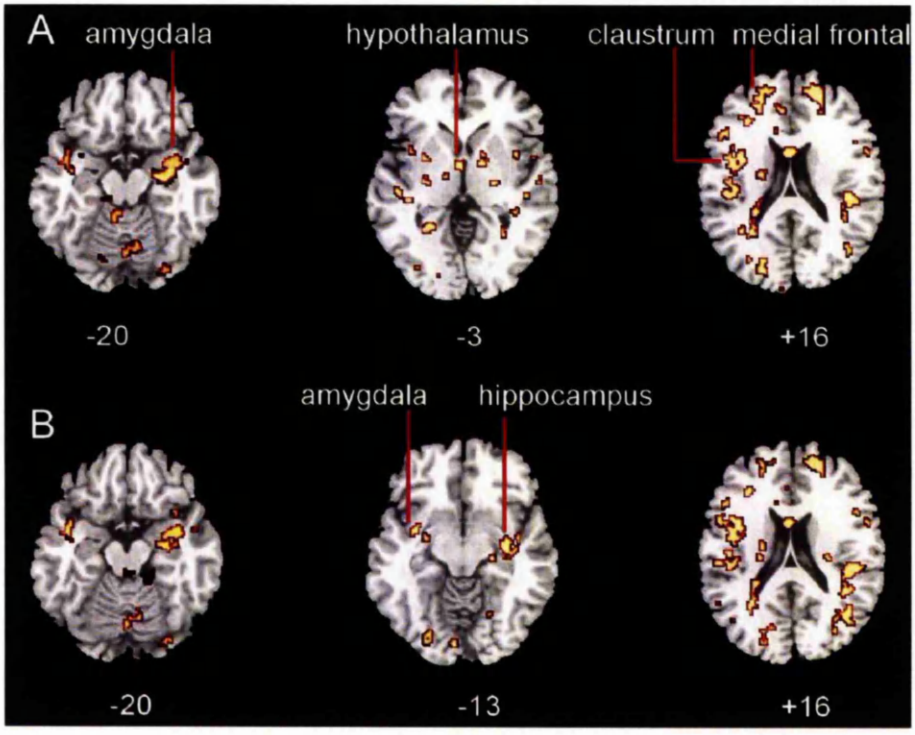

Figure 6.2 Brain activation maps **A**: representative images of activity in areas more correlated to neuroticism when viewing happy faces alone compared with happy faces plus pain (i.e. areas of reducing activity but not necessarily inactivity with increasing neuroticism for visceral pain induced dyshedonia) **B**: representative images of activity in areas more correlated to extroversion when viewing happy faces combined with pain compared with viewing happy faces alone (i.e. areas of increasing activity with increasing extroversion for visceral pain induced dyshedonia) (number at base of each brain slice = z- Talairach co-ordinate level). All activations shown are at significance level $p<0.00002$ and cluster size > 10. See table 6.1 for other areas of brain activations and Talairach co-ordinates.

6.4.4. Additional brain activation analyses

Happy faces vs. neutral; happy faces plus pain vs. neutral; and happy faces vs. happy faces plus pain

Group brain activations were additionally determined for 1) happy faces vs. neutral faces and 2) happy faces plus pain vs. neutral faces. The results for these are given in table 6.2 A&B. Group brain activations were also determined for an analysis of covariance (ANCOVA) of happy faces vs. happy faces plus pain. The results of this are shown in table 6.2 C&D. Table 6.2C therefore shows areas of brain more active in happy faces plus pain compared to happy faces alone and equates to those areas

more active during visceral pain induced dyshedonia. Table 6.2D shows areas of brain more active during happy faces alone i.e. those areas of brain less active (but not necessarily inactive) during visceral pain induced dyshedonia.

Analysis type	Size	x,y,z	Side	BA	Location
A Group : happy faces vs. neutral faces all p < 0.007	27	-17,-41,30	L	31	posterior cingulate gyrus
	21	32,-45,-13	R	37	fusiform gyrus
	36	17,-43,-20	R		cerebellum
	36	-19,-46,-30	L		cerebellum
B Group: happy faces plus pain vs. neutral faces all p <0.009	34	0, -16, 40	L	24	anterior cingulate gyrus
	11	3, -80, 33	R	19	cuneus
	11	0, -79, 26,	L	18	cuneus
	17	48, -16, 16	R	43	post-central gyrus
	43	46, -21, 7,	R	13	superior temporal gyrus
	18	46, -29, 16,	L	41	superior temporal gyrus
	13	46, -20, 13,	R	41	transverse temporal gyrus
	59	-46, -23, 10,	L	41	transverse temporal gyrus
	12	-13, 46, 13	L	10	medial frontal gyrus
	11	-1, -16, 46	L	31	paracentral lobule
	59	42, -16, 3	R		insula
	14	-43, 0, -3	L		insula
	39	36, 4, 3,	R		claustrum
	20	23, -54, -26	R		cerebellum
	41	4, -43, -30	L		cerebellum
C ANCOVA NEG (happy plus pain > happy alone) all p<0.007	55	4,27,26	R	32	anterior cingulate gyrus
	43	6,-12,40	R	24	anterior cingulate gyrus
	53	-16,36,23	L	9	cingulate gyrus
	38	-6,11,33	L	24	anterior cingulate gyrus
	31	3,-93,20	R	18	cuneus
	24	-3,-84,26	L	19	cuneus
	62	46,-20,7	R	13	superior temporal gyrus
	52	45,-23,13	R	41	transverse temporal gyrus
	48	-45,-21,10	L	41	transverse temporal gyrus
	17	-49,-41,10	L	22	middle temporal gyrus
	17	1,-14,46	R	31	paracentral lobule
	33	-16,36,20	L	9	medial frontal gyrus
	163	42,-14,3	R		insula
	55	-46,-9,13	L		insula

	14	32,-2,-3	R		claustrum
	12	29,4,7	R		putamen
D ANCOVA POS (happy alone>happy plus pain) all p<0.01	25	-14,-41,30	L	31	posterior cingulate
	28	-23,-52,3	L	30	parahippocampal gyrus
	44	32,-45,-16	R	37	fusiform gyrus
	28	-1,-48,-26	L		cerebellum

Table 6.2: areas of brain activation seen for the group as a whole **A**. for viewing happy faces compared with neutral faces as baseline **B** for viewing happy faces plus pain compared with neutral faces as baseline **C** ANCOVA of brain areas more active for condition happy faces plus pain than for viewing happy faces alone (i.e. more active in visceral pain induced dyshedonia) **D** ANCOVA of brain areas more active for condition viewing happy faces alone than for happy faces plus pain (i.e. less active but not necessarily inactive during visceral pain induced dyshedonia) (BA = Brodmann area; xyz = Talairach co-ordinates L = left, R = right).

Personality correlations for happy faces and happy faces plus pain

Negative and positive correlations of brain activity with neuroticism and extroversion scores were also calculated separately for the conditions of viewing happy faces alone and then for happy faces plus pain. These are shown in table 6.3A-H.

Analysis type	Cluster size	x,y,z	Side	BA	Location
A Negatively correlated with Neuroticism (Happy faces alone) all p < 0.00002	11	-3, 29, 26	L	32	anterior cingulate gyrus
	20	0, -45, 20	L	30	posterior cingulate gyrus
	12	-19, -46, 7	L	30	parahippocampal gyrus
	12	20,-89,-16	R	18	Fusiform gyrus
	34	-25, -77, -16	L	19	fusiform gyrus
	60	-3, -79, 23	L	18	cuneus
	14	-33, -82, 10	L	19	middle occipital gyrus
	11	-20, -59, 43	L	7	precuneus
	10	48, -23, 10,	R	41	superior temporal gyrus
	11	-40, -62, 7	L	37	middle temporal gyrus
	12	12, 11, 13	R		caudate body
	15	1, -61, -13	R		cerebellum
	12	-4, -12, -7,	L		mamillary body
B Positively correlated	15	16, -41, 40,	R	31	posterior cingulate gyrus
	23	-4, -9, 36	L	24	anterior cingulate

with Neuroticism (happy faces alone) all p < 0.00002	10	7, -41, 0,	R	30	parahippocampal gyrus
	25	-27, 0, -20	L		amygdala
	46	27, -80, -7,	R	18	middle occipital gyrus
	34	13, -88, 0	R	17	Lingual gyrus
	15	4, -95, 7	R	18	cuneus
	11	1, 27, 36,	R	8	medial frontal gyrus
	16	-10, -16, 46	L	6	medial frontal gyrus
	30	32, -30, -3	R		hippocampus
	80	-38, -57, 30	L	39	superior temporal gyrus
	20	23, 9, 0	R		putamen
	17	6, -9, 7,	R		thalamus
	17	20, -4, -3	R		globus pallidus
	16	-9, -4, -3	L		hypothalamus
	19	-14, -36, -23,	L		pons
C Positively correlated with Extroversion (happy faces alone) all p < 0.00001	12	-6,-55,26	L	31	posterior cingulate gyrus
	12	-13,-32,-7	L	30	parahippocampal gyrus
	14	-42,-61,7	L	37	middle temporal gyrus
	18	48,-25,7	R	41	Superior temporal gyrus
	12	48,-21,10	R	41	transverse temporal gyrus
	11	6,-66,36	R	7	precuneus
	10	-26,-5,13	L		putamen
	10	13,11,13	R		caudate body
	16	38,-11,7	R		claustrum
	30	-3,-79,23	L	18	cuneus
	17	-25,-77,-16	L	19	fusiform gyrus
	27	-13,-80,0	L	18	lingual gyrus
	18	-38,23,10	L	13	inferior frontal gyrus
	25	-4,-41,-23	L		anterior cerebellum
	17	0,-30,-7	L		midbrain
	15	7,-46,-23	R		anterior cerebellum
	18	4,-27,-16	R		midbrain
D Negatively correlated with Extroversion (happy faces alone) all p<0.00002	16	-3,-30,26	L	23	cingulate gyrus
	14	-22,-16,36	L	24	anterior cingulate gyrus
	22	-29,0,-20	L		amygdala
	93	-38,-54,23	L	39	Superior temporal gyrus
	12	35,-57,13	R	19	middle temporal gyrus
	20	-20,-21,26	L		caudate body
	12	-7,7,0	L		caudate head

	56	36,-7,16	R		insula
	33	12,-9,13	R		thalamus
	28	22,-4,0	R		globus pallidus
	44	25,-88,-7	R	18	inferior occipital gyrus
	11	4,-96,0	R	17	cuneus
	17	-13,-20,46	L	6	medial frontal gyrus
	21	38,-5,33	R	6	pre-central gyrus
	24	-13,-36,-23	L		pons
	13	0,-70,-20	R		posterior cerebellum
E Negatively correlated with Neuroticism (happy faces plus pain) all p < 0.00002	27	10, -12, 40,	R	24	anterior cingulate gyrus
	12	23, -62, 16	R	31	posterior cingulate gyrus
	29	-25, -4, -20	L		amygdala
	18	-25, -18, -16,	L		hippocampus
	15	16, -82, 23,	R	18	cuneus
	11	-16, -84, -13,	L	18	lingual gyrus
	21	36, -30, 13	R	41	superior temporal gyrus
	12	-40, -55, 26	L	39	middle temporal gyrus
	11	-26, -9, 46,	L	6	middle frontal gyrus
	13	29, 34, 26,	R	9	middle frontal gyrus
	11	-12, -16, 46,	L	6	medial frontal gyrus
F Positively correlated with Neuroticism (happy faces plus pain) all p < 0.00002	12	-3, 36, 23	L	32	anterior cingulate gyrus
	15	38, -39, -7	R	37	fusiform gyrus
	16	20, -84, 3,	R	17	lingual gyrus
	25	-25, -86, 10,	L	19	middle occipital gyrus
	13	9, -50, 33	R	31	precuneus
	15	-13, -50, 43	L	7	precuneus
	28	39, -18, 20	R		insula
	16	14, 11, 13	R		caudate
	12	0, -14, -7,	L		mamillary body
G Negatively correlated with Extroversion (happy faces plus pain) all p < 0.00002	10	-3,36,23	L	32	anterior cingulate gyrus
	26	-25,-86,10	L	19	middle occipital gyrus
	11	38,-39,-7	R	37	fusiform gyrus
	17	-14,-41,50	L	7	precuneus
	28	35,-21,36	R	3	post-central gyrus
	12	-4,-4,13	L		thalamus
	21	39,-21,23	R		insula
	20	-23,-57,-36	L		cerebellum
H Positively	26	-23,-18,-16	L	28	parahippocampal gyrus

correlated	14	-26,-18,-13	L		hippocampus
with	11	-16,-23,36	L	31	posterior cingulate gyrus
Extroversion	15	23,-62,16	R	31	posterior cingulate gyrus
(happy faces	20	35,-34,13	R	41	transverse temporal gyrus
plus pain)	10	29,34,26	R	9	middle frontal gyrus
all p<0.00002	14	-32,-16,20	L		insula
	12	-1,-39,-13	L		midbrain
	10	1,-38,-30	R		pons

Table 6.3: areas of brain activation positively and negatively associated with personality scores **A.** viewing happy faces negatively associated with neuroticism **B** viewing happy faces positively associated with neuroticism **C** viewing happy faces positively associated with extroversion **D** viewing happy faces negatively associated with extroversion **E** happy faces plus pain negatively associated with neuroticism **F** happy faces plus pain positively associated with neuroticism **G** happy faces plus pain negatively associated with extroversion **H** happy faces plus pain positively associated with extroversion (BA = Brodmann area; xyz = Talairach co-ordinates L = left, R = right.

6.5 Discussion

My results show for the first time that oesophageal pain reduces the perception of intensity of a positive emotional stimulus in healthy females, a phenomenon I have described as "dyshedonia". Furthermore, the magnitude of this "dyshedonic" effect is greater in more introvert and more neurotic individuals but less in more extrovert and more emotionally stable individuals. My imaging findings are consistent with the existence of a homeostatic processing network involving insula and anterior cingulate cortices and with the amygdala as a key structure in mediating individual personality effects during pain and emotion.

These behavioural findings of dyshedonia make sense within a conceptual framework in which emotion and pain are not sharply demarcated phenomena but rather interact in a bi-directional manner. Previous work by our group (Phillips et al. 2003) has shown that a negative emotional context can influence the perception of a non-painful visceral sensation, i.e. *concordant* negative visceral and emotional stimuli may tend to *amplify* the negative experience. I have now shown conversely, that a painful visceral sensation can in turn influence the perceived intensity of the emotional context. In particular I have seen that when *discordant* positive emotional and negative painful stimuli interact, there may be a tendency to *diminish* the positive

emotional experience. This effect is greater in people that score highly on neuroticism scales and lesser in those who score highly on extroversion scores.

This has important clinical implications since it may be necessary to treat both negative affect and pain simultaneously in order to optimize outcome. This may be especially so for more neurotic and more introvert individuals. These results also suggest that clinical trials of acute and chronic pain treatments may benefit from stratification of patients according to their personality trait and affective state (Tanum and Malt 2000).

I found that a number of structures implicated previously in studies of emotion and pain were also associated with personality scores during the dyshedonic effect. In particular, it was only when individual differences in personality were incorporated into the analysis that I saw differential activation in amygdala, hippocampus and hypothalamus during the processing of the pain and emotional context. This interaction was not seen at the group level indicating that a richer dataset can be obtained by incorporating known measures of individual variance into the analysis. The "nomothetic" approach to brain imaging studies, which is the commonest approach, tends to treat individual differences as noise to be excluded whereas the "idiographic" approach exemplified here considers individual differences to be a signal of primary interest (Pennebaker and Epstein 1983; Schafer 1999; Grice 2004; Kristjansson et al. 2007).

The neuroanatomic findings in this study are also consistent with previous imaging studies exploring the effects of personality on amygdala activation and thus they provide some insight into the neurophysiological basis of personality differences. Personality effects appear to involve differential activation within a widely distributed network of structures implicated in pain and emotion processing. Given that the neuroticism dimension of personality is defined in terms of "emotionality"(Eysenck 1967), correlations of activity in this network with neuroticism are not surprising. Hans Eysenck believed that functional differences in the "visceral brain" may underlie increasing neuroticism (Eysenck 1967) which is supported by my data showing that insula and anterior cingulate activations were associated with personality during emotion and pain processing separately [see table 6.3]. Conversely, Eysenck believed the extroversion dimension was sub-served by the reticular activating

system mediating cortical arousal for which I could not find supporting evidence, although the fMRI imaging modality may not be best able to test this.

Gray, and more recently Gray and MacNaughton (Gray and McNaughton 2000; McNaughton and Corr 2004) have suggested that neuroticism and extroversion are best thought of as "surface" traits (Corr 2004) which relate tangentially to underlying neurobiological behavioural activation and inhibition systems, including most pertinently for pain the defensive fight-freeze-flight systems. Within these hierarchically organized systems there is a network including prefrontal cortex, anterior and posterior cingulate, amygdala, septo-hippocampal system, medial hypothalamus and peri-aqueductal gray (PAG). With the exception of the latter structure I found evidence of involvement of all of these areas. Involvement of the PAG and related brainstem structures such as nucleus tractus solitarius and nucleus ambiguus are poorly delineated by fMRI currently and may better be explored using measures of brain-stem autonomic function (Porges 2007; 2007).

My data demonstrate that although there was no difference in absolute pain ratings, neurotics and introverts were more sensitive to pain input in terms of the effects this subsequently had on emotional processing since they exhibited a greater dyshedonic effect. This is consistent with "sensitivity" as a core component of neuroticism, introversion and anxiety (Aron and Aron 1997; Dunn 2001; Craig 2004; Stelmack 2004).

Precise mapping of personality traits onto brain structures may not be possible (Matthews 2004) due in part to well documented problems with functional localization attempts in cognitive neuroscience (Uttal 2001). A full account of personality, emotion and pain may require explanations including "virtual cognitive architecture" which support information processing and the meaning of processing with respect to personal goals. Inclusion of these levels of description in addition to neural function, physiology and systems biology has been called "explanatory pluralism" (Matthews 2004). Furthermore a dynamic systems approach of loosely and dissociably coupled bio-oscillators may ultimately be a better heuristic model for understanding relationships between structure and function at the biological level than relatively static homeostatic structures and networks (Thayer and Friedman 2002).

Nonetheless, I propose based on my data, that the amygdala in particular may play a key role associated with personality differences in dynamic situations relating emotion and pain. The role of genotype, in particular in the serotenergic system which has been related both to neuroticism and amygdala activation could be usefully explored further in this regard (Hariri et al. 2002). Previous work has shown neuroticism is a vulnerability factor for the development of chronic emotion and pain disorders when a visceral injury occurs in the presence of psychological stress (Gwee et al. 1999). My findings may represent a neurobiological substrate for this vulnerability and therefore may be useful in risk stratification for developing functional disorders and determining future therapeutic strategies.

Chapter 7 Summary, General Discussion and Conclusion

7.1 What this work adds to what is known

The work in this thesis was conducted to explore the psychophysiology of pain. This was in response to my perception of a mechanistic hiatus for unexplained medical symptoms, particularly the functional gut disorders (section 1.3). I focussed on the experience of pain as being an archetypal symptom. The strategy was to explore the psychophysiology of pain in healthy humans in an attempt to dissect some of the fundamental mechanisms of visceral and somatic pain.

In summary, I have shown that the ANS in general and cardiac vagal control (CVC) in particular, together with areas of the central nervous system involved in ANS control, form part of a mind-body continuum by which pain-emotion interactions (state) are modulated by personality (trait).

In my PhD thesis I have made several original contributions in the related fields of psychophysiology and cognitive neuroscience:-

1. A pluralistic psychophysiological model:

The starting point for my studies was at a theoretical level. I discerned a convergence in the modern literature on pain, emotion, personality and interoception with evidence on the one hand for the existence of a homeostatic afferent processing network (section 1.5) and on the other hand an integrated and expanded role for the ANS, specifically the vagus nerve, under hierarchical sub-cortical and cortical control in both affiliative and defence behaviours (section 1.7). This led me to the development of a pluralistic working model synthesised from these strands which places pain and gastrointestinal sensorimotor activity within a holistic, hierarchical, dynamic and integrated model [see figure 7.1, section 7.5]

2. Novel applications of new technology - real time non-invasive selective ANS responses:

At the methodological level I have demonstrated that selective ANS responses can be obtained for distal oesophageal balloon inflation evoked pain (chapters 3&4). I also included the use of a less well known measure of cardiac sympathetic activity – the Cardiac Sympathetic Index, since hitherto putative sympathetic measures in visceral pain research have been unsatisfactory (chapter 3&4). In order to explore the time course of the ANS changes more closely I have employed a novel technique of

beat-to-beat CVC measurement using the Neuroscope. This was because the time course of ANS pain responses required better time resolution than traditional CVC measures provide (chapter 4).

3. Novel observations of patterned ANS pain responses:

i) Post oesophageal intubation, a sustained elevated heart rate mediated by sustained CVT withdrawal was observed following return of SNS measures to baseline. This was a novel observation that showed the SNS & PNS were not simply reciprocal in their actions but can operate semi-independently (chapter 4 and see section 1.8) ii) Co-activation of SNS and PNS with elevated heart rate and vasodepression during visceral and (deep) somatic pain was demonstrated. This confirms data from recent animal studies and extends these findings to humans (chapter 4 and see section 1.8). Again this demonstrates that the ANS is not a simple reciprocal system.

4. Novel observations of bi-directional emotion-pain interactions and their central responses:

i) This is the first study to demonstrate the central concomitants of visceral hyperalgesia evoked by a negative emotional context (chapter 5). It extends previous imaging research which demonstrated visceral allodynia (Phillips et al. 2003). ii) Visceral pain induced dyshedonia (chapter 6) – this was a novel psychophysical phenomenon by itself but further original observation was to demonstrate its central correlates. These findings of bi-directional emotion-pain interactions confirm and extend the background knowledge outlined in sections 1.5 and 1.6 of the relations between emotion and pain and their neurobiological concomitants.

5. Novel observations of relations between psychological state, trait, ANS and CNS function:

I have demonstrated that personality traits can affect: - i) ANS function at baseline and to visceral and somatic pain stimuli (chapters 3&4). ii) pain sensitivity (balloon volumes vs. extroversion – chapter 3) iii) CNS function to visceral pain and emotional context changes both separately and in their interactions (chapters 5&6) iv) the degree of dyshedonia induced by visceral pain (chapter 6). These findings confirm and extend the background knowledge reviewed in sections 1.4, 1.5, 1.6 and 1.8 of relationships between personality, emotion, pain and ANS and CNS function.

7.2 Limitations of the studies

Sex of subjects

In the imaging studies (chapters 5&6) only females were studied. Psychophysics and imaging studies have shown systematic differences between males and females in pain responses (Rhudy and Williams 2005; Wiesenfeld-Hallin 2005) and so the results of the imaging studies cannot be directly extrapolated to men. Nonetheless, from a clinical perspective, females outnumber males 3:1 for most functional pain syndromes and are therefore the more clinically relevant group to study. In the second ANS study (chapter 5) the sex mix was heavily skewed towards females. Furthermore there was no control for stage of oestrous cycle in the females which has also been shown to affect pain sensitivities. None of the studies were powered or stratified to permit sex or age differences to be studied.

Statistics: small numbers and cluster analysis

The studies performed were very labour intensive in terms of data handling, processing and analysis. Additionally imaging studies are very expensive. These logistical factors limited the number of subjects that could be studied. Nonetheless the powering of the imaging studies was satisfactory according to current conventions for this type of study. Future ANS studies could benefit from larger numbers. The novel finding of the psychophysiological phenotypes would benefit from a prevalence study in larger numbers. Cluster analysis is open to criticism that it always finds clusters. "Elbow criteria" may be preferable to dendritic distance for cluster classification.

Reproducibility of results

It was logistically feasible to attempt to reproduce the findings of the first ANS study (chapter 3) in only 6 of the original subjects. The qualitative findings in these subjects were reproduced but re-testing larger numbers on at least 3 occasions in the future would be beneficial. The second ANS study (chapter 4) did not reproduce exactly the relations between personality variables and ANS mean summary measures seen in chapter 3. The subjects however differed between the studies in chapters 3&4 and this is a likely explanation for the differences in outcome. Nonetheless the second study confirmed and extended the relations seen in chapter 3 between neuroticism-introversion and PNS measures using the summary slope measure. No attempts have been made to reproduce the imaging findings owing to logistical and financial constraints at this time.

7.3 Generic limitations of psychophysiology and cognitive neuroscience – a commentary.

7.3.1 Technological preoccupations?

There is a proliferation of inter-related scientific disciplines which share common goals, assumptions and experimental paradigms yet different names. These include cognitive neuroscience, affective neuroscience, biological psychology, psychological physiology, psychophysiology and various other combinations of the words emotion, cognitive, neuroscience, physiology, biology and psychology.

The defining differences chiefly exist at the socio-political-economic rather than scientific level or appear tied to particular technologies and methodologies rather than subject-matter. For example the British Psychophysiological Society recently changed its name to the British Association of Cognitive Neuroscience in an attempt to move away from the *"blood, sweat and spit brigade"* and encompass the *"sexier"* brain-imaging fraternity (personal communication from former secretary to the BPS).

In a recent critique on the localisationist project within cognitive neuroscience William Uttal wrote: *"The development of the magnificent imaging machines has driven most incipient consideration of the germane conceptual issues into the background. For one thing, it has driven purely psychological studies totally from the pages of at least one of the most prestigious journals (Science) and from the halls of some of our most prestigious universities"* (Uttal 2002)(see also "a comment on the Zeitgeist", Appendix B, p 227(Uttal 2001)).

Shifts in theoretical emphasis have also played a role in changing disciplinary affiliations, for example Panksepp has lamented and LeDoux documented post-behavioural "cognitive imperialism" in the psychological sciences (LeDoux 2000; Panksepp 2003).

7.3.2 Bottom up or Top down?

Within psychophysiology and cognitive neuroscience there is a continuing debate over whether "top-down" regulation, i.e. central influencing peripheral somatovisceral (Frith and Dolan 1997) or "bottom up" regulation, i.e. peripheral somatovisceral influencing central, predominates (Berntson et al. 2003). There is evidence that the flow is bi-directional or more accurately dynamically reciprocal rather than these polarized options.

Although this peripheral-central top-down/bottom up distinction is artificial to some degree, nonetheless an interesting and difficult dilemma remains over the degree to which the differentiation of visceral perception arises from peripheral or central components of this network. Cacioppo and Berntson who are "leading lights" within the discipline of psychophysiology (Cacioppo et al. 2000) reviewed the literature on the relative roles of peripheral (bodily) and central (cognitive) components in emotion perception (Cacioppo et al. 1992). They concluded that models largely fell into two extremes a) models that hold that discrete emotional experiences stem from distinct somatovisceral patterns (a bottom-up emphasis) (Ekman et al. 1983; Levenson et al. 1990) and b) models that hold that discrete emotional experiences derive from cognitive appraisals that were initiated by the perception of undifferentiated physiological arousal (a top-down emphasis) (Schachter and Singer 1962). This debate has continued between antagonists Zajonc (primarily bodily components) and Lazarus (primarily cognitive appraisals and hence appraisalist) an argument summarised and criticised by Panksepp (Panksepp 2003). Friston favours top-down supremacy in a review of neuroimaging findings (Friston 2002).

Cacioppo and Berntson suggest that these are not mutually exclusive views but rather can operate to different degrees at different times and also propose a "third way" of partially differentiated ambiguous somato-visceral afference giving rise to "visceral illusions" by way of comparison with "visual illusions" from visual cognitive neuroscience (Cacioppo et al. 1992).

The same authors warn 10 years later that "just because you are imaging the brain doesn't mean you can stop using your head" when it comes to orienting central imaging findings within a coherent social neuroscience functional framework (Cacioppo et al. 2003). Ultimately, this debate reflects some very basic and unresolved epistemological difficulties in relating mind to brain and to body.

7.3.3 Metaphysical qualifiers

"Without consciousness the mind-body problem would be much less interesting. - With consciousness it seems hopeless"
(Nagel 1974)

Consciousness and qualia

Scientific attempts to research perceptual phenomena biologically, such as pain and emotion, frequently bypass implications of a considered reflection that they are fore mostly first person subjective experiences, consciously perceived and subsequently communicated.

Understanding the relationships between consciousness & "qualia" (i.e. "what it feels like to....") on the one hand and biology on the other is the central challenge. Psychophysiology and cognitive/affective neuroscience are in the primary business of making claims as to how mind/emotion relates to the brain and to the body. If Nagel is correct in the quotation above as to the hopelessness of the mind-body problem then symptoms research is in trouble!

This is not an esoteric problem but has potentially far-reaching practical implications (Sarter et al. 1996; Uttal 2001; Cacioppo et al. 2003; Davidson 2003; Matthews 2004; Sohrabi and Brook 2005). William Uttal shares Nagel's pessimism and cautions that the resource stakes are high if decomposability of mind-brain structures is ultimately impossible:

"It is no longer a matter of relative optimism or pessimism but, rather, of a critical and realistic evaluation of what mathematics and other sciences tell us that should guide our future efforts.... appreciate the magnitude of the potential waste, both intellectual and resource-wise, that would occur if the as yet unanswered question of decomposability or modularity is ultimately answered in the manner in which I think it will be" (Uttal 2002).

Ontological monism but epistemological dualism?

Ray Tallis, in his article "Brains and minds: a brief history of neuromythology", suggests that there is ontological naivety amongst neuroscientists (Tallis 2000). That is to say, the relationships between the type of "stuff"/matter there is (ontology) and how we can know it (epistemology) have not been properly thought through or applied. Uttal feels this is especially so for the status of cognitive constructs and

definitions (Uttal 2001). At one end of the ontological spectrum is the "reductionist-materialist" perspective and at the other the "mentalist, mysterion or phenomenological". Whilst the reductionist-materialist posits that mental phenomena are identical with neural activity, an extreme phenomenological view is that all reality is perceived through filters of constructs and therefore not directly knowable or measurable.

Uttal opts for a half-way house: ontological monism (there's only one kind of stuff) but epistemological dualism (we can only know about mind and matter in categorically different ways). His ontological monism is therefore an unprovable a-priori assumption whilst he is empirically a dualist. Sperry arrived at similar conclusions: *"mind-brain interaction: mentalism, yes; dualism, no"* (Sperry 1980).

In agreement with Tallis, Uttal says that *"the real problem is the bridge between the neural response and cognition, not the one between the neural response and the fMRI image"* (Uttal 2002). He believes that *"the essential level of psychoneural equivalence is to be found at the much more microscopic level of the enormous numbers involved in the network of interacting neurones rather than the level of chunks of the brain dealt with by the relatively low resolution imaging devices"* (Uttal 2002). Since this is unmeasurable it leaves mind as a biologically unknowable black box. Tallis is still more iconoclastic and doesn't even permit the possibility for psychoneural equivalence as an ontological leap of faith (Tallis 2000).

Matthews argues for "explanatory pluralism" - biological, syntactic/symbolic and semantic levels of knowledge/explanation which cannot be mapped directly one onto the other (Matthews 2004).

Ineffability of qualia: a "category error" between phenomenal and propositional knowledge?

Both Jakab and Musacchio have independently come to the conclusion that the explanatory mind-body gap may not really be a metaphysical ontological problem but rather a linguistic one which they term the "ineffability of qualia" (Jakab 2000; Musacchio 2002). Put simply, what we experience (phenomenal or perceptual knowledge – or qualia) is linguistically inexpressible (ineffable) because these qualia are the very irreducible building blocks of language itself. *"the ineffability of qualia is due to their **physicality**, not to their mysterious character"* (Musacchio 2002)p342.

Musacchio believes what is being perpetrated in the explanatory gap conundrum is a "category error" between phenomenal and propositional knowledge.

"Natural language ultimately refers through the phenomenal, to brain processes, models or transformations of the diverse forms of energy that affect our senses. Thus, phenomenal knowledge is an absolute prerequisite for the development of language and propositional language" (Musacchio 2002) p355). If this is true then it may explain the neurobiological and neurophysiological success of using "naturalistic" language as a basis for personality.

The philosophical concept of category error first originated from Gilbert Ryle in his prominent work "the concept of mind" in a consideration of Descartes' mind-body dualism (Ryle 1949). He said "The "reduction" of the material world to mental states and processes, as well as the "reduction" of the mental states and processes to physical states and processes, presuppose the legitimacy of the disjunction "either there exist minds or there exist bodies (but not both)". It would be like saying, "either she bought a left-hand and a right-hand glove or she bought a pair of gloves (but not both)".

The category mistake is made when philosophers talk about mind and matter as if they were "... terms of the same logical type". While it does make sense to talk about mental processes and events, claims Ryle, the "... phrase 'there occur mental processes' does not mean the same sort of thing as 'there occur physical processes', and, therefore, that it makes no sense to conjoin or disjoin the two". Cartesian dualism makes the mistake of assuming that it is sensible to ask of a given cause, process, or event, whether it is mental or physical (with the implication that it cannot be both). Ryle illustrated this with a prospective student who visits a university, he or she will see the library, the labs, the sports arena, but then may very well ask the tour guide, "but where is the university?", having been under the assumption that it is a different place altogether. According to Ryle, the mistake made by the student is a failure to realize that "university" and "library" are terms belonging to different logical categories.

Similarly, dualism establishes mind and body as polar opposites. At the language level, the mental properties are logical negations of the physical properties. So they belong, in accordance with the concept of category, to the same logical types, given that the expressions that are used for the descriptions of mental events are always mere negatives of the expressions used for the descriptions of material

events. Ryle then says that such use implies a 'categorical mistake' for the descriptions of mental events that do not properly belong to the categories used for describing the bodily events.

The "body-minded" brain and the embodiment of mind

Ryle also originated the phrase "the ghost in the machine" to refer to Descartes model. Descartes popularised a dualistic notion of mind and body which became the dominant model for western medicine, and this *"Cartesian split pervades both research and practice"* (Damasio 1994).

Antonio Damasio has recently championed that *"the comprehensive understanding of the human mind requires an* ***organismic perspective;*** *that not only must the mind move from a non-physical cogitum to the realm of biological tissue, but it must also be related to a whole organism possessed of integrated body proper and brain and fully interactive with a physical and social environment"* (Damasio 1994)p251-252.

It is therefore an additional problem for a reductionist approach to mind and cognition (i.e. that the total is simply the sum of the parts) if in fact mind is an ***emergent property*** of the whole system. This is corrected in "organicism for the 21st century" (Gilbert and Sarkar 2000). It also facilitates the concept that cognition is a property of a distributed network contra localisationist attempts to find homuncular/phrenological pain or emotion centres (Uttal 2001; Friston 2002; Mundale 2002).

By contrast, conscious perception needs to be set in the proper context that consciousness is merely the tip of the "cognitive iceberg". Indeed it has been estimated that only 5% of human behaviour is consciously determined: the "unbearable automaticity of being" (Bargh and Chartrand 1999). Automaticity is the rule for emotional processing (LeDoux 1996; Morris et al. 1999; Vuilleumier et al. 2002; Dolan and Vuilleumier 2003); facial processing (Winston et al. 2002); and visceral afferent and efferent activity (Adam 1998; Cameron 2002) indeed it is consciousness which is the exception! A PET study showed that the majority of brain sites involved in emotion generation are sub-cortical and generally associated with automatic processes (Damasio et al. 2000; Panksepp 2003). Many neuroscientists now believe that very basic automatic/autonomic/homeostatic processes form the

foundation and basis for self-consciousness and "agency" within the body-minded brain (Salzen 1998; Damasio 1999; Rolls 2000).

Summary of section 7.3.3

(i) The philosophical problem of the "mind-body gap" may have practical implications for cognitive neuroscience/psychophysiology as there may be no knowable level of psychoneural equivalence: the gap may be unbridgeable! Some have opted for a Cartesian dualistic epistemology in response. (ii) Some philosophers have suggested that the very irreducibility of the language of perception (the ineffability of qualia) points towards its biological basis and the mind-body gap is simply a category error. (iii) A Cartesian dualistic ontology/epistemology may undermine research in this field. This has been countered by notions of the "body-minded brain" and the "embodied mind". (iv) Emphasis on explicit aspects of consciousness may diminish appreciation of automatic/unconscious underpinnings.

7.3.4 What do physiological changes actually index?

Physiological measures in general and ANS measures in particular are multiply determined. As an example, cardiac vagal control (CVC) includes relatively "simple" reflex and peripheral physiology such as baro-receptor modulation and respiratory modulation as outlined in section 1.8. These reflexes sub serve "consciousness" at its most mundane homeostatic level, i.e. getting blood and oxygen to the body and brain to sustain conscious life. CVC also receives modulatory input from sub-cortical centres including peri-aqueductal gray matter, amygdala (Julu 2001) and ultimately from the pre-frontal cortices (Thayer and Friedman 2002). CVC has been used therefore to putatively index very diverse physiological and psychological processes from cardiovascular fitness and risk to neonatal pain reactivity and attention to a global index of central inhibition and disinhibition (Thayer and Friedman 2002; Berntson et al. 2007).

At the most basic level however, physiological measures such as CVC (but also serum hormone levels or any other physiological measure) have only a very "limited vocabulary" in that they can vary both tonically and phasically in only binary directions i.e. they can increase or decrease (or remain unchanged). Therefore only 4 combinations of autonomic or other physiological change are generally possible:

reduced tone with either increase/decrease in phasic changes and increased tone with either increase/decrease in phasic changes.

When recovery time, rebound changes and habituation/slope of phasic changes are incorporated, this repertoire is increased further, but the number of possible physiological permutations is nonetheless generally outstripped in number by the diverse interpretations available as to their physiological or psychological "meaning" at any given moment.

Carefully controlled experimental conditions and concomitant time-locked measures such as brain-imaging and electrophysiological measures; precise psychophysics or pharmacological manipulation can give us some external anchors as to what level of analysis a given physiological change is working at. This can lead however to the danger of limiting definition of a physiological change to operational parameters i.e. those used in the experimental set-up. To operationally define the meaning of a physiological change may be a "category error" since the physiological parameter could be influenced by all several explanatory levels simultaneously. If the latter is the case then it is difficult to discern specific "higher meaning" with any great certitude from binary physiological changes (or even the more complex functional surface of "autonomic space" (Berntson et al. 1991).

There are several interpretive possibilities open therefore in psychophysiological studies:

1. Physiological changes may solely reflect physiological function, for example reflex haemodynamic auto regulation for CVC. Correlations with higher constructs, such as personality factors, anxiety, and pain; may therefore be random or spurious which may explain difficulties in reproduction.

2. Correlations with higher constructs are real but "fragile" due to a given physiological change being multiply determined and therefore may only be seen under certain conditions and given particular subject characteristics.

3. There may be simultaneous mathematical relations of physiological changes both to higher processes and to basic physiological processes but to disentangle their relative contribution requires a level of mathematical sophistication presently beyond our grasp. This may be resolved ultimately with developments and application in mathematics, e.g. chaos theory at a level beyond the scope of current spectral decomposition techniques. An analogy is that spectral decomposition has helped differentiate respiratory parasympathetic influences on HRV from other influences and

so a similar mathematical/technological advance may help dissect competing sources of influence on CVC. This explanation for difficulties in reproduction of psychophysiological associations is that the correlations between physiological and higher constructs only emerge using current mathematical applications when haemodynamic and higher influences either diverge or converge in particular ways and at other times the conjoined influences are lost to the techniques.

It does not seem possible at present to be sure which of these 3 possibilities pertains in psychophysiological studies. It is challenging therefore to envisage how currently available neurophysiological techniques (from autonomics through to brain imaging techniques, brain stimulation/lesioning techniques and pharmacological manipulation) can reliably be translated into sensitive and specific discriminatory biomarkers for "higher" trait constructs or syndrome phenotypes.

7.3.5 What do "brain" activity changes actually index?

Everything just said about physiological measures can equally be applied to brain imaging. Again brain activity changes are a fairly binary physiological output (e.g. BOLD effect phasic increases or decreases) albeit that they are both spatially and temporally distributed. Some imaging techniques, such as MEG, have increased degrees of freedom with changes in power spectra but even these are again relatively restricted when compared with the complexity and diversity of cognitive events purportedly attributed to them.

Brain blood flow seems a reasonable indirect index of metabolic and electrical activity (Uttal 2002), however the question then arises as to what metabolic and electrical activity really index? This is unknown, but it is doubtful that even the most comprehensive chaos theory driven analysis of the neurochemical, spatial, temporal and frequency activity of the whole brain's metabolic and electrical input and output would shed light as to which of these is ultimately responsible for an organisms "thoughts", "feelings" and "decisions" let alone the content of what those thoughts/feelings/decisions actually were. Decoding the genome has been called a task of some order of magnitudes lower than that which is needed for the cognitive neuroscience enterprise of deciphering the functions inside the mind's "black box" (Uttal 2001; 2002). This is where the metaphysical questions dealt with in section 7.3.3 become of practical significance – to properly attribute cognitive processes to

brain physiology events one has to assume a level of psychoneural equivalence which may be incorrect.

The subtraction analysis technique which is foundational to most functional brain imaging is itself a target for criticism. In particular, it would seem highly likely that some differences in regional blood flow between subtracted images would always be detected regardless of experimental condition (Uttal 2001). Thus, differences detected could simply be statistical epiphenomena or non-specific signals that the brain is connected to the body and is "on" (Mason et al. 2007). The trouble is that there is no externally valid way of choosing between these options. Region of interest analysis can help by putting all the awkward inexplicable non-specific, i.e. not operationally or circularly defined, areas of activation out of sight and so literally "out of mind".

Psychophysiology has been described as "taking shots at moving targets with wobbly sights" (Matthews 2004). This highlights the difficulties of both adequately tight psychological constructs (the moving targets) with methodology that is itself imprecise (wobbly sights). These are the same problems encountered with functional brain imaging.

Regardless of the origin or nature of the physiological recordings (cardiac or brain, electrical or haemodynamic) we are left with simple correlations between these and subjectively reported accounts of what is happening internally. This is an unbridgeable epistemic divide which is unlikely ever to diminish. Both psychophysiology and cognitive neuroscience are subject to these identical constraints and limitations. The two disciplines are defined and distinguished simply by the physiological outputs measured i.e. the technology (section 7.3.1).

Precise biological isomorphism of mind and physiology (brain or body) is probably an unrealistic and unrealisable goal. The metaphor of "explanatory pluralism" is useful here whereby multiple measures are taken simultaneously at multiple levels including (i) physiology (brain and body hardware) (ii) the "virtual cognitive architecture" (software) and (iii) wider contextual organismic/societal level goals (Matthews 2004). The aim of explanatory pluralism is to build up a bigger picture rather than to simply try to map one level directly on the other.

Conversely, without any attempts to constrain (iii) contextual goals and (ii) "virtual cognitive architecture" by (i) biological or environmental anchors - the worst

excesses of unfalsifiable mythology may ensue, therefore biological explanations should remain at the forefront of explanatory attempts for symptom perception.

7.3.6 What do psychological constructs actually mean/index?

Personality models and other cognitive constructs such as anxiety and pain catastrophising have had significant heuristic success in producing multiple correlations with biological events and clinical conditions. What they seem to lack however are fundamental clinical properties of specificity, sensitivity and repeatability with sufficient finesse to make them viable discriminatory diagnostic tools or biomarkers for therapeutic tracking.

For William Uttal it is the, at times, relative arbitrariness of operational definitions of cognitive constructs which is the most insurmountable obstacle in the localisationist cognitive neuroscience enterprise (Uttal 2001). William James famously said "everybody knows what is meant by attention" – but it seems there are limited objective criteria for moving beyond such folk definitions. Personality theory superseded Galenic observations by using factor analysis of dictionary descriptors. Eysenck took this further by using factor analysis of clinical descriptors but his personality theories are still ultimately rooted in lexical properties (Corr 2004).

The primary issue is therefore the relations between neural events, syntactical events and symbolic events. Isomorphism between these seems unlikely. Abandoning isomorphism however shouldn't mean casting off all attempts to constrain syntactical and symbolic levels biologically nor in turn to relate biological events to syntactical and symbolic levels, since this is where they may ultimately arise from (Musacchio 2002). It does however require insight into these limitations to inform expectations and mitigate over-hasty or over-speculative conclusions.

7.4 So then, so what? – back to medically unexplained symptoms: clinical implications and potential for translation

At the start of the thesis, an epidemic of medically unexplained symptoms and functional syndromes was documented (section 1.3). The findings in this thesis have implications and applications for functional syndromes: i) in our understanding of the bi-directional relations between pain and emotion based on common biological substrates and processes and ii) in the role of personality traits effected through central and autonomic mechanisms.

7.4.1 "State" – bodily sensations/symptoms and emotional perception are inextricably linked

Rationale for antidepressants for pain

It is already common practice for antidepressants to be used for chronic functional pain disorders. My findings of dyshedonia induced by visceral pain and visceral hyperalgesia induced by negative emotional context provide rationales for why and how anti-depressant therapy might work. In other words they provide evidence that changing emotional perceptions can affect pain perceptions and vice-versa. This should be the case equally for pharmacological and psychological therapies. It is possible that co-morbid emotional problems may be under treated in functional syndromes where the emphasis is sometimes on more typical "anti-nociceptive" therapies, which may be thus rendered less effective. The implication here is that rather than treating either pain or emotion, *both* need to be tackled as they may be mutually re-enforcing.

7.4.2 "Trait" – inter-individual psychophysiological differences at baseline and in pain: vulnerability factors for unexplained symptoms?

The picture that has emerged from the literature and from this programme of work is that extroversion-introversion is linked to SNS reactivity and to pain intensity thresholds whereas neuroticism-stability is linked with PNS changes and to general emotional responsivity.

It is possible that these personality related differences in emotion-pain interactions and ANS/CNS pain responses represent neurobiological vulnerabilities or risk factors for the development of chronic pain and affective disorders. Certainly the role of neuroticism as a general risk factor is well established but its lack of specificity raises concerns as to its utility (Claridge and Davis 2001; Ormel et al. 2004; Yousfi et al. 2004). Establishing these endophenotypic biomarkers for neuroticism may be helpful in increasing its mechanistic explanatory utility and clinical discriminatory validity. In particular if the characteristic biological markers are found in response to provoking stimuli, in conjunction with the surface traits, it may help to determine further diagnostic or therapeutic strategies.

In particular, the finding of a neurotic surface trait together with a specific endophenotypic pattern of pain response might encourage early anti-depressant

therapy for unexplained pain. Invasive investigations could be deferred until there is failure of therapeutic response which itself could be potentially monitored by the biomarkers for dosing adequacy. Conversely, extrovert surface traits together with endophenotypic bio-markers might encourage a more aggressive initial investigative work up and less aggressive antidepressant therapy.

7.4.3 What has experimentally evoked acute pain got to do with clinical symptoms?

Acute pain experimental models may not be directly translatable to clinical syndromes. In particular clinical syndromes usually consist of chronic symptoms not only of pain but also of many concomitant symptoms such as fatigue. Certainly caution should be exercised in making such leaps. Ethically it is problematic to induce chronic symptoms in healthy humans. Confirmation of the relevance of the observations and mechanisms identified for clinical populations will certainly require studying clinical populations. It would however be quite legitimate to use similar experimental paradigms in clinical populations since the hypothesis might be that there is an increased prevalence of the neurotic profile, physiological brain and body responses in clinical populations.

Another approach might be to use sensitising agents (e.g. capsaicin/oesophageal acidification) to see how the responses may be changed in healthy populations but even these are sub-acute rather than truly chronic symptom models.

7.4.4 Can functional syndromes be mechanistically dissected?

The metaphysical possibility strongly exists that there is no measurable level of psychoneural equivalence and that the mind-brain-body gap may be epistemically unbridgeable (Tallis 2000). If this is so then symptoms such as pain, nausea and satiety which are primary sensory percepts (or "ineffable qualia" - linguistically irreducible perceptual experiences) will not be completely reducible mechanistically. Since functional syndromes are simply collections of ineffable qualia they would also be mechanistically irreducible. It may be possible to determine *necessary* biological components (e.g. a functioning neocortex) but not *sufficient* causes of symptoms. This means it may be impossible to obtain any "objective" biological measure(s)

which can sufficiently discriminate between different aetiological possibilities for a given symptom.

I am not arguing here that there may not be remediable occult infectious/inflammatory components in some "functional symptoms" in some patients nor indeed that there may not be remediable "functional disturbances of the nervous system". I am simply addressing the question as to whether functional syndromes can truly be completely mechanistically dissected. In so far as this question is really a "smokescreen" for attempts to mechanistically dissect qualia (including symptoms) this may be epistemically impossible. Herein the art of medical practice may never be fully superseded by the science.

7.5 Future research strategies

7.5.1 Psychophysiological phenotypes

The ANS psychophysiological phenotypes identified in chapter 3 can be taken further by exploring:

1. Prevalence in the "normal" population – This would require several hundreds of individuals to be studied in order to be meaningful. An alternative approach would be to screen large numbers with psychological measures and then study the extremes in detail for their psychophysiological responses. Stability could be assessed further in a subset by repeat provocation studies. The prevalence in clinical populations could also be studied thereafter to see if there is an over-representation of the phenotype.

2. Sex and age differences – this could be performed as part of a prevalence study by powering sufficiently and with stratification to enable sex and age influences to be established.

3. State anxiety differences – This would need to be controlled for in prevalence studies but also is a subject worthy of further exploration experimentally. State could be manipulated in dimensions of arousal and valence.

4. Genetic influences – candidate genotypes would include choline transporter polymorphisms, serotonin transporter polymorphisms, a2adrenoceptor polymorphisms and COMT - covering cholinergic, adrenergic, serotenergic and dopaminergic/opioidergic central and peripheral influences.

5. Further mechanistic studies of subset extremes could include a) concurrent ANS studies with brain imaging using MEG b) Pharmacological manipulation of ANS parameters (serotonergic, opiodergic, adrenergic, cholinergic) c) physiological manipulation of cardiac vagal control (paced breathing, exercise/fitness) d) Differential effects of sensitisation/injury response d) Differential effects to stressors

6. Prospective clinical studies could be performed for example by phenotyping people prior to elective abdominal surgery for risk of post-operative pain development

7. Therapeutic clinical studies e.g. roles of Vagal Nerve Stimulation/manoeuvres to increase baseline vagal tone (exercise, respiratory) in selected populations of patients with the "at-risk" phenotype.

7.5.2 Imaging

The findings from the imaging studies in chapters 5&6 could be taken forward in similar ways to those of the psychophysiological studies. Specifically in the ideal world and in subjects pre-selected for psychophysiological traits, exploring genotypic influences, concurrent imaging and ANS measures with pharmacological modulation of dyshedonia and hyperalgesia (e.g. using antidepressants) would be useful future imaging strategies to explore.

7.5.3 Developing more sophisticated models

Current clinical and experimental models are inadequate for dealing with unexplained medical symptoms and syndromes. They tend to produce dichotomised Cartesian diagnostic labels and therapeutic strategies. There is a need therefore to develop new theoretical and experimental models refined by theoretical and experimental advances.

The review of the literature has suggested that missing elements from current schemata include:-

1) Dynamism – existing models tend to be too *static* in the following dimensions:

a) *Neuroanatomically* in attributing structure to function. Dynamic system approaches counter a tendency towards reification of structures and constructs (Thayer and Friedman 2002). Dynamic systems emphasise subsystems comprising dissociable and loosely coupled bio-oscillators which coalesce or disjunct with others

to provide increased repertoires of functional flexibility for different purposes under different conditions, rather than sub serving any particular function.

b) *Origins* –little attention is generally paid to *ontogeny* - the developmental trajectory of the individual and *teleology* – the developmental trajectory of the species. Ontogeny can be addressed by measures of distal (early life) and recent stress whereas the teleology can be addressed by phylogenetic comparative studies. Lastly, *adaptation* puts the model in a dynamic framework of survival goals and defence responses.

c) *Trajectory* – taking into account individual and societal expectations and goals will help with this level of dynamism.

2) Inhibition at the apex of hierarchy of control – models have tended to emphasise behavioural activation and sensitisation over inhibition. This could be corrected by emphasising inhibitory and disinhibitory processes. In particular the pre-frontal cortices (PFC) serve this function centrally, [see for example the accounts of Phineas Gage (Damasio 1994)] and cardiac vagal control does this peripherally. There is need for further exploration therefore of the PFC-CVC inhibitory axis (Thayer and Friedman 2002).

3) Afferent limb (feedback/feedforward) – models have tended to emphasise the effector limbs of the circuit, particularly for the ANS. This can be redressed by considering:

a) the role of *interoception*, sensory sensitivity and sensation seeking in personality models

b) the roles of the *insula cortex*, *sensory vagus* and vagal nerve stimulation in physiological models and recognition of the heuristic construct of a "homeostatic afferent processing network".

4) Role of endophenotypes – models have tended to emphasise "surface traits". This can be redressed by using:

a) endophenotype personality models e.g. behavioural inhibition systems/fight flight-freeze systems/behavioural activation systems (BIS-FFFS-BAS), sensation seeking

b) endophenotype bio-markers such as ANS and CNS reactivity.

5) Organicism – models tend to be reductionist i.e. "bottom-up" assuming that the whole can be explained by the sum of its parts. However, it seems likely that mind is an *emergent property* of brain-body function. This can be redressed by "organicism for the 21st century" (Gilbert and Sarkar 2000) and "explanatory pluralism" (Matthews 2004).

I have synthesised a pluralistic conceptual working model in which I have sought to place GI sensorimotor (interoceptive) function in a context which is holistic, hierarchical, integrated and dynamic. The model aims to clarify the "big picture" involved in psychophysiological/cognitive neuroscience studies with emphasis on the neglected elements drawn from my own experimental findings and the particularly salient elements of the literature [figure 7.1]. These elements from the literature are:

(i) MacNaughton-Gray personality model (McNaughton and Corr 2004)

(ii) Thayer-Friedman dynamical systems model (Thayer and Friedman 2002)

(iii) Matthews "explanatory pluralism" (Matthews 2004)

(iv) Porge's Polyvagal model (Porges 2007)

(v) Craig homeostatic afferent processing network model (Mayer et al. 2006)

(vi) Bandler-Lumb-Paton experimental work (Bandler et al. 2000; Lumb 2002; Paton et al. 2005).

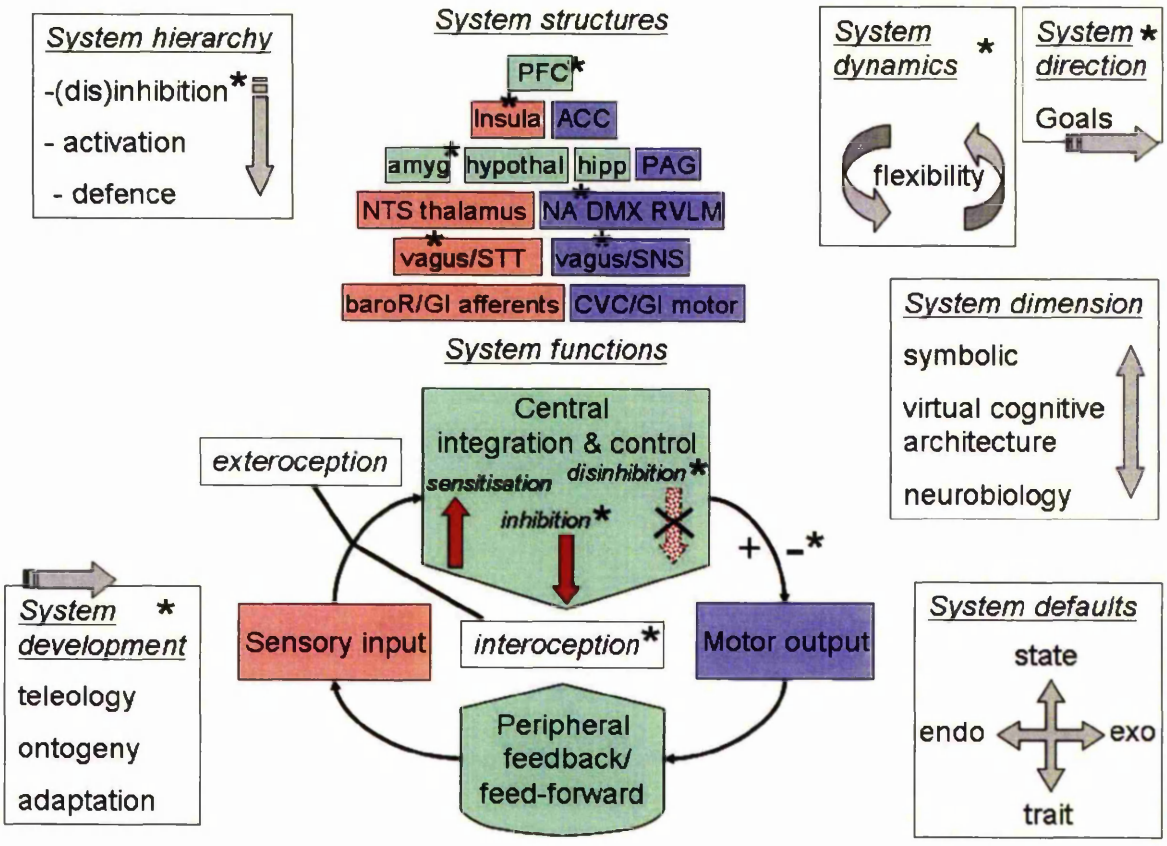

Figure 7.1 a pluralistic, holistic, hierarchical, integrated and dynamic conceptual-working model. Genetic polymorphisms (not shown here) can influence any aspect of the system.
* asterixes highlight elements of the model that have generally been overlooked or neglected. PFC – pre-frontal cortex, ACC – anterior cingulate cortex, amyg – amygdala, hypothal – hypothalamus, hipp – hippocampus, PAG – peri-aqueductal gray, NTS – nucleus of the solitary tract, NA – nucleus ambiguus, DMX – dorsal motor nucleus of vagus, RVLM – rostral ventrolateral medulla, STT – spinothalamic tracts, SNS – sympathetic nervous system, baroR – baroreceptors, GI – gastrointestinal, CVC – cardiac vagal control. Transparent red boxes represent structures involved in sensory input and transparent blue boxes those involved in motor output.

7.6 Conclusions

1. There is an epidemic of functional syndromes comprising medically unexplained symptoms which includes gastrointestinal pain.

2. The scientific study of pain requires a pluralistic account incorporating measures including (i) psychophysical (subjective experience of pain) (ii) stimulus characteristics (iii) personality trait (iv) emotional state (v) brain, brainstem and body physiological parameters (vi) sociological meaning/context

3. Psychophysiological endophenotypes exist for visceral pain which relate neuroticism and extroversion to differentiated patterned ANS responses and pain sensitivities.

4. Visceral and somatic pain increase heart rate with co-activation of sympathetic and parasympathetic nervous systems but reduced sympathetic vasomotor activity. Personality factors correlate with rate of change of Cardiac Vagal Control responses to pain in particular.

5. Negative emotional context induces visceral hyperalgesia which correlates with a widespread network of brain structures differentially active according to personality type.

6. Visceral pain induces dyshedonia. The degree of dyshedonia and activation in a widespread network of cortical and sub-cortical brain structures including the amygdala is related to personality type.

7. Symptoms are ineffable qualia (linguistically irreducible perceptual experiences) that mechanistically may not be fully reducible to brain-body physiological concomitants. This could mean that clinically sensitive and specific biological markers for functional syndromes may not be possible. However:

i) the endophenotypes identified in this thesis may be clinically useful for stratifying risk and vulnerability in healthy individuals for the subsequent development of functional syndromes. This could be studied further in clinical prevalence studies.

ii) the psychological and central mechanisms identified in this body of work may be clinically useful for informing clinical management of functional syndromes – in particular for encouraging concomitant treatment of emotional and pain symptoms, and also may be useful for clinical pharmaco-imaging studies by providing biomarkers of efficacy (e.g. reduction in brain activity markers of negative emotion induced visceral hypersensitivity).

Appendices

Psychological trait measures used in this thesis

Big Five Inventory (BFI)

Here are a number of characteristics that may or may not apply to you. For example, do you agree that you are someone who likes to spend time with others? Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement.

Disagree strongly	Disagree a little	Neither agree nor disagree	Agree a little	Agree Strongly
1	2	3	4	5

I see myself as someone who

___ 1. Is talkative
___ 2. Tends to find fault with others
___ 3. Does a thorough job
___ 4. Is depressed, blue
___ 5. Is original, comes up with new ideas
___ 6. Is reserved
___ 7. Is helpful and unselfish with others
___ 8. Can be somewhat careless
___ 9. Is relaxed, handles stress well
___ 10. Is curious about many different things
___ 11. Is full of energy
___ 12. Starts quarrels with others
___ 13. Is a reliable worker
___ 14. Can be tense
___ 15. Is ingenious, a deep thinker
___ 16. Generates a lot of enthusiasm
___ 17. Has a forgiving nature
___ 18. Tends to be disorganized
___ 19. Worries a lot
___ 20. Has an active imagination
___ 21. Tends to be quiet
___ 22. Is generally trusting
___ 23. Tends to be lazy
___ 24. Is emotionally stable, not easily upset
___ 25. Is inventive
___ 26. Has an assertive personality
___ 27. Can be cold and aloof
___ 28. Perseveres until the task is finished
___ 29. Can be moody
___ 30. Values artistic, aesthetic experiences
___ 31. Is sometimes shy, inhibited
___ 32. Is considerate and kind to almost everyone
___ 33. Does things efficiently
___ 34. Remains calm in tense situations
___ 35. Prefers work that is routine
___ 36. Is outgoing, sociable
___ 37. Is sometimes rude to others
___ 38. Makes plans and follows through with them
___ 39. Gets nervous easily
___ 40. Likes to reflect, play with ideas
___ 41. Has few artistic interests
___ 42. Likes to cooperate with others
___ 43. Is easily distracted
___ 44. Is sophisticated in art, music, or literature

Please check: Did you write a number in front of each statement?

Anxiety Sensitivity Index (ASI)

Anxiety Sensitivity Index

Name/Code Number **Age:** **Male/Female**

The following questionnaire measures anxiety. Please rate each item by circling the number which most represents how you generally feel. Please answer all of the questions. Thank you.

	Very little	A little	Some	Much	Very much
1. It is important for me not to appear nervous	0	1	2	3	4
2. When I can't keep my mind on a task, I worry that I might be going crazy	0	1	2	3	4
3. It scares me when I feel "shaky" (trembling)	0	1	2	3	4
4. It scares me when I feel faint	0	1	2	3	4
5. It is important for me to stay in control of my emotions	0	1	2	3	4
6. It scares me when my heart beats rapidly	0	1	2	3	4
7. It embarrasses me when my stomach growls.	0	1	2	3	4
8. It scares me when I am nauseous	0	1	2	3	4
9. When I notice that my heart is beating rapidly, I worry that I might have a heart attack	0	1	2	3	4
10. It scares me when I am short of breath	0	1	2	3	4
11. When my stomach is upset, I worry that I might be seriously ill	0	1	2	3	4
12. It scares me when I am unable to keep my mind on the task	0	1	2	3	4
13. Other people notice when I feel shaky	0	1	2	3	4
14. Unusual body sensations scare me	0	1	2	3	4
15. When I am nervous, I worry that I might be mentally ill	0	1	2	3	4
16. It scares me when I am nervous	0	1	2	3	4

Spielberger State Anxiety Index (STAI-S)

Spielberger state

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately So	Very Much So
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable.	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Spielberger Trait Anxiety Index (STAI-T)

Spielberger Trait
A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Almost Never	Sometimes	Often	Almost Always
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that doesn't really matter	1	2	3	4
30. I am happy.	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interest	1	2	3	4

Sensory Processing style Q1-15

Adult sensory profile

Name/Code Number **Age:** **Male/Female**

Please rate each item by circling the number which most represents how you generally feel. Please answer all of the questions. Thank you.

	Almost never (5% or less)	Seldom (about 25% of time)	Occasionally (about 50% of time)	Frequently (about 75% of time)	Almost always (95% or more)
1. I leave or move to another section when I smell a strong odor in a store (e.g. bath products, candles, perfumes)	1	2	3	4	5
2. I add spice to my food	1	2	3	4	5
3. I don't smell things that other people say they smell	1	2	3	4	5
4. I enjoy being close to people who wear perfume or cologne	1	2	3	4	5
5. I only eat familiar foods	1	2	3	4	5
6. Many foods taste bland to me (in other words food tastes plain or does not have lots of flavour)	1	2	3	4	5
7. I don't like strong tasting mints or candies	1	2	3	4	5
8. I go over to smell fresh flowers when I see them	1	2	3	4	5
9. I'm afraid of heights	1	2	3	4	5
10. I enjoy how it feels to move about (e.g. dancing, running)	1	2	3	4	5
11. I avoid elevators and/or escalators because I dislike the movement	1	2	3	4	5
12. I trip or bump into things	1	2	3	4	5
13. I dislike the movement of riding in a car	1	2	3	4	5
14. I choose to engage in physical activities	1	2	3	4	5
15. I am unsure of footing when walking on the stairs (e.g. I trip, lose balance, need to hold the rail)	1	2	3	4	5

Sensory Processing style Q16-33

	Almost never (5% or less)	Seldom (about 25% of time)	Occasionally (about 50% of time)	Frequently (about 75% of time)	Almost always (95% or more)
16. I become dizzy easily (e.g. after bending over, getting up too fast)	1	2	3	4	5
17. I like to go places that have bright lights and that are colorful	1	2	3	4	5
18. I keep the shades down during the day when I am at home	1	2	3	4	5
19. I like to wear colorful clothing	1	2	3	4	5
20. I become frustrated when trying to find something in a crowded drawer or messy room	1	2	3	4	5
21. I miss the street, building, or room signs when trying to go somewhere new	1	2	3	4	5
22. I am bothered by unsteady or fast moving visual images in movies or TV	1	2	3	4	5
23. I don't notice when people come into the room	1	2	3	4	5
24. I choose to shop in smaller stores because I'm overwhelmed in large stores	1	2	3	4	5
25. I become bothered when I see lots of movement around me (e.g. at a busy mall, parade, carnival)	1	2	3	4	5
26. I limit distractions when I am working (e.g. I close the door, or turn off the TV)	1	2	3	4	5
27. I dislike having my back rubbed	1	2	3	4	5
28. I like how it feels to get my hair cut	1	2	3	4	5
29. I avoid or wear gloves during activities that will make my hands messy	1	2	3	4	5
30. I touch others when I'm talking (e.g. I put my hand on their shoulder or shake their hands)	1	2	3	4	5
31. I am bothered by the feeling in my mouth when I wake up in the morning	1	2	3	4	5
32. I like to go barefoot	1	2	3	4	5
33. I'm uncomfortable wearing certain fabrics (e.g. wool, silk, corduroy, tags in clothing)	1	2	3	4	5

Sensory Processing style Q34-50

	Almost never (5% or less)	Seldom (about 25% of time)	Occasionally (about 50% of time)	Frequently (about 75% of time)	Almost always (95% or more)
34. I don't like particular food textures (e.g. peaches with skin, applesauce, cottage cheese, chunky peanut butter)	1	2	3	4	5
35. I move away when others get too close to me	1	2	3	4	5
36. I don't seem to notice when my face or hands are dirty	1	2	3	4	5
37. I get scrapes or bruises but don't remember how I got them	1	2	3	4	5
38. I avoid standing in lines or standing close to other people because I don't like to get too close to others	1	2	3	4	5
39. I don't seem to notice when someone touches my arm or back	1	2	3	4	5
40. I work on two or more tasks at the same time	1	2	3	4	5
41. It takes me more time than other people to wake up in the morning	1	2	3	4	5
42. I do things on the spur of the moment (in other words I do things without making a plan ahead of time)	1	2	3	4	5
43. I find time to get away from my busy life and spend time by myself.	1	2	3	4	5
44. I seem slower than others when trying to follow an activity or task	1	2	3	4	5
45. I don't get jokes as quickly as others	1	2	3	4	5
46. I stay away from crowds	1	2	3	4	5
47. I find activities to perform in front of others (e.g. music, sports, public speaking and answering questions in class)	1	2	3	4	5
48. I find it hard to concentrate for the whole time when sitting in a long class or meeting	1	2	3	4	5
49. I avoid situations where unexpected things might happen (e.g. going to unfamiliar places or being around people I don't know)	1	2	3	4	5
50. I hum, whistle, sing or make other noises	1	2	3	4	5

Sensory Processing style Q51-60

	Almost never (5% or less)	Seldom (about 25% of time)	Occasionally (about 50% of time)	Frequently (about 75% of time)	Almost always (95% or more)
51. I startle easily at unexpected or loud noises (e.g. vacuum cleaner, dog barking, telephone ringing)	1	2	3	4	5
52. I have trouble following what people are saying when they talk fast or about unfamiliar topics	1	2	3	4	5
53. I leave the room when others are watching TV or I ask them to turn it down	1	2	3	4	5
54. I am distracted if there is a lot of noise around	1	2	3	4	5
55. I don't notice when my name is called	1	2	3	4	5
56. I use strategies to drown out sound (e.g. close the door, cover my ears, wear ear plugs)	1	2	3	4	5
57. I stay away from noisy settings	1	2	3	4	5
58. I like to attend events with a lot of music	1	2	3	4	5
59. I have to ask people to repeat things	1	2	3	4	5
60. I find it difficult to work with background noise (e.g. fan, radio)	1	2	3	4	5

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