

**MULTIDISCIPLINARY PAIN MANAGEMENT:
PSYCHOSOCIAL OUTCOMES AND EFFECT ON
NEUROPHYSIOLOGICAL RESPONSES TO PAIN**

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ABSTRACT

Background

The efficacy of UK National Health Service (NHS) multidisciplinary pain management programmes (PMPs) is currently measured using self-report questionnaires. Whilst subjective measurements provide important information about personal experiences, they cannot reveal underlying changes in cortical activity related to pain that may also accompany PMP treatment. There is no objective measurement of treatment efficacy currently available. This thesis contains studies of two NHS PMPs that differ in their psychological approach. The effect of these treatments was assessed using self-report questionnaire measures, and a newly developed neurophysiological assessment technique.

Methods

Studies examined the effect of a cognitive-behavioural therapy (CBT) based PMP, and an acceptance and commitment therapy (ACT) based PMP, upon questionnaire measures of psychological, physical, and social health, as well as measures of coping and acceptance. Further studies examined pre- to post-treatment changes in patients' cortical pain processing measured using electroencephalography (EEG), as well as in healthy and patient (waiting list/treatment as usual) control groups. The effect of treatment on contact heat evoked potentials (CHEPs), and on changes in power spectral density (PSD) following exposure to medium duration tonic pain (90s cold pressor test) was investigated.

Results

Small but significant ($p < .05$) improvements in self-report measures of mental health, coping, and acceptance were found in patients following both CBT- and ACT-based PMPs. There were differences in the effect of PMPs on measures of anxiety, depression and catastrophising, with the ACT-based programme data showing slightly larger effect sizes. Neurophysiological testing revealed no pattern of effect upon CHEPs, however there were pre- to post-treatment differences in the effect of tonic pain upon PSD. Alpha (α) and theta (θ) rhythms were significantly ($p < .05$) reduced pre-treatment in the CBT group ($n=12$); post-treatment this effect was not

observed. There were no pre- to post-treatment differences in the ACT group (n=4) and there were also no changes in either healthy (n=14) or waiting list (n=13) control groups between test sessions.

Conclusion

Both PMPs studied brought about small but significant improvements in patients' perceived mental and physical health. Despite their differences both programmes were clinically beneficial to patients in terms of self-report measures. Measurable change was observed in the cortical response to pain pre- to post-treatment with a CBT-based PMP, most likely due to a change in cognitive appraisal of painful signals brought about by taking part in the PMP. Results imply the possible use of neurophysiological assessment to identify patients who may benefit most from treatment, to match treatments to patients' individual psychological and neurophysiological profile, and to more closely monitor treatment efficacy.

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ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ACT	Acceptance and Commitment Therapy
AEPs	Auditory Evoked Potentials
α	Alpha
BCU	Birmingham City University
β	Beta
c.EEG	Continuous Electroencephalography
CB	Cerebellum
CBT	Cognitive Behavioural Therapy
CHEPs	Contact Heat Evoked Potentials
CHEPS	Contact Heat Evoked Potential Stimulator
CNS	Central Nervous System
CPM	Conditioned Pain Modulation
CRPS	Chronic Regional Pain Syndrome
CS	Central Sensitisation
CSSEPs	Chemosomatosensory Evoked Potentials
DNIC	Diffuse Noxious Inhibitory Controls
DRG	Dorsal Root Ganglion
δ	Delta
EEG	Electroencephalography
ERP	Event Related Potential
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
GCT	Gate Control Theory
γ	Gamma
HSCIC	Health and Social Care Information Centre
HSE	Health Survey for England
HTM	High Threshold Mechanoreceptors
IASP	International Association for the Study of Pain
IBS	Irritable Bowel Syndrome
ISI	Interstimulus Interval

kΩ	Kilo Ohms
LBP	Low Back Pain
LEPs	Laser Evoked Potentials
M1	Primary Motor cortex
MBSR	Mindfulness Based Stress Reduction
MDT	Multidisciplinary Treatment
μV	Microvolts
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
PAG	Periaqueductal Grey
PCC	Posterior Cingulate Cortex
PENS	Percutaneous Electrical Nerve Stimulation
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PMP	Pain Management Programme
PSD	Power Spectral Density
QST	Quantitative Sensory Testing
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RHH	Russells Hall Hospital
S1	Primary Somatosensory cortex
S2	Secondary Somatosensory cortex
SG	Substantia Gelatinosa
SSEPs	Somatosensory Evoked Potentials
STT	Spinothalamic Tract
T-cell	Transmission cell
TCD	Thalamocortical Dysrhythmia
tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation
θ	Theta
WHO	World Health Organisation

PUBLICATIONS AND PRESENTATIONS RELATED TO RESEARCH PRESENTED WITHIN THIS THESIS

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Hylands-White N., Sparkes E., Duarte R.V., Ashford R.L., & Raphael J.H. (2011). Evaluation of the use of EEG in the assessment of chronic pain syndromes: a systematic literature review. *Regional Anaesthesia and Pain Medicine*, 36 (7), E186.

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Hylands-White N, Biggs S, LeMarchand K, Ashford R, Raphael JH. Coping strategies and psychophysical health in patients attending a group cognitive-behavioural therapy pain management programme. Poster presentation at IASP 14th World Congress on Pain, 2012, Milan, Italy.

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CHAPTER 1

INTRODUCTION

Pain is usually a finite experience that is felt in response to illness or injury, and which disappears following recovery. Yet for some, pain may appear without apparent physical cause, or does not subside upon recovery from illness or injury, resulting in a long-term condition characterised by the symptom of ‘chronic’ pain. The treatment of pain begins by addressing the physical cause of pain – tissue damage is allowed to heal, whilst pain medication is used to modify nerve signals relating to the damage and ease suffering. If pain were a purely physical phenomenon, with its origin in the damaged tissues, this treatment would be all that was required. However, pain is a ‘sensory and emotional’ experience which results from a complex interaction of physiological and psychological factors; therefore modern treatments for chronic pain consist of a mix of pharmacological, physiological, and psychological approaches, which mirror the present theoretical understanding of pain as a biopsychosocial phenomenon. One treatment in particular which offers respite from suffering in those patients who do not achieve satisfactory relief through medication is the pain management programme (PMP). Based upon a psychotherapeutic approach, the PMP aims to promote recovery from chronic pain by exploiting the role of psychological factors that contribute to the pain experience.

At present, the success of PMP treatment is measured using questionnaires concerning psychosocial health, examining such factors as anxiety, depression, pain catastrophising, coping strategies, daily activity, and beliefs about pain. These measures have demonstrated that the treatment can be effective (Morley, Eccleston &

A. Williams 1999). Such subjective reporting of improvement by patients is arguably the most important assessment of treatment efficacy, as it relates directly to the goal of treatment, which is to promote better patient health. Two PMPs delivered by regional treatment centres in the West Midlands region of the UK are focused on in this study. The first is based on the psychological principles of cognitive-behavioural therapy (CBT), and the second based on the principles of acceptance and commitment therapy (ACT). Since their inception, several hundred patient questionnaires have been collected by the staff of both programmes. Two chapters of this thesis (Ch. 3 & 5) are dedicated to the analysis and presentation of these questionnaire datasets.

Questionnaire data can provide a detailed picture of the efficacy of PMPs in terms of subjective improvement from pre- to post-treatment. However, the questionnaires cannot reveal biological mechanisms and underlying changes in the brain accompanying treatment success or failure in these patients (Linden 2006). Advances in the field of functional brain imaging over the past decades have made it possible to measure brain structure and brain activity with high spatial and temporal resolution and it has now become possible to examine the biological consequences of psychotherapeutic interventions using the techniques available (Etkin et al. 2005). This thesis therefore also explores the possibility that the neuroimaging technique of electroencephalography (EEG) can be used to record measurable changes in electrical brain activity as a consequence of PMP treatment for chronic pain, either in CBT-based (Ch. 4) or ACT-based (Ch. 6) programmes. The relationship between questionnaire and EEG data is also explored in a short case series (Ch. 6).

The studies contained within this work were designed following a thorough exploration of pain theory, pain treatment, and the use of questionnaires and neuroimaging to assess pain and the effects of pain treatment. Background information

relevant to the studies is presented in the literature review (Ch. 2), which ends with a summary of the theoretical basis for the study and an accompanying rationale.

The final chapter (Ch. 7) contains discussion of the main findings from this work, the implications, and recommendations for future research. Figure 1.1 illustrates the structure of the thesis.

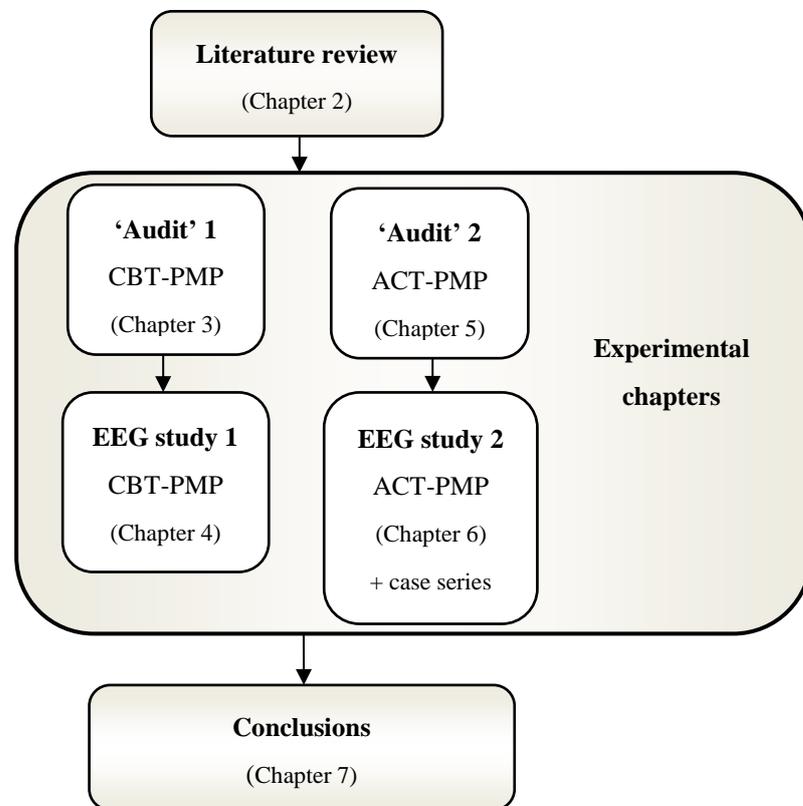


Figure 1.1 Flow chart illustrating the structure of the thesis.

1.1 AIMS AND OBJECTIVES

The aims of this study are:

- (1) To assess the efficacy of two pain management programmes, which are either based on principles of CBT or ACT, in terms of patient self-report in the form of questionnaires.
- (2) To identify measurable changes in brain activity related to the processing of painful stimuli brought about by treatment using a pain management programme (based on CBT or ACT).

The objectives of this study are:

- (1) To investigate changes in psychophysical health and pain related thinking (measured by self-report questionnaires) in the population of patients which have attended either the CBT-based Dudley Group of Hospitals NHS trust PMP or the ACT-based Royal Wolverhampton NHS trust PMP.
- (2) To perform an assessment of cortical electrical activity following painful stimulation (measured using EEG) in samples of chronic pain patients and control participants over a time period during which a subset of patients will partake in one of the above PMPs.

CHAPTER 2

LITERATURE REVIEW

2.1 HISTORY OF PAIN THEORIES

“Nature has placed in the front part of man, as he moves, all those parts which when struck cause him to feel pain; and this is felt in the joints of the legs, the forehead and the nose, and has been so devised for the preservation of man, because if such pain were not felt in these limbs they would be destroyed by the many blows they receive.”

Leonardo Da Vinci (n.d.), Thoughts on Art and Life, 82.

The search for a working model, or theory, of how pain works has probably been going on as long as the concept of pain has been in existence. According to Gatchel (1999) descriptions of pain treatment were recorded as early as 4000 B.C. in ancient Egypt, and acupuncture therapy for pain reduction was first used in ancient China nearly 2000 years ago. Throughout history, several theories of pain have dominated current thinking. With advances in our understanding of biology, psychology, and with the advent of new medical technologies, older theories have been replaced or updated.

2.1.1 Specificity Theory

Descartes' (1664) concept of the pain system (Figure 2.1) was of a 'straight-through' channel running from the skin to the brain, which transmits the sensation of pain from one place to another.



Figure 2.1 Descartes' pain system (from Descartes 1664, in Descartes & Hall 2003).

The central premise of specificity theory held the existence of a specific pain system which carried messages from pain receptors in the skin to a pain area in the brain. Through experiments in anatomy and physiology, it was known that nerve pathways existed and that these were responsible for conveying sensory messages to the brain. It was clear that nerves were capable of carrying messages from specific sense organs which described a variety of sensations – sight, sound, touch, taste, and smell – however it was not clear how these qualities were translated into experiences felt by the mind. Sensory properties of nerves were thought to be determined by the brain area in which the nerve terminated. Areas of the brain responsible for vision and hearing had already been located, and it was reasoned that specific brain areas for touch, taste,

smell and pain also existed. The evidence for a specific pain centre in the brain was lacking, however Head and colleagues (1920) suggested it was located in the thalamus, as lesions or removal of the thalamus tended to worsen pain.

Specificity theory could not explain the 'phantom limb' pain felt by amputees, and also the failure of complete transections of the spinal cord to abolish pain. It was also known that pain could be elicited by non-noxious stimulation in some patients, and that patients would complain of pain in the absence of any stimulus, which was not possible under specificity theory.

Specificity theory was also unable to account for the effect of pain on the mind. In order to bring together the physiological and psychological aspects of pain, Hardy, Wolff and Goodell (1952) proposed an extension to specificity theory, which stated that pain was made up of two components: the perception of pain and the reaction to pain. In their theory, there remained a one-to-one relationship between the intensity of the stimulus and the pain message arriving at the brain; however it was possible for an individual to react to the pain differently depending on psychological factors. This theory of pain as a sensory and affective experience was able to account for individual differences in reactions to painful stimuli which could not be explained by specificity theory; however the body and mind were treated as separate entities and there was no notion that the mind could exert influence over the sensory system.

2.1.2 Sensory Interaction Theory

Noordenbos (1959) took ideas from Goldscheider's (1894) pattern theory and combined them with recent evidence that showed the existence of two separate fibre systems (fast and slow) responsible for transmitting sensory information to the spinal cord. Pattern theory took into account the effect of stimulus intensity on the pattern of nerve firing, and suggested that pain sensation is felt when the total output of nerve cells exceeds a

certain threshold level. Sensory interaction theory held that the rapidly conducting sensory fibre system had inhibitory control over the more slowly conducting system that carries the signal for pain. When the activity in the slow fibre system overcame the inhibition of the fast 'control' system, a summation of pain signals at a spinal ganglion resulted in the transmission of a pain signal to the brain. This theory displayed a marked departure from the idea of a straight through pain system from the periphery to the brain.

2.1.3 Gate Control Theory (GCT)

During the early 1960s a great deal of research was carried out to examine the properties of the sensory nerve fibres which had been identified by Noordenbos and others described above. In 1960 Patrick Wall published work in which he described recordings from single cells in the spinal cord which responded to input from both fast and slow fibres in a characteristic manner. The 'gate control system' represents the area of the spinal cord containing the afferent synapses of the peripheral sensory nerves, the substantia gelatinosa, and the transmission cells (T-cells) which project to the 'action system' (Figure 2.2). The transmission of afferent impulses to the T-cells is controlled by a gating mechanism which acts to facilitate or inhibit the incoming signals. This gating mechanism is influenced by the relative activity in the large and small-diameter fibres; more small fibre activity tends to facilitate transmission (open the gate); more large fibre activity tends to inhibit transmission (close the gate). Large, fast-transmitting fibres (the central control trigger) transmit signals direct to the brain, activating cognitive processes which in turn return signals which can influence the gating mechanism. When output of the T-cells reaches a threshold level, the action system is activated, resulting in the response and perception of pain (Melzack & Wall 1996; Bonica & Loeser 2001).

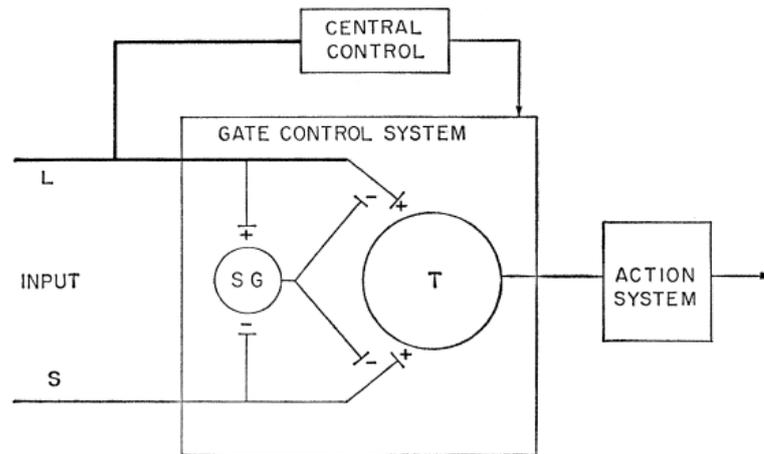


Figure 2.2 Diagram of the gate control theory of pain. The large (L) and small (S) fibres project to the substantia gelatinosa (SG) and first central transmission (T) cells. The inhibitory effect exerted by the SG on the afferent fibre terminals is increased by activity in the L fibres and decreased by activity in the S fibres. The central control trigger is represented by a line running from the large fibre system to the central control mechanisms; these mechanisms, in turn, project back to the gate control system. The T-cells project to the entry cells of the action system. + = excitation, - = inhibition (from Melzack & Wall 1965, p.975).

The GCT was successful in refuting many of the claims made by specificity theory, particularly that a specific system was involved in pain transmission and that there was a one-to-one relationship between stimulus intensity and pain perception. However, large parts of the theory were still theoretical and had not yet been empirically proven, thus opening up a number of avenues for research to proceed along in the following years – mainly in the areas of the fine detail of the physiology of the sensory system and in the role of the brain and cognitive processes in the perception of pain. The next section will describe our current understanding of nervous system physiology as it is related to pain.

2.2 PHYSIOLOGY OF PAIN

“It is customary to describe the somatosensory system by proceeding from the peripheral receptors...to areas in the brain. However, it is essential to remember that stimulation of receptors does not mark the beginning of the pain process...Stimulation produces neural signals that enter an active nervous system...already the substrate of past experience, culture, anticipation, anxiety and so forth.”

R. Melzack & P.D. Wall (1996). *The Challenge of Pain*, p.81.

The role of the nociceptive system is to protect the organism from harmful stimulation. Nociception is accomplished using a relatively simple process: a stimulus of sufficient intensity to cause tissue damage activates a specialised nerve ending, which sets off a signal that is transmitted along a chain of nerves until it reaches a group of muscle cells which activate to move the organism away from the point of stimulation. This nociceptive signal may also pass into more complex systems and networks of nerves where it is assessed, encoded and interpreted as something more than mere nociception. It may affect the behaviour, cognitions, and emotions of the organism, resulting in the organism feeling this nociception as something more than actual or potential tissue damage. The feeling of pain is the result of a complex exchange between signalling systems, modulation from higher centres and the unique perception of the individual (Steeds 2009) (Figure 2.3).

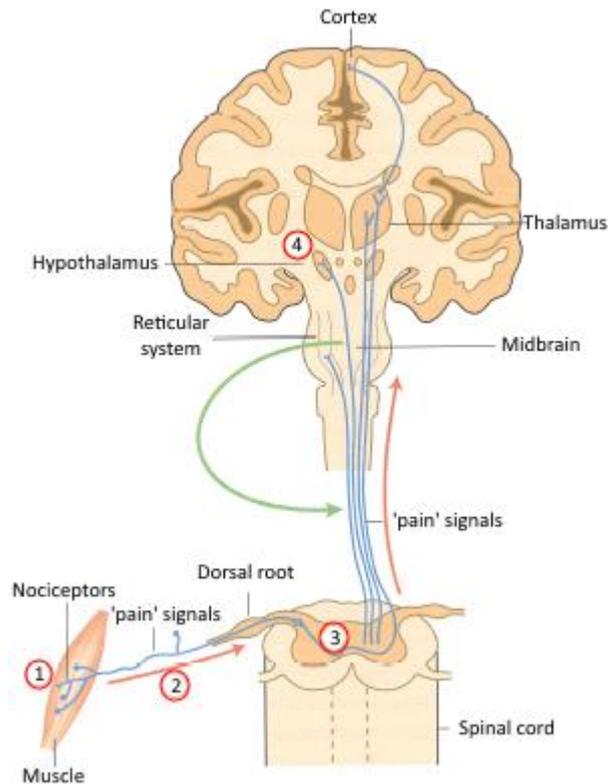


Figure 2.3 The path of pain – 1) Transduction: the conversion of a noxious stimulus into electrical energy by peripheral nociceptors – 2) Transmission: propagation of the signal through the peripheral nervous system via first-order neurons – 3) Modulation: adjustment of pain intensity at the point where first-order neurons synapse with second-order neurons in the dorsal horn of the spinal cord – 4) Perception: the cerebral cortical response to nociceptive signals projected to the brain by third-order neurons. Stimulation of the descending pathway from the brain (green arrow) sends modulatory signals back to the spinal cord that may facilitate or inhibit further transmission (adapted from Cepeda et al. 2007, p.11).

2.2.1 The Nociceptors and Peripheral Nerves

The skin, musculo-skeletal system, and viscera are penetrated by widely branching, bushy networks of nerve fibres which are sensitive to temperature, pressure, and chemical stimulation. Three types of fibres are known to exist: A-beta ($A\beta$), A-delta ($A\delta$), and C-fibres (Table 2.1). The $A\beta$ -fibres respond only to light mechanical pressure and are not involved in nociception; the $A\delta$ - and C-fibres respond to a wide

range of temperature, pressure, and chemical influences, and are thus capable of detecting potentially damaging stimulation.

Table 2.1 Properties of different types of afferent fibres.

	Myelinated		Unmyelinated
Fibre type	A-beta ($A\beta$)	A-delta ($A\delta$)	C
Diameter	5-15 μm	1-5 μm	0.25-1.5 μm
Conduction velocity	30-100 m/sec	6-30 m/sec	1.0-2.5 m/sec
Receptor type	specialised & free	free	free
Respond to *	light pressure	1 light pressure 2 heavy pressure 3 heat ($45^\circ\text{C} +$) 4 chemicals 5 cooling	1 light pressure 2 heavy pressure 3 heat ($45^\circ\text{C} +$) 4 chemicals 5 warmth

* Each fibre in the $A\delta$ and C may respond to only one or to more than one of the types of stimuli; for example, there are C 'polymodal fibres' that respond to heavy pressure, heat, and chemicals (adapted from Melzack & Wall 1996, p.86).

Transduction of a noxious stimulus into an electrical signal occurs at the peripheral nociceptor through the activation of receptors positioned around the nerve ending. The process by which stimuli are converted into a nerve impulse is thought to be mediated by cell membrane proteins of the transient receptor potential (TRP) family of ion channels (Ramsey et al. 2006). The details of TRP channels are beyond the scope of this thesis, suffice it to say that receptors exist that are specialised to respond to mechanical, heat, cold and chemical stimuli. $A\delta$ - and C-fibres do not respond equally to all types of stimulation; instead there are fibres that respond preferentially to one or other stimulus, or do not respond to some stimuli at all. This may allow for the different aspects of nociceptive sensation (e.g. burning, itch, pricking, aching) due to the enhanced discrimination made possible by a mixture of response properties. The $A\delta$ -nociceptors are separated into two categories: Type-I $A\delta$ nociceptors, or high-threshold mechanoreceptors (HTM), typically respond to mechanical and chemical

stimuli, but are also activated by high (>50°C) temperatures; Type-II A δ nociceptors respond preferentially to noxious thermal stimuli, and most show no response to mechanical stimuli. The C-fibre nociceptors contain populations of neurons responding to either mechanical, heat or cold stimuli; there are C-fibre nociceptors that are affected by mechanical and heat stimuli; and also so called 'silent' nociceptors, which develop sensitivity to heat and chemical stimuli in the presence of inflammatory chemicals released following tissue damage (Porreca 2010).

In the event of intense stimulation, the myelinated A δ -fibres transmit the initial sensations: the intense, sharp pain felt immediately following pinprick, pinch or noxious heat. The unmyelinated C-fibres transmit the delayed, unpleasant sensations which are more dull, diffuse, throbbing and/or burning than the initial pain. This 'nociceptive' pain warns of potential tissue damage. In the event of tissue damage, a range of inflammatory chemicals will be released, including bradykinin and prostaglandins which sensitise the terminals of A δ -HTM and C-fibres, meaning that pain will persist in and around the injured tissues for minutes, hours, or days.

2.2.2 The Spinal Cord

The final destination of the first order sensory neurons is the dorsal horn of the spinal cord, which they enter after passing through the dorsal root ganglion (DRG). The DRG is a nodule which contains the cell bodies of the primary afferent fibres and lies just outside the spinal cord.

2.2.3 Central Modulation and Descending Pathways

Transmission of nociceptive signals from the dorsal horn is modulated by descending pathways from brainstem structures, the periaqueductal grey and the rostral ventromedial medulla (Fields et al. 2006). These structures are part of a descending modulatory circuit with inputs from multiple cortical sites including the hypothalamus,

amygdala, and anterior cingulate cortex, which acts to facilitate or inhibit nociceptive traffic in the spinal cord (Ossipov et al. 2010).

2.2.4 Cortical Processing

Axons of both types of second order neurons ascend to regions of the brainstem and thalamus in the spinothalamic tract (STT). The fibres of the lateral STT terminate in several locations, including the brainstem reticular formation and medial nuclei of the thalamus, which project third order neurones to limbic structures and the frontal cortex, parts of the brain associated with emotion, memory and decision making. Fibres in the anterior STT terminate in the lateral nuclei of the thalamus where they synapse with neurones which pass signals to the somatosensory cortex. The somatosensory cortex is the initial site of sensory processing, encoding information regarding location and intensity of stimulation. Following these initial points of entry into the cortex, further processing of information received from the periphery across multiple sites (collectively known as the pain matrix) gives rise to the conscious feeling of pain.

2.2.5 From Nociception to Pain

A large distributed network of brain areas are activated during the processing of nociceptive information. These include the thalamus, basal ganglia, hippocampus, amygdala, cerebellum, primary and secondary somatosensory cortices (S1 and S2), primary motor cortex (M1), insular cortex, amygdala, anterior cingulate cortex (ACC), and prefrontal cortex (PFC). There is no single pain centre where the feeling of pain is generated; instead there exists an interconnected matrix of areas which work in concert to give rise to the complex experience of pain. The sensory-discriminatory (e.g. location, intensity, duration) aspects of pain are thought to be processed by S1, S2, thalamus and posterior insula; the affective-cognitive-evaluative (e.g. unpleasantness, emotion, motivation) aspects are encoded in the ACC, PFC, and anterior insula. The

precise level of involvement of each brain area in the experience of pain varies considerably depending not only on the location and severity of injury, but also on less tangible factors such as mood, cognition, environment, and past experience, which means that the pain matrix is not a strictly defined entity (Tracey 2010).

2.3 CURRENT UNDERSTANDING OF PAIN

2.3.1 The Biopsychosocial Model

One of the strengths of the GCT was that sensory mechanisms were not solely responsible for the experience of pain. Cognitive, emotional, and situational factors such as memory, arousal, and context also played a part. However, medicine at the time was ill equipped to deal with such a symptom which spanned the body and the mind. The biomedical model that had prevailed since the renaissance assumed that symptoms could be traced to a purely biological origin, and that illness was treated by correcting the specific body structure or organ system at fault. In the cases of mental illness and chronic pain, where no fault could be found, the biomedical model was of no use. A paper by George L. Engel published in 1977 called for a new ‘biopsychosocial’ medical model. Under this model, diagnosis and treatment of illness would be made not solely on the basis of laboratory findings, but also by investigating the psychological, behavioural, and social circumstances which led to the patient arriving in the healthcare system (Figure 2.4a).

Loeser (1982) applied the biopsychosocial model to the concept of pain, describing four interrelated dimensions: nociception, pain, suffering (the emotional responses triggered by pain, such as anxiety or depression), and pain behaviour (the visible responses to pain, such as avoiding activities and seeking treatment) (Figure 2.4b).

Each of the four dimensions becomes a target for treatment, and pain is no longer the most important element of the illness.

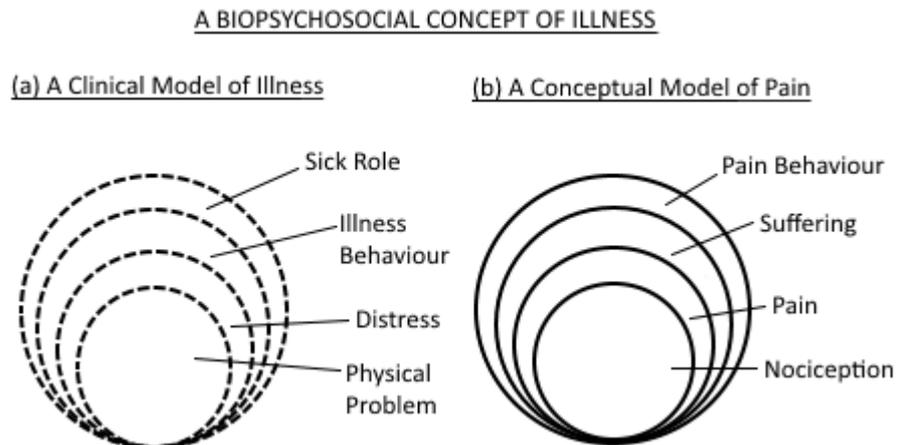


Figure 2.4 Diagram of the biopsychosocial concept of illness (a) general model, (b) applied to pain (adapted from Waddell 1987, p.637).

2.3.2 Neuromatrix Theory

“We don’t need a body to feel a body.”

R. Melzack (1989), p.4.

The greatest problem with GCT was that it could not explain the phantom limb pains of patients who had a completely severed spinal cord, and therefore no connection between the gate control system and the brain. The new theory proposed by Melzack (1989) described a network of nerve cells distributed around the entire brain that work together to hold a representation of the whole body, termed ‘the body-self neuromatrix’. Crucially, the inputs to this neuromatrix are not only limited to sensory

afferents from the periphery, but also include inputs from within the brain itself, representing cognitive, emotional, and motivational processes. These inputs are processed by the neuromatrix in a series of converging and diverging neuronal loops, generating a unified output termed the ‘neurosignature’. The neurosignature flows continuously into the brain areas which generate a constantly changing stream of awareness, in order for the body to experience sensation and emotion; and also to areas that initiate muscle activity, generating behavioural responses. Neuromatrix theory allowed for the explanation of phantom limb pain, even with a severed spinal cord: the neuromatrix contains a representation of the missing limb, and inputs from within the brain itself can activate the neuromatrix in such a way that produces a neurosignature for pain in the phantom limb.

Figure 2.5 presents a diagram describing the body-self neuromatrix, including the outputs of the neuromatrix: pain perception, action programs, and stress-regulation programs.

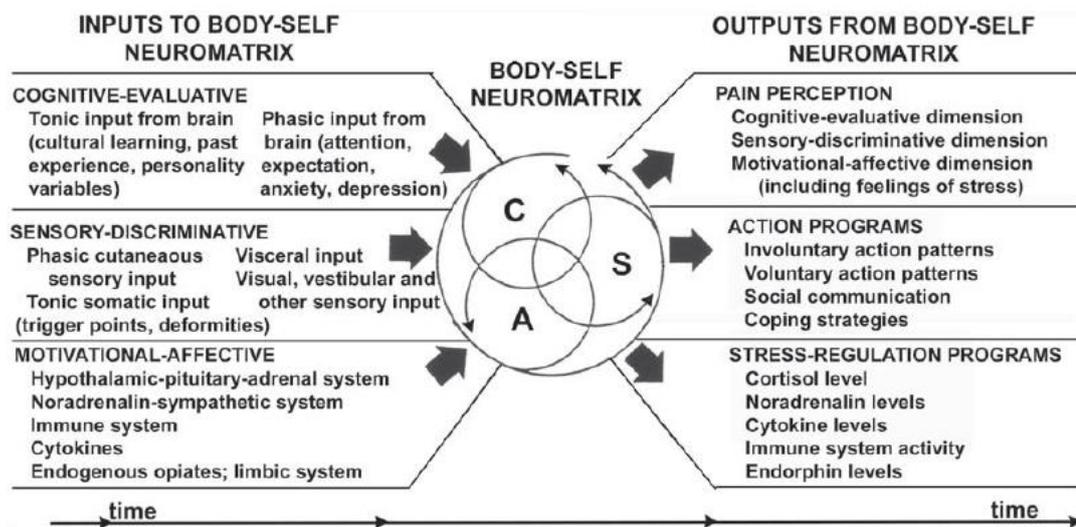


Figure 2.5 Factors that contribute to the patterns of activity generated by the body-self neuromatrix, which comprises sensory (S), affective (A), and cognitive (C) neuromodules. The output patterns from the neuromatrix produce the multiple dimensions of pain experience as well as concurrent homeostatic and behavioural responses (adapted from Melzack 2001, p.1382).

A key concept in the theory was that the pattern generating mechanism (the body-self neuromatrix) was not a fixed system. The initial spatial distribution and synaptic architecture of the neuromatrix was determined genetically, but there is plasticity – the neuronal connections are constantly being updated and altered by the chemical mediators of sensory, cognitive, and emotional experiences. This meant that the theory could account for almost any pain phenomenon. Previous experience, be it injury, pathology, hormonal stress, or psychology, could shape the neuromatrix in such a way that the pain neurosignature could be generated by a combination of angst, context, and emotion, in the absence of any physical stimulation. Furthermore, the theory suggested that chronic pain could be modulated by treatments targeting cognitive, emotional, and behavioural factors.

2.4 CHRONIC PAIN

Pain is unpleasant, but it is also a useful mechanism that promotes the healing process, forcing the sufferer to rest the affected area and seek out medical assistance. When pain continues for extended periods of time – either beyond the usual amount of time expected for an injury to heal, or in the absence of injury – it is referred to as chronic pain (Turk & Melzack 2011). The International Association for the Study of Pain (IASP) define chronic pain as pain which lasts for longer than three months (IASP 1986). Chronic pain syndromes, such as low back pain, fibromyalgia, or sciatica, commonly begin following injury or disease, but may be perpetuated by factors other than the cause of the pain (Loeser & Melzack 1999). The pain persists long after it can serve any useful function and is no longer just a symptom of injury or disease but becomes a medical problem in its own right (Melzack & Wall 1996).

2.4.1 Epidemiology of Chronic Pain

It has been estimated that disorders characterised by chronic pain account for 21.3% of the worldwide total years lived with disability – more than diabetes and cancer combined (Vos et al. 2012). Low back pain and neck pain are the first and fourth (respectively) leading causes of disability worldwide (Vos et al. 2012). In a meta-analysis of 13 studies examining chronic pain conducted in Europe, Israel, Canada, and Australia, the prevalence of chronic pain ranged from 10.1–55.2% (Harstall & Ospina 2003). Another study of 46,394 people (aged ≥ 18 years) across 15 European countries and Israel (including 3,800 from the UK), screened for chronic pain lasting ≥ 6 months, with an intensity of ≥ 5 on the 10-point Numerical Rating Scale (NRS, 1 = no pain, 10 = worst pain imaginable). Using these specific criteria, prevalence ranged from 12–30%, with the UK at 13% (Breivik et al. 2006). Further analysis revealed that chronic pain sufferers in the UK had a mean age of 49.2 years, mean pain duration of 5.9 years, and 49% were female; 37% reported they received inadequate pain control, highlighting how difficult it is to achieve successful treatment of chronic pain. More recently, the Health Survey for England (HSE) 2011 interviewed 8,610 adults, finding 31% of men and 37% of women had suffered pain for more than 3 months (HSCIC 2012). Finally, analysis of a large scale dataset from UK Biobank, which included 503,325 people aged 40–69 years, put the prevalence of pain lasting ≥ 3 months at 42.9% (Macfarlane et al. 2015).

2.4.2 Living with Chronic Pain

Patients with chronic pain frequently present with a number of other psychological and social complaints which may have preceded or been brought on by the stress of living in near constant pain. Many patients may have to stop working, cancel enjoyable physical and social activities, and withdraw from contact with friends and family due

to their disability (Kemler & Furnée 2002). The HSE 2011, which included over 4,000 pain patients, documented that for 22% of men and 24% of women, pain had limited daily activities for over 14 days in the past three months (HSCIC 2012). Chronic pain is likely to alter traditional family roles, to cause financial difficulties, result in deterioration of marital and sexual relationships, and create distress for other family members, as well as for the patient (Turk et al. 1987). Elevated rates of depressive, anxiety, substance use, somatoform, and personality disorders have been noted in chronic pain patients (Dersh et al. 2002).

2.4.3 The Development and Maintenance of Chronic Pain

Biomedical explanations for chronic pain can be categorised into four broad syndromes: nociceptive pain; inflammatory pain; dysfunctional pain; and neuropathic pain (Costigan et al. 2009). The reasons for the development and maintenance of three of the pain syndromes are easily identified: prolonged noxious stimulation (nociceptive pain); chronic inflammation (inflammatory pain); nerve lesions or disease (neuropathic pain). However in the case of dysfunctional pain there is no obvious reason for the occurrence of persistent pain.

In contrast to biomedical explanations, psychosocial theories of pain do not place emphasis on the origin of pain, but instead focus on how pain in general can affect and be affected by an individual's cognitions, behaviours, and environment. Not only is the relationship between tissue damage and pain highly variable, but also the relationship between the experience of pain and the level of functional disability is far from absolute. Patients may experience intense pain without suffering any disability (Vlaeyen et al. 2007). Psychological and social theories attempt to explain this variable relationship by recognising that the person and their environment play active roles in the pain experience.

2.4.3.1 Behavioural theory

Wilbert Fordyce applied the principles of behavioural psychology to explain the development, maintenance, and treatment of pain behaviours (Fordyce, Fowler, & DeLateur 1968; Fordyce, Fowler, Lehmann, et al. 1968). Behaviourism places emphasis on observable actions, which are an objective, visible measure – “for the behaviourist, the crying (plus the kicking, facial expression, and other overt activities) is itself the pain” (Rachlin 1985, p.48). Fordyce recognised that there was a variable relationship between pain reports and pain behaviours, and believed that behaviour held the key to the maintenance of or recovery from pain.

2.4.3.2 Cognitive theory

In contrast to behaviourism, cognitive theory recognises the contribution of thought processes in the development of an illness and the corresponding behaviours. The pioneer of cognitive theory, A.T. Beck, believed that an individual’s emotion and behaviour were largely determined by the way in which they structure the world and the reciprocal influences of thoughts, feelings and behaviours (Figure 2.6) (Beck 1967; Beck et al. 1979).

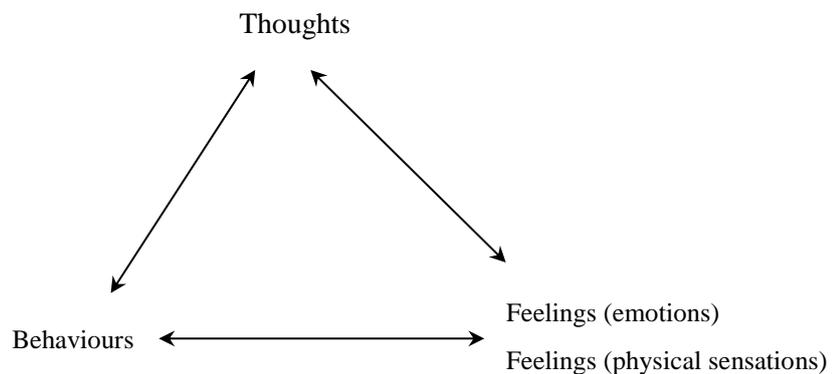


Figure 2.6 The cognitive-behavioural model (from Simmons & Griffiths 2009, p.21).

A number of cognitive-psychological processes are involved with pain and may contribute to the development of a persistent pain problem (Linton & Shaw 2011). Cognitions such as beliefs, attributions, expectations, self-efficacy, attention, catastrophising, coping, and locus of control can all influence the way in which an individual interprets and reacts to feelings of pain:

Beliefs and attributions about pain can affect the way in which patients engage with their problem, and may lead to maladaptive coping, exacerbation of pain, increased suffering, and greater disability (Turk & Monarch 2002). Patients who believe that their pain is due to ongoing tissue damage report more severe pain than patients with an identical condition who believe that the pain is a stable symptom of a condition that may improve (Spiegel & Bloom 1983).

Expectations include anticipation of pain and the fear of pain. When patients believe that activities will result in pain, they are likely to engage in avoidance behaviours to prevent a potential painful experience (Vlaeyen & Linton 2000).

Self-efficacy is concerned with a person's judgement of their capabilities to perform activities, and their perceived control over events (Bandura et al. 1987). In samples of chronic pain patients, perceived self-efficacy is significantly correlated with actual physical performance of exercise tasks (Council et al. 1988), and has been shown to be predictive of pain behaviours and avoidance behaviours, even when controlling for actual pain severity, chronicity, and disability (Asghari & Nicholas 2001).

Attention to acute pain is beneficial, interrupting ongoing tasks with a signal to bodily threat that urges escape (Vlaeyen et al. 2007). In the case of chronic pain, where the signal may be considered unhelpful, pain still demands attention. The individual in chronic pain can become fixated on the pain, closely monitoring every fluctuation and

constantly searching for causes and treatments – a state known as hypervigilance (Crombez et al. 2005). When repeated attempts to relieve or cure the pain end in failure, patients experience physical, emotional, and cognitive distress, further worsening their overall health (Aldrich et al. 2000).

Catastrophic thinking about pain, or catastrophising, is characterised by negative self-statements and exaggerated pessimistic thoughts and ideation (Rosenstiel & Keefe 1983). Patients and healthy subjects who show a tendency to catastrophic thinking are likely to report more intense pain and emotional distress during painful stimulation than non-catastrophisers (Keefe et al. 1989; Sullivan et al. 1995).

Locus of control concerns the degree to which a person believes that outcomes are controlled by their own behaviours (internal locus) or by external factors such as chance or other people (external locus) (Rotter 1966). One study measuring locus of control over pain has shown that patients who score highly on the internality dimension report their pain as less intense and frequent than those with lower scores (Toomey et al. 1991). Locus of control has been studied in relation to coping strategies used in chronic pain patients (Crisson & Keefe 1988). Patients who perceived outcomes as controlled by ‘chance’ or ‘luck’ were likely to use maladaptive coping strategies such as catastrophising, diverting attention, praying or hoping, and report that they had little control over their pain. In both of the above studies, ‘internals’ showed reduced levels of physical and psychological symptoms and responded better to treatment than ‘externals’ (Main & Waddell 1991).

2.4.3.3 The fear-avoidance model

Bringing together both behavioural and cognitive factors to explain the development of musculoskeletal pain problems, the fear-avoidance model has been highly influential (Lethem et al. 1983; Vlaeyen, Kole-Snijders, Boeren et al. 1995; Vlaeyen,

Kole-Snijders, Rotteveel et al. 1995; Vlaeyen & Linton 2000). Under the model (Figure 2.7), patients suffering from acute pain may either engage in confrontation or avoidance behaviours in order to deal with the pain. The avoidance of feared activities leads to an overall reduction in activity, which can be the beginning a downward spiral of disability and pain.



Figure 2.7 The fear-avoidance model. If pain (possibly caused by an injury) is interpreted as threatening (pain catastrophising), pain related fear evolves. This leads to avoidance behaviours, and hypervigilance to bodily sensations followed by disability, disuse, and depression (adapted from Vlaeyen & Linton 2000, p.329).

The strength of the fear-avoidance model is that it brings together a number of psychological factors which are related to chronic pain and combines them into a unified cognitive-behavioural model with clear targets for psychosocial treatment.

2.4.3.4 The psychological flexibility model

This model has evolved as a response to the limitations of behavioural theory (which does not deal with cognition) and the complex and mechanistic nature of cognitive theory (in which numerous discrete modules of cognition interact). It is a general

model of psychopathology and not specific for pain, however the treatment which emerges from the theory (Acceptance and Commitment Therapy, ACT) has proven useful as a therapeutic approach to chronic pain (discussed later, Section 2.5.8). Under the psychological flexibility model, behaviour is viewed as a function of the individual interacting with and in the context of an experience. The model has six interrelated processes which contribute to psychopathology: experiential avoidance, cognitive fusion, preoccupation with the past or future, inability to take a perspective separate from thoughts and feelings, failures in clarity or pursuit of values, and rigid persistence or impulsive avoidance (Hayes 2004a; McCracken & Morley 2014).

Experiential avoidance can be a particular source of distress to the chronic pain patient, as no matter how much the person avoids activities or thoughts that are related to pain, the pain itself cannot be avoided. Cognitive fusion describes the manner in which a person becomes automatically guided by their elaborate relational networks without awareness of the process involved; making the individual less in contact with here-and-now experiences and more dominated by verbal rules and evaluations (Hayes 1989). In the pain patient, every environmental stimulus can become linked to pain through a relational network, meaning that everyday life becomes more stressful if the person unquestioningly believes their automatic thoughts and feelings.

2.4.4 Summary

The term chronic pain describes a biopsychosocial syndrome, characterised by persistent physical pain, disability, emotional disturbance, and social withdrawal symptoms existing together and influencing one another, in what Bandura (1978) has termed ‘reciprocal determinism’. Prolonged bodily stress and psychological distress lead to a deprived social environment and a dependence on medical and social support.

Constant pain leads to a fear of movement and a catastrophic belief that more pain and injury will occur, and it is likely that the patient will become depressed.

Treatment of chronic pain requires a biopsychosocial approach. The next section will discuss available treatments including pain relieving drugs, as well as cognitive and behavioural strategies to manage pain, increase functional ability, and increase wellbeing.

2.5 TREATMENTS FOR CHRONIC PAIN

2.5.1 Analgesic Medication for Pain

Pain reducing medications range from common ‘painkillers’ which can be found in any pharmacy or supermarket in the UK, to powerful opioids and antidepressants which are prescribed only for severe or chronic pain.

In treating a case of pain the physician usually follows the steps on the World Health Organisation (WHO) analgesic ladder (Ventafridda et al. 1985; Figure 2.8). Initially developed for the treatment of cancer pain, but applicable to most pain conditions, the ladder suggests that analgesic medications should be given orally with increasing dose and potency until pain relief has been achieved. It is a simple and inexpensive approach that produces pain relief in 80-90% of patients (WHO 2015). The first step consists of non-opioid analgesics, such as paracetamol or Non-Steroidal Anti-Inflammatory drugs (NSAIDs), which act to reduce inflammation and provide pain relief by reducing the sensitisation and stimulation of nociceptors by chemicals released during inflammation. The second step adds weak opioids. Opioid drugs mimic the effects of naturally occurring pain reducing chemicals (endorphins) which activate opioid receptors in the central nervous system that attenuate transmission of nociceptive signals. The third step calls for strong opioids, which are more potent but also have

more severe side effects than weak opioids. At each step, adjuvant medications may be given to relieve fear and anxiety caused by the pain (Table 2.2).

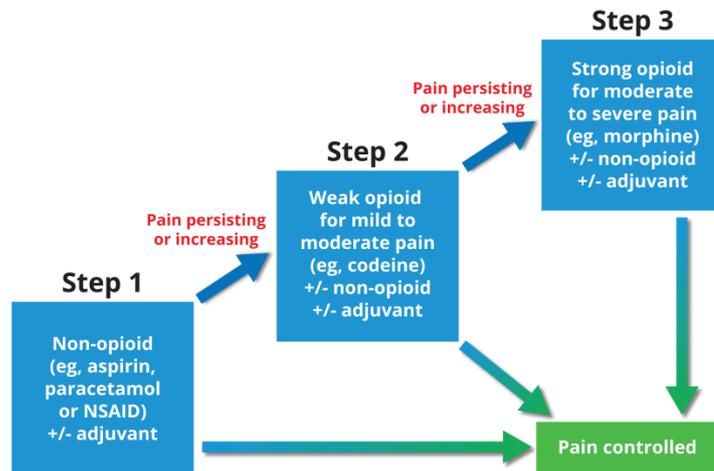


Figure 2.8 The WHO analgesic ladder (adapted from Ventafriidda et al. 1985, p.94).

Table 2.2 Common analgesic medications, mechanisms, and side-effects.

Category	Drug	Use(s)	Mechanism of action	Side-effects
Non-opioids	Paracetamol	Mild to moderate pain	COX-3 inhibition?	None at normal doses
	NSAIDs			
	Aspirin			
	Ibuprofen		COX-1 and 2 inhibition	Risk of GI bleed, impair renal function
	Diclofenac			
	Naproxen			
	Celecoxib	Arthritis pain	COX-2 inhibition	Risk of CV event
	Etoricoxib			
Weak opioids + Paracetamol	Codeine Dihydrocodeine Co-codamol Co-dydramol	Mild to moderate pain	Opioid receptor agonist	Constipation
Other opioid	Tramadol	Severe pain	Weak opioid agonist, inhibits noradrenaline uptake and serotonin release	Dizziness, no respiratory depression
Strong opioids	Morphine Oxycodone Fentanyl Buprenorphine	Severe pain	Opioid receptor agonists	Sedation, respiratory depression, constipation, nausea, itching, tolerance and dependence, euphoria
Anti-depressants	TCA's Amitriptyline Nortriptyline SNRIs Venlafaxine Duloxetine	Neuropathic pain	Unknown, may include opioid receptor activation, sodium channel blockade	Sedation, confusion, weight gain, dry mouth, constipation Nausea, agitation, diarrhoea
Anti-epileptics	Gabapentin Pregabalin Carbamazepine	Neuropathic pain Trigeminal neuralgia	Calcium channel blockade, glutamate suppression Sodium channel blockade	Sedation, ataxia

NSAID=Non-steroidal anti-inflammatory drug; COX=Cyclo-oxygenase; GI=Gastrointestinal; CV=Cardiovascular; TCA=Tricyclic antidepressant; SNRI=Serotonin and noradrenaline reuptake inhibitor (Rang et al. 2012; Gilron 2010; Mico et al. 2006; Perucca 2005; Dworkin et al. 2007).

2.5.2 Invasive Procedures

The WHO pain treatment guidelines take in most of the available analgesics, however it is mainly concerned with oral preparations, and invasive procedures are not included. These include nerve block injections, denervation surgery, implantable drug delivery systems, and nerve stimulators. Invasive procedures are often risky and expensive, so they are usually reserved for cases of severe pain that do not respond to oral and systemic analgesics.

2.5.3 Pain Relief by Counter-irritation

A well-known phenomenon in traditional medicine, the ‘pain inhibiting pain effect’ (Reinert et al. 2000) or ‘counter-irritation’ (Wand-Tetley 1956) is the relief of pain by application of intense stimulation to the painful area or another area of the body. The mechanism of action by which pain relief is achieved depends upon the technique used. Counter-irritation techniques for pain relief include transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), acupuncture, topical capsaicin, and application of heat or cold.

Experimental studies, in which brief noxious stimuli are applied to an area, whilst another area receives ongoing painful stimulation (known as conditioned pain modulation, CPM); shed light on a common mechanism that may subserve counter-irritation. An endogenous, anti-nociceptive neural process termed ‘diffuse noxious inhibitory controls’ (DNIC) is characterised by a reduction in the activity of pain signalling neurons in the spinal dorsal horn and trigeminal nuclei in response to noxious stimuli applied to a remote area of the body (LeBars et al. 1979; Moont et al. 2010). Although the phenomenon of DNIC has only been observed under experimental conditions, it may explain the beneficial effects of counter-irritation which have been observed in patients.

2.5.4 Biopsychosocial Treatment

Neuromatrix theory suggests that in the absence of overt physical damage, it is the psychological factors of emotion and cognition that can contribute most to the experience of pain. In turn, these psychological factors are influenced by the social and cultural environment in which the patient is living. Biopsychosocial treatment draws on the knowledge of several healthcare disciplines including physicians, psychologists, specialist nurses, physiotherapists, and occupational therapists,

combined to deliver ‘multidisciplinary pain management’. In the UK, a patient will be referred by their general practitioner to the local pain clinic for multidisciplinary treatment. In 2010, there were 214 pain clinics in the UK (Price et al. 2012). Upon entering the pain clinic system the patient will usually meet individually with each member of the team in order to discuss their situation and how treatment should proceed. Patients may continue to meet regularly with team members to receive ongoing treatment and monitor progress, however it is likely that the patient will eventually be recommended to attend a series of group treatment sessions, known as the pain management programme (PMP) (of which there were 97 in the UK in 2013; S. Williams 2013). This section will look at the separate treatments available in the pain clinic before discussing the components of PMPs.

2.5.4.1 Physiotherapy

Physiotherapy represents a variety of treatment modalities ranging from passive manipulation, stretching, and movements to intensive exercise and activity simulation. In the case of treating chronic pain the goal of physiotherapy is to maximise and maintain the patients’ functional ability, without contributing to any increase in pain. Patients are taught that pain does not necessarily imply that tissue damage is taking place, and that avoiding activity can actually worsen pain in the long run through deconditioning.

2.5.4.2 Occupational therapy

Occupational therapy is concerned with enabling patients to maintain, recover, or develop the skills needed for daily living and for work. In the patient with chronic pain, interventions focus on increasing physical capacities, mastery of self and the environment through activities, and productive and satisfying performance of life tasks and roles (Engel 2013). Patients are taught early on that rest is not a good way to deal

with chronic pain, and that the performance of a baseline level of daily activity is the key to recovery. Activity levels are increased gradually over time, and the patient is able to perform more activity without the pain worsening. Activities are planned in advance, including regular breaks for rest – a technique known as pacing.

2.5.4.3 Pain specialist nursing

The nurse specialising in pain can advise patients on their medications, explaining the reasons why they have been prescribed, and suggesting the best time of day to take them to minimise the impact of side effects. Patients can be confused and worried when they are prescribed an antidepressant for their pain, which may lead to non-compliance; if patients understand why they are taking particular medications, they are more likely to take them (Claxton et al. 2001).

2.5.4.4 Clinical psychology

The clinical psychologist is concerned with the impact that the pain condition has on the mental health and wellbeing of the patient. Initial assessment involves a psychological screening to ascertain how the pain has affected mood, sleep, appetite, motivation, daily activities, relationships, work, and finances. Patients' may be unsure why they are seeing a psychologist for pain treatment; that it somehow implies that their pain is a psychological rather than a physical problem. The psychologist must take care to explain the role of non-physiological factors in the maintenance of pain symptoms and their responses to treatment (Turk & Monarch 2002). Of vital importance to recovery are the ways in which the patient reacts to, and copes with physical pain and the emotional suffering that accompanies it. There are numerous approaches to psychological treatment, including: motivational interviewing, psychodynamic psychotherapy, operant therapy, cognitive-behavioural therapy (CBT), biofeedback, hypnosis, graded exposure, mindfulness based stress reduction,

acceptance and commitment therapy (ACT), and solution-focused brief therapy. In a pain clinic setting, patients are often invited to attend a group pain management programme which combines elements of psychological treatment from various approaches with physiotherapy, occupational therapy, information on medication, pain physiology, sleep hygiene, local support groups, and relaxation techniques.

2.5.5 Multidisciplinary Pain Management Programmes

“A PMP aims to improve the physical, psychological, emotional and social dimensions of quality of life of people with persistent pain, using a multidisciplinary team working according to behavioural and cognitive principles. The problems of people with persistent pain are formulated in terms of the effects of persistent pain on the individual’s physical and psychological wellbeing, rather than as disease or damage in biomedical terms, or as deficits in the individual’s personality or mental health.”

British Pain Society (2007), p.6.

The basic concepts, goals and content are in general quite similar across different types of pain management programmes. Typically, patients are treated in groups of 5-15, over a course of 8-12 sessions taking place once or twice a week on an outpatient basis. PMPs are delivered in a group format because this normalises the experience of pain for the patients and maximises opportunities to draw on the experiences of group members; it is also cost effective (British Pain Society 2013, p.8). Sessions last 3-4 hours and consist of physical, psychological, medical, and occupational themes. The treatment team usually consists of a specialist nurse, physiotherapist, psychologist,

occupational therapist, and pain physician. Each session will generally proceed using the same structure of five components, the contents of which change from session to session: exercise, education, skills training, relaxation, and homework.

2.5.5.1 Exercise

Led by the physiotherapist, stretches and light exercises aim to increase flexibility and strength. Patients are encouraged to perform stretches regularly at home between sessions. Some examples are shown in Figure 2.9.

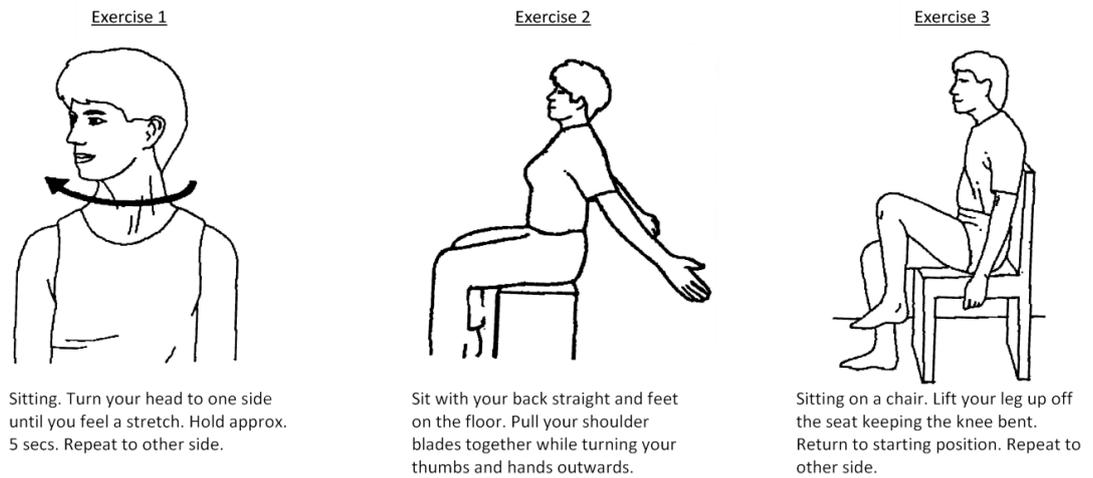


Figure 2.9 Stretches and light exercises (adapted from New Cross Hospital PMP Exercise Diary, unpublished).

2.5.5.2 Education

All members of the treatment team are involved in leading lecture type teaching sections covering topics that deal with a variety of problems faced by chronic pain patients (Table 2.3). These may differ slightly according to the needs of the group and the psychological basis of the PMP.

Table 2.3 Patient education topics.

Pain mechanisms	Depression
Gate control theory	Effects of exercise and inactivity
Biomechanics	Role of surgery
Medication use	Dealing with doctors
Disability benefit	Maintenance of gains
Expert patient visit	Cognitive-behavioural theory
Acute vs. Chronic pain	ACT theory
Healing and disuse	

Adapted from Loeser & Egan (1989) in Loeser & Turk (2001), p.2073.

2.5.5.3 Skills Training

Patients are taught skills to assist them in living with chronic pain (Table 2.4). These include topics such as activity-rest cycling (Gil et al. 1988), also known as pacing, which is designed to help patients avoid a pattern of over activity followed by a flare-up of extreme pain followed by a period of prolonged rest; and replace it with periods of planned moderate activity and limited rest. CBT-based programmes will go into detail on cognitive strategies for dealing with stress, depression, and anger responses to pain, guided by the relationship between thoughts, feelings, and behaviours. ACT programmes will address these problems using acceptance and cognitive diffusion strategies, including mindfulness practice.

Table 2.4 Topics for skills training.

Stress management	Assertiveness training
Relaxation training	Cognitive strategies
Coping skills	Communication skills
Anger management	Dealing with depression
Pain behaviours	Crisis management
Sleep hygiene	Costs/meanings of pain
Physiology of stress	Mindfulness meditation
Planning/pacing	

Adapted from Loeser & Egan (1989) in Loeser & Turk (2001), p.2073.

2.5.5.4 Relaxation

Each session will typically include a period of guided relaxation led by the psychologist or other member of the team. ACT programmes use guided mindfulness exercises for relaxation, acceptance, and cognitive diffusion, whereas CBT programmes use a variety of techniques including progressive muscle relaxation (Jacobson 1965), visualisation, and breathing exercises.

2.5.5.6 Homework

Patients are asked to complete homework assignments in order practice what they have learned in class whilst they are in their usual environment (Table 2.5). Patients' feedback to the treatment team and other group members on challenges and successes they have encountered. ACT programmes include a daily mindfulness exercise to work towards automatic use of this technique in daily life. CBT-based programmes also include homework tasks designed to test negative assumptions that patients may have about their ability to cope with pain – with the aim of helping patients prove to themselves that these assumptions are false and unreliable, fostering cognitive change and increased self-efficacy.

Table 2.5 Homework topics.

Goal setting	Testing assumptions
Time management	Relaxation practice
Setback/flare-up planning	Mindfulness practice
Rewarding self (reinforcement)	Activity-rest cycling/pacing

The present study investigated patient outcomes in two pain management programmes. These programmes were based on different psychological theories – CBT and ACT, both of which have been demonstrated to be effective in improving patient health and wellbeing.

2.5.6 Cognitive Behavioural Therapy (CBT)

CBT is intended to recognise, evaluate, and rectify maladaptive conceptualisations and dysfunctional beliefs that patients have about themselves and their pain. Patients are taught to become aware of the connections between thoughts, feelings, and behaviours – to recognise that negative thoughts and feelings about the pain are directly linked to maladaptive behaviours and exacerbation of symptoms (Eccleston 2001). Unrealistic or unhelpful thoughts about pain and pain catastrophising are identified and replaced with thoughts that are oriented towards adaptive behaviour and positive functioning, through cognitive restructuring. Pain symptoms themselves are reconceptualised during the therapy process, with patients learning that they can control their symptoms to an extent by employing the cognitive and behavioural skills acquired during therapy (Turk et al. 1983). CBT for pain develops coping skills for pain management and improved mental health, including structured relaxation, planned daily activities and scheduling of pleasurable events, assertive communication, and pacing of behaviour

to avoid exacerbation of pain flares (Sturgeon 2014). The goals of CBT are summarised in Box 2.1.

Box 2.1 Goals of CBT.

- Reconceptualisation of patients' views of their problems from overwhelming to manageable (*combat demoralization*)
- Convince patients that skills necessary for responding to problems more adaptively will be included in treatment (*enhance outcome efficiency*)
- Reconceptualisation of patients' views of themselves from being passive, reactive, and hopeless to active, resourceful, and competent (*foster self-efficacy*)
- Ensure that patients learn how to monitor their thoughts, feelings, behaviours, and physiology and learn interrelationships among these (*break up automatic, maladaptive patterns*)
- Teach patients how to use and when to use adaptive overt and covert behaviours required for adaptive response to problems associated with chronic pain (*skills training and use*)
- Encourage patients to attribute success to their own efforts (*self-attribution*)
- Anticipate problems and discuss these as well as ways to deal with them (*facilitate maintenance and generalisation*)

Adapted from Turk (2002), p.144.

2.5.7 Evidence for Efficacy of CBT

A large number of studies have investigated the effectiveness of CBT for chronic pain, and since 1994 a number of meta-analyses and reviews have collected together the evidence for CBT. Morley, Eccleston, and A. Williams (1999), in a meta-analysis of 25 randomised controlled trials (RCTs), compared the effectiveness of cognitive-behavioural treatments with the waiting list control and alternative treatment control conditions upon questionnaire-based measures of psychophysical health. Cognitive-behavioural treatments were associated with significant effect sizes (median effect size

= 0.5) on all domains of measurement, when compared to waiting list (i.e. treatment as usual). Pain experience, positive cognitive coping and appraisal, and reduced behavioural expression of pain were improved significantly by CBT compared to other active treatments (including information, physiotherapy, and relaxation). No difference was found between CBT and alternatives on measures of mood (depression etc.), negative coping and appraisal (e.g. catastrophising), and social role functioning (Morley et al. 1999). Another meta-analysis of 22 controlled studies of psychological treatment for low back pain concluded that CBT was efficacious in improving measures of pain intensity, pain-related interference, health-related quality of life, and depression (Hoffman et al. 2007). Finally, in an update to their 1999 review, A. Williams, Eccleston, and Morley (2012) performed a Cochrane review of CBT for chronic pain (excluding headache) in 35 RCTs with 4,788 participants. The benefits of CBT emerged almost entirely from comparisons with treatment as usual/waiting list, not with active controls, and CBT was effective in improving measurements of mood and catastrophising. There was some evidence that improvements were maintained after 6 months, and they conclude that CBT is a useful approach to the management of chronic pain (A. Williams et al. 2012). Taken together, these studies present convincing evidence that psychological therapies including CBT are more effective in bringing about improvements in coping and mental health than pharmaceutical treatment alone. It should also be noted that CBT may not bring about a reduction in pain *per se*; however this is not a goal of the treatment.

2.5.8 Acceptance and Commitment Therapy (ACT)

ACT is an approach to treatment designed around processes from the psychological flexibility model (Hayes et al. 1999; Hayes 2004a; Hayes 2004b; Hayes et al. 2006; McCracken & Morley 2014). Thoughts, feelings and behaviours are not seen as the

problem which must be addressed; rather it is the response to these factors which is the target for change. For example in chronic pain, the tendency to react in maladaptive ways and fight against the pain is what causes suffering, rather than the pain itself. The patient is encouraged to question whether their current courses of action are preventing them or helping them move towards their life goals and values. The goal of ACT is to help the patient develop their ability to follow the six core processes of psychological flexibility (Box 2.2). Mindfulness is an important technique which is employed to foster acceptance, to help view the self as separate from thoughts and emotions, and to aid defusion and letting go of automatic thoughts. The essence of mindfulness is paying attention to the present moment without attaching meaning or judgmental language to thoughts that arise (Kabat-Zinn 1994). Patients practice mindfulness techniques that promote a distancing from, and a non-judgemental awareness of thoughts, such as imagining watching ones thoughts as they float by like leaves on a stream (Hayes 2004b). Seeing thoughts as transient events separate from the self, cultivates psychological flexibility, allowing the patient to deal with difficult thoughts and feelings that might otherwise become barriers to pursuing their goals. ACT differs from CBT in the regard that it does not attempt to change thoughts and feelings: how a person has dealt with their problems in the past is not important. Patients can learn to use the skills taught in ACT to begin living a fulfilling life right away, without first “winning a war with their own history” (Hayes 2004b, p.652).

Box 2.2 Core Processes of Psychological Flexibility

- (1) *Acceptance*: a broad-based willingness to have pain or discomfort.
- (2) *Defusion*: a lack of dominance of verbal, often cognitive, content or narrowing of perspective such that it is predominately focused on this content.
- (3) *Moment-to-Moment Awareness*: a purposeful, non-judgmental, and fluid attending to present experiences.
- (4) *Self-as-Context*: a conscious perspective taking on the content of one's experience where a distinction is made between the person having the experience and the experiences themselves.
- (5) *Values Orientation*: freely identified (e.g., noncoerced) directions for activity that bring meaning, importance, or vitality to living.
- (6) *Committed Action*: a pattern of behaviour that encompasses a flexible persistence oriented towards valued living.

Adapted from Vowles et al. (2014), p.391.

2.5.9 Evidence for Efficacy of ACT

The use of ACT as a treatment approach for chronic pain problems has grown steadily over the past 15 years. During this time evidence has accumulated that supports the use of ACT as a good alternative to CBT, with similar effects on a range of treatment outcomes (Veehof et al. 2011). A systematic review and meta-analysis of acceptance based interventions for chronic pain management by Veehof and colleagues (2011) concluded that the treatments were not superior, but a good alternative to CBT. A systematic review of ten RCTs using ACT in 623 adults with chronic pain concluded that ACT was effective in increasing physical functioning, and decreasing anxiety, depression, and distress, compared to inactive treatments (Hann & McCracken 2014).

2.6 TECHNIQUES FOR MEASURING PAIN

Pain is a complex sensation; it has location, intensity, frequency, texture, and emotional unpleasantness, all of which may change from one moment to the next. To make matters more complicated, it is also not only the consequence of tissue damage ('actual or potential'), but also the product of the environmental circumstances and the psychological characteristics of the person experiencing it. To reduce these many factors into a manageable and useful report is clearly challenging, and there are compromises to be made between the practicality of the measure and the level of detail it can achieve. Single measurements are quickly taken, but at the cost of leaving out all other information. Highly detailed reports are comprehensive but time consuming. A number of different self-report and observational measures have been developed for use under a variety of circumstances where pain and associated factors are to be assessed.

A simple method is to ask the patient to rate their pain on a numerical scale from zero to ten, where zero is 'no pain' and ten is 'the worst pain imaginable'; known as the Numerical Rating Scale (NRS). However, pain is subjective – what constitutes a 'ten' to one person might conceivably constitute an 'eight' in another person, or a 'five' in another; one has no way of standardising and comparing different scores across a population. By contrast, one can observe the *impact of pain* on a person's behaviour – such as distance walked or amount of pain medication required; or on a person's physiology – such as brain structure or brain activity. These more objective observations can be used as indirect measures of pain. The limitation to using objective measures is that the observations are of behaviours or reactions related to pain, not of the pain itself, therefore the subjective qualities of pain are not recorded.

2.6.1 Subjective measures: Self-report questionnaires

In contrast to the unidimensional NRS, questionnaires have the potential to assess multiple dimensions of the pain experience including sensory, emotional, and cognitive aspects. Such aspects are experienced subjectively by the individual and therefore must be assessed via self-report. Information revealed from self contains introspective and motivational data that cannot be accessed through any other method. Measurements that rely on self-assessment have the potential for response bias. This may be caused by a desire to ‘look good’ (social-desirability bias), by a misunderstanding in what is being measured, or by inaccurate evaluation of past events (recall bias). Such biases can be minimised by use of questionnaires that have been well tested for reliability and validity, and proven to be useful measurement tools. Self-reports can help to provide a wider range of responses than many other data collection instruments, and also have the advantages of being easy to administer and easy to interpret.

As well as assessment of the sensation of pain itself, questionnaires can be used to assess the impact of chronic pain on patient quality of life – in terms of psychological factors, behavioural changes, and perceived health status, as discussed above. The present research made use of a variety of questionnaires to measure the effect of pain management programmes upon psychosocial health, coping strategies, and attitudes towards pain. The questionnaires were selected on good evidence that they are both valid and reliable measures of the constructs under investigation, and this is discussed further in the methods sections of subsequent experimental chapters.

2.6.2 Behavioural Measures

The experience of pain motivates protection of the painful area and the seeking of treatments to reduce pain. These behaviours may be observed and thus provide an

indication of the amount of pain being suffered. The frequency of verbal or non-verbal complaints, facial grimaces, rubbing, bracing, sitting or lying down, and use of (or demand for) medications have all been employed as observational measures of pain (Richards et al. 1982; Keefe & Block 1982; Chapman et al. 1985). The utility of these measures depends not only on agreement between observers, but also on agreement between observer and sufferer. A movement recorder (accelerometer) can be used to objectively measure a person's activity levels throughout the day (Sanders 1983).

2.6.3 Recording Brain Activity during Pain

Advances in non-invasive functional brain imaging mean that it is now possible to record the brain activity that takes place during the perceptual experience of pain. Techniques used include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG), and magnetoencephalography (MEG). These techniques differ in terms of the type of information they provide. fMRI and PET measure the change in blood flow following neuronal activation, which is a surrogate measure of cell activity, and are capable of providing an image of the entire brain with a spatial resolution of up to 1mm³. However, the data for each image takes a long time to collect, and their temporal resolution is limited. In contrast, EEG and MEG directly measure the electric and magnetic field disturbances generated by neuronal activity, with millisecond temporal accuracy, by the use of multiple sensors placed over the scalp. EEG and MEG record data outside the skull, therefore their spatial resolution is limited, as the signal reaching the sensor reflects a combination of sources. Over the past 20 years, numerous studies have examined the neural correlates of acute painful stimulation in normal subjects, revealing a network of cortical and sub-cortical structures that are consistently activated. These include S1, S2, the ACC, insula, PFC, and thalamus, collectively

referred to as the pain matrix (Figure 2.10) (Melzack 1999; Treede et al. 1999; Derbyshire 2000; Apkarian et al. 2005; Lee & Tracey 2010).

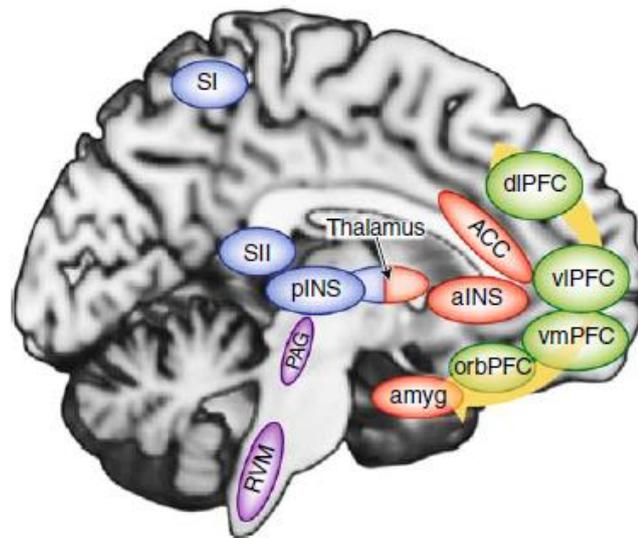


Figure 2.10 The Pain Matrix. Anterior cingulate cortex (ACC), anterior insular cortex (aINS), amygdala (amyg), primary and secondary somatosensory areas (SI and SII), posterior insular cortex (pINS), dorsolateral (dl), ventrolateral (vl), ventromedial (vm), orbital (orb), prefrontal cortex (PFC), periaqueductal grey (PAG), rostral ventromedial medulla (RVM) (adapted from Lee & Tracey 2010, p.126).

Activations of S1 and S2 reflect nociceptive input underlying the perception of sensory features of pain, and a number of studies have noted that activity in these areas is correlated with perceived pain intensity (Coghill et al. 1999; Bushnell et al. 1999; Bornhove et al. 2002; J.I. Chen et al. 2002). The ACC and insular cortex are both components of the limbic system; activation of these regions has been linked to the affective processing of pain, and activity has been shown to correlate with perceived stimulus unpleasantness (Rainville et al. 1997; Fulbright et al. 2001). Activation in PFC and parietal association areas may reflect cognitive factors, such as evaluation of

the stimulus or memory (Coghill et al. 1999; Bornhovd et al. 2002; Strigo et al. 2003). Subcortical activation in the thalamus is also regularly observed in studies of pain, likely reflecting the transmission of nociceptive inputs from the spinothalamic pathway (Coghill et al. 2003). Motor and pre-motor cortex activations are occasionally reported, although not reliably, and this may be due to secondary effects of stimulation such as pain-evoked movements or suppression of movement (Apkarian et al. 2005). These findings are consistent with the concept of the neuromatrix as described by Melzack, reflecting the interaction of sensory, affective, cognitive, and motoric components to generate the pain experience.

After more than two decades of functional brain imaging studies, there is still debate over whether or not the network of brain areas activated during pain actually represents a specific, objective signature for pain. The fact that these areas are integral to the pain experience is certain; however some researchers have recently argued that the pain matrix represents a non-specific salience network, triggered by any salient stimulus occurring in the sensory environment, regardless of its sensory modality (Iannetti et al. 2008; Iannetti & Mouraux 2010; Legrain et al. 2011).

The following sections: **2.7, 2.8, 2.9** are based on literature discovered in the writing of the abstract below, which was published in *Regional Anaesthesia and Pain Medicine*, 36 (7, Suppl.), p.E186.

30th Annual ESRA Congress · Abstract: A-384-0005-00532

Title: Evaluation of the use of EEG in the assessment of chronic pain syndromes: a systematic literature review.

Background and aims: Clinical pain syndromes are difficult to diagnose, and often require trials of different forms of treatment before patients experience reliable pain relief. Furthermore, standard objective assessment of treatment efficacy is lacking, with clinicians having to rely on subjective report from patients. EEG equipment is relatively inexpensive, compact, non-invasive, safe, and found in most hospitals. The aim of this review was to investigate the use of EEG in diagnosis and assessment of chronic pain.

Methods: Systematic literature review was undertaken by searching databases EBSCOhost (CINAHL, EMBASE, Medline & PsycINFO) using search terms (EEG, electroencephalogra*, diagnos*, assess*, chronic pain, pain measurement). This yielded 52 papers, 24 of which were considered relevant. A hand search of references yielded 5 further papers.

Results: The evoked response potential to phasic noxious stimulation is a robust finding, and reliably comprises 4 components (N1, N2, P2, P3), of which the N2-P2 amplitude correlates with perceived pain intensity. In continuous EEG data, the peak α frequency is related to subjective perception of tonic pain intensity, and relative changes in slow wave power (δ , θ , α) are linked to subjective pain control.

Conclusions: It may be possible to utilise EEG in the objective assessment of pain treatment efficacy. The capacity for diffuse noxious inhibitory controls, habituation, sensitisation, and temporal summation is differentially affected across conditions, opening the possibility for EEG guided diagnosis and treatment in the future: many conditions are yet to be investigated in this way.

2.7 THE STUDY OF PAIN PERCEPTION USING EEG

2.7.1 Evoked Response Potentials

The characteristic pattern of electrical activity in the brain following a stimulus is known as the evoked response potential (ERP). Painful heat delivered to the skin by a CO₂ laser stimulator was first shown to elicit fluctuations in ongoing EEG by Carmon and colleagues in 1976. Subsequent studies have used similar brief heat stimuli to investigate the electrical activity of the brain in response to painful peripheral stimulation. Pain ERPs tend to reflect the dual pain sensation elicited by the two types of nociceptive sensory afferent fibres from the skin. Small myelinated A δ fibres and large unmyelinated C fibre afferents both respond to changes in skin temperature and pressure, with rapidly conducting A δ fibres delivering the initial sharp pain sensation at around 100-200ms (Treede et al. 1988) followed by the dull aching pain sensation being delivered by the slow conducting C fibres around 1000ms later (Iannetti et al. 2003).

EEG source analysis of laser evoked potentials (LEPs) (Garcia-Larrea et al. 2003; Tarkka & Treede 1993; B. Bromm & A.C.N. Chen 1995) suggests that the earliest ERP component (N1 ~160ms) originates from contralateral S1 and S2 cortices, and represents the arrival of the nociceptive signal at the cortex. The next observed components (the N2-P2 complex ~240ms) originate from bilateral S2 and ACC, respectively, and represent the early stages of pain processing by the brain.

2.7.1.1 Contact heat evoked potentials

More recently, brief painful stimulation using heat delivered via a thermode placed into contact with the skin has been used as an alternative to laser stimulation. The Contact Heat Evoked Potential Stimulator (CHEPS: Medoc, Ramat Yishai, Israel) is a safe and reliable method for generating ERPs in both healthy (e.g. A.C.N. Chen et al.

2001; LePera et al. 2002; Greffrath et al. 2007; Warbrick et al. 2009) and patient samples (Atherton et al. 2007; Chi et al. 2008; Truini et al. 2007; Staud et al. 2008). CHEP studies have reported a slightly different ERP time course than LEP studies, with longer component latencies (N1 ~450ms, N2-P2 ~550ms) and smaller amplitudes (A.C.N. Chen et al. 2001, 2006; LePera et al. 2002; Granovsky et al. 2005; Iannetti et al. 2006; Greffrath et al. 2007; Roberts et al. 2008; Warbrick et al. 2009). The longer latency of the CHEP is due to the fact that the thermode used to deliver stimuli heats up at ~70°C/sec, compared to ~10,000°C/sec for laser stimuli (A.C.N. Chen et al. 2001). The rapid heating achieved with laser stimuli results in a more coherent afferent volley of nerve input to the brain, and a larger ERP than contact heat stimuli (Figure 2.11, upper panels).

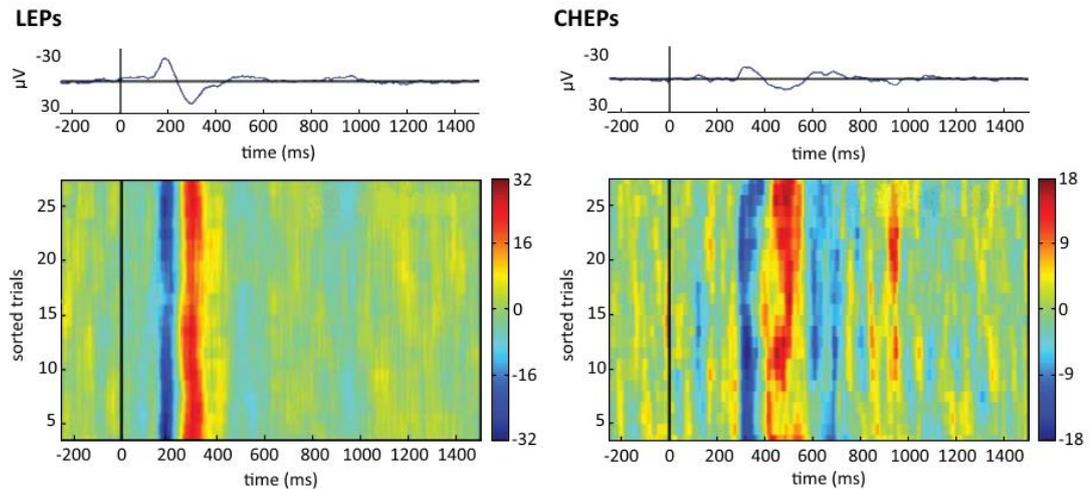


Figure 2.11 Comparison of average waveforms (upper panels) and stacked plots of single trials (lower panels) obtained using laser (left side) and contact heat (right side) stimulation. Recorded from the Cz electrode in the same subject, showing the N2 and P2 waves after stimuli were applied to dorsum of left hand. To assess trial-to-trial consistency, one stacked plot of single-trial responses is shown for each stimulus modality (adapted from Iannetti et al. 2006).

The slow temperature increase of the CHEPS thermode also generates greater variability in response latencies (known as latency jitter) of CHEP compared to LEP signals, which is apparent when viewing a stacked plot of the single trial data (Figure 2.11, lower panels). Latency jitter has the effect of attenuating the peak amplitudes and distorting the waveform when averaging across multiple trials. To avoid such loss of information it is preferential to extract peak amplitude from each trial individually, and then use these numbers to calculate a more accurate average of peak amplitude (Iannetti et al. 2005, 2006). A method of automated single-trial analysis was developed by Mayhew and colleagues (2006) using a multiple linear regression approach. Briefly, a basis-set is constructed from the subject average ERP waveform; regressors are formed that represent the N and the P peak of interest, then this basis set is regressed against each single-trial in the data. The regression coefficients between the data and the basis-set are used to reconstruct a fit for each trial and then the amplitudes and latencies are measured from this (Mayhew et al. 2006). This method has been shown to reliably generate a more consistent ERP average and is considered the desired method for analysis of CHEPs (Iannetti et al. 2006; Hu et al. 2010; Mayhew et al. 2013).

Stimulus location effects ERP latencies, with trigeminal (facial) stimulation producing much shorter latencies than lower limb stimulation, simply because of the shorter distance that the nerve signal has to travel to the brain (Truini et al. 2007; Warbrick et al. 2009). Also a late P3 (~1000ms) component is occasionally but not reliably reported across CHEP studies; it has been suggested that it represents either a processing of noxious information carried by slower conducting C-fibres (A.C.N. Chen et al. 2001), or that it represents a shift of attention towards a novel stimulus (Lorenz & Garcia-Larrea 2003; Kakigi et al. 2005). Finally, both amplitude and latency of CHEPs and

LEPs have not been shown to differ between male and female participants (Truini et al. 2005; I.A. Chen et al. 2006).

2.7.2 Phenomena of Pain Perception

2.7.2.1 Correlation of ERPs with pain ratings

A large number of studies have demonstrated a significant positive correlation between the amplitude of pain ERPs and the subjective perception of pain intensity using electrical (Harkins & Chapman 1978; A.C.N. Chen et al. 1979; de Lima et al. 1982), laser (Carmon et al. 1978; Kakigi et al. 1989; Beydoun et al. 1993; Arendt-Nielsen 1994; Garcia-Larrea et al. 1997; Iannetti et al. 2005), and contact heat stimuli (A.C.N. Chen et al. 2001; A.C.N. Chen et al. 2002; LePera et al. 2002; Granovsky et al. 2005, 2006, 2008; Greffrath et al. 2007; Roberts et al. 2008). Only two studies reported no significant correlation between ERPs and pain ratings (I.A. Chen et al. 2006; Warbrick et al. 2009; both CHEP studies). The majority of the studies above compared the mean pain rating with the mean ERP amplitude when calculating the correlation. In the case of the Iannetti and colleagues (2005) study, the authors extracted ERP amplitude data at the single-trial level, and found that ERP amplitude correlated with participant's trial-by-trial ratings of pain intensity, thus reinforcing the finding that there is a correlation between evoked brain activity and perceived pain intensity.

2.7.2.2 Habituation

The phenomenon of habituation describes a reduction in response with repeated stimulation. In healthy subjects, perceptual habituation (of subjectively reported pain intensity ratings) has been observed with interstimulus intervals (ISI) of anywhere between 3 and 80 seconds and has been attributed to nociceptor suppression or fatigue (Price et al. 1977; Kleinböhl et al. 2006). Similar studies in chronic pain patients reveal that habituation is reduced in conditions characterised by increased pain sensitivity –

such as fibromyalgia (Smith et al. 2008), chronic low back pain (Flor et al. 2004), and migraine (Valeriani et al. 2003), and it has been suggested that deficits in habituation may play a role in the development of some chronic pain conditions (Smith et al. 2008).

Habituation can also be observed in the pain ERP, as a reduction in N2-P2 peak-to-peak amplitudes with repeated stimulation. Two types of habituation of evoked potentials have been documented, peripheral and central. Peripheral habituation occurs rapidly when the stimuli are applied to a fixed location, and reflects nociceptor fatigue (Greffrath et al. 2006, 2007). Single trial ERPs are seen to gradually decrease over the first three or four stimuli of a block and then plateau at around 50% of the size of the initial ERP (Greffrath et al. 2007), with the result that the N2-P2 complex is greatly reduced in the average waveform (Warbrick et al. 2009). Central habituation occurs at a much longer timescale when stimuli are applied to non-overlapping locations, with amplitude reduction becoming visible after 20-30 trials (Valeriani et al. 2005; Warbrick et al. 2009). Central habituation is not due to peripheral nociceptor fatigue, as stimuli applied to other areas of the body once habituation has been induced also result in attenuated ERPs (Arendt-Nielsen 1990; Hüllemann et al. 2013). Reduced habituation of LEPs has been reported in patients with migraine compared to control subjects (Valeriani et al. 2003).

2.7.2.3 Sensitisation

The application of repeated identical nociceptive stimuli, at a greater frequency than 0.33 Hz, results in a progressive increase in perceived pain intensity in healthy subjects known as sensitisation (sometimes called ‘temporal-summation’, or ‘wind-up’) (Price et al. 1977; Herrero et al. 2000; Kleinbohl et al. 2006; Meeus & Nijs 2007). This is thought to be due to a central mechanism, as the firing of peripheral C-nociceptors has been observed to remain the same or decline with stimulus repetition (Price et al.

1977). Perceptual sensitisation has also been shown to be correlated with levels of anxiety and catastrophising in healthy individuals (Granot et al. 2006), and with fear-avoidance beliefs and catastrophising in LBP patients (George et al. 2007), indicating the influence of psychological factors on pain sensitivity. In patients suffering with fibromyalgia, sensitisation is induced at lower frequencies and lower temperatures of stimulation, and can be maintained with less frequent stimulation than in healthy control subjects (Staud et al. 2001, 2009; Price et al. 2002). Enhanced perceptual sensitisation is also found in other chronic pain conditions such as osteoarthritis (Arendt-Nielsen et al. 2010), whiplash (Curatolo et al. 2001), migraine (Weissman-Fogel et al. 2003), and temporomandibular disorder (Sarhani et al. 2004).

2.7.2.4 Attention/distraction

A review of the effects of attending to painful stimuli, or attending to other sensory modalities or tasks (i.e. distraction from painful stimuli) by Lorenz and Garcia-Larrea (2003) reported that the N2-P2 complex was strongly enhanced by purposeful attention towards painful stimuli. The habituation to stimuli over a session may be due to a decrease in attention towards the stimuli (vigilance) as participants become accustomed to the sensations.

2.7.2.5 Conditioned pain modulation (pain inhibiting pain)

The phenomenon of conditioned pain modulation (CPM) refers to a reduction in ongoing pain brought about by a painful stimulus applied to another area of the body. It is mediated by a mechanism of endogenous analgesia acting via descending modulatory systems, known as diffuse noxious inhibitory control (DNIC) (LeBars et al. 1979). When exploring this effect in an experimental setting the most commonly used paradigm is to compare the response to a brief (phasic) stimulus presented alone, known as the test stimulus, to the response to the same stimulus in the presence of a

long-lasting (tonic) stimulus, known as the conditioning stimulus (Pud et al. 2009). The observed effect of the conditioning stimulus on the response to the test stimulus is known as CPM (Yarnitsky et al. 2010) (the term ‘heterotopic noxious conditioning stimulation’ has also been used; Sprenger et al. 2011), and this effect is mediated by DNIC. A systematic review and meta-analysis of 30 controlled studies of CPM in clinical populations revealed that some chronic pain conditions (including fibromyalgia, osteoarthritis, migraine, and irritable bowel syndrome) are associated with impaired DNIC (overall effect size 0.78) (Lewis et al. 2012).

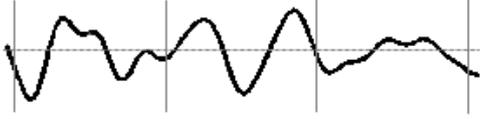
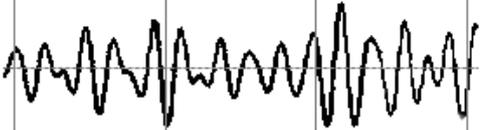
The effect of dual (tonic and phasic) painful stimulation on the nociceptive ERP has rarely been studied. Two studies have investigated the effect of ischaemic muscle pain (the conditioning stimulus) on somatosensory evoked potentials (SSEPs) elicited by painful electrical stimulation (the test stimulus) (A.C.N. Chen et al. 1985; Reinert et al. 2000). The earlier study reported that SSEPs were depressed during and after concurrent tonic pain (A.C.N. Chen et al. 1985). In the later study, after tonic pain was induced, SSEPs were attenuated and remained so for up to 20 minutes afterwards, indicating a long lasting effect of tonic pain stimulation. Subjective pain ratings also remained reduced for 10 minutes after ischaemic muscle work, and there was an increase in beta power which also persisted for 10 minutes after tonic stimulation. DNICs are believed to be the cause of the reduced SSEP amplitudes, as auditory evoked potentials recorded before and after tonic pain were unaffected (Reinert et al. 2000).

2.7.3 Power Spectral Density

EEG data can be converted into a set of simple sine waves representing the power of the signal at discrete frequencies (known as the power spectral density or ‘PSD’) using a mathematical process called Fourier analysis. Recordings of different brain states are

dominated by certain frequency bands which are thought to be connected to different states of arousal (Niedermeyer 2005; M.P. Jensen et al. 2008; Table 2.6).

Table 2.6 Examples of filtered bandwidths and the states usually associated with them (adapted from M.P. Jensen et al. 2008, p.195; Sherlin 2009, p.87).

Frequency Band	Frequency Bandwidth	State Associated with Bandwidth	Example of Filtered Bandwidth
Delta (δ)	0.5-4 Hz	Deep Sleep	
Theta (θ)	4-7 Hz	Drowsy	
Alpha (α)	8-12Hz	Relaxed	
Beta (β)	13-30 Hz	Engaged	

The effect of pain upon PSD in healthy subjects has been investigated in several studies, using a variety of tonic pain stimuli (Table 2.7). There is a definite trend of an overall increase in power in the presence of tonic pain. β - (and occasionally δ -) frequencies appear to increase relatively more than other bands, accompanied by a relative decrease in α -power. θ -power changes are occasionally observed. Two of the studies observed that pain was accompanied by an initial decrease in α -power which then increased towards the end of stimulation (Backonja et al. 1991; Chang et al. 2001b). Three of the studies noted that during stimulation, the EEG was subject to contamination by muscle activity artefacts in the high β -range (18-30 Hz), particularly at temporal recording sites (Backonja et al. 1991; Veerasarn & Stohler 1992; Dowman

et al. 2008). Furthermore, one study recorded EEG during a period of imagined pain, finding that the results were similar to those obtained with experimental pain, suggesting that the effects on β -frequency are non-specific to pain (Veerasarn & Stohler 1992). Two studies reported that power spectrum changes remained measurable from one minute (Stevens et al. 2000) to ten minutes (Reinert et al. 2000) after the tonic pain stimulus was removed.

Table 2.7 overleaf.

Table 2.7 Effects of tonic experimental pain on EEG power spectra in healthy subjects (grouped by stimulus type).

Study	Stimulus	Delta (δ)	Theta (θ)	Alpha (α)	Beta (β)
ACN Chen et al. (1989)		↑ (P)	–	–	↑ (P)(β_2)
Backonja et al. (1991)		–	↑ (<i>i.F</i>)	↓, ↑ (FP)	↑ (FP)(β_1)
ACN Chen & Rappelsberger (1994)	Cold	–	–	↓ (C)	↑ (C)
Ferracuti et al. (1994)	pressor	↑ (F)	–	↓ (<i>c.P</i>)(α_2)	–
Stevens et al. (2000)		↑	↑	↓ (α_2)	↑ ($\beta_{1,2}$)
Chang et al. (2002a)		↑ (F)	↑ (F)	↓ (O)($\alpha_{1,2}$)	↑ (T)(β_2)
Dowman et al. (2008)		–	↓ (FCT)	↓ (<i>c.T</i>), ↑ (P)	↑ (β_2)
Shao et al. (2012)			↓	↓	↑ (β_2)
Huber et al. (2006)	Contact heat	↑	↓ (<i>i.FT</i>)	↓ (FT)(α_1)	↑ (<i>i.T</i>)(β_1)
Giehl et al. (2013)		↑ (PO)	–	↓ (C)($\alpha_{1,2}$)	–
Zhang et al. (2013)		–	–	↓ (<i>c.CT</i>)	–
Veerasarn & Stohler (1992)		–	–	–	↑ (T)
Le Pera et al. (2000)	Hypertonic saline i.m.	↑	–	↑ (<i>c.P</i>)(α_1)	–
Chang et al. (2002b)		–	–	↓ (PO)(α_1)	–
Chang et al. (2003)		–	–	↓, ↑ ($\alpha_{1,2}$)	↑ (β_2)
Reinert et al. (2000)	Ischemic muscle work	–	–	–	↑
Chang et al. (2001a)	Capsaicin injection i.d.	–	↓ (CP)	↓ (CP)($\alpha_{1,2}$)	–
Chang et al. (2001b)	Capsaicin injection i.m.	–	–	↓ (O)($\alpha_{1,2}$)	↑ (β_2)

Key: i.m. = intramuscular injection, i.d. = intradermal injection, *i.* = area ipsilateral to stimulation, *c.* = area contralateral to stimulation, ↑ = general relative increase in power following stimulation, ↓ = general relative decrease in power following stimulation, F = frontal area, C = central area, T = temporal area, P = parietal area, O = occipital area, α_1 , α_2 , β_1 , β_2 = sub-divided alpha- and beta-power bands (if reported).

The changes in relative power spectral density of these frequency bands have been attributed to quite general shifts in brain activity not specific to painful stimulation:

2.7.3.1 Delta band (δ)

Increased δ -oscillatory activity has been recorded in response to pain, reward, and fatigue; also patients with schizophrenia, depression, and anxiety have raised baseline δ -power; and it has been speculated that δ -rhythms are associated with more primitive motivational urges triggered by motivational rewards and dangers (Knyazev 2012). A review of experimental studies reporting δ -activity changes reported that power increases were observed in states of ‘internal concentration’ such as working memory tasks, and also during the inhibition of movement in a Go/No-Go task (Harmony 2013). Studies have also shown that experienced meditators have increased resting δ -power in prefrontal areas compared to controls (Faber et al. 2008, Tei et al. 2009). fMRI has also revealed evidence of reduced prefrontal cortex activity in experienced meditators, suggesting that the δ -rhythm is involved in inhibition of brain activity (Holzel et al. 2007).

2.7.3.2 Theta band (θ)

Theta frequency power changes have previously been associated with meditative states, focused attention, and hypnotic susceptibility (Schacter 1977; Doppelmayr et al. 2008; Baijal & Srinivasan 2010; Finnigan & Robertson 2011). Also, evidence from two case studies has shown that enhanced θ -activity is related to a conscious effort to lower the perception of pain. Larbig and colleagues (1982) measured cerebral responses in anticipation of a painful stimulus and during pain in a fakir (person with incredible self-discipline) and 12 male controls; both before and during pain the fakir showed more θ -power relative to controls. In a second study the same author found enhanced θ -wave activity during pain control demonstrations by the fakir (Larbig

1994, cited by B. Bromm & Lorenz 1998). θ -activity has also been associated with task performance in trained subjects under the extreme environmental conditions of deep sea diving (Lorenz et al. 1992) and prolonged confinement (Lorenz et al. 1996). Finally, a study investigated pain report and PSD following CPT in four groups: women with borderline personality disorder who do, and do not report pain during self-harm, women with major depression, and healthy women (Russ et al. 1999). Results showed that θ -power after CPT was significantly higher in the group who do not report pain compared to depressed and healthy groups; θ -power was also correlated with scores on the Dissociative Experiences Scale (Bernstein & Putnam 1986) suggesting a link between raised θ -power and dissociation from pain.

2.7.3.3 Alpha (α) and beta (β) bands

A desynchronisation of α -activity upon stimulation of any type is commonly observed (B. Bromm & Lorenz 1998) and is termed event related desynchronisation (ERD; Pfurtscheller & Aranibar 1977). The opposite, event related synchronisation (ERS; Pfurtscheller 1992) also occurs in response to a stimulus, and may be observed in the same frequency band at a different location to the ERD, or in the same location in a different band (Pfurtscheller & Lopes da Silva 1999). The α -reduction and β -enhancement following painful stimulation which dominates the findings in Table 2.8 are therefore unlikely to be pain specific. B. Bromm and Lorenz (1998) suggest that α -frequency changes may indicate selectivity of salient features of stimulation in preparation for a motor response to the painful interruption and the increase in β -activity may indicate the replacement of α -activity by faster rhythms.

2.7.3.4 Correlation of PSD with pain ratings

A relationship between aspects of PSD and subjective pain ratings has also been reported, but not to the same extent as the ERP based correlation. The peak frequency

in the α -band during noxious stimulation (cold pressor), and the same measured at rest, has been shown to correlate positively with pain intensity ratings in healthy subjects, indicating that peak α -frequency may provide a measure of pain experience during stimulation, and may also predict sensitivity to tonic painful stimuli (Nir et al. 2010). A recent study using techniques to measure the PSD of different brain structures (frequency-domain EEG source analysis) reported negative correlations between (cold pressor) pain ratings and left medial frontal, left superior frontal θ -activity; anterior cingulate α activity; and posterior cingulate β activity (Shao et al. 2012).

2.8 THE USE OF EEG TO STUDY CHRONIC PAIN

2.8.1 ERP Studies

In pain conditions characterised by nerve damage and dysfunction of nociceptive pathways, ERPs from noxious stimuli applied to the affected area are attenuated or absent – syringomelia (Treede et al. 1991), peripheral neuropathy (Kakigi et al. 1992), central neuropathic pain (Garcia-Larrea et al. 2002), post-herpetic neuralgia (Truini et al. 2003). In fibromyalgia, a condition characterised by heightened pain sensitivity, LEPs are enhanced compared to controls (Brown & Jones 2009; de Tommaso et al. 2010). Some chronic pain conditions exhibit normal ERPs from noxious stimuli – migraine/chronic tension type headache (Valeriani et al. 2003), CBP (Flor et al. 2004), and cardiac syndrome X (Valeriani et al. 2005). Several studies have also reported that the normal reduction in ERP amplitude seen with repeated stimulation (i.e. habituation) does not occur. Conditions in which ERP habituation is absent include: migraine (Valeriani et al. 2003; de Tommaso et al. 2005; Coppola et al. 2010), CBP

(Flor et al. 2004, Vossen et al. 2015), cardiac syndrome X (Valeriani et al. 2005; Sestito et al. 2008), and fibromyalgia (de Tommaso et al. 2010).

ERPs have also been used to investigate DNIC. One study investigated this using electrical stimulation as a phasic stimulus and intramuscular injection of glutamate as the tonic stimulus, in groups of chronic tension type headache patients and healthy controls (Buchgreitz et al. 2008). Compared to phasic stimulation presented alone, ERPs during tonic stimulation were attenuated in the healthy group, but remained unaffected in the patient group, which the authors posit to be due to a deficiency in DNIC related to their condition (Buchgreitz et al. 2008, p.3237). Self-reported pain intensity was not recorded in the study, so it is not possible to know if the reduced ERPs reflected a reduction in pain intensity. In contrast, another study investigated DNIC in osteoarthritis patients using electrical stimulation as a phasic stimulus, and provoked osteoarthritis pain to cause the tonic painful stimulus (by holding a slightly hyperextended joint position), measuring perceived pain intensity by self-report and brain activity using EEG and MEG (Quante et al. 2008). Despite not rating the phasic stimulus as any less painful during the tonic pain condition, N2-P2 complex amplitudes evoked by phasic stimulation were reduced by over 50% during tonic pain compared to the phasic pain alone condition. The lack of a reduction in reported pain intensity agrees with the finding that DNIC is impaired in chronic pain conditions including osteoarthritis (Lewis et al. 2012). However, the lack of a reduction in subjectively reported pain when ERPs were so clearly reduced is interesting, as pain intensity and ERP amplitude have been shown to be correlated in many studies using healthy samples. Quante and colleagues (2008) suggest that as the N2-P2 complex originates in the cingulate cortex, it is related to the cognitive and emotional dimension of pain rather than the sensory dimension (which is localised to the somatosensory

cortex; Lorenz & Garcia-Larrea 2003). Some authors have suggested that ERP magnitude is determined by stimulus saliency in general rather than by absolute pain intensity (Iannetti et al. 2008), which may explain the difference between perceived intensity and N2-P2 complex amplitude observed by Quante and colleagues (2008). The study did not include a control group, meaning it is hard to know if the observations were specific to the patient group or not. Also, patients were given local anaesthetic injection into the painful joint to reverse the provoked osteoarthritis pain, which could have introduced further effects on nociceptive transmission alongside DNIC, leaving uncertainty over the effect that was actually being measured.

2.8.2 PSD Studies

PSD of EEG frequency bands recorded at rest appear to be similar in chronic pain patients and healthy controls: one study found no difference in frequency composition between CBP patients and healthy controls (Schmidt et al. 2012); another study compared resting PSD between a mixed group of patients (CBP, IBS, and fibromyalgia) and controls and also found no difference in relative δ -, θ -, α -, and β -power (Vossen et al. 2014). A notable study has investigated PSD in a sample of spinal cord injury patients, half of which experienced pain as a result of injury and half who did not (Braden et al. 2011). The PSD of the 'in pain' group displayed relative decreases in α -power and increases in β -power compared to the 'no pain' group. This result is similar to observations made of healthy subjects stimulated with tonic pain (i.e. decreased α -power and increased β -power compared to rest; Table 2.8). Another study compared EEG PSD changes in response to tonic pain induced by the CPT between fibromyalgia patients and healthy controls (Stevens et al. 2000). During immersion in the cold pressor, both groups displayed significant increases in δ -, θ -, and β -power compared to rest; however, α -power decreased in the healthy group but

increased slightly in the patient group. The reason for this is unclear; Stevens and colleagues (2000) speculate that it reflects an increased thalamic processing of painful stimuli in fibromyalgia patients.

An interesting set of studies has investigated the relationship between θ - and β -oscillations and their origin within the brain in a set of patients with neuropathic/neurogenic pain. Using MEG to measure spontaneous brain activity and perform source analysis, two studies have demonstrated a coherent increase in θ - and β -rhythms in neurogenic pain patients compared to healthy controls, which results from a resonant interaction between thalamus and cortex – known as thalamocortical dysrhythmia (TCD; Llinás et al. 1999; Schulman et al. 2005). These observations are supported by EEG findings of increased coherent θ - and β -activation in similar patient groups (Sarnthein et al. 2006; Stern et al. 2006; Sarnthein & Jeanmonod 2008). It has been suggested that the loss of afferent input to the thalamus following nerve damage gives rise to spontaneous discharges in thalamic neurones that sustain the observed TCD, causing neurogenic pain (Sarnthein & Jeanmonod 2008).

Finally a number of studies have reported that the dominant frequency peak in the PSD of some groups of pain patients is lower than that of healthy controls. For example in neuropathic pain (Llinás et al. 1999; Sarnthein et al. 2006; Boord et al. 2008; Wydenkeller et al. 2009); chronic regional pain syndrome (Walton et al. 2010); and chronic pancreatitis (Olesen et al. 2011; deVries et al. 2013). This slowing of the dominant frequency is thought to be a result of TCD (Llinás et al. 1999; Sarnthein et al. 2006).

2.8.3 Psychological Correlates of EEG Activity in Chronic Pain

A small number of studies have investigated relationships between psychological measures (e.g. depression, catastrophising) and abnormalities in brain structure and

function in chronic pain patients. In a study examining habituation of LEPs in fibromyalgia patients, as well as finding that both ERPs and pain ratings showed significantly reduced habituation to repeat stimuli in patients compared to controls, it was observed that self-reported depression scores were negatively correlated with the extent of habituation in the patient group (de Tommaso et al. 2010). Operant reward conditioning increased N2-peak ERP amplitudes in response to identical stimulation in CBP patients and controls, which displayed a slower rate of extinction in the CBP patient group (Flor et al. 2002). Finally, a very recent study by M.P. Jensen and colleagues (2015) investigated the predictive value of frontal α -power asymmetry on catastrophising scores measured two years later in a sample of spinal cord injury patients. Based on the theories that right frontal activity is related to 'negative' feelings and left frontal activity 'positive' (Davidson 2004), and that increases in α -power are associated with inhibitory activity (Klimesch et al. 2007), the authors hypothesised that asymmetry in frontal α -power (left > right) would be related to catastrophising scores measured in the future. In a sample of spinal cord injury patients, this hypothesis was supported (M.P. Jensen et al. 2015). These findings not only demonstrate that physiological brain activity is related to psycho-behavioural phenomena, but also that it may be possible to detect the emergence of such phenomena using physiological measures.

2.9 THE USE OF EEG TO ASSESS PAIN TREATMENT

2.9.1 Surgical Treatments

Studies have investigated the effect of a surgical lesion to the thalamus (central lateral thalamotomy, CLT) in neurogenic pain patients exhibiting the increased coherent θ -

and β -activations of TCD (Sarnthein et al. 2006; Stern et al. 2006). In both studies, θ - and β -activations were significantly reduced 12 months after successful surgery, which paralleled a reduction in reported pain intensity. These studies point to TCD as the underlying mechanism for chronic neurogenic pain, and also demonstrate that EEG can be used as a tool both for diagnosis of this condition, and for monitoring the effects of CLT treatment.

2.9.2 Pharmacological Treatments

The effects on brain activity of medications used to treat chronic pain have rarely been studied in patient groups, however a number of studies have been carried out in healthy samples. The majority of these have been placebo controlled investigations of the effect of drugs on the ERP in response to painful stimulation. The almost universal finding has been that ERP amplitudes are reduced in the presence of the medication compared to placebo, paralleled by reductions in perceived pain intensity. Studies which have computed PSD tended to find increases in δ -, β -, and most commonly θ -power, occasionally reduced α -power is reported. The present study recruited pain patients into groups which varied in their medication use. Patients could not be expected to change their medication regimen for the purpose of controlling the confounding effects of drugs on the EEG. However, as individual patients did not change their medication throughout the study it can be assumed that these effects remained constant over time. By comparing data within each participant it is expected that any effects due to medication would remain constant and cancel out, and that observed changes (if any) are due to the experimental intervention.

2.9.3 Psychological Treatments

Research into the effect of psychological treatment upon brain physiology explores the boundary between cognitive and biological processes. It attempts to quantify the

outcomes of therapy intended to change the mind by measuring changes in the brain. This type of research is not only important from a neuroscience point of view, but also provides the most objective method by which to measure the outcome of psychological therapy. There is evidence for efficacy of these therapies when applied to chronic pain in terms of improvements in pain intensity, physical activity, wellbeing, anxiety, depression, catastrophising, and other questionnaire based, subjective report outcome measures. What makes the use of EEG and other measures of brain activity to assess therapy outcomes interesting is that they are almost entirely free of subjective influence (with the exception of the subjective confirmation of painful stimulus intensity) and therefore permit investigation of physiological changes associated with therapy, and their relationship with subjective measures.

2.9.3.1 Cognitive-behavioural therapy

To date only two studies have investigated the effect of CBT on brain activity in chronic pain patients. Lackner and colleagues (2006) scanned a group of eight female irritable bowel syndrome (IBS) patients using PET to record activity at rest and in response to painful bowel stimulation, before and after a ten-week group CBT programme. Post-treatment, patients displayed significantly reduced resting state activity in the cingulate cortex and parahippocampal gyrus compared to pre-treatment. This reduction in activity was correlated with reductions in measures of vigilance and attention to pain and may reflect these psychological changes (Lackner et al. 2006). K.B. Jensen and colleagues (2012) recorded fMRI in response to painful stimulation in a randomised, waiting-list controlled trial of a 12-week group CBT programme in 43 female fibromyalgia patients. As well as significant improvements on anxiety and depression measures, the CBT group also displayed increased post-treatment activations in the venterolateral PFC, which correlated with the change in anxiety. The

authors note that this brain region is associated with executive cognitive control and the appraisal of pain, and suggest that CBT led to the increased involvement of this brain area in pain processing (K.B. Jensen et al. 2012).

2.9.3.2 Mindfulness

The effect of mindfulness based therapies upon brain activity, measured using EEG, has been investigated in two studies. The first was a controlled study of the effects of an 8-week mindfulness based PMP on laser-evoked potentials, as well as measures of physical and mental health, physical pain, ability to control pain, and mindfulness, in a mixed group of 28 patients with chronic musculoskeletal pain (Brown & Jones 2013). The therapy, similar to the ACT-based PMP discussed earlier, was delivered in group sessions by a private company and has previously been shown to have positive effects on measures of physical and mental health (Cusens et al. 2010). Brown and Jones (2013) found those patients who participated in the PMP reported improvements in mental health and control over pain, and the P2 component amplitude (measured at the C2 electrode) decreased in the intervention group, and increased in the control group from baseline to follow-up. The authors did not comment on the meaning of the attenuated P2 component; however source-analysis revealed that deactivation of the dorsolateral PFC in anticipation of pain was reduced after treatment in the intervention group, which the authors speculate to be due to increased cognitive processing in the emotional regulation of pain (Brown & Jones 2013). The second study investigated the effects of an 8-week mindfulness based stress reduction (MBSR; Kabat-Zinn 1982) programme upon EEG spectral density and measures of mental and physical health in a single group of 22 CBP patients (Schmidt et al. 2015). The therapy was not tailored to pain management, did not contain any education on pain, and was focused on mindfulness practice, mindfulness during stressful situations, and dynamic yoga.

Patients made improvements in quality of life, health satisfaction, and depression, however there was no significant difference in PSD between pre- and post-intervention (Schmidt et al. 2015).

2.9.3.3 Other non-pharmacological pain treatments

Finally, two studies by M.P. Jensen and colleagues (2013a, 2014) have demonstrated that measurable change occurs in the PSD of continuous EEG from pre- to post-treatment with a number of different psychologically mediated therapies. In the first study, the PSD of 31 spinal cord injury patients with chronic pain was measured before and after they had each partaken in a single 20 minute session of four non-pharmacological pain treatments: hypnosis, meditation, biofeedback, transcranial direct current stimulation (tDCS), and a control condition of sham tDCS. Treatment sessions were counterbalanced across participants and took place weekly to reduce carry over effects. Each treatment yielded a different pattern of pre- to post-session changes in PSD. Hypnosis was associated with general increases in θ - and α -power, and was accompanied by a significant reduction in reported pain intensity, as was meditation, which produced central electrode increases in α - and β -power. Biofeedback produced an increase in occipital β -power, tDCS increased θ -power generally, and sham tDCS was associated with an increase in general α -power (M.P. Jensen et al. 2013a). The active treatments yielded different results compared to the placebo condition, meaning that observed changes were not merely a placebo effect. Reductions in pain intensity were not significantly correlated with PSD changes meaning the authors could not associate a particular pattern of activity with the experience of pain; however it is possible that the observed PSD changes reflected some other psychological variable that was not measured. The second study used a similar group of patients and employed the same non-pharmacological treatments

given in a single 20 minute session; however this time the authors investigated the relationship between pre-treatment PSD and the pre- to post-session change in subjects' pain intensity. Baseline θ -power was correlated with response to hypnosis, with higher θ -power predicting pain reduction; α -power was also correlated with response to meditation, with lower α -power predicting pain reduction (M.P. Jensen et al. 2014). Although correlation does not imply causation, these results suggest that hypnosis and meditation achieve pain relief via different mechanisms, and that treatment efficacy might be improved by matching patients to treatments based on their baseline brain activity.

2.10 RESEARCH CARRIED OUT IN THIS THESIS

2.10.1 Theoretical Basis and Rationale

The following list summarises the reasoning behind pursuing the research which follows, based on information presented in the literature review:

1. Questionnaire measures are the current 'gold' standard to assess the efficacy of psychological pain management. Improvements in patient quality of life, mental and physical health, daily activity, and a shift from maladaptive to adaptive pain coping strategies have regularly been observed. A problem inherent with using self-report questionnaires to assess treatment outcomes is that they are a measure of subjective experience and cannot reveal underlying physiological mechanisms that may accompany successful treatment.
2. Studies have shown that successful pain treatments (surgical, pharmacological, and psychological) are associated with measurable changes in brain activity, however to date no such study has investigated these measures pre-/post-PMP.

3. EEG is a sensitive tool by which to measure brain activity related to pain processing. Literature reviewed above has illustrated that both ERP and PSD information is not only altered in patients with chronic pain compared to healthy controls, but also that it is sensitive to the effects of certain pain treatments in certain groups of patients. From a practical viewpoint, EEG is a relatively cheap, portable, and uncomplicated measurement tool which can be used at multiple sites by a single investigator.
4. The development of an objective measure of PMP efficacy which can confirm the subjective measures currently used has the potential to not only reveal mechanisms by which this treatment affects the brain, but also to indicate which patients might benefit most from treatment based on baseline brain activity.

2.10.2 Overview of the Studies

This research investigated psychosocial health and brain activity in patients attending two different NHS pain management programmes, one based on CBT, the other based on ACT. In order to determine efficacy of each PMP using the current standard of assessment, studies were undertaken in which questionnaire data collected since the inception of each programme was analysed (henceforth referred to as ‘audits’). These audits looked retrospectively at the whole population of patients that had attended the PMP. Next, in order to investigate the effect of the PMP on brain activity related to pain processing, prospective studies (henceforth, ‘EEG studies’) were conducted. The studies of the CBT-based PMP (both audit and EEG) were carried out first, and the results of these studies prompted the investigation of a second, ACT-based PMP, in a similar manner. The thesis has been structured so that studies are presented in chronological order, with Chapters 3 and 4 containing the audit and EEG study of the

CBT-PMP, and Chapters 5 and 6 containing the audit and EEG study of the ACT-PMP. The case series, which examined the relationship between self-report measures and EEG data in two patients, is included in Chapter 6 (Figure 2.12).

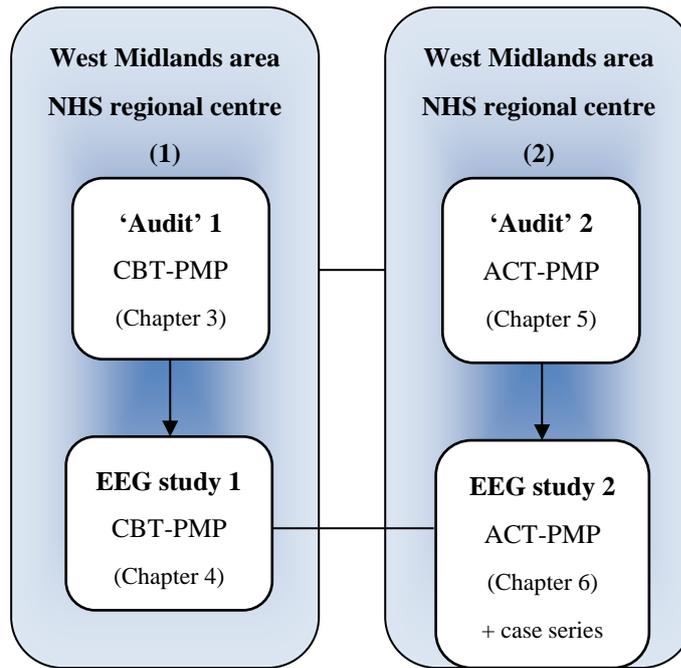


Figure 2.12 An overview of the studies contained within this research.

2.10.3 Experimental design

The following observational studies looked at groups of participants before and after they underwent treatment in a pain management programme. Some groups did not partake in treatment and acted as control groups. The inclusion of patients in either treatment or control groups was not randomised. Such experimental design is known as a quasi-experimental, or pre-post intervention, design. Quasi-experiments aim to evaluate interventions but that do not use randomisation. Similar to randomised trials,

quasi-experiments aim to demonstrate causality between an intervention and an outcome. Although the randomised controlled trial is generally considered to have the highest level of credibility with regard to assessing causality, randomisation may not be possible or viable for a number of reasons. For example, if the intervention under study incorporates an accepted, well-established therapeutic intervention, it would not be ethically sound to withhold such treatment from patients who stand to benefit from it. In the studies presented here, observations were made during routine clinical practice, therefore patients could not be randomised to groups.

Hypothesis testing

The following studies investigate the effect of pain management therapy upon several psychological and physiological parameters. Hypotheses are not explicitly stated. In the cases of the audits, past research has already demonstrated the hypothesis that there is an effect of treatment upon self-report measures. These studies were conducted to make observations about the treatments and discuss them in context of past research. In the EEG studies, outcomes could not be hypothesised from prior research. The findings were exploratory and intended to reveal patterns that could inform future work. It should be noted however, that statistical testing (i.e. null-hypothesis significance testing) was used to demonstrate that differences in parameters from pre- to post-intervention were unlikely to have arisen by chance and were in fact a consequence of the intervention.

CHAPTER 3

PSYCHOPHYSICAL HEALTH AND PAIN COPING STRATEGIES IN PATIENTS ATTENDING A COGNITIVE- BEHAVIOURAL THERAPY (CBT) PAIN MANAGEMENT PROGRAMME

3.1 ABSTRACT

(This abstract has been published in *British Journal of Pain*, 6(2), 75. It has been reformatted to fit with the overall PhD thesis).

Background: Cognitive-behavioural therapy (CBT) for pain management seeks to identify and correct problematic behaviour patterns that can contribute to increased pain and reduced quality of life in chronic pain patients. A typical pain management programme contains sessions which focus on increasing patients' understanding of pain; training in behavioural and cognitive coping skills; and training in relaxation techniques. The goals of CBT are to change the way in which the patient thinks about their pain, and to equip patients with the tools to manage living with chronic pain. This study aimed to investigate changes in pain coping strategies and psychophysical health in a cohort of patients throughout CBT for pain management.

Methods: 360 patients attended the pain management programme at a West Midlands NHS trust regional hospital between Oct 1997 and May 2010. All patients were asked to complete the Pain Coping Strategies Questionnaire, the Hospital Anxiety

Depression Scale, the Frenchay activity questionnaire, and the Short-Form-36 general health questionnaire at baseline (pre-course), at outcome (end-course), and at follow-up (three months). In order to be included in the analysis patients were required to have completed questionnaires at a minimum of two time points (n = 195, mean age 46.2 ±10.21, range 22-68).

Results: There was a significant improvement in use of the coping strategy ‘cognitive coping/suppression’ between baseline and outcome ($p < .05$). There was also a significant decrease in the maladaptive coping strategy ‘helplessness’ between baseline and outcome ($p < .01$), which was also significant between baseline and follow-up ($p < .05$). There were also significant decreases in anxiety ($p < .01$) and depression ($p < .01$); and improvements in activity ($p < .01$), physical function ($p < .05$), social function ($p < .05$) and mental health ($p < .05$) between baseline and follow-up. Correlations of the changes in scores over time revealed that ‘cognitive coping/suppression’ was positively related to improvement in psychophysical health ($p < .05$) while ‘helplessness’ was negatively related to psychophysical health changes ($p < .05$).

Conclusion: The pain management programme has been instrumental in bringing about significant improvements in psychophysical health and daily activity of patients. It has also contributed to a significant change in coping strategies used by chronic pain patients, with an increase in ‘cognitive coping/suppression’ and a decrease in ‘helplessness’.

3.2 BACKGROUND

The West Midlands NHS trust regional hospital (henceforth: Centre A) PMP is conceptually based on the behavioural (Fordyce et al. 1968, 1973, 1984) and cognitive-behavioural models of pain (Turk et al. 1983; Flor & Turk 1984; Turk & Flor 1984). The programme has three basic elements: education; behavioural and cognitive coping strategies; and progressive relaxation training. The programme is delivered by the Centre A multidisciplinary pain clinic team, consisting of psychologist, specialist nurse, physiotherapist, and occupational therapist. The psychologist and specialist nurse are trained in CBT and experienced in applying CBT to patients who have persistent pain. This PMP has previously been shown to be effective in reducing patient anxiety and depression, improving general wellbeing, daily activity, and use of adaptive coping strategies as measured by subjective report in 95 patients (LeMarchand & Raphael 2008). Due to the small number of patients this research was underpowered and the present study will update these findings by including data from an additional 265 patients who have since attended the programme.

Upon being enrolled into the programme, patients are asked by the clinical staff to fill in several questionnaires: the Short Form 36-item general health questionnaire (SF-36); the Hospital Anxiety and Depression Scale (HADS); the Pain Coping Strategies Questionnaire (PCSQ); and the Frenchay Activities Index (FAI). Patients are asked to fill in the same questionnaires at the end of the programme, and at a follow-up session approximately three months later.

Since the inception of the CBT-based PMP at Centre A in October 1997, up until the time that this study was conducted (May 2010), the programme has been run 40 times, and 360 patients have attended.

3.2.1 Aim

The aim of this study was to assess the efficacy of the CBT-based PMP at Centre A.

3.2.2 Objectives

The objectives of this study were to gather the entire available patient generated questionnaire data together into a single dataset, and to analyse this dataset to reveal overall changes in psychosocial health and pain coping strategies from baseline to outcome and baseline to follow-up.

3.3 METHODS

3.3.1 Study Design

The study used a longitudinal retrospective design to assess the impact of a CBT-based PMP treatment upon questionnaire measures collected from patients at three time points (baseline, outcome, follow-up). In order to be included in the analysis patients were required to have completed questionnaires at a minimum of two time points.

3.3.1.1 Power calculation

To determine the required sample size, an a priori power calculation was carried out using G*Power software (version 3.1.9; Faul et al. 2007). Population effect size was estimated using the results of two large scale meta-analyses which examined the effects of CBT for pain upon behavioural measures. Morley, Eccleston, and Williams

(1999) reported significant effect sizes (median = 0.5) on all measurement domains (including pain, mood, cognitive coping, activity, and social functioning). However, a later study by the same group (Williams et al. 2012) included a larger number of studies and reported smaller effect sizes on pain (0.21), mood (0.38), disability (0.26), and catastrophising (0.53), effect on coping was not measured. The present study included a measure of pain, so estimated effect size was set conservatively at 0.21 for the power calculation. Probability of type 1 error (α) was set at 0.05 and power was set at 0.8, as is the convention suggested by Cohen (1969, 1992) that is typically used in behavioural sciences research (Sullivan & Feinn 2012).

The calculation using the above parameters reported that a sample size of 142 participants would be required for power to be above the 0.8 level.

3.3.2 Pain Management Programme Design

Outpatient programmes ran approximately three times per year, depending upon patient demand and staff availability. Patients were required to attend 12 sessions of approximately 150 minutes each, given over an 11 week period. The programme followed the same timetable (Table 3.1) and consisted of two sessions per week in the first three weeks, a two week break, and then one session per week for the remaining six weeks.

Table 3.1 Timetable of the Centre A Pain Management Programme.

Session 1 Introduction to the Programme Relatives Session Exercise Circuit Pain Journey	Session 2 Exercise Exercise & Posture talk Relaxation Theory (breathing)
Session 3 Exercise Theories of Pain Pacing Relaxation	Session 4 Exercise Goal Setting Goals Relaxation
Session 5 Exercise Art Work Being Believed Relaxation	Session 6 Exercise Coping/Fear avoidance Sleep Relaxation
Session 7 Exercise Medication Goal Review Relaxation	Session 8 Exercise Thoughts and Feelings Relaxation
Session 9 Exercise Stress Expert Patient Goal Review Relaxation	Session 10 Exercise Memory Assertiveness Relaxation
Session 11 Exercise Change Setback Planning Relaxation	Session 12 Exercise Circuit Revisit Goals What Next? Questions & Answers Relaxation

3.3.3 Questionnaires of Psychological and Health-related Variables

3.3.3.1 Short form 36-item general health questionnaire (SF36)

The SF36 questionnaire is a 36-item self-report questionnaire that measures health related functions in eight domains: general health, physical functioning, role limitations due to physical health, role limitations due to emotional problems, social functioning, bodily pain, vitality, and mental health (Ware & Sherbourne 1992). The score on each item ranges from 0 to 100, with higher scores representing better health and well-being (Hays et al. 1993).

A number of studies support reliability and validity of the SF-36 in both general (Brazier et al. 1992; McHorney et al. 1993) and patient (Garratt et al. 1993; McHorney et al. 1994) populations (discussed in detail in McDowell 2006, pp.649-665). Garratt and colleagues (1993) report good consistency between the items; correlation coefficients within the eight domains all exceed the accepted level of 0.4 (Kline 1986); internal consistency measured by Cronbach's α (Cronbach 1951) for all scales exceeds the accepted level of 0.7 (Nunnally & Bernstein 1994). The SF-36 has also been shown to be sensitive to changes in patient health over a course of treatment (Kopjar 1996; Hemmingway et al. 1997).

3.3.3.2 Hospital anxiety and depression scale (HADS)

The HADS consists of 14 self-scored items designed to assess levels of anxiety and depression. Each item is related to either symptoms of anxiety or depression and has four responses which are scored from 0 to 3 according to symptom severity (e.g. I feel tense and wound up: most of the time (3); a lot of the time (2); from time to time (1); not at all (0)). The HADS consists of two independent scales: anxiety (HADS-A) and depression (HADS-D), each with seven items, leading to a score between 0 and 21. A score of 0 to 7 is considered normal; 8 to 10 suggests the presence of the mood

disorder; a score 11 or higher indicates a valid case of anxiety or depression (Zigmond & Snaith 1983; Snaith 2003).

The HADS has been validated against psychiatric interviews (Zigmond & Snaith 1983) and against other scales for the measurement of anxiety and depression (Aylard 1987) in patient groups. A review of 747 studies using the HADS concluded that it was a suitable measure for assessing anxiety and depression in both patient and healthy populations (Bjelland et al. 2002). Internal consistency of both subscales has been verified in a study of a large mixed sample of 64,648 persons, which reported a Cronbach's α of 0.80 for HADS-A and 0.76 for HADS-D (Mykletun et al. 2001).

3.3.3.3 Pain coping strategies questionnaire (PCSQ)

The PCSQ is a self-administered, 44-item questionnaire designed to elicit which cognitive and behavioural coping strategies are put into use when an individual experiences pain (Rosenstiel & Keefe 1983). 42 of the items are rated by the responder on the same 7-point Likert-type scale ranging from 0 (never do) to 6 (always do that) in response to statements designed to assess six different coping strategies (diverting attention, reinterpreting pain, catastrophising, ignoring sensations, praying or hoping, coping self-statements, increased activities). The final two items: 'control over pain' and 'ability to decrease pain' are also scored on a 7-point scale. Scores from subscales are combined to generate three coping factors: cognitive coping/suppression (reinterpreting + ignoring + coping); helplessness (catastrophising - increased activities - control - ability); and diverting attention/praying (diverting attention + praying), with higher scores indicating greater use of the coping strategy.

The PCSQ was developed in conjunction with samples of chronic LBP patients (Rosenstiel & Keefe 1983), however it has since been shown to be a valid tool for use in a variety of chronic pain conditions including rheumatoid arthritis, diabetic neuropathy, cancer, chronic headache, and neuralgia (Keefe et al. 1989; Lawson et al. 1990; Geisser et al. 1994; Snow-Turek et al. 1996). Rosenstiel and Keefe (1983) reported that the subscales all have satisfactory internal consistency, with Cronbach's α scores all above 0.7.

The 6-item catastrophising scale within the PCSQ was used to assess pain catastrophising in participants. The score was the total of all 6 items, with higher scores indicating a higher degree of catastrophising. This subscale has been reported to be the most useful measure of catastrophising, when compared to other psychometric tools in a sample of LBP patients (Main & Waddell 1991).

3.3.3.4 Frenchay activities index (FAI)

The FAI is a 15-item self-report questionnaire that provides a measure of everyday activities of normal living (Holbrook & Skilbeck 1983). The total score reflects overall lifestyle activity, with higher scores conferring greater activity. The scale was originally developed for use in stroke patients, and has been found to be suitable for use in that population; with acceptable internal reliability (Cronbach's $\alpha > .7$) (Schuling et al. 1993). The FAI has also been assessed for reliability and validity in a large sample drawn from the general population (Turnbull et al. 2000); this study reported that the scale has high test-retest reliability, and good construct validity, particularly in middle aged and elderly people. The FAI contains items relating to very basic activities (such as housework) and is sensitive to changes in patient groups whose basic daily activities are compromised as a result of illness.

3.3.4 Participants

360 patients attended one of the 40 programmes between October 1997 and May 2010. Patients were included in the analysis if they had completed questionnaires at baseline, and either outcome, or follow-up time points, in order to maximise the data available for paired comparisons. Patients who had completed questionnaires at only one time point were excluded.

3.3.5 Data Processing and Analysis

Questionnaires were scored according to their prescribed marking schemes. Raw scores were recorded using Excel 2007 (Microsoft, Redmond, WA) and further analysis was performed with SPSS 20 (Statistics Package for the Social Sciences, IBM, Chicago, IL). The data were analysed as two separate datasets, the first dataset containing data from pairs of baseline and outcome questionnaires (baseline/outcome), and the second dataset containing data from pairs of baseline and follow-up questionnaires (baseline/follow-up). Paired comparisons were computed using Student's related samples *t*-test. Effect sizes were calculated using Cohen's *d* (Cohen 1969, 1992). Correlations between changes in scores from baseline to outcome and baseline to follow-up were calculated using the Pearson product-moment *r* correlation. Cases with missing data points were excluded from the analyses in a pair-wise fashion.

3.4 RESULTS

195 patients completed or part-completed questionnaires at baseline and at least one other time point (mean age = 46.2 ±10.21, age range = 22-68), 123 (63%) females and 72 (37%) males. 132 completed questionnaires at the baseline and outcome time points; 123 at baseline and follow-up; (60 at all three time points). Overall means and standard deviations are shown for each subscale in Table 3.2.

Table 3.2 Descriptive statistics of scores on all scales at the three time points.

Questionnaire (Subscale)	Baseline	Outcome	Follow-up
	Mean (n) ±SD	Mean (n) ±SD	Mean (n) ±SD
SF36 (General health)	33.6 (195) ±15.2	35.8 (141) ±16.3	34.7 (128) ±16.6
SF36 (Physical functioning)	23.2 (195) ±20.1	25.6 (141) ±20	25.8 (128) ±21.8
SF36 (Role limitations due to physical health)	13.9 (195) ±16.9	17.6 (141) ±19.5	14.4 (128) ±20.0
SF36 (Role limitations due to emotional problems)	30.3 (195) ±40.6	34.0 (141) ±40.7	37.5 (128) ±42.7
SF36 (Social functioning)	37.6 (195) ±23.3	42.0 (141) ±22.1	41.7 (128) ±23.4
SF36 (Bodily pain)	23.7 (195) ±16.9	24.6 (141) ±15.6	24.9 (128) ±14.9
SF36 (Vitality)	24.5 (195) ±17.3	27.1 (141) ±17	27.6 (128) ±16.8
SF36 (Mental health)	47.9 (195) ±18.7	53.7 (141) ±19.4	52.9 (128) ±18.1
HADS (Anxiety)	11.7 (164) ±4.3	10.6 (108) ±4	10.4 (96) ±3.9
HADS (Depression)	10.4 (164) ±3.7	9.8 (108) ±3.6	9.6 (97) ±4.1
FAI	23.9 (172) ±9.1	22.8 (116) ±8.9	26.3 (99) ±9.2
PCSQ (Catastrophising)	17.0 (164) ±8.6	14.8 (107) ±7.9	15.1 (95) ±8
PCSQ (Cognitive coping /suppression)	33.7 (164) ±17.6	36.1 (107) ±18	36.3 (95) ±18.8
PCSQ (Helplessness)	-1.5 (164) ±11.8	-6.7 (107) ±11.7	-4.1 (95) ±12.5
PCSQ (Diverting attention/praying)	23.9 (164) ±13.2	24.5 (107) ±12.6	24.9 (95) ±13.5

SD = Standard Deviation; SF36 = Short form 36 item general health survey; PCSQ = Pain coping strategies questionnaire; HADS = Hospital Anxiety and Depression Scale; FAI = Frenchay Activities Index.

3.4.1 Differences between Baseline and Outcome Scores

Between baseline and outcome, paired *t*-tests revealed a significant difference in scores of: the general health, social functioning, and mental health subscales of the SF36; the anxiety subscale of the HADS; and in the catastrophising subscale, and cognitive coping/suppression and helplessness factors of the PCSQ (Table 3.3).

Table 3.3 Baseline and outcome questionnaire scores from patients in the Centre A PMP, significance values shown for paired *t*-tests.

Questionnaire (Subscale)	Baseline Mean ±SD	Outcome Mean ±SD	Paired <i>t</i> -test outcome	Effect size (Cohen's <i>d</i>)
SF36 (General health)	32.7 ±15.1	35.1 ±16.3	<i>t</i> = -2.7, <i>df</i> (131), <i>p</i> = .008*	-0.24 ^s
SF36 (Physical functioning)	25.0 ±21.2	26.2 ±20.3	<i>t</i> = -0.8, <i>df</i> (131), <i>p</i> = .447	-0.07
SF36 (Role limitations due to physical health)	14.7 ±15.6	17.7 ±20.1	<i>t</i> = -1.7, <i>df</i> (131), <i>p</i> = .101	0.14
SF36 (Role limitations due to emotional problems)	28.5 ±40.0	34.8 ±41.2	<i>t</i> = -1.7, <i>df</i> (131), <i>p</i> = .093	0.15
SF36 (Social functioning)	37.7 ±22.5	42.0 ±22.3	<i>t</i> = -2.5, <i>df</i> (131), <i>p</i> = .014*	-0.22 ^s
SF36 (Bodily pain)	23.5 ±16.0	24.6 ±15.8	<i>t</i> = -0.7, <i>df</i> (131), <i>p</i> = .470	0.06
SF36 (Vitality)	24.7 ±16.6	26.9 ±17.0	<i>t</i> = -1.4, <i>df</i> (131), <i>p</i> = .172	-0.12
SF36 (Mental health)	48.3 ±18.9	54.0 ±19.7	<i>t</i> = -3.6, <i>df</i> (131), <i>p</i> < .001*	-0.31 ^s
HADS (Anxiety)	12.0 ±4.5	10.7 ±4.1	<i>t</i> = 4.2, <i>df</i> (103), <i>p</i> < .001*	0.41 ^s
HADS (Depression)	10.4 ±3.6	9.8 ±3.7	<i>t</i> = 1.8, <i>df</i> (103), <i>p</i> = .077	0.17
FAI	23.3 ±8.4	22.7 ±9.1	<i>t</i> = 0.8, <i>df</i> (99), <i>p</i> = .416	0.08
PCSQ (Catastrophising)	16.8 ±8.0	14.9 ±8.0	<i>t</i> = 2.5, <i>df</i> (102), <i>p</i> = .015*	0.24 ^s
PCSQ (Cognitive coping /suppression)	32.8 ±17.0	36.1 ±18.2	<i>t</i> = -2.5, <i>df</i> (102), <i>p</i> = .016*	-0.24 ^s
PCSQ (Helplessness)	-1.7 ±11.0	-6.4 ±11.8	<i>t</i> = 4.9, <i>df</i> (102), <i>p</i> < .001*	0.48 ^s
PCSQ (Diverting attention/praying)	23.1 ±12.4	24.7 ±12.4	<i>t</i> = -1.8, <i>df</i> (102), <i>p</i> = .072	-0.18

SD = Standard Deviation; SF36 = Short form 36 item general health survey; PCSQ = Pain coping strategies questionnaire; HADS = Hospital Anxiety and Depression Scale; FAI = Frenchay Activities Index; * = significant difference between scores ($\alpha = .05$); ^s = small effect size ($d = 0.2-0.5$).

3.4.2 Differences between Baseline and Follow-up Scores

Between baseline and follow-up, paired *t*-tests revealed a significant difference in scores of: physical functioning and mental health subscales of the SF36; anxiety and depression subscales of the HADS; daily activity measured by the FAI; and the helplessness factor of the PCSQ (Table 3.4).

Table 3.4 Baseline and follow-up questionnaire scores from patients in the Centre A PMP, significance values shown for paired *t*-tests.

Questionnaire (Subscale)	Baseline Mean ±SD	Follow-up Mean ±SD	Paired <i>t</i> -test outcome	Effect size (Cohen's <i>d</i>)
SF36 (General health)	34.5 ±16.0	34.5 ±16.8	$t = 0.04, df(122), p = .970$	0.003
SF36 (Physical functioning)	22.4 ±19.9	26.1 ±22.3	$t = -2.1, df(122), p = .043^*$	-0.18
SF36 (Role limitations due to physical health)	14.7 ±19.0	14.4 ±20.3	$t = 1.2, df(122), p = .903$	-0.01
SF36 (Role limitations due to emotional problems)	33.6 ±41.3	36.9 ±42.4	$t = -0.8, df(122), p = .416$	0.07
SF36 (Social functioning)	37.2 ±23.9	40.9 ±23.3	$t = -1.7, df(122), p = .085$	-0.16
SF36 (Bodily pain)	24.6 ±17.0	25.1 ±15.0	$t = -0.4, df(122), p = .689$	0.04
SF36 (Vitality)	25.9 ±17.9	27.1 ±16.6	$t = -0.7, df(122), p = .467$	-0.07
SF36 (Mental health)	48.8 ±18.6	52.7 ±18.4	$t = -2.5, df(122), p = .013^*$	-0.23^s
HADS (Anxiety)	11.4 ±4.2	10.3 ±3.9	$t = 3.1, df(91), p = .003^*$	0.32^s
HADS (Depression)	10.4 ±3.6	9.6 ±4.1	$t = 2.8, df(91), p = .006^*$	0.29^s
FAI	24.7 ±9.2	26.4 ±9.4	$t = -2.8, df(91), p = .007^*$	-0.29^s
PCSQ (Catastrophising)	16.7 ±8.9	15.2 ±8.1	$t = 1.9, df(89), p = .058$	0.20
PCSQ (Cognitive coping /suppression)	32.8 ±17.0	36.5 ±19.2	$t = -1.6, df(89), p = .104$	-0.17
PCSQ (Helplessness)	-2.0 ±12.4	-4.1 ±12.6	$t = 2.1, df(89), p = .038^*$	0.22^s
PCSQ (Diverting attention/praying)	25.2 ±13.8	24.9 ±13.1	$t = 0.3, df(89), p = .781$	0.03

SD = Standard Deviation; SF36 = Short form 36 item general health survey; PCSQ = Pain coping strategies questionnaire; HADS = Hospital Anxiety and Depression Scale; FAI = Frenchay Activities Index; * = significant difference between scores ($\alpha = .05$); ^s = small effect size ($d = 0.2-0.5$).

3.4.3 Correlations between Changes in Scores from Baseline to Outcome and Baseline to Follow-up

From baseline to outcome, the increase in scores on the cognitive coping and suppression factor of the PCSQ was correlated with improvements in physical functioning, role limitations due to physical health, and a decrease in depression (Table 3.5). The decreases in scores on the catastrophising and helplessness factors were correlated with improvement in scores of: general health, role limitations due to physical health, role limitations due to emotional problems, bodily pain, mental health, anxiety, and depression. The increase in scores on the diverting attention/praying factor was positively correlated with change in FAI scores.

From baseline to follow-up, the change in helplessness scores correlated with mental health and depression. Also, the increase in scores on the diverting attention/praying factor was positively correlated with change in FAI scores.

Table 3.5 Correlations (Pearson's *r*) between the changes in factor scores on the PCSQ, and subscales on the SF36, HADS, and FAI, from baseline to outcome, and baseline to follow-up

PCSQ factor:	Catastrophising	Cognitive coping /suppression	Helplessness	Diverting attention/praying
Baseline/Outcome (N)				
(SF36) General Health (99)	-.21**	-	-.20*	-
Physical Functioning (99)	-	.26*	-	-
Role limitations due to Physical health (99)	-.31**	-	-.29**	-
Role limitations due to Emotional problems (99)	-	.42**	-.35**	-
Social Functioning (99)	-	-	-	-
Bodily Pain (99)	-.33**	-	-.25*	-
Vitality (99)	-	-	-.21*	-
Mental Health (99)	-.37**	-	-.33**	-
(HADS) Anxiety (103)	.37**	-	.41**	-
(HADS) Depression (103)	.36**	-.22*	.45**	-
FAI (91)	-	-	-	.22*
Baseline/Follow-up (N)				
(SF36) Mental Health (90)	-	-	-.28**	-
(HADS) Depression (90)	-	-	.24*	-
FAI (84)	-	-	-	.25*

SF36=Short form 36 item general health survey; PCSQ=Pain coping strategies questionnaire; HADS=Hospital Anxiety and Depression Scale; FAI = Frenchay Activities Index; * = $p < .05$, ** = $p < .01$.

3.5 DISCUSSION

In this study of 195 patients attending a CBT-based PMP, there were small but significant improvements in several measures of psychophysical health and pain coping strategies between baseline/outcome and baseline/follow-up. Scores on domains of mental health, anxiety, and helplessness improved significantly between both baseline/outcome and baseline/follow-up. However, significant improvements in general health, social functioning, catastrophising, and cognitive coping/suppression that occurred between baseline/outcome were not observed between baseline/follow-up. Conversely, there were significant improvements in measures of physical function, daily activity, and depression between baseline/follow-up that were not observed between baseline/outcome.

Looking at improvements made from baseline to outcome, the immediate benefit of attending the PMP was to change patients' use of coping strategies and improve their perceived general physical and mental health. Use of the maladaptive coping strategies of catastrophising and helplessness (which are closely related) significantly decreased, while use of the positive coping strategy – cognitive coping/suppression – increased significantly. These results agree with the Cochrane review of CBT for pain management (A. Williams et al. 2012), which found the treatment was effective in improving measures of mood and catastrophising. Catastrophising has consistently been associated with increased pain and psychophysical dysfunction in patient groups (Sullivan et al. 2001; Turner et al. 2002). This study has revealed that change in catastrophising scores are negatively correlated with change on psychophysical health domains including bodily pain, anxiety, and depression. Whether the change in catastrophising represents the cause or the effect of psychophysical improvement

in patients is unclear due to the correlational nature of the data used. Taken together, these findings confirm that the CBT components of the PMP, such as goal setting, coping with pain, fear avoidance, coping with stress, and relaxation, are effective in bringing about positive mental health changes in patients pre- to post-treatment.

Alongside CBT, the PMP also contained a substantial physical component: every session began with 15-20 minutes of physiotherapy. At outcome, physical domain scores had not improved compared to baseline; however at follow-up, scores on the physical functioning scale of the SF36 and on the FAI significantly improved compared to baseline. This data suggests that physical improvement may not be an immediate benefit of attending a PMP, with the benefit emerging over a longer period of time. Patients' also reported better mental health, less anxiety and depression, and reduced helplessness at follow-up compared to baseline. Mental health improvements were also observed between baseline and outcome, suggesting that the mental health benefits are maintained after the treatment program has ended. Perceived reduction in disability and increased daily activity may contribute to long-term maintenance of mental health improvements: a recent overview of Cochrane reviews (Geneen et al. 2017) reported that exercise and physical activity was linked to positive effects on mental health and quality of life in chronic pain patients.

3.5.1 Limitations

There were some methodological limitations to the study. Firstly, given the longitudinal nature of the available data, collected at three time-points, an ideal method of analysis would have been repeated-measures ANOVA. To make the best use of the available data, to maximise group size and statistical power, the present study instead used paired *t*-tests to compare patient scores between baseline/outcome and baseline/follow-up, meaning that change in scores between outcome/follow-up

was not directly measured. To put into context the lack of data available to perform a repeated-measures ANOVA: of the 195 patients studied, only 60 (partially) filled in questionnaires at all three time-points (25 fully completed all questionnaires at all time-points). This meant that there were a large number of absent data points that could not be corrected without making significant assumptions. The retrospective design of the study makes missing data an inevitable and unavoidable problem. A second limitation to the study is that data regarding the patients' diagnosed pain condition was not collected. It is possible that if patients had been grouped according to disease or disorder there may have been differential effects of the treatment upon collected measures. Such information would be of benefit to clinical decision making regarding treatment options. However, some have argued that disease phenotype is not helpful in predicting how a patient will respond to psychological interventions, and a more relevant approach to classification is on the basis of psychological factors (Turk 1990, 2005; Vlaeyen & Morley 2005). Such classification could reveal patient groups that respond better to treatment, however the criteria for classification are not yet clear (Kindermanns et al. 2011; Morley et al. 2013).

3.5.2 Directions for Future Study

One aspect of psychology to explore in future study is the patients' beliefs regarding locus of control, and how this changes from pre- to post-treatment (Rotter 1966). Patients who believe outcomes to be controlled by chance are more likely to use maladaptive coping strategies (Crisson & Keefe 1998); those who believe pain is controlled by external factors tend to score more highly on measures of disability (Turner et al. 2002) and respond worse to treatment (Tota-Foucette et al. 1993); and patients who have a more internal locus of control report their pain as less intense and frequent (Toomey et al. 1991) and respond better to treatment (Lame et al.

2008). Given this evidence that locus of control is a contributing factor to psychophysical health and treatment efficacy in patients, its measurement should be included in future investigations of PMP efficacy.

Another direction for future study concerns the method used to measure the effect of treatment. It is important to note that despite the treatment having some significant effects upon questionnaire measures between the time-points, these effects were generally small (i.e. less than half of one standard deviation). Effect sizes reported by previous studies of CBT for pain management (reviewed in A. Williams et al. 2012) were also of similar magnitude. For a treatment that has been in widespread use for over 25 years, it is unclear why the effect on patients' perceived health status is not greater. It is possible that patients who have been living with chronic pain, which often presents without overt physical evidence and is not responsive to treatment, may develop a pattern of behaviour which seeks validation of their condition from healthcare staff. The patients' may be reluctant to report significant health improvements in case it results in withdrawal of treatment; therefore, even following several weeks of treatment in a PMP, only small effects are observed on these subjectively reported measures of health. This subjectivity is a drawback to using self-report questionnaires, which are the *de facto* gold-standard for measuring the efficacy of psychological treatment.

The next chapter explores the possibility of measuring the effect of a PMP using a more objective method, in the form of EEG, as suggested by literature reviewed in Sections 2.7–2.9.

CHAPTER 4

EEG MEASURES OF PAIN PROCESSING IN PATIENTS BEFORE AND AFTER ATTENDING A COGNITIVE- BEHAVIOURAL THERAPY (CBT) PAIN MANAGEMENT PROGRAMME

4.1 ABSTRACT

Background: The Centre A pain management programme (PMP) has previously been shown to bring about significant improvements in questionnaire measures of psychophysical health and pain coping strategies in a large sample (Chapter 3). Studies reviewed in Sections 2.7-2.9 suggest that neurophysiological differences exist between patient and healthy groups, and also that cortical electrical activity can change following treatment. In the present study, patients from the Centre A PMP underwent periods of EEG recording during experimentally induced pain, both before and after treatment, to investigate the effect of treatment upon the cortical response to pain.

Methods: Two studies were carried out. In study A, EEG recording of the cortical response to brief, painful contact heat stimulation was conducted in a sample of 12 patients, both before and after attending a CBT-based PMP. Low-frequency, high-frequency, and conditioned pain modulation conditions were used. Evoked response potentials (ERPs) were extracted from EEG data for comparison. In study B, continuous EEG recording was carried out at rest and following medium duration (90s) tonic painful stimulation using the cold pressor test. Recording sessions were

carried out with 12 patients, both before and after attending a CBT-based PMP; and also with 14 healthy control participants over a 12 week period. Participants also filled in questionnaires to measure psychophysical health and pain coping strategies, as per the earlier study (Chapter 3), including a measure of locus of control.

Results: Study A: Group mean ERPs were not significantly affected either by the different stimulation conditions, or by the treatment programme. There were a few significant effects at an individual level, however these did not show any consistent pattern across the sample. *Study B:* In the patient group, paired *t*-tests revealed the effect of cold pressor pain pre-PMP to be significant reductions in θ - and α - power ($p < .05$). There were no significant effects of cold pressor pain post-PMP. There were no significant effects of cold pressor pain in the healthy control group. Behavioural data from the patient group showed a significant improvement in general health, anxiety, depression, catastrophising and helplessness scores from pre- to post-PMP ($p < .05$), there was no effect upon the measure of locus of control. Questionnaire scores did not change significantly in the control group.

Conclusion: The effect of cold pressor pain upon θ - and α -activity is modulated following a CBT-based PMP. This may be due to a change in cognitive appraisal of painful signals brought about by taking part in the PMP, supported by the reduction in catastrophising and feelings of helplessness post-PMP. Patients also learned relaxation techniques for dealing with periods of increased pain, which they may have employed during cold pressor pain, and which may have contributed to the observed stability of θ - and α -power measured post-PMP. Results imply the possibility of an objective measure of the outcome of psychological therapy for chronic pain. Data should be collected from a waiting-list control group in order to confirm findings.

4.2 BACKGROUND

Previous studies, reviewed in Sections 2.7–2.9, demonstrated that neurophysiological differences in pain processing (measured using EEG) exist between chronic pain patient and healthy groups, and also that measurable changes can occur from pre- to post-treatment. This chapter describes two studies carried out to investigate the effect of a CBT-based PMP on EEG measures of pain processing. Participants underwent EEG test sessions before and after they had attended a CBT-based PMP which has proven efficacy in improving psychophysical health and pain coping strategies from baseline to outcome (see Chapter 3). The first study (Study A) investigated the effect of the treatment upon ERPs in response to brief painful stimulation. The second study (Study B) investigated the effect of treatment upon EEG power spectral density (PSD) over a period of continuous EEG recording, both at rest and following continuous painful stimulation.

4.2.1 Choice of Stimuli

4.2.1.1 Brief (phasic) painful stimulation

Early studies used a CO₂ laser to rapidly heat a small area of skin at around 10,000°C/sec (Carmon et al. 1976), and this method continues to be used by some researchers; however the device must be carefully controlled by a skilled operator to avoid the danger of damage to the skin. A method which is far safer and easier to control is contact heat stimulation (Contact Heat Evoked Potential Stimulator; CHEPS: Medoc, Ramat Yishai, Israel). The CHEPS equipment delivers contact heat stimulation using a thermode (a heating thermo-foil covered with a 25µm layer of thermo-conductive plastic) which is placed into contact with the skin and heated using electrical current. The thermode is programmed to heat rapidly (70°C/sec) to a

pre-set temperature and is then cooled immediately (at 40°C/sec) by heat exchange with a coolant pumped into the thermode. This process ensures a controlled stimulus is delivered for an extremely brief duration (100 ms) at sufficient intensity to induce an evoked response. As the whole process is computer controlled, the system will deliver identical repeated stimuli to every participant. Further safety measures incorporated into the CHEPS are a maximum thermode temperature of 55°C, computer controlled safety checks carried out before each block of trials, and an emergency stop button which is easy to identify and activate. The CHEPS equipment has been used numerous times in both healthy (e.g. A.C.N. Chen et al. 2001; LePera et al. 2002; Greffrath et al. 2007; Warbrick et al. 2009) and patient (Atherton et al. 2007; Chi et al. 2008; Truini et al. 2007; Staud et al. 2008) samples, no problems have ever been reported.

To ensure that the intensity of stimulation is sufficient to generate a feeling of pain in the participant, it is common to either use a range of stimulus intensities during the experiment, each of which are rated using a verbal or numerical scale; or to carry out a pre-test in which participants are exposed to the stimulus at varying intensities, so that a painful level may be agreed upon before collecting ERP data.

4.2.1.2 Continuous (tonic) painful stimulation

Experimentally induced pain of moderate intensity and medium duration can be set up using a number of methods. Three choices are available: chemical, muscle fatigue, and temperature. Chemically induced pain using capsaicin is difficult to control, often resulting in prolonged skin irritation and distress. Muscle fatigue induced by performing muscle work (such as squeezing a tennis ball) whilst restricting blood flow using a tourniquet, results in a moderate to high intensity pain due to ischaemia. As the participant controls of the intensity of the stimulation, it is

difficult to ensure similar levels of stimulation across participant groups. A more reliable method of inducing tonic pain at a consistent level in all participants is by immersion of the hand into cold water (~4°C) for a set time period. This method is known as the cold pressor test (CPT; Hilgard 1975). A water bath is prepared and maintained at constant temperature by the addition of ice. After the participant has immersed their hand in the water for a few minutes, they experience a medium intensity pain which continues for 5-10 minutes. The CPT carries no risk of lasting damage, a little reddening of the skin is to be expected but this returns to normal within 5-10 minutes of withdrawing the hand from the water. The effects of the CPT have been thoroughly investigated (Walsh et al. 1989) and this method has been used as an experimental pain stimulus in numerous studies (A.C.N. Chen et al. 1989; Russ et al. 1999; Mitchell et al. 2004; Arendt-Nielsen et al. 2008).

4.2.2 General Aspects

The studies were approved by the National Research Ethics Service Committee West Midlands-Solihull (granted: 15/12/2011, ref: 11/WM/0407) and the Research and Development committees at Russells Hall Hospital, Dudley (granted: 14/02/2012, ref: ID1004), and was sponsored by Birmingham City University (granted: 24/10/2011). The study protocol, participant information sheets, and informed consent forms were all approved by the above NHS research ethics committees.

4.3 STUDY A: THE EFFECT OF PMP TREATMENT UPON CONTACT HEAT EVOKED POTENTIAL MEASURES

A.1 BACKGROUND

Previous studies have shown that sensitisation to repetitive heat stimuli, as measured by verbal self-report of pain intensity, occurs in healthy subjects at stimulation frequencies greater than 0.33 Hz (Price et al. 1977; Herrero et al. 2000; Kleinbohl et al. 2006; Meeus & Nijs 2007). Studies have also shown that sensitisation occurs at lower frequencies in chronic pain patients suffering from fibromyalgia (Staud et al. 2001), osteoarthritis (Arendt-Nielsen et al. 2010), whiplash (Curatolo et al. 2001), migraine (Weissman-Fogel et al. 2003), temporomandibular disorder (Sarhani et al. 2004), and chronic fatigue syndrome (Meeus & Nijs 2007). The present study explored sensitisation using CHEPs as a measure of pain intensity instead of a verbal rating. A number of studies have demonstrated a significant positive correlation between the amplitude of pain ERPs and the subjective perception of pain intensity using contact heat stimuli (A.C.N. Chen et al. 2001; A.C.N. Chen et al. 2002; LePera et al. 2002; Granovsky et al. 2005, 2006, 2008; Greffrath et al. 2007; Roberts et al. 2008). The effect of conditioned pain modulation (CPM) has previously been shown to attenuate ERP amplitudes in both healthy (A.C.N. Chen et al. 1985; Reinert et al. 2000) and patient groups (Quante et al. 2008). How multidisciplinary pain treatment affects ERP amplitudes has not previously been studied.

This study was designed to investigate CHEP amplitudes in chronic pain patients, under three conditions measured before and after PMP treatment. The first condition

measured ERPs during low-frequency painful stimulation, where stimuli were presented every 6-8 seconds. The relatively long period between stimuli was chosen to mitigate any effects of habituation and sensitisation upon ERPs, and this condition provided a reference ERP amplitude for comparison with the next two conditions. In second condition, stimuli were presented at a high-frequency, every 4-6 seconds, in order to reveal any increase in ERP amplitudes as a result of sensitisation, which is enhanced in chronic pain patients (Brown & Jones 2009; de Tommaso et al. 2010), and which may also be related to pain catastrophising (Granot et al. 2006; George et al. 2007). The third condition used a conditioned pain modulation paradigm (Yarnitsky et al. 2010) where tonic pain was induced using the CPT, and contact heat stimuli were then presented at a low-frequency. This condition was used to investigate the presence or absence of DNICs (see Section 2.7.2.5).

A.1.1 Aim

The aim of this study was to assess CHEPs in patients pre- and post-treatment in the CBT-based PMP at Centre A.

A.1.2 Objectives

The objectives of this study were to measure CHEPs under conditions of low- and high-frequency stimulation and under a conditioned pain modulation paradigm, and to investigate how the differences between measures changed from pre- to post-treatment. Questionnaire data was collected to verify the efficacy of the treatment in the patients studied.

A.2 METHODS

A.2.1 Study Design

The study used a prospective cohort design to assess the impact of a CBT-based PMP treatment upon CHEPs and questionnaire measures collected from patients at two time points (baseline and outcome).

A.2.1.1 Power calculation

Optimum group size was calculated using the software application G*Power 3.1.2 (Faul et al. 2007) and with advice from Peter Nightingale, a statistician at University Hospitals Birmingham NHS Foundation Trust. In order to detect a large effect size (d) of 0.8 (Cohen 1988) from a two-tailed paired test, with a type-I error probability of 0.05, the required group size was calculated to be 19–24.

A.2.2 Stimulation Equipment

Contact heat stimulation was delivered using the Contact Heat Evoked Potential Stimulator (CHEPS; Medoc, Ramat Yishai, Israel). Heat pain tolerance thresholds were assessed using a peltier-based thermode with a 30x30 mm thermo-sensory stimulator (PATHWAY model ATS). Contact heat stimulation for the generation of ERPs was delivered by a circular thermode with an area of 572.5mm², and a heating thermo-foil (Minco Products Inc., Minneapolis, MN) covered with a 25μm layer of thermo-conductive plastic (Kapton®, thermal conductivity at 23°C of 0.1–0.35 W/m/K). Two thermocouples are embedded 10 μm within this conductive coating, which contacts the skin directly, thus providing an estimate of the skin temperature at the thermode surface (Granovsky et al. 2008). The maximum thermode heating rate was 70°C/s (~200ms to reach 51°C from 32°C baseline) and the maximum cooling rate was 40°C/s.

Tonic cold pain was induced using the standard cold pressor test (CPT) procedure (Hines & Brown 1932; Wolf & Hardy 1941; Walsh et al. 1989). A water bath was prepared and maintained at 4°C (\pm 1°C) by the addition of ice crystals.

A.2.3 EEG Equipment Setup

EEG data was recorded using a 10 channel system (VAmP, BrainProducts, Munich, Germany). The EEG cap consisted of 9 Ag/AgCl scalp electrodes distributed according to the 10–20 system (AFz (ground), Fz, FCz (reference), Cz, Pz, C3, C4, T7, T8) with one additional electrode attached below the left eye (on the lower orbital portion of the orbicularis oculi muscle) for detection of eyeblink artefacts. Data was sampled at 2 kHz, using FCz as a reference. Impedance at all recording electrodes was less than 10 k Ω . The amplified EEG signals were transmitted to a recording computer running Brain Vision Recorder software version 1.10 (BrainProducts, Munich, Germany), where it was down sampled to 500 Hz and saved to disk. The EEG recording software received stimulus timing information from the CHEPS equipment via a cable which was connected to the EEG amplifier.

A.2.4 Participants

12 participants (10 female, 2 male, mean age = 52, range = 39–64) were recruited consecutively from the population of chronic pain patients who had been enrolled into the PMP at Centre A. Test sessions took place at Centre A and were carried out in two-week periods before and after patients attended the 11-week CBT-based PMP (described in Chapter 3). All data was collected by the author. For the duration of the test session, participants sat in a quiet, dimly lit room. Participants were fitted with EEG recording equipment and given time to become familiar with the contact heat and cold water bath stimuli prior to testing. This ensured that participants were as relaxed as possible once recording began and also that participants were used to the

stimuli, thus minimising any brain activity related to the novelty of the stimuli, which has been shown to affect ERPs in previous studies (Granovsky et al. 2005; Iannetti et al. 2008; Legrain et al. 2012).

A.2.5 Calibration of Contact Heat Testing Temperature

In order to determine the testing temperature, heat pain tolerance thresholds were measured with the thermo-sensory stimulator applied to the right volar forearm and held firmly in place by the investigator. This step also allowed the participants to become familiar with the equipment and contact heat sensations. Pain tolerance thresholds were assessed using the 'Limits' programme provided with PATHWAY software version 4.0.11.0 (Medoc, Ramat Yishai, Israel). The thermo-sensory stimulator temperature was increased from 32°C at a rate of 1°C/sec to a maximum of 52°C. This heating rate was chosen to minimise any artificially high readings caused by reaction time (i.e. as the temperature continues to rise during the reaction time between subjective tolerance and button press, which has previously been found to be an issue with rates > 2°C/sec; Yarnitsky & Ochoa 1990). Pain tolerance threshold was defined as the point at which the subject could no longer tolerate the pain. Participants were asked to press a button indicating when this point had been reached. Participants were shown the following scale as a reference: 0, no pain; 1, slight intense; 2, mild intense; 3, moderate intense; 4, slight pain (pain threshold); 5, mild pain; 6, moderate pain; 7, moderate–strong pain; 8, strong pain; 9, severe pain; 10, unbearable pain (Niddam et al. 2001). The thermo-sensory stimulator was programmed to return to baseline at a rate of 5°C/sec once the button had been pressed. The procedure was repeated three times in order to generate a mean value. The thermode was moved after each stimulus to one of three adjacent, non-overlapping locations on the right volar forearm.

The temperature set point for the phasic heat stimulation trials was then calibrated. This was the temperature which consistently elicited a rating from the participant of 7 out of 10 on the NRS. This rating was selected based on previous studies which used a range of temperatures and collected ratings for each level, finding that an average rating of between 5.8 and 6.5 on an 11-point NRS was required to consistently elicit CHEPs (A.C.N. Chen et al. 2001; LePera et al. 2002; Granovsky et al. 2005; I.A. Chen et al. 2006). Using the 'Pulses' programme provided with the PATHWAY software, 5 consecutive stimuli (inter-stimulus interval (ISI) 4-6s) were delivered at the tolerance threshold temperature and the participant was asked to verbally rate the pain intensity immediately after each stimulus was felt (thermode moved after each stimulus). If the rating was consistently below 7, the temperature was increased by 1°C for another 5 stimuli. If the rating was above 7, the temperature was reduced by 1°C for another 5 stimuli. The process was repeated until the desired temperature was reached, or until the maximum temperature of the stimulator (55°C) was reached. This set the temperature to be used during both test sessions, therefore this part was not repeated during the outcome session.

A.2.6 CHEPS Stimulation and Recording

CHEPs were recorded in three blocks of trials, each consisting of 30 consecutive stimuli at the test temperature (Figure 4.1). In order to investigate the effect of the frequency of stimulation, the first block of trials used a variable ISI of 6-8s (low-frequency) and the second block used a variable ISI of 4-6s (high-frequency) delivered to the right volar forearm. When the thermode temperature passed 37°C a signal was sent from the CHEPS machine to the EEG amplifier to indicate the onset of each stimulus. In order to reduce the peripheral habituation effect caused by nociceptor fatigue, the thermode was moved to one of three adjacent, non-

overlapping locations after every two pulses (Mayhew et al. 2013). There was a break of two minutes between blocks.

A.2.6.1 Conditioned pain modulation: CHEPS and cold pain stimulation

The CPT described earlier was used to induce a tonic pain stimulus lasting around 10 minutes. Participants were asked to place their left hand and wrist into the cold water bath for a period of 90 seconds. EEG data was not recorded during the CPT procedure due to the risk of EEG data contamination from involuntary body movements and facial muscle activity caused by exposure to the cold water bath. Previous work has shown that the effect of tonic pain upon the EEG continues for some minutes after the stimulus has been withdrawn (Reinert et al. 2000; Stevens et al. 2000), and that peak discomfort occurs after around 90 seconds (Walsh et al. 1989). Participants removed their hand from the water and placed it onto a towel, and a third block of 30 low-frequency stimulation CHEPs was recorded.

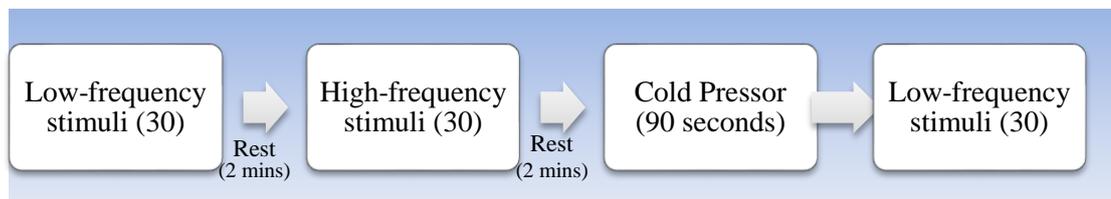


Figure 4.1 Diagram of the test procedure.

A.2.7 Data Processing and Analysis

EEG data were processed and analysed using four software applications: Brain Vision Analyzer v2.0 (BrainProducts, Munich, Germany); EEGLAB 8.0 (Delorme & Makeig 2004; Swartz Centre for Computational Neurosciences, La Jolla, CA; <http://www.sccn.ucsd.edu/eeglab>) running on Matlab 2007b (MathWorks, Natick, MA); Excel 2007 (Microsoft, Redmond, WA); and SPSS 20 (IBM, Chicago, IL).

A.2.7.1 EEG data pre-processing

Raw EEG files were divided into three periods of contact heat stimulation, being low-frequency stimulation (henceforth: CHEPS-low), high-frequency stimulation (henceforth: CHEPS-high), and low-frequency stimulation following tonic cold stimulation with the CPT (henceforth: CHEPS-cold). Data were filtered to remove non-physiological noise using a band-pass filter between 0.53Hz and 70Hz. CHEPS data periods were further divided into peristimulus epochs -1000ms to +2000ms around the event marker, therefore retaining EEG data which occurred in the one second preceding and the two seconds following the contact heat stimulation. In order to eliminate voltage offset in each epoch caused by the fluctuating signal, baseline correction was applied by subtracting the mean prestimulus voltage (-500 to -5 ms) from the entire epoch. Epochs were visually inspected, and those contaminated with obvious eyeblinks were discarded. Eyeblinks were defined as any activity which exceeded +/- 100 μ V occurring in the -500 to +1000ms time window.

A.2.7.2 Analysis of evoked response potentials

For each block of trials the remaining epochs were combined to produce an averaged waveform for each electrode. The electrode channel (either Cz or Pz) which displayed the most obvious ERPs was selected for further analysis of the waveform. N2 and P2 single trial peak latencies and amplitudes were extracted from epochs using the automated method (Mayhew et al. 2006). A basis-set is constructed from the subject average ERP waveform, then regressors are formed that represent the N and the P peak of interest and then this basis set is regressed against each single-trial in the data. The regression coefficients between the data and the basis-set are used to reconstruct a fit for each trial and then the amplitudes and latencies are measured from this. The single-trial amplitude and latency data were then visually inspected

for errors in the automated extraction method: any N2 and P2 amplitude results that were expressed as negative numbers were discarded as they did not represent the ERP of interest. The main effects of frequency of stimulation (CHEPS-low vs. CHEPS-high) at the two time points; and stimulation in the presence of cold pain (CHEPS-low vs. CHEPS-cold) at the two time points on N2-P2 peak-to-peak amplitude were calculated using the Wilcoxon test for paired samples (as Shapiro-Wilk tests indicated that some data could not be assumed to come from a normally distributed population; Wilcoxon 1945; Shapiro & Wilk 1965). Comparisons were also performed on a per participant basis using a Mann-Whitney *U* test (Mann & Whitney 1947).

A.2.8 Questionnaire Data Collection and Analysis

In the period one week prior to the EEG test session, a pack was sent to participants containing five questionnaires: Short Form 36-item general health questionnaire (SF-36); Hospital Anxiety and Depression Scale (HADS); Pain Coping Strategies Questionnaire (PCSQ); Frenchay Activities Index (FAI); Multidimensional Health Locus of Control Scale Form C (MHLC-C), together with instructions that they should bring the completed questionnaires with them to the subsequent test session. Questionnaire scores were collated and analysed in a pair-wise fashion as per the previous audit (as described in Section 3.3.5).

A.3 RESULTS

A.3.1 CHEPs Data

In each block of 30 trials, an average of 2.1 trials per block were discarded due to contamination by eyeblinks. Of the remaining 27.9 trials, 7.2 trials did not contain an

identifiable N2-P2 ERP complex. Each block of 30 trials therefore generated an average of 20.7 data points.

A.3.1.1 Effect of frequency

At baseline, the Wilcoxon test indicated that as a group, there was no significant difference in N2-P2 amplitudes between low- and high-frequency stimulation (Figure 4.2, blue line). When analysed individually, two participants had significantly smaller N2-P2 amplitudes at high-frequency compared to low at baseline. These were participant 7 (Low, 4.51 vs. High, 1.96; $U = 47$, $p < .001$) and participant 14 (Low, 7.43 vs. High, 4.01; $U = 79$, $p = .022$).

At outcome, the Wilcoxon test indicated that as a group, there was no significant difference in N2-P2 amplitudes between low- and high-frequency stimulation (Figure 4.2, red line). When analysed individually, the N2-P2 amplitude of participant 8 was larger at high-frequency compared to low at outcome (Low, 15.29 vs. High, 19.18; $U = 300$, $p = .044$) and the N2-P2 amplitude of participant 11 was smaller at high-frequency compared to low at outcome (Low, 10.82 vs. High, 5.62; $U = 272$, $p = .049$).

Main effect of stimulation frequency on ERP amplitude at baseline and outcome.

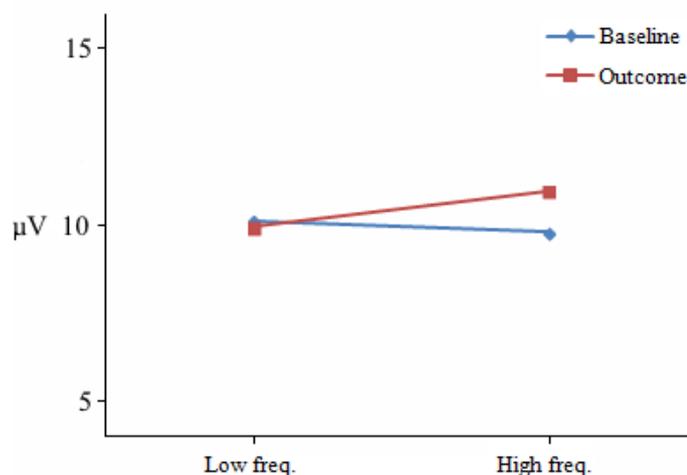


Figure 4.2 Group mean N2-P2 peak-to-peak amplitude of low- and high-frequency contact heat stimulation at baseline (blue line) and outcome (red line).

A.3.1.2 Effect of conditioned pain modulation

At baseline, the Wilcoxon test indicated that as a group, there was no significant difference in N2-P2 amplitudes between stimulation alone or following immersion in the CPT (Figure 4.3, blue line). When analysed individually the N2-P2 amplitude of participant 8 was larger following CPT compared to stimulation alone (Low, 14.88 vs. Low + CPT, 20.36; $U = 423, p = .005$) and the N2-P2 amplitude of participant 7 was smaller following CPT compared to stimulation alone (Low, 5.21 vs. Low + CPT, 2.91; $U = 99, p = .005$)

At outcome, the Wilcoxon test indicated that as a group, there was no significant difference in N2-P2 amplitudes between stimulation alone or following immersion in the CPT (Figure 4.3, red line). When analysed individually the N2-P2 amplitude of participant 8 was larger following CPT compared to stimulation alone (Low, 15.29 vs. Low + CPT, 22.31; $U = 284, p = .049$) and the N2-P2 amplitudes of participants 2

and 5 were smaller following CPT compared to stimulation alone (participant 2: Low, 19.43 vs. Low + CPT, 7.74; $U = 96$, $p < .001$; participant 5: Low, 13.38 vs. Low + CPT, 9.21; $U = 140$, $p = .031$)

Main effect of conditioned pain modulation on ERP amplitude at baseline and outcome.

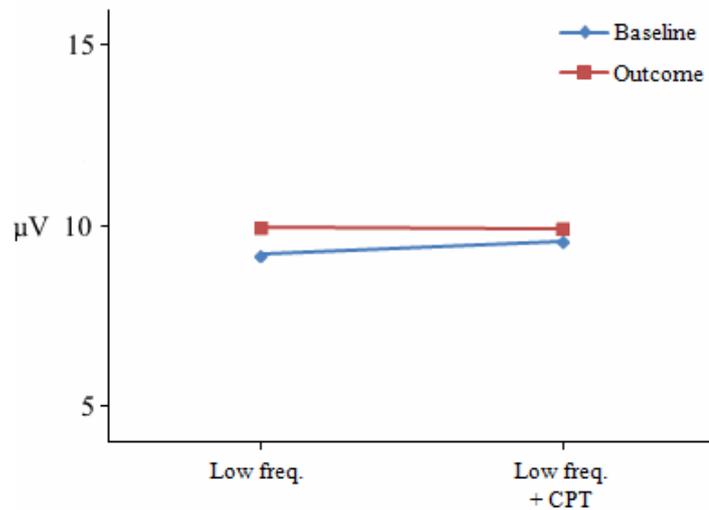


Figure 4.3 Group mean N2-P2 peak-to-peak amplitude of low-frequency contact heat stimulation alone and following CPT at baseline (blue line) and outcome (red line).

A.3.2 Questionnaire Data

Comparisons were performed on participants' questionnaire subscale scores between baseline and outcome using Student's *t*-test for related samples. There were significant improvements on the SF-36 subscales of general health, social functioning, and mental health; all subscales of the PCSQ; and in scores of anxiety and depression. Results are summarised in Table 4.1 below.

Table 4.1 Baseline and outcome questionnaire scores from patients in the CHEPS study, significance values and effect sizes shown for paired sample t-tests.

Questionnaire (Subscale)	Baseline (n = 12) Mean ±SD	Outcome (n = 12) Mean ±SD	<i>p</i>	<i>d</i>
SF36 (General health)	24.7 ±13.6	44.0 ±17.0	.001	-1.2 ^{<i>l</i>}
SF36 (Physical functioning)	22.5 ±11	25.1 ±20.7	–	–
SF36 (Role limitations due to physical health)	93.8 ±15.5	79.8 ±27.8	–	–
SF36 (Role limitations due to emotional problems)	71.1 ±26.4	69.3 ±38.8	–	–
SF36 (Social functioning)	30.3 ±19.9	45.6 ±22.1	.038	-0.7 ^{<i>m</i>}
SF36 (Bodily pain)	79.1 ±12.6	67.6 ±22.4	–	–
SF36 (Vitality)	23.3 ±15.7	32.7 ±23.1	–	–
SF36 (Mental health)	41.4 ±19.4	57.8 ±23.3	.01	-0.9 ^{<i>l</i>}
PCSQ (Catastrophising)	21.1 ±8.4	14.0 ±7.5	.01	0.9 ^{<i>l</i>}
PCSQ (Cognitive coping and suppression)	32.5 ±10.4	46.3 ±18.5	.008	-0.9 ^{<i>l</i>}
PCSQ (Helplessness)	3.8 ±12.8	-12.2 ±11.8	.001	1.4 ^{<i>l</i>}
PCSQ (Diverting attention/praying)	25.4 ±15	33.6 ±14.2	.041	-0.7 ^{<i>m</i>}
HADS (Anxiety)	13.6 ±5.4	10.5 ±4.1	.027	0.8 ^{<i>l</i>}
HADS (Depression)	11.1 ±4.1	8.0 ±3.7	.007	1.0 ^{<i>l</i>}
Frenchay Activities Index	28.8 ±10.8	30.6 ±12.4	–	–
MHLC-C (Internal)	16.6 ±7.8	17.7 ±6.8	–	–
MHLC-C (Chance)	15.3 ±8.1	15.6 ±7.3	–	–
MHLC-C (Doctors)	8.1 ±2.9	8.1 ±3.7	–	–
MHLC-C (Others)	7.6 ±2.7	6.6 ±2.8	–	–

SD = Standard Deviation; SF36 = Short form 36 item general health survey; PCSQ = Pain coping strategies questionnaire; HADS = Hospital Anxiety and Depression Scale, MHLC-C = Multidimensional Health Locus of Control questionnaire form C; ^{*m*} = medium effect size ($d > 0.5$), ^{*l*} = large effect size ($d > 0.8$).

A.4 DISCUSSION

A.4.1 Contact Heat Evoked Potential Amplitudes

A.4.1.1 Effect of stimulus frequency

Group mean N2-P2 peak-to-peak ERP amplitudes were generally unaffected by the frequency of stimulation, remaining around 10 μ V. N2-P2 amplitudes were actually significantly smaller during high- compared to low-frequency in two participants (7, 14) at baseline, and in one participant (11) at outcome. This decrease in amplitude

may have been due to habituation carrying over from one block of trials to the next. Central habituation to non-overlapping stimuli has previously been observed after 20-30 trials (Valeriani et al. 2005; Warbrick et al. 2009). In the present study each block consisted of 30 trials separated by a two minute break; as such the observed reductions would be consistent with previous accounts of central habituation. However, this was not a reliable observation across participants and there may be other explanations, such as variations in attention towards stimuli which may change as participants become accustomed to the sensations (Lorenz & Garcia-Larrea 2003). Looking at the results of all participants, it can be seen that there were almost the same number of increases as decreases in amplitude between blocks, suggesting that – either there was some habituation between blocks which masked any sensitisation that may have occurred in participants, or there was in fact no reliable observable effect of stimulus frequency. Most visible differences were non-significant, which is likely due to the combination of a large variation in amplitudes across trials and a small number of trials that was made smaller by discarding contaminated trials. Future work may benefit by controlling for habituation by counterbalancing the order of high- and low-frequency blocks and taking longer breaks between blocks to allow recovery. Larger numbers of trials would reduce the impact of variance on statistical tests, and could be achieved by adding further blocks of trials, however the added discomfort caused to participants by adding further stimuli and prolonging the session may cause participants to withdraw from the study.

One participant (8) showed a significant increase in amplitude at high- compared to low-frequency at outcome, that was also visually obvious but non-significant at baseline; this could be due to sensitisation and would fit with previously observed abnormal sensitisation in fibromyalgia patients (Staud et al. 2001). Participant 8 is

diagnosed with fibromyalgia; however other members of the group also suffering from fibromyalgia (11, 14, 15) did not show similar results. In the present study the use of a heterogeneous group of patients meant that any trend would need to be universal across conditions in order to be noticed. A homogenous group of patients would be the ideal method to control for the effects of condition, however to recruit sufficient numbers of similar patients would have either required a lot more time, or a larger number of sites feeding into the study. To further counter this point, it could be argued that the use of a heterogeneous sample is more representative of the real world and therefore may provide more clinically useful information than a study of a particular condition.

A.4.1.2 Effect of conditioned pain modulation

A conditioned pain modulation (CPM) paradigm was used to investigate diffuse noxious inhibitory control (DNIC) in patients and the effect of a PMP on this measure. CHEPs recorded alone and during a period of tonic pain (induced by CPT) were compared, and one would expect to observe a reduction of ERP amplitudes during the CPM trials if there was any DNIC effect. Such a reduction has previously been found in a healthy sample, but was absent in a specific patient group (i.e. chronic tension type headache; Buchgreitz et al. 2008); however, in osteoarthritis patients a reduction in ERP amplitudes has been observed (Quante et al. 2008). The effect of a PMP upon these measures has not previously been reported. The results do not reveal a consistent pattern of DNIC (or lack of) across participants at either baseline or outcome. At both time points the average N2-P2 peak-to-peak amplitude was slightly larger in the CPM condition compared to the phasic stimulation alone condition. Looking at individual participant data there were similar numbers of increases and decreases at both time points; the most parsimonious explanation for

this is the test paradigm was not reliably inducing an observable DNIC effect and that observations are the result of natural variation in ERPs. In those patients where a significant reduction was observed, this is unlikely to be due to habituation from previous blocks of stimuli as there was a long break between blocks during which the CPT water bath was prepared, the hand immersed, and a period of resting EEG recording. A significant increase in amplitudes was observed at both time points in participant 8, which may have been due to abnormal central sensitisation characteristic of fibromyalgia; however other members of the group also suffering from fibromyalgia (11, 14, 15) did not show similar results.

It is possible that no DNIC was observed because the effects of cold pressor pain on DNIC had diminished by the time ERPs were recorded. Patients had already withdrawn their hand before commencement of the CHEPS recording, allowing some recovery time, although patients did casually report that the hand remained painful for some minutes following CPT. This problem could have easily been avoided by having the patients immerse their hand into the cold pressor during the CHEPs recording, thereby ensuring that maximum tonic pain was being experienced at the same time as phasic stimuli were applied. The reason for not pursuing this methodology was that in the author's personal experience of administering dozens of CPTs, participants do not remain in a relaxed physical state during the immersion period – shivering, clenching of muscles, verbal outbursts, and breath holding often occur – all of which affect the quality of EEG data. This may be taken into consideration in future work by providing participants with a period of training or familiarisation with the CPT during which they can practice remaining as relaxed as possible in the interest of good quality EEG recording; however this would require

more time, either as a longer test session or even a separate session before EEG recording.

A.4.1.3 CHEPS artefact

A final observation to note is the presence of an artefact in the CHEPs data. This was observed as a large deflection which peaked around 240ms post-stimulus. The artefact was observed in most of the participants' data, and varied in amplitude both between and within sessions. Such an artefact is created by an electric field disturbance originating in some part of the CHEPS equipment, and has previously been noted in a study which compared CHEPs and LEPs, which found the artefact was peculiar to CHEPs epochs and absent from LEPs epochs (Iannetti et al. 2006, p.240). As the artefact occurs both at the same time in each trial and before the start of the ERP of interest, it does not contaminate the ERP and should not be cause for concern. If CHEPS stimulation was being applied to a site more proximal to the head (e.g. the face compared to the arm), nerve conduction times would be shortened and therefore ERPs may overlap with the artefact. The artefact can be eliminated by ensuring that all electrodes are connected with an impedance that it as close to zero as possible ($< 5 \text{ k}\Omega$) and this would explain why the artefact is not consistently reported in CHEPs studies. In practice it is not always possible to achieve such low impedance due to individual variations in scalp and hair characteristics which impact on the quality of connection between electrode and scalp, and for the present study an impedance of $< 10 \text{ k}\Omega$ was acceptable.

A.4.2 Questionnaire Scores

The effect of cognitive-behavioural therapy and multidisciplinary pain management upon questionnaire measures of psychophysical health and pain coping strategies have been discussed in the preceding Chapters. The PMP used in this study has been

shown to bring about small effects in measures of general health, social functioning, mental health, anxiety, catastrophising, cognitive coping/suppression, and helplessness. The effect of treatment on questionnaire scores collected from the small sample of patients in the present study were significant improvements on scores of general health, social functioning, mental health, anxiety, depression, catastrophising, cognitive coping/suppression, and helplessness. The effect of treatment upon questionnaire scores was therefore highly similar to the earlier audit carried out with large number of patients.

Following the previous audit, a measure of locus of control was also administered to patients in the present study. Earlier work suggested that patients who believe outcomes to be controlled by chance are more likely to use maladaptive coping strategies (Crisson & Keefe 1998), however no such relationship was found in the present sample (results not shown). From baseline to outcome, there was very little change in any of the dimensions measured using the MHLC-C.

4.4 STUDY B: THE EFFECT OF PMP TREATMENT UPON POWER SPECTRAL DENSITY AT REST AND DURING TONIC PAIN

B.1 BACKGROUND

This study was designed to investigate the effects of PMP treatment upon the EEG power spectral density (PSD) of participants, under two conditions measured before and after treatment. In the first condition continuous EEG data was recorded from participants during a period of rest. In the second condition continuous EEG data was recorded during a period of tonic pain that was induced using the CPT. Comparative data was also recorded from a control group consisting of healthy participants. Previous work (discussed earlier in Section 2.7.3) has shown that the effect of CPT upon PSD in healthy subjects is a general increase in δ -, θ -, and β -power accompanied by a decrease in α -power (A.C.N. Chen et al. 1989; Backonja et al. 1991; A.C.N. Chen & Rappelsberger 1994; Ferracuti et al. 1994; Stevens et al. 2000; Chang et al. 2002a; Dowman et al. 2008; Shao et al. 2012). Some of these studies also reported regional effects on PSD, with α -power decreases observed in either frontal, central, temporal, and parietal areas; two studies observed decreased α -power in areas contralateral to the stimulated limb (Ferracuti et al. 1994; Dowman et al. 2008).

The effect of CPT upon PSD in chronic pain patients is less well studied. Two studies have reported no differences in the resting PSD between pain patients and healthy controls (Schmidt et al. 2012; Vossen et al. 2014). The effect of CPT upon PSD was studied in fibromyalgia patients and healthy controls (Stevens et al. 2000);

the findings were an increase in δ -, θ -, and β -power compared to rest in both groups, in the healthy group there was a decrease in α -power, whereas α -power increased slightly in the patient group for a short time after immersion in the cold pressor.

Brief sessions of non-pharmacological pain treatments (hypnosis, meditation, biofeedback, and tDCS) have been shown to affect PSD in chronic pain patients (discussed in Section 2.9.3.3; M.P. Jensen et al. 2013a, 2014). One study investigated the effect on PSD of an 8-week course of MBSR in pain patients and found no difference (Schmidt et al. 2015). To date there has been no study of the effects of a PMP upon PSD in chronic pain patients. The present study will investigate the effects of a CBT-PMP upon PSD at rest and during induced pain, and upon the difference between PSD in the rest and pain conditions.

B.1.1 Aims

The aims of this study were to assess PSD at rest and during induced pain, in patients pre- and post-treatment in the CBT-based PMP at Centre A, and to compare this with data from healthy controls.

B.1.2 Objectives

The objectives of this study were: to record continuous EEG at rest and during CPT induced pain in a group of patients before and after treatment, and to take the same measurements in a group of healthy controls. Questionnaire data was also collected to verify the efficacy of the treatment in the patients studied.

B.2 METHODS

B.2.1 Study Design

The study used a prospective cohort design to assess the impact of a CBT-based PMP treatment upon PSD and questionnaire measures collected from patients and healthy controls at two time points (baseline and outcome).

There were 12 participants in the patient group (10 female, 2 male, mean age = 52, range = 39–64), recruited consecutively from the population of chronic pain patients who had been enrolled into the PMP at Centre A. Test sessions were carried out in two-week periods before and after patients attended the Centre A CBT based PMP, and took place at Centre A.

The control group consisted of 14 participants (10 female, 4 male, mean age = 36, range = 20–68), recruited consecutively from the population of staff and students at Birmingham City University. Volunteers were excluded if they reported having any history of chronic pain, long term use of analgesics or history of psychological treatment. Test sessions took place under laboratory conditions at Birmingham City University, Edgbaston. All data was collected by the author. For the duration of the test sessions, participants sat in a quiet, dimly lit room. Participants were fitted with EEG recording equipment and given time to become familiar with the cold water bath stimuli prior to testing.

B.2.2 Test Procedure

EEG data was recorded with the same equipment setup as used in **Study A** (see Section A.2.3 above). There were two periods of EEG recording, before and after exposure to the CPT (Figure 4.4).

B.2.2.1 Continuous EEG recording at rest

EEG data was recorded for 180 seconds with the subject sitting still and relaxed and eyes open. The first 90 seconds of the recording period were discarded as participants often moved around to get comfortable during this time.

B.2.2.2 Continuous EEG recording during cold pressor induced pain

The CPT described earlier was used to induce a tonic pain stimulus lasting around 10 minutes. Participants were asked to place their left hand and wrist into the cold water bath for a period of 90 seconds. EEG data was not recorded during the CPT procedure due to the risk of EEG data contamination from involuntary body movements and facial muscle activity caused by exposure to the cold water bath. Previous work has shown that the effect of tonic pain upon the EEG continues for some minutes after the stimulus has been withdrawn (Reinert et al. 2000; Stevens et al. 2000), and that peak discomfort occurs after around 90 seconds (Walsh et al. 1989). Participants then removed their hand from the water and placed it onto a towel. Continuous EEG data was then recorded for 90 seconds whilst participants sat still with eyes open.



Figure 4.4 Diagram of the test procedure.

B.2.3 Data Processing and Analysis

The last 90 seconds of the initial rest period (henceforth: rest-rest) and the 90 second period following stimulation with the CPT (henceforth: cold-rest) were filtered to

remove non-physiological noise using a band-pass filter between 0.53Hz and 150Hz, with a notch filter applied at 50Hz to remove noise caused by mains electricity (i.e. alternating current which oscillates at 50Hz). Data were converted from the time domain to the frequency domain using the Fast Fourier Transformation (FFT) function in Brain Vision Analyser 2.0. For EEG data the FFT takes a signal which describes fluctuations in voltage over time and converts it into an output which describes the power at each frequency in the entire time period. The FFT was set to run with a 0.2Hz resolution, use a Hanning window of 10% length, apply variance correction, and output in units of power (μV^2). The power contained within the four commonly used frequency bands was calculated at each electrode, the bands defined as: Delta (δ) 0.6–4.0Hz; Theta (θ) 4.2–7.4Hz; Alpha (α) 7.6Hz–12.4Hz; Beta (β) 12.6–30.0Hz. In order to control for global power fluctuations between sessions, the absolute spectral power in each band was converted to the relative spectral power in each band at each electrode and expressed as a percentage. The power from the left hemisphere electrodes (C3, T7) were combined, as were the right hemisphere electrodes (C4, T8), to examine the power fluctuations in each hemisphere region. The main effect of treatment/time upon the relative spectral power in each band (over each hemisphere in the rest-rest period within each group) was calculated using a Wilcoxon Signed-Rank test for related samples (as the Shapiro-Wilk test indicated that some data could not be assumed to come from a normally distributed population). The main effect of the CPT upon the relative spectral power within each frequency band (over each hemisphere at the two time points within each group) was calculated using Wilcoxon Signed-Rank tests. Between-group differences in the effect of the CPT on relative spectral power within each frequency band (over each hemisphere in each rest period) were calculated using Mann-Whitney U tests.

B.3 RESULTS

B.3.1 EEG power – analysis of the effect of CPT

B.3.1.1 Within-group differences

Relative EEG spectral power in each of the four bands, in left and right hemisphere regions, was compared within each group between the rest-rest and cold-rest recording periods. Results are illustrated for the patient group in Figure 4.5 and for the healthy control group in Figure 4.6.

In the patient group, at baseline, there were significant decreases in relative spectral power following the CPT in the theta (θ) band in both the left ($Z = -2.93, p = .003$) and right ($Z = -2.40, p = .016$) hemispheres. There were also significant decreases in relative spectral power following the CPT in the alpha (α) band in both the left ($Z = -2.58, p = .009$) and right ($Z = -2.05, p = .041$) hemispheres. There were no significant differences in the delta or beta bands.

At outcome, there were no significant differences in any of the four power bands.

Effect of CPT upon relative spectral power in the PMP patient group

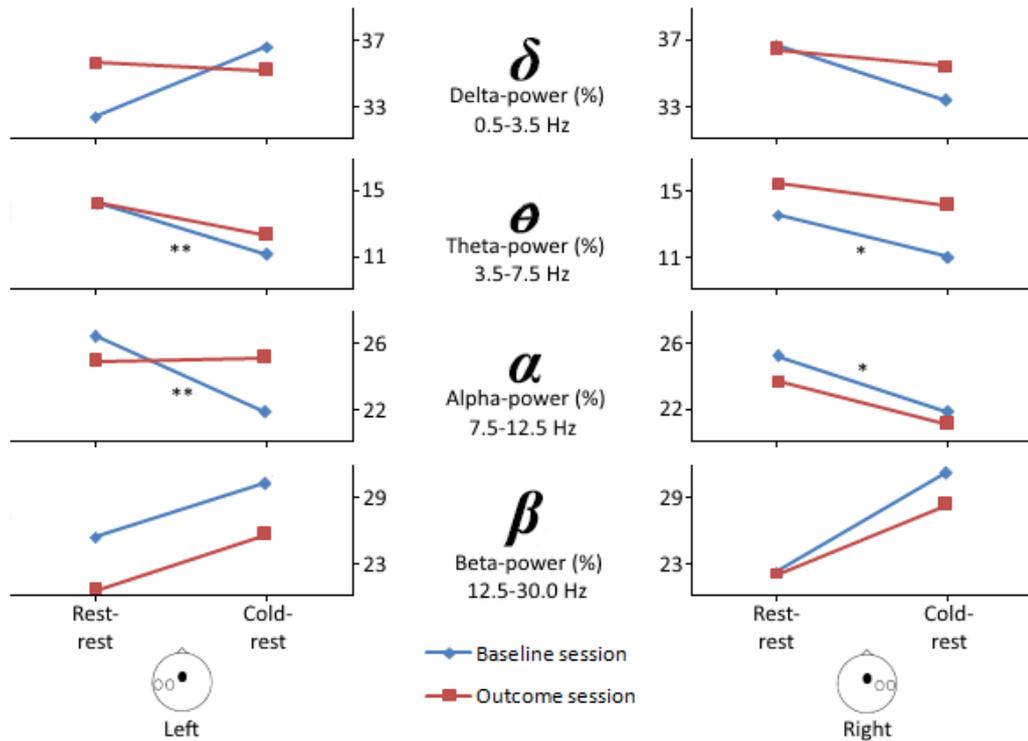


Figure 4.5 Effect of cold pressor on relative spectral power in each of the four bands in the left and right hemisphere electrodes (PMP patients group). At baseline (blue lines) there were significant within-session decreases in theta and alpha power in both hemispheres after immersion in the cold pressor, * = significant at $p < .05$ level, ** = significant at $p < .01$ level. There were no between-session significant differences.

In the healthy control group, at baseline and at outcome, there were no significant differences in relative spectral power following CPT, in any of the four power bands.

Effect of CPT upon relative spectral power in the healthy control group

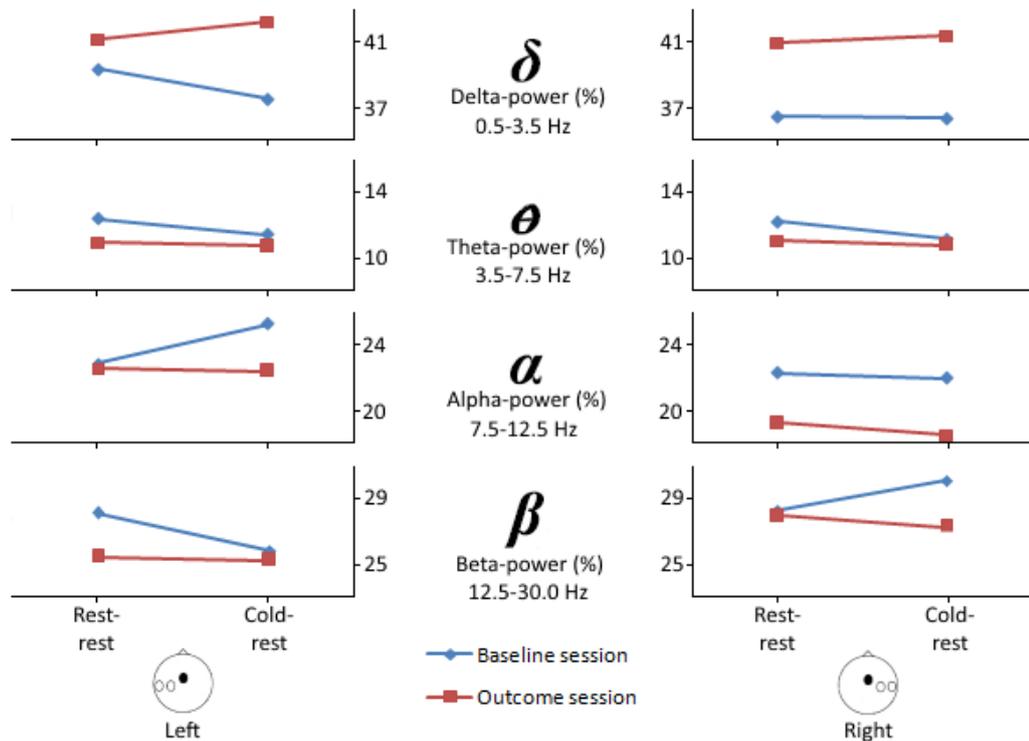


Figure 4.6 Effect of cold pressor on relative spectral power in each of the four bands in the left and right hemisphere electrodes (healthy control group). There were no significant differences in power, either within- or between-sessions.

B.3.1.2 Between-group differences

The change in relative spectral power from rest-rest to cold-rest in each of the four bands in each hemisphere was compared between-groups at baseline and outcome time-points. Results are illustrated in Figure 4.7. At baseline, there were significant differences between the groups in the alpha band over the left hemisphere (Patient median = -2.86, Control median = 1.99, $Z = 2.71$, $p = .005$) and the theta band over

the right hemisphere (Patient median = -2.59, Control median = -0.84, $Z = 2.15$, $p = .031$). At outcome, no significant differences were observed between the groups.

Baseline: effect of CPT on spectral power in left and right hemisphere electrodes



Outcome: effect of CPT on spectral power in left and right hemisphere electrodes



Figure 4.7 Effect of cold pressor test (CPT) on spectral power in patient and control groups at baseline (upper) and outcome (lower). At baseline, there were significant differences between groups in the effect of CPT on alpha power in the left hemisphere and theta power in the right hemisphere, * = significant at $p < .05$ level, ** = significant at $p < .01$ level.

B.4 DISCUSSION

PSD was calculated for periods of continuous EEG recorded during periods of rest, both before and after the induction of tonic pain by the CPT. Previous work has either investigated the effect of tonic pain upon PSD, or the effect of a treatment upon PSD; the present study was designed to measure both of these effects. In addition, because the effect of tonic pain upon PSD was measured both before and after treatment it was possible to also investigate the effect of treatment upon this variable. As any pre- to post-treatment differences could have been unrelated to the treatment, both groups were measured in the same fashion to provide comparative data. The use of a control group also meant that between-group comparisons could be made, however these should be viewed with caution as individual differences between-groups such as effects of medication upon PSD were not controlled for.

B.4.1 Within-group differences

B.4.1.1 Patient treatment group

At baseline, there were significant decreases in θ -power and α -power following exposure to the cold pressor in the patient group. Following the treatment programme, there were no significant changes in relative power spectral density. Post-treatment θ -power stability could represent patients maintaining a more relaxed state in the presence of pain (Sherlin 2009). Previous studies have also linked θ -power increase during pain with efforts to control pain in experienced meditators (Larbig et al. 1982; Larbig 1994), and with reduced pain perception in a patient sample (Russ et al. 1999). Lack of decrease in the present PT sample is not the same

as an increase, but it does show a change in the expected direction if the PMP treatment – which included relaxation, and other exercises in pain control – did affect top-down pain control in patients. The lack of a decrease in α -power at follow-up compared to baseline may be related to effects of treatment; however it has previously been suggested that α -frequency changes indicate selectivity of salient features of stimulation. A decrease in α -power in preparation for a motor response to the painful stimulus is accompanied by an increase in β -power (B. Bromm & Lorenz 1998). The absence of a significant α -power decrease at follow-up may represent a reduction in stimulus salience for the patients, having already experienced the cold pressor in the baseline session. There were consistent, but not significant, increases in β -power following stimulation which likely represent high-frequency afferent nociceptive activity processing by the cortex.

B.4.1.2 Healthy control group

Studies reviewed in Section 2.7.3 and Table 2.8 investigated the effect of tonic pain upon PSD in healthy subjects, finding an inconsistent pattern of results: δ -power was seen to increase or not change; θ -power was observed to increase, decrease, or not change depending on the study; α -power tended to decrease, rarely was there no change; β -power often increased or there was no change. In the present study the PSD of the healthy control group was not significantly affected by tonic pain from the CPT, at both baseline and follow-up test sessions (Figure 4.6). It could be argued that this result agrees with previous studies, as between those studies using the CPT in Table 2.8, no change was observed in each of the different power bands at least once (A.C.N. Chen et al. 1989; Backonja et al. 1991; A.C.N. Chen & Rappelsberger 1994; Ferracuti et al. 1994; Dowman et al. 2008; Shao et al. 2012). However, the

most common finding of a decrease in α -power accompanied by an increase in β -power was not observed in the healthy control group.

B.4.2 Between-group differences

Before discussing between-group differences in PSD it should be noted that participants were recruited conveniently and consecutively into the study, therefore groups were not intentionally matched in terms of age, gender, pain condition, or medication use. All groups contained a majority of female participants and were also closely matched in age; however these similarities reflect the characteristics of the populations in general and were not planned in advance.

At baseline, there were significant differences between groups in the effect of cold pressor pain upon PSD. The changes in left hemisphere α -power and right hemisphere θ -power were significantly different between the two groups at baseline. There were no significant differences between the groups at follow-up (Figure 4.7). The absence of difference between groups at follow-up could represent an effect of the treatment, acting to normalise the cortical response to cold pressor pain in the patients. Previously, only one study had compared the effect of CPT on PSD in healthy and pain patient (fibromyalgia) groups (Stevens et al. 2000), finding that the effect on EEG spectra was largely similar in both groups.

In the present study, there was a slight decrease in α -power following CPT in both groups at both time points, with the exception that α -power increased in left hemisphere electrodes in the healthy group at baseline. The reduction in α -power likely represents an event related desynchronisation (ERD) in response to somatosensory stimulation that is not specific to pain (Pfurtscheller & Aranibar

1977; B. Bromm & Lorenz 1998; see also Section 2.7.3.3 of this work). The increase in α -power observed may be related in a similar fashion, representing an event related synchronisation (ERS) that also occurs in response to a stimulus, and may be observed in the same frequency band at a different location to the ERD, or in the same location in a different band (Pfurtscheller 1992; Pfurtscheller & Lopes da Silva 1999). Indeed, in the present samples, there were also slight increases in β -power following stimulation that may be explained by ERS.

The significant difference in right hemisphere θ -power observed at baseline may represent efforts to block out, or dissociate from feelings of pain, with previous work suggesting there is a link (Larbig et al. 1982; Bernstein & Putnam 1986; Russ et al. 1999). A tentative explanation would be that pain patients tended to focus more on the pain at baseline (pre-treatment) than the healthy group, hence the difference in θ -power. At follow-up (post-treatment) the θ -power change was similar between groups, with even a slight increase in in the patient group over the healthy group – this may represent a positive effect of the treatment. Patients may have employed relaxation techniques learned during treatment in order to block out the feeling of pain.

B.4.3 Limitations and suggestions for further study

A limitation to the study was the absence of a patient control group drawn from the same population. Without comparison to such a group it is possible that the observed differences between baseline and follow-up in the patient treatment group could have been due to the effects of familiarity with and repetition of the cold pressor. Whilst efforts were made to familiarise participants with the stimulus before recording, this is a possibility that cannot be ruled out without a patient control group

A second limitation concerns the heterogeneity of the patient group studied. It has been discussed earlier (Sections 2.8-2.9) that the effects of painful stimulation and pain treatments can differ across different diagnostic groups. The present study used a convenience sample in which patients were recruited consecutively into the study, regardless of diagnosis, in order to gather the maximum data in the time available. Using a mix of patients has the disadvantage that for any effect to be observed, it must be robust across all patients, or be a large effect in enough patients to generate a significant statistical test overall. In homogenous patient groups it is possible to detect smaller effects as the confounding variable of different conditions is removed. The advantage to a heterogeneous group is that it more accurately represents the real world. The PMP under investigation is intended to be effective across a wide range of chronic pain conditions and therefore it would be expected to produce effects that are shared by a mix of patients.

The observed effect of treatment upon changes in θ -power following CPT in the present study points to the possibility that psychologically based pain treatment can affect the way in which the brain processes, or reacts to painful stimulation. Previous literature has linked θ -power to efforts to block out, or dissociate from feelings of pain (Larbig et al. 1982; Bernstein & Putnam 1986; Russ et al. 1999). The CBT-based PMP programme did not explicitly train patients in techniques to help them dissociate from feelings of pain. There were guided relaxation sessions throughout the course that may have led patients to learn that they can mentally influence their pain experience. Future work might benefit from the study of a PMP that teaches patients explicitly a technique for dissociation from pain. A treatment such as the ACT-based PMP (Sections 2.5.8–2.5.9) in which the technique of mindfulness is taught to and practised by the patients, would be ideal for such an investigation.

B.4.4 Conclusion

The effect of cold pressor pain upon θ - and α -activity is modulated following a CBT-based PMP. This may be due to a change in cognitive appraisal of painful signals brought about by taking part in the PMP, supported by the reduction in catastrophising and feelings of helplessness post-PMP. Patients also learned relaxation techniques for dealing with periods of increased pain, which they may have employed during cold pressor pain, and which may have contributed to the observed stability of θ - and α -power measured post-PMP. Results imply the possibility of an objective measure of the outcome of psychological therapy for chronic pain. Future work should include data collected from waiting-list control and different treatment (ACT-based PMP) groups in order to confirm and extend findings.

CHAPTER 5

PSYCHOSOCIAL HEALTH AND ATTITUDES TO PAIN IN PATIENTS ATTENDING AN ACCEPTANCE AND COMMITMENT THERAPY (ACT) PAIN MANAGEMENT PROGRAMME

5.1 ABSTRACT

Background: The use of ACT as a treatment approach for chronic pain problems has grown steadily over the past 15 years. During this time evidence has accumulated that supports the use of ACT as a good alternative to CBT, with similar effects on a range of treatment outcomes (Veehof et al. 2011). In contrast to CBT, thoughts, feelings and behaviours are not seen as the problem which must be addressed; rather the patients' response to these factors is the target for change. This study aimed to investigate changes in psychosocial health and attitudes to pain in a cohort of patients throughout a course of ACT for pain management.

Methods: Between June 2012 and August 2015, 258 patients attended the PMP at the West Midlands NHS regional hospital (Centre B). Before (baseline) and after (outcome) treatment patients were asked to complete the Hospital Anxiety and Depression Scale (HADS), the Pain Catastrophising Scale (PCS), the Psychological Inflexibility to Pain Survey (PIPS), the Chronic Pain Acceptance Questionnaire (CPAQ), the Acceptance of Illness Scale (AIS), and the Fear Avoidance Beliefs Questionnaire (FABQ). In order to be included in the analysis patients were required

to have at least part-completed questionnaires at both time points (n = 131, mean age = 52.9 ±11.98, age range = 27-82).

Results: There were significant improvements ($p < .01$) in scores on all scales between baseline and outcome, with the exception of the FABQ ‘work’ subscale.

Conclusion: The pain management programme has been instrumental in bringing about significant improvements in psychosocial health and attitudes to pain in patients.

5.2 BACKGROUND

The West Midlands NHS regional hospital (henceforth: Centre B) PMP is conceptually based upon acceptance and commitment therapy (ACT) for the treatment of chronic pain (discussed earlier in Section 2.5.8). The programme is delivered by the Centre B multidisciplinary pain clinic team, consisting of psychologist, specialist nurse, physiotherapist and occupational therapist. The psychologist is trained in ACT and experienced in applying its principles to the management of chronic pain.

Upon being enrolled into the programme, patients are asked by the clinical staff to fill in several questionnaires: the Hospital Anxiety and Depression Scale (HADS), the Pain Catastrophising Scale (PCS), the Psychological Inflexibility to Pain Survey (PIPS), the Chronic Pain Acceptance Questionnaire (CPAQ), the Acceptance of Illness Scale (AIS), and the Fear Avoidance Beliefs Questionnaire (FABQ). Patients are also asked to fill in the same questionnaires at the end of the programme.

Since the inception of the ACT-based PMP in Centre B in June 2012, until the time that this study was conducted (August 2015), the programme has been run 27 times, and 258 patients have attended.

5.2.1 Evidence for Efficacy of ACT for Chronic Pain

A systematic review and meta-analysis of 19 acceptance based interventions for chronic pain by Veehof and colleagues (2011) found medium effect sizes for pain intensity, depression, anxiety, physical wellbeing, and quality of life. A later systematic review of ten RCTs concluded ACT was effective in increasing physical functioning, and decreasing anxiety, depression, and distress, compared to inactive treatments (Hann & McCracken 2014).

5.2.2 Programme structure (and comparison to CBT-based programme)

The programme follows a timetable (Table 5.1) which is similar in many respects to the previously studied CBT-based PMP at Centre A. Both programmes include regular exercise; goal setting exercises and homework tasks; educational presentations on the physiology of pain, pain medications, pacing of activity, sleep hygiene, the interaction between thoughts, feelings and behaviours; discussion with an expert patient; and weekly relaxation exercises. There are differences between the two programmes which reflect the differing approaches of CBT and ACT. One of the main tenets of CBT is identifying maladaptive or irrational thoughts and challenging their veracity, with the goal of changing the way in which such thoughts are interpreted and thus lessening their impact on mental wellbeing. In contrast, ACT teaches clients to accept negative thoughts as part of normal life and to deal with them through a process of non-judgemental awareness, where they do not get ‘caught up’ in negative thoughts and emotions, thereby lessening their impact on mental wellbeing. The programmes also differed in the type of relaxation techniques that

were taught. The CBT approach contained deep breathing and guided visualisation sessions designed to encourage a relaxed body and mind. The ACT programme included periods of guided mindfulness meditation which were intended to not only relax the body, but also as an exercise to practice the skill of non-judgemental awareness.

Table 5.1 Timetable of Centre BPain Management Programme.

Session 1	Session 2
Introduction to the programme	Exercise
Ice-breaker discussion	What is ACT? What is mindfulness?
Pain physiology	Pacing
Introduction to exercise (diary)	Goal setting
Mindfulness/Relaxation	Mindfulness/Relaxation
Session 3	Session 4
Exercise	Exercise
Acceptance and Control	Occupational therapy – functional session
Values	Expert patient
Mindfulness/Relaxation	Mindfulness/Relaxation
Session 5	Session 6
Exercise	Exercise
Committed action	How to talk about pain
Thoughts, feeling and behaviours	The spine
Mindfulness/Relaxation	Healthy living
	Mindfulness/Relaxation
Session 7	Session 8
Exercise	Exercise
Sleep	Medication
Pain theories and TENS theory	Relapse prevention and flare-ups
Acupuncture	Neighbourhood support service
Mindfulness/Relaxation	Mindfulness/Relaxation

Psychophysical outcomes have been shown to be similar in both ACT- and CBT-based treatments for chronic pain. A systematic review and meta-analysis (mentioned above, Veehof et al. 2011) reported that the effects of ACT on pain intensity ($d = 0.37$) and depression ($d = 0.32$) were comparable to those of CBT (reported to be

0.21 & 0.38, respectively, by Williams et al. 2012). One RCT has directly compared CBT and ACT treatment for chronic pain (Wetherell et al. 2011). Outcomes from the two types of treatment were equivalent: there were no significant differences in improvement on any outcome variables. Participants found the CBT rationale more credible and had higher expectations for improvement, and ACT participants reported significantly higher levels of satisfaction than CBT participants. The study also investigated possible mediators for improvement on measures of pain interference: in both CBT and ACT conditions, perceived pain control was significantly negatively correlated with pain interference, whereas pain acceptance was not. This finding was contrary to the findings of other studies which placed importance on acceptance over control-oriented strategies (Wetherell et al. 2011). A more recent study has investigated the mediating role of acceptance in multidisciplinary CBT for chronic pain (Åkerblom et al. 2015). Despite not targeting acceptance in their CBT approach, pain-related acceptance was reported as the strongest mediator of change in measures of pain interference, pain intensity, and depression. These results suggest that the therapeutic mechanism underlying CBT and ACT might share common ground in the psychological flexibility model, which emphasises pain-acceptance and control over the effects of pain (McCracken & Vowles 2014; McCracken & Morley 2014).

5.2.3 Aims

The primary aim of this study was to assess the efficacy of the ACT-based PMP at Centre B. The secondary aim was to compare these findings where possible to the results of the earlier audit of a CBT-based PMP.

5.2.4 Objectives

The objectives of this study were to gather the entire available patient generated questionnaire data together into a single dataset, and to analyse this dataset to reveal overall changes in psychosocial health and attitudes to pain from baseline to outcome.

5.3 METHODS

5.3.1 Study Design

The study used a longitudinal retrospective design to assess the impact of an ACT-based PMP treatment upon questionnaire measures collected from patients at two time points (baseline and outcome). In order to be included in the analysis patients were required to have completed questionnaires at both time points.

5.3.1.1 Power Calculation

To determine the required sample size, an a priori power calculation was carried out using G*Power 3.1.9 software (Faul et al. 2007), in a similar manner to that described in the earlier study of the Centre A PMP (Section 3.3.1.1). Population effect size was estimated at 0.32 using the results of the meta-analysis by Veehof and colleagues 2011. Probability of type 1 error (α) was set at 0.05 and power was set at 0.8, as is the convention suggested by Cohen (1969, 1992) that is typically used in behavioural sciences research (Sullivan & Feinn 2012).

The calculation using the above parameters reported that a sample size of 79 participants would be required for power to be above the 0.8 level.

5.3.2 Pain Management Programme Design

Centre B ran two programmes in parallel per three month period. The programme consisted of eight sessions of approximately 150 minutes each given over a period of eight consecutive weeks to groups of 8-10 patients.

5.3.3 Questionnaires of Psychosocial Health and Attitudes to Pain

5.3.3.1 Hospital Anxiety and Depression Scale (HADS)

The HADS consists of 14 self-scored items designed to assess levels of anxiety and depression. Each item is related to either symptoms of anxiety or depression and has four responses which are scored from 0 to 3 according to symptom severity (e.g. I feel tense and wound up: most of the time (3); a lot of the time (2); from time to time (1); not at all (0)). The HADS consists of two independent scales: anxiety (HADS-A) and depression (HADS-D), each with seven items, leading to a score between 0 and 21. A score of 0 to 7 is considered normal, 11 or higher indicates probable presence of the mood disorder, and 8 to 10 being suggestive of the presence of the mood disorder (Zigmond & Snaith 1983; Snaith 2003).

The HADS has been validated against psychiatric interviews (Zigmond & Snaith 1983) and against other scales for the measurement of anxiety and depression (Aylard 1987) in patient groups. A review of 747 studies using the HADS concluded that it was a suitable measure for assessing anxiety and depression in both patient and healthy populations (Bjelland et al. 2002). Internal consistency of both subscales has been verified in a study of a large mixed sample of 64,648 persons, which reported a Cronbach's α of 0.80 for HADS-A and 0.76 for HADS-D (Mykletun et al. 2001).

5.3.3.2 The Pain Catastrophising Scale (PCS)

The PCS is a self-administered, 13-item questionnaire designed to assess specific elements of catastrophising – helplessness, rumination, magnification. Participants are asked to reflect on past painful experiences and indicate the extent to which they experienced the 13 thoughts or feelings when experiencing pain (Sullivan et al. 1995). There are five levels of response ranging from 0 (not at all) to 4 (all the time).

The PCS uses five items taken from the catastrophising subscale of the PCSQ (Pain Coping Strategies Questionnaire, Rosentiel & Keefe 1983), plus eight statements derived from examples of catastrophising ideation by Sullivan and colleagues (1995). The scores from the 13 items load onto three factors (helplessness, rumination, magnification). This three factor structure has been confirmed in samples of chronic pain patients (Osman et al. 1997), pain-free adults (Osman et al. 2000), and has also been shown to be consistent across sexes and across patient and non-patient groups (D'Eon et al. 2004; Quartana et al. 2009). The PCS has good internal consistency with Cronbach's α overall = 0.87, rumination = 0.87, magnification = 0.66, and helplessness = 0.78 (Sullivan et al. 1995).

5.3.3.3 The Psychological Inflexibility in Pain Scale (PIPS)

The PIPS is a 16-item questionnaire developed to assess processes underlying the efficacy of acceptance and exposure based treatments for pain (Wicksell et al. 2007). Items are scored according to a two-factor model (avoidance of pain, cognitive fusion). The avoidance subscale measures the self-reported tendency to engage in certain behaviours that function to avoid pain and related distress (e.g. "I avoid scheduling activities because of my pain"), while the fusion subscale assesses the frequency of thoughts that, if they are acted on, are likely to lead to avoidance behaviours (e.g. "I need to understand what is wrong in order to move on"). Items

are rated on a 7-point Likert-type scale from “never true” (1) to “always true” (7), with higher scores indicating greater psychological inflexibility (Wicksell et al. 2010a).

The PIPS has been shown to be sensitive to change following psychological treatment for chronic pain based upon exposure and acceptance (Wicksell et al. 2008). The two factor structure (avoidance, fusion) has been confirmed in samples of patients suffering from chronic back pain (Barke et al. 2015) and fibromyalgia (Rodero et al. 2013).

5.3.3.4 The Chronic Pain Acceptance Questionnaire (CPAQ)

The CPAQ is a 20-item questionnaire designed to measure pain-related acceptance (McCracken et al. 2004). Scores load onto two subscales (activity engagement, pain willingness). Activity engagement measures the extent to which pain restricts behaviour, and pain willingness measures the degree of effort put into controlling pain. Respondents are asked to rate the truth of each statement (e.g. “I am getting on with the business of living no matter what my level of pain is”) on a 7-point scale from 0 (never true) to 6 (always true). The subscale and total scores from the CPAQ have been validated against measures of avoidance, emotional distress, and patient functioning in cross-sectional analyses, and also show good internal consistency (Cronbach’s $\alpha = 0.78\text{--}0.82$; McCracken et al. 2004).

5.3.3.5 The Acceptance of Illness Scale (AIS)

The AIS is an 8-item scale designed to assess acceptance of an illness and the presence of negative emotions associated with the illness (Felton et al. 2001). Respondents indicate the extent to which they agree with the eight statements (e.g. “I have problems adapting to limitations imposed by my illness”) on a 5-point scale from 1 (strongly agree) to 5 (strongly disagree). A higher score indicates more

acceptance of the illness. The scale has been shown to have good internal consistency with a Cronbach's α of 0.85 (Juczyński 2001).

5.3.3.6 The Fear Avoidance Beliefs Questionnaire (FABQ)

The FABQ is a 16-item scale designed to assess the level of fear avoidance beliefs (Waddell et al. 1993). Patients are required to rate their agreement with each of the 16 statements on a 7-point scale (0 = completely disagree to 6 = completely agree). There are two subscales: the work subscale consisting a seven items (e.g. 'My pain was caused by my work or by an accident at work') and a four-item physical activity subscale (e.g. 'Physical activity makes my pain worse'). The FABQ has been shown to be a valid measure of fear-avoidance beliefs in samples of chronic pain patients (Crombez et al. 1999; Kovacs et al. 2006). Both subscales have good internal consistency (Cronbach's α = 0.75-0.82; Swinkels-Meewisse et al. 2003).

5.3.4 Participants

258 patients attended one of the 27 programmes between June 2012 and April 2015. In order to maximise the data available for paired comparisons, patients were included if they had part-completed questionnaires. Patients were excluded if they had not filled in questionnaires at both time points.

5.3.5 Data Processing and Analysis

Questionnaires were scored according to their prescribed marking schemes. Raw scores were recorded using Excel 2007 and further analysis was performed with SPSS 20. Paired comparisons between questionnaire scores at baseline and outcome were computed using Student's related samples *t*-test. Effect sizes were calculated using Cohen's *d*. Cases with missing data points were excluded from the analyses in a pair-wise fashion.

5.4 RESULTS

131 patients completed or part-completed questionnaires at baseline and outcome (mean age = 52.9 ±11.98, age range = 27-82), 114 (87%) females and 17 (13%) males.

5.4.1 Differences between Baseline and Outcome Scores

Between baseline and outcome, paired *t*-tests revealed a significant difference in scores of: the anxiety and depression subscales of the HADS; the rumination, magnification, and helplessness subscales of the PCS; the cognitive fusion and avoidance subscales of the PIPS; the engagement and pain willingness subscales of the CPAQ; the AIS; and the activity subscale of the FABQ (Table 5.2).

Table 5.2 Baseline and outcome questionnaire scores from patients in the Centre B PMP, significance values shown for paired *t*-tests.

Questionnaire (Subscale)	Baseline Mean ±SD	Outcome Mean ±SD	Paired <i>t</i> -test outcome	Effect size Cohen's <i>d</i>
HADS (Anxiety)	12.6 ±4.9	10.7 ±4.9	t = 6.0, df(129), <i>p</i> < .001*	0.53 ^{<i>m</i>}
HADS (Depression)	11.1 ±4.4	8.7 ±4.4	t = 8.0, df(130), <i>p</i> < .001*	0.70 ^{<i>m</i>}
PCS (Rumination)	10.6 ±4.3	8.4 ±4.7	t = 5.2, df(97), <i>p</i> < .001*	0.53 ^{<i>m</i>}
PCS (Magnification)	6.3 ±2.9	5.1 ±3.2	t = 4.1, df(97), <i>p</i> < .001*	0.41 ^{<i>s</i>}
PCS (Helplessness)	14.2 ±5.7	11.2 ±6.2	t = 5.3, df(97), <i>p</i> < .001*	0.53 ^{<i>m</i>}
PIPS (Cognitive fusion)	23.6 ±4.1	21.0 ±5.6	t = 5.7, df(104), <i>p</i> < .001*	0.55 ^{<i>m</i>}
PIPS (Avoidance)	40.0 ±11.5	32.0 ±11.6	t = 8.0, df(103), <i>p</i> < .001*	0.79 ^{<i>m</i>}
CPAQ (Engagement)	33.4 ±11.9	40.1 ±12.5	t = -5.2, df(102), <i>p</i> < .001*	-0.52 ^{<i>m</i>}
CPAQ (Pain willingness)	16.5 ±8.6	20.2 ±9.2	t = -4.5, df(101), <i>p</i> < .001*	-0.44 ^{<i>s</i>}
AIS (Total)	19.6 ±9.0	23.5 ±6.0	t = -4.7, df(116), <i>p</i> < .001*	-0.43 ^{<i>s</i>}
FABQ (Activity)	17.1 ±4.8	12.4 ±6.1	t = 4.0, df(16), <i>p</i> = .001*	0.98 ^{<i>l</i>}
FABQ (Work)	23.1 ±13.6	20.9 ±10.9	t = 0.8, df(12), <i>p</i> = .421	0.23 ^{<i>s</i>}

SD = Standard Deviation; HADS = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophising Scale; PIPS = Psychological Inflexibility to Pain Survey; CPAQ = Chronic Pain Acceptance Questionnaire; AIS = Acceptance of Illness Scale; FABQ = Fear Avoidance Beliefs Questionnaire; * = significant difference between scores ($\alpha = .05$), ^{*s*} = small effect size ($d = 0.2-0.5$); ^{*m*} = medium effect size ($d = 0.2-0.8$); ^{*l*} = large effect size ($d > 0.8$).

5.4.2 Correlations between Changes in Scores from Baseline to Outcome

From baseline to outcome, the increase in scores on the anxiety and depression subscales of the HADS were correlated with several other measures (Table 5.3).

Table 5.3 Correlations (Pearson's *r*) between changes in subscale scores on the HADS, and subscale scores on the PCS, PIPS, CPAQ, AIS, and FABQ, from baseline to outcome.

Scale	Subscale (N)	Anxiety	Depression
PCS	Rumination(100)	.31**	.28**
	Magnification (100)	-	.28**
	Helplessness (100)	.37**	.41**
PIPS	Cognitive fusion (105)	.27**	.27**
	Avoidance (104)	.34**	.38**
CPAQ	Engagement (103)	-	-.31**
	Pain willingness (102)	-	-
AIS	Acceptance (115)	-.31**	-.30**
FABQ	Fear of activity (15)	-	-
	Fear of work (11)	-	-

** = significant at $p < .01$ level. HADS = Hospital Anxiety and Depression Scale; PCS = Pain Catastrophising Scale; PIPS = Psychological Inflexibility to Pain Survey; CPAQ = Chronic Pain Acceptance Questionnaire; AIS = Acceptance of Illness Scale; FABQ = Fear Avoidance Beliefs Questionnaire.

5.5 DISCUSSION

In this study of 131 patients attending an ACT-based PMP, there were significant improvements in several measures of psychosocial health and attitudes towards pain from baseline to follow-up. The majority of questionnaires used focused on the way patients' responded to and dealt with pain, and therefore were well-suited to assess the efficacy of the delivery of the programme. The general measure of mental health (HADS) also demonstrated a significant improvement in both feelings of anxiety and

depression in the patients, with mean scores on both scales falling to < 11 following the programme. Correlational analysis demonstrated that reductions in anxiety and depression scores correlated with reduced catastrophising and inflexibility to pain and increased acceptance of pain. This agrees with earlier studies (McCracken & Eccelston 2005; Vowles et al. 2008, 2014), which consistently show that increased acceptance is associated with improved emotional, social, and physical functioning, as well as decreased use of healthcare and medication, and better work status.

5.5.1 Limitations and suggestions

The present study did not include measures of patient general health, physical function, daily activity, social function, or pain intensity. Such measures could have been included to give a more rounded picture of changes in patient quality of life across the duration of the programme, and also to investigate correlations between the change in attitudes to pain and more general health outcomes. For example, the ACT-based programme contained an exercise/physiotherapy component; however there was no record made of patient activity. The inclusion an activity scale such as the FAI, or the SF-36 general health status questionnaire is recommended for future assessment of this PMP.

5.5.2 Comparison with audit of CBT-based programme (Chapter 3)

Direct comparison with the CBT programme audit is difficult because only the HADS was a common measure in both groups. Both studies revealed a significant improvement in anxiety scores from baseline to outcome, however effect size was slightly larger in the ACT sample. Depression scores did not significantly improve at outcome in the CBT sample, but there was a significant improvement in the ACT group. One explanation for this finding is that ACT teaches acceptance of negative thoughts as part of normal life and how to deal with them through a process of non-

judgemental awareness, thereby lessening their impact on mental wellbeing. At the follow-up data collection point in the CBT sample, depression scores were significantly improved over baseline, which indicates that this benefit of treatment took longer to emerge, and this may be due to differences in treatment approach compared to ACT.

The PCS is comparable to the catastrophising subscale of PCSQ as it uses some of the same statements, however the scoring is different – PCS uses 3 subscales. Both CBT and ACT audits showed significant improvements in catastrophising scores, however the effect size was larger in the ACT group. Acceptance has been suggested to have a mediating effect on catastrophising in chronic pain (Vowles et al. 2008) and this could explain the larger effect of ACT on catastrophising compared to CBT that was observed.

The CBT audit had a follow-up data collection point, which was not available in the ACT audit. A follow-up data collection would ideally be included reveal the longer-term effects of the ACT treatment, as the earlier CBT audit revealed that some treatment benefits did not emerge until the follow-up data collection point. The questionnaires used to assess the ACT-based programme mainly focused on mental health and pain acceptance, whereas the CBT audit also surveyed changes in general health and in daily physical activity. In order to gain a more complete picture of patient outcomes such questionnaires should be added to the battery used to assess the ACT-PMP patients in future.

CHAPTER 6

EEG MEASURES OF TONIC PAIN PROCESSING IN PATIENTS BEFORE AND AFTER ATTENDING AN ACCEPTANCE AND COMMITMENT THERAPY (ACT) PAIN MANAGEMENT PROGRAMME

6.1 ABSTRACT

Background: The ACT-based pain management programme at Centre B has been shown to bring about significant improvements in psychosocial health and attitudes to pain in a large sample (Chapter 5). Previous work in this thesis (Chapter 4: Study B) revealed that CBT-based treatment may affect the cortical electrical response to pain. The present study used the identical test paradigm in a sample of patients before and after ACT-based treatment. To confirm findings, a waiting-list/treatment as usual control group was also tested in a similar manner.

Methods: Continuous EEG recording was carried out at rest and following medium duration (90s) tonic painful stimulation using the cold pressor test. Recording sessions were carried out with 4 patients, both before and after attending an ACT-based PMP; and also with 13 waiting-list/treatment as usual control patients over a 12 week period. Participants also filled in questionnaires to measure psychophysical health and pain coping strategies, as per earlier studies.

Results: There were no significant effects of cold pressor pain upon EEG spectral power in either the patient treatment or patient control group. Questionnaire scores did not change significantly between baseline and follow-up sessions in either the

patient treatment or patient control group. Comparing the effect of the CPT on spectral power between all four groups (including the CBT and healthy control groups), spectral power changes were not similar between all patient groups at baseline; at follow-up, the effects of CPT on PSD were different from baseline, but there was no consistent pattern to suggest treatment effects.

Conclusion: The earlier finding that θ - and α -power are reduced in a patient group at baseline following cold pressor pain was not supported in either of the patient groups tested in this study. Group size in the treatment (ACT) group was small (4) meaning statistical tests lacked power and small/medium effects of the CPT (if any) could not be identified. Patient control group size was equivalent to group sizes used in the earlier study, yet the effect of the CPT at the baseline session did not match that of the earlier patient group. Results cast doubt on earlier significant findings, and these should be ideally be confirmed by repeating the study with larger patient groups.

6.2 BACKGROUND

This study was designed to investigate the effects of PMP treatment upon the EEG power spectral density (PSD) of participants, under two conditions, measured before and after treatment. The study used an identical protocol to that of the earlier study (Chapter 4, Study B) with one major difference: the treatment programme was based upon principles of ACT rather than CBT. Participants underwent EEG test sessions before and after they had attended an ACT-based PMP, which has proven efficacy in improving psychosocial health and attitudes towards pain from baseline to outcome (Chapter 5). Comparative data was also recorded from a ‘treatment as usual’ control

group consisting of patients who were on the waiting list for the treatment programme.

The earlier study of patients attending a CBT-based PMP revealed that the effect of cold pressor pain upon relative PSD at baseline (before treatment) was a significant reduction in both θ - and α -power in both left- and right-hemispheres, compared to PSD recorded at rest. Following treatment, these significant changes in relative PSD in response to cold pressor pain were no longer observed. Furthermore, in comparison to a healthy control group, pre-treatment between-group differences in left-hemisphere α -power and right-hemisphere θ -power were not observed post-treatment. These results suggest the possibility that treatment can effect brain activity in response to painful stimulation in patients, bringing it closer to brain activity of healthy persons. A waiting list control group was included in the present study to provide comparative data, to confirm that the change in brain activity previously observed in patients was related to the treatment, and not due to the effect of familiarity with the stimuli from the baseline to the outcome test session.

To investigate the relationship between changes in questionnaire scores and changes in EEG data pre-post treatment, a short case series was also performed. Two patients were chosen as cases, being those who had the largest and the smallest change in EEG PSD pre-post treatment (across both EEG studies). This may reveal a correlation between certain self-report measures and brain activity.

6.2.1 Aims

The aims of this study were to assess PSD at rest and during induced pain, in patients pre- and post-treatment in the ACT-based PMP at Centre B, and to compare this with data from a control group of waiting list/treatment as usual patients, as well as with data from the previous EEG study (Chapter 4: Study B). A case series was also

performed to investigate the relationship between changes in questionnaire scores and changes in EEG data.

6.2.2 Objectives

The objectives of this study were: to record continuous EEG at rest and during CPT induced pain in a group of patients before and after treatment, and to take the same measurements in a group of patient controls. Questionnaire data was also collected to verify the efficacy of the treatment in the patients studied.

6.2.3 General Aspects

The study was approved by the National Research Ethics Service Committee West Midlands-Solihull (granted: 15/12/2011, ref: 11/WM/0407) and the Research and Development committees at Russells Hall Hospital, Dudley (granted: 14/02/2012, ref: ID1004) and New Cross Hospital, Wolverhampton (granted: 18/02/2013, ref: 12CRIT01), and was sponsored by Birmingham City University (granted: 24/10/2011). The study protocol, participant information sheets, and informed consent forms were all approved by the above NHS research ethics committees.

6.3 METHODS

6.3.1 Study Design

The study used a prospective cohort design to assess the impact of an ACT-based PMP treatment upon PSD and questionnaire measures collected from treated patients and waiting list controls at two time points (baseline and outcome).

There were 4 participants in the patient group (3 female, 1 male, mean age = 49, range = 39–56), recruited consecutively from the population of chronic pain patients who had been enrolled into the PMP at Centre B. Test sessions were carried out in two-week periods before and after patients attended the Centre B PMP, and took place at Centre A.

The control group consisted of 13 participants (12 female, 1 male, mean age = 49, range = 33–64), recruited consecutively from the population of chronic pain patients who were on the waiting list of the PMP at Centre B. Test sessions were carried out 10 weeks apart, and took place at Centre A. All data was collected by the author. For the duration of the test sessions, participants sat in a quiet, dimly lit room. Participants were fitted with EEG recording equipment and given time to become familiar with the cold water bath stimuli prior to testing.

6.3.2 Test Procedure

EEG data was recorded with the same equipment setup as used in **Chapter 4** (see Section A.2.3). The test procedure was identical to that used in **Chapter 4: Study B** (see Section B.2.2), consisting of two periods of EEG recording, before and after exposure to the CPT (Figure 6.1).

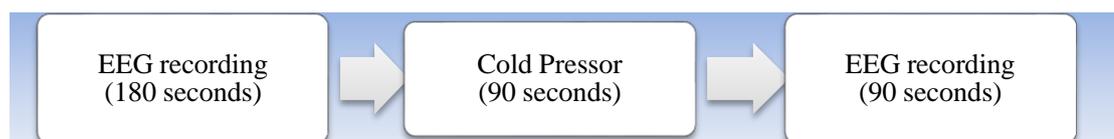


Figure 6.1 Diagram of the test procedure.

6.3.3 Data Processing and Analysis

Data from recording periods were filtered, converted from the time domain to the frequency domain using the Fast Fourier Transformation (FFT), and relative spectral power in each of the four bands (δ , θ , α , β) calculated for the left and right hemispheres in an identical manner to **Chapter 4: Study B** (see Section B.2.3). The main effect of treatment/time upon the relative spectral power in each band (over each hemisphere in the rest-rest period within each group) was calculated using a Wilcoxon Signed-Rank test for related samples (as the Shapiro-Wilk test indicated that some data could not be assumed to come from a normally distributed population). Between-group differences in the relative spectral power within each frequency band (over each hemisphere in each rest period) were calculated using a Mann-Whitney U test. The main effect of the CPT upon the relative spectral power within each frequency band (over each hemisphere at the two time points within each group) was calculated using Wilcoxon Signed-Rank tests.

6.3.4 Questionnaire Data Collection and Analysis

In the period one week prior to the EEG test session, a pack was sent to participants containing five questionnaires: Short Form 36-item general health questionnaire (SF-36); Hospital Anxiety and Depression Scale (HADS); Pain Coping Strategies Questionnaire (PCSQ); Frenchay Activities Index (FAI); Multidimensional Health Locus of Control Scale Form C (MHLC-C), together with instructions that they should bring the completed questionnaires with them to the subsequent test session. Questionnaire scores were collated and analysed in a pair-wise fashion as per the previous studies (see Section 3.3.5).

6.3.5 Comparison of PSD Data with Data from the Previous Study

PSD data from the waiting list control group was compared with PSD data obtained from the patient treatment and healthy control groups from the earlier study (Chapter 4: Study B). Between-group differences in the effect of the CPT on relative spectral power within each frequency band (over each hemisphere in each rest period) were calculated using a Kruskal-Wallis test for k independent samples ($k > 2$) (Kruskall & Wallis 1952). Post-hoc testing was performed using Dunn's test (Dunn 1964), adjusted p -values were used to correct for multiple comparisons.

6.4 RESULTS

6.4.1 EEG power – analysis of the effect of CPT

6.4.1.1 Within-group differences

Relative EEG spectral power in each of the four bands, in left and right hemisphere regions, was compared within each group between the rest-rest and cold-rest recording periods. Results are illustrated for the patient treatment group in Figure 6.2 and for the waiting list control group in Figure 6.3.

In the patient treatment group, at baseline and at outcome, there were no significant differences in relative spectral power following CPT, in any of the four power bands.

Effect of CPT upon relative spectral power in the patient treatment group

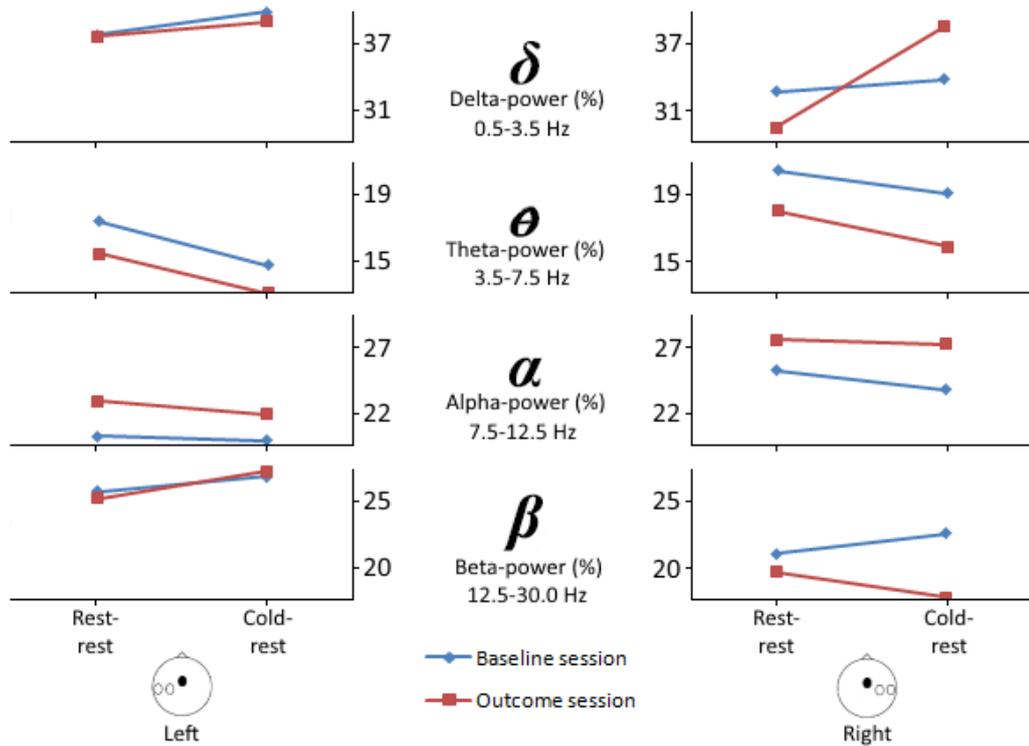


Figure 6.2 Effect of cold pressor on relative spectral power in each of the four bands in the left and right hemisphere electrodes (patient treatment group). There were no significant differences in power, either within- or between-sessions.

In the waiting list control group, at baseline and at outcome, there were no significant differences in relative spectral power following CPT, in any of the four power bands.

Effect of CPT upon relative spectral power in the waiting list control group

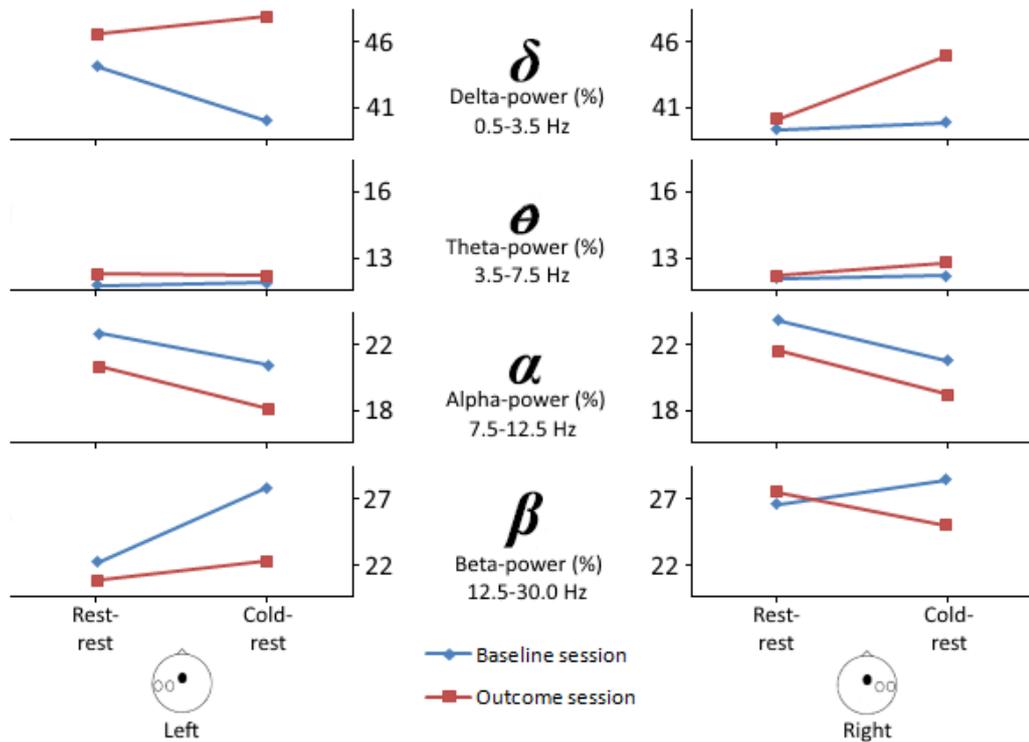


Figure 6.3 Effect of cold pressor on relative spectral power in each of the four bands in the left and right hemisphere electrodes (waiting list control group). There were no significant differences in power, either within- or between-sessions.

6.4.1.2 Between-group differences

The change in relative spectral power from rest-rest to cold-rest in each of the four bands in each hemisphere was compared between-groups at baseline and outcome time-points. There were no significant differences between the two groups.

6.4.2 Questionnaire Data

Comparisons were performed on participants' questionnaire subscale scores between baseline and outcome using Student's *t*-test for related samples. There were no significant differences in any scores between baseline and follow-up. Results are summarised in Table 6.1 below.

Table 6.1 Baseline and outcome questionnaire scores from patients in Centre B PMP and waiting-list controls.

Questionnaire (Subscale)	Treatment group (n =4)		Control group (n = 13)	
	Baseline Mean \pm SD	Outcome Mean \pm SD	Baseline Mean \pm SD	Outcome Mean \pm SD
SF36 (General health)	32.7 \pm 0.0	54.0 \pm 23.7	33.6 \pm 23.7	37.8 \pm 27.1
SF36 (Physical functioning)	25.0 \pm 0.0	22.5 \pm 21.0	18.5 \pm 23.3	23.5 \pm 28.9
SF36 (Role limitations due to physical health)	0.0 \pm 0.0	0.0 \pm 0.0	8.0 \pm 20.9	9.6 \pm 24.0
SF36 (Role limitations due to emotional problems)	25.0 \pm 0.0	41.5 \pm 49.9	22.4 \pm 36.8	12.8 \pm 29.0
SF36 (Social functioning)	37.5 \pm 0.0	42.8 \pm 14.4	32.9 \pm 23.6	39.1 \pm 25.4
SF36 (Bodily pain)	25.0 \pm 0.0	34.0 \pm 31.3	20.4 \pm 17.0	18.5 \pm 17.5
SF36 (Vitality)	25.0 \pm 0.0	26.9 \pm 17.0	21.3 \pm 20.2	23.2 \pm 20.0
SF36 (Mental health)	48.3 \pm 18.9	71.0 \pm 10.5	45.9 \pm 14.8	48.9 \pm 21.1
PCSQ (Catastrophising)	16.8 \pm 5.3	12.0 \pm 6.6	11.2 \pm 3.9	11.2 \pm 5.4
PCSQ (Cognitive coping and suppression)	32.8 \pm 14.7	54.0 \pm 15.4	12.0 \pm 4.6	10.0 \pm 4.2
PCSQ (Helplessness)	-1.7 \pm 13.9	-18.4 \pm 7.6	22.5 \pm 12.1	27.2 \pm 11.2
PCSQ (Diverting attention/praying)	23.1 \pm 12.4	35.5 \pm 15.9	18.5 \pm 10.5	16.6 \pm 10.0
HADS (Anxiety)	11.8 \pm 5.3	7.9 \pm 3.4	33.9 \pm 15.7	42.9 \pm 18.7
HADS (Depression)	10.0 \pm 3.8	6.7 \pm 3.7	3.3 \pm 14.7	-1.4 \pm 13.7
Frenchay Activities Index	30.5 \pm 11.7	35.0 \pm 14.2	23.6 \pm 10.9	21.0 \pm 9.4
MHLC-C (Internal)	12.8 \pm 6.4	14.0 \pm 4.2	18.5 \pm 6.6	18.2 \pm 7.5
MHLC-C (Chance)	8.5 \pm 2.9	12.0 \pm 2.6	12.5 \pm 6.3	13.8 \pm 5.0
MHLC-C (Doctors)	6.3 \pm 1.9	6.5 \pm 4.5	7.8 \pm 1.9	7.6 \pm 2.0
MHLC-C (Others)	8.3 \pm 2.9	6.5 \pm 2.9	6.9 \pm 2.4	6.8 \pm 2.9

SD = Standard Deviation; SF36 = Short form 36 item general health survey; PCSQ = Pain coping strategies questionnaire; HADS = Hospital Anxiety and Depression Scale; FAI = Frenchay Activities Index, MHLC-C = Multidimensional Health Locus of Control questionnaire form C.

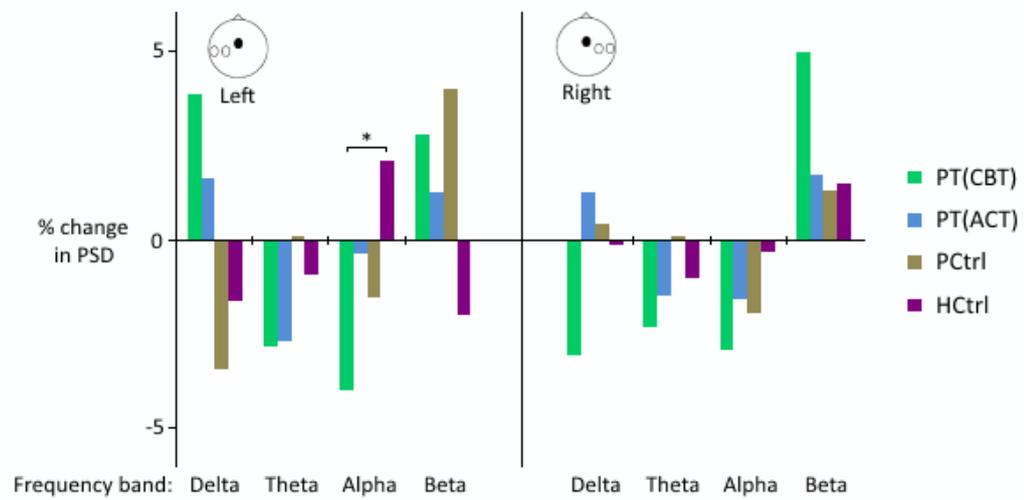
**6.4.3 EEG data – comparison with data from previous study (Chapter 4:
Study B)**

Table 6.2 Demographic information for all participant groups.

	Patient Treatment (ACT) n = 4	Patient Treatment (CBT) n = 12	Patient Control n = 13	Healthy Control n = 14
Gender (N)	M (1); F (3)	M (2); F (10)	M (1); F (12)	M (4); F (10)
Age (years) \pm SD	49 \pm 6.4	52 \pm 8.8	49.2 \pm 10.4	36 \pm 14.6
Pain Condition:				
Fibromyalgia (FM)	2	4	4	-
Back/neck pain	-	2	1	-
Disc degeneration	1	3	2	-
Post injury pain	1	1	1	-
Arthritis (OA/RA)	-	2	3	-
Neuropathic pain	-	-	2	-

A Kruskal-Wallis test was conducted to compare the change in relative spectral power from rest-rest to cold-rest in each of the four bands in each hemisphere between-groups at baseline and outcome time-points. The test showed that at baseline there was a statistically significant difference in the change in left hemisphere α -power (χ^2 (3, N = 39) = 8.42, p = .038). Post-hoc comparisons using Dunn's test indicated that the mean change in left hemisphere α -power for the patient treatment (CBT) group (M = -3.96, SD = 4.0) was significantly different than the healthy control group (M = 2.13, SD = 5.0, z = -2.87, p = .025). At outcome there were no statistically significant differences between the three groups. Results are illustrated in Figure 6.4.

Baseline: effect of CPT on spectral power in left and right hemisphere electrodes



Outcome: effect of CPT on spectral power in left and right hemisphere electrodes

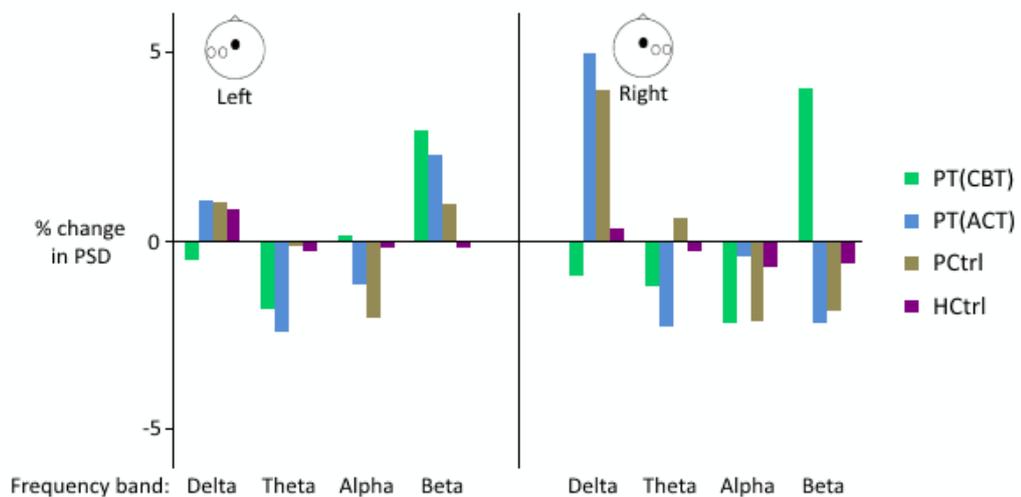


Figure 6.4 Effect of cold pressor test (CPT) on spectral power in patient treatment (PT) (CBT and ACT groups), patient control (PCtrl) and healthy control (HCtrl) groups at baseline (upper) and outcome (lower). At baseline, there was a significant difference between the PT (CBT) and HCtrl groups in the effect of CPT on alpha power in the left hemisphere, * = significant at $p < .05$ level.

6.5 DISCUSSION

6.5.1 Within-group differences

6.5.1.1 Patient treatment group

At both baseline and outcome sessions, there was no significant change in EEG spectral density following immersion in the cold pressor. Also questionnaire scores revealed no significant differences in psychophysical health and attitudes to pain at a group level. The group size was small (4 participants), meaning that statistical significance tests of the effects of the CPT on PSD, or of the treatment on questionnaire scores were heavily influenced by variance in individual data points. For example, there were obvious changes in questionnaire subscale mean scores from pre- to post-treatment (Table 6.1), however these were smaller than one standard deviation.

The effect of CPT upon spectral power was similar across sessions: δ - and β -power increases were accompanied by decreases in θ - and α -power (Figure 6.2). If there was any effect of the treatment upon the response to cold pressor pain, it was too small to be identified. Large, consistent effects across all participants were absent, and the small group size meant that small/medium effects would not be picked up.

6.5.1.2 Patient control group

The patient control group showed that treatment as usual has no significant effect on psychosocial parameters measured using self-report questionnaires and this was as expected.

In response to the CPT, α -power decreased in both sessions, θ -power did not change in both sessions, whereas δ -power decreased slightly at baseline, but increased

slightly at follow-up, also β -power increased at baseline but decreased at follow up. None of the changes were significant, but the slight differences between sessions may indicate some effect of familiarity with the stimulus.

6.5.2 Between-group differences (including groups from previous study)

At baseline, the effect of CPT on PSD in the patient groups was not similar between all three groups (Figure 6.4, upper). Alpha-power was significantly reduced by the CPT in the CBT patient treatment group, visibly reduced (non-significantly) in the patient control group, and barely changed in the ACT patient group. The effect on θ -power was similar between the two treatment groups; there was a visible decrease in both groups, however in the patient control group there was no observable change. All patients were drawn from a similar population and were at same stage of treatment (baseline/pre-treatment), and would be expected to show similar response to CPT. The earlier finding that θ - and α -power are significantly reduced following cold pressor pain was not supported by either of the patient groups tested in this study.

There was a consistent increase in left-hemisphere β -power following CPT in all patient groups, but in the healthy control group there was a decrease in β -power. Beta-power increases could have been the result of muscle activity artefacts, which have previously been found to contaminate high- β frequencies (Backonja et al. 1991). Indeed, as the left hand had been placed in the cold pressor, it is possible that the left side increase in β -power was due to left arm, shoulder, and neck muscle movements made by the participants in response to discomfort in the left hand.

Previous studies have reported inconsistent or absent θ -power changes in response to CPT in healthy subjects (Table 2.8). The one study that tested a patient sample (Stevens et al. 2000; fibromyalgia) reported an increase in θ -power during tonic pain

compared to rest. The present study tested groups of patients with a mix of conditions, meaning that the effect of tonic pain on θ -power could not be predicted based on earlier work that tested patients with the same condition together. Such contrasting findings between three groups drawn from the same population could suggest that θ -power changes are not a reliable effect of tonic pain, and if the study were repeated with new samples, quite different results may be found. It must be noted that group sizes were smaller than planned in this study, meaning that the effect of individual data on the group average is relatively greater compared to larger sample sizes, and this may have influenced the result. The desired group size of 19 participants was not attained due to difficulties in recruiting and retaining sufficient participants in the time available. Individual differences were controlled for where possible by the use of paired comparisons to analyse the group data; each participant was only compared to him/herself under different conditions, meaning it was the difference between the conditions that was analysed, rather than absolute values. In this way, any participants exhibiting abnormal absolute values would not overly influence the group average.

6.5.3 Limitations and suggestions

These inconsistent findings may be due to methodological inconsistencies between the present studies and previous research in this area. In the present studies participant EEG was not recorded whilst the hand was immersed in the cold pressor and significant effects on PSD may have subsided by the time that recording was started following withdrawal from the CPT. Two earlier studies performed EEG recording during and after immersion in the cold pressor: A.C.N. Chen and colleagues (1989) reported that post-CPT readings remained slightly different to rest but not to the significant extent seen during immersion in the CPT; also Stevens and

colleagues (2000) recorded a post-CPT EEG at one minute after withdrawal, δ -power remained elevated compared to rest but other bands displayed no real difference compared to rest. These studies therefore make a convincing case for recording during immersion in the cold pressor to ensure the observation of maximal change in PSD. In the present studies, recording was not conducted during CPT in order to minimise EEG contamination from muscle activity caused by participants not being relaxed. Whilst the advantage of this method is a period of relatively artefact-free recording, it has the disadvantage of not recording the data from the time when the effect of tonic pain upon PSD was at its peak. The alternative method, favoured by almost all of the earlier CPT studies (Table 2.8), has been to record EEG during immersion in the cold pressor and then remove artefact contaminated data in a pre-processing step before performing FFT. In these earlier studies the finding that tonic pain causes a temporary decrease in α -power and increase in β -power is relatively consistent. The reason that this outcome was not found across participant groups at baseline in the present study is most likely due to the fact that EEG was recorded after CPT rather than during CPT, meaning that the effect of tonic pain upon the EEG was not at maximum during recording.

The present study also neglected to remove artefacts from the continuous EEG data, on account of the participants being at rest during the recording, which meant that movements were minimal. The presence of movement artefacts may have influenced the result, however this is unlikely based upon previous studies. Movement artefacts may not be a problem when studying $< 25\text{Hz}$ activity, as at least two studies have shown that muscle activity does not interfere with these frequencies. Dowman and colleagues (2008) tried to control for muscle artefacts by recording a control condition in which participants made a wincing facial expression.

A final limitation is that there was no control for vigilance. The frequency composition of resting EEG may fluctuate according to the level of vigilance or arousal of the subject at the time of recording, which may also vary across sessions and subjects. It is therefore possible that the observed effects of tonic pain upon PSD were solely due to increased arousal and vigilance compared to the resting condition. Guidelines from the international pharmaco-EEG society suggest that vigilance can be controlled by having subjects perform some continuous cognitive task whilst at rest, incorporating a fixation point to minimise eye movement artefacts; also sleep pattern over the preceding few days, the time since last meal, and type of food consumed can affect vigilance levels and should be taken into account (Jobert et al. 2013).

6.5.4 Conclusion

The earlier finding that θ - and α -power are reduced in a patient group at baseline following cold pressor pain was not supported in either of the patient groups tested in this study. Group size in the patient treatment (ACT) group was small (4) meaning statistical tests lacked power and small/medium effects of the CPT (if any) could not be identified. Patient control group size was equivalent to group sizes used in the earlier study, yet the effect of the CPT at the baseline session did not match that of the earlier patient group. EEG recording may yield more consistent results if brain activity is sampled during immersion in the cold pressor. Results did not support earlier significant findings, and these should be confirmed by repeating the studies with the suggested methodological change using a larger group of participants.

6.6 CASE SERIES

To investigate the relationship between changes in questionnaire scores and changes in EEG data pre-post treatment, a short case series was also performed. Two patients were chosen as cases, being those who had the largest and the smallest change in EEG PSD pre-post treatment (across both EEG studies). A relationship between the change of PSD and in certain questionnaire scores may indicate a psychological basis for changes in brain activity.

6.1 Case study 1: Patient A

Patient A showed the largest differences in the effect of the CPT upon PSD pre-post treatment. More specifically, large fluctuations in δ -, θ -, and β -power following exposure to the CPT pre-treatment were far less pronounced post-treatment, whereas there was the opposite effect of CPT on α -power (small change pre-treatment, large change post-treatment).

Pre-post treatment questionnaire scores for patient A showed improvement on all scales, particularly SF36 (Role limitations due to emotional problems), SF36 (Social functioning), daily activity, and catastrophising.

6.2 Case study 2: Patient B

Patient B showed the least differences in the effect of the CPT upon PSD pre-post treatment. At both pre- and post-treatment test sessions there was little effect of exposure to the CPT upon PSD.

Pre-post treatment questionnaire scores for patient B were a mix of improvements on some scales (for example use of the cognitive coping and suppression pain coping strategy), and worsening on other scales, particularly SF36 (Physical functioning),

SF36 (Social functioning), and catastrophising. Daily activity score remained at the same level pre-post treatment.

6.3 Case series discussion

Patient A improved on all scales of the self-report measures post-treatment, as well as displaying large fluctuations in PSD following CPT at baseline, which reduced at follow up (with the exception of an increase in α -power). Conversely, the PSD of Patient B was relatively unaffected by exposure to the CPT at baseline and follow-up; and fewer improvements on questionnaire scores were seen, in fact some scores worsened. Given these findings, it is suggested that baseline EEG fluctuation following exposure to a tonic pain stimulus might be a possible indicator of future PMP treatment efficacy. As this interpretation is based on just two cases, caution must be advised, however it does give a useful direction to proceed in future work.

Also interesting to note is that in Patient A the changes in PSD (increased α -power) accompanied improvements in catastrophising, social functioning, and daily activity scores; whereas in Patient B there was little change in PSD and scores on the same scales actually worsened following treatment. Previous studies have made a link between α -power and catastrophising scores, suggesting that the α -activity may be related to a suppression of negative feelings (Davison 2004, Klimesch et al. 2007, M.P. Jensen et al. 2015). This is a tentative link, however future work might focus on how α -activity is related to catastrophising based on these findings.

CHAPTER 7

CONCLUSIONS

7.1 INTRODUCTION

Studies reported in this thesis have investigated the effect of two multidisciplinary pain management programmes upon psychosocial measures in the form of self-report questionnaires, and also upon neurophysiological responses to pain recorded using EEG. Experimental Chapters 3 and 5 contained investigations of whole populations of patients who had attended either the Centre A CBT-based PMP or the Centre B ACT-based PMP since they were started. These studies both revealed significant improvements in self-report questionnaire scores from pre- to post-treatment.

Literature reviewed in Chapter 2 showed that successful treatments for pain (surgical, pharmacological, and psychological) are associated with measurable changes in brain activity. However, studies had not previously investigated the effect of group multidisciplinary pain management upon brain activity related to pain processing. Based on these findings, neurophysiological experiments were performed in samples of patients from each programme, and also in patient and healthy control groups, both to identify brain activity in response to painful stimulation, and to examine any pre- to post treatment changes in this brain activity. These were reported in Chapters 4 and 6. In the CBT-based PMP patient group, cold pressor pain caused a significant reduction in α - and θ -power at baseline, which was no longer significant following treatment. Both control groups showed very little intra- and inter-session difference in spectral density. The ACT-based PMP patient group

ultimately lacked sufficient numbers, meaning the results could not be used to make meaningful comparisons between the two programmes. However, the effect of cold pressor pain upon θ - and α -activity was found to be modulated following a CBT-based PMP. These findings lend support to the understanding of pain as a biopsychosocial phenomenon – a treatment such as the PMP which focuses on the ‘psycho’ and ‘social’ components of the biopsychosocial model not only brings about change in measures of those components, but also in measures of brain activity (the ‘bio’ part of biopsychosocial).

7.2 SUMMARY OF FINDINGS

The effect of both treatment programmes was a significant, but small, improvement in the majority of questionnaire measures, pre- to post-treatment. These findings agree with previous studies which have also found that psychologically-based, multidisciplinary pain management tends to bring about small but significant improvements in patients, and is more effective than treatment as usual (Morley et al. 1999; Hoffman et al. 2007; Veehof et al. 2011; A. Williams et al. 2012; Hann & McCracken 2014). These improvements followed treatment with PMPs that were based on cognitive theory (CBT-based PMP) or the psychological-flexibility model (ACT-based PMP). The questionnaires used in the two audit studies differed in their assessment of the underlying theory of the treatment programme. The CBT-based programme audit focused on aspects of the cognitive triad (thoughts, feelings, behaviours) such as coping strategies, catastrophising, mental health, and daily activity. Conversely the ACT-based PMP audit looked at psychological-flexibility and acceptance, as well as mental health. Therefore, each audit lent weight to the theory underlying the treatment programme; however the cognitive model, being elegant in its simplicity, offers a neat framework for understanding the efficacy of

pain treatment by PMP. Despite this, the inherent problem with using self-report questionnaires to assess treatment outcomes is that they are a measure of subjective experience and cannot reveal underlying *physiological* mechanisms that may accompany successful treatment. Nonetheless, subjective measures are important in understanding the psychosocial changes that occur across treatment, and these changes are known to influence the initiation, exacerbation, attenuation, and maintenance of pain (Jensen & Turk 2014).

The EEG studies revealed that the effect of tonic pain upon spectral power was different between healthy and patient samples, and that there were measurable changes pre- to post-treatment that were not seen in the treatment as usual sample. In the treated group of patients, the effect of tonic pain pre-treatment were significant decreases in θ - and α -power, accompanied by an observed increase in β -power. Post-treatment, θ - and α -power were less effected by tonic pain, an increase in β -power was still observed. Decreased α -power accompanied by an increase in β -power is a characteristic response to salient events (B. Bromm & Lorenz 1998), and has often been explained as an event-related desynchronisation (Pfurtscheller & Aranibar 1977) of resting rhythms (α) with the corresponding synchronisation of faster (β) rhythms as the brain reacts to the event (Pfurtscheller 1992; Pfurtscheller & Lopes da Silva 1999). Decrease of slow θ - and α -rhythms in the patient treatment group indicates an interruption of resting brain activity by the tonic pain stimulus, and the increased β -power indicates arousal. Post-treatment, the less severe reduction in θ - and α -rhythms means that the pain stimulus did not interrupt resting brain activity to the same extent as at pre-treatment, indicating there was an effect of treatment upon the cortical response to painful stimulation. This may have been due to a change in cognitive appraisal of painful signals brought about by taking part in the PMP,

supported by the reduction in catastrophising and feelings of helplessness post-treatment. Patients also learned relaxation techniques for dealing with periods of increased pain, which they may have employed during exposure to cold pressor pain, and which may have contributed to the observed stability of θ - and α -power measured at outcome. A caveat to this is that observations may have been due to a familiarity with the stimulus at the outcome session, however this is unlikely, as the control groups tested did not exhibit significant differences between baseline and outcome measurements. The case studies hinted at a link between improved catastrophising scores and the effect of experimental pain upon EEG spectral density, suggesting a possible cortical basis for the effect of psychological treatment.

PMP treatment has a measurable effect upon brain activity related to pain. This is a novel finding that has the potential to influence the way in which treatment for chronic pain is assessed and even how it is delivered. Treatments which modulate EEG activity could potentially be beneficial to individuals with chronic pain in helping them learn to regulate their experience of pain. Evaluations of treatment-related brain activity changes might also allow for sub-grouping of patients and help to develop individualised treatments. The effects of psychological treatments on cortical activity could form the basis of a neuropsychological model of pain, which may be used to guide future research in understanding the mechanisms of clinical psychological treatments and the brain states that may facilitate treatment response.

7.3 CLINICAL IMPLICATIONS AND SUGGESTIONS FOR FURTHER STUDY

7.3.1 Programme delivery

The two PMP audits both showed that patients made significant improvements on domains of measurement pre- to post-treatment regardless of specific psychological format (CBT or ACT). This finding agrees with the observations made by other researchers that different psychological treatments tend to result in similar outcomes (Wetherell et al. 2011; A. Williams et al. 2012). However, there was one notable difference between the two programmes other than the psychological basis – the CBT-based programme had been running for over 15 years, whereas the ACT-based programme was just into its third year. The fact that both programmes significantly improved measures of psychological health and wellbeing, suggests that outcomes are less dependent on the particular contents of the programme and expertise of staff, and may be due to a more vague and general group behaviour effect. Patients' chronic pain is a private experience that is difficult to communicate to others, especially to the majority of people who only understand pain as an acute sensation. Treatment within a group who all suffer from similar problems can have a positive impact on the individual. A shared experience, a sense of not having to 'go it alone', opportunities to discuss their problems with people who have also experienced similar, and a feeling of intra-group connectedness can only be achieved in the group therapy setting, and these factors may be just as important as the content of the programme.

The provision of pain management programmes tends to be limited to larger cities and towns due to the availability of trained staff and specialists required to run the treatment. If group treatment can be beneficial even when delivered by less

experienced and specialised staff, this would mean that more programmes can be rolled out into the community and at a greatly reduced cost. Physically impaired patients often find it difficult to attend treatment due to the inconvenience of travelling to and from larger centres. Local programmes would make it easier for patients to comply with the demands of attending and mean that ultimately many more patients would have access to treatment and support for their condition.

7.3.2 Maintenance of improvements

The audit of the CBT-based PMP contained data collected at baseline, outcome, and at a follow-up session three months after the programme had ended. Improvements in mental health were seen at outcome and remained improved at follow-up, compared to baseline. There was no change in scores on measures of physical activity at outcome, but at follow-up significant improvements had been made. This suggests that patients continued to put into practice themselves what they had learned on the programme, particularly activity pacing which requires a gradual increase in daily activity and could explain why the significant physical activity improvements emerged only at follow-up. Conversely, significant decrease in the use of maladaptive coping strategies and increase in adaptive cognitive coping and suppression seen at outcome were not observed at follow-up, with scores not significantly different from baseline. The cognitive aspect of self-management may therefore be difficult to maintain in the absence of weekly treatment sessions.

Studies which contain several follow-up data collection points over periods of months, years, or decades provide valuable insight into the long-term maintenance of initial positive benefits. The problem with such studies is that over time many patients are lost to follow-up, particularly those who no longer attend regular visits to healthcare providers where they can be surveyed. The patients who have maintained

positive improvements do not provide long-term data, meaning that later follow-up collection of data may only represent those patients who have relapsed to pre-treatment levels, which emphasises the perceived lack of long-term benefit.

A possible solution to the problem of long-term maintenance of benefits and to diminishing compliance with research is the use of technology. Online pain management programmes, software applications, automated email and text based communication, multi-user video telecommunication, and other methods of service delivery offer exciting opportunities that can address long-term self-management, barriers to treatment, social support, and the rising cost of healthcare (Murray et al. 2005). Further research might examine the effects of these technologically driven treatments in order to monitor and refine their positive benefits, as well as identify the types of patients who might benefit most from them.

7.3.3 Neurophysiological testing

Pre- to post-treatment differences in the effect of tonic pain upon EEG power spectral density may be attributed to the effects of the pain management treatment programme. It is possible that specific aspects of the treatment were responsible for the observed effects on brain activity. If this were the case, it might be possible to make treatment programmes more streamlined to achieve the positive outcomes while using fewer resources. Future work in this area could therefore study outcomes in a group of patients that are tested before and after attending several sessions containing isolated components of the multidisciplinary programmes studied – for example: physiotherapy, relaxation techniques, pain education, mindfulness, and so on. A counterbalanced design would control for order effects, and this may even reveal an additive or subtractive effect depending on the order of treatment.

It is also important to bear in mind that individual patients will respond differently to treatment, and it is unlikely that one approach will benefit all patients. Chronic pain patients are usually grouped by clinicians' conception of the pain phenotype, which is limited by lack of objective signs and reliance of patient account. If response to treatment can be measured objectively using EEG, and indeed is related to pre-treatment measurements, it may be the case that certain patients respond differently to the treatment depending upon baseline physiology. Patients could be identified as more likely to be 'responders' before adding them to a treatment programme waiting-list. Patients who are classed as 'non-responders' could be given different forms of treatment sooner, rather than pursuing ineffective treatment which ultimately leads to a worsening of their overall condition. Such a strategy would improve outcomes for patients whilst also being more cost-effective than the current approach, where pain management programmes are delivered based on the preferences of the clinicians providing the treatment rather than on individual patient requirements. Ideally, treatment is flexible and not 'one-size-fits-all', and can be adapted depending on patient preferences and ongoing changes in both psychological and physiological measures.

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