Exploring the Processes and Psychological Factors Involved in Hypnotic Modulation of Chronic Pelvic Pain

Steven Coen

D.Clin.Psy. thesis (Volume 1)

2016

University College London

UCL Doctorate in Clinical Psychology

Thesis declaration form

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

Signature:

Name: Steven Coen

Date:

Overview

Part 1 is a literature review exploring the functional neuroanatomy of pain and psychological modulation of the pain experience. The focus of the review is a description and evaluation of peer reviewed research on functional brain imaging of hypnosis induced pain relief. The findings are summarised and discussed in the context of generalizability. Future research and clinical implications are then outlined.

Part 2 is a research study exploring the processes, application, clinical benefits and potential mechanisms of hypnosis for chronic pelvic pain. A mixture of quantitative and qualitative methods were employed to assess a number of psychological and sensory (i.e. pain) changes from baseline to end of treatment. All participants completed the study. Overall, the results suggest that participants benefited from hypnosis treatment but that such benefits varied between individuals in terms of sensory, psychological and behavioural effects such as pain relief, acceptance of pain and engaging in more activity. Several of these benefits were clinically significant and reliable, notably in terms of pain reduction and less catastrophizing.

Part 3 is a critical appraisal. Here reflections on the research process, from conducting the study for the empirical paper are discussed.

Table of contents

List of Tables

Part 1: Literature Review

Part 2: Empirical Paper

List of Figures

Part 1: Literature Review

Part 2: Empirical Paper

Acknowledgements

I am indebted to my research supervisor, Dr. Amanda Williams for all her support, direction and knowledge imparted during each stage of my research.

I also owe a great deal to Dr. Anna Mandeville and Dr. Raj Sharma for giving their time and expertise in providing the hypnosis intervention that was pivotal to the success of this project. I appreciate the efforts made, especially when the pressure was on to complete intervention in time for submission of my thesis. I thank Dr. Sharma in particular for stepping in late on in the project, without which the project would surely not have been a success.

My family, mother and mother-in-law have also been very supportive in reducing the burden of childcare on my wife towards the end of my thesis, when I spent a significant amount of time in the library! I thank my father, who is sadly no longer with us but who was, and still is, with me every step of the way.

Finally, and most importantly I owe so much to my wonderful wife who has supported me throughout my thesis and the entire doctorate, during the good and challenging times of the past three years of which there have been many. Thank you for being so understanding. With your support I may manage to get the thesis submitted before the arrival of our next child, which is very much imminent!

Part 1: Literature Review

Functional Neuroanatomy of Hypnotic Analgesia in Chronic Pain: What Have we Learned From Functional Neuroimaging?

1.1 Abstract

Background: Hypnosis is commonly used as an intervention for treating chronic pain, the mechanisms of which are likely to be neuropsychological. Whilst mechanisms of modulating chronic pain in health has been well described, there is a paucity of available synthesised information on mechanisms in individuals suffering with chronic pain. **Aims:** The aim of this review is to assess and critically evaluate current knowledge on the role of the brain in hypnotic analgesia of patients suffering with chronic pain. **Methods:** A systematic search of PsychINFO, Medilne and Embase was carried out. This search identified nine papers suitable for addressing the research aims. **Results:** The studies reviewed highlighted considerable variability in methodology and outcomes of research on brain mechanisms of hypnosis induced analgesia in chronic pain. Nonetheless, the most common brain regions implicated in the studies reviewed (anterior cingulate cortex, insula, thalamus, secondary somatosensory cortex and frontal cortex) overlap with those show to be involved in processing of pain in health and chronic pain. Moreover, these regions are predominately those previously implicated in more emotional and cognitive modulation of pain. In addition, baseline brain state appears to be linked to effectiveness of hypnotic analgesia. **Conclusions:** Given the relatively small number of studies available for review, there are limitations on the conclusions that can be drawn. As such, recommendations are made for future research including the need for larger sample sizes and more complex brain image acquisition

and analysis. Baseline brain state may predict response to hypnotic analgesia. There may be a role for assessing this before commencing hypnosis treatment.

1.2 Introduction

Overview of review

The aim of this review is to assess and critically evaluate current knowledge on the role of the brain in hypnotic analgesia of patients suffering with chronic pain. An overview of pain, functional brain imaging and the neuroanatomy of pain will be presented, followed by a description of clinical hypnosis and summary of research on brain processing of hypnosis. There follows a description of systematic search methods used to identity current literature on functional brain imaging of hypnotic analgesia in chronic pain patients. Finally a summary and critical evaluation of the current literature will be presented with implications for future research and clinical practice.

1.3 The Pain 'Matrix'

What is pain?

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (Merskey & Bogduk, 1994). Importantly, this definition avoids linking pain to the stimulus that produced it and highlights the emotional ("unpleasant") and cognitive aspects ("potential" tissue damage). This definition reflects the fact that pain can originate centrally and is therefore often experienced in the absence of observable organic sensory pathology (often referred to as functional pain syndrome or unexplained chronic pain) and is commonly associated with psychological factors such as mood and attention.

Chronic pain

Chronic pain occurs when symptoms persist beyond the normal acute period of tissue damage and healing time (greater that 3-6 months). It is debilitating physically and psychologically, affects approximately 20%-40% of the population and is a global phenomenon (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). It is generally well accepted that in chronic pain disorders psychological factors such as emotional and cognitive processing, as well as stress, play an important role in symptomatology. This is reflected in the high association of anxiety and depression in individuals suffering with chronic pain (estimated at between 20-40% (McWilliams, Cox, & Enns, 2003)).

Dimensions of Pain

Broadly speaking, contemporary theories consider pain a multidimensional experience consisting of *sensory* (localisation and intensity of pain), *cognitive (*aspects such as attention to pain), *affective (*level of negative affect associated with pain) and behavioural components rather than the somewhat dated dualistic approach which viewed pain as "organic" or "psychological" (R. Melzack, 1999, 2001, 2005; Ronald Melzack & Casey, 1968; Treede, Kenshalo, Gracely, & Jones, 1999). These theories emphasize the fact that the experience of pain is not simply related to the level of nociceptive input but is modulated by "top-down" factors such as mood, pain memories and hypervigilance, for example.

Sensory-Discriminative Dimension of Pain

The sensory-discriminative component of pain refers to the localisation of a painful event to a specific region of the body as well as identifying the intensity of the noxious stimulus (Bushnell et al., 1999; Treede et al., 1999). Several studies have shown that the sensory-discriminative aspect of pain can be modulated by affective and cognitive components of the pain experience, resulting in changes in pain tolerance,

pain intensity ratings and ability to localize the region of painful stimulation (see section on psychological modulation of pain).

Affective-Motivational Dimension of Pain

The affective-motivational dimension of pain is more complex and comprises several aspects that contribute to the emotional experience of pain including unpleasantness, fear and anxiety during and immediately following a painful event.
In addition, this dimension also refers to emotional feelings regarding the long-term implications of living with ongoing, persistent pain such as hopelessness, depression and anger (Price, 2000)(Donald D. Price & Harkins, 1992).

Cognitive-Evaluative dimension of Pain

The cognitive-evaluative component of the pain encompasses aspects such as attention, learning and anticipation (Bantick et al., 2002; Coen et al., 2008; Gregory et al., 2003; Ploghaus et al., 1999; I. Tracey et al., 2002; Treede et al., 1999; Yaguez et al., 2005) as well as past experience of pain, beliefs about pain and constructs such as acceptance (R. Melzack, 1999; Ronald Melzack & Casey, 1968; R. Melzack & Chapman, 1973).

1.4 Psychological modulation of pain

The three components of pain processing interact such that one can affect another. For example, using experimentally induced pain, experimenters have demonstrated that negative emotional states can increase pain perception and reduce pain tolerance (Hertel & Hekmat, 1994; Meagher, Arnau, & Rhudy, 2001; Phillips et al., 2003; N. K. Y. Tang et al., 2008; Weisenberg, Raz, & Hener, 1998; Whipple & Glynn, 1992; Zelman, Howland, Nichols, & Cleeland, 1991). whilst a positive emotional state

has been shown to increase pain tolerance and decrease pain perception (Roy, Peretz, & Rainville, 2003; Villemure, Slotnick, & Bushnell, 2003; Whipple & Glynn, 1992; Zelman et al., 1991; Zillmann, de, King-Jablonski, & Jenzowsky, 1996). Furthermore, experimenters have reported increased pain thresholds and lowered pain scores when volunteers are distracted from a painful stimulus (Bushnell et al., 1999; Levine, Gordon, Smith, & Fields, 1982; Miron, Duncan, & Bushnell, 1989; Rode, Salkovskis, & Jack, 2001). And that when individuals focus their attention towards pain they report higher pain scores, suggesting that focussing attention on pain enhances pain perception (Levine et al., 1982; Miron et al., 1989).

Furthermore, individual differences in personality traits such as neuroticism and trait anxiety have also been shown to be related to inter-individual differences in pain tolerance and pain perception (Farmer et al., 2013; Ruffle et al., 2015; J. Tang & Gibson, 2005).

The mechanisms of the psychological modulation of nociception are not fully understood but it is clear from numerous studies that the brain is where pain perception and thus modulation takes place (Bingel & Tracey, 2008).

1.5 **Functional neuroanatomy of pain processing**

Much of what we know about the functional role of brain regions involved in the processing of nociception come from functional neuroimaging studies, which have increased exponentially since the introduction of brain imaging methods such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) approximately 20 years ago. These studies have reported brain activation in response to a variety of pain stimuli (e.g. mechanical, chemical, heat, electrical) in health and chronic pain using a range of brain imaging methods (e.g. fMRI, PET, cortical evoked potentials [CEPs) and electroencephalography [EEG]).

The main underlying principles of the most commonly used functional neuroimaging imaging approaches are summarised in Figure 1.1. Electrophysiological approaches (MEG and EEG) detect direct electrical activity, thereby providing excellent temporal resolution of function (milliseconds). However, these approaches are limited in their spatial resolution and largely confined to measuring cortical activity with limited validity in accuracy of localization when measuring subcortical activity i.e. MEG. As a result of these limitations, electrophysiological approaches are mostly employed to assess temporal aspects of cortical function to acute stimuli. In addition to stimulus evoked activity, EEG has also been used extensively to measure spontaneous fluctuations in electrical activity (e.g. alpha, theta, gamma waves) at rest and during experimental challenges such as pain or hypnotic induction.

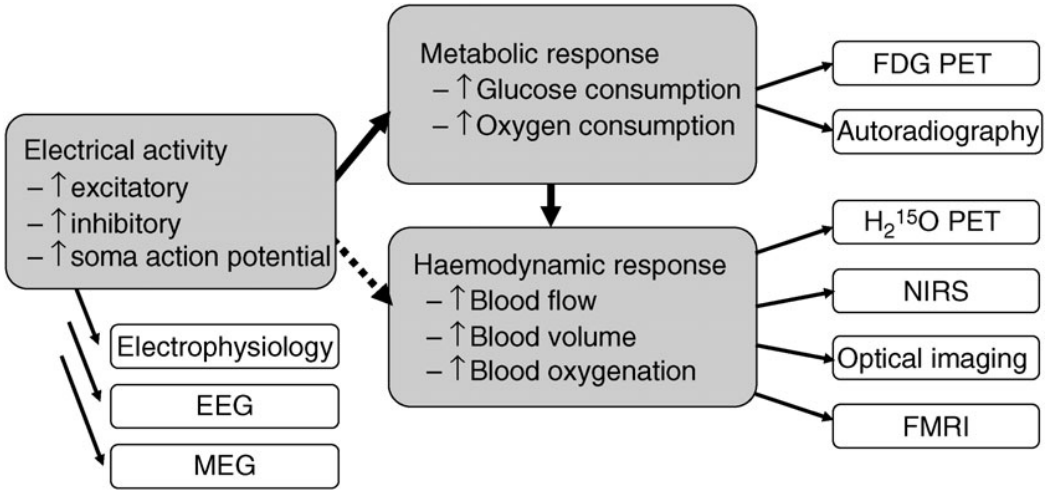


Figure 1.1 Summary of main principles of various neuroimaging techniques

In contrast, PET and fMRI measure blood flow, blood oxygenation or local metabolic changes that are indirect measures of neuronal activity. These methods are the most extensively used approaches in functional neuroimaging research. PET and fMRI have lower temporal resolution than the electrophysiological approaches (PET >60 seconds; fMRI 2-3 seconds) but have the advantage of excellent spatial resolution and ability to measure activity in subcortical structures. Whilst fMRI is a non-invasive

approach, PET requires injection of a radioligand and although this limits serial scans it does provide a window for examining specific neurotransmitters or receptors, giving it a biological specificity, unlike fMRI (Mayer et al., 2009).

Despite the heterogeneity in study methods a consensus has been reached regarding a network of brain regions involved in pain processing, commonly referred to as the pain neuromatrix. This cerebral signature of pain is most commonly defined as the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), prefrontal cortex (PFC), insula, and the thalamus, see Figure 1.2 (Apkarian, Bushnell, Treede, & Zubieta, 2005; I. Tracey, 2008). Given the multi-factorial influences on pain perception, the pain neuromatrix can be considered somewhat simplistic and researchers have acknowledged that this neuromatrix overlaps with other cognitive, emotional and sensory (non-nociceptive) stimuli and may represent a common brain response to salient sensory and emotional stimuli (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Mouraux, Diukova, Lee, Wise, & Iannetti, 2011; I. Tracey, 2008). Nevertheless, the cerebral signature of pain, as it is now commonly described (Irene Tracey & Mantyh, 2007), is a summary of current knowledge on brain involvement and has been defined as comprising lateral (sensory-discriminatory, including regions such as the S1, S2, posterior insula and thalamus) and medial (affective-cognitive-evaluative components, including regions such as the PFC, anterior insula and ACC) functional neuroanatomical divisions (I. Tracey, 2008). Other regions that are also commonly reported in functional neuroimaging studies on pain include the amygdala, cerebellum and hippocampus. The exact nature of activity in any given study depends on a multitude of factors including the population being studied (chronic pain patients/healthy volunteers), stimulus type, imaging modality and experimental design. Although the influence of inter-individual variability is diminished by studying and summarising groups in functional imaging studies, there are likely to be differences in

genetics, neurotransmitters, autonomic function and psychological responses to pain that also contribute to the composite of brain activity reported in any given study (Farmer et al., 2013). For a schematic summary of the main factors known to modulate pain perception see Figure 1.3.

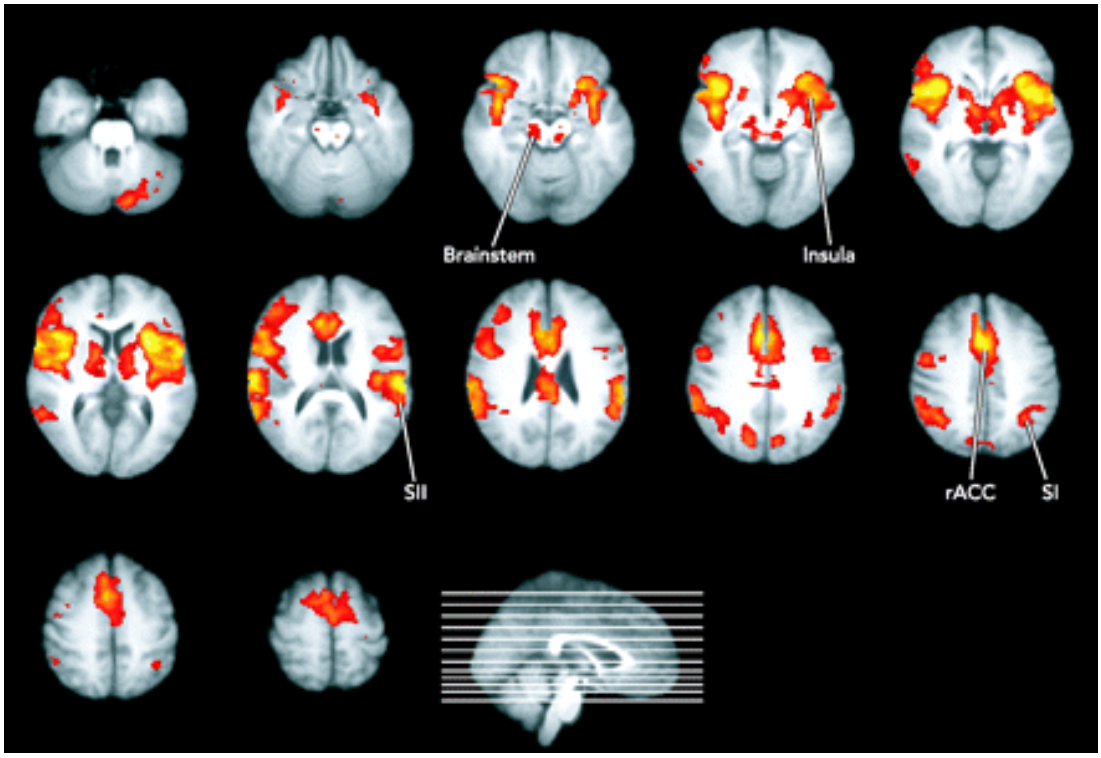


Figure 1.2 Cerebral signature of pain. fMRI data rendered onto structural MRI image, depicting brain activity (from bottom to top of brain) during pain in the brainstem (thalamus), insula primary and secondary somatosensory cortices and the anterior cingulate cortex. Figure adapted from Bingel & Tracey (2008).

Overview of main brain regions involved in pain processing

Primary Somatosensory Cortex:

Previous functional imaging studies have shown evidence that the primary somatosensory cortex has an important role to play in processing visceral and somatic sensations (Aziz et al., 2000; Bushnell et al., 1999; Coghill, Sang, Maisog, & Iadarola, 1999; Craig, Reiman, Evans, & Bushnell, 1996; S. W. Derbyshire et al., 1997; Kenshalo & Willis, 1991; Porro, Cettolo, Francescato, & Baraldi, 1998). Many of these studies have highlighted the role of the SI in processing sensory-discriminative aspects of non-

painful and painful somatic and visceral sensations, such as spatial discrimination and intensity. Indeed, several studies have shown brain activity in this region increases with rising sensory input suggesting the intensity of a stimulus is encoded in the SI (Bushnell et al., 1999)(Coen et al., 2008; Coen et al., 2007).

Several studies have also suggested the SI may be also important in processing affective (Hofbauer, Rainville, Duncan, & Bushnell, 1998; D. D. Price, 2000; D. D. Price & Verne, 2002) and cognitive dimensions of pain (Bushnell et al., 1999; Coghill et al., 1999; Porro et al., 1998).

Secondary Somatosensory Cortex:

The secondary somatosensory cortex receives afferents from the primary somatosensory cortex, and also from the thalamus (Stevens, London, & Apkarian, 1993). There is evidence to suggest that S2 plays a role in serial secondary processing of incoming sensory information after processing has taken place in the S1 (Mauguiere et al., 1997). However. it has also been suggested that the S2 may be involved in attention to painful events rather than being involved in the sensory discriminative aspects of sensations (Kenshalo & Willis, 1991). However, lesion studies in primates have provided evidence to suggest that S2 contributes to texture and shape discrimination (somethetic function) (Garcha & Ettlinger, 1978, 1980; Murray & Mishkin, 1984).

Anterior Cingulate Cortex:

The anterior cingulate cortex (ACC) has been activated in many studies of pain processing and sensory stimulation. It is generally broken down into two regions; the perigenual region of the ACC (BA32) and the mid-ACC (BA24).

The perigenual region of the cingulate (BA32) has direct connections with brainstem autonomic nuclei and is believed to play a role in the management of

autonomic and emotional reactions to external stimuli, (Devinsky, Morrell, & Vogt, 1995; Vogt, Derbyshire, & Jones, 1996). The mid-ACC (BA24) has connections with the motor cortex and has been shown to be mainly involved in response decisions, attention and preparatory motor functions (Devinsky et al., 1995; Vogt et al., 1996) as well as being involved in the anticipation of pain (Yaguez et al., 2005). The mid-anterior cingulate gyrus has also been shown to be activated by negative emotions (Bush, Luu, & Posner, 2000; George et al., 1995; Phillips et al., 2003; Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Tolle et al., 1999) and processing the unpleasantness of pain which has been shown to positively correlate with activity in this region (Rainville et al., 1999; Rainville et al., 1997; Tolle et al., 1999).

Several studies have also shown association of activity in this region with level of sensory input such that activity increases with increasing pain, suggesting a function of encoding of stimulation intensity and therefore in sensory-discriminative aspects of pain processing (Bernstein et al., 2002; Binkofski, 2000; Brooks, Nurmikko, Bimson, & Roberts, 2002; Porro et al., 1998). More recent findings suggest a multi-functional role of the mid ACC in processing sensory and cognitive aspects of painful stimulation (Coen et al., 2008).

Insula:

The insula is perhaps the most common area of brain activation following painful stimulation (Apkarian et al., 2005; Peyron, Laurent, & Garcia-Larrea, 2000) and is generally divided into the anterior and posterior regions.

There is little evidence to suggest the insula is specific to pain as activation in this region has been shown in response to a variety of non-noxious stimuli including electrical, tactile, vibratory and thermal sensations (Coghill, Sang, Berman, Bennett, &

Iadarola, 1998; Coghill et al., 1994; Craig et al., 1996; Iadarola et al., 1998; Mauguiere et al., 1999). However, functional imaging studies have shown that mid-posterior insula activity increases with intensity of thermal stimulation (Coghill et al., 1999; Peyron et al., 1999).

In contrast, the anterior insula is believed to be involved in the affective responses to pain (Coen et al., 2009; Phillips et al., 2003) and interoception (Craig, 2002, 2003). Injury in the form of lesions to the anterior insula results in diminished affective responses, but does not affect the spatial discriminative aspects of a painful experience.

Thalamus:

The thalamus is made up of several nuclei and is where nociception information enters the brain from the periphery; from this region sensory information is transmitted to limbic and cortical brain regions. As well as being implicated in pain processing, activation of the thalamus has been shown to increase during periods of vigilance or attention suggesting the thalamus has a more specific role in mediating general arousal reactions to pain (Lowey AD, 1990).

Pre-frontal cortex:

Previous studies involving pain have identified the right ventrolateral prefrontal cortex as being involved in corticolimbic inhibition of pain (Berman et al., 2008; Lorenz, Minoshima, & Casey, 2003; Mayer, Naliboff, & Craig, 2006). There is a well-characterized opiate-sensitive descending pathway which descends from the frontal cortex to the amygdala, PAG, rostral ventral medulla to the spinal dorsal horn (Fields, 2000; Villemure & Bushnell, 2002) that is thought to be involved in pain inhibition. Other researchers have also found increased activity in the dorsolateral PFC associated with a decrease in pain ratings during cognitive processes such as placebo analgesia and

distraction from pain (Coen et al., 2008; Kong et al., 2006; Kong, Kaptchuk, Polich, Kirsch, & Gollub, 2007).

1.6 **Brain function in chronic pain**

Studies have shown that brain activity in patients with chronic pain overlaps with that seen in normal subjects to experimental pain but that there is a tendency for lower activity in clinical populations in most regions. However, it has also been suggested that PFC activity is more prevalent in functional imaging studies involving patients with chronic pain and that the activity reflects the added burden of cognitive and affective impact of chronic pain (Apkarian et al., 2005). It should be noted however that differences between clinical and healthy populations may be accounted for by various factors, not least the effect of co-morbid symptoms commonly found in clinical pain populations (Elsenbruch et al., 2010). Moreover, the causality i.e. whether brain activity was different in chronic pain patients as a result of chronic pain or prior to pain symptoms is not clear and requires longitudinal imaging studies are required that also assess other biological, psychological and environmental factors that contribute to chronic pain.

1.7 **Functional neuroanatomy of psychological modulation of pain**

As previously described, experimental evidence suggests that pain tolerance increases during distraction and positive emotional modulation. but decreases when attention is focused on pain or during negative emotional modulation (Coen et al., 2008; Phillips et al., 2003; N. K. Y. Tang et al., 2008; I. Tracey et al., 2002; Villemure et al., 2003; Zelman et al., 1991). Using brain imaging techniques, researchers have shown a neurological basis of psychological modulation of pain which typically involves regions such as the anterior insula and anterior cingulate cortex ([ACC] emotional modulation)

(Berna et al., 2010; Coen et al., 2009; Phillips et al., 2003; Rainville, 2002; Rainville et al., 1997) and frontal cortex and ACC (cognitive modulation) (Bantick et al., 2002; Coen et al., 2008; Dunckley et al., 2007; Kulkarni et al., 2005; Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000; Tolle et al., 1999; Valet et al., 2004). In addition, several studies have shown activity of the cerebral signature of pain during the anticipation of pain (in the absence of a physical stimulus), highlighting the importance of expectation on the pain experience (Ploghaus et al., 1999; Villemure & Bushnell, 2002; Yaguez et al., 2005). Finally, several studies have also shown the periaqueductal grey matter and hippocampal network to be important in emotional and cognitive inhibition and facilitation of pain (Ploghaus et al., 2001; I. Tracey et al., 2002).

More recently, there has been a shift away from correlating individual loci of pain activity with function and a move towards studying networks (e.g. emotional arousal, salience and sensorimotor networks) involved in psychological modulation through the use of connectivity analysis (Denk, McMahon, & Tracey, 2014; Garcia-Larrea & Peyron, 2013; Labus et al., 2009; Labus et al., 2008; Mayer, Labus, Tillisch, Cole, & Baldi, 2015; Ploner, Lee, Wiech, Bingel, & Tracey, 2010; Wager et al., 2013).

1.8 **Summary of neuroanatomy of pain processing**

In summary, functional neuroimaging studies have helped delineate a pain pathway whereby afferent nociceptive information is transmitted through the thalamus to the S1, S2, IC, ACC and PFC. Whilst there appear to be differences between chronic and experimental pain (i.e. more activity seen in PFC in chronic pain, less activity in other areas), the brain signature is broadly consistent across populations. Furthermore, a wealth of studies have shown how modulation of pain perception is associated with changes in various loci considered part of the pain signature.

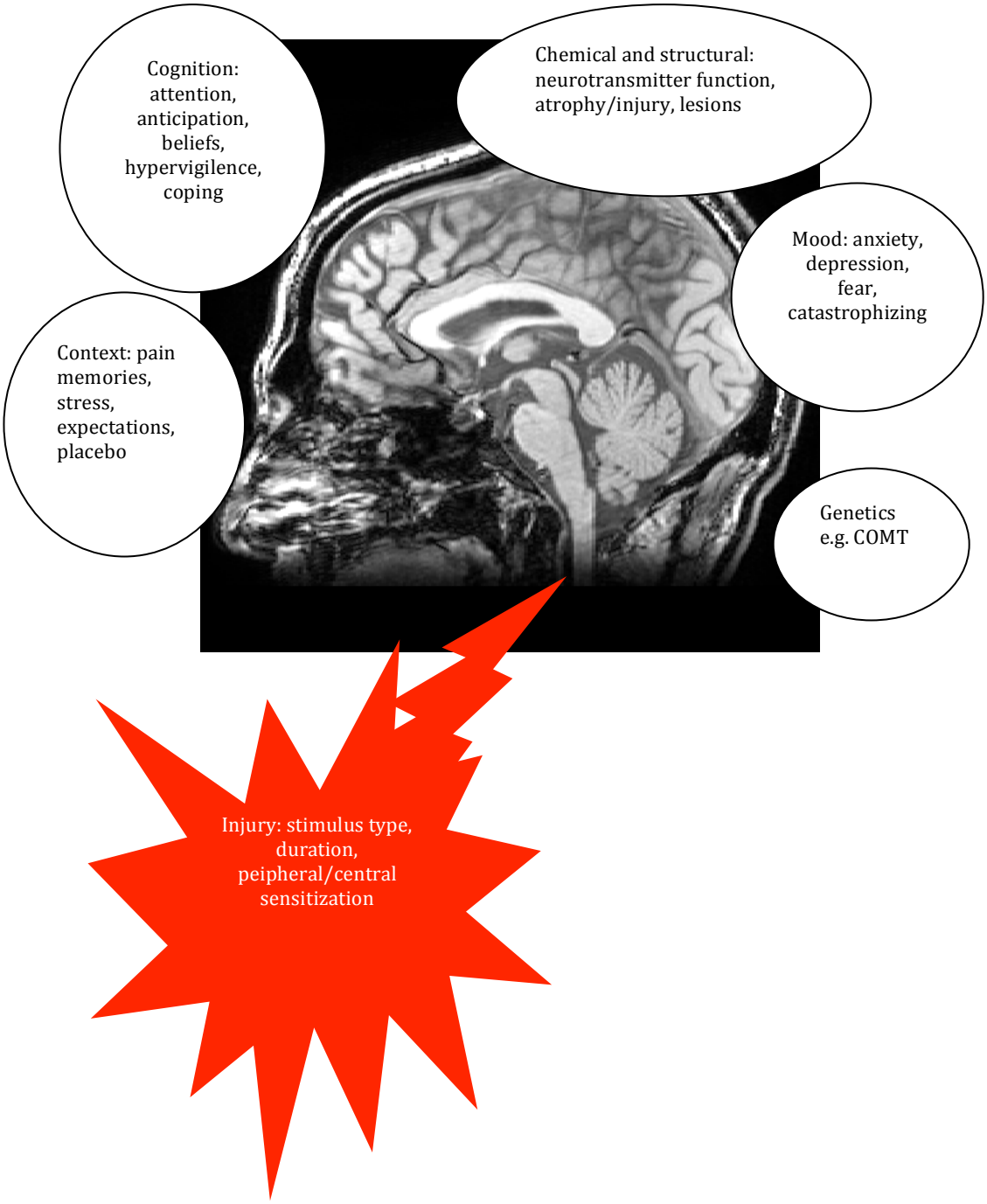


Figure 1.3 Schematic summary of most common factors known to modulate human perception of nociceptive input, overlaid onto structural MRI of candidate's (Steven Coen) brain. Peripheral nerves transmit nociceptive signals through the spinal column to the brain, the perception of the signal is influenced by factors such as attention and mood which can amplify or reduce the individual experience of pain.

1.9 **Clinical Hypnosis**

Clinical hypnosis is a procedure that results in a temporary change in individual state such that peripheral awareness is reduced, attention is focused and responsiveness to suggestion is increased. In order to achieve a hypnotic state or trance, hypnotherapy typically involves the use of a series of instructions such as focusing on breathing rhythms or using guided imagery both of which can result in a focused and absorbed attentional state. It is in this state or trance that targeted suggestions for a desired treatment are delivered. The individual is guided by the hypnotherapist to respond to suggestions for changes in subjective experience (e.g. level of pain), perception, sensation, emotion, thought or behaviour. The suggestions are often idiosyncratic depending on the presentation and goals of the patient (M. P. Jensen, Day, & Miro, 2014). Hypnosis for pain often uses imagery to change the sensation of pain (e.g. imagining a pain dial being turned down) as well as focusing of cognitive influences on pain (e.g. coping, acceptance and catastrophizing) and behavioural (such as increasing daily function and activity). The number of sessions varies but typically intervention is delivered over 6-8 sessions lasting between 30 to 60 minutes. It is common for patients to rehearse scripts (self hypnosis) between sessions which is often achieved by the use of in session recordings that the patient uses outside the therapy sessions.

There is a growing area of research on hypnosis for treating chronic pain in a variety of pain conditions including musculoskeletal pain, visceral pain (e.g. irritable bowel syndrome) and neuropathic pain (Flik et al., 2011; Gonsalkorale & Whorwell, 2005; Oneal, Patterson, Soltani, Teeley, & Jensen, 2008; Prior, Colgan, & Whorwell, 1990). These studies, which have largely focused on outcomes such as pain reduction, have provided good evidence for reducing pain and there are now several RCTs showing efficacy of hypnosis for reducing pain in a range of chronic pain disorders (M. P. Jensen & Patterson, 2014; Tan et al., 2014). In addition, recent evidence has also

highlighted other beneficial side effects such as reduction in pain unpleasantness, and improved sleep quality, self-efficacy and confidence, mood and socializing (Crasilneck, 1979; H. J. Crawford, 1998; Grundy et al., 2006; M. P. Jensen, 2006; R. Melzack & Perry, 1975; Sachs, Feuerstein, & Vitale, 1977).

The mechanisms of hypnosis for reducing pain are still relatively poorly understood, although it is widely accepted that the brain is the central channel through which psychological (e.g. coping, hypervigilance) and physiological (e.g. autonomic function, muscle tension) modulation occurs. Recent developments have been achieved through neuroimaging work that has shown hypnosis results in changes in brain activity in the pain neuromatrix, suggesting top-down modulation of pain. The brain regions involved appear to depend on the nature of the hypnotic suggestions, i.e. whether there is a sensory, emotional or attention focus. Taken together these data suggest an alteration in the integration of sensory, cognitive and affective aspects of the pain experience following hypnosis.

1.10 **Functional neuroanatomy of hypnosis**

Before reviewing neuroimaging studies on the hypnotic modulation of pain, it is important to first consider the role of the brain in hypnotic modulation alone.

Research exploring the possible mechanisms behind hypnosis has accelerated rapidly in the past two decades with the introduction of neuroimaging techniques such as fMRI and PET. As with pain, the functional neuroanatomy of hypnosis is complex and there is no "hypnosis center" in the brain. (Jensen 2015). Instead, there are several regions thought to be important in the efficacy of hypnosis. The complexity is made all the more multifaceted as studies involving brain imaging have largely compared groups of individuals based on how susceptible they are to hypnotic induction (high versus low). Furthermore, the nature of the brain involvement in hypnotic modulation is not

simple as the direction of activity (increased v decreased) has shown to be dependent on the type of hypnotic suggestion as well as inter-individual differences in hypnotic susceptibility.

Nevertheless, these studies have produced a body of evidence that suggests there is a consistent pattern of neural responding during hypnotic induction particularly in the frontal cortices, mid and anterior cingulate gyrus (Helen J. Crawford, 1994; De Benedittis, 2003; Faymonville, Boly, & Laureys, 2006; Mark P. Jensen et al., 2015; Rainville, 2002; Vanhaudenhuyse, Laureys, & Faymonville, 2014) along with increased functional and structural connectivity between these regions (Hoeft et al., 2012; Mark P. Jensen et al., 2015; Oakley & Halligan, 2013). In addition, EEG studies have shown a consistent dominance in theta wave activity in people who are highly hypnotizable (Helen J. Crawford, 1994; H. J. Crawford & Gruzelier, 1992). These individuals typically exhibit greater theta activity at rest and during hypnotic induction. Theta activity (between 4-8Hz) is associated with drowsiness, memory function and focused attention. In addition, hypnotic induction and suggestion has been associated with changes in gamma activity (>38Hz) which is thought to be important in memory and recall, and coherence of cross-modal sensory processing (e.g. synthesizing parallel sensory processing from different brain regions for example sound, sight and smell) (Mark P. Jensen et al., 2015). However, the direction of gamma activity is not consistent, with some researchers showing a decrease in gamma activity in highly hypnotizable subjects (Vilfredo De Pascalis, 2007; V. De Pascalis, Cacace, & Massicolle, 2004; V. De Pascalis, Marucci, Penna, & Pessa, 1987). Whilst others show a decrease (Akpinar, Ulett, & Itil, 1971; Schnyer & Allen, 1995).

1.11 **Review Questions**

Taken together, these studies have shown that hypnosis results in changes in brain activity in several brain regions that are also considered important in pain processing. Whilst there are several reviews assessing the brain involvement in hypnotic analgesia of experimental pain, there are very few focused on chronic pain. Therefore, the aim of the current review is to examine the current research findings on the brain processing during hypnotic analgesia in chronic pain. Specifically the aims of the current review are assess:

1. What are the brain mechanisms of hypnotic analgesia in chronic pain?
2. How generalizable are the findings from the current literature; a discussion of study design
3. What are the clinical and research implications?

1.12 **Methods**

Systematic search strategy

Potential studies for review were identified using a systematic approach to searching.

An online search for relevant journal articles was carried out using three electronic databases; PsychINFO, Medline and Embase. The following search terms were applied:

Chronic pain or pain or nociception or pain perception

AND

Hypnosis or Hypnotherapy or clinical hypnosis or hypnoanalgesia or hypnotic analgesia or hypnotic

AND

Functional magnetic resonance imaging or FMRI or positron emission tomography or PET or arterial spin labelling or ASL or electroencephalogram or EEG or magnetoencephalography or MEG or functional neuroimaging

Inclusion criteria for search

- Studies on individuals with chronic pain
- Using functional brain imaging
- Clinical hypnotic modulation of chronic pain
- Examined brain response during hypnotic modulation of actual pain (i.e. not imagined pain)
- Participants were adult humans
- Written in English
- Published between 1995 (to coincide with the first use of functional MRI) and the present day
- Published in a peer-reviewed journal

Following this, records were screened for duplicates across databases. Abstracts were then screened for inclusion/exclusion criteria. Finally, full text articles were assessed in further detail for eligibility based on inclusion criteria.

1.13 **Results**

A schematic overview of the search process can be found in Figure 1.4. A total of 437 articles were identified across the 3 databases (Embase 259, Medline 99, PsychINFO 79). An initial screen excluded 48 animal studies, 44 articles that were not published in English, and 23 articles that were published before 1995, resulting in a remaining 322 articles. Duplicates were then removed, resulting in 218 articles (Embase

192, Medline 16 and PsychINFO 20). Following this, the abstracts and titles of the articles identified were screened against inclusion/exclusion criteria. Of these, 180 articles were excluded. A significant number (76) were excluded as they were not functional neuroimaging studies on hypnotic modulation of pain; a large number of these were studies on pharmacokinetics and anaesthesia, pharmacological modulation of brain activity, studies on the hypnotic effects of opioids and studies on insomnia. A further 104 were excluded for the following reasons; 67 were review articles, 27 were conference proceedings/abstracts, 5 were book chapters and 5 were editorials.

The remaining 38 articles were screened further by reading the full publication. 29 of these were excluded as they did not include hypnotic modulation of chronic pain and were focused on functional brain imaging of acute experimental pain or imagined pain in normal healthy volunteers. This resulted in 9 studies eligible for inclusion in the current review (Abrahamsen et al., 2010; S. W. G. Derbyshire, Whalley, & Oakley, 2009; M. P. Jensen, 2013; M. P. Jensen et al., 2016; M. P. Jensen, Sherlin, et al., 2014; Nusbaum et al., 2011; Rosen, Willoch, Bartenstein, Berner, & Rosjo, 2001; Wik, Fischer, Bragee, Finer, & Fredrikson, 1999; Willoch et al., 2000), summarized in Table 1.1.

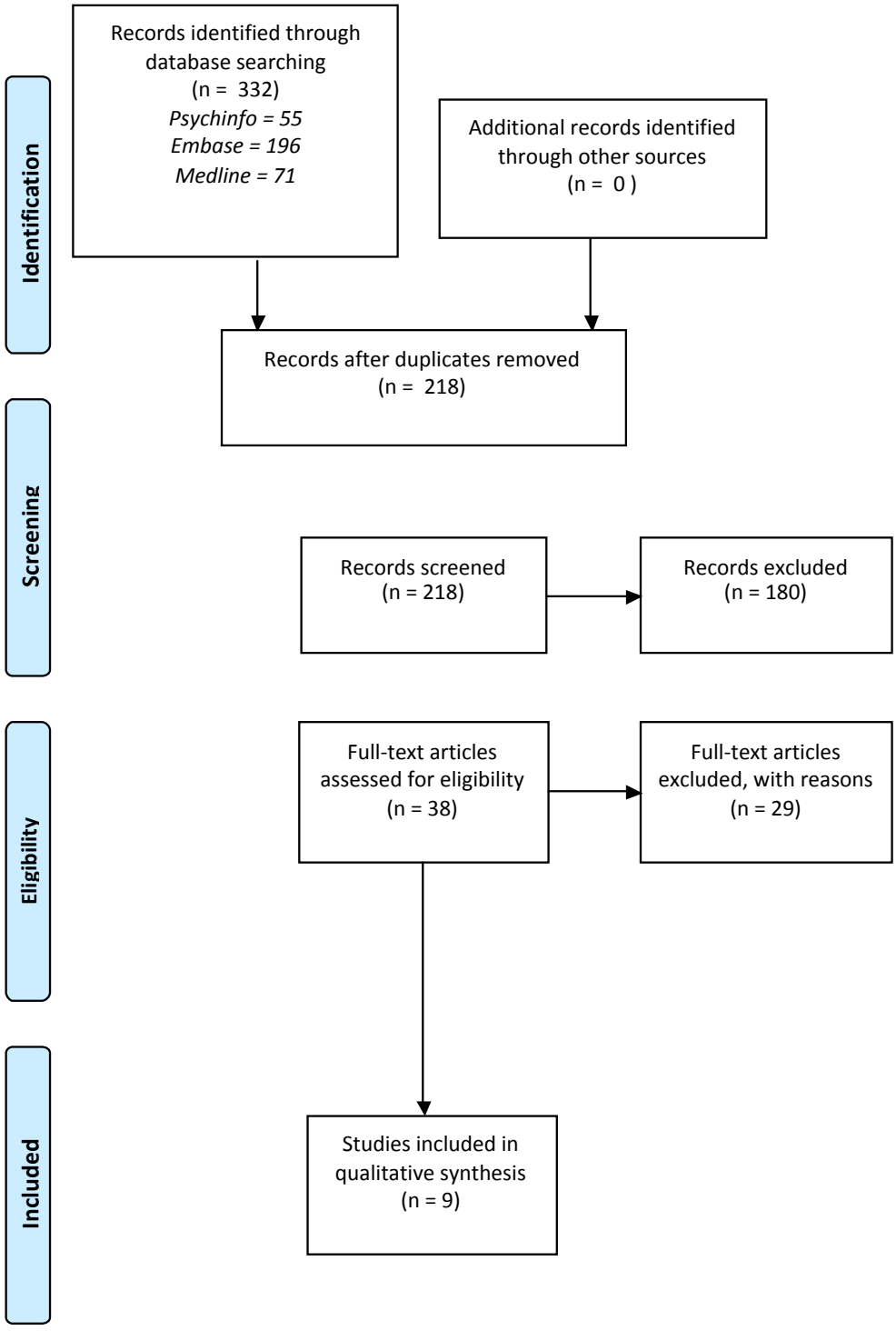


Figure 1.4 PRISMA flowchart showing an overview of systematic search strategy and results (Moher, Liberati, Tetzlaff, & Altman, 2009)

Table 1.1 Summary of studies induded in review. PET=Positron emission tomography; fMRI=functional magnetic resonance imaging; EEG=Electroencephalography; CP=chronic pain; PL=phantom limb; NS=not stated; ACC=anterior cingulate cortex; S2=secondary somatosensory cortex; PFC=prefrontal cortex; SMA=supplementary motor area; S1=primary somatosensory cortex; BA=Brodmann area

Author	Imaging technique	N (mean age)	Pain stimulus	Pain disorder	Chronic Pain duration	Brain regions modulated by hypnotic analgesia
Jensen et al., 2016	EEG	20 (12 female, mean age 49 years)	None – modulation of on-going CP	Multiple sderosis	>6 months	*Increased*: theta activity, left frontal cortex
Jensen et al., 2014	EEG	30 (22 male, mean age 49 years)	None – modulation of on-going CP	Spinal cord injury	>6 months	*Increased*: theta activity, frontal and posterior cortical areas and less significant in central areas *Decreased*: gamma activity, left frontal cortex
Jensen et al., 2013	EEG	30 (22 male, mean age 49 years)	None – modulation of on-going CP	Spinal cord injury	>6 months	*Increased*: theta activity, left frontal cortex; Alpha activity, diffuse and non-localized (whole cortex) *Decreased*: gamma activity, non-localised, mainly central regions of the cortex
Nusbaum et al., 2011	PET	14 (all male, mean age 41 years)	None – modulation of on-going CP	Chronic lower back pain	>3 months	*Increased activity:* Anterior insula, ACC (BA32), medial prefrontal cortex, Caudate nudeus accumbens
Abrahamsen et al., 2010	fMRI	19 (18 male, mean age 41 years)	Pressure – pin prick	Temporomandibular disorder (TMD)	>6 months	*Decreased activity:* Right posterior insula, S2, middle temporal cortex
Derbyshire et al., 2009	fMRI	13 (all female, mean age 51 years)	None – modulation of on-going CP	Fibromyalgia	NS	*Increased activity:* Midbrain, thalamus, ACC (BA24), S1, S2, insula, inferior parietal cortex, prefrontal cortex
Rosen et al., 2001	PET	2 (all male, mean age 30 years)	Imagined painful position or movement of PL	Phantom limb (PL)	>6 months	*Increased activity:* right insula, right ACC *Decreased activity:* bilateral thalamus, bilateral SMA, bilateral S1
Willoch et al., 2000	PET	8 (6 male, mean age? range 25-68)	Imagined painful position or movement of PL	Phantom limb (PL)	NS	*Increased activity*: SMA, S1
Wik et al., 1999	PET	8 (all female, mean age 47 years)	None – modulation of on-going CP	Fibromyalgia	NS	*Increased activity:* bilateral PFC, bilateral subcallosal cingulate gyrus, right thalamus, left S2. *Decreased activity:* bilateral mid ACC (BA24), bilateral posterior CC

Relevant review

There have been several reviews over the past decade on the functional neuroanatomy of hypnosis (e.g. (Dillworth, Mendoza, & Jensen, 2012)). The systematic search identified the most recent and most relevant review to the present review (Del Casale et al., 2015), published in 2015. Del Casale et al., reported on the recent functional neuroimaging studies on pain perception and hypnosis. In their review, they reported brain correlates during imagined pain, experimental pain in patients and healthy volunteers during hypnotic analgesia.

The proposed review aims to build on that by Del Casale et al., in several ways. Firstly, the current review includes findings from studies using EEG which was a technique excluded by Del Casale et al. As a result, the present review includes four additional studies on chronic pain, compared to the five studies described by Del Casale et al. In addition, whilst Del Casale et al. described the findings from the studies included in their review, they did not offer a critique on the methodological approaches of the studies and therefore the generalizability of the findings summarized in their review is unclear. A second additional aim of the present review therefore is to critically evaluate the current literature on neuroimaging studies of chronic pain and hypnosis and propose areas for development in future research.

Summary of findings

As can be seen in Table 1, the most commonly reported areas involved in hypnoanalgesia are the ACC, insula, thalamus, S2 and frontal cortex. Whilst the EEG studies are limited in the localization of activity, it is clear that there is predominance towards prefrontal cortex activity implicated in hypnoanalgesia. However, despite an apparent similarity between studies, it is also noteworthy that despite common regions implicated, there are no studies that report the same 'network' of regions. Furthermore,

there are differences in direction of activity, with some showing increased activity during hypnoanalgesia and others showing decreases in the same regions. All studies, with the exception of one (Abrahamsen et al., 2010) show increases in brain activity during hypnoanalgesia, with two of those also showing decreased activity.

1.14 **Discussion**

Review aim 1; What are the brain mechanisms of hypnotic analgesia in chronic pain?

Hypnoanalgesia involves regions involved in the pain processing: Not surprisingly perhaps, the most common regions implicated in the studies reviewed (ACC, insula, thalamus and S2 and frontal cortex) overlap with those show to be involved in processing of pain in health and chronic pain. Perhaps unexpectedly, these regions are predominately those previously implicated in more emotional and cognitive modulation of pain and not sensory processing per se. This is surprising as all studies reported a decrease in pain during hypnoanalgesia, which one might expect would result in a change in activity in sensory areas, most notably the S1. This may suggest that the peripheral/sensory component of the pain has not been altered but that emotional and cognitive aspects have been modulated through hypnosis treatment.

Frontal cortex: The majority of the studies (6 out of 9) suggest a role of the frontal cortex in hypnoanalgesia. This is in line with previous suggestions that this area is pivotal in a descending modulatory (pain inhibiting) pathway (Berman et al., 2008; Fields, 2000; Lorenz, Minoshima, & Casey, 2003; Mayer, Naliboff, & Craig, 2006; Villemure & Bushnell, 2002). It is also a region that has been shown to be more prominent in patients with chronic pain (Apkarian, Bushnell, Treede, & Zubieta, 2005).

Baseline brain function and hypnotic modulation: The three EEG studies, most notably Jensen et al. (2014), provide an insight into how resting brain function might be

involved in hypnotic analgesia of pain. In contrast to the PET and fMRI studies described, these data are not focused entirely on measuring change in response to evoked pain during hypnotic modulation. They describe brain states, in particular increased theta activity in the PFC is related to hypnotic analgesia, whereby greater theta activity is associated with pain reduction during hypnosis. Jensen et al. (2016) also demonstrated how neurofeedback training in theta activity enhances hypnotic analgesia. One could argue that theta activity is not specific to hypnotic analgesia and is related to hypnosis in general, however the effects described above were not shown in other neuromodulatory pain treatments, providing stronger evidence of this effect being specific to hypnotic analgesia (Jensen, 2013).

Review aim 2: How generalizable are the findings from the current literature; a discussion of study design

Despite synthesizing the results of the studies reviewed as a whole, it is also clear that whilst a consensus can be argued, there is also a significant amount of variability in the findings. In part, this is likely to be due to the small number of studies reported on the particular topic reviewed, with such a small number there is likely to be more variability.

Sources of variability between studies

Method of stimulation: There was a range of types of pain and methods of evoking pain described across the studies reviewed ranging from imagined limb movement (e.g. Rosen et al., 2001) to pin prick (Abrahamsen et al., 2010). This offers several sources of variability including stimulation of different afferent pain pathways (e.g. a variety of pain fibers activated depending on stimulation method) which has been show to involve differing brain regions and stimulus duration (e.g. pin prick is a short sharp pain (milliseconds/second), compared to constant ongoing background pain (e.g. Wik et al.,

1999). Evoked pain compared with ongoing background pain also has a number of other psychological differences related to anticipation, threat and salience which are also known to influence brain activity during pain (Gregory et al., 2003; Naliboff et al., 2008; Ploghaus et al., 2001; Ploghaus et al., 2000).

Sample size: There was also a wide range of sample sizes and types of chronic pain groups studied. Sample size ranged from 2 to 30, with the majority (six studies) involving fewer than 20 participants. Although the exact number of participants required to adequately power a functional neuroimaging study is unclear, it is generally accepted that a minimum of 12-16 volunteers are required in order to begin generalizing the findings. Certainly, the case series described by Rosen et al (2001) which reported data on two individual patients lacks statistical power and therefore the findings are very limited in terms of generalization. These data are likely to be considerably affected by type I and type II errors, as are the findings of Willoch (2000) and Wik (1999). However, the later studies described (from 2009 – 2016) appear to be adequately powered to detect significant effects without such error.

Study populations: There was also a variety of pain conditions studied in the papers reviewed (2 fibromyalgia; 2 phantom limb pain; 1 chronic lower back pain; 1 TMD. 2 spinal cord injury; 1 multiple sclerosis). One could argue that aside from the different peripheral input, all pain is essentially processed in the same way at a central level. However, there is likely to be significant heterogeneity in both physiological and psychological processing of different types of pain which would contribute to variability between the studies described.

Image processing and analysis approach: Across the studies there was a wide range of statistical analysis package used to analyse brain imaging data, the use of which can result in significantly different findings as the philosophy behind the analysis can be extremely different e.g. parametric (e.g. SPM, http://www.fil.ion.ucl.ac.uk/spm/) versus

non-parametric (e.g. XBAM, http://brainmap.co.uk/), approaches to brain data (Brammer et al., 1997; Penny, Friston, Ashburner, Kiebel, & Nichols, 2011). There is no consensus on which package to use, with the approach taken often driven by factors such as the Institute in which the study is situated and the availability of analysis software and support. Whilst there has been a move towards using two approaches (SPM (Penny et al., 2011)and FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012)) there will still be difficulty in interpreting differences found by research teams using differing approaches. Making data available to several research groups through collaboration may enable these differences to be assessed which could be a research implication of the findings described herein. This is something that is already happening in many pain fields.

In addition to analysis software, there were other differences in analysis approach i.e. whole brain versus a priori region of interest (ROI) approach (2 studies ROI, 2 ROI and whole brain, 5 whole brain only). Such differences are likely to produce significant variability across studies. Using an a-priori approach reduces the number of multiple comparisons required (compared to whole brain) and arguably makes it more likely to find significant effects in those brain regions examined. However, this approach risks missing potentially important changes in other areas of the brain not hypothesized to effect change. This means excluding potentially pivotal, novel findings that may contribute to existing knowledge on brain mechanisms of hypnoanalgesia. Given the limited understanding of mechanisms of hypnoanalgesia it could be argued that a more exploratory, whole-brain approach is warranted before ROI approaches are used to examine more nuanced, hypothesized effects. It is likely that the two studies exclusively using an ROI approach (Rosen, Willoch, Bartenstein, Berner, & Rosjo, 2001; Willoch et al., 2000) did so as a result of the low sample size, which would be more affected by

correction for multiple comparison across a while brain compared to several a priori regions.

Review aim 3; What are the clinical and research implications?

Despite the variability across studies in terms of methods and techniques, there are several clinical and research implications to consider as a result of the findings described.

Assessing connectivity of brain regions: Compared to other area of research using functional brain imaging, the current literature on hypnotic analgesia in chronic pain seems somewhat dated. The studies found largely report modulation of individual brain regions with little attempt to explore how those brain regions might be related or connected, other than through interpretation. Brain imaging acquisition and analysis techniques now permit the investigation of how brain regions talk to one another by using connectivity analysis approaches. This has moved functional imaging away from phrenology, and somewhat deductive interpretation and towards a more realistic discussion of networks of regions acting in symphony. Such research has identified emotional arousal networks, salience networks and homeostatic networks, amongst others. Such networks may prove to be important in mediating hypnosis effects on pain, not least given EEG data showing widespread synchronous activity as being pivotal in hypnotic responding.

Other brain imaging modalities: In addition to connectivity analysis, other pain research has also moved ahead in terms of using other more suitable brain imaging techniques to study chronic pain. fMRI and PET are largely reliant on study design that use evoked, transient stimuli and are not particularly well suited to measuring brain activity to ongoing, chronic pain, which perhaps explains the paucity of chronic pain data in relation to hypnosis. The relatively recent introduction of Arterial Spin Labeling

(ASL) provides an alternative approach which is more suited to studying less transient effects such as hypnotic analgesia and provide an absolute measure of perfusion in the brain. Indeed, it has recently been used to brain activity during normal fluctuations in pain (Hodkinson et al., 2013; Howard et al., 2012; Owen, Bureau, Thomas, Prato, & St Lawrence, 2008; Wasan et al., 2011)

Brain stem imaging: Given the importance of the brain stem in pain facilitation and inhibition, there is a rationale for studying this region in detail when examining pain modulation by using an ROI approach and high resolution imaging of this region. Given the role of nuclei within this region in autonomic control it is surprising that there appear to be no studies that have examined this region in hypnotic modulation of pain, not least given the relaxation element of hypnosis which involves autonomic arousal/rest which is known to be controlled by brainstem autonomic nuclei. Whilst this is a less exploratory, hypothesis driven and perhaps 'risky' approach it may provide valuable information on mechanisms of hypnotic pain modulation.

What works for whom?: The findings by Jensen et al. (2014 & 2016) suggest a possible role for EEG in treatment of chronic pain. Firstly, they suggest that it may be possible to identify individuals more likely to respond to hypnotic analgesia, thereby streamlining clinics and avoiding treating 'non-responders'. Secondly, these results also suggest that training people using neurofeedback has a beneficial, additive effect on hypnotic analgesia. Taken together, these data if applied to clinical practice could conceivably result in more efficient use of hypnosis as a treatment option. Caution is required however, as these results are preliminary and require replication, and testing on larger samples and across different pain conditions. In addition, there are practical considerations of using an EEG in clinics which in itself may be costly and time consuming. Perhaps as psychologists, our role could be to phenotype 'responders' and

develop a questionnaire and validate it against EEG data to provide an alternative, easy to administer way of assessing suitability for treatment.

The apparent role of the frontal cortex in hypnoanalgesia, combined with the role of theta activity in this area suggests a possible role for trans-cranial magnetic stimulation (TMS). TMS uses a magnetic coil to stimulate brain local cortical brain areas without the need for invasive electrode implants. There is already evidence for use of TMS in several centrally mediated problems including pain (J.-P. Lefaucheur et al., 2014; J. P. Lefaucheur, 2012). This is a speculative clinical implication that would require further exploration and research however, recent research has shown an additive effect of TMS of the prefrontal cortex on hypnotic suggestibility (Dienes & Hutton, 2013). Given the findings of the current review it is possible that there may be a similar role for TMS in hypnotic analgesia.

1.15 **Summary and conclusions**

Taken together, functional brain imaging studies on hypnotic modulation of pain suggest hypnoanalgesia recruits a number of brain regions previously implicated in cognitive and emotional modulation of pain. However, there is a paucity of functional neuroimaging studies investigating brain mechanisms involved in hypnotic analgesia in chronic pain. Those reported vary significantly in imaging approach, populations studied and method of stimulation. Furthermore, the data reported describe independent brain regions showing change in the context of an evoked pain. Future research would benefit from exploring connectivity between regions and networks involved in pain modulation as well as using alternative methods such as ASL to examine absolute changes in perfusion in response to hypnotic modulation of pain. EEG data provide a rationale for exploring baseline brain activity predicts pain modulation. Such studies may offer potential clinical implications such as pre-selection of patients more likely to benefit

from a hypnosis approach to pain management. Finally, the long-term impact of hypnosis on pain and brain function remains an unexplored area. Research here may help clarify whether pain and brain changes following hypnosis are transient or stable and long lasting.

1.16 **References**

Abrahamsen, R., Dietz, M., Lodahl, S., Roepstorff, A., Zachariae, R., Ostergaard, L., & Svensson, P. (2010). Effect of hypnotic pain modulation on brain activity in patients with temporomandibular disorder pain. *Pain, 151*(3), 825-833.

Akpinar, S., Ulett, G. A., & Itil, T. M. (1971). Hypnotizability predicted by digital computer-analyzed EEG pattern. *Biol Psychiatry, 3*(4), 387-392.

Apkarian, A. V., Bushnell, M. C., Treede, R.-D., & Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9*(4), 463-463. doi:10.1016/j.ejpain.2004.11.001

Aziz, Q., Thompson, D. G., Ng, V. W., Hamdy, S., Sarkar, S., Brammer, M. J., . . . Williams, S. C. (2000). Cortical processing of human somatic and visceral sensation. *Journal of Neuroscience, 20*(7), 2657-2663.

Bantick, S. J., Wise, R. G., Ploghaus, A., Clare, S., Smith, S. M., & Tracey, I. (2002). Imaging how attention modulates pain in humans using functional MRI. *Brain, 125*(Pt 2), 310-319.

Berman, S. M., Naliboff, B. D., Suyenobu, B., Labus, J. S., Stains, J., Ohning, G., . . . Mayer, E. A. (2008). Reduced brainstem inhibition during anticipated pelvic visceral pain correlates with enhanced brain response to the visceral stimulus in women with irritable bowel syndrome. *Journal of Neuroscience, 28*(2), 349-359.

Berna, C., Leknes, S., Holmes, E. A., Edwards, R. R., Goodwin, G. M., & Tracey, I. (2010). Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. *Biol Psychiatry, 67*(11), 1083-1090. doi:10.1016/j.biopsych.2010.01.014

Bernstein, C. N., Frankenstein, U. N., Rawsthorne, P., Pitz, M., Summers, R., & McIntyre, M. C. (2002). Cortical mapping of visceral pain in patients with GI disorders using functional magnetic resonance imaging. *Am.J.Gastroenterol., 97*(2), 319-327.

Bingel, U., & Tracey, I. (2008). Imaging CNS Modulation of Pain in Humans. *Physiology, 23*(6), 371-380.

Binkofski, F. (2000). Limbic and somatic cortex activations in electrical pelvic floor stimulation. *Neuroimage, Volume 11, Issue 5, Supplement 1*, Page S893.

Brammer, M. J., Bullmore, E. T., Simmons, A., Williams, S. C., Grasby, P. M., Howard, R. J., . . . Rabe-Hesketh, S. (1997). Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. *Magn Reson.Imaging, 15*(7), 763-770.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur. J. Pain, 10*, 287-333.

Brooks, J. C. W., Nurmikko, T. J., Bimson, W. E., & Roberts, N. (2002). fMRI studies of themosensation and nociception using graded thermal stumuli. *Abstract.ISMRM*.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci., 4*(6), 215-222.

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J. I., & Carrier, B. (1999). Pain perception: is there a role for primary somatosensory cortex? *Proc.Natl.Acad.Sci.U.S.A, 96*(14), 7705-7709.

Coen, S. J., Aziz, Q., Yaguez, L., Brammer, M., Williams, S. C., & Gregory, L. J. (2008). Effects of attention on visceral stimulus intensity encoding in the male human brain. *Gastroenterology, 135*(6), 2065-2074, 2074.

Coen, S. J., Gregory, L. J., Yaguez, L., Amaro, E., Jr., Brammer, M., Williams, S. C., & Aziz, Q. (2007). Reproducibility of human brain activity evoked by esophageal stimulation using functional magnetic resonance imaging. *Am.J.Physiol Gastrointest.Liver Physiol, 293*(1), G188-G197.

Coen, S. J., Yaguez, L., Aziz, Q., Mitterschiffthaler, M. T., Brammer, M., Williams, S. C., & Gregory, L. J. (2009). Negative mood affects brain processing of visceral sensation. *Gastroenterology, 137*(1), 253-261, 261.

Coghill, R. C., Sang, C. N., Berman, K. F., Bennett, G. J., & Iadarola, M. J. (1998). Global cerebral blood flow decreases during pain. *J.Cereb.Blood Flow Metab, 18*(2), 141-147.

Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (1999). Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J.Neurophysiol., 82*(4), 1934-1943.

Coghill, R. C., Talbot, J. D., Evans, A. C., Meyer, E., Gjedde, A., Bushnell, M. C., & Duncan, G. H. (1994). Distributed processing of pain and vibration by the human brain. *Journal of Neuroscience, 14*(7), 4095-4108.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat.Rev.Neurosci., 3*(8), 655-666.

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Curr.Opin.Neurobiol., 13*(4), 500-505.

Craig, A. D., Reiman, E. M., Evans, A., & Bushnell, M. C. (1996). Functional imaging of an illusion of pain. *Nature, 384*(6606), 258-260.

Crasilneck, H. B. (1979). Hypnosis in the control of chronic low back pain. *Am J Clin Hypn, 22*(2), 71-78.

Crawford, H. J. (1994). Brain Dynamics and Hypnosis: Attentional and Disattentional Processes. *International Journal of Clinical and Experimental Hypnosis, 42*(3), 204-232. doi:10.1080/00207149408409352

Crawford, H. J. (1998). Hypnotic analgesia: 1. Somatosensory event-related potential changes to noxious stimuli and 2. Transfer learning to reduce chronic low back pain. *Int. J. Clin. Exp. Hypn., 46*, 93-132.

Crawford, H. J., & Gruzelier, J. H. (1992). Contemporary Hypnosis Research (pp. 227-266).

De Benedittis, G. (2003). Understanding the multidimensional mechanisms of hypnotic analgesia. *Contemp. Hypn., 20*, 59-80.

De Pascalis, V. (2007). Phase-ordered gamma oscillations and the modulation of hypnotic experience. In G. A. Jamieson (Ed.), *Hypnosis and Conscious States: The Cognitive Neuroscience Perspective* (pp. 67-89): Oxford University Press.

De Pascalis, V., Cacace, I., & Massicolle, F. (2004). Perception and modulation of pain in waking and hypnosis: Functional significance of phase-ordered gamma oscillations. *Pain, 112*(1-2), 27-36.

De Pascalis, V., Marucci, F. S., Penna, P. M., & Pessa, E. (1987). Hemispheric activity of 40 Hz EEG during recall of emotional events: differences between low and high hypnotizables. *Int J Psychophysiol, 5*(3), 167-180.

Del Casale, A., Ferracuti, S., Rapinesi, C., Serata, D., Caltagirone, S. S., Savoja, V., . . . Girardi, P. (2015). Pain perception and hypnosis: Findings from recent functional neuroimaging studies. *International Journal of Clinical and Experimental Hypnosis, 63*(2), 144-170.

Denk, F., McMahon, S. B., & Tracey, I. (2014). Pain vulnerability: a neurobiological perspective. *Nat Neurosci, 17*(2), 192-200. doi:10.1038/nn.3628

Derbyshire, S. W., Jones, A. K., Gyulai, F., Clark, S., Townsend, D., & Firestone, L. L. (1997). Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain, 73*(3), 431-445.

Derbyshire, S. W. G., Whalley, M. G., & Oakley, D. A. (2009). Fibromyalgia pain and its modulation by hypnotic and non-hypnotic suggestion: An fMRI analysis. *European Journal of Pain, 13*(5), 542-550.

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

Dienes, Z., & Hutton, S. (2013). Understanding hypnosis metacognitively: rTMS applied to left DLPFC increases hypnotic suggestibility. *Cortex, 49*(2), 386-392. doi:http://dx.doi.org/10.1016/j.cortex.2012.07.009

Dillworth, T., Mendoza, M. E., & Jensen, M. P. (2012). Neurophysiology of pain and hypnosis for chronic pain. *Transl Behav Med, 2*(1), 65-72. doi:10.1007/s13142-011-0084-5

Dunckley, P., Aziz, Q., Wise, R. G., Brooks, J., Tracey, I., & Chang, L. (2007). Attentional modulation of visceral and somatic pain. *Neurogastroenterol Motil, 19*(7), 569-577. doi:10.1111/j.1365-2982.2007.00908.x

Elsenbruch, S., Rosenberger, C., Enck, P., Forsting, M., Schedlowski, M., & Gizewski, E. R. (2010). Affective disturbances modulate the neural processing of visceral pain stimuli in irritable bowel syndrome: an fMRI study. *Gut, 59*(4), 489-495. doi:10.1136/gut.2008.175000

Farmer, A. D., Coen, S. J., Kano, M., Paine, P. A., Shwahdi, M., Jafari, J., . . . Aziz, Q. (2013). Psychophysiological responses to pain identify reproducible human clusters. *Pain, 154*(11), 2266-2276. doi:10.1016/j.pain.2013.05.016

Faymonville, M. E., Boly, M., & Laureys, S. (2006). Functional neuroanatomy of the hypnotic state. *Journal of Physiology Paris, 99*(4-6), 463-469.

Fields, H. L. (2000). Pain modulation: expectation, opioid analgesia and virtual pain. *Prog.Brain Res., 122*, 245-253.

Flik, C. E., van Rood, Y. R., Laan, W., Smout, A. J., Weusten, B. L., Whorwell, P. J., & de Wit, N. J. (2011). A randomised controlled trial on hypnotherapy for irritable bowel syndrome: design and methodological challenges (the IMAGINE study). *BMC Gastroenterol, 11*, 137. doi:10.1186/1471-230X-11-137

Garcha, H. S., & Ettlinger, G. (1978). The effects of unilateral or bilateral removals of the second somatosensory cortex (area SII): a profound tactile disorder in monkeys. *Cortex, 14*(3), 319-326.

Garcha, H. S., & Ettlinger, G. (1980). Tactile discrimination learning in the monkey: the effects of unilateral or bilateral removals of the second somatosensory cortex (area SII). *Cortex, 16*(3), 397-412.

Garcia-Larrea, L., & Peyron, R. (2013). Pain matrices and neuropathic pain matrices: a review. *Pain, 154 Suppl 1*, S29-43. doi:10.1016/j.pain.2013.09.001

George, M. S., Ketter, T. A., Parekh, P. I., Horwitz, B., Herscovitch, P., & Post, R. M. (1995). Brain activity during transient sadness and happiness in healthy women. *Am.J.Psychiatry, 152*(3), 341-351.

Gonsalkorale, W. M., & Whorwell, P. J. (2005). Hypnotherapy in the treatment of irritable bowel syndrome. *Eur J Gastroenterol Hepatol, 17*(1), 15-20.

Gregory, L. J., Yaguez, L., Williams, S. C., Altmann, C., Coen, S. J., Ng, V., . . . Aziz, Q. (2003). Cognitive modulation of the cerebral processing of human oesophageal sensation using functional magnetic resonance imaging. *Gut, 52*(12), 1671-1677.

Grundy, D., Al-Chaer, E. D., Aziz, Q., Collins, S. M., Ke, M., Tache, Y., & Wood, J. D. (2006). Fundamentals of neurogastroenterology: basic science. *Gastroenterology, 130*(5), 1391-1411. doi:10.1053/j.gastro.2005.11.060

Hertel, J. B., & Hekmat, H. M. (1994). Coping with cold-pressor pain: Effects of mood and covert imaginal modeling (Vol. 44, pp. 207-220). (Reprinted from: NOT IN FILE).

Hodkinson, D. J., Krause, K., Khawaja, N., Renton, T. F., Huggins, J. P., Vennart, W., . . . Howard, M. A. (2013). Quantifying the test–retest reliability of cerebral blood flow measurements in a clinical model of on-going post-surgical pain: A study using pseudo-continuous arterial spin labelling(). *NeuroImage : Clinical, 3*, 301-310. doi:10.1016/j.nicl.2013.09.004

Hoeft, F., Gabrieli, J. D. E., Whitfield-Gabrieli, S., Haas, B. W., Bammer, R., Menon, V., & Spiegel, D. (2012). Functional brain basis of hypnotizability. *Archives of General Psychiatry, 69*(10), 1064-1072.

Hofbauer, R. K., Rainville, P., Duncan, G. H., & Bushnell, M. C. (1998). Cognitive modulation of pain sensation alter activity in the human cerebral cortex (Vol. 24, pp. 447.445).

Howard, M. A., Sanders, D., Krause, K., O'Muircheartaigh, J., Fotopoulou, A., Zelaya, F., . . . Williams, S. C. (2012). Alterations in resting-state regional cerebral blood flow demonstrate ongoing pain in osteoarthritis: An arterial spin-labeled magnetic resonance imaging study. *Arthritis Rheum, 64*(12), 3936-3946. doi:10.1002/art.37685

Iadarola, M. J., Berman, K. F., Zeffiro, T. A., Byas-Smith, M. G., Gracely, R. H., Max, M. B., & Bennett, G. J. (1998). Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain, 121 (Pt 5)*, 931-947.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage, 62*(2), 782-790. doi:http://dx.doi.org/10.1016/j.neuroimage.2011.09.015

Jensen, M. P. (2006). Satisfaction with, and the beneficial side effects of, hypnotic analgesia. *Int. J. Clin. Exp. Hypn., 54*, 432-447.

Jensen, M. P. (2013). Effects of non-pharmacological pain treatments on brain states. *Clin. Neurophysiol., 124*, 2016-2024.

Jensen, M. P., Adachi, T., Tomé-Pires, C., Lee, J., Osman, Z. J., & Miró, J. (2015). MECHANISMS OF HYPNOSIS:: Toward the Development of a Biopsychosocial Model. *Int J Clin Exp Hypn, 63*(1), 34-75. doi:10.1080/00207144.2014.961875

Jensen, M. P., Day, M. A., & Miro, J. (2014). Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nat Rev Neurol, 10*(3), 167-178. doi:10.1038/nrneurol.2014.12

Jensen, M. P., Gianas, A., George, H. R., Sherlin, L. H., Kraft, G. H., & Ehde, D. M. (2016). Use of Neurofeedback to Enhance Response to Hypnotic Analgesia in Individuals with Multiple Sclerosis. *International Journal of Clinical and Experimental Hypnosis, 64*(1), 1-23.

Jensen, M. P., & Patterson, D. R. (2014). Hypnotic approaches for chronic pain management: clinical implications of recent research findings. *Am Psychol, 69*(2), 167-177. doi:10.1037/a0035644

Jensen, M. P., Sherlin, L. H., Fregni, F., Gianas, A., Howe, J. D., & Hakimian, S. (2014). Baseline Brain Activity Predicts Response to Neuromodulatory Pain Treatment. *Pain Med.* doi:10.1111/pme.12546

Kenshalo, D. R., & Willis, W. D. (1991). The role of the cerebral cortex in pain sensation. In a. E. G. J. A.Peters (Ed.), *In: Cerebral Cortex* (Vol. 9, pp. 153-212). New York Plenum .

Kong, J., Gollub, R. L., Rosman, I. S., Webb, J. M., Vangel, M. G., Kirsch, I., & Kaptchuk, T. J. (2006). Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. *Journal of Neuroscience, 26*(2), 381-388.

Kong, J., Kaptchuk, T. J., Polich, G., Kirsch, I., & Gollub, R. L. (2007). Placebo analgesia: findings from brain imaging studies and emerging hypotheses. *Rev.Neurosci., 18*(3-4), 173-190.

Kulkarni, B., Bentley, D. E., Elliott, R., Youell, P., Watson, A., Derbyshire, S. W., . . . Jones, A. K. (2005). Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur.J.Neurosci., 21*(11), 3133-3142.

Labus, J. S., Naliboff, B. D., Berman, S. M., Suyenobu, B., Vianna, E. P., Tillisch, K., & Mayer, E. A. (2009). Brain networks underlying perceptual habituation to repeated aversive visceral stimuli in patients with irritable bowel syndrome. *Neuroimage, 47*(3), 952-960. doi:10.1016/j.neuroimage.2009.05.078

Labus, J. S., Naliboff, B. N., Fallon, J., Berman, S. M., Suyenobu, B., Bueller, J. A., . . . Mayer, E. A. (2008). Sex differences in brain activity during aversive visceral stimulation and its expectation in patients with chronic abdominal pain: a network analysis. *Neuroimage, 41*(3), 1032-1043. doi:S1053-8119(08)00225-5 [pii]
10.1016/j.neuroimage.2008.03.009

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., . . . Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology, 125*(11), 2150-2206. doi:http://dx.doi.org/10.1016/j.clinph.2014.05.021

Lefaucheur, J. P. (2012). Analgesic effects of repetitive transcranial magnetic stimulation of the motor cortex in neuropathic pain: influence of theta burst stimulation priming. *Eur. J. Pain, 16*, 1403-1413.

Legrain, V., Iannetti, G. D., Plaghki, L., & Mouraux, A. (2011). The pain matrix reloaded: A salience detection system for the body. *Progress in Neurobiology, 93*(1), 111-124. doi:http://dx.doi.org/10.1016/j.pneurobio.2010.10.005

Levine, J. D., Gordon, N. C., Smith, R., & Fields, H. L. (1982). Post-operative pain: effect of extent of injury and attention. *Brain Res., 234*(2), 500-504.

Lorenz, J., Minoshima, S., & Casey, K. L. (2003). Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain, 126*(Pt 5), 1079-1091.

Mauguiere, F., Frot, M., Peyron, R., Garcia-Larrea, L., Laurent, B., & Michel, D. (1999). The role of parietal opercular and insular cortex in pain sensation in humans: data from PET activation studies and intracortical recordings of CO2 laser evoked potentials (LEPs). *Electroencephalogr.Clin.Neurophysiol.Suppl, 49*, 255-260.

Mauguiere, F., Merlet, I., Forss, N., Vanni, S., Jousmaki, V., Adeleine, P., & Hari, R. (1997). Activation of a distributed somatosensory cortical network in the human

brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation timing of SEF sources. *Electroencephalogr.Clin.Neurophysiol., 104*(4), 281-289.
Mayer, E. A., Aziz, Q., Coen, S., Kern, M., Labus, J. S., Lane, R., . . . Tracey, I. (2009). Brain imaging approaches to the study of functional GI disorders: a Rome working team report. *Neurogastroenterol.Motil., 21*(6), 579-596.
Mayer, E. A., Labus, J. S., Tillisch, K., Cole, S. W., & Baldi, P. (2015). Towards a systems view of IBS. *Nat Rev Gastroenterol Hepatol, 12*(10), 592-605. doi:10.1038/nrgastro.2015.121
Mayer, E. A., Naliboff, B. D., & Craig, A. D. (2006). Neuroimaging of the brain-gut axis: from basic understanding to treatment of functional GI disorders. *Gastroenterology, 131*(6), 1925-1942.
McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain, 106*(1–2), 127-133. doi:http://dx.doi.org/10.1016/S0304-3959(03)00301-4
Meagher, M. W., Arnau, R. C., & Rhudy, J. L. (2001). Pain and emotion: effects of affective picture modulation. *Psychosom.Med., 63*(1), 79-90.
Melzack, R. (1999). From the gate to the neuromatrix. *Pain, Suppl 6*, S121-126.
Melzack, R. (2001). Pain and the neuromatrix in the brain. *J Dent Educ, 65*(12), 1378-1382.
Melzack, R. (2005). Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. *Pain Pract, 5*(2), 85-94. doi:10.1111/j.1533-2500.2005.05203.x
Melzack, R., & Casey, K. L. (1968). Sensory, motivational and central control determinants of pain: a new conceptual model. *The skin senses, 1*.
Melzack, R., & Chapman, C. R. (1973). Psychologic aspects of pain. *Postgrad Med, 53*(6), 69-75.
Melzack, R., & Perry, C. (1975). Self-regulation of pain: the use of alpha-feedback and hypnotic training for the control of chronic pain. *Exp. Neurol., 46*, 452-469.
Merskey, H., & Bogduk, N. (1994). Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms (pp. 178). Seattle: IASP Press. (Reprinted from: NOT IN FILE).
Miron, D., Duncan, G. H., & Bushnell, M. C. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain, 39*(3), 345-352.
Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ, 339*. doi:10.1136/bmj.b2535
Mouraux, A., Diukova, A., Lee, M. C., Wise, R. G., & Iannetti, G. D. (2011). A multisensory investigation of the functional significance of the "pain matrix". *Neuroimage, 54*(3), 2237-2249. doi:http://dx.doi.org/10.1016/j.neuroimage.2010.09.084
Murray, E. A., & Mishkin, M. (1984). Relative contributions of SII and area 5 to tactile discrimination in monkeys. *Behav.Brain Res., 11*(1), 67-83.
Naliboff, B. D., Waters, A. M., Labus, J. S., Kilpatrick, L., Craske, M. G., Chang, L., . . . Ornitz, E. (2008). Increased acoustic startle responses in IBS patients during abdominal and nonabdominal threat. *Psychosom Med, 70*(8), 920-927. doi:PSY.0b013e318186d858 [pii]
10.1097/PSY.0b013e318186d858
Nusbaum, F., Redoute, J., Le Bars, D., Volckmann, P., Simon, F., Hannoun, S., . . . Sappey-Marinier, D. (2011). Chronic low-back pain modulation is enhanced by

hypnotic analgesic suggestion by recruiting an emotional network: A PET imaging study. *International Journal of Clinical and Experimental Hypnosis, 59*(1), 27-44.

Oakley, D. A., & Halligan, P. W. (2013). Hypnotic suggestion: opportunities for cognitive neuroscience. *Nat. Rev. Neurosci., 14*, 565-576.

Oneal, B. J., Patterson, D. R., Soltani, M., Teeley, A., & Jensen, M. P. (2008). Virtual reality hypnosis in the treatment of chronic neuropathic pain: a case report. *Int J Clin Exp Hypn, 56*(4), 451-462. doi:10.1080/00207140802255534

Owen, D. G., Bureau, Y., Thomas, A. W., Prato, F. S., & St Lawrence, K. S. (2008). Quantification of pain-induced changes in cerebral blood flow by perfusion MRI. *Pain, 136*(1-2), 85-96. doi:10.1016/j.pain.2007.06.021

Penny, W. D., Friston, K. J., Ashburner, J. T., Kiebel, S. J., & Nichols, T. E. (2011). *Statistical Parametric Mapping: The Analysis of Functional Brain Images*: Elsevier Science.

Petrovic, P., Petersson, K. M., Ghatan, P. H., Stone-Elander, S., & Ingvar, M. (2000). Pain-related cerebral activation is altered by a distracting cognitive task. *Pain, 85*(1-2), 19-30.

Peyron, R., Garcia-Larrea, L., Gregoire, M. C., Costes, N., Convers, P., Lavenne, F., . . . Laurent, B. (1999). Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. *Brain, 122 (Pt 9)*, 1765-1780.

Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol.Clin., 30*(5), 263-288.

Phillips, M. L., Gregory, L. J., Cullen, S., Coen, S., Ng, V., Andrew, C., . . . Aziz, Q. (2003). The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. *Brain, 126*(Pt 3), 669-684.

Ploghaus, A., Narain, C., Beckmann, C. F., Clare, S., Bantick, S., Wise, R., . . . Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *Journal of Neuroscience, 21*(24), 9896-9903.

Ploghaus, A., Tracey, I., Clare, S., Gati, J. S., Rawlins, J. N., & Matthews, P. M. (2000). Learning about pain: the neural substrate of the prediction error for aversive events. *Proc.Natl.Acad.Sci.U.S.A, 97*(16), 9281-9286.

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M., & Rawlins, J. N. (1999). Dissociating pain from its anticipation in the human brain. *Science, 284*(5422), 1979-1981.

Ploner, M., Lee, M. C., Wiech, K., Bingel, U., & Tracey, I. (2010). Prestimulus functional connectivity determines pain perception in humans. *Proceedings of the National Academy of Sciences, 107*(1), 355-360. doi:10.1073/pnas.0906186106

Porro, C. A., Cettolo, V., Francescato, M. P., & Baraldi, P. (1998). Temporal and intensity coding of pain in human cortex. *J.Neurophysiol., 80*(6), 3312-3320.

Price, D. D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science, 288*(5472), 1769-1772.

Price, D. D., & Harkins, S. W. (1992). The affective-motivational dimension of pain A two-stage model. *APS Journal, 1*(4), 229-239. doi:http://dx.doi.org/10.1016/1058-9139(92)90054-G

Price, D. D., & Verne, G. N. (2002). Does the spinothalamic tract to ventroposterior lateral thalamus and somatosensory cortex have roles in both pain sensation and pain-related emotions? *J.Pain, 3*(2), 105-108.

Prior, A., Colgan, S. M., & Whorwell, P. J. (1990). Changes in rectal sensitivity after hypnotherapy in patients with irritable bowel syndrome. *Gut, 31*(8), 896-898.

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology, 12*(2), 195-204.

Rainville, P., Carrier, B., Hofbauer, R. K., Bushnell, M. C., & Duncan, G. H. (1999). Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain, 82*(2), 159-171.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science, 277*(5328), 968-971.

Rode, S., Salkovskis, P. M., & Jack, T. (2001). An experimental study of attention, labelling and memory in people suffering from chronic pain. *Pain, 94*(2), 193-203.

Rosen, G., Willoch, F., Bartenstein, P., Berner, N., & Rosjo, S. (2001). Neurophysiological processes underlying the phantom limb pain experience and the use of hypnosis in its clinical management: An intensive examination of two patients. *International Journal of Clinical and Experimental Hypnosis, 49*(1), 38-55.

Roy, M., Peretz, I., & Rainville, P. (2003). Effects of emotion induced by music on experiemental pain. *Pain Research and Management, (supplement)*, 33B.

Ruffle, J. K., Farmer, A. D., Kano, M., Giampietro, V., Aziz, Q., & Coen, S. J. (2015). The influence of extraversion on brain activity at baseline and during the experience and expectation of visceral pain. *Personality and Individual Differences, 74*, 248-253. doi:http://dx.doi.org/10.1016/j.paid.2014.10.024

Sachs, L. B., Feuerstein, M., & Vitale, J. H. (1977). Hypnotic self-regulation of chronic pain. *Am. J. Clin. Hypn., 20*, 106-113.

Schnyer, D. M., & Allen, J. J. (1995). Attention-related electroencephalographic and event-related potential predictors of responsiveness to suggested posthypnotic amnesia. *International Journal of Clinical and Experimental Hypnosis, 43*(3), 295-315. doi:10.1080/00207149508409972

Stevens, R. T., London, S. M., & Apkarian, A. V. (1993). Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey. *Brain Res., 631*(2), 241-246.

Tan, G., Rintala, D. H., Jensen, M. P., Fukui, T., Smith, D., & Williams, W. (2014). A randomized controlled trial of hypnosis compared with biofeedback for adults with chronic low back pain. *Eur J Pain*. doi:10.1002/ejp.545

Tang, J., & Gibson, S. J. (2005). A psychophysical evaluation of the relationship between trait anxiety, pain perception, and induced state anxiety. *J.Pain, 6*(9), 612-619.

Tang, N. K. Y., Salkovskis, P. M., Hodges, A., Wright, K. J., Hanna, M., & Hester, J. (2008). Effects of mood on pain responses and pain tolerance: An experimental study in chronic back pain patients. *Pain, 138*(2), 392-401. doi:10.1016/j.pain.2008.01.018

Tolle, T. R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., . . . Bartenstein, P. (1999). Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. *Ann.Neurol., 45*(1), 40-47.

Tracey, I. (2008). Imaging pain. *British Journal of Anaesthesia, 101*(1), 32-39. doi:10.1093/bja/aen102

Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation. *Neuron, 55*(3), 377-391. doi:http://dx.doi.org/10.1016/j.neuron.2007.07.012

Tracey, I., Ploghaus, A., Gati, J. S., Clare, S., Smith, S., Menon, R. S., & Matthews, P. M. (2002). Imaging attentional modulation of pain in the periaqueductal gray in humans. *Journal of Neuroscience, 22*(7), 2748-2752.

Treede, R. D., Kenshalo, D. R., Gracely, R. H., & Jones, A. K. (1999). The cortical representation of pain. *Pain, 79*(2-3), 105-111.

Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., . . . Tolle, T. R. (2004). Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. *Pain, 109*(3), 399-408.

Vanhaudenhuyse, A., Laureys, S., & Faymonville, M. E. (2014). Neurophysiology of hypnosis. *Neurophysiologie Clinique, 44*(4), 343-353.

Villemure, C., & Bushnell, M. C. (2002). Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain, 95*(3), 195-199.

Villemure, C., Slotnick, B. M., & Bushnell, M. C. (2003). Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain, 106*(1-2), 101-108.

Vogt, B. A., Derbyshire, S., & Jones, A. K. (1996). Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. *Eur.J.Neurosci., 8*(7), 1461-1473.

Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., & Kross, E. (2013). An fMRI-Based Neurologic Signature of Physical Pain. *New England Journal of Medicine, 368*(15), 1388-1397. doi:10.1056/NEJMoa1204471

Wasan, A. D., Loggia, M. L., Chen, L. Q., Napadow, V., Kong, J., & Gollub, R. L. (2011). Neural Correlates of Chronic Low Back Pain Measured by Arterial Spin Labeling. *Anesthesiology, 115*(2), 364-374. doi:10.1097/ALN.0b013e318220e880

Weisenberg, M., Raz, T., & Hener, T. (1998). The influence of film-induced mood on pain perception. *Pain, 76*(3), 365-375.

Whipple, B., & Glynn, N. J. (1992). Quantification of the effects of listening to music as a noninvasive method of pain control. *Sch Inq.Nurs.Pract., 6*(1), 43-58.

Wik, G., Fischer, H., Bragee, B., Finer, B., & Fredrikson, M. (1999). Functional anatomy of hypnotic analgesia: A PET study of patients with fibromyalgia. *European Journal of Pain, 3*(1), 7-12.

Willoch, F., Rosen, G., Tolle, T. R., Oye, I., Wester, H. J., Berner, N., . . . Bartenstein, P. (2000). Phantom limb pain in the human brain: Unraveling neural circuitries of phantom limb sensations using positron emission tomography. *Annals of Neurology, 48*(6), 842-849.

Yaguez, L., Coen, S., Gregory, L. J., Amaro, E., Jr., Altman, C., Brammer, M. J., . . . Aziz, Q. (2005). Brain response to visceral aversive conditioning: a functional magnetic resonance imaging study. *Gastroenterology, 128*(7), 1819-1829.

Zelman, D. C., Howland, E. W., Nichols, S. N., & Cleeland, C. S. (1991). The effects of induced mood on laboratory pain. *Pain, 46*(1), 105-111.

Zillmann, D., de, W. M., King-Jablonski, C., & Jenzowsky, S. (1996). Drama-induced affect and pain sensitivity. *Psychosom.Med., 58*(4), 333-341.

Part 2: Empirical Paper

Exploring the Processes and Psychological Factors Involved in Hypnotic Modulation of Chronic Pelvic Pain

2.1 Abstract

Background and Aims: Chronic pelvic pain (CPP) is a debilitating condition often associated with significant psychological difficulties such as anxiety and depression. There is increasing experimental and clinical evidence for the effectiveness of hypnosis in treating a variety of chronic pain problems, although the usefulness of hypnosis for treating CPP has not been reported. Given the paucity of psychological interventions for CPP and the increasing evidence of effectiveness of hypnosis in other pain disorders, the aim of the current research was to assess the use of hypnosis for reducing pain and psychological distress and improving function in people suffering with CPP.

Methods: A multiple single case approach was employed. 5 patients diagnosed with chronic pelvic or abdominal pain participated in the study. Participants attended 2 baseline visits, followed by 5 treatment sessions and one post treatment visit. A mixed methods approach to data collection taken, combining self-report measures and semi-structured interview to assess a number of outcomes measures before and after treatment. Visual, graphical analysis, was used to explore the relationship between psychological variables and change in the pain experience of participants before and after treatment. Post treatment interviews assessing use and experience of hypnosis were qualitatively analysed using Thematic Analysis.

Results: All participants completed the study. Overall, the results suggest that participants benefited from hypnosis treatment but that such benefits varied between individuals in terms of sensory, psychological and behavioural effects such as pain relief,

acceptance of pain and engaging in more activity. Several of these benefits were clinically significant and reliable, notably in terms of pain reduction and less catastrophizing.

Conclusions: the present study suggest that hypnosis is a valuable treatment approach to managing chronic pain and can influence the experience of pain on a number of domains including sensory, psychological and behavioural such as pain relief, acceptance of pain and engaging in more activity. The varied nature of hypnosis effects was reflected in the variety of ways in which hypnosis is applied and practiced. The findings also propose a number of potential factors involved in mediating the effects of hypnosis on pain relief including psychological (acceptance) and psychophysiological (relaxation, worry). Larger sample sizes and more complex analysis (such as regression) are required to assess these hypotheses further.

2.2 Introduction

Pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (Merskey & Bogduk, 1994). Importantly, this definition avoids linking pain to the stimulus that produced it and highlights the emotional ("unpleasant") and cognitive aspects ("potential" tissue damage). This definition reflects the fact that pain can originate centrally and is therefore often experienced in the absence of observable organic sensory pathology (often referred to as functional pain syndrome or unexplained chronic pain) and is commonly associated with psychological factors such as mood and attention.

Psychological influences on pain processing

The impact of psychological variables on the experience of pain has been well recognised in the earliest theories of pain (Zarem, 1966). These and others concluded that there was significant "top down" modulation of pain perception by the brain, particularly via descending pain modulatory pathways from the cortex via the midbrain structures such as the periaqueductal grey matter (Melzack & Chapman, 1973). Contemporary theories consider pain a multidimensional experience consisting of *sensory* (localisation and intensity of pain, *cognitive (*aspects such as attention to pain), and *affective (*level of negative affect associated with pain) components rather than the somewhat dated dualistic approach which viewed pain as "organic" or "psychological" (Melzack, 2001, 2005). Despite evidence to the contrary, a dualistic approach still dominates the lay medical model of pain and is still prevalent in medical practice.

Experimental evidence suggests that pain tolerance increases during distraction and positive emotional modulation but decreases when attention is focused on pain or

during negative emotional modulation (Coen et al., 2008; Phillips et al., 2003; Tang et al., 2008; I. Tracey et al., 2002; Villemure, Slotnick, & Bushnell, 2003; Zelman, Howland, Nichols, & Cleeland, 1991). Using brain imaging techniques such as functional magnetic resonance imaging (fMRI), researchers have shown a neurological basis of psychological modulation of pain which typically involves regions such as the anterior insula and anterior cingulate cortex ([ACC] emotional modulation) and frontal cortex and ACC (cognitive modulation) (Bantick et al., 2002; Coen et al., 2008; Dunckley et al., 2007; Kulkarni et al., 2005). Notwithstanding the sensory component of pain, these findings highlight the importance of considering psychological factors in the assessment and intervention of individuals suffering with chronic pain conditions.

Chronic pain

Chronic pain occurs when symptoms persist beyond the normal acute period of tissue damage and healing time (greater that 3-6 months). It is debilitating physically and psychologically, affects approximately 20%-40% of the population and is a global phenomenon. It is generally well accepted that in chronic pain disorders psychological factors such as emotional and cognitive processing, as well as stress, play an important role. This is reflected in the high association of anxiety and depression in individuals suffering with chronic pain (estimated at between 20-40% (McWilliams, Cox, & Enns, 2003)).

The effectiveness of standard medical treatment for chronic pain is limited (Turk, Wilson and Cahana 2001). For example, a recent meta-analysis exploring the efficacy of opioids for chronic pain suggested this pharmacological treatment results in relatively small improvements in pain intensity relative to placebo (Baron R (Baron, Binder, & Wasner, 2010). Furthermore, the reliance on analgesic medications such as opioids which can have significant side effects, limited long-term efficacy, abuse

(Ballantyne & Mao 2003; Ballantyne & Sullivan, 2015) or problems with treatment adherence has led to an increased interest in the use of psychological therapies for managing chronic pain.

Chronic pelvic pain

CPP has been defined as 'chronic or persistent pain perceived in structures related to the pelvis', including bladder and bowel symptoms (Engeler et al., 2013). CPP is a prevalent pain condition with a high burden. The multifactorial nature of CPP makes it challenging for clinicians and patients. The lack of relationship between pain and extent of pathology can exacerbate the challenge of CPP. Despite surgical and pharmacological interventions, many individuals remain in pain without a firm diagnosis (chronic pain).

Treatment of chronic pelvic pain

NICE guidelines (Engeler et al., 2013; Fall et al., 2010) suggest CPP in males and females is treated according to several algorithms. If underlying tissue pathology is identified then treatment is commonly delivered through surgery or pharmacological management. These interventions are often unsuccessful, surgery in particular, as often the pain is likely to result from central sensitization and is therefore no longer originating in the organ or tissue (Arendt-Nielsen & Graven-Nielsen, 2003; Moshiree, Zhou, Price, & Verne, 2006; Nijs et al., 2012; Woolf, 2007, 2011; Zambreanu, Wise, Brooks, Iannetti, & Tracey, 2005). When CPP occurs in the absence of an identifiable disease, and the absence of organ specific pain symptoms, then a multidisciplinary, holistic approach is recommended which includes some or all of sexology, psychology, physiotherapy and pain medicine. Despite these recommendations, there is no clear evidence base or recommendation regarding the psychological intervention for CPP.

Indeed, a recent Cochrane review of non-surgical interventions for the management of chronic pelvic pain suggested that urgent research is required on the effectiveness of psychological interventions for CPP (Cheong, Smotra, & Williams, 2014)). However, the authors did suggest one approach to research and clinical practice is to extrapolate findings from general chronic pain management to that of CPP.

Clinical Hypnosis and pain

One psychological intervention for chronic pain that has received considerable attention in the past decade is hypnosis. This is particularly the case where other treatments, including psychological based interventions, have failed (M. P. Jensen & Patterson, 2014). Clinical Hypnosis is a procedure in which suggestions for imaginative experiences are presented after a hypnotic induction that often includes practice of relaxation, deep breathing or focused attention. The individual is guided by the hypnotherapist to respond to suggestions for changes in subjective experience (e.g. level of pain), perception, sensation, emotion, thought or behaviour. The suggestions are often idiosyncratic depending on the presentation and goals of the patient (M. P. Jensen, Day, & Miro, 2014).

There is a growing area of research on hypnosis for treating chronic pain in a variety of pain conditions including musculoskeletal pain, visceral pain (e.g. irritable bowel syndrome) and neuropathic pain (Flik et al., 2011; Gonsalkorale & Whorwell, 2005; Oneal, Patterson, Soltani, Teeley, & Jensen, 2008; Prior, Colgan, & Whorwell, 1990). These studies, which have largely focused on outcomes such as pain reduction, have provided good evidence for reducing pain and there are now several RCT's showing efficacy of hypnosis for reducing pain in a range of chronic pain disorders (M. P. Jensen & Patterson, 2014; Tan et al., 2014). In addition, recent evidence has also highlighted other beneficial side effects such as reduction in pain unpleasantness, and

improved sleep quality, self-efficacy and confidence, mood and socializing (Crasilneck, 1979; Crawford, 1998; Grundy et al., 2006; M. P. Jensen, 2006; Melzack & Perry, 1975; Sachs, Feuerstein, & Vitale, 1977).

Despite all the evidence above, the mechanisms of hypnosis for reducing pain are still relatively poorly understood. Developments have been made through recent neuroimaging work that has shown hypnosis results in changes in brain activity in several brain regions that overlap with the those considered part of the cerebral signature of pain (Faymonville, Boly, & Laureys, 2006; Irene Tracey & Mantyh, 2007; Vanhaudenhuyse, Laureys, & Faymonville, 2014), suggesting hypnosis may work through a top-down modulation of pain. The brain regions involved appear to depend on the nature of the hypnotic suggestions, i.e. whether there is a sensory, emotional or attention focus (Mark P. Jensen et al., 2015). Taken together these data suggest an alteration in the integration of sensory, cognitive and affective aspects of the pain experience following hypnosis.

Perhaps the strongest rationale for using hypnosis is that it is a neuromodulatory approach that targets supraspinal processing of pain rather than the sensory input itself. This is in line with contemporary understanding of pain, i.e. that the pain experience is the result of what the brain does with the sensory input rather than the sensory input itself. This approach is particularly pertinent in those disorders where there is no evidence of sensory dysfunction such as that seen in CPP.

2.3 **Research problem**

Despite the wealth of evidence showing the efficacy of hypnosis for a range of chronic pain problems, there is a paucity of research examining how individuals respond to the use of hypnosis in treating CPP. This is important as although hypnosis for

chronic pain appears to show good efficacy for chronic pain in general, there is variation in treatment response between different pain conditions (Dillworth, Mendoza, & Jensen, 2012; M. P. Jensen et al., 2014; Stoelb, Molton, Jensen, & Patterson, 2009). Moreover, there are very few studies exploring the processes involved in the effectiveness of hypnosis; for example, hypnosis interventions typically rely on individuals engaging in self-hypnosis on a daily basis between treatment sessions but little is known about the way in which self-hypnosis is practiced (i.e. frequency, duration, time of day). For example, some individuals may use self-hypnosis when their pain reaches a certain level whilst others may use it before or after activity. It would be interesting to explore the relationship between self-hypnosis use and change in pain outcomes during and following hypnosis treatment.

In addition, particularly lacking is an exploration of how psychological factors such as attention, emotion processing, catastrophizing and hypervigilance may be involved in mediating the effect of hypnosis. All these factors are known to be important in the exacerbation and maintenance of chronic pain (Bergbom, Boersma, Overmeer, & Linton, 2011; G. Crombez, D. M. Van Ryckeghem, C. Eccleston, & S. Van Damme, 2013; Eccleston & Crombez, 1999; Garland, 2012; Goubert, Crombez, & Van Damme, 2004; Lumley et al., 2011; Westman, Boersma, Leppert, & Linton, 2011). Despite this, the majority of hypnosis studies thus far have used global, rudimentary measures such as the Hospital Anxiety and Depression scale (HADS)(Zigmond & Snaith, 1983) and SCL-R 90 Symptom Checklist-Revised (Derogatis & Unger, 2010), largely ignoring other functional and psychological outcomes.

Finally, it is likely, given the proposed mechanisms of hypnosis, that the effect of hypnoanalgesia extends beyond purely inhibiting sensory input and that some of the psychological factors thought to influence the experience of pain (as mentioned above)

are mediating factors in the usefulness of hypnosis. To date, these factors have not been assessed.

2.4 **Research aims**

Using mixed quantitative and qualitative outcomes, and adopting an inductive approach, the aim of the study is to generate knowledge on how patients with chronic pelvic pain use hypnosis and how that is related to a variety of pain and functional outcome measures. This knowledge can then be used to formulate hypotheses for future studies in larger cohorts with the aim of assessing the effectiveness and/or efficacy of hypnosis for CPP in a more systematic and controlled manner e.g. in controlled experiments and randomised controlled trials.

Research questions

1. Does hypnosis affect intensity and unpleasantness of pain in people with CPP?
2. How do individuals practice self-hypnosis?
3. What are the psychological mechanisms that might be involved in mediating response to hypnosis?

2.5 **Methods**

Participants

Five volunteers (3 male; mean age 35 years, range 19-51 years) participated in the study after informed, written consent; the study had ethical approval from the South West – Cornwall and Plymouth Research Ethics Committee (reference 15/SW/0345). Participants were identified and recruited, following informed consent, from consecutive referrals for hypnosis from within the Pain Management Centre at the National Hospital for Neurology and Neurosurgery (NHNN), University College London Hospitals (UCLH) Queen Square, London. All participants had a diagnosis of chronic pelvic or abdominal pain. Potential participants with further planned surgery, pelvic inflammatory disease, other major neurological, neurodevelopmental or medical illness were excluded. A summary of participant characteristics is presented in Table 2.1.

Table 2.1 Summary of patient demographics, clinical history and therapist allocation

Participant number	Age	Gender	Duration of pain	Ethnicity	Location of pain/diagnosis	Co-morbid problems	Therapist
P1	27	male	5 years	White British	Pelvic pain	PTSD	1
P2	35	male	13 years	White British	Pelvic pain	-	1
P3	61	female	2 years	Arabic	Abdominal Pain	Chronic Lower Back Pain (following a fall 2 years ago)	2
P4	26	male	18 months	Indian	Abdominal pain	IBS, chronic constipation	2
P5	19	female	8 years	White British	Abdominal pain	JHS, CFS	2

JHS=joint hypermobility syndrome; IBS=irritable bowel syndrome; PTSD=post-traumatic stress disorder.

Design

A prospective case series approach was employed to address the aims of the research proposal. Participants completed mixed quantitative and qualitative measures to assess outcomes of the study such as change in average and worst pain intensity and distress, psychological functioning (e.g. attentional bias, emotional distress) and experience of hypnotherapy for chronic pain. Given the heterogeneity in the delivery and proposed mechanisms of hypnosis as well as the multidimensional nature of the pain experience, the outcomes selected for this study were broad and aimed at covering sensory, cognitive and emotional factors that are hypothesised to change during intervention.

Pre-intervention and post intervention outcomes were collected using self-report measures (see questionnaire pack, below) and qualitative interview. In addition, daily measures of pain (e.g. pain intensity and pain unpleasantness) and pain related psychological functioning (e.g. catastrophizing, worry about pain and attention to pain, pain interference) were recorded using an electronic daily diary. For a schematic overview of the protocol see the appendix.

Procedure

Recruitment and informed consent: Potential participants were identified by screening consecutive referrals to the pain team at the NHNN, UCH. Participants were then contacted by telephone to briefly assess suitability for hypnosis and interest in volunteering for the research, after which they were invited to attend a clinical assessment appointment at UCH with one of the qualified hypnotherapists involved in the study (see section on clinical hypnosis procedure). Following this, participants were sent a participant information sheet and appointment letter for their assessment, thereby giving them a minimum of 48 hours to consider the study and their participation before

informed consent was obtained. At their assessment appointment (prior to clinical assessment) participants were met by me to discuss and answer any questions about the research and obtain informed consent to participate in the study.

Baseline phase: Following informed consent, participants completed a questionnaire pack containing several self-report questionnaires (see below) and a Pain-Stroop task (see below for more details). After this, they were given instructions and a demonstration on how to complete an online dairy diary (see below for more detail) which they agreed to complete from that day forward until two weeks after the end of treatment. Approximately two weeks later, participants attended their first treatment session, prior to which the outcome measures described above were repeated (questionnaire pack and Stroop task). This pre-treatment phase was aimed at establishing a baseline level of functioning and symptoms prior to hypnosis treatment.

Intervention phase: during treatment, participants attended their clinical hypnosis outpatient appointments as normal at UCLH based on the availability of clinician and participant. During this time they also completed an online daily diary.

Post intervention phase: following the end of treatment, participants completed the online daily diary for approximately two weeks. At the end of this period, they attended a final research appointment where the baseline measures described above (questionnaire pack and Pain-Stroop task) were repeated. Participants were then interviewed to assess their experience of using hypnosis and any effects of treatment on their symptoms or functioning.

For a summary of measurements used and the time points at which measures were administered see Table *2.2*.

Self-report questionnaires (Questionnaire Pack)

Self-report measures were used to assess a range of study outcomes. Participants complete all the questionnaires listed below at baseline (twice) and approximately two weeks following the end of treatment.

The choice of questionnaires was pragmatic and aimed at assessing the psychosocial, sensory, cognitive and emotional aspects of pain whilst not over-burdening participants. In addition to being pragmatic, this approach was aimed at ensuring the quality of responses to the questions was not affected by questionnaire-fatigue.

Psychosocial functioning:

A common outcome measure in chronic pain research is interference of pain in the ability to engage in routine, daily physical activities, otherwise known as health related quality of life (HRQOL). This was assessed using the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994). The BPI is a recommended measure of HRQL when researching pain (Dworkin et al., 2005) and provides a reliable assessment of pain severity and the interference of pain with physical functioning. It has been translated into many languages and studied in diverse chronic pain conditions in multiple countries. Validation studies include The BPI contains 11 items, comprised of a pain severity scale (4 items) and pain interference scale (7 items), each item scored from 0 to 10. It is a relatively simple questionnaire to complete, score and interpret and is applicable across a variety of pain aetiologies (Keller et al., 2004). Means for the severity and interference scales are calculated with higher scores representing more severe pain levels (range 0-10) and more interference (range 0-10). The psychometric properties of the BPI have been explored recently with findings suggesting a good psychometric profile: internal reliability 0.82-0.95 (assessed by comparing two groups of chronic pain

patients), criterion validity α=0.61-0.74 (assessed by comparing with SF-36 bodily pain scale). Furthermore, they also noted that BPI was sensitive to changes in disability for the sample they studied (Keller et al., 2004).

Psychological distress:

The Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress. The HADS is comprised of fourteen items designed to assess levels of anxiety and depression through two, 7 item subscales HADS-A and HADS-D (Zigmond & Snaith, 1983). The questionnaire was validated within health populations, showing good psychometric properties with a Cronbach's α=.89-.93 (Zigmond & Snaith, 1983), test-retest reliability r=.72. In addition, comparisons with other questionnaires of psychological distress have shown good convergent validity (r.49 to .83) (Bjelland, Dahl, Haug, & Neckelmann). Although there are other measures available to specifically assess anxiety and depression, the HADS is preferable when measuring such constructs in clinical populations with chronic pain as it does not contain somatic descriptions of psychological distress that may overlap with symptoms of chronic pain. This reduces the chance of artificially inflated scores of anxiety and depression. Despite being developed and validated for use in assessing anxiety and depression separately, the HADS has been shown to be more valid as a single measure of psychological distress (Cosco, Doyle, Ward, & McGee, 2012). Total HADS scores range from 0 to 42 with greater scores representing higher levels of psychological distress.

Worry:

The Pain Catastrophizing Scale (PCS, (Sullivan, Bishop, & Pivik, 1995) is a self-report measure containing 13 items that assess catastrophizing, overestimation of threat and underestimation of coping, and tendency to attend to pain. Studies have shown

high internal consistency (Cronbach's α=0.91, (Sullivan et al., 1995) whilst the test-retest reliability is moderate for the scale as a whole (ICC=0.82) (Chatzidimitriou et al., 2006). Respondents are required to rate frequency of responses to pain from 0 (not at all) to 4 (all the time), range of total score 0 to 52 with higher scores representing increased levels of pain catastrophizing.

The Pervasive Thinking Questionnaire (Ehring et al., 2011) was used as an additional measure of worry as it has been suggested that this tool assesses a different construct to the PCS that may be important in maintaining pain (Flink, Boersma, & Linton, 2013). The PTQ contains 15 items designed to measure extent of repetitive negative thinking (RNT). Unlike several other questionnaires measuring RNT, the PTQ does not focus on a particular disorder-specific content and is therefore useful for measuring RNT across a range of presenting problems where RNT is hypothesised to be important, including chronic pain. On a 5-point scale, respondents are requested to indicate how they typically think about their problems or negative experiences (e.g. pain) with each item rated from 0 (never) to 4 (almost always). Higher scores indicate higher levels of repetitive thinking (range 0-60). The internal consistency of the PTQ is good (Cronbach's alpha=0.94-0.95), and convergent validity with other similar measures is also reasonable (r=0.63) (Ehring et al., 2011). The PTQ has also been recently validated within other clinical populations showing similar psychometric properties (Černis et al., 2016) and highlighting the utility of the PTQ in measuring a transdiagnostic process (Ehring et al., 2011).

Electronic daily diary assessment

Participants completed an 8 question online diary at the end of each day during a pre-treatment baseline period and throughout treatment, to assess sensory, emotional and cognitive components of their pain experience. Participants were reminded to

complete the diary each day at 7 pm by means of a text message with a link to the questionnaire, an example of which can be found at the following url http://www.surveygizmo.com/s3/2850663/Hypnosis-and-Pain-Research-Example. All items were rated using an 11-point numerical rating scales ranging from 0-10. These scales and questions are based upon previous pain studies assessing psychological mechanisms involved in pain processing (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013; Van Ryckeghem et al., 2013). Daily questions assessing pain intensity are based on those recommended as a core outcome measure in clinical trials of chronic pain treatments (Dworkin et al., 2005; D. C. Turk & Dworkin, 2004; D. C. Turk et al., 2003). For a list of questions used see Appendix 1.

Pain Stroop

The Stroop task (Stroop, 1935) provides an objective measure of attentional bias and has been adapted for use in measuring attentional bias towards pain (Crombez, Hermans, & Adriaensen, 2000; G. Crombez, D. M. Van Ryckeghem, et al., 2013; Pearce & Morley, 1989). In the present study, the Stroop was employed as an objective measure to assess whether one of the mechanisms of hypnosis might be in reducing attentional bias towards pain and increasing ability to disengage from pain. The task typically involves presentation of a list of words written in different colours. Participants are asked to name the colour the word is written in whilst ignoring the meaning of the word. The task becomes more difficult when the written word is salient to the person performing the task resulting in longer response latencies (the Stroop effect). Previous studies have shown increased latencies when reading pain congruent words in chronic pain patients. This effect is thought to be larger when the words are particularly salient to type of pain an individual is experiencing and when the word is a sensory pain word

(e.g. throbbing, sharp) rather than emotional pain word (e.g. nasty, punishing) (G. Crombez, D. M. Van Ryckeghem, et al., 2013).

In the present study, participants completed the Stroop task twice during the baseline period and once following treatment in order to assess any effect of hypnosis treatment on attentional biases (latency times). The Stroop task used was based on that previously described by Morley et al 1989. Briefly, participants were presented with four word lists 1) colour Stroop control; where each word was written in the corresponding g coloured ink e.g. blue written in blue ink; 2) colour Stroop, where ink colour and word colour were incongruent e.g. blue written in red ink; 3) pain Stroop control; a list of neutral words written in coloured ink 4) pain Stroop; a list of pain related words written in coloured ink. Lists were present on A4 card in two columns of 25 words (50 words per list in total) containing equal numbers of words printed in blue, red, yellow, brown and green ink. Words in each control list were matched for length and frequency of use. The pain Stroop control and pain Stroop words were the same as those described by Pearce and Morley (1989). Word order was pseudo-randomised such that no word or colour could appear twice in succession. A practice list was given before testing with two columns of Xs written in the five colours described above to ensure participants understood the task and could accurately report the colours. A stop watch was used to record latency times for the time taken to read each list from the moment the each participant began reading the first word. For examples of the word lists used see Appendix 4 and 5.

Table 2.2 Measurement time points

Time point	**Measures administered**
Baseline 1	BPI, HADS, PTQ, PCS, DD, STP
Baseline 2	BPI, HADS, PTQ, PCS, DD, STP
Intervention	DD
End point	BPI, HADS, PTQ, PCS, DD, STP, PII

BPI=Brief Pain Inventory; HADS=Hospital anxiety and depression scale; PTQ=perseverative thinking questionnaire; PCS=Pain catastrophizing scale; DD=daily diary; STP=Stroop; PII=post intervention interview.

Clinical Hypnosis

Hypnosis treatment was delivered over 5 sessions by two clinicians qualified and experienced in using clinical hypnosis for treating chronic abdominal/pelvic pain. For a summary of clinician experience and training in hypnosis see Table 2.3. A standardised protocol was used by both clinicians, incorporating factors known to be important in delivering hypnosis for chronic pain such considering social (e.g. social avoidance/isolation), behavioural (e.g. avoidance of activity), cognitive (e.g. acceptance) and emotional (e.g. rumination) factors as well as pain sensation. However, specific targets for treatment were driven by formulation of each individual client. As such, suggestions used during hypnosis were tailored to the needs of the patient as this has been shown to be the most effective intervention and is the approach employed in previous clinical hypnosis research on chronic pain, (M. P. Jensen & Patterson, 2014; Kirsch, Montgomery, & Sapirstein, 1995). Nonetheless, each clinician adhered to a standardized protocol as described below and summarized in Table 2.4.

Overview of hypnosis protocol: Briefly, the first session was aimed at familiarisation with hypnotic induction, using relaxation induction and deepening with imagery

combined with use of suggestions for comfort and relaxation. During session two, pain sensation was targeted through the use of pain imagery (e.g. pain dial) to help transform (e.g. dampen down) the pain sensation. Suggestions aimed at changing relationship to pain (e.g. pain becoming less bothersome) were also incorporated. Session three was aimed at exploring behavioural context in relation to pain such as avoiding social situations/activity through appropriate suggestions and imagery, e.g. imaginal exposure. During session four, progress was reviewed and problem solving used to explore any barriers/problems, integrated into another hypnotic induction. Session five, targeted optimisation of current hypnosis strategies as was as using suggestions for maintenance or improvement.

Each session was recorded on a smart phone and participants were encouraged to practice self-hypnosis using the recordings at between sessions.

Table 2.3 Summary of clinician training and experience of using hypnosis for management of chronic pain

Therapist 1	**Therapist 2**
Qualifications relevant to hypnosis intervention: • BSc (Hons) Psychology • DClinPsy (2007) • Diploma in Clinical Hypnosis, UCL (2006)	*Qualifications relevant to hypnosis intervention:* • Doctorate in general medicine, MD (2003) • MSc Hypnosis, UCL (2007) • Diploma in Hypnosis, UCL (2006)
Experience relevant to hypnosis intervention: Psychology Lead for Complex Pain Team and Abdominal Pelvic Pain Pathway, University College London Hospitals (UCLH) NHS Foundation Trust. Over 15 years of experience treating chronic pain, 10 years of treating chronic pain with clinical hypnosis.	*Experience relevant to hypnosis intervention:* History of using hypnosis for treating chronic pain since 2005. Established the first NHS hypnosis service to treat a wide range of conditions including pain. President-elect of the Hypnosis and Psychosomatic Medicine Section, Royal Society of Medicine.

Table 2.4 Hypnosis intervention summarised session by session

Session number	Session content
Session 1	• Familiarisation with hypnotic induction • Relaxation induction and deepening with imagery combined with use of suggestions for comfort and relaxation
Session 2	• Pain sensation was targeted through the use of pain imagery (e.g. pain dial) to help transform (e.g. dampen down) the pain sensation. • Suggestions aimed at changing relationship to pain (e.g. pain becoming less bothersome)
Session 3	• Exploration of behavioural context in relation to pain such as avoiding social situations/activity. • Exposure to avoided situations using appropriate suggestions and imagery, e.g. imaginal exposure
Session 4	• Review session. Problem solving any difficulties in engagement/use of hypnosis
Session 5	• Optimisation of current hypnosis strategies • Suggestions for maintenance or improvement of hypnosis practice

Post treatment Semi-structured interview

Approximately two weeks (depending on participant availability) after their final hypnosis treatment session, participants attended a final appointment with me. During this appointment, participants completed a final questionnaire pack and Stroop, after which they were interviewed to assess experience of hypnosis such as what they found most helpful and how they think hypnosis affected their pain and well-being. The interview, developed in consultation with the research supervisor and hypnosis clinicians, was designed to gain an idiographic measurement of experience and benefit of hypnosis rather than relying purely on quantitative methods. Interviews lasted between 25-40 minutes, were recorded on Dictaphone and transcribed by me. The interview was semi-structured and based on a list of pre-defined areas of interest aimed

at addressing the study outcomes including practice of self-hypnosis and effects of hypnosis on pain and quality of life/daily functioning, as well as probing cognitions about pain. The list of topics for discussion can be found in the interview schedule (Appendix 7). Although the interview was structured, the schedule was used as a guide and alternative or follow-up questions were used where appropriate, these are also contained in Appendix 7. Many of the additional questions that were used were analogous to those used in the standardized client change interview (Elliott, 1999), although questions were focused on addressing research questions of the study and were therefore not as broad as the interview by Elliot and colleagues.

Statistical Analysis

Questionnaire, daily diary and Stroop

Due to the small sample size, the use of group level inferential statistics was not possible as a minimum number of approximately twelve is required in order to have enough statistical power to detect an effect and avoid type II error. As a result, analysis of baseline-endpoint data was calculated at an individual level using reliable change and clinically significant change were possible (Jacobson, Roberts, Berns, & McGlinchey, 1999; Jacobson & Truax, 1991; Morley & Dowzer, 2014). Reliable change (RC) refers to a change in score that is more than the expected error of the measurement tool, whilst clinically significant change (CSC) refers to a reliable change that is also clinically relevant. Briefly, clinical significance, in the absence of an established cutoff for clinical caseness, is estimated using one of 3 criteria; criterion A) when scores are outside the range of a clinical population (more than 1.96 standard deviations towards a non-clinical reference sample); criterion B) when scores fall within the range of a non-clinical population; criterion C) when scores fall closer to the mean of the comparison group

than the clinical group, see Figure 2.1. When calculating CSC it is preferable to use criterion B or C when data for a non-clinical population is available (Jacobson & Truax, 1991; S. Morley & Dowzer, 2014). However, as there were no normative population statistics available for the BPI, criterion A was used in this instance. For all other measures where normative data was available (HADS, PCS, PTQ), criterion B was applied.

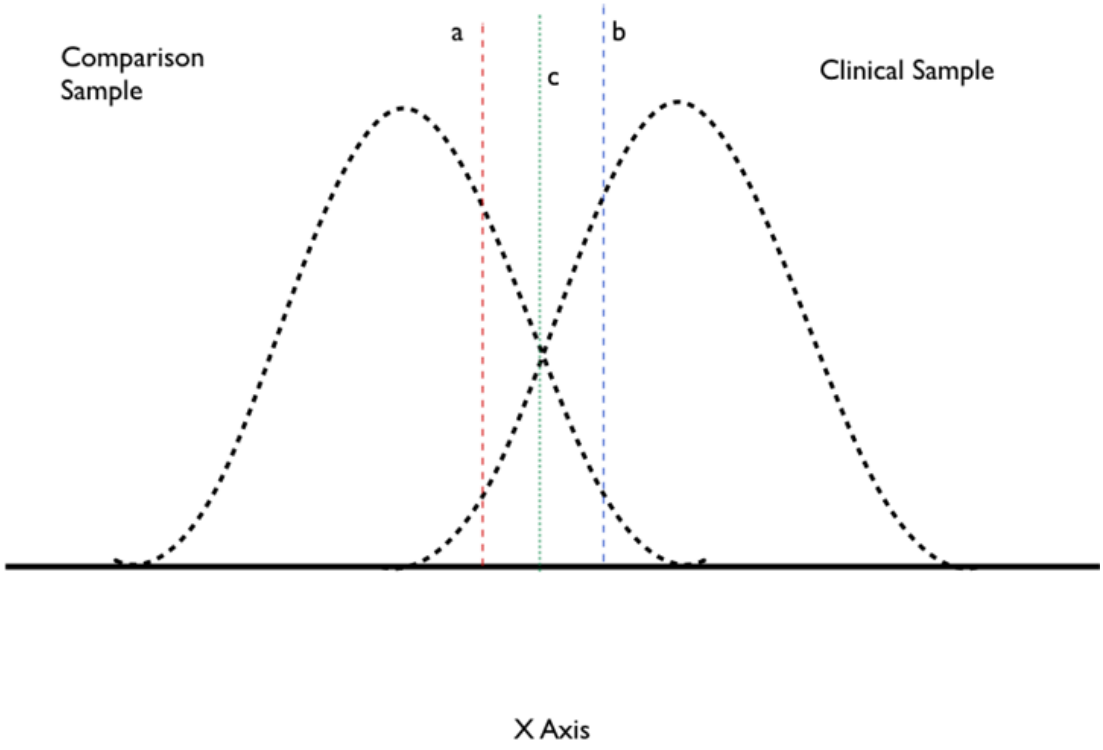


Figure 2.1. Schematic of Jacobson's criteria for estimating clinically significant change, taken directly from Morley & Dowzer (2014).

Using the criterion described above, reliable and clinically significant change were calculated using statistics summarised in Table *2.5* and according to the method described by Morley & Dowzer (2014).

Where RC or CSC was not possible, qualitative analysis was applied by graphically analysing data for each individual, according to previous guidelines for single-case data (Morley & Adams, 1991).

Baseline:

A composite baseline score was used (calculated by obtaining the mean value of baseline measure 1 and baseline measure 2) as a representative baseline score for all self-report questionnaire data (HADS, PCS, BPI and PTQ) but not daily diary outcomes. This score was then used to compare with outcomes obtained at the end of treatment.

Self-report questionnaires:

For each participant, mean scores were calculated for the BPI pain severity and pain interference constructs at baseline and post intervention. These data were plotted graphically and analysed for RC and CSC. For HADS, PCS and PTQ, total score was calculated for each participant at baseline and post intervention for each measure and plotted graphically then analysed for RC and CSC.

Pain Stroop:

Latency times for each condition at baseline and end of treatment were plotted graphically for each participant and analysed visually.

Daily diary:

Data were summarized by calculating mean weekly scores for each outcome (e.g. pain intensity, pain unpleasantness, avoidance) for each participant. These were plotted graphically to show change weekly from baseline to post intervention. Error bars were calculated and added to each graph to represent variability in scores for each mean calculated. In addition, baseline and end of treatment scores were calculated for pain intensity and pain distress measures in order to assess if there was a clinically significant change in pain ratings (30% change from baseline)(Dworkin et al., 2005).

Table 2.5 Reliable change statistics for all measures

Measure	Published clinical population	Clinical population mean (SD)	Reliability coefficient
BPI	(Keller et al., 2004) (Tan, Jensen, Thornby, & Shanti, 2004)	P=6.98 (1.79) I=7.56 (2.01)	α=0.84-0.95
HADS	(Morley, Williams, & Hussain, 2008)	20.85 (7.2)	α=0.89-0.93
PCS	(Osman et al., 1997)	20.9 (12.5)	α=0.93
PTQ	(Ehring et al., 2011)	28.1 (13.23) NCS	α=0.95

BPI=Brief Pain Inventory (P=Pain subscale, I=Interference subscale); HADS=Hospital anxiety and depression scale; PTQ=perseverative thinking questionnaire; PCS=Pain catastrophizing scale; NCS=non clinical sample

Interview data:

Thematic analysis (TA) was used to analyse and interpret the data gathered at post intervention interview as this provided the most pragmatic approach to answering the research question (Pistrang & Barker, 2012). Thematic analysis is a systematic method involving several pre-defined stages (see below) of analysis that is suitable for identifying and analysing patterns of meaning in qualitative data sets (Joffe, 2011). Unlike some alternative qualitative methods, TA allows a combination of a deductive (researcher led ideas, hypotheses or topics are used to interpret data) and inductive (content of the data drives topics, idea and themes and outcomes) approach to data analysis reflecting the fact that it is a suitable approach for research from different epistemological positions (Braun & Clarke, 2006, 2012). Although a primarily deductive approach was taken in analysis of the interview transcripts, TA was selected as it also

enabled opportunity for emergence of themes outside the hypothesis and research questions of the project (inductive).

Transcripts were analysed across three domains which reflected the research questions and structure and content of the interview; 1) Practice of self-hypnosis, 2) Effects of hypnosis on pain levels, 3) Effects of hypnosis on psychosocial functioning (e.g. behavior, cognitions and emotions about pain).

Thematic analysis procedure: A six stage protocol was used to analysis the data as previously described by Braun and Clarke (2006). Each recording was transcribed verbatim by the researcher, ensuring any personal information was removed that might make participants identifiable. This process is a useful step if carried out by the researcher as it adds an extra layer of familiarisation with the data compared to outsourcing transcription. Following transcription, all transcripts (data) were read and preliminary comments were noted. The data were then re-read and any text that seemed to describe (explicitly or latently) phenomena congruent with the research questions were noted. These items were given initial codes, which refers to the most basic element of the raw data (Braun & Clarke, 2006). Using these codes, themes were then identified by grouping conceptually similar codes, leading to a preliminary thematic map of the data for each individual. Following this, the complete data set (all participants' transcripts) were read again and reviewed to ensure themes were heterogeneous and codes homogenous. During this stage any necessary recoding or changes to themes were made as a result of the review of the entire data set. This resulted in an updated thematic map that closely mirrored the data and consistently and accurately reflected elements of the research question. Following this, themes were defined and labeled. Finally, in order to illustrate the occurrence of themes in individual participant responses, extracts of raw data were selected which reflected each theme.

Researcher perspective

It is well described that researchers bring their own perspective to analysis of any type of data and that this can influence the data analysis, data collection and interpretation and are therefore active agents in the research process (Braun & Clarke, 2012). This influence is particularly relevant when considering qualitative analysis. As such qualitative methodology guidelines recommend that perspectives of the researcher are disclosed so that the results can be better evaluated by the audience. I am a white male in my mid-thirties from an Irish working class background. I am a clinical psychologist trainee at UCL, prior to which I spent several years working as an experimental psychologist conducting research in functional brain imaging and pain. Through this work I have developed a good knowledge of top-down modulation on pain (cognitive and emotional) whilst also gaining a good understanding of the physiology of pain. As a result I adopt a biopsychosocial approach to assessment and understanding of chronic pain. I have personal experience of long-term mild pain as a result of several sporting injuries, but this does not affect my physical activity. I also have experience of relatives with pain conditions, secondary to other physical health problems and have seen the effect pain can have on physical ability and emotional well-being. Through these experiences I have noticed the disparity between level of pain/injury and level of disability/ function and observed how psychological factors mediate this difference in functional outcomes between individuals. In summary, I have personal and professional experience with chronic pain which will influence my interpretation of the data and perhaps my follow-up interview questions. In order to reduce personal bias in the research process, I have used regular research meetings, supervision and personal reflection to acknowledge and partition my own beliefs and assumptions (Hill et al., 2005). Furthermore, an example transcript was independently

coded by another researcher involved in the study ad differences in coding were clarified and updated as necessary.

2.6 **Results**

All participants completed baseline, intervention and post intervention visits. In addition, they attended all their clinical sessions. Due to differences in clinician and participant availability there was a range of treatment period from 6-8 weeks.

Daily diary

Response: all participants responded to the daily diary requests. However there was some variability in number of daily responses, with all participants responding a minimum of twice per week (range 2-7 responses per week). On days where volunteers responded, all questions in the diary were answered. In total, individual responses varied from 61% completion to 100% completion (P1=90%, P2=83%, P3=100%, P4=61%, P5=79%). Average weekly responses to each question are summarised graphically in Figure 2.2 to Figure 2.9.

Pain intensity and pain unpleasantness: visual graphical analysis revealed that all participants showed a decrease in pain intensity and unpleasantness ratings from baseline to end of treatment. Visual analysis suggested the changes in PI were mirrored by changes in PU except in P1 who showed a greater gradual decrease in PU. When baseline and end of treatment scores were analysed for CSC, results demonstrated that there was a CS reduction in PI and PU in P4 and P5, whilst P1 showed a CS reduction in PU only. Most of the changes observed show a gradual slow decrease over the period of treatment (e.g. P1, P2, P3). However, the graph of PU and PI for P4 show a big at week 3 when treatment started whereas the drop in PU and PI seen in P5 seem show most change after the final treatment session.

Finally, error bars show some variability in within each week for all volunteers. This was most notable for P4 and P5, who showed very high variability in scores, suggesting pain levels were dramatically changing on a daily basis. Anecdotally this is analogous to verbal reports from P4 and P5 who suggested their pains are very episodic and changed day to day compared to P1-P3 who reported more steady pain levels.

Focus on pain and distraction by pain: visual inspection of the FP and DP graphs show that responses over time were mirrored for these daily questions, reflecting the fact they were measuring similar outcomes. Overall, scores show high between subject variability in how much people focused on their pain or were distracted by pain from low (P1, P5) to moderate (P2, P3). P1 and P2 showed little notable change from baseline to end of treatment with low variability from week to week. P3 and P5 showed a gradual decrease in DP and FP scores from beginning to end of treatment. P4 showed high variability in scores at during baseline with very high scores before treatment and a dramatic drop at the start of treatment which was then mostly stable week by week (low for the rest of the study). Both P4 and P5 showed high variability in scores within each week, reflected by large error bars.

Worry about pain: reported worry about pain varied between subjects with some reported low (P1, P5), moderate (P2, P3) and high levels (P4). Worry was stable across time for P1 and P2 with no change from baseline. P5 showed a reduction from low worry to no worry from baseline to end of treatment. P3 and P4 showed changes in weekly worry levels that fluctuated around moderately high levels but there was no apparent change when scores at the beginning and end of study were assessed.

Effects of pain on activity: Scores on HA, SD, ad AV questions showed remarkably similar weekly plots, reflecting the fact these questions measured similar effects of pain on daily activity. P1 reported low scores on all measures, with a small reduction over time suggesting pain did not limit daily activity substantially before treatment and

therefore there was a floor effect for this participant on this outcome. Nevertheless, it does appear that variability decreased over time with more days at the beginning than at the end of treatment when pain affected daily activity. P2 showed moderate levels of effect of pain on activity, but this effect showed very little variability week by week and there was no notable change from beginning to end of treatment. P3, P4 and P5 all showed a change in HA, SD and AV scores from baseline to end of treatment. Graphs of P3 and P4 suggest a gradual decrease of influence of pain on activity from start to end of treatment whilst the change in P4 appears to be a result of a considerable drop in scores when treatment commenced. As with previous measures, P4 and P5 showed high variability in weekly scores (large error bars) suggesting scores varied substantially day to day.

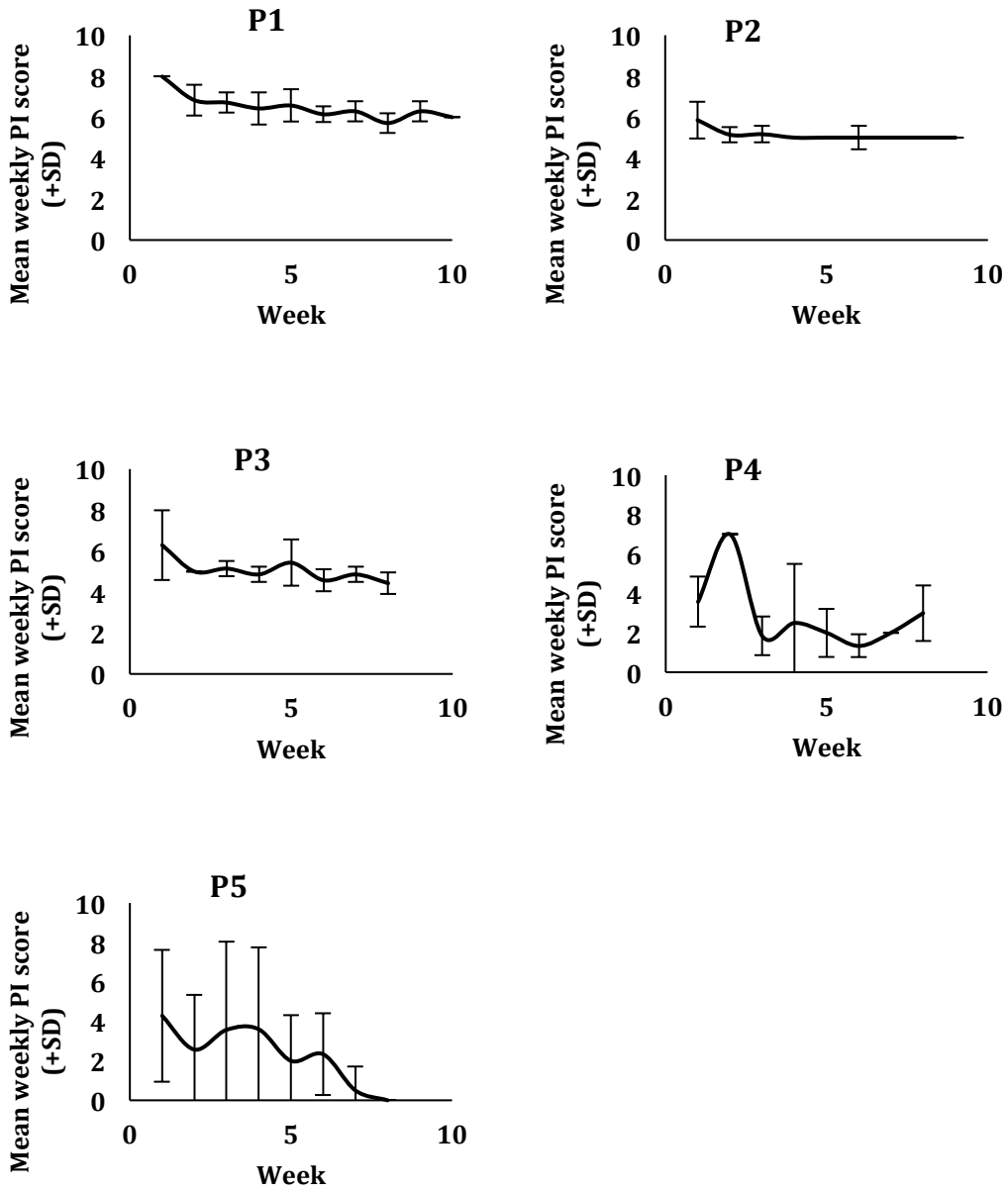


Figure 2.2 Mean weekly pain intensity scores. Each graph shows weekly changes in pain intensity for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *Please rate your pain intensity by indicating the number that best describes your pain on average in the last 24 hours* were recorded using daily dairy and summarised as weekly averages.
PI=pain intensity; P=participant; SD=standard deviation; 0=no pain, 10= extreme pain

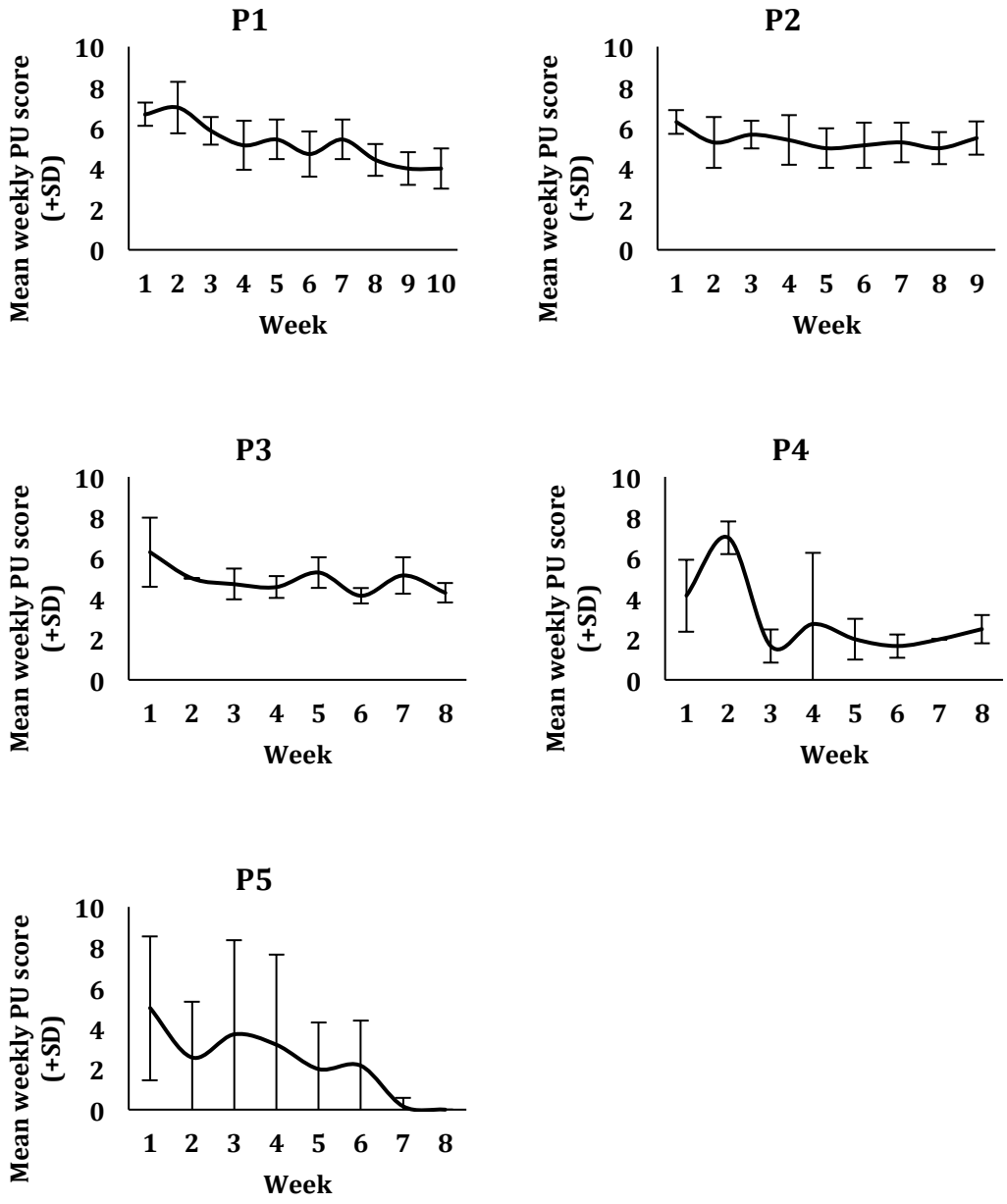


Figure 2.3 Mean weekly pain unpleasantness scores. Each graph shows weekly changes in pain unpleasantness for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *Please rate you're the unpleasantness of you pain by indicating the number that best describes your pain on average in the last 24 hours* were recorded using daily dairy and summarised as weekly averages.
PU=pain unpleasantness; P=participant; SD=standard deviation; 0=no unpleasantness, 10= extremely unpleasant

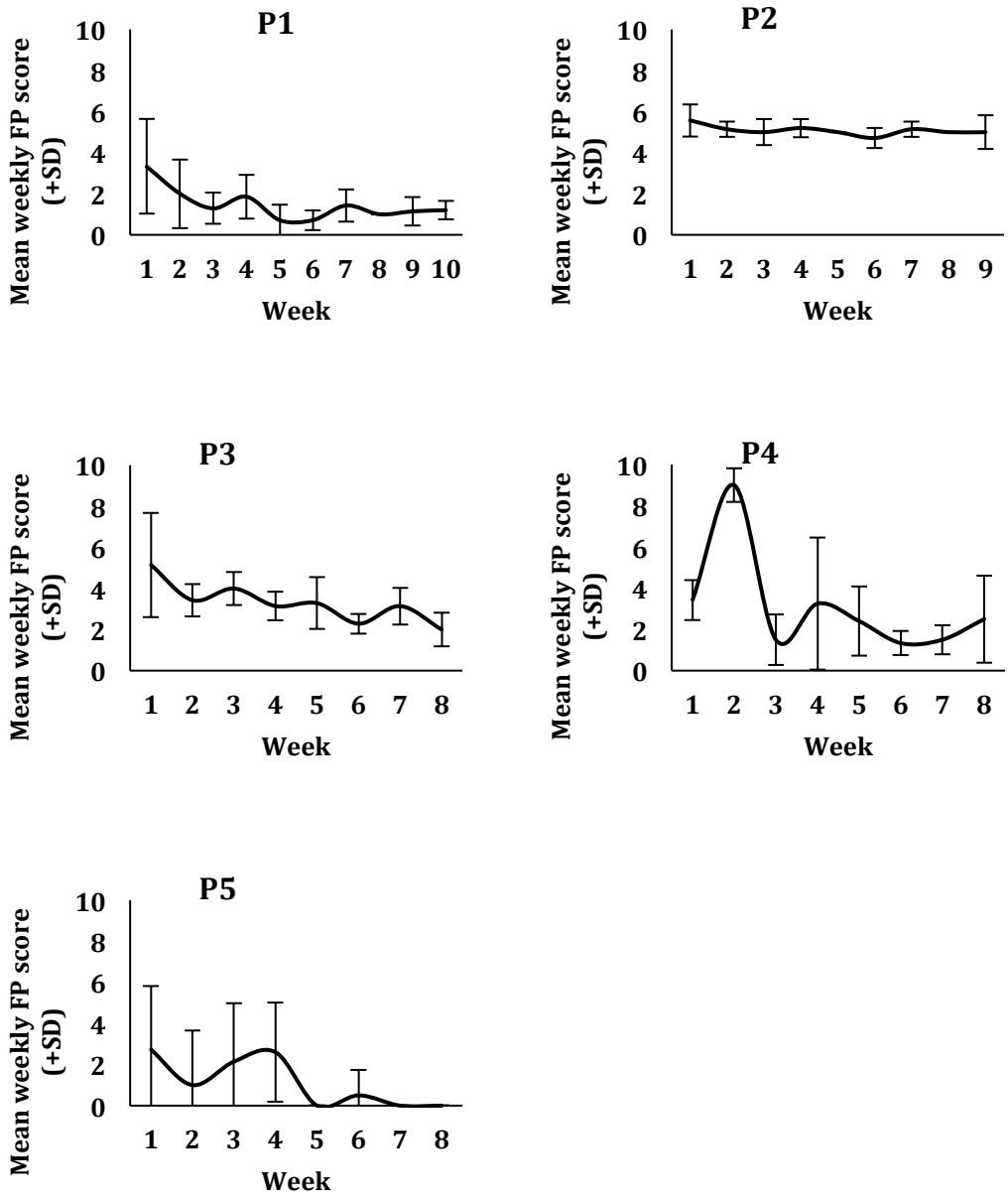


Figure 2.4 Mean weekly focus on pain scores. Each graph shows weekly changes in level of focus on pain for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *Today I have been focussing on my pain* were recorded using daily dairy and summarised as weekly averages.
FP=focused on pain; P=participant; SD=standard deviation; 0=not at all, 10= completely focused

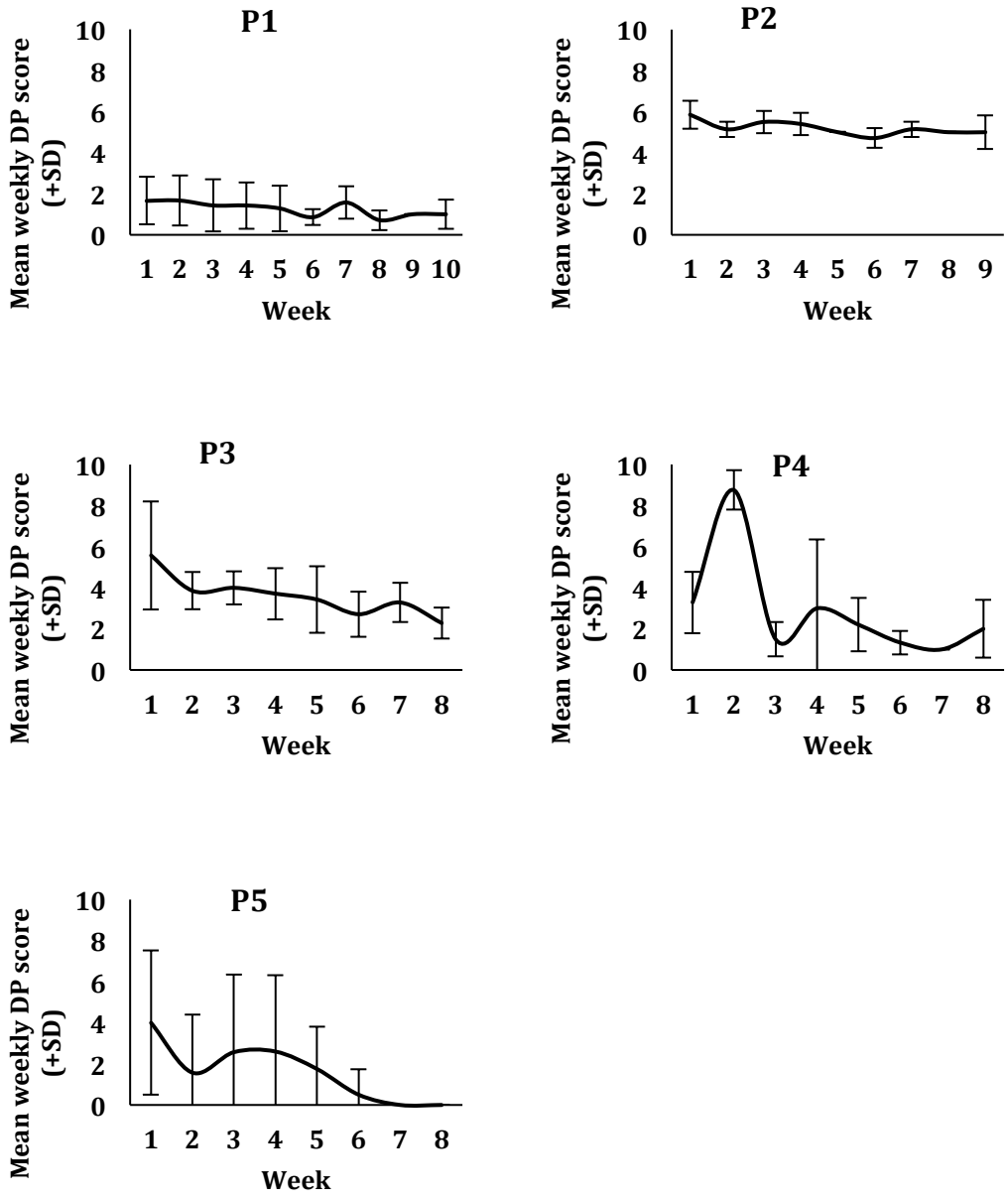


Figure 2.5 Mean weekly distracted by pain scores. Each graph shows weekly changes in level of distraction by pain for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *Today I am distracted by my pain* were recorded using daily dairy and summarised as weekly averages.
DP=distracted by pain; P=participant; SD=standard deviation; 0 = not at all – 10 = completely distracted.

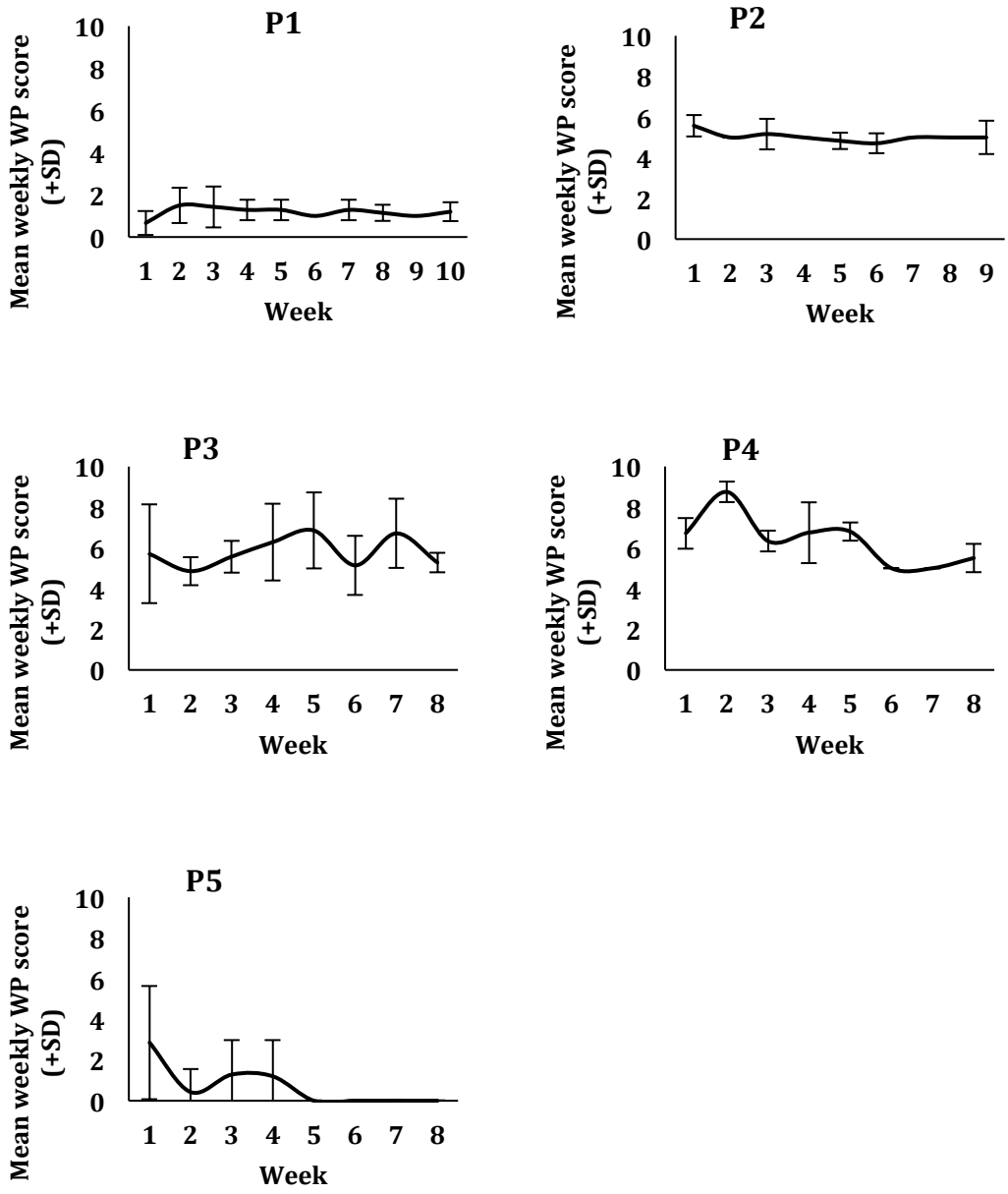


Figure 2.6 Mean weekly worry about pain scores. Each graph shows weekly changes in level of worry about pain for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement I am worried about my pain were recorded using daily dairy and summarised as weekly averages.
WP=Worry about pain; P=participant; SD=standard deviation; 0 = not at all – 10 = completely.

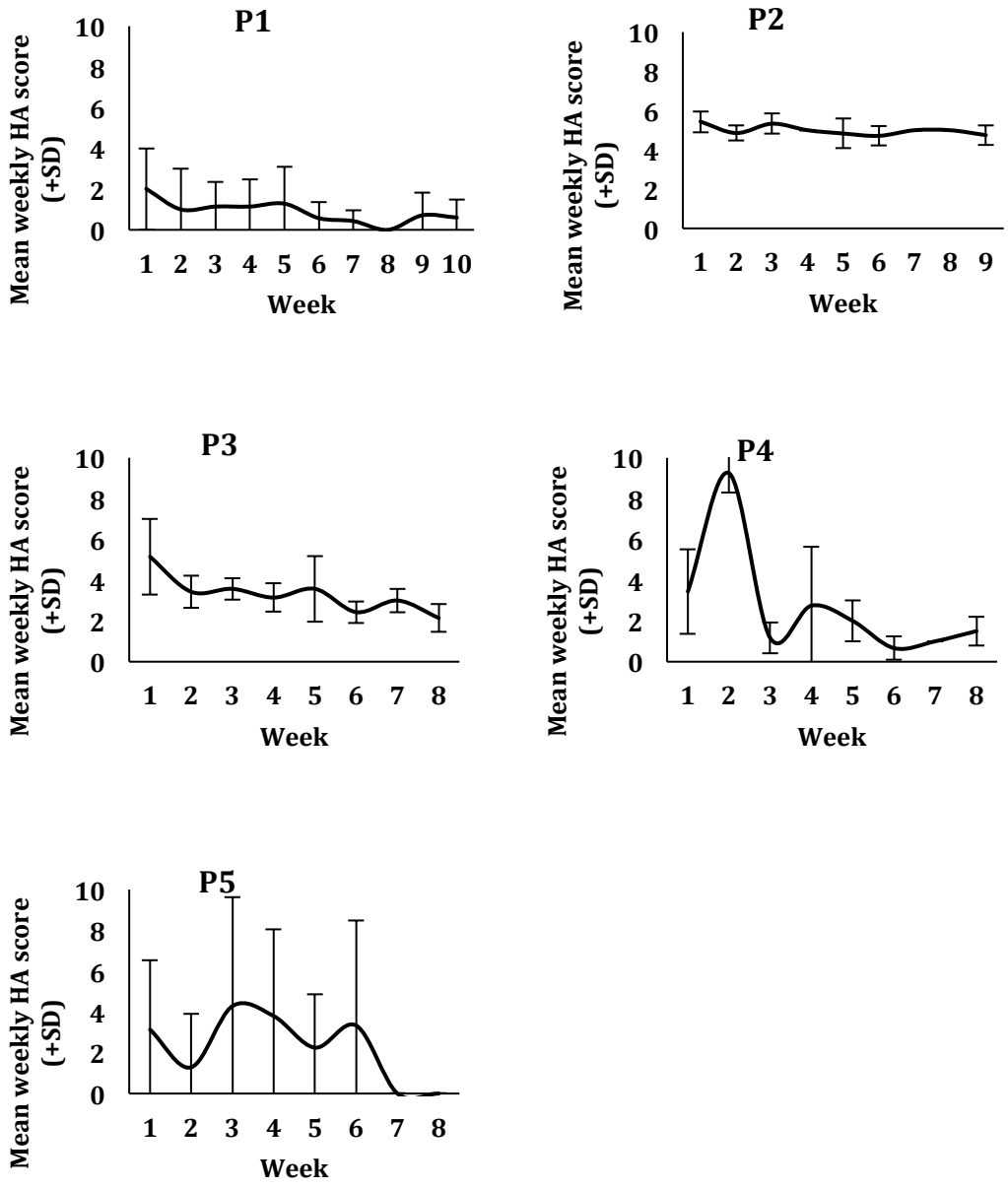


Figure 2.7 Mean weekly pain hindrance scores. Each graph shows weekly changes in hindrance of planned activity due to pain for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *To what extent did pain hinder your planned activities* were recorded using daily dairy and summarised as weekly averages.
HA=Hindered activity; P=participant; SD=standard deviation; 0 = not at all – 10 = completely hindered.

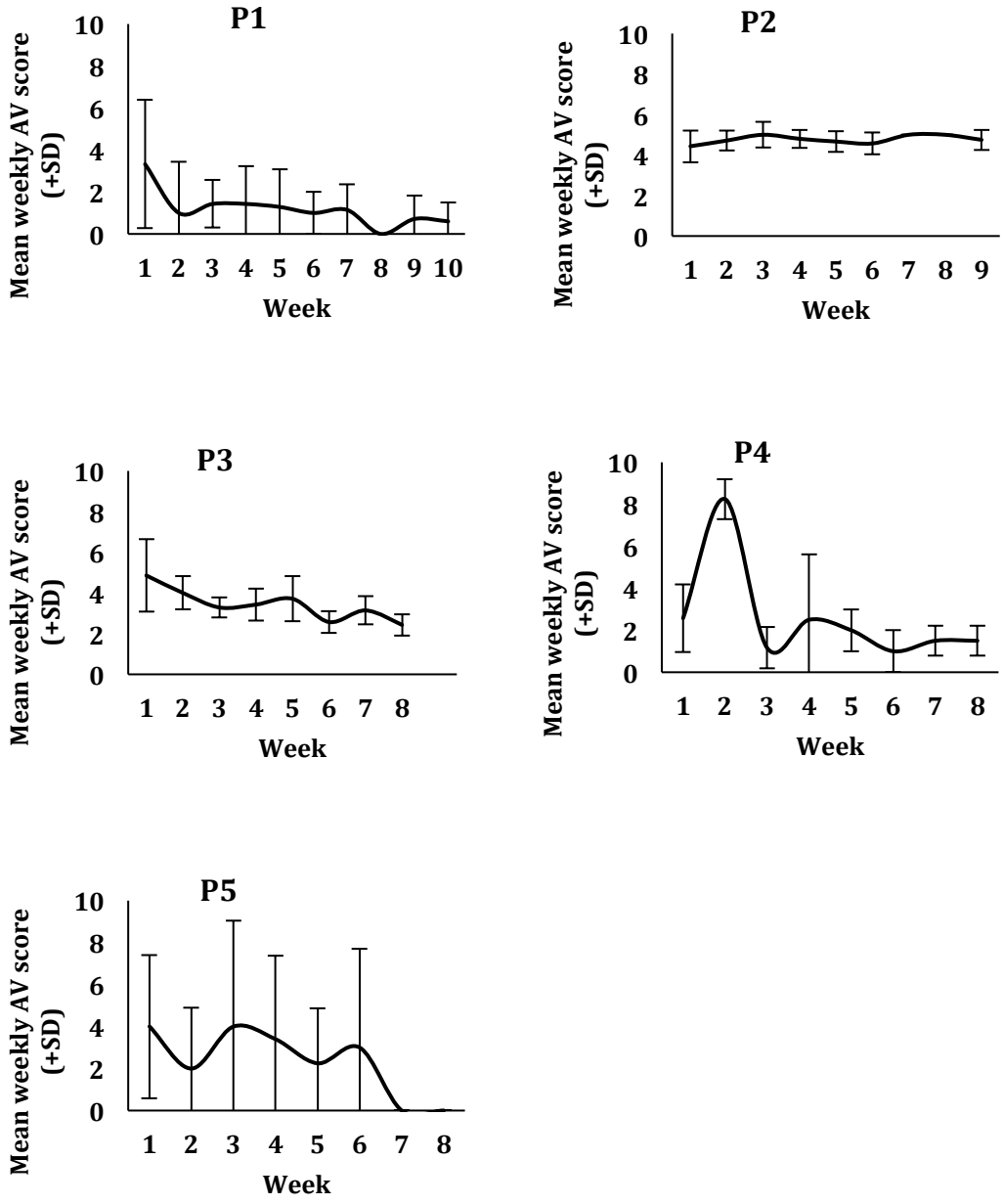


Figure 2.8 Mean weekly pain avoidance scores. Each graph shows weekly changes in avoidance of activity due to pain for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *To what extent did you avoid daily activities today because of pain* were recorded using daily dairy and summarised as weekly averages.
AV=Avoided activity; P=participant; SD=standard deviation; 0 = not at all – 10 = completely.

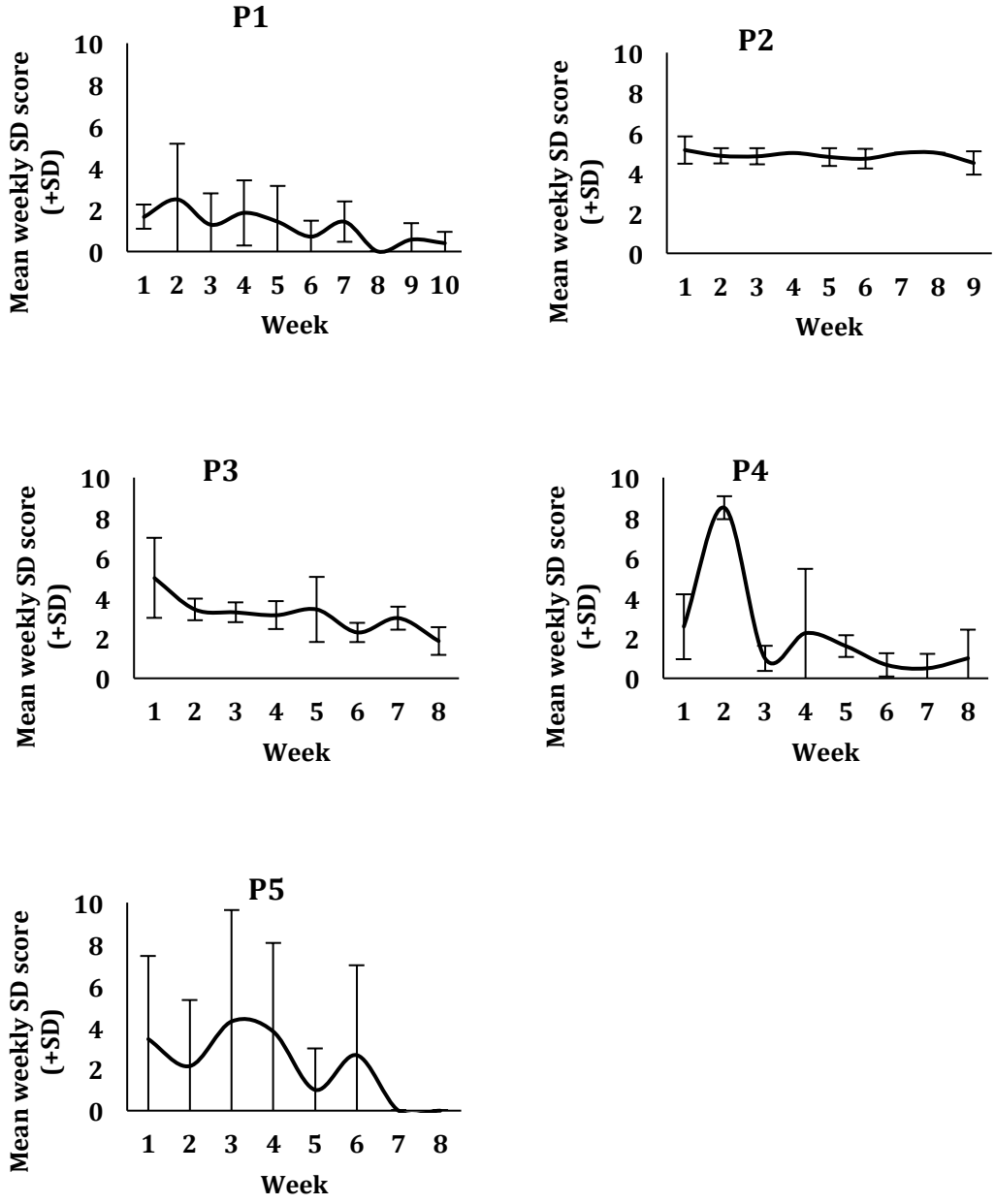


Figure 2.9 Mean weekly pain stopped me from doing things scores. Each graph shows weekly changes in effect of pain on stopping activity for an individual participant from baseline (week 1 and 2) to end of treatment. Daily responses to the statement *Today my pain has stopped me from doing things* were recorded using daily dairy and summarised as weekly averages.
SD=Stopped me from doing things; P=participant; SD=standard deviation; 0 = not at all – 10 = completely.

Self-report questionnaire data

All participants completed all questionnaires at baseline and end of treatment. A summary of baseline and end of treatment scores for each measure can be found in Figure 2.11 (BPI), Figure 2.10 (HADS), Figure 2.12 (PCS) and Figure 2.13 (PTQ). RC and CSC for each measure is summarised in Table *2.6* and plotted in Figures 2.13 to 2.17.

HADS: Overall psychological distress ranged from low (P5) to moderately high ((P2, P3). Scores between baseline and end of treatment reduced for 4 out of the 5 participants (P1-P4), but none of these changes observed were reliable or clinically significant. In contrast to other participants, P5 reported an increase in psychological distress scores at the end of treatment: see Figure 2.10 and Table *2.6* for detailed information on scores.

BPI: Overall, pain intensity and unpleasantness levels were moderate to high across the group of participants, with the exception of P1 who reported low pain intensity at baseline and end of treatment.

Pain intensity scores (BPI-I) reduced in two participants (P2, P3), showed no change in P1 and P4 and increased to more than double in P5. Analysis of CSC and RC demonstrated that only one participant (P3) showed a reliable decrease in pain from baseline, with no CS reductions in pain.

In terms of pain interference on daily life (BPI-I), 3 participants (P1, P2, P3) reported reduced interference. However, only one (P1) of these changes was CS and reliable. P4 showed no notable change whilst P5 reported increased interference from a mean of 1 at baseline to 8 at end of treatment. See Figure 2.11 and Table *2.6* for detailed information on scores.

PCS: Scores across the group varied from low (P1) to moderate (P4) levels of pain catastrophizing. Levels of catastrophizing reduced in all participants from baseline to end of treatment. These changes were CS and reliable for P2, P3 and P5. Although catastrophizing dropped in P4, scores were high and reduced very slightly. P1 reported low catastrophizing at baseline and a small drop from this at end of treatment. See Figure 2.12 and Table *2.6* for detailed information on scores.

PTQ: Overall, scores on ruminative thinking about pain varied from low (P1) to moderate (P4). Graphical analysis revealed that scores reduced from baseline to end of treatment for 3 participants (P1, P3, P5) of which one was CS and reliable (P3). P2 and P4 reported no notable change in scores from baseline. See Figure 2.13 and Table *2.6* for detailed information on scores.

When the profile of PCS and PTQ scores are viewed graphically, it appears that scores were very similar for each individual, suggesting a similar construct was being measured.

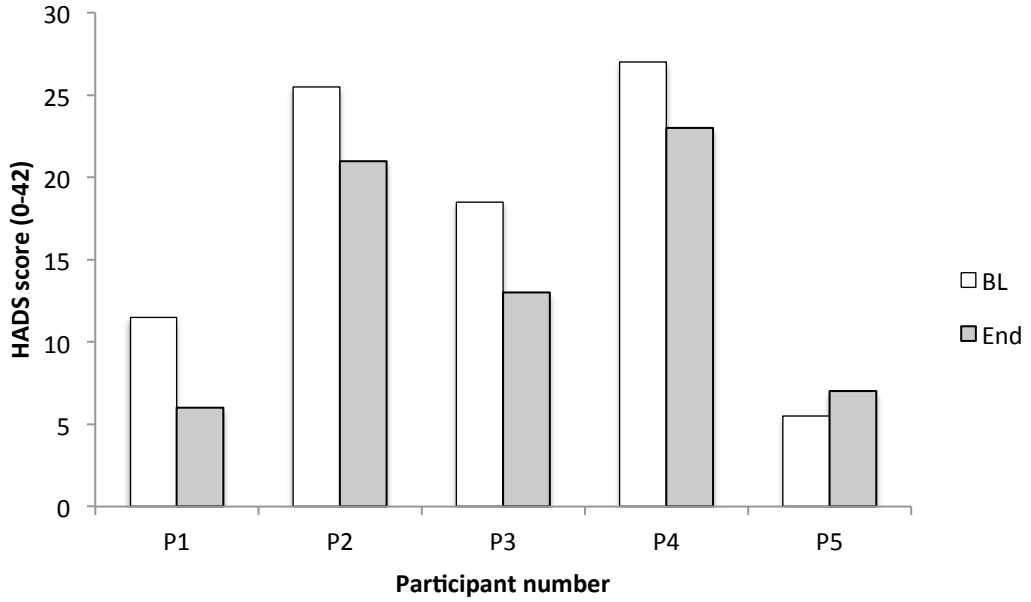
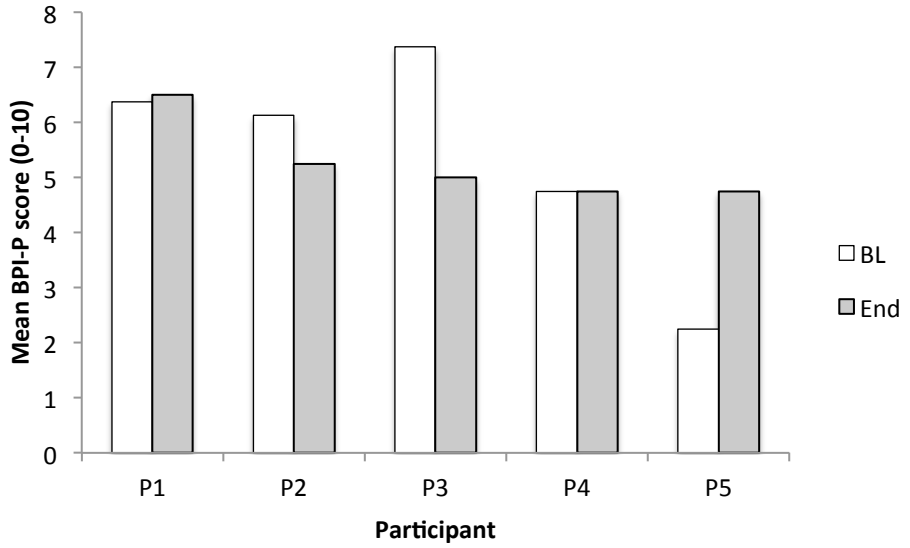


Figure 2.10 HADS scores before and after treatment. Higher scores represent higher levels of psychological distress.
HADS=Hospital anxiety and depression score; P=participant; BL=baseline; End=end of treatment

A)



B)

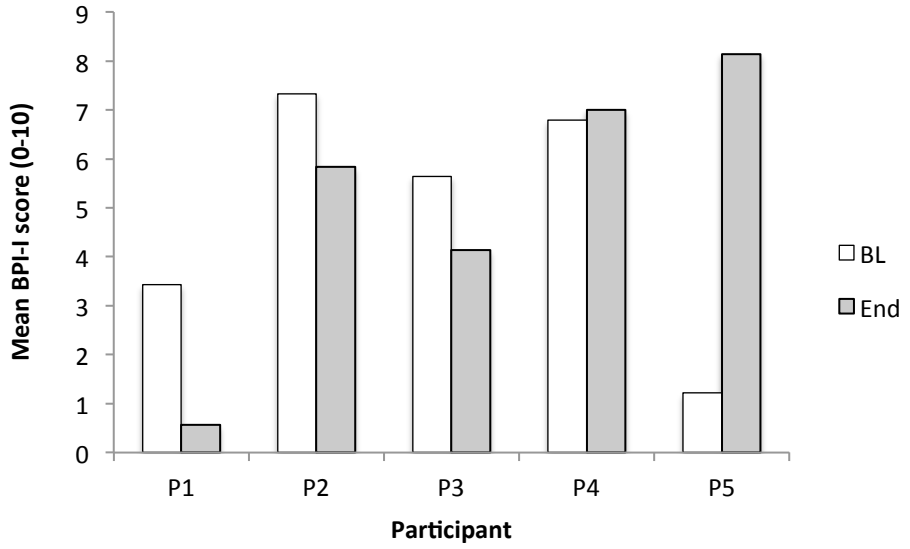


Figure 2.11 BPI pain and interference scores before and after treatment. Each graph shows pain level (a) and interference level (b) for each volunteer at baseline and after intervention. Higher scores represent higher levels of pain and interference respectively.
BPI=Brief pain inventory; P=participant; BL=baseline; End=end of treatment

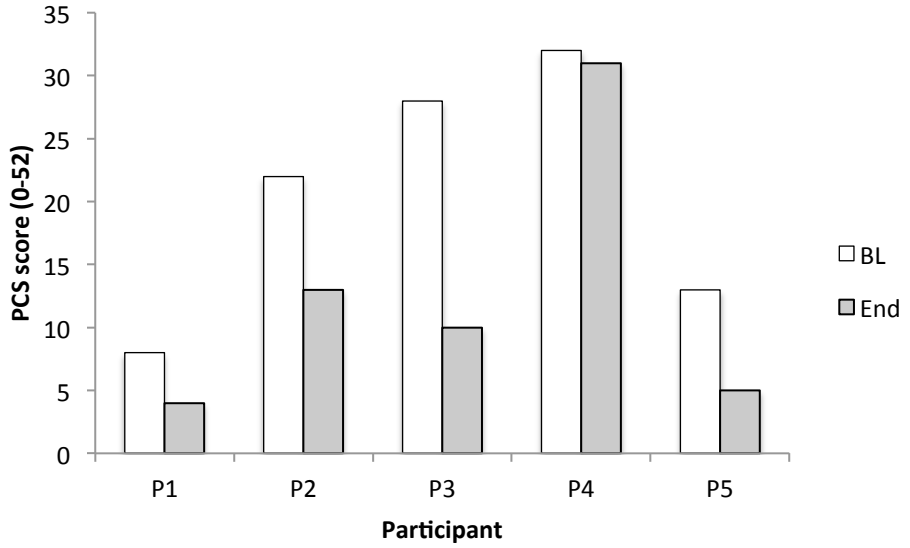


Figure 2.12 PCS scores before and after treatment. Higher scores represent higher levels of pain catastrophizing.
PCS=Pain catastrophizing scale; P=participant; BL=baseline; End=end of treatment.

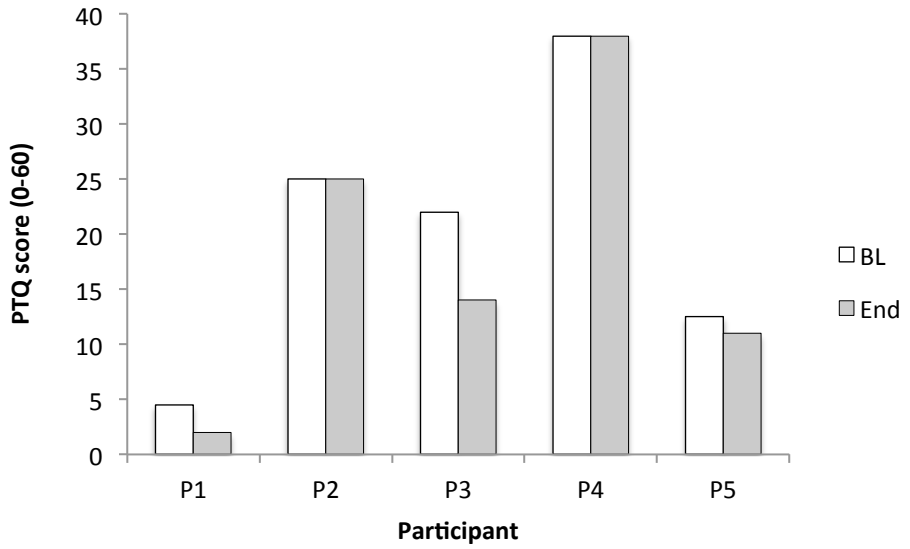


Figure 2.13 PTQ scores before and after treatment. Higher scores represent higher levels of ruminative thinking about pain.
PTQ=Perseverative thinking questionnaire; P=participant; BL=baseline; End=end of treatment.

Table 2.6 Summary of outcome scores for baseline and end of treatment with reliable change and clinically significant change indicated

Measure	**P1**	**P2**	**P3**	**P4**	**P5**
PI, DD					
Baseline	7	6	6	5	3
Endpoint	6	5	4	3	0
Change	-19%	-9%	-22%	-45% [CSC]	-100% [CSC]
PU, DD					
Baseline	7	6	6	6	4
Endpoint	4	6	4	3	0
Change	-41% [CSC]	-5%	-24%	-56% [CSC]	-100% [CSC]
HADS					
Baseline	12	26	19	27	6
Endpoint	6	21	13	23	7
Change	-6	-5	-6	-5	+1
BPI-I					
Baseline	3	7	6	7	1
Endpoint	1	6	4	7	8
Change	-2[RC, CSC]	-1	-2	0	+7
BPI-P					
Baseline	6	6	7	5	2
Endpoint	7	5	5	5	5
Change	+1	-1	-2 [RC]	0	+3
PCS					
Baseline	8	22	28	32	13
Endpoint	4	13	10	31	5
Change	-4	-9[RC, CSC]	-18[RC, CSC]	-1	-8[RC, CSC]
PTQ					
Baseline	5	25	22	38	13
Endpoint	2	25	14	38	11
Change	-3	0	-8 [RC, CSC]	0	-2

[RC]=reliable change; [CSC]=clinically significant change; PI=pain intensity, PU=pain unpleasantness, DD=daily diary; BPI=Brief Pain Inventory (P=Pain subscale, I=Interference subscale); HADS=Hospital anxiety and depression scale; PTQ=perseverative thinking questionnaire; PCS=Pain catastrophizing scale.

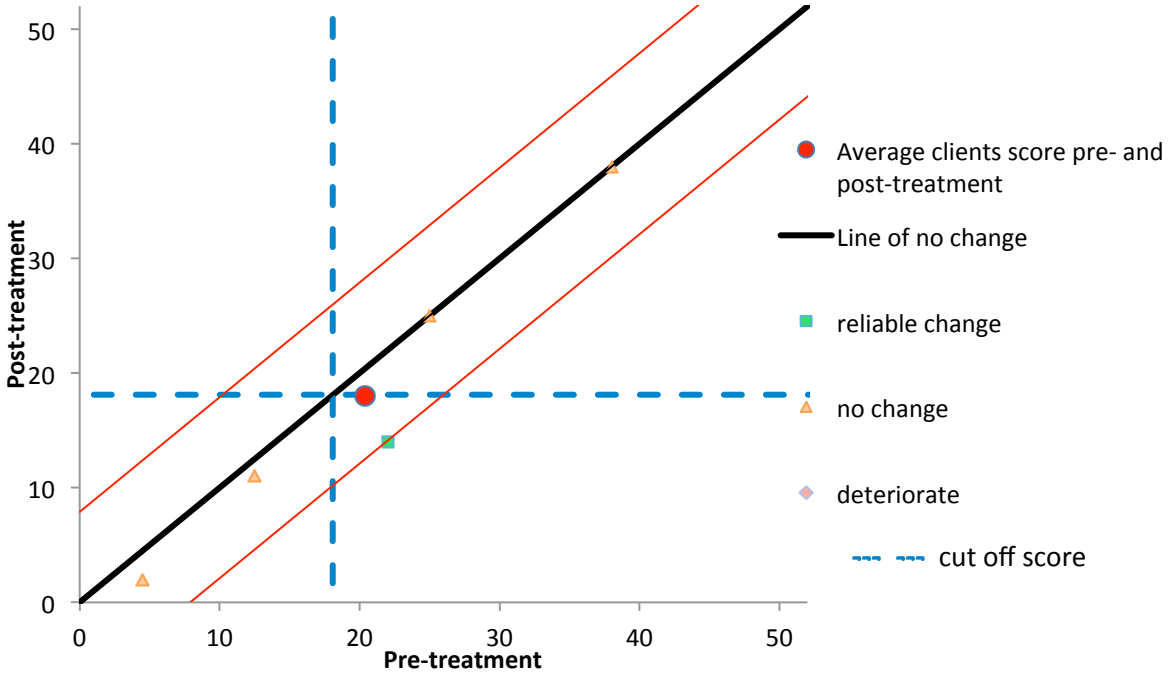


Figure 2.14 Plot of PTQ scores pre and post treatment with reliable change margins and clinical cut-offs illustrated

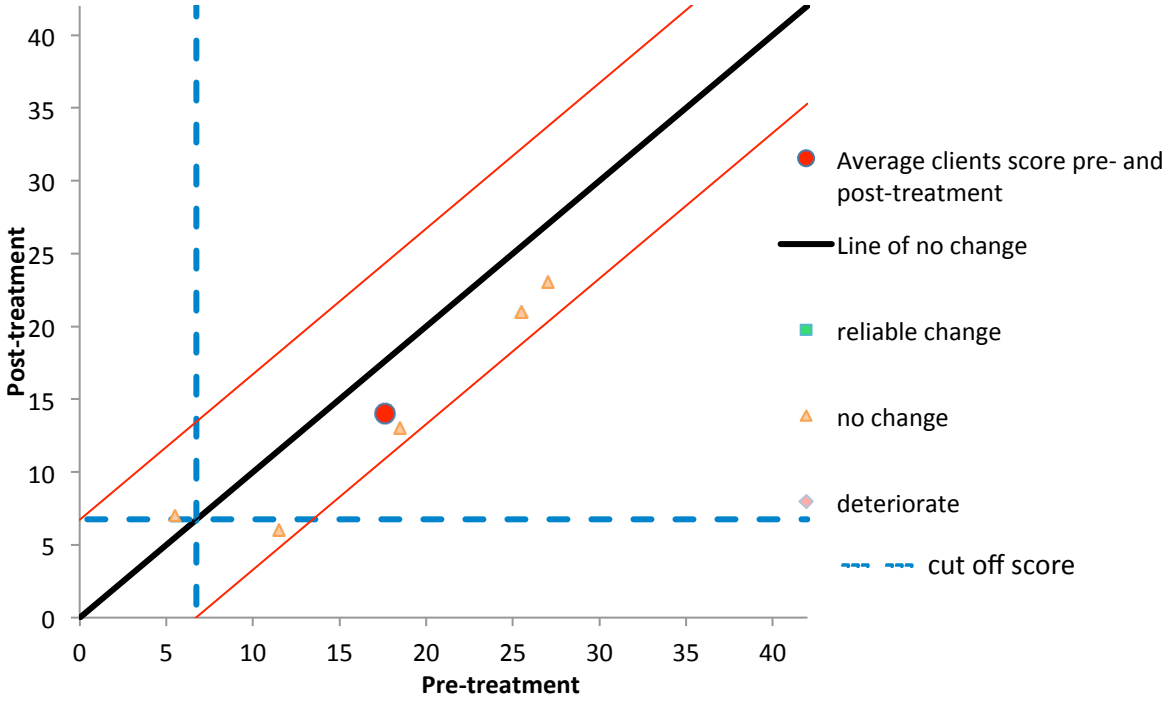


Figure 2.15 Plot of HADS scores pre and post treatment with reliable change margins and clinical cut-offs illustrated.

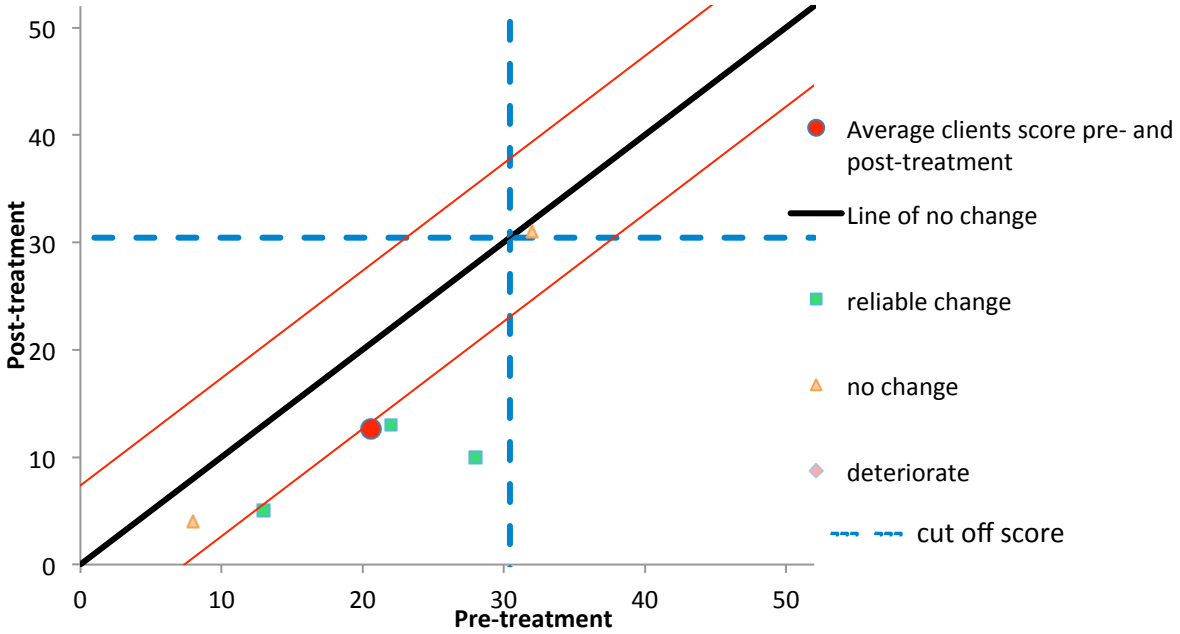


Figure 2.16 Plot of PCS scores pre and post treatment with reliable change margins and clinical cut-offs illustrated.

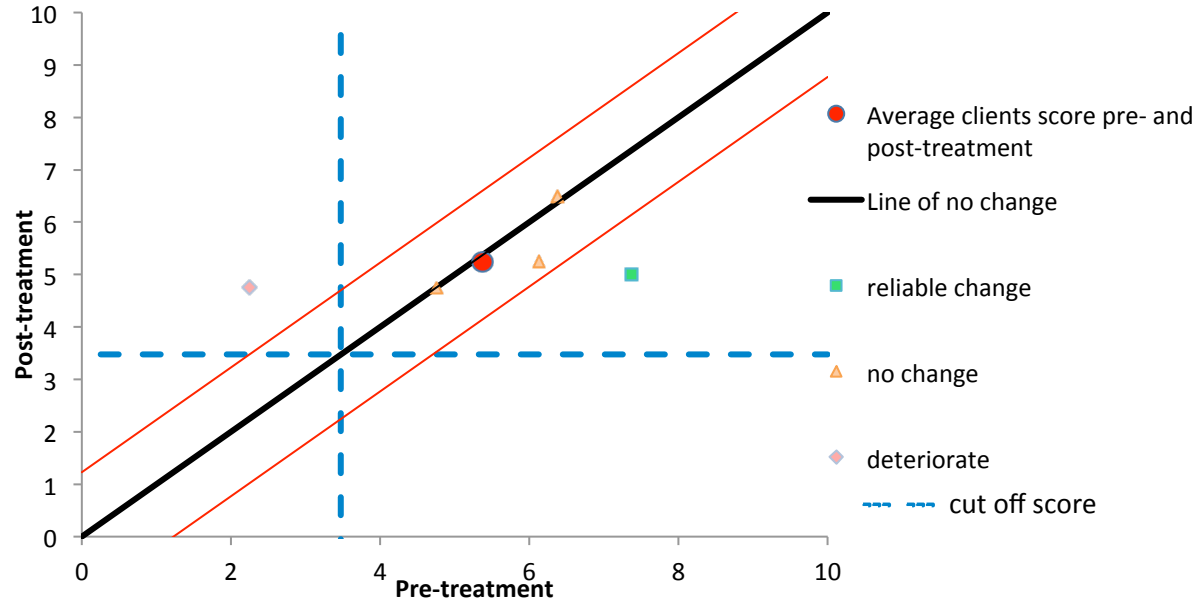


Figure 2.17 Plot of BPI-P scores pre and post treatment with reliable change margins and clinical cut-offs illustrated.

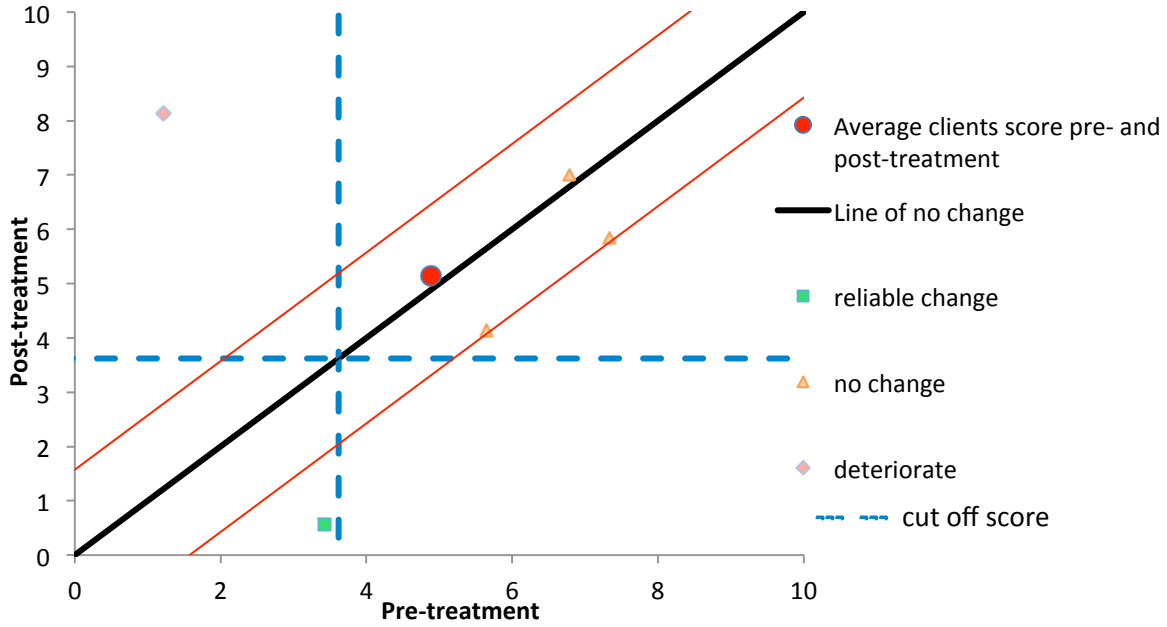


Figure 2.18 Plot of BPI-I scores pre and post treatment with reliable change margins and clinical cut-offs illustrated.

Stroop data

Stroop latencies for classic Stroop task and pain Stroop are summarised in Figure 2.19 and Figure 2.20.

Classic Stroop: All participants showed increased latencies to SI lists compared to SC at baseline. All participants showed similar responses at end of treatment.

Pain Stroop: Overall, latencies to PS and PC showed variability within and between subjects at baseline and end of treatment. P1 and P4 showed a slightly longer response time to PS relative to PC at baseline whilst P2 and P3 showed shorter response times and P5 showing little difference.

At the end of treatment P2 and P3 showed increased latencies during PS relative to PC whilst P4 showed a decrease and P1 showed no difference.

When PS latencies are compared at baseline and end of treatment, two participants (P1 & P4) show a decrease in latency whilst all other participants show an increase in response times.

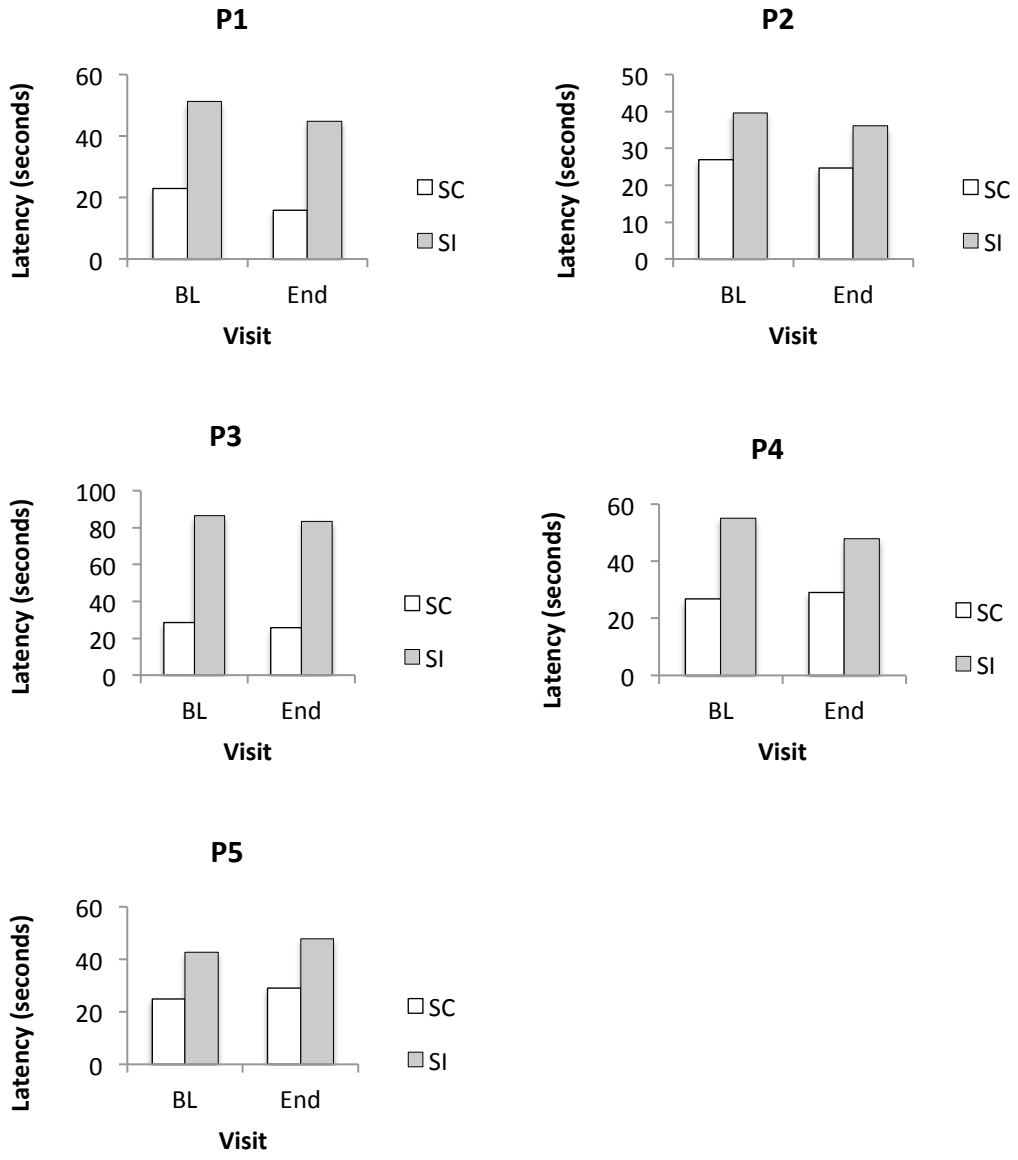


Figure 2.19 *L*atencies for Stroop congruent and Stroop incongruent trials at baseline and end of treatment.
SC=Stroop congruent; SI=Stroop incongruent

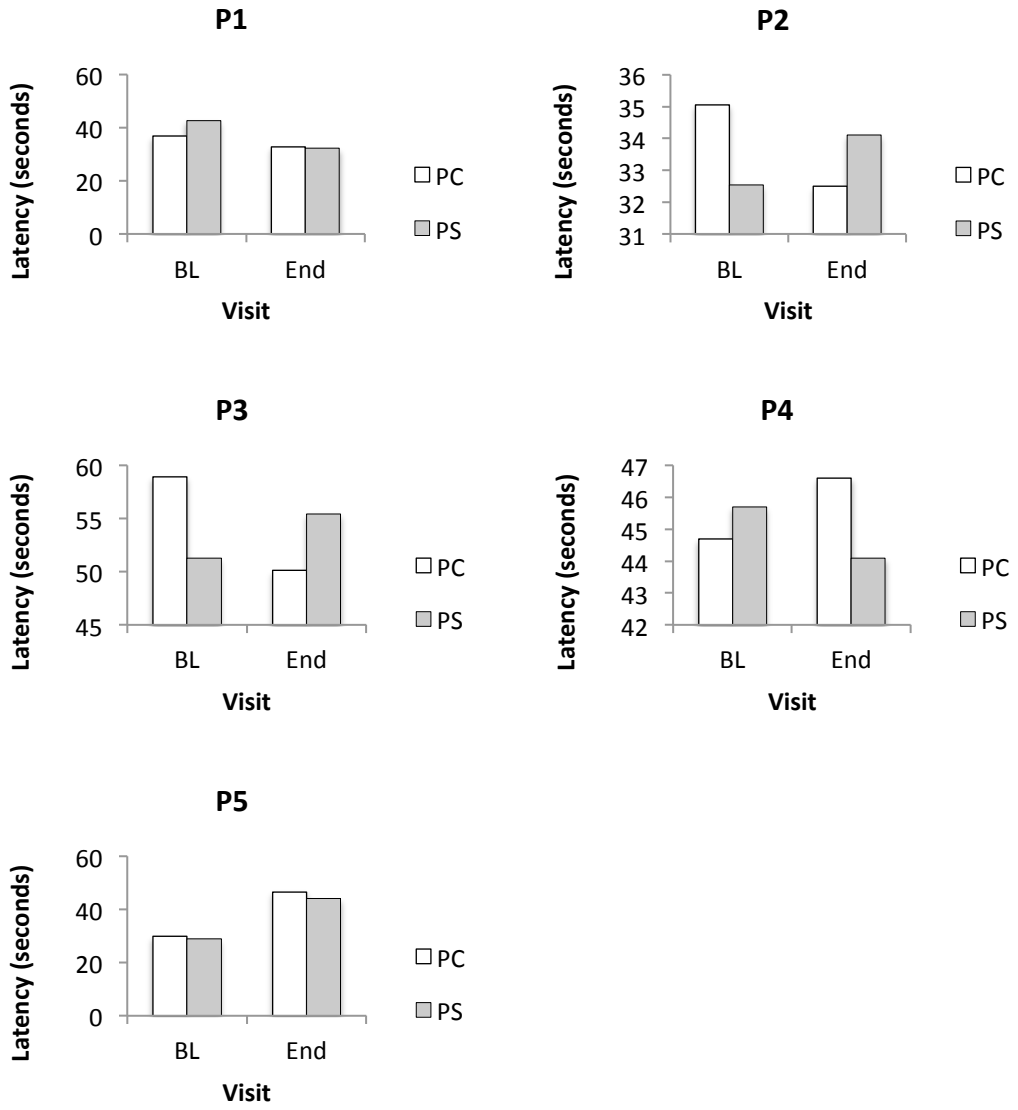


Figure 2.20 *L*atencies for Pain control and Pain Stroop trials at baseline and end of treatment. PC=Pain control; PS=Pain Stroop

Interview data

Thematic analysis of the interview data was aimed at addressing research questions on practical application of hypnosis outside sessions, effects of hypnosis on pain sensation, and effects of hypnosis on behavioral and psychological functioning. Several themes were identified through analyzing participant's responses, these are described below with examples to highlight data.

Theme 1: Effect of treatment on pain

There was a consensus between participants in describing how treatment had affected the physical nature of their pain symptoms. Several talked about expectations of change prior to treatment, with most suggesting they had little or no expectation on hypnosis changing their pain level:

P1: *I knew it wasn't one of these things that just stops pain or cuts it down drastically*

P2: …*although I knew that a mental approach or attitude does help and have some effect but you know I wasn't expecting my pain to disappear or anything like that.*

With the exception of P4 who described high expectations:

P4: …*I was going in the hope that it's going to uncover something and from uncovering that it's going to be a big breakthrough in terms of how the pain is affecting me and I was hoping that maybe I would fully recover*

When discussing change, most participants described little of no change in their pain sensation since the beginning of treatment:

P1: *No, no change in the pain but I am able to tolerate it a lot more than what I was…the only hard part I found is the pain dial, turning the dial down. I could only turn it down so far and then it feels like it is getting stuck*

P2: *I'd say no (impact of treatment on pain) because I think simply it is a physical thing that is happening (to me).*

P4: *the pain was bad and when the pain gets bad it's really bad and using the recordings doesn't do too much…I realise that it does relax me. But when the pain kicks in it is not helpful at all…its helped me in many ways that I probably won't even understand but it hasn't done anything for the pain directly for me*

P5: *No I don't have any change in my level of pain more in the way I look at it if that kind of makes sense*

Many individuals suggested that rather than changing pain sensation, the treatment had changed the way the think about their pain:

P1: *In a way yeah. It's not taken the pain down but it has helped me work with it and understand it a lot more.*

P3: *I just do it (the hypnosis) because I feel it keeps me away from the pain because I've got the strength not to think of my pain in front of me.*

P4: … *it has changed my mentality, it's made my mood much better so that in itself is a big thing.*

P5: *It doesn't change the time length of the pain it just changes the way that I think about it*

Theme 2: Varied application of self-hypnosis

Several participants noted how they use the hypnosis to manage pain either before activity or when the pain is very bad. Others described how they used hypnosis routinely, each night before bed. Several participants also stated that they were using the hypnosis to help with other problems such as worry, low mood and helping them to sleep, not just for their pain management directly.

P1: *No (not routinely) I use it as and when I need it. So in response to pain or if I'm sort of planning on walking into town today I'll get into that mind set, that zone and just start walking in that zone and it helps me go that little bit further so I'm sort of using it for prior, planning…If I'm struggling walking I'll try and get the pain dial down so that I can just go that bit further*

P5: *Erm, maybe once or twice a week. I don't use it every time when I am in pain but sometimes if it is really bad then I will use it to try and see if it will help.*

As stated, several participants described using self-hypnosis for a variety of applications:

P1: *Yeah I use it for everything yeah, not just for pain. Daily, anytime during the day. Basically if I can't sleep I'll use it while sleeping*

P1: *Well I use it as relaxation to get through stressful periods. I used it recently to help me with a recent bereavement. It helped me feel more upbeat and to get me through a tough time. It helped me a lot.*

P3: *It helps me to sleep. Let me explain, when you put the news on it can be good, bad, horrible you know it stressed you. But this, when you listen to it nothing…it releases your stress of the day because there is nothing sad or bad or happy or anything so it's totally pure it is and you just sleep nicely because you don't have to share or feel you know. Even when you listen to music sometimes it could be sad music so it affects your feeling, you're emotional but this makes you forget the whole world, be yourself relax and sleep.*

P4: *I'd get myself relaxed in bed and then I'd put the recording on a while before I go to sleep but just to sort of relax me and calm me down and everything and yeah it worked. Sometimes in the morning before I got up but not as often erm and sometimes on the bus.*

In relation to this, participants gave several examples of using a variety of self-hypnosis tapes depending on the problem facing them at any given time.

P5: *Erm one of them if I have like a really bad day then I use the one that focus more on the main sensation of pain if I am having a down day I will use the one that takes you to your calm place if it's a medium day but I feel like I need it then I use the one that focuses on background pain and things like that.*

P1: *I vary them just depending on…well I like a bit of variety so I'll…it's very much spontaneous what I will use. I mean I think if I'm going for a longer activity I'll use the last session because it was more about the pain dial, trying to get control the pain a little bit. So there are certain ones I'll use for certain activities but other than that it's just very varied.*

Theme 3: Relationship to pain

Perhaps the most common and broad theme was related to how participants relate to their pain. Indeed, several elements of this this theme overlap with other themes described. Several participants gave the impression that whilst the pain had not changed, their relationship with their pain had changed in several ways. Many participants described fighting less with their pain:

P1*: And just thought we can stop arguing and work together sometimes. I know it's always going to have a say and say no you can't do that but at least I can try to build that relationship up so that it is not such a hindrance and more of a working relationship sort of thing… I am able to tolerate it a lot more than what I was. I am able to just work with it rather than fight against it all the time…I am able to tolerate it a lot more than what I was. I am able to just work with it rather than fight against it all the time*

P3: *Accept it and don't fight it. I was fighting myself asking why this, and very angry you know and angry with doctors thinking why can't they sort out that problem for me but now I'm finding a way to control it and accept that it happens and there is nothing you can do*

P5: *Yeah (I was fighting with the pain), I think before treatment I would be thinking I really can't do anything why is it like this. Whereas now I am like okay it's going to be like that I'll just go and do something else.*

There were also several examples of participants showing greater acceptance of their pain:

P1: *Yeah, I see my pain as more of a hindrance now than a big, massive problem. It's just something I've got to learn to adapt to. That's how I see it now, adapt and get used to it and I have done…I think I've always know that I would need to accept the pain. It's going to be there for life, it's not going to go away*

P2: *Yeah I think so, it's sort of…I suppose there is an acceptance there in that it will flare up so why worry about it flaring up, you know yeah.*

P3: *Yes I gave up (fighting and searching for a cause), I gave up I just think ok they can't put their finger on it so just live with it…yeah, just accept that to get…to accept things, accept your circumstances that is the main thing really. So now I have come to terms with my condition but not with anger*

P5: *Sort of knowing that it might not go away but that there are still things that I can do to help it or while I am in pain there are still things that I can do. Yeah that and sort of working on myself deciding that there isn't anything I can do when I am in pain but when I am not in pain I can go and do all the things I normally do. So just look forward to the good parts rather than focusing on the bad.*

Theme 4: Relaxation

A further theme that was found suggested that in addition to relating to pain differently, participants found that they were more relaxed than prior to treatment. This was reflected in several areas. For example, a more relaxed style of thinking:

P1: *Well I use it as relaxation to get through stressful periods. I used it recently to help me with a recent bereavement. It helped me feel more upbeat and to get me through a tough time. It helped me a lot.*

P2: *I know it will automatically flare up because of any sort of slight anxiety or whatever, it will just make it worse but I think I have slightly more confidence now that it's not the end of the world if that happens … Its really difficult but I suppose it does give you a bit more strength to sort of tell yourself that you are not going to die or anything and it's going to be okay.*

P3: *Before yes I thought about it (the pain) all the time. Now I don't I try not to, I keep myself busy with something.*

P4: *Erm I've realized that if you relax more it's going to help pain regardless of how it's affecting you… I suppose the relaxation element is the main thing (that has helped). I guess it's kind of obvious that when you are stressed and thinking and all of that all the time any pain feels worse so your nerves flare up or something and you feel the pain a lot more intensely and when you are relaxed you feel it less…So I'd use it to just sort of relax me because often when I am relaxed I stop thinking so much about all the negatives and all that.*

Participants also described a physical feeling of relaxation and feeling less anger:

P3: *First of all it takes that anger out of you because it's true that I was so angry, it takes the anger out of your system. So it is very helpful, it gives you hand up you know…. I mean the tension in side of you it comes out when you talk about it*

Theme 5: Doing More

The majority of participants described being much more active since starting treatment. Several described that they were being active despite being in pain, which is something they were not doing prior to treatment:

P1: *But I'm just I'm more in that mind set of just keep going at it now. Definitely don't let anything get in the way. I'm not letting the pain dictate what I can and can't do. I'm working with the pain and dictating to it that look we can do this, it's not a big drama.*

P3: *It does, like today I really felt pain but I didn't stop I just kept going, I prepared food this morning, went to the GP, chemists and I am sitting here now uncomfortable but I am not letting it stop me*

P4: *I mean I'm not, it's not that I recover from an episode and I'm straight in there doing loads of things and I'm continuing with my life but I'm able to do more. I don't feel as if the pain is going to come back on.*

In addition, others described being more flexible in terms of choosing activity and valuing alternative activity

P5: *it doesn't mean that I can't do things. I can still enjoy things I used to or some of the things I used to even though I am in pain like reading a book or watching a video or something or talking to friends. It doesn't mean I can't do them it just means that physically I can't get out to do something like go to the park with friends but I can still talk to them*

With some people suggesting that the treatment had given them more confidence to do more than they were doing before:

P2: *The biggest thing for me is dealing with, well not dealing with but just interacting with people. I think maybe more so when I was doing it, it gave me a little more confidence I think when I was having hypnosis sessions every week*

2.7 **Discussion**

The aim of the study was to assess how people use self-hypnosis, and the effect of hypnosis on pain reporting psychosocial function. Within this, the aim was to use changes reported in psychosocial functioning, as assessed through quantitative and qualitative methods, to build hypotheses on potential mediators of hypnosis. The aim of the discussion is to synthesize and consider the findings in relation to these aims.

Summary of results

Overall, the results suggest that participants benefited from hypnosis treatment but that such benefits varied between individuals in terms of sensory, psychological and behavioural effects such as pain relief, acceptance of pain and engaging in more activity.

Summary of Quantitative outcomes: Self-report and daily diary measures suggest a variable experience of hypnosis amongst participants. Overall, there was a general (non-significant) effect on all the outcome measures (psychological and sensory) whereby scores reduced at the end of treatment compared to baseline. This was seen with the exception of P5 who reported greater scores in most domains at the end of treatment. This is likely a result of an episode of severe pain that P5 reported (incidentally) during the final end of treatment appointment. This is supported by scores on daily diary, which was completed before the end of treatment interview session and shows a general decrease in scores for this participant.

Summary of Qualitative outcomes: The results of the qualitative analysis suggest that individuals use hypnosis in a variety of ways, not limited to direct management of pain. Indeed, the qualitative results point towards a utility of hypnosis outside management of sensory symptoms of pain and more towards psychosocial e.g. acceptance and engaging more with valued activities and management of pain related symptoms such as worry,

physiological arousal and problems with sleep. These factors may be important in mediating clinical reduction in pain, as described by the quantitative data.

Effects of hypnosis on pain

Interestingly, there was a disparity between daily dairy and BPI-I scores which both assess sense The BPI-P data suggests no significantly reduced in pain levels in any participants whereas the daily diary data suggests 3 participants reported clinically significant change in pain (unpleasantness and intensity). This perhaps highlights the importance of collecting more than one post-intervention measure as this could be influenced by how the participant is feeling on the data of the measurement rather than a more general picture of functioning since treatment. In addition, it supports the notion that it is important to measure both intensity and unpleasantness (D. C. Turk et al., 2003). This disparity may also be a result of the different parameters used to assess CSC between the two measures. However, the fact that P5 reported completed reduction in pain on daily diary measures and more than double an increase on the BPI-P suggests otherwise.

Compared to quantitative data, it was clear at interview that all participants felt there was no change in pain sensation. One could suggest that this perhaps reflects the treatment approach which, whilst including some focus on reducing pain symptoms, predominately addressed issues beyond pain reduction. However, this finding is consistent with literature suggesting patients who notice change and are satisfied with treatment do not always report changes in pain levels and that hypnosis has significant benefits beyond pain relief (M. P. Jensen & Patterson, 2014; Dennis C. Turk, Okifuji, Sinclair, & Starz, 1998). More generally the aim of treatment targets beyond pain relief is reflected in guidelines for outcome measure in pain research and practice, which

emphasizes the need for measures of HRQoL (D. C. Turk & Dworkin, 2004; D. C. Turk et al., 2003).

Psychosocial function

Activity: Scores on the BPI-I showed no significant effect of pain on psychosocial function, except in one participant. The data gathered at interview however was more effective at elucidating change in daily functioning. All participants described being more active at the end of treatment and that they were able to act on goals and desires inspire of still experience pain. For some this meant changing the type of activity whilst for others it was more about pacing and using hypnosis to calm the pain or worries about engaging in activity.

Relationship to pain: Perhaps the most rich and common theme identified by analysis of the interview data was the way in which participants' described a change in the way they relate to their pain. Interestingly, the changes that several participants described in relation to this theme were analogous to goals of acceptance and commitment therapy (ACT), a third wave CBT approach to pain management. This approach moves away from targeting symptoms of pain and towards behavioural and psychological responses to the symptoms. ACT emphasis the need for psychological flexibility when living with a long term condition, encourages patients to acknowledge their pain but rather than focus on it and allow it to dominate it aims to encourage individuals to accept the pain is there but act in ways according to their values (Hayes, Strosahl, & Wilson, 1999; McCracken & Vowles, 2014). Such psychological flexibility is something that often appears to reduce when people are living with chronic pain. For example, they may ruminate on the significant targets they cannot achieve whilst de-valuing other activities they previously engaged in. Examples of how ACT aims to address such patterns of thinking and behaving may be by, being flexible in choice of

activity depending on how the pain is on a given day, and learning to find alternative ways to socialize (e.g. via the telephone). These are behaviours and ways of thinking about pain that individuals reported as changing during treatment the current study. Whilst such changes are made at a cognitive level, they have the added benefit of increasing activity and daily function, which is known to have a beneficial effect on pain. Including elements of ACT has been proposed as important in updating approach to traditional CBT methods when treating chronic pain (McCracken & Vowles, 2014) and has also be hypothesised to be a possible target when applying clinical hypnosis to chronic pain (M. P. Jensen & Patterson, 2014). The results of the current study suggest that this is a realistic and clinically effective approach.

Pain catastrophizing: Interestingly, there were reliable and clinically significant reductions in pain catastrophizing in two of the three participants who reported CSC in pain intensity, which may suggest thinking style could be a possible mediator in terms of change in pain responses and other variables such as change in activity. Alternatively, this change in catastrophizing could simply reflect a change in emotional meaning of pain. Finally, the reduction in catastrophizing may have been effected by the benefits of relaxation which was a theme identified at interview.

Disparity of qualitative and quantitative outcomes

It is interesting to note that many of the scores reported using self-report measure at beginning and end of treatment were in conflict with changes described by participants at interview. An example of this is that all participants reflected on the fact they are doing much more at the end of treatment in spite of their pain but only one person showed CS and reliable change on the measure used for assessing this (BPI-I). This is likely to reflect the fact that the BPI-I measures more than just functional interference (also emotional too) but perhaps also highlights the limitation of using

quantitative outcomes that can be relatively blunt tools, depending on how well a measure fits with a research outcome. In contrast, pain scores on daily diary and BPI-P suggested that in total 3 individuals reduced in pain unpleasantness and pain intensity over the course of treatment which conflicts with the fact that at interview all participants suggested the intervention did not change their pain level. Such discrepancies could be due to gathering retrospective data at interview compared with the 'real-time' daily measurements of pain.

Factors mediating change

Despite areas of discrepancy in the data, when the quantitative and qualitative data are combined then it appears that there was a reduction in pain and an increase in daily activity, overall. There was also a reduction in several psychological outcomes such as worry, anxiety and relationship to pain. It is challenging to determine what effect comes first i.e. does the pain reduction allow for a more active, enjoyable life or does engaging in activity lead to psychological benefits and learning that encourages more movement which has a beneficial effect on pain levels and/or pain reporting.

For many patients, the reality when they reach the point of psychological intervention is that several attempts (physical therapy, surgical and or/pharmacological) have been made to influence the physical element of pain, with limited success. It is understandable therefore that treatments that are more psychologically based, such as hypnosis described in the present study, do not focus explicitly on pain reduction as a primary target and instead emphasize the factors that may be exacerbating pain or indeed the beliefs around pain and activity, for instance. Through these approaches, a side effect may be pain reduction but it is the way an individual adapts and lives within a context of chronic pain that is often a primary goal of the patient and the clinician.

One theory is that the physiological component of pain remains constant but the reporting of those symptoms and impact of the problem on the person is reduced as patients find ways of coping and getting on with life. In the present study one of the factors mediating this could be acceptance.

Biopsychosocial formulation: One query that commonly arises in relation to hypnosis is in relation to how it works. It is of course likely that the mediating effects of hypnosis on pain outcomes is multi-factorial as discussed above. Given this, it may be helpful when considering the factors mediating change in the present study by considering a biopsychosocial formulation, summarized in Figure 2.21. Using the data from the current study there are several interacting features that may explain the changes described. The effect of relaxation is both biological and psychological in that it is known to reduce *physiological* arousal and has an analogous effect on *psychological* arousal. These effects of relaxation in the present study are therefore likely to reduce level of rumination, catastrophizing, worry which are factors known to facilitate pain. In addition, reduced physiological arousal is also known to reduce pain facilitation via engagement of parasympathetic ANS activity and reduction of sympathetic activity (Farmer et al., 2014). Furthermore, physiological arousal has also been linked with a pain facilitating effect via inflammatory pathways and upregulation of genes involved in pain transmission, for example (Peace et al., 2012). Relaxation is likely to reduce such effects. In addition to relaxation, psychological changes such as increased acceptance is likely to result in participants being more able to disengage from pain, thereby lowering hypervigilance and rumination which are both known to facilitate pain. Finally, increased activity is known to increase positive affect and in the case of the present study is useful in testing beliefs about the effect of activity increasing pain (which is often described by people suffering with chronic pain), improving muscle function and tone and enable more opportunities for distraction from pain, all of which are known to

inhibit pain. Given all the above, it is likely that the effect of hypnosis is mediated through various interacting biopsychosocial mechanisms (Mark P. Jensen et al., 2015; M. P. Jensen & Patterson, 2014).

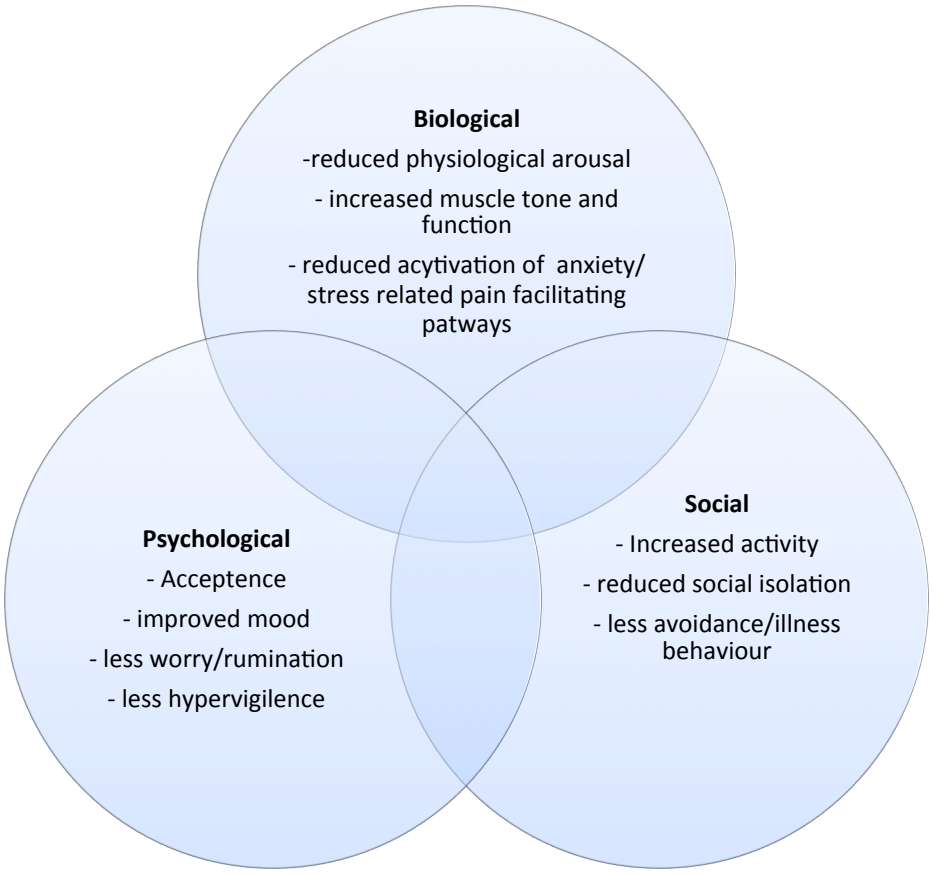


Figure 2.21: Shows the hypothesized mediating effects of hypnosis by using a biopsychosocial formulation of pain

Stroop

The Stroop task was employed as an objective measure to assess whether one of the mechanisms of hypnosis might be in reducing attentional bias towards pain and increasing ability to disengage from pain. The fact participants responded with increased latencies to the SI task compared to SC at baseline and end of treatment indicates that volunteers understood the task and that methodology (i.e. contextual extraneous variable such as setting, word size, colour) was suitable for eliciting a Stroop effect. The results of the pain Stroop were extremely variable which makes interpretation

challenging. Nonetheless, there was no evidence to suggest that participants in the present study 'Strooped' thereby indicating there was no change in attentional bias in the sample studied.

This finding is possibly due to the fact that the majority of participants did not appear to excessively focus on pain, as is evidenced by daily scores of DP and FP. In fact, the only participant (P4) who showed high FP/DP scores at baseline which reduced at the end of treatment was the only individual to show a change in attentional bias i.e. removal of pain Stroop effect after treatment.

However, it is more likely the results described in the present study are due to the reliability of the Stroop. Whilst effects have been shown, there is substantial variability in observing the pain Stroop effect with small effect sizes (G. Crombez, I. Viane, et al., 2013). Indeed, several authors have suggested that attentional bias to pain related information in chronic pain in general may not be as robust as often assumed (Schoth, Nunes, & Liossi, 2012; Van Ryckeghem & Crombez, 2014). Given the small effect sizes seen when measuring attentional bias, it is likely that the small sample size and fact that data was analysed on an individual level rather than group level is also a critical factor in ability to detect attention bias in the present study.

Furthermore, it has been suggested that the pain Stroop effect is best accounted for by mood state of chronic pain patients rather than pain per se (Pincus, Fraser, & Pearce, 1998). This may well account for the fact that the only participant (P4) who showed Stroop effect also reported the highest levels of psychological distress whilst the majority of the rest of the sample reported low to moderate levels of distress.

The use of the Stroop may have been improved by using individualised pain descriptions in the word list as that has been shown to increase the effect (G. Crombez, D. M. L. Van Ryckeghem, C. Eccleston, & S. Van Damme, 2013).

Clinical implications

Evaluating outcomes at a patient and service level: The findings from the present study demonstrates the importance of gathering quantitative and qualitative outcomes in evaluating change and feeding back change to patients but also in service evaluation. As studying questionnaire outcomes in present study would suggest small clinical gains, however, patient descriptions suggested significant changes to their quality of life. If such outcomes are overlooked, the benefits may be of treatment difficult to justify and service funding may be affected or a patient may not receive the most effective treatment.

For similar reasons, the value in gathering data on a more frequent basis is clearly important, particularly given the variability seen in daily pain scores in the present study. This could be possible via a measure of daily pain using an electronic online diary as an outcome. Such data may capture clinically significant changes that are not gathered at start and end of treatment alone.

Use of hypnosis in chronic pain management: The hypnosis treatment approach applied in the present study is very similar to pain management programs or one to one psychological treatment for chronic pain but implemented over fewer sessions. It is possible that the effect of changing rigid cognitive styles (such as catastrophizing/acceptance) in relatively few sessions may be achieved in the unconscious delivery of information which is unique to hypnosis. Indeed, although not reported in the results, it was clear during interviews that participants were not consciously aware of the suggestions employed by the therapist and mentioned only the relaxation element of the tapes used for self-hypnosis. This suggests that therapeutic objectives for change were delivered without the normal 'cognitive filter' applied. The obvious clinical value of this is reduced number of treatment sessions, which is

beneficial to services and service users alike. There may also be a clinical benefit in the unconscious delivery of suggestions for behavioral and cognitive change, particularly for those patients who are extremely resistant to change or to the application of clinical psychology in pain management.

Limitations

The aim of the study was to recruit a sample of 12 patients. However, as a result of a various number of factors including R&D approval, clinician availability for hypnosis and difficulty recruiting suitable patients the final sample was considerably affected. Whilst this is a significant limitation for studies relying on group analysis, the nature of a case series is that it is not dependent on large sample sizes and what is lost in numbers is balanced by richness and depth of the data. Nonetheless, with a larger sample it may have been possible to (cautiously) employ group level inferential statistics to explore if some of the observed changes may have reached statistical significance at a group level. It should be noted however that even with 12 participants the conclusions and generalizability of such analysis would be limited.

In relation to the above point, due to changes in availability of clinician resource to deliver hypnosis treatment it was necessary to use to clinicians to administer treatment. Whilst this may have introduced some variability into the study, it was necessary in order to complete the study on schedule. The potential effects were limited by clinicians agreeing a protocol for intervention and also by each participant receiving treatment by only one clinician. Furthermore, it is likely that there is within clinician variability in treatment due to the formulation driven nature of the intervention. This may reduce the expected added variability of a second clinician, as described above.

In order to address several of the research questions, I used an interview schedule that was developed and approved by myself, supervisor and hypnosis

therapists. The interview questions were designed to specifically address the research aims and hypotheses. As such, the breadth of questions was relatively narrow and focused on probing specific hypotheses. Whilst this was helpful in gaining specific responses to our research questions, there is an increased risk of introducing bias in responses and questions could be considered leading. An alternative approach would have been to use a broader interview schedule such at the Client Change Interview Schedule (Elliott, 1999). This would help reduce bias and perhaps allow a more 'natural' narrative of change, thereby providing information outside the hypothesised mechanisms. As with all approaches to gathering such data, there is no gold standard or 'correct' method. However, there are clearly techniques and approaches that can be employed to reduce potential bias. It is worth noting that whilst conducting interviews I monitored my questions and was mindful of introducing bias. In doing so, I found myself using broader questions similar to those found in the more standardised, broader Client Change Interview. Future studies may benefit from using a broader tool such as the Client Change Interview with more specific, hypothesis driven queries appended.

Some mention of the design of the case series employed in the current study is worthy of discussion. The present study employed an AB design with multiple baseline measures (daily diary and self-report questionnaires) and one post-intervention outcome. Such designs have been criticised for lacking the potential to experimentally reverse treatment and observe effects on dependent variables, which can serve to strengthen the association between treatment and effect, thereby increasing internal validity (Morley, 2015).

This AB approach was chosen for several pragmatic reasons such as time available to complete the study in the context of a clinical doctoral training programme and patient/therapist availability. In order to utilize more eloquent approaches (such as

multiple baseline, randomised treatment onset, on-off interventions, and repeated measures or replication) it would have required more therapist/patient availability and flexibility, which was identified as a threat to the completion of the study during planning and choosing the study design. In addition, some of the alternative case series design options are perhaps not suitable for investigating hypnosis treatment which is something that requires several sessions and practice over time, compared with other approaches such as pharmaceutical treatments which may be more amenable to 'switching' on and off. Furthermore, other approaches such as varying treatment dose may not be suitable options for similar reasons associated with the nature of hypnosis treatment.

Despite being limited in choice of design for pragmatic reasons, the design employed was optimised from the simplest AB designs by including multiple baseline measures and daily measures during the intervention which allowed for exploration of how outcomes were changing throughout intervention rather than capturing discrete before/after treatment data. Finally, despite the limitations of AB designs, they do perhaps contain an ecologically valid assessment of treatment in the real world, which is often follows the same format of an AB design (i.e. a single treatment intervention programme).

Summary and conclusions

Despite limitations, the results of the present study suggest that hypnosis is a valuable treatment approach to managing chronic pain and can influence the experience of pain on a number of domains including sensory, psychological and behavioural such as pain relief, acceptance of pain and engaging in more activity. The varied nature of hypnosis effects was reflected in the variety of ways in which hypnosis is applied and practiced. The findings also propose a number of potential factors involved in

mediating the effects of hypnosis on pain relief including psychological (acceptance) and psychophysiological (relaxation, worry). Larger sample sizes and more complex analysis (such as regression) are required to assess these hypotheses further.

The findings also highlight the importance of how outcomes are measured and how data is gathered influence the quality of the data obtained. Here we described differences in approach to asking questions (self-report questionnaire, NRS and interview) and varying temporal aspects (real time, high resolution (DD); retrospective (interview)) and low resolution retrospective (self-report measures at BL/End of treatment). Using a variety of approaches enriched the data but was also important in enabling identification of change that would otherwise have been missed. This highlights the need for a variety of outcome measures when assessing change in research and clinical practice.

2.8 **References**

Arendt-Nielsen, L., & Graven-Nielsen, T. (2003). Central sensitization in fibromyalgia and other musculoskeletal disorders. *Curr Pain Headache Rep, 7*(5), 355-361.

Ballantyne , J. C., & Mao , J. (2003). Opioid Therapy for Chronic Pain. *New England Journal of Medicine, 349*(20), 1943-1953. doi:doi:10.1056/NEJMra025411

Ballantyne, J. C., & Sullivan, M. D. (2015). Intensity of Chronic Pain — The Wrong Metric? *New England Journal of Medicine, 373*(22), 2098-2099. doi:doi:10.1056/NEJMp1507136

Bantick, S. J., Wise, R. G., Ploghaus, A., Clare, S., Smith, S. M., & Tracey, I. (2002). Imaging how attention modulates pain in humans using functional MRI. *Brain, 125*(Pt 2), 310-319.

Baron, R., Binder, A., & Wasner, G. (2010). Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol, 9*(8), 807-819. doi:10.1016/S1474-4422(10)70143-5

Bergbom, S., Boersma, K., Overmeer, T., & Linton, S. J. (2011). Relationship among pain catastrophizing, depressed mood, and outcomes across physical therapy treatments. *Phys Ther, 91*(5), 754-764. doi:10.2522/ptj.20100136

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. The validity of the Hospital Anxiety and Depression Scale. *Journal of Psychosomatic Research, 52*(2), 69-77. doi:10.1016/S0022-3999(01)00296-3

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3*(2), 77-101. doi:10.1191/1478088706qp063oa

Braun, V., & Clarke, V. (2012). *Thematic analysis*

APA handbook of research methods in psychology, Vol 2: Research designs: Quantitative, qualitative, neuropsychological, and biological.

Černis, E., Dunn, G., Startup, H., Kingdon, D., Wingham, G., Evans, N., . . . Freeman, D. (2016). The Perseverative Thinking Questionnaire in Patients with Persecutory Delusions. *Behavioural and Cognitive Psychotherapy, 44*(04), 472-481. doi:doi:10.1017/S1352465815000533

Chatzidimitriou, A., Georgoudis, G., Manousou, A., Argira, E., Vadalouka, A., Anastasopoulou, D., . . . Siafaka, I. (2006). Topic G: Diagnosis, Assessment and Reviews. *European Journal of Pain, 10*(Supplement 1), S237-S238. doi:10.1016/S1090-3801(06)60921-X

Cheong, Y. C., Smotra, G., & Williams, A. C. (2014). Non-surgical interventions for the management of chronic pelvic pain. *Cochrane Database Syst Rev, 3*, CD008797. doi:10.1002/14651858.CD008797.pub2

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore, 23*(2), 129-138.

Coen, S. J., Aziz, Q., Yaguez, L., Brammer, M., Williams, S. C., & Gregory, L. J. (2008). Effects of attention on visceral stimulus intensity encoding in the male human brain. *Gastroenterology, 135*(6), 2065-2074, 2074.

Cosco, T. D., Doyle, F., Ward, M., & McGee, H. (2012). Latent structure of the Hospital Anxiety And Depression Scale: a 10-year systematic review. *J Psychosom Res, 72*(3), 180-184. doi:10.1016/j.jpsychores.2011.06.008

Crasilneck, H. B. (1979). Hypnosis in the control of chronic low back pain. *Am J Clin Hypn, 22*(2), 71-78.

Crawford, H. J. (1998). Hypnotic analgesia: 1. Somatosensory event-related potential changes to noxious stimuli and 2. Transfer learning to reduce chronic low back pain. *Int. J. Clin. Exp. Hypn., 46*, 93-132.

Crombez, G., Hermans, D., & Adriaensen, H. (2000). The emotional stroop task and chronic pain: what is threatening for chronic pain sufferers? *Eur J Pain, 4*(1), 37-44. doi:10.1053/eujp.1999.0149

Crombez, G., Van Ryckeghem, D. M., Eccleston, C., & Van Damme, S. (2013). Attentional bias to pain-related information: a meta-analysis. *Pain, 154*(4), 497-510. doi:10.1016/j.pain.2012.11.013

Crombez, G., Van Ryckeghem, D. M. L., Eccleston, C., & Van Damme, S. (2013). Attentional bias to pain-related information: A meta-analysis. *Pain, 154*(4), 497-510. doi:http://dx.doi.org/10.1016/j.pain.2012.11.013

Crombez, G., Viane, I., Eccleston, C., Devulder, J., & Goubert, L. (2013). Attention to pain and fear of pain in patients with chronic pain. *J Behav Med, 36*(4), 371-378. doi:10.1007/s10865-012-9433-1

Derogatis, L. R., & Unger, R. (2010). Symptom Checklist-90-Revised *The Corsini Encyclopedia of Psychology*: John Wiley & Sons, Inc.

Dillworth, T., Mendoza, M. E., & Jensen, M. P. (2012). Neurophysiology of pain and hypnosis for chronic pain. *Transl Behav Med, 2*(1), 65-72. doi:10.1007/s13142-011-0084-5

Dunckley, P., Aziz, Q., Wise, R. G., Brooks, J., Tracey, I., & Chang, L. (2007). Attentional modulation of visceral and somatic pain. *Neurogastroenterol Motil, 19*(7), 569-577. doi:10.1111/j.1365-2982.2007.00908.x

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., . . . Immpact. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain, 113*(1-2), 9-19. doi:10.1016/j.pain.2004.09.012

Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull, 125*(3), 356-366.

Ehring, T., Zetsche, U., Weidacker, K., Wahl, K., Schönfeld, S., & Ehlers, A. (2011). The Perseverative Thinking Questionnaire (PTQ): Validation of a content-independent measure of repetitive negative thinking. *Journal of Behavior Therapy and Experimental Psychiatry, 42*(2), 225-232. doi:http://dx.doi.org/10.1016/j.jbtep.2010.12.003

Elliott, R. (1999). Client change interview protocol. *Network for Research on Experiential Psychotherapies website:* http://experiential-researchers. *org/instruments/elliott/changei. html.*

Engeler, D. S., Baranowski, A. P., Dinis-Oliveira, P., Elneil, S., Hughes, J., Messelink, E. J., . . . European Association of, U. (2013). The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur Urol, 64*(3), 431-439. doi:10.1016/j.eururo.2013.04.035

Fall, M., Baranowski, A. P., Elneil, S., Engeler, D., Hughes, J., Messelink, E. J., . . . European Association of, U. (2010). EAU guidelines on chronic pelvic pain. *Eur Urol, 57*(1), 35-48. doi:10.1016/j.eururo.2009.08.020

Farmer, A. D., Coen, S. J., Kano, M., Naqvi, H., Paine, P. A., Scott, S. M., . . . Aziz, Q. (2014). Psychophysiological responses to visceral and somatic pain in functional chest pain identify clinically relevant pain clusters. *Neurogastroenterol Motil, 26*(1), 139-148. doi:10.1111/nmo.12245

Faymonville, M. E., Boly, M., & Laureys, S. (2006). Functional neuroanatomy of the hypnotic state. *Journal of Physiology Paris, 99*(4-6), 463-469.

Flik, C. E., van Rood, Y. R., Laan, W., Smout, A. J., Weusten, B. L., Whorwell, P. J., & de Wit, N. J. (2011). A randomised controlled trial on hypnotherapy for irritable

bowel syndrome: design and methodological challenges (the IMAGINE study). *BMC Gastroenterol, 11*, 137. doi:10.1186/1471-230X-11-137
Flink, I. L., Boersma, K., & Linton, S. J. (2013). Pain catastrophizing as repetitive negative thinking: a development of the conceptualization. *Cogn Behav Ther, 42*(3), 215-223. doi:10.1080/16506073.2013.769621
Garland, E. L. (2012). Therapeutic mechanisms of a mindfulness-based treatment for IBS: effects on visceral sensitivity, catastrophizing, and affective processing of pain sensations. *J. Behav. Med., 35*, 591-602.
Gonsalkorale, W. M., & Whorwell, P. J. (2005). Hypnotherapy in the treatment of irritable bowel syndrome. *Eur J Gastroenterol Hepatol, 17*(1), 15-20.
Goubert, L., Crombez, G., & Van Damme, S. (2004). The role of neuroticism, pain catastrophizing and pain-related fear in vigilance to pain: a structural equations approach. *Pain, 107*(3), 234-241. doi:S030439590300455X [pii]
Grundy, D., Al-Chaer, E. D., Aziz, Q., Collins, S. M., Ke, M., Tache, Y., & Wood, J. D. (2006). Fundamentals of neurogastroenterology: basic science. *Gastroenterology, 130*(5), 1391-1411. doi:10.1053/j.gastro.2005.11.060
Hayes, S. C., Strosahl, K., & Wilson, K. G. (1999). *Acceptance and Commitment Therapy: An experiential approach to behavior change*. New York: Guilford Press.
Hill, C. E., Knox, S., Thompson, B. J., Williams, E. N., Hess, S. A., & Ladany, N. (2005). Consensual qualitative research: An update. *Journal of Counseling Psychology, 52*(2), 196-205. doi:10.1037/0022-0167.52.2.196
Jacobson, N. S., Roberts, L. J., Berns, S. B., & McGlinchey, J. B. (1999). Methods for defining and determining the clinical significance of treatment effects: description, application, and alternatives. *J Consult Clin Psychol, 67*(3), 300-307.
Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol, 59*(1), 12-19.
Jensen, M. P. (2006). Satisfaction with, and the beneficial side effects of, hypnotic analgesia. *Int. J. Clin. Exp. Hypn., 54*, 432-447.
Jensen, M. P., Adachi, T., Tomé-Pires, C., Lee, J., Osman, Z. J., & Miró, J. (2015). MECHANISMS OF HYPNOSIS:: Toward the Development of a Biopsychosocial Model. *Int J Clin Exp Hypn, 63*(1), 34-75. doi:10.1080/00207144.2014.961875
Jensen, M. P., Day, M. A., & Miro, J. (2014). Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nat Rev Neurol, 10*(3), 167-178. doi:10.1038/nrneurol.2014.12
Jensen, M. P., & Patterson, D. R. (2014). Hypnotic approaches for chronic pain management: clinical implications of recent research findings. *Am Psychol, 69*(2), 167-177. doi:10.1037/a0035644
Joffe, H. (2011). Thematic Analysis *Qualitative Research Methods in Mental Health and Psychotherapy* (pp. 209-223): John Wiley & Sons, Ltd.
Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., & Cleeland, C. S. (2004). Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain, 20*(5), 309-318.
Kirsch, I., Montgomery, G., & Sapirstein, G. (1995). Hypnosis as an adjunct to cognitive-behavioral psychotherapy: A meta-analysis. *Journal of Consulting and Clinical Psychology, 63*(2), 214-220. doi:10.1037/0022-006X.63.2.214
Kulkarni, B., Bentley, D. E., Elliott, R., Youell, P., Watson, A., Derbyshire, S. W., . . . Jones, A. K. (2005). Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur.J.Neurosci., 21*(11), 3133-3142.

Lumley, M. A., Cohen, J. L., Borszcz, G. S., Cano, A., Radcliffe, A. M., Porter, L. S., . . . Keefe, F. J. (2011). Pain and emotion: a biopsychosocial review of recent research. *J Clin Psychol, 67*(9), 942-968. doi:10.1002/jclp.20816

McCracken, L. M., & Vowles, K. E. (2014). Acceptance and commitment therapy and mindfulness for chronic pain: Model, process, and progress. *American Psychologist, 69*(2), 178-187. doi:10.1037/a0035623

McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain, 106*(1–2), 127-133. doi:http://dx.doi.org/10.1016/S0304-3959(03)00301-4

Melzack, R. (2001). Pain and the neuromatrix in the brain. *J Dent Educ, 65*(12), 1378-1382.

Melzack, R. (2005). Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. *Pain Pract, 5*(2), 85-94. doi:10.1111/j.1533-2500.2005.05203.x

Melzack, R., & Chapman, C. R. (1973). Psychologic aspects of pain. *Postgrad Med, 53*(6), 69-75.

Melzack, R., & Perry, C. (1975). Self-regulation of pain: the use of alpha-feedback and hypnotic training for the control of chronic pain. *Exp. Neurol., 46*, 452-469.

Merskey, H., & Bogduk, N. (1994). Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms (pp. 178). Seattle: IASP Press. (Reprinted from: NOT IN FILE).

Morley, S. (2015). Single cases are complex. *Scandinavian Journal of Pain, 7*, 55-57. doi:10.1016/j.sjpain.2015.02.004

Morley, S., & Adams, M. (1991). Graphical analysis of single-case time series data. *British Journal of Clinical Psychology, 30*(2), 97-115. doi:10.1111/j.2044-8260.1991.tb00926.x

Morley, S., & Dowzer, C. N. (2014). Manual for the Leeds Reliable Change Indicator: Simple Excel(tm) applications for the analysis of individual patient and group data. Leeds, UK: University of Leeds.

Morley, S., Williams, A., & Hussain, S. (2008). Estimating the clinical effectiveness of cognitive behavioural therapy in the clinic: evaluation of a CBT informed pain management programme. *Pain, 137*(3), 670-680. doi:10.1016/j.pain.2008.02.025

Moshiree, B., Zhou, Q., Price, D. D., & Verne, G. N. (2006). Central sensitisation in visceral pain disorders. *Gut, 55*(7), 905-908. doi:10.1136/gut.2005.078287

Nijs, J., Meeus, M., Van Oosterwijck, J., Ickmans, K., Moorkens, G., Hans, G., & De Clerck, L. S. (2012). In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *Eur J Clin Invest, 42*(2), 203-212. doi:10.1111/j.1365-2362.2011.02575.x

Oneal, B. J., Patterson, D. R., Soltani, M., Teeley, A., & Jensen, M. P. (2008). Virtual reality hypnosis in the treatment of chronic neuropathic pain: a case report. *Int J Clin Exp Hypn, 56*(4), 451-462. doi:10.1080/00207140802255534

Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'Neill, E. (1997). Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med, 20*(6), 589-605.

Peace, R. M., Majors, B. L., Patel, N. S., Wang, D., Valle-Pinero, A. Y., Martino, A. C., & Henderson, W. A. (2012). Stress and gene expression of individuals with chronic abdominal pain. *Biol Res Nurs, 14*(4), 405-411. doi:10.1177/1099800412458350

Pearce, J., & Morley, S. (1989). An experimental investigation of the construct validity of the McGill Pain Questionnaire. *Pain, 39*(1), 115-121.

Phillips, M. L., Gregory, L. J., Cullen, S., Coen, S., Ng, V., Andrew, C., . . . Aziz, Q. (2003). The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. *Brain, 126*(Pt 3), 669-684.

Pincus, T., Fraser, L., & Pearce, S. (1998). Do chronic pain patients 'Stroop' on pain stimuli? *Br J Clin Psychol, 37 (Pt 1)*, 49-58.

Pistrang, N., & Barker, C. (2012). Varieties of qualitative research: A pragmatic approach to selecting methods. In H. Cooper, P. M. Camic, D. L. Long, A. T. Panter, D. Rindskopf, & K. J. Sher (Eds.), *APA handbook of research methods in psychology, Vol 2: Research designs: Quantitative, qualitative, neuropsychological, and biological* (pp. 5-18). Washington, DC, US: American Psychological Association.

Prior, A., Colgan, S. M., & Whorwell, P. J. (1990). Changes in rectal sensitivity after hypnotherapy in patients with irritable bowel syndrome. *Gut, 31*(8), 896-898.

Sachs, L. B., Feuerstein, M., & Vitale, J. H. (1977). Hypnotic self-regulation of chronic pain. *Am. J. Clin. Hypn., 20*, 106-113.

Schoth, D. E., Nunes, V. D., & Liossi, C. (2012). Attentional bias towards pain-related information in chronic pain; a meta-analysis of visual-probe investigations. *Clinical Psychology Review, 32*(1), 13-25. doi:http://dx.doi.org/10.1016/j.cpr.2011.09.004

Stoelb, B. L., Molton, I. R., Jensen, M. P., & Patterson, D. R. (2009). The Efficacy of Hypnotic Analgesia in Adults: A Review of the Literature. *Contemp Hypn, 26*(1), 24-39. doi:10.1002/ch.370

Stroop, J. R. (1935). *Studies of interference in serial verbal reactions.* (Ph D), George Peabody College for Teachers, Nashville, Tenn.

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment, 7*(4), 524-532. doi:10.1037/1040-3590.7.4.524

Tan, G., Jensen, M. P., Thornby, J. I., & Shanti, B. F. (2004). Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain, 5*(2), 133-137. doi:10.1016/j.jpain.2003.12.005

Tan, G., Rintala, D. H., Jensen, M. P., Fukui, T., Smith, D., & Williams, W. (2014). A randomized controlled trial of hypnosis compared with biofeedback for adults with chronic low back pain. *Eur J Pain*. doi:10.1002/ejp.545

Tang, N. K. Y., Salkovskis, P. M., Hodges, A., Wright, K. J., Hanna, M., & Hester, J. (2008). Effects of mood on pain responses and pain tolerance: An experimental study in chronic back pain patients. *Pain, 138*(2), 392-401. doi:10.1016/j.pain.2008.01.018

Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation. *Neuron, 55*(3), 377-391. doi:http://dx.doi.org/10.1016/j.neuron.2007.07.012

Tracey, I., Ploghaus, A., Gati, J. S., Clare, S., Smith, S., Menon, R. S., & Matthews, P. M. (2002). Imaging attentional modulation of pain in the periaqueductal gray in humans. *Journal of Neuroscience, 22*(7), 2748-2752.

Turk, D. C., & Dworkin, R. H. (2004). What should be the core outcomes in chronic pain clinical trials? *Arthritis Res Ther, 6*(4), 151-154. doi:10.1186/ar1196

Turk, D. C., Dworkin, R. H., Allen, R. R., Bellamy, N., Brandenburg, N., Carr, D. B., . . . Witter, J. (2003). Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain, 106*(3), 337-345.

Turk, D. C., Okifuji, A., Sinclair, J. D., & Starz, T. W. (1998). Differential responses by psychosocial subgroups of fibromyalgia syndrome patients to an interdisciplinary treatment. *Arthritis & Rheumatism, 11*(5), 397-404. doi:10.1002/art.1790110511

Van Ryckeghem, D. M., & Crombez, G. (2014). Attentional bias and chronic pain: where to go from here? *Pain, 155*(1), 6-7. doi:10.1016/j.pain.2013.10.025

Van Ryckeghem, D. M., Crombez, G., Goubert, L., De Houwer, J., Onraedt, T., & Van Damme, S. (2013). The predictive value of attentional bias towards pain-related information in chronic pain patients: a diary study. *Pain, 154*(3), 468-475. doi:10.1016/j.pain.2012.12.008

Vanhaudenhuyse, A., Laureys, S., & Faymonville, M. E. (2014). Neurophysiology of hypnosis. *Neurophysiologie Clinique, 44*(4), 343-353.

Villemure, C., Slotnick, B. M., & Bushnell, M. C. (2003). Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain, 106*(1-2), 101-108.

Westman, A. E., Boersma, K., Leppert, J., & Linton, S. J. (2011). Fear-avoidance beliefs, catastrophizing, and distress: a longitudinal subgroup analysis on patients with musculoskeletal pain. *Clin J Pain, 27*(7), 567-577. doi:10.1097/AJP.0b013e318219ab6c

Woolf, C. J. (2007). Central sensitization: uncovering the relation between pain and plasticity. *Anesthesiology, 106*(4), 864-867. doi:10.1097/01.anes.0000264769.87038.55

Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain, 152*(3 Suppl), S2-15. doi:10.1016/j.pain.2010.09.030

Zambreanu, L., Wise, R. G., Brooks, J. C., Iannetti, G. D., & Tracey, I. (2005). A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. *Pain, 114*(3), 397-407. doi:10.1016/j.pain.2005.01.005

Zarem, P. (1966). The psychology of pain. *Bull Mich Dent Hyg Assoc, 12*(1), 16-18.

Zelman, D. C., Howland, E. W., Nichols, S. N., & Cleeland, C. S. (1991). The effects of induced mood on laboratory pain. *Pain, 46*(1), 105-111.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr.Scand., 67*(6), 361-370.

Part 3: Critical Appraisal

Previous experience and research orientation

Prior to clinical training, I spent several years working as an experimental psychologist in the field of neuroscience and pain. I worked at several research institutions where I conducted many research studies, including clinical trials, typically aimed at manipulating single independent variables within a controlled environment. My research background is very much one where quantitative methodology and analysis dominated and a where there was a focus on 'objective' outcome measures such as change in brain activity or reduction in inflammatory markers in response to an intervention.

This previous experience influenced my research approach and choice of topic of research for my research thesis. Firstly, I wanted to continue in an area I had experience and published in as this is something I plan to continue after training. Secondly, I wanted to improve my research options in terms of methodology and analysis away from the predominately quantitative methods and analysis I had previously employed and which is most commonly employed in pain research. In addition, I viewed the research project as an opportunity to learn and train under one of the leading researchers in the field of chronic pain and psychology, which is after all the purpose of training. Finally, I was curious about hypnosis as I have heard narratives about how it can work well for treating common visceral pain problems such as IBS (Whorwell, 2005, 2008) but was aware of a distinct lack on knowledge on how hypnosis works (e.g. psychological mechanisms) and how people use it.

Given my background, at the planning stage of the current research project, I initially struggled with the lack of control and sources of variability such a project is likely to encounter. As such, my early study designs included fixed clinical visits with

one clinician, with set intervals between visits, a fixed baseline period, and a completely standardised hypnosis protocol that would be applied to all participants. In addition to I aimed to control contextual factors such as always using the same clinic room and having appointments at the same time, amongst others. This was because I was already considering how to analyse and interpret any data that would be collected and felt it would be to challenging to make sense of data with so much 'background noise'. To some extent I still believe the study would have been improved with all the above measures in place. However, I became more aware of the fact that a single case series design would enable a more realistic picture of a clinical intervention and outcome that would therefore be more relative to future clinical work and perhaps provide a better measure of clinical effectiveness. Indeed, it could be argued that such research with all its extraneous variables is more similar to clinical practice and therefore what it lacks in assessing efficacy it more than makes up for it in measuring effectiveness and therefore is more clinically relevant research.

Furthermore, at the outset of the analysis I was very much aware of an apparent subjectivity in visual graphical analysis and in conducting thematic analysis. However, the more I understood the approach in particular the TA method, the more I valued the data it provides. This was highlighted by the visual analysis of graphs which highlighted the variability in pain scores over time which otherwise would not have been apparent in studies examining mean changes at beginning and end of treatment. Furthermore, the idiosyncratic nature of the data gathered at interview very much suits the idiosyncratic method of clinical intervention which, if formulation driven, is individualised. I also valued the data the interview could access that a group of pre-selected self-report measures could not assess. These are values I plan to bring to my future research and clinical practice (when considering service outcome).

Recruitment and working as a research team

As an experienced researcher, I was aware at the outset of the study that conducting clinical research is significantly more challenging and time consuming than healthy volunteer research for several reasons, most notably; recruitment (particularly in terms of identifying a homogenous patient group) and reliance on experienced clinicians for providing the intervention. These challenges were exacerbated by the limited time and flexibility I had for attending research visits due to placement commitments. Overall, I found this area (recruitment and reliance on other clinicians) perhaps the most challenging component of the research process.

The clinicians involved in the study were excellent and did everything they could to make the project work. It was due to factors outside their control that problems arose. These problems, although personal to my research, are likely to affect anyone conducting clinical research alongside NHS commitments. Through no fault of her own, my external supervisor's NHS role was in a state of constant uncertainty whilst we were awaiting ethical approval and did indeed change when the study had approval and was set to commence. This change of role resulted in less time to recruit and complete intervention and also the amount of time dedicated to project per week was reduced. In order to overcome this problem, I enrolled the help of a second clinician and agreed a necessary change in the study accepting that the sample size would be less than expected but that by combining qualitative and quantitative data collection, the dataset would be richer and thicker than initially planned. I also conceded that the follow-up part of the study would need to be omitted. In addition, I combined the first baseline visit with clinical assessment which was less than ideal but necessary in order to complete the study on schedule.

This set of circumstances and management of the research highlights the importance of flexibility when conducting research in general. Although it is important

to aim for the best possible study design, the reality of clinical research is that compromises are often made in order to commence and complete the work. This flexibility is something that a case series design permits but is not so straightforward if conducting other more tightly controlled experiments, such as a RCT for example. Of course, were it not for the need to complete the project within a strict timeframe it may have been possible to delay the study and limit compromise. However, in my experience, research with patients is very rarely without such compromise and the limiting factors are often out of the control of the researcher e.g. patient recruitment. Such issues are not uncommon and it raises debate about the feasibility of clinical trainees conducting clinical research from conception to conclusion. It is possible for instance to join an existing clinical study or conduct healthy volunteer research. However, despite all the problems I encountered, I still consider being involved from conception/study design, navigating the NHS ethical approval process and becoming familiar with the realities of clinical research a valuable experience for clinical psychologists in training who wish to conduct patient research in the future.

Difficulties in dissemination

Perhaps one of the challenges of single case methods is disseminating information in a way that is accessible and meaningful to the wider scientific community, clinicians and indeed funding bodies (clinical and research). Whilst the data can be very rich, as I have found it is sometimes challenging to formulate a cohesive, coherent narrative that can be summarised, communicated and therefore easily digested by interested parties. This is particularly important in terms of the utility of findings to clinical application such that results need to be summarised in a simple enough form to prove useful in translating to the clinic. In contrast, larger studies using predominately quantitative based methods can reduce clinical practice and outcomes down to a single unit or measure, pinpointing particular components of an intervention and weighting

them on their importance to change (e.g. through multiple regression). Whilst this minimizes individual experience, it provides something tangible to clinicians and researchers alike.

Perhaps, in terms of the present study some of the difficulties may be due to the inherent variability that exists in small samples. It may be more realistic to use the current findings to formulate hypothesis for larger studies with outcomes tailored to the factors that participants cited as key in effecting change so that these 'mechanisms' can be tested empirically.

Successes and failures

I found the use of daily diary very enlightening in that it highlighted the extremely high variability in pain experience and the need for 'real time' outcomes measures when assessing pain. This was the first time I employed such technology for research outcomes and it worked extremely well and was very accessible and not invasive for patients (i.e. no time consuming).

In contrast, the Stroop task did not work so well. This element of the research was included as a more innovative and potentially risky outcome which is why it was conceptualized as a pilot arm to the research and not one of the main aims of the project. Nonetheless, it highlights the importance of only including outcomes which it is possible to make sense of. It is possible this may have been less problematic had the originally anticipated a sample size been recruited, which may have given more weight to using quantitative statistics and reduced variability, thereby enabling a clearer picture to emerge.

Influence of dual role of clinician and researcher

One area that occurred to me as potentially important in the present study that might be applied to my research in the future is maintaining balance between clinical and research skills. I was aware at several points during the post-treatment interview

that I wandered into my clinical role, which was apparent by the type of questions I asked or the fact I often reflected back or summarised information in a clinical way e.g. "it sounds like you are more accepting of the pain now". It is now an automatic process when engaged in a patient-clinician relationship to continually formulate, reflect, hypothesis and summarize. As I was aware this was happening, I was quickly able to move back on track in the interviews. However, this highlights the fact that maintaining neutrality when asking questions from a research capacity is key to avoiding potential researcher bias influencing participant responses. For example, my summary suggesting greater acceptance may have led to acquiescence and therefore compromised the quality of the data.

It is equally important to maintain a good rapport with a patient in order to gather as much data as possible at interview. It is perhaps a socially learned behaviour that when interviewing individuals familiar with healthcare interactions, the interviewee will draw the clinician into their clinical role and that the clinician will naturally gravitate towards a clinical role when called upon. It is therefore a two-way process as a patient will, most likely, respond differently to someone who is a clinical psychologist compared with someone who is a laboratory researcher. In summary, it appears that when conducting clinical research as a clinician, it is important to be mindful of the trade-off between using clinical skills to establish good rapport and facilitate drawing out information from patients. Whilst at other times using a more neutral focused approach may reduce experimenter bias and keep the interview on track towards gathering research relevant outcomes.

Multifactorial nature of pain

One of the constant challenges when conducting my research (and the literature review) was holding in mind all the factors that contribute to chronic pain. The complexity of pain is enormous and it was at times overwhelming to reduce that

complexity down to a few common factors, psychological mechanisms or behaviours. This was apparent in design (i.e. choosing appropriate outcome measures) analysis and interpretation. I was always aware that whilst it was not practically possible to measure all potential mediating factors, I was missing potentially important outcomes such as ANS response which may have been crucial given the number or participants who cited relaxation as an important beneficial factor of hypnosis treatment. In addition, at times I largely omitted (not deliberately) the physical component of pain, focusing more on the emotional and cognitive aspects. This perhaps is natural given the objectives of the research but also comes from a personal perspective on chronic pain given my role as psychologist and past research interests. What this amounts to is the reality that I was only studying a part of the picture/puzzle of hypnotic analgesia for pain. It is perhaps unrealistic to think that it is possible to isolate particular causes or moderators of pain given the bio psychosocial nature of the condition.

Research design process

Patient involvement: Given the limited amount of time available to clinical psychologist trainees to conduct research, the time available during the design of the research is relatively restricted. In future work it would be ideal to have more space to discuss and review protocols amongst the research team but also to extend that discussion to other stakeholders, most notably the patient group being studied. It is now a pre-requisite for many research projects to have consulted patient representatives prior to seeking funding or ethical approval. Given the time constraints this opportunity was not taken up. In retrospect this may have been a valuable process as whilst conducting the research several participants provided helpful constructive feedback on what could have been included/omitted from the research protocol. Perhaps the reluctance (in addition to the time constraint) to consult service user groups was that often, in the past, I have found expectations of patients to be very high, unrealistic or outside the

scope of the research project being planned. *Piloting research:* With this in mind, I think that perhaps the most useful approach would be to fully pilot a study such as the one conducted incorporating opportunity for formal feedback and constructive criticism from the patients participating in the study. This enables relevant, realistic patient input and also provides the research team with an opportunity to notice any potential flaws or pitfalls and make any necessary changes to the protocol before studying larger groups. Although this may be a time consuming process in the short term, this is something I will consider when conducting research in the future as it may save time in the long term.

Conclusion

Overall, my research experience during clinical training has broadened my research horizons and I have learnt a great deal, despite previous extensive research experience. I have learnt that it is about using the right tools for the research question at hand, so if a technique such as TA is suitable then I will certainly use it again in the future. Moreover, my positive experience of the research is a reflection of the excellent research and statistical training clinical psychologists receive and the opportunities available for clinical research whilst on training. It is not surprising that I have noticed how psychologists are valued by other clinical professions (e.g. medicine, nursing) for their research knowledge and expertise e.g. on study design and statistics. Yet I have also noticed a disparity in the knowledge and training psychologists receive, and the confidence and/or desire to carry out research. Furthermore, despite clinical training emphasizing the role of the scientist-practitioner psychologist there is a lack of dedicated time within clinical roles given to research, which is perhaps the biggest barrier to clinical psychologists continuing to build on research skills developed during training. With ever-increased waiting lists, this is no doubt a result of the demands of clinical practice within the NHS. My current research however, has given me the

confidence that useful research can be conducted on a case-by-case basis, using appropriate outcomes measures alongside normal clinical practice and in keeping with models of practice based evidence.

3.1 **References**

Whorwell, P. J. (2005). Review article: The history of hypnotherapy and its role in the irritable bowel syndrome. Aliment Pharmacol Ther, 22(11-12), 1061-1067. doi:10.1111/j.1365-2036.2005.02697.x

Whorwell, P. J. (2008). Hypnotherapy for irritable bowel syndrome: the response of colonic and noncolonic symptoms. J Psychosom Res, 64(6), 621-623. doi:10.1016/j.jpsychores.2008.02.022

Appendix

Appendix 1 - Electronic Daily Diary Questions

Pain intensity and unpleasantness:

1. **Please rate your pain intensity by indicating the number that best describes your pain on average in the last 24 hours** (0=no pain, 10= extreme pain)

2. **Please rate the unpleasantness of your pain by indicating the number that best describes your pain on average in the last 24 hours** (0=not at all unpleasant, 10=pain as unpleasant as you can imagine)

Avoidance:

3. **To what extent did you avoid daily activities today because of pain?** (0 = ''not at all'' – 10 = ''completely avoid '').

Attention:

4. **Today I have been focussing on my pain** (0 = ''not at all'' – 10 = ''completely focused'').

5. **Today I am distracted by my pain** (0 = ''not at all'' – 10 = ''completely distracted).

Disability:

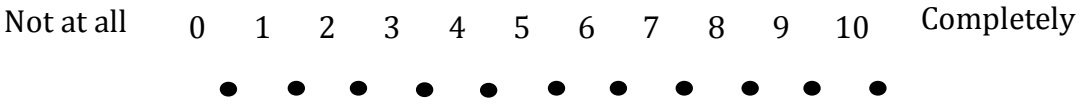
6. **'To what extent did pain hinder your planned activities?** (0 = ''not at all'' – 10 = 'completely hindered).

7. **Today my pain has stopped me from doing things** (0 = ''not at all'' – 10 = ''completely'').

Worry:

8. **I am worried about my pain** (0 = ''not at all'' – 10 = ''completely").

Example scale:



Appendix 2 –Perseverative thinking Questionnaire

Instruction: In this questionnaire, you will be asked to describe how you *typically* think about negative experiences or problems. Please read the following statements and rate the extent to which they apply to you when you think about negative experiences or problems.

		never	**rarely**	**sometimes**	**often**	**almost always**
1.	The same thoughts keep going through my mind again and again.	0	1	2	3	4
2.	Thoughts intrude into my mind.	0	1	2	3	4
3.	I can't stop dwelling on them.	0	1	2	3	4
4.	I think about many problems without solving any of them.	0	1	2	3	4
5.	I can't do anything else while thinking about my problems.	0	1	2	3	4
6.	My thoughts repeat themselves.	0	1	2	3	4
7.	Thoughts come to my mind without me wanting them to.	0	1	2	3	4
8.	I get stuck on certain issues and can't move on.	0	1	2	3	4
9.	I keep asking myself questions without finding an answer.	0	1	2	3	4
10.	My thoughts prevent me from focusing on other things.	0	1	2	3	4
11.	I keep thinking about the same issue all the time.	0	1	2	3	4
12.	Thoughts just pop into my mind.	0	1	2	3	4
13.	I feel driven to continue dwelling on the same issue.	0	1	2	3	4
14.	My thoughts are not much help to me.	0	1	2	3	4
15.	My thoughts take up all my attention.	0	1	2	3	4

Appendix 3 –BPI-P (pain scale)

BPI- Pain Scale

1. Please rate your pain by circling the one number that best describes your pain at its worst in the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No pain										*Pain as bad as you can imagine*

2. Please rate your pain by circling the one number that best describes your pain at its least in the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No pain										*Pain as bad as you can imagine*

3. Please rate your pain by circling the one number that best describes your pain on average

0	1	2	3	4	5	6	7	8	9	10
No pain										*Pain as bad as you can imagine*

4. Please rate your pain by circling the one number that tells how much pain you have right now

0	1	2	3	4	5	6	7	8	9	10
No pain										*Pain as bad as you can imagine*

Appendix 4 – BPI-I (interference scale)

BPI – Interference scale

5. Circle the one number that describes how, during the past 24 hours, pain has interfered with your

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

D. Normal work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										*Completely interferes*

Appendix 5 – Pain Stroop Control Example

Footnotes	Hail
Hail	Upper
Rendered	Flew
Coasted	Descend
Descend	Footnotes
Sleeve	Rendered
Mention	Flew
Coasted	Mention
Rendered	Flowed
Footnotes	Sleeve
Flowed	Mention
Upper	Hail
Flew	Footnotes
Sleeve	Rendered
Coasted	Flowed
Footnotes	Descend
Descend	Coasted
Mention	Flowed
Hail	Sleeve
Flowed	Mention
Descend	Coasted
Sleeve	Rendered
Upper	Upper
Flew	Flew
Upper	Hail

Appendix 6 -Pain-Stroop Example

Appendix 7 Post Treatment interview Schedule

- **What were your initial expectations of hypnosis, prior to treatment?**
    - Was your experience similar/different to expectation?
    - What were your thoughts about how it might affect your pain?

- **How have you been using the self-hypnosis techniques?**
    - Where e.g. at home, work, bedroom, outside, whilst shopping etc?
    - When e.g. routinely at certain time of day, when pain or emotion is particularly bad, before/after activity?
    - Duration, frequency (daily, weekly, minutes)
    - Has your use changed over the course of treatment e.g. slow start but now routine?

- **What impact has hypnosis had?**
    - Was it useful/not useful?
    - Are there any specific aspects that have been helpful i.e. suggestion v relaxation?

- **Do you understand your pain differently now?**

- **Has your thinking about pain changed in any way?**
    - Worry, daily bother from pain, acceptance

- **Has using hypnosis changed anything in your daily life?**

- **Do you plan to continue using self-hypnosis?**

Common alternative/follow-up questions

- If you feel there have been changes, what do you attribute those changes to (including anything else that was happening in your life outside hypnosis therapy that may have influenced change)?
- What ideas do you have about how hypnosis works?
- Is there anything you would change about hypnosis therapy (add or take away)?
- Is there anything you found unhelpful about your treatment experience?
- Has anyone you know noticed/commented on anything different about you since you started therapy?
- Would I notice you doing anything differently now compared with before treatment

Appendix 8 – Research Ethical Committee Approval letter

NHS
Health Research Authority
South West - Cornwall & Plymouth Research Ethics Committee
Level 3
Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

07 December 2015

Dr Amanda Williams
Research Department of Clinical, Educational and Health Psychology, University College London
1-19 Torrington place
London
WC1E 6BT

Dear Dr Williams

Study title:	**Exploring the Processes and Psychological Factors Involved in Hypnotic Modulation of Chronic Pelvic Pain**
REC reference:	**15/SW/0345**
IRAS project ID:	**178051**

Thank you for your letter of 4th December 2015, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Georgina Castledine, [redacted]. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Covering letter on headed paper [Cover letter]	1	13 November 2015
GP/consultant information sheets or letters [GP letter]	1	16 September 2015
Interview schedules or topic guides for participants [qualitative interview]	2	10 August 2015
IRAS Checklist XML [Checklist_04122015]		04 December 2015
Letters of invitation to participant [Patient invitation letter]	1	17 November 2015
Other [Stroop task example]	2	10 August 2015
Other [Daily Diary Questions]	2	10 August 2015
Other [Letter of response to REC comments]	1	04 December 2015
Participant consent form	2	15 September 2015
Participant information sheet (PIS) [PIS with changes highlighted]	4	03 December 2015
Participant information sheet (PIS) [PIS clean version]	4	03 December 2015
REC Application Form [REC_Form_17112015]		17 November 2015
Referee's report or other scientific critique report [Review acceptance report]		27 March 2015
Referee's report or other scientific critique report [Reviewer comments/report]		14 November 2014
Research protocol or project proposal [Project proposal]	2	10 August 2015
Summary CV for Chief Investigator (CI) [CI CV]		21 July 2015
Summary CV for student [Student CV]		15 July 2015
Summary CV for supervisor (student research) [supervisor 2 CV]	1	16 November 2015
Summary, synopsis or diagram (flowchart) of protocol in non technical language [flowchart]	2	10 August 2015
Validated questionnaire [Pain catastrophizing scale]		15 July 2015
Validated questionnaire [Pervasive thinking Questionnaire]		15 July 2015
Validated questionnaire [Brief Pain Inventory]		15 July 2015
Validated questionnaire [HADS]		15 July 2015
Validated questionnaire [IPQ]		15 July 2015
Validated questionnaire [McGill Pain Questionnaire]		15 July 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/SW/0345	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp. [redacted]

Ian Ainsworth-Smith
Chair

Email: [redacted]

Copy to: *Ms Smaragda Agathou*

Appendix 9 – Participant Information Sheet

Dept. of Clinical, Educational and Health Psychology
University College London
1-19 Torrington Place
WC1E 7HB

Participant Information Sheet

Full Title: Exploring the Processes and Psychological Factors Involved in Hypnotic Modulation of Chronic Pelvic Pain

Invitation

- You are being invited to take part in a medical research study based at University College London Hospitals (UCLH).
- The study being conducted forms part of a Doctorate in Clinical Psychology Thesis project
- Before you decide whether to take part it is important that you understand why the research is being conducted and what your participation will involve.
- Please take time to read this information sheet carefully and discuss it with friends, relatives and your GP if you wish. Feel free to ask any questions if you are unclear about the study or if you would like further information.

Important things you need to know

- We are interested in how people use hypnosis as part of their normal treatment as this is currently poorly understood
- Understanding this better may help inform the best ways for patients to use hypnosis in the future so that it can be of most benefit
- You will receive your treatment as normal but with some extra questionnaires and tasks to complete before or after your clinical visits
- This study fits into your normal treatment so there are no extra clinical visits but there will be two additional visits for research purposes
- You can stop taking part in the study at any time

Brief summary the Study

Hypnosis is often used as part of a clinical team approach to help treat people suffering from chronic pain. Despite the fact that many patients who use hypnosis for the treatment of chronic pelvic pain, there have been no studies to assess how people use the hypnosis and how they find it helpful.

If we understand better how individuals use hypnosis and what aspects they find beneficial, it may help inform better treatments in the future that are more tailored to individuals suffering with chronic pelvic pain.

The study will work around your clinical appointments for hypnosis and will use a combination of questionnaires, a short pen and pencil task and an interview to information about how you use hypnosis and how it may affect your overall well-being.

Can I Take Part?

We are recruiting participants with a diagnosis of chronic pelvic or abdominal pain. There are certain things listed here that would mean you cannot take part in the study which you need to read before deciding if you can take part.

(1) If you have any planned surgery
(2) If you have a diagnosis of pelvic inflammatory disease.
(3) If you have any other major neurological, neurodevelopmental or medical illness.

If you are not sure if any of these apply to you please ask us to clarify this for you.

Do I Have To Take Part?

Participating in this research trial is entirely voluntary and will not influence your clinical care. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason.

What Will Happen To Me If I Take Part?

You will need to attend UCLH as normal to receive your hypnosis treatment as usual.
This will involve an initial consultation with your clinician and then four to six sessions of hypnosis treatment and training.

In terms of the research component, you will need to attend 2 extra visits – two weeks and six weeks after the end of your hypnosis treatment.

At the beginning of your first clinical consultation visit we will clarify any questions concerning the study and if you are still happy to continue you will then complete the consent form.

The research component will involve completing questionnaires and a short pencil and paper task at your first clinical consultation visit, your first hypnosis session, 2 weeks after your final clinical visit and 6 weeks after your final hypnosis session. For more details on the questionnaires and pen and pencil task see below.

In addition, you will be asked to complete daily electronic questions about your pain and daily functioning, on your phone or computer. These are very brief and will take approximately 5 minutes to complete in total. A reminder to complete these will be sent to you every day. If you do not have electronic access or email these questionnaires will be provided as paper copies for you to complete daily, as described above.

Finally, 2 weeks after your final hypnosis session we will conduct a short interview asking you some questions about your experience of hypnosis, for example how you used it and was it helpful.

These means there are 4 visits in total that form part of the research, two of which will coincide with your clinical appointments.

Further details on questionnaires, pen and pencil task, and interview

Questionnaires
As mentioned above, on four occasions we will give you some questionnaires to complete which assess your current daily activity and quality of life, and your attitudes, beliefs and worries about your pain.
In addition, we will also give you some standard health questionnaires assessing your current mood. The questionnaires will not ask for any personal or clinical history and will be anonymised so that your personal details are not on them. The completion of the questionnaires will take approximately 25-30 minutes in total.
We will also ask you to complete a brief set of questions every day assessing different aspects of your pain experience which should only take roughly 5 minutes to complete each day.

Short pen and pencil task
As mentioned above, on four occasions you will have to complete a short pen and pencil task that involves you reading a list of twenty words on a piece of paper. The words on the list will be presented in a variety of colours. Once positioned comfortable at a desk, we will present the list of words and ask you to read aloud the colour of each word as quickly and as accurately as possible. We will make a note of how accurately and promptly you read this list.

Interview
Two weeks after your final hypnosis session we will conduct a short interview asking you to describe your experience of using hypnosis and whether you think it has been helpful. The interview will be recorded on a voice recorder to enable us to accurately detail your responses. The recording will be anonymised and destroyed after it has been transcribed by a member of the research team.

What Are The Side Effects of Taking Part?
As the research is largely focused on using questionnaires and a short interview, there should be no short or long-term side effect from taking part as the research. However, you may find the questionnaires take up some of your time each day during the study.

What Are The Possible Benefits of Taking Part?
You may benefit from a greater insight into the best way to use hypnosis for treating your chronic pain.

Travel Expenses

We will reimburse for any travel expenses to and from the study appointments that you have so please keep receipts. Payments will be made after you have completed your final visit. If you do not complete the study, you will still be reimbursed for travel expenses up to the point at which your participation in the study ended.

What will happen if I withdraw from the study?

You are free to withdraw from the study at any time without having to provide an explanation. If you decide to withdraw it will not have any impact on your clinical treatment sessions (hypnosis) and you will continue to receive these as part of your care plan as discussed with your clinician.

Will My Taking Part Be Confidential?

All information which is collected about you during the course of this research is kept strictly confidential and is made untraceable to you. All data collected will be stored against a number, not your name, in a password-protected computer that only the investigators of the study will have access to. Paper questionnaires will also be annoymised and stored in a locked cupboard within the research department.

When reporting the outcome of the study, we may use quotations from participants'. However, these will be edited in order to remove any identifiable information.

If you consent to take part, we will inform your GP about your enrolment.

What Will Happen To The Results Of The Study?

It is anticipated that the results will be submitted for publication as a Doctoral thesis at University College London and in an international research journal. You will not be able to be identified in any way in this publication. The final report will be available to you should you wish to have a copy.

Who Is Organising The Research?

The study is organised by the Research Department of Clinical, Educational & Health Psychology, University College London (UCL).

Who Has Reviewed The Study?

This study has undergone both internal and external peer review processes and has been reviewed and given favourable opinion by the by the South West Cornwall and Plymouth Research Ethics Committee (REC reference 15/SW/0345). The study has also been approved by the Joint Research and Development Office for UCL.

Who Do I Contact If I Wish To Make A Complaint About The Way In Which The Research Is Conducted

If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. If you are harmed by taking part in this research project, but it is not due to negligence then you will be given further advice on whom to contact and your case would be considered as per NHS guidelines. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, please contact the Complaints Officer

(details below). Alternatively, any complaints may be directed to Dr. Steven Coen, the Chief Investigator of the study.

Complaints
In the event of a complaint about the conduct of the study, the complaints can be directed to the study researcher (Dr Steven Coen, contact details below). If your complaint is with regards to the clinical service, you can direct any concerns to one of the clinicians delivering your care (Dr Anna Mandeville or Dr Raj Sharma) or to the clinical service lead clinician, Dr Natasha Curran.

If you prefer, you may also direct any complaints regarding the research or clinical care to the Patient Advice and Liaison Service (PALS) at UCLH. You can contact the PALS by post at:

PALS
Box 25
National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG

Or by email to PALS@uclh.nhs.uk

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise."

Contact For Further Information?
Further information can be obtained by contacting Dr Steven Coen [redacted]

Thank you for taking the time to read this information.

Appendix 10 – consent form

Dept. of Clinical, Educational and Health Psychology
University College London
1-19 Torrington Place
WC1E 7HB

Centre Number:
Study Number:
Participant Identification Number for this trial:

CONSENT FORM

Title of Project: **Exploring the Processes and Psychological Factors Involved in Hypnotic Modulation of Chronic Pelvic Pain**

Name of Researcher: Dr. Steven Coen

Please initial box

1. I confirm that I have read the information sheet dated.....15th September 2015... (version...2....) for The above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the NHS Trust, where it is relevant to my taking part in this study. I give permission for these individuals to have access to my records. ☐
4. I give permission for my comments regarding hypnosis, during the structured interview, to be recorded and transcribed. ☐
5. I agree to my General Practitioner being informed of my participation in the study. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 11: Schematic Overview of Experimental Protocol