The influence of discouragement, anxiety and anger on pain: An examination of the role of endogenous opioids

Ashley Frew

BA (Hons, Psychology)

This thesis is presented for the degree of Doctor of Philosophy
of Murdoch University, Western Australia, 2004.

I declare that this thesis is my own account of my research and contains as its main content work that has not previously been submitted for a degree at any tertiary education institution.

_____

Ashley Frew

ABSTRACT

Animal research suggests that exposure to inescapable stressors can lead to an endogenous opioid-mediated form of pain inhibition, known as *stress-induced analgesia (SIA)*. Similar results have been found with humans, although the literature is much less extensive and at times contradictory where uncontrollable stressors have led to an increase, rather than a decrease in pain. More recently, there has been some suggestion that emotions play an important role in pain modulation, and that particular negative moods are associated with opioid-mediated hypoalgesia. This research aimed to clarify the psychological (cognitive and affective) factors underlying endogenous opioid-mediated pain inhibition in humans.

The purpose of Study 1 was to examine the effects of stressor controllability and predictability on pain intensity (PI) and unpleasantness (UP) ratings during a cold pressor task (CPT) in 56 male and female subjects. The stressor involved a timed mental arithmetic task during which three moderately noxious electrical shocks were delivered. Although subjects were informed that shock delivery was contingent on math performance, the shock schedule was preset and identical across conditions. Perceived control over the shocks was manipulated between subjects by altering the difficulty of the math task. Shock predictability was manipulated by changing the colour of the computer screen to warn of an impending shock. Subjects were randomly allocated to four experimental conditions (controllable-predictable, controllable-unpredictable, uncontrollable-predictable, and uncontrollable-unpredictable shocks). Visual analogue ratings of 'perceived self-efficacy' (to avoid the shocks) and mood (anxiety, confusion, discouragement, anger, sluggishness, liveliness) were completed before, during and after the math task. Significantly greater discouragement and lower self-efficacy was reported in 'uncontrollable' conditions indicating that 'controllability' was manipulated effectively. Results indicated that a perceived lack of control over shocks during the math task led to significantly greater decreases in PI, but not UP, ratings during the last stages of a 4-minute fixed interval CPT after the math task. Shock predictability failed to influence subjective pain ratings alone; however, unpredictability interacted with lack of

control to initially increase pain, followed by analgesia. Stress-induced increases in negative affect (anxiety, discouragement, anger) were associated with decreases in cold pressor PI, but with increased shock PI and UP during the math task. It was concluded that lack of control over an aversive event and negative affect led to SIA during a prolonged pain stimulus, whereas shock predictability had little influence on pain.

In Study 2, 70 male and female subjects received either an opioid antagonist (naltrexone) or a placebo before the math task (using a double-blind, counterbalanced design), in order to determine the role of endogenous opioids in SIA. Subjects were randomly assigned to one of three experimental conditions to investigate whether the shocks themselves may have contributed to analgesia observed after the math task: (1) easy task-few shocks, (2) hard task-few shocks, (3) hard task-many shocks. Increases in systolic blood pressure (SBP), diastolic blood pressure (DBP), anxiety, anger and discouragement indicated that negative affect and sympathetic arousal were induced during the math task. Endogenous opioids inhibited the rise in anger, but not discouragement or anxiety, during the math task. There was some evidence that perceived lack of control over shocks, and not the shocks themselves, led to opioid-mediated decreases in cold pressor UP after the math task. In correlational analyses, discouraged subjects under opioid blockade reported more cold pressor UP after the math task than their placebo counterparts. However, this effect was not strong enough to reach statistical significance in regression analyses. Anxiety, anger, discouragement and lack of control over shocks increased shock PI and UP during the math task.

A growing body of research with normotensive subjects has linked increased cardiovascular activity with insensitivity to pain, but the role of endogenous opioids remains contentious. In addition to the investigations outlined above, Study 2 aimed to examine the contribution of endogenous opioids in the cardiovascular-pain relationship. However, there was no evidence of an interaction between pain and cardiovascular activity in this study.

Study 3 was carried out to investigate opioid involvement in the effects of an uncontrollable stressor and stress-induced negative mood on cold pressor PI, UP and

pain tolerance, and onset/thresholds of the nociceptive flexion reflex (RIII). Forty-three male and female subjects were administered either naltrexone or a placebo using a double-blind, counterbalanced design before completing a timed mental arithmetic stressor (identical to the 'hard task-many shocks' condition in Study 2). Increases in physiological (SBP, DBP) and affective measures (anxiety, anger and discouragement) indicated that the math task induced a marked state of stress. Negative affect increased shock PI and UP during the task, whereas self-efficacious subjects taking the placebo experienced less shock pain. However, uncontrollable stress led to an opioid-antagonised increase in cold pressor UP. Stressor controllability had a similar, but marginal, effect on cold pressor PI, but not pain tolerance. Tolerance of cold pressor pain was not associated with subjective PI and UP ratings, but was positively associated with endurance to non-painful, but unpleasant tasks (Valsalva Manoeuvre, Letter-Symbol Matching Task), indicating that pain tolerance was measuring the ability to tolerate discomfort, in addition to pain. Results of hierarchical multiple regressions demonstrated that increases in discouragement were positively related to increases in cold pressor UP after the math task, for naltrexone recipients only. These findings suggest that discouragement inhibits the UP of a prolonged pain stimulus via opioid mechanisms. RIII latencies and thresholds were not affected by the math task or by opioid blockade; however, these null effects may be due to methodological limitations. Unlike Study 2, higher blood pressure was associated with shock and cold pressor pain inhibition in normotensive subjects, and this relationship appeared to be mediated by opioids.

The strong association between chronic pain and depression has led to speculation that the endogenous opioid system and pain modulatory mechanisms may be impaired in depression. At the time that this research was carried out, no studies had examined whether this was the case. In Study 4, the effect of a cognitive stressor (math task used in Study 3) on foot cold pressor PI, UP and pain tolerance and the nociceptive, or R2 component, of the blink reflex was investigated in 61 participants with or without major depression (as met by DSM-IV diagnostic criteria and confirmed by psychometric testing). Naltrexone or placebo was administered to subjects an hour before the math task using a double-blind, counterbalanced design. Increases in physiological (SBP, DBP) and affective measures (anxiety, anger and discouragement) confirmed that the math task induced the targeted emotional state.

An opioid-mediated reduction in anxiety occurred mid-way through the math task. Opioid-mediated decreases in foot cold pressor PI and UP were observed in depressed and non-depressed subjects after the math task. R2 onset to 10 mA was facilitated after the task regardless of opioid blockade, suggesting that endogenous opioids are not involved in the modulation of the BR. Increased anxiety and discouragement led to opioid-mediated inhibition of shock PI and UP during the task and, to a lesser extent, foot cold pressor PI and UP after the math task. Anger increased shock pain without being influenced by opioid blockade. Pain tolerance was not influenced by depression, opioid blockade or mood. These findings failed to support the idea that SIA is impaired in major depression, suggesting instead that uncontrollable aversive events and negative mood (anxiety, discouragement) lead to opioid activation and insensitivity to acute pain. Multiple regression analyses revealed that the inverse relationship between resting blood pressure and foot cold pressor PI and UP was opioid-mediated in controls only, suggesting that opioid dysregulation in depression might influence regulatory functions other than SIA.

In Study 4, opioid involvement in hetero-segmental pain inhibitory phenomena termed diffuse noxious inhibitory controls (DNIC) was examined separately, before psychological stress. Specifically, the effect of a heterotopic noxious conditioning stimulus (CS i.e., hand CPT) on R2 onset latency was compared before and after drug absorption (before the math task). An inhibitory effect of the first CS was detected at each electrical stimulus intensity consistent with a DNIC effect. However, this effect was not detected during the second CS, suggesting that some other process masked the DNIC effect.

In summary, the findings indicate that uncontrollable aversive events and negative emotion (primarily discouragement) activates endogenous opioids and inhibits pain in human subjects, whether depressed or not. Notably, opioids inhibited the affective component of pain perception, or pain UP, more consistently than PI, suggesting that the antinociceptive function of opioids may be secondary to an important emotional-modulatory role. Endogenous opioids also appeared to mediate the cardiovascular-pain relationship in normotensive non-depressed subjects, suggesting an important stress-regulatory role for these peptides. Opioid-mediated masking of this relationship in major depression suggests that functioning of the endogenous opioid

system may be impaired in baroreceptor-mediated analgesia. This finding provides preliminary support for the notion that opioid antinociceptive system dysfunction may contribute to cardiovascular disease in depression.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACTH	=	adrenocorticotrophic hormone
ANS	=	autonomic nervous system
BDI-II	=	Beck Depression Inventory, Second Edition
BP	=	blood pressure
CHD	=	coronary heart disease
CMS	=	chronic mild stress model
CNS	=	central nervous system
CPT	=	cold pressor task
CRF	=	corticotrophin releasing factors
CS	=	conditioning stimulus (i.e., hand cold pressor task)
CSF	=	cerebrospinal fluid
DASS	=	Depression, Anxiety, Stress Scales
DBP	=	diastolic blood pressure
DNIC	=	Diffuse Noxious Inhibitory Controls
DSM-IV	=	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DST	=	Dexamethasone Suppression Test
EFS	=	'easy task-few shocks' condition, Study 2
EMG	=	electromyographic
fCPT	=	foot cold pressor task
GABA	=	gamma amino butyric acid
HFS	=	'hard task-few shocks' condition, Study 2
HMS	=	'hard task-many shocks' condition, Study 2
HPA	=	hypothalamic-pituitary-adrenal axis
LH	=	learned helplessness
LSMT	=	Letter Symbol Matching Task
M-VAS	=	mechanical visual analogue scale
PBQ	=	phenylbenzoquinone
PET	=	positron emission tomography
PI	=	pain intensity

List of abbreviations.....continued.

RDC	=	Research Diagnostic Criteria
REM	=	rapid eye movement
RIA	=	radioimmunoassay
RRA	=	radio-receptor assay
R2	=	nociceptive component of the blink reflex
RIII	=	nociceptive flexion reflex
SBP	=	systolic blood pressure
SCID-CV	=	Structured Clinical Interview for DSM-IV Axis I Disorders - Clinician Version
SIA	=	stress-induced analgesia
STAI	=	State-Trait Anxiety Inventory
TENS	=	transcutaneous electrical nerve stimulation
TS	=	test stimuli (i.e., electrical pulses) to elicit the blink reflex
UFC	=	urinary free cortisol
UP	=	pain unpleasantness
VAS	=	visual analogue scale
VM	=	Valsalva manoeuvre
VRS	=	verbal rating scale

CHAPTER ONE

1. GENERAL INTRODUCTION

1.1 PURPOSE OF THIS RESEARCH

The identification of psychological factors leading to the activation of *endogenous* pain control mechanisms (e.g., stress-induced analgesia, SIA) has important implications for pain control in acute and chronic pain disorders, as new discoveries might inform new treatments (Maier, Sherman, Lewis, Terman, & Liebeskind, 1983). Current *exogenous* pain control techniques involve the prescription of addictive opiate drugs (e.g., morphine, pethidine, codeine), and/or destructive analgesic surgical techniques (Maier et al., 1983). These treatments pose problems for the management of chronic pain conditions, such as the development of tolerance. Furthermore, the reliance on external pain control techniques serves to remove an individual's control over their pain, and may contribute to feelings of depression and anxiety and lead to avoidant and/or helpless behaviour.

There is a well-established correlation between depression and pain, and some suggestion that depression may be involved in the aetiology or exacerbation of pain syndromes by chronically activating and eventually exhausting natural pain-modulatory systems. However, existing evidence does not allow a causal direction to be determined. Therefore, by clarifying how negative mood and cognitions influence the body's capacity to modulate pain, the role of mood disorders (such as major depression) in the aetiology of chronic pain may be elucidated. Additionally, the establishment of a causal relationship between negative mood and pain could highlight the importance of treating pathological mood in affectively ill patients with or without chronic pain. For instance, patients could learn not to exhaust endogenous pain systems by refraining from particular cognitions or emotions known to precipitate stress and the activation of finite pain inhibitory mechanisms. Furthermore, teaching depressed patients to appraise life events as non-threatening

could reduce the risk of chronic pain. This could also lessen immunosuppressive effects or immune pathophysiology linked to endogenous opioid release in depression (Leonard, 1990; Maes, De Meester, Scharpe, Desnyder, Ranjan, & Meltzer, 1996; Maes, Goossens, Scharpe, Meltzer, D'Hondt, & Cosyns, 1994).

Thus, this research aims to:

- Identify the psychological factors leading to SIA in humans.
- Investigate the influence of negative mood on opioid-mediated endogenous pain inhibitory mechanisms in healthy humans.
- Investigate whether chronic negative mood, manifesting in disorders such as major depression, alters the functioning of endogenous pain inhibitory mechanisms.

1.2 CHAPTER OVERVIEW

This chapter will introduce the notion of 'pain' as a multi-dimensional, complex concept involving sensory, affective, cognitive and behavioural components. Following this is a brief overview of theories of pain transmission, including a description of the neurophysiological circuitry and neurochemical mediators involved. Next, stimuli that activate endogenous pain control systems, including physical and psychological factors, are reviewed. Animal research is presented briefly to provide a context for the discussion of human studies. Of particular interest for this thesis is the phenomenon of SIA. Therefore, evidence of SIA in various types of settings (experimental, clinical) and subject samples (pain-free subjects, acute/chronic pain patients) is presented in detail. Finally, the issue of whether negative mood facilitates and/or inhibits pain is discussed.

1.3 THE MULTI-DIMENSIONAL EXPERIENCE OF PAIN

Classically, pain has been viewed as a uni-dimensional sensory phenomenon involving a physiological response to a painful stimulus that is proportional to the number of pain receptors stimulated (Hirsch & Liebert, 1998). However, from advances in areas such as functional brain imaging (Coghill, Derbyshire, &

Ploghaus, 2004), it is clear that pain is a complex multidimensional phenomenon in which sensory (i.e., intensity, location) and affective components (emotional reactions/expectations) contribute significantly to the experience of pain (Ahles, Blanchard, & Leventhal, 1983). Contemporary theorists are careful to distinguish between *nociception* and the subjective, conscious experience termed *pain* (Craig, 1989). Briefly, nociception involves the peripheral activation of primary afferents in response to noxious stimuli, whereas *pain* refers to the sensory-perceptual, cognitive-evaluative, affective-motivational, and behavioural products resulting from the sensory input (Melzack & Wall, 1982). Each component of pain, and the interaction between them, will be explored in the sections below.

1.3.1 Nociception

Nociception refers to "the processes regulating the transduction, transmission, and modulation of noxious stimuli in the nervous system" (Craig, 1995, p 305). Tracing a pathway from the periphery to the central nervous system (CNS), the nociceptive system includes primary afferent nociceptors (from the periphery), interneurons in the spinal cord or in the trigeminal system of the brain stem, ascending tracts, and thalamic and cerebral cortex neurons within the brain (Willis, 1995). Primary afferent *nociceptive* fibres selectively respond to noxious stimuli that may endanger or cause damage to the skin, joints, muscles, and internal organs, resulting in varying qualities and intensities of pain.

Nociceptive information sent via afferent pathways is processed within the dorsal horn of the spinal cord, which houses both excitatory and inhibitory neurons. The dorsal horn facilitates nociceptive reflexes and modulates ascending-transmission cells (t-cells) via descending inhibitory and facilitatory influences that originate supra-spinally in the brainstem and higher centres of the brain. These descending influences originate in the periaqueductal gray, nucleus raphe magnus and medullary reticular formation (Willis, 1995). Theories speculating as to the action and location of endogenous pain control systems are still tentative at present, and will be discussed at length later on.

1.3.2 Sensory-discriminative component of pain

The sensory-discriminative dimension refers to the location, quality, duration and intensity of pain (Gracely, McGrath, & Dubner, 1978). Extensive empirical evidence has revealed that sensory ratings, although being affected by the physical qualities of a painful stimulus, are relatively unaffected by contextual factors (e.g., Gracely et al., 1978; Hirsch & Liebert, 1998). This is in stark contrast to affective responses to pain (see below).

1.3.3 Affective-motivational component of pain

Affective-motivational aspects refer to the unpleasant or uncomfortable nature of pain sensations, and the drive to seek pain relief (Weisenberg, Raz, & Hener, 1998). Unlike sensory components, affective components of pain are highly susceptible to psychological and (perceived or actual) environmental factors. For instance, Hirsch and Liebert (1998) examined the effects of aversive labelling of cold pressor stimuli on sensory and affective ratings of pain and pain tolerance. Affective ratings increased and pain tolerance decreased when aversive and painful-sounding labels were used, whereas sensory ratings remained the same. Pain tolerance, like pain affect, is also influenced heavily by contextual and affective-motivational factors (see *1.3.5 Behavioural reactions to pain*, p 24). Ahles et al. (1983) found that subjects attending to affective/emotional versus sensory qualities of a cold pressor task (CPT) reported higher levels of distress and pain unpleasantness (UP), despite the task being identical across groups. Therefore, attention to emotional components of the pain stimulus increased fearful expectations, and facilitated emotional processing. It has also been established that moods such as anxiety play an important role in determining pain affect and behavioural elements of pain perception (Gracely et al., 1978) (see *1.8.1 Mood modulation of pain: Anxiety and pain*, p 63).

The differentiation between affective and sensory aspects of pain has resulted in the development of separate scales measuring ‘unpleasantness/discomfort’ and ‘intensity/severity’, respectively (Price, Bush, Long, & Harkins, 1994). Although related, each scale represents a unique component of the pain experience, as demonstrated by different nociceptive stimulus response functions (Price et al., 1994;

Price, McGrath, Rafii, & Buckingham, 1983), and differential effects on the magnitude of each aspect following sensory or affective manipulations (Gracely et al., 1978). Positron emission tomography (PET) has revealed that pain UP is encoded in different areas of the cortex (anterior cingulate cortex) than perceptions of pain intensity (PI) (somatosensory cortex) (Rainville, Duncan, Price, Carrier, & Bushnell, 1997).

Clinical studies of patients who have undergone a frontal lobotomy (the disconnection of prefrontal lobes from the thalamus) dramatically demonstrate the distinction between sensory and affective components of pain, as these patients report sensory aspects of noxious stimuli but no longer appear distressed or complain about them (Melzack, 1986). Similar results have been found in patients who are congenitally insensitive to pain or who suffer from pain asymbolia (lesions to the parietal lobe and frontal cortex) (Melzack, 1986). In summary, PET, laboratory and clinical findings support the notion that pain is encoded on different perceptive dimensions in different areas of the brain and that regulation of these areas is not identical.

1.3.4 Cognitive-evaluative component of pain

Cognitive appraisal, involving the perception, recognition and judgement of sensation, is heavily influenced by an individual's assumptions or beliefs, their prior experience, and the meaning they assign to noxious stimuli (Weisenberg, 1989). An individual's appraisal or interpretation of sensory input largely governs the coping strategies they implement and the affect they experience (Weisenberg, 1989). For instance, outcomes of previous attempts at pain management influence perceptions of current ability to manage pain, and the choice of coping technique (Haerkaepaeae, Jaervikoski, & Vakkari, 1996). Appraisals of noxious stimuli involving threat, harm, or loss are usually associated with dependent coping, higher PI and greater levels of depression (Schiaffino & Revenson, 1995). On the other hand, the belief in the ability to *respond successfully* to noxious stimuli - termed self-efficacy - often results in greater persistence and more effort expended to cope with current stressors (Lackner, Carosella, & Feuerstein, 1996). Self-efficacy and the related construct 'locus of control' are examined in more detail in the next section.

Locus of control and self-efficacy

It is widely accepted that locus of control and self-efficacy are two cognitive factors that influence pain tolerance, negative affect (e.g., stress and anxiety) and choice of coping strategies (Arntz & Schmidt, 1989; Haerkaepaeae et al., 1996; Schermelleh-Engel, Eifert, Moosbrugger, & Frank, 1997). Some researchers suggest that these two factors are the most important factors in predicting long-term change for those dealing with pain disorders (Schermelleh-Engel et al., 1997). Internal locus of control differs from self-efficacy, in that the former refers to the perception that a response (behavioural/overt, cognitive/covert) can alter the outcome, whereas self-efficacy refers to the perception that the individual has the *capacity* to exert control in potentially controllable situations (Bandura, O'Leary, Taylor, Gauthier, & Gossard, 1987).

Individuals who perceive that noxious stimuli are within their control (i.e., have an internal locus of control), often experience less negative affect and display higher pain tolerance (Litt, 1988; Martin, Holroyd, & Penzien, 1990). Davison and Valins (1969) demonstrated this relationship by measuring the effects of a placebo drug (that subjects thought had analgesic qualities), on electro-cutaneous pain threshold and tolerance. Prior to taking the so-called 'analgesic', subjects underwent a shock pain threshold/tolerance test. During subsequent testing, the shock intensities were covertly halved. Subjects who were told that they had received a placebo drug perceived subsequent shocks as *less* intense and tolerated more pain than subjects who continued to believe that the drug reduced the pain of electric shocks. Thus, when attributing pain relief to their own abilities rather than an analgesic drug, subjects demonstrated a higher tolerance for electric shocks. Similarly, Hill, Chapman, Kornell, Sullivan, Saeger and Benedetti (1990) found that cancer patients taught to self-regulate analgesic medication experienced less stress, higher pain tolerance and used 50% less morphine to achieve a similar level of pain control than patients whose medication regime was controlled by hospital staff. Arntz and Schmidt (1989) state that control *per se* does not influence stimulus aversiveness, but that the meaning assigned to the controllable stimulus does. For instance, control signifies that a stimulus will not exceed tolerance levels, such that the individual is

free to attend to other external signals. Consequently, the pain is perceived as less threatening and more tolerable.

Individuals with high self-efficacy in relation to control over pain utilise more adaptive, or active coping strategies (e.g., coping self-statements, reinterpretation/ignoring sensations, distraction by increasing behavioural activities) and rely less on analgesic medication than those who feel that they do not have the ability to influence their experience of pain (Drummond & Holroyd, 2000). Therefore, self-efficacy reflects an individual's motivation to persist with aversive stimulation, and has been strongly related to outcomes such as pain tolerance (Weisenberg et al., 1998).

Coping strategies

Coping strategies can be cognitive or behavioural in nature, and involve coping self-statements, reinterpretation/ignoring sensations, cognitive/behavioural distraction, increased analgesic medication, catastrophisation and praying and hoping for a cure or relief from pain (Rosenstiel & Keefe, 1983). Distraction has proved to be the single most effective coping strategy in reducing pain-related distress and PI (Arntz & Schmidt, 1989). This is as long as the task leading to distraction results in a positive emotional outcome (McCaul, Monson, & Maki, 1992), and the level of PI is relatively mild and has risen slowly (Drummond & Holroyd, 2000; Melzack & Wall, 1982). Catastrophisation about pain, worrying, resting, hoping/wishing for a cure, and the dependence on others for coping predicts a decrease in functional status and greater levels of disability (Evers, Kraaimaat, Geenen, & Bijlsma, 1998). Ruminations about pain (e.g., 'Why me?') are usually associated with depressed mood, cognitive deficits and the use of maladaptive coping strategies such as praying/hoping and catastrophising (Schiaffino & Revenson, 1995). An unwillingness to accept one's pain is related to greater depression, disability and anxiety, and poorer adjustment (McCracken, 1998).

1.3.5 Behavioural reactions to pain

In addition to assessing experimental pain via subjective sensory and affective ratings, pain can be measured behaviourally by way of pain threshold and tolerance parameters. In fact, several researchers have argued that separate measurement of each dimension of pain (i.e., sensory, affective and behavioural) is paramount in gaining a comprehensive understanding of an individual's pain experience (e.g., Hirsch & Liebert, 1998; Melzack & Wall, 1982).

Pain threshold has been defined as "that point at which the subject just begins to feel pain in an ascending trial, or at which pain just disappears in a descending trial" (Wolff, 1978, p150). Although once viewed as a relatively objective measure of pain with high physiological loadings, pain thresholds have been found to be influenced by contextual factors (e.g., instructions - Blitz & Dinnerstein, 1968) and mood (Wolff, 1978). Nonetheless, when using rigorous methodology (e.g., excluding first trials, standardising stimulus application), the pain threshold has proven to be a highly reliable pain parameter.

Wolf (1978) defined pain tolerance as "that point at which the individual terminates noxious stimulation" (p 154), and is the highest level of experimental pain that a subject is willing to endure (Hirsch & Liebert, 1998). Pain tolerance is usually reliable (Wolff, 1978); however, as was demonstrated in Hirsch and Liebert (1998), this behavioural measure is highly susceptible to manipulation and other psychological variables. Further examples have come from Gelfand (1964), Wolff, Krasnegor and Farr (1965) and Neumann, Kugler, Seelbach and Krueskemper (1997) who found that tolerance to ultra-sound, cutaneous electrical stimulation and pressure pain differed depending on the permissiveness of instructions or nondirective suggestions given for coping with pain. These methodological manipulations had no impact upon pain threshold. Other contextually-manipulated factors such as monetary incentives (Baker & Kirsch, 1991; Blitz & Dinnerstein, 1968; Wolff et al., 1965), quota setting (Dolce, Doleys, Raczynski, Lossie, Poole, & Smith, 1986), locus of control (Kanfer & Seidner, 1973), self-efficacy (Baker & Kirsch, 1991; Stevens, 1993; Vallis & Bucher, 1986), and naturally occurring factors such as life stressors (Stevens, 1993) and personal reactivity (Kohn, Cowles, & Dzinas, 1989) have also

been demonstrated to influence pain tolerance. Thus, pain tolerance appears to have higher psychological than physiological loadings (Wolff, 1978).

In conclusion, sensory, affective, cognitive and behavioural dimensions of pain interact in complex ways to either facilitate or inhibit the subjective experience of pain. Examination of the *mechanisms* by which psychological factors modulate pain may provide explanations for these complex relationships (Chapman, 1995). Several theories addressing the issue of pain transmission will now be discussed.

1.4 THEORIES REGARDING THE TRANSMISSION OF NOXIOUS STIMULI

Three theories concerning the transmission of aversive signals have been proposed: the specificity, pattern and spinal gate control theories (Schiffman, 1990). The *specificity theory* proposes that pain is a discrete sensory modality, involving specific pain receptors in the peripheral regions of the body. These receptors transmit signals to the CNS, which are subsequently interpreted as painful. The *pattern theory* proposes that pain is determined not by specific fibres, but by the general intensity or summation of impulses travelling along afferent fibres to the CNS. Neither theory has been empirically validated, as a simple relationship between stimulus intensity and the magnitude of pain has not been found (Schiffman, 1990).

Melzack and Wall's (1965) *spinal gate control theory* is the most widely accepted and influential theory of pain transmission to date. According to this theory, two different types of nerve fibres (i.e., large diameter-myelinated and small diameter-unmyelinated) transfer nerve impulses to transmission-neurons (t-cells) in a gating mechanism within the substantia gelatinosa in the dorsal horn of the spinal cord, wherein the signals are facilitated or inhibited by interneurons prior to reaching central cells in the brain. Specifically, small diameter fibres transfer dull, burning sensations that 'turn off' the inhibitory influence of interneurons on t-cells, which in turn 'open' the gate. Conversely, large diameter fibres relay sensations of vibration and pressure that excite inhibitory interneurons and subsequently 'close' the pain gate. Signals from large diameter afferent fibres inhibit those of small diameter fibres; however, sensations from either fibre that are ongoing and of a higher

intensity are more likely to open the spinal gate, transferring painful stimuli. This theory offers an explanation regarding the progression of acute to chronic pain, as the prolonged transfer of noxious impulses results in a relatively open gate and a high intensity of pain (Schiffman, 1990). The efficacy of acupuncture, low-intensity electrical stimuli (Transcutaneous Nerve Stimulation, TENS), and other stimuli-based procedures in the treatment of clinical pain provide support for this theory (Schiffman, 1990).

Melzack and Wall also described a 'central control' component of pain perception that descends from the brain to have a profound effect on the spinal gate and transmission of noxious stimuli. They proposed that past experiences, perceptions (e.g., attention), cognitions, and emotions serve to modulate the transmission of noxious stimuli at the spinal gate by means of descending inhibitory and facilitatory influences on t-cells from the brain (Schiffman, 1990). *Pain* is said to occur when the number of sensory signals transmitted from the spinal cord to brain structures responsible for pain perception exceeds a threshold (Melzack, 1986).

1.5 ENDOGENOUS PAIN MODULATORY SYSTEMS

1.5.1 Neurophysiological circuitry

Although knowledge about pain transmission (in particular the site and mechanics of the hypothesised spinal gate) has advanced, far greater attention has been paid to factors comprising the 'central control' component of pain than the actual transmission of nociceptive signals. The detailed study of central pain modulatory factors began in earnest after it was discovered that electrical stimulation of certain sites in the brain led to analgesia (Watkins & Mayer, 1986). Since then, neurobiological circuitry and neurochemical mediators involved in endogenous systems of pain modulation have been studied comprehensively. A number of pain modulatory systems have been identified, including those that are endocrine-mediated and centrally-mediated (Watkins & Mayer, 1986). Each endogenous pain modulatory system will now be discussed.

Endocrine-mediated pain modulation

The attenuation of analgesia both in humans and animals following hypophysectomy (removal of the pituitary gland), and adrenalectomy (removal of adrenal glands) provided strong evidence for a hormonally-mediated pain modulation system (Jackson, Maier, & Coon, 1979; Watkins & Mayer, 1982). Foot-shock analgesia in rats has been traced to the pituitary gland and sympathetic-adrenal-medullary axis (Watkins & Mayer, 1986). However, front paw foot-shock analgesia and other forms of analgesia (e.g., classically conditioned analgesia) were not eliminated by the removal of the pituitary or the adrenal glands, suggesting that other pain modulation systems existed (Watkins, Cobelli, Newsome, & Mayer, 1982b; Watkins, Wiertelak, Grisel, Silbert, & et al., 1992).

Neurally-mediated pain modulation

Watkins, Mayer and colleagues (e.g., Watkins, Cobelli, & Mayer, 1982a; Watkins & Mayer, 1982; Watkins & Mayer, 1986; Watkins et al., 1992) demonstrated the existence of two neurally-mediated pain modulatory mechanisms in the CNS of animals based on different responses to front and back paw shock in rats who had parts of descending circuitry lesioned. The first neurally-mediated system to be identified inhibited pain via descending circuitry that exit the rostral ventromedial medulla (i.e., nucleus raphe magnus, reticularis magnocellularis) via the dorsolateral funiculus within the spinal cord. Therefore, lesions of the dorsolateral funiculus in the spinal cord abolished front paw foot-shock induced analgesia in rats (Watkins et al., 1982a).

Hind paw foot-shock induced analgesia was only partially abolished by lesions of the rostral ventromedial medulla, dorsolateral funiculus in the spinal cord or spinal transection, suggesting that a second neurally-mediated system existed intra-spinally, including a possible descending centrifugal pathway originating in the medulla. A variation of this intra-spinal system, where nociceptive stimuli were inhibited in the dorsal horn by noxious impulses projected from remote areas of the body, was termed diffuse noxious inhibitory controls (DNIC) by Le Bars and colleagues (Le Bars, Bouhassira, & Villanueva, 1995; Le Bars, Willer, & de Broucker, 1992).

Although likened to segmental inhibitory phenomena (e.g., conventional TENS, acupuncture - Price & McHaffie, 1988), the mechanisms of DNIC were found to be transient with a rapid onset and much shorter duration (Kakigi, 1994), and only occur with noxious heterotopic stimuli. In consideration of the temporal qualities of DNICs, Price and McHaffie (1988) concluded that these controls resembled a reflex response (Le Bars et al., 1995).

Finally, a third neurally mediated analgesic pathway involving supra-spinal structures was discovered using a classical conditioning paradigm. In addition to being abolished by lesions of the spinal dorsolateral funiculus or rostral ventromedial medulla, classically conditioned analgesia was also abolished by decerebration. Other brainstem structures such as the periaqueductal gray and periventricular gray have also been implicated in this phenomenon.

In humans, it has been proposed that the cerebral cortex modulates the sensory and affective domains of pain nociceptive input by transmitting pain-related cognitions, emotions, attention and information about past pain experiences to the reticular formation and dorsal horn, where signals are ultimately modulated (Melzack, 1986). However, involvement of the cerebral cortex in pain perception remains a contentious issue as processing of noxious stimuli is thought to be limited to the limbic system (hippocampus, amygdala), thalamus and hypothalamus in the forebrain (Willis, 1995). Specifically, limbic structures modulate affective-motivational components of pain, whilst the thalamus (which receives afferent input via neospinothalamic and spinocervical tracts) is primarily responsible for modulating sensory-discriminative components of pain in humans (Melzack, 1986).

1.5.2 Neurochemical mediators

Neural pain modulatory systems are mediated by two categories of endogenous chemicals: opioids and neurotransmitter monoamines such as serotonin, noradrenaline and dopamine (Amit & Galina, 1986). Intrathecally or systemically administered exogenous opiates (e.g., morphine) and synthetic neurotransmitters can also produce analgesia (Price, 1999).

Endogenous opioids

The analgesic effects of morphine and similar compounds have been recognised for many years; however, the discovery of opioid receptor sites and endogenous opioid peptides in the CNS and endocrine tissues has only been made in the last few decades (Rosenzweig, Leiman, & Breedlove, 1996). It is now known that morphine and endogenous ligands bind to the same receptors to modulate pain, but that only a small part of their chemical structure is the same. This necessitated the distinction between *exogenous opiates* (e.g., morphine) and *endogenous opioids* (e.g., beta-endorphins). Endogenous opioid peptides and opiate receptors are distributed throughout endocrine tissues (pituitary and adrenal glands) and neural pain modulatory circuitry in the spinal cord dorsal horn, dorsolateral funiculus, nucleus raphe magnus, midbrain, and brainstem structures (i.e., periaqueductal gray and rostral ventral medulla). Opioid peptides are also present in areas that modulate mood (i.e., amygdala, hippocampus, locus coeruleus, cerebral cortex) and the autonomic nervous system (i.e., medulla) (Reisine & Pasternak, 1996). Therefore, the target receptors of opioids lie in endocrine tissues, and the peripheral, autonomic and CNS (Drolet, Dumont, Gosselin, Kinkead, Laforest, & Trottier, 2001).

Endogenous opioids occur in at least five naturally-derived forms, including beta-endorphins, leu-enkephalins, met-enkephalins, a-neoendorphins and dynorphins (Horn & Munafo, 1997). Four opiate receptor subtypes have been identified including delta, mu (both heavily located in the periaqueductal gray), kappa (located in the spinal cord), and sigma (located in the limbic system) receptors (Pfister & Maffesoni, 1992). The function of each receptor has been associated with specific effects of opioids such as analgesia (mu, kappa, delta), euphoria (mu, delta), dysphoria and depersonalisation (sigma), and respiratory depression (mu). For instance, enkephalins and dynorphins bind to mu receptors in the dorsal horn, thus mediating analgesia in the spinal cord.

Opioids inhibit the release of pain-transmitters (Substance P) from afferent terminals to achieve an antinociceptive result. However, small doses have been found to have the opposite effect, where descending pain inhibitory systems are inhibited at the dorsal horn and medullary level, facilitating the transmission of nociceptive signals

(Gebhart, 1982; Gillman & Lichtigfeld, 1985; Simonnet & Rivat, 2003). In some cases, the affective response to pain (anxiety, anger, distress, depression) is altered by opioids but the sensation of pain is not changed (Reisine & Pasternak, 1996). A reduction in suffering can lead to marked increases in pain tolerance (Reisine & Pasternak, 1996).

Nonopioids (Neurotransmitters)

The evidence for nonopioid-mediated pain modulatory mechanisms is unequivocal in studies of endogenous pain modulation (Messing & Wilcox, 1987). Brain and spinal cord monoamines (or neurotransmitters) such as serotonin, noradrenaline and, and to a lesser extent, dopamine have been reliably implicated in pain modulation. Lesions to supra-spinal sites rich in serotonin-containing neurons (i.e., dorsal raphe nucleus) have resulted in hyperalgesia (Gillman & Lichtigfeld, 1985), and serotonin antagonists have significantly reduced SIA (Amit & Galina, 1986). Although not conclusive, noradrenergic-mediated effects on analgesia act primarily at the level of the spine. Noradrenaline is released supra- and intra-spinally to have an inhibitory effect on pain transmission (mostly via small diameter A-delta and A-beta fibres), and a facilitatory effect on the transmission of innocuous stimuli (Yaksh, 1985). Nonetheless, when the relative importance of each was assessed in animals, serotonin proved more important in the spinal transmission of nociceptive information than noradrenaline (Amit & Galina, 1986). Nonopioid-mediated pain inhibitory mechanisms originate in both spinal and supra-spinal structures such as the periaqueductal gray and dorsal raphe nucleus (Watkins & Mayer, 1986).

Neurotransmitters also interact with endogenous/exogenous opioids to influence opioid-mediated analgesia. For example, serotonin is metabolised faster when in the presence of opioids during periods of stress (Messing & Wilcox, 1987). Also, the availability of tryptophan (a precursor amino acid of serotonin) mediates (i.e., potentiates or attenuates) the analgesic effects of morphine (Gillman & Lichtigfeld, 1985). Furthermore, noradrenaline-mediated analgesia at the level of the spine is potentiated by the action of supra-spinal endogenous opioids (Gillman & Lichtigfeld, 1985).

Other substances including gamma amino butyric acid (GABA-which is found in the same neurons as serotonin in the CNS), acetylcholine, prolactin, adrenocorticotrophic hormone (ACTH), glutamate, cholecystokinin, and thyroid releasing hormones have also been implicated in nonopioid-mediated pain modulation or analgesia (Gillman & Lichtigfeld, 1985). Unlike serotonin and noradrenaline, ACTH antagonises opioid-mediated analgesia at high doses. However, this hormone has agonistic characteristics at low doses. ACTH also reverses opioid-induced secretion of prolactin.

1.6 ACTIVATION OF ENDOGENOUS PAIN INHIBITORY SYSTEMS

Environmental conditions that activate neural and hormonal pain inhibitory systems, whether opioid- or nonopioid-mediated, have been of great interest to scientists over the past 30 years. Early on, research was limited to animals and has only been extended to humans more recently (Amit & Galina, 1986). It was by way of research with animals that the phenomenon, now referred to as SIA, was discovered in three different laboratories in the 1970s (Amit & Galina, 1986). Other pain inhibitory phenomena involve baroreceptors in the cardiovascular system, and age-old counter-stimulation techniques where non-painful (i.e., acupuncture or TENS) or painful stimuli (i.e., DNIC) are applied segmentally or hetero-segmentally to the site of pain to induce analgesia. Counter-irritation is also known as *stimulation produced analgesia*. Therefore, the transmission of peripheral pain signals can be inhibited at the spinal and/or supraspinal level via a number of endogenous mechanisms.

Since psychologically activated endogenous pain inhibitory systems are the main focus of this thesis, blood pressure-mediated and stimulation-produced analgesia will be discussed briefly followed by an in-depth exploration of factors leading to SIA.

1.6.1 Blood pressure and pain

Randich and Maixner (1984) state that cardiovascular and pain regulatory systems are interrelated, whereby primary afferents from peripheral baroreceptors (in heart, lungs and arteries) synapse in the caudal medulla (or nucleus tractus solitarius), and

secondarily in various other supra-medullary structures responsible for cortical inhibition and anti-nociception (i.e., nucleus reticularis gigantocellularis, nucleus raphe magnus). Some contend that the cardiovascular-pain relationship is mediated by endogenous opioids (e.g., McCubbin, Wilson, Bruehl, Ibarra, Carlson, Norton, & Colclough, 1996). In support of this contention, opioid receptors have been located in these central sites of pain and cardiovascular regulation (Bruehl, McCubbin, & Harden, 1999). Nonetheless, opioids as sole mediators of blood pressure-derived hypoalgesia remains controversial as others have found the relationship between pain and blood pressure (BP) to be mediated in part by nonopioid mechanisms (Bruehl et al., 1999; McCubbin & Bruehl, 1994).

Beta-endorphins and enkephalins are thought to inhibit cardiovascular stress reactivity, and decrease the risk of hypertensive conditions (McCubbin, 1993; McCubbin et al., 1996). However, much of the data demonstrating an opioid-mediated association between BP and pain has been found in hypertensive animals and humans (e.g., Fontana, Bernardi, Spampinato, Boschi, De Iasio, & Grossi, 1997; Luna & Taylor, 2001; McCubbin et al., 1996; Szilagyi, 1991). It has been hypothesised that hypertensive individuals respond to stress with exaggerated cardiac output, which activates baroreflex pain dampening mechanisms, completing the baroreceptor reflex arc (France, 1999; Randich & Maixner, 1984). Alternative hypotheses state that hypertensive subjects react abnormally to stress by releasing high levels of beta-endorphins peripherally and centrally, therefore producing opioid-mediated hypoalgesia (France, 1999; McCubbin, Surwit, & Williams, 1985; McCubbin, Surwit, & Williams, 1988). In support of this, high levels of plasma beta-endorphins have been found in hypertensive individuals (Fontana et al., 1997).

More recent research, however, suggests that opioid-mediation of the blood pressure-hypoalgesia relationship may occur at other ranges of BP. For instance, a small number of studies have demonstrated a possible opioid-mediated inverse relationship between resting BP and pain sensitivity in normotensive subjects (Bragdon, Light, Costello, Sigurdsson, Bunting, Bhalang, & Maixner, 2002; McCubbin & Bruehl, 1994). However, in these studies effect sizes are generally weak and differences between placebo and opioid blockade conditions do not always achieve statistical significance. Others have found a direct relationship between pain tolerance, plasma

beta-endorphin levels and blood pressure increases in response to stress in normotensive subjects (Rosa, Ghione, Mezzasalma, Pellegrini, Basile Fasolo, Giaconi, Gazzetti, & Ferdeghini, 1988).

The inverse relationship between resting BP and pain has been replicated in other studies with normotensive human (Bruehl, Carlson, & McCubbin, 1992) and animal populations (Sun, Liu, Li, & Ingenito, 1996). Unfortunately, the neurochemical substrates involved were not assessed in these studies.

1.6.2 Stimulation-produced analgesia

Segmental Inhibition

In the case of techniques such as TENS or acupuncture, experimentally- or clinically-induced afferent pain signals mediated by small-diameter fibres are inhibited in the dorsal horn of the spinal cord by segmentally produced input mediated by A-beta or A-delta large diameter fibres. The convergence of large cutaneous afferents and nociceptive afferents onto the same pool of spinal inter-neurones exerts an inhibitory effect on nociceptive messages associated with the initial painful stimulus (Freeman, Campbell, & Long, 1983; Willer, Roby, Boulu, & Albe-Fessard, 1982a; Willer, Roby, Boulu, & Boureau, 1982b). This mechanism has been referred to as 'segmental inhibition' or 'gating', and is accounted for by Melzack and Wall's gate control theory (Melzack & Wall, 1965). Origins of segmental inhibition are indisputably situated in the spinal cord, as gating can be demonstrated both in 'spinal' animals (i.e., animals lesioned at the level of the spinal cord) and intact animals (Le Bars, Dickenson, & Besson, 1979b).

Recent evidence suggests that this local synaptic mechanism may be mediated by endogenous opioids. It has been found for example that TENS increases concentrations of beta-endorphins in cerebrospinal fluid (CSF) (Marchand, Sluka, Le Bars, & Rainville, 2004) and blood plasma (Facchinetti, Sandrini, Petraglia, Alfonsi, Nappi, & Genazzani, 1984), and can lead to a naloxone-reversible analgesia (Kalra, Urban, & Sluka, 2001; Mayer, Price, & Rafii, 1977; Woolf, Mitchell, & Barrett, 1980). The failure to reverse TENS effects with high doses of naloxone in other

studies (e.g., Freeman et al., 1983; Willer et al., 1982b) however, suggests that these results may have been induced with noxious TENS, leading instead to a DNIC phenomenon, also known to be mediated by opioids. The mechanism underlying DNIC is explained in the next section.

Diffuse Noxious Inhibitory Controls (DNIC) - Heterosegmental inhibition

The mechanism whereby a painful stimulus is inhibited by a second noxious stimulus applied to a part of the body remote from the peripheral excitatory field of the first, has been utilised for centuries to reduce pain. This mechanism is known as counter-irritation, and has more recently been characterised by Le Bars and colleagues (Le Bars, Dickenson, & Besson, 1979a; Le Bars et al., 1979b) as DNIC. Functionally, DNIC are believed to assist with the coding of incoming/competing nociceptive signals by inhibiting background noise, which may include either noxious or innocuous signals. In amplifying or 'signalling pain', the potential alarm function of nociceptive signals is augmented (Villanueva & Le Bars, 1995). DNIC also reflect a 'coding' system where the inhibition of one population of neurones and excitation of another creates a contrast within the nociceptive system, assisting with the coding of such signals (Price & McHaffie, 1988).

The last two decades have seen an expansion of research into the neural schema involved in DNIC, which have primarily been located in the spinal cord and more recently thought to be influenced by supraspinal structures. Le Bars and colleagues demonstrated that heterotopic noxious conditioning stimuli (CS)[1] powerfully inhibited activity in almost all wide dynamic range cells found in the spinoreticular and spinothalamic tracts, the spinal trigeminal nucleus, and the spinal cord dorsal horn, whilst nociceptive-specific neurones were not affected (Le Bars et al., 1979a; Le Bars et al., 1979b). Wide dynamic range neurones are so called because they are located in both deep and superficial laminae of the spinal cord, and receive input from both A- and C-fibres (Hu, 1990).

[1] In this context a conditioning stimulus refers to an initial stimulus that 'conditions' or alters a response to subsequent stimuli. No part of the DNIC protocol reflects actual conditioning.

The most compelling evidence that DNIC recruit a complex spinal-supraspinal-spinal loop has come from 'spinal animals' whose spinal cord had been transected at the cervical level (Le Bars et al., 1979b). In these animals, wide dynamic range neurones responded to both A- and C-fibre input such as touch, heat, pressure and pinch. However, none of these responses were inhibited by noxious CS, suggesting that DNIC are not confined to the spinal cord and that ascending signals must reach supraspinal structures in order to activate inhibitory influences. The lack of DNIC influences in patients with tetraplegia (i.e., paralysis of all four limbs stemming from clinically complete spinal cord transection) and Wallenberg's syndrome (in which lateral elements of the medulla die due to lack of blood supply) also supports the role of brainstem structures in DNIC (Villanueva & Le Bars, 1995). Further evidence that DNIC recruit a complex system involving supraspinal structures can be found in a set of studies conducted by Bouhassira and colleagues (Bouhassira, Bing, & Le Bars, 1990; Bouhassira, Bing, & Le Bars, 1992a; Bouhassira, Bing, & Le Bars, 1993; Bouhassira, Chitour, Villaneuva, & Le Bars, 1995; Bouhassira, Villanueva, & Le Bars, 1992b).

Some sceptics have attributed DNIC to the distracting nature of the painful stimuli, rather than endogenous pain inhibitory mechanisms. The most compelling evidence against these criticisms came from research with unilateral thalamic or parietal cortical lesioned patients, in which noxious electrical CS substantially inhibited the nociceptive flexion reflex (RIII) in the absence of subjective perceptions of pain (de Broucker, Cesaro, Willer, & Le Bars, 1990). That is, RIII inhibition could not be attributed to distracting influences of the remotely applied noxious stimulus as these patients typically perceived no pain. In other evidence against the distraction hypothesis, discriminative ability on control tasks (arithmetic subtraction) failed to change during heterotopic noxious CS (Plaghki, Delisle, & Godfraind, 1994; Talbot, Duncan, & Bushnell, 1989). Furthermore, distraction does not explain how noxious thresholds (such as dental pain thresholds) rise in response to a heterotopically applied stimulus, whereas tactile thresholds (i.e., upper lip sensitivity) remain relatively unchanged (Pertovaara, Kemppainen, Johansson, & Karonen, 1982).

Research demonstrating DNIC in both animals and humans is discussed below:

Animal studies: Le Bars and colleagues found that a variety of noxious CS (e.g., pinch, heat), when applied outside of the excitatory receptive field of the test stimulus (TS), inhibited both noxious and innocuous TS in animals (e.g., Le Bars et al., 1979a; Le Bars et al., 1979b). However, the application of innocuous stimuli (e.g. stroking, jets of air, warm water) to remote areas failed to inhibit test responses. These findings have been reliably replicated in many types of mammals (cats - Duggan, 1985; rats - Hu, 1990).

In an inventive animal model of DNIC in chronic pain states, Kraus, Le Bars and Besson (1981) measured the threshold of vocalisation in rats to electrical TS applied to the tail in the presence of phenylbenzoquinone (PBQ). The authors suggested that the visceral, dull pain induced by PBQ resembled pain experienced by chronic pain patients. A rise in vocalisation thresholds when PBQ was administered suggested that chronic pain could act as a heterosegmentally-applied painful stimulus and mobilise DNIC to inhibit acute pain – providing an explanation for higher pain thresholds found in some chronic pain patients when compared with pain-free subjects.

Human studies: As in animals, DNIC phenomena have been reliably demonstrated in humans. For instance, Talbot, Duncan, Bushnell and Boyer (1987) applied non-painful and painful heat (42-48°Celsius) to the faces of subjects before, during and after a noxious hand CPT (5 °Celsius). The CPT powerfully increased pain thresholds and decreased subjective pain ratings for noxious and innocuous heat stimuli. Furthermore, DNIC phenomenon continued to inhibit the TS beyond the application of the CPT. Similarly, Price and McHaffie (1988) applied a noxious (47-51°Celsius) and innocuous (43°Celsius) heat stimulus to each subject's abdomen and one of their feet. Noxious (15 mA) and innocuous (6-12 mA) electrical impulses were simultaneously applied to the ankle of the contralateral foot. Subjective pain reports demonstrated that only the noxious CS inhibited both noxious and innocuous TS. Witting, Svensson, Arendt-Nielsen and Jensen (1998) extended these findings by measuring the *area* and *intensity* of capsaicin-induced pain (both spontaneous and

brush-evoked) on the forearm, during a CPT applied to the contralateral forearm. DNIC inhibited the intensity but not the *area* of both types of pain, suggesting that inhibitory effects on spinal neurones were specific and not generalised.

Opioid and nonopioid mediation of DNIC: Research investigating the effect of opioids on DNIC found that a low dose of morphine blocked these inhibitory effects in rats and humans (Villanueva & Le Bars, 1995; Willer & Le Bars, 1995). Specifically, intrathecal morphine blocked DNIC by segmentally depressing nociceptive messages coming from all convergent neurones, preventing the spinal initiation of DNIC (Villanueva & Le Bars, 1986). Others found that DNIC were blocked by opioid antagonists such as naloxone and naltrexone (Villanueva & Le Bars, 1995; Willer, Le Bars, & de Broucker, 1990; Willer, Roby, & Le Bars, 1984), providing credence to the notion that supraspinal structures responsible for endogenous opioid analgesia (i.e., periaqueductal gray, rostral ventromedial medulla, nucleus raphe magnus) indirectly modulate this inhibitory loop, and that DNIC are mediated by opioids (Villanueva & Le Bars, 1995).

Although exploratory, there is evidence that nonopioid substrates may also mediate DNIC phenomena. For instance, animals lacking in 5-hydroxy-tryptamine, or serotonin, failed to activate DNIC in response to noxious CS suggesting that DNIC may also be mediated by descending serotonergic pathways (Chitour, Dickenson, & Le Bars, 1982; Le Bars et al., 1979b).

1.6.3 Stress-induced analgesia (SIA)

Knowledge about the activating factors of SIA has advanced considerably. Intensive investigation has not only uncovered various factors that activate SIA, but has also identified conditions that mobilise either opioid- or nonopioid-mediated analgesia. However, prior to a discussion of these factors in the context of (first) animal and (second) human research, 'stress' will be defined, and the function of SIA and techniques of measuring analgesia will be described.

Stress defined

Historically there has been a lack of consistency in the literature with regard to the definition of stress. For the purposes of this research, a *stressor* is defined as "any stimulus, internal or external to an individual, that poses a real or perceived threat to the individual's homeostasis" (Drolet et al., 2001, p 731). A *stress response* involves a range of defensive behavioural and physiological reactions to the stressor that are necessary to protect the integrity of the individual (Amit & Galina, 1986; Drolet et al., 2001). Finally, *stress* refers to the outcome of an interaction between the stressor and accompanying stress response.

The function of SIA

SIA is activated automatically and enables the organism to adapt to a changing environment without falling prey to events that may threaten its survival. Specifically, the suppression of pain reduces distracting noxious sensations enabling the organism to learn the 'right' response (e.g., to remain and defend themselves or to escape quickly) in a threatening situation (Bandura, Cioffi, Taylor, & Brouillard, 1988; van der Kolk, Greenberg, Boyd, & Krystal, 1985). Also, analgesia may lessen pain-related behaviour in situations in which it is vital to remain still and not attract the attention of the aggressor (Amit & Galina, 1986; Molina, Heyser, & Spear, 1994). Thus, in a highly threatening situation SIA may lessen the physiological and emotional impact of the stressor, promoting defensive behaviour, survival and recovery through healing later on (Bandler & Shipley, 1994; Fanselow, 1986).

Opioid-mediated analgesia appears to be associated with more intense and extended noxious stimuli, and thus is activated to protect organs/structures important for survival in a life-threatening situation (e.g., front paw shock elicits opioid-mediated analgesia in rats who assumes a boxing-position when engaging in self-defence) (Amit & Galina, 1986; Watkins et al., 1982b). Furthermore, the ability to reinstate opioid analgesia many hours after experiencing an uncontrollable stressor (Flor, Birbaumer, Schulz, Grusser, & Mucha, 2002) may enable an organism to remain alert, and ready to respond (Maier, 1986). However, because all physiological systems are interdependent, the prolonged reliance on endogenous analgesia has

detrimental effects on other systems. For example, extended reliance on opioid analgesia has deleterious effects on the immune system by impairing cellular components and increasing vulnerability to infections (Bandura et al., 1988). Moreover chronic opioid activation can result in opioid receptor desensitisation and/or down-regulation, rendering endogenous pain inhibitory mechanisms less effective (Bragdon et al., 2002).

Measuring SIA

Analgesia in animals has been measured by tests of reflexes and of behavioural escape or avoidance of a noxious stimulus. The endogenous neurochemical mediators of analgesia have been investigated by the use of opioid agonistic and antagonistic substrates within these and other paradigms with humans. Finally, the surgical transection of neural tracts and removal of analgesic structures has helped to identify anatomical sites of analgesia.

Empiricists have found that parameters of stimulus intensity, duration, timing and anatomical locale alter the activation of endogenous analgesic reactions. Therefore, the choice of pain induction method and test of analgesia is important to reliably and validly make deductions about the factors that activate SIA. Each experimental method is briefly discussed below.

Reflex tests: The most common measure of analgesia involves behavioural tests of a motor reflex, such as tail-flick, flinch-jump (or jump-escape), vocalisation, writhing, and paw-lick to aversive stimuli (i.e., radiant heat to the tail/paws via a hot-plate; electrical shocks/pinches to the body) (Amit & Galina, 1986). Responses are triggered by a neuronal loop through the spinal cord; therefore, the latency of the behavioural response or *behavioural threshold* to the aversive stimuli is taken as the measure of analgesia (Amit & Galina, 1986). A 'behavioural threshold' is the lowest intensity of the stimulus to which an animal makes a response. Reflex tests have a high level of construct validity because behavioural thresholds of animals to thermal and electrical stimuli are similar to human thresholds.

Operant conditioning paradigms: In an operant paradigm, the animal learns to execute a behavioural response to avoid an aversive stimulus. For example, an animal may learn to terminate an electric shock transmitted to their foot by depressing a lever, or by escaping to another compartment where shocks are not transmitted. Alterations in the animal's response signify changes in pain threshold and levels of analgesia. These responses involve learning and hence are thought to be mediated centrally, rather than just at the level of the spinal cord (Amit & Galina, 1986).

Although tests of reflexes and operant conditioning offer reliable measures of analgesia, these tests confound the concept of pain and stressor. Because these procedures are both painful and aversive to the animal, it is difficult to distinguish the factors responsible for the activation of SIA. The methodology utilised in human research, where pain is measured after a stressful stimulus (e.g., cognitive stressor), has partly resolved this difficulty.

Opioid antagonists: Endogenous opioid activation has been investigated with the use of opioid antagonists, which work by displacing endorphins from their receptors, thereby altering the function of opioids (Volavka, Anderson, & Koz, 1982). *Naloxone* and *naltrexone* are amongst the most common antagonists used. Naloxone is a competitive antagonist at some, but not all opioid receptors, unless administered in high doses (Amit & Galina, 1986). In contrast, *naltrexone* has been classified as a relatively pure antagonist, displacing agonists and non-selectively binding to all opioid receptors (Gonzalez & Brogden, 1988). Naltrexone has several other advantages over naloxone. For instance, naltrexone is more orally efficient (e.g., rapid absorption rate, where peak plasma levels are reached in 60 minutes; higher percentage reaches systemic circulation) and has a longer duration of action than naloxone (Kleber, 1985; Reisine & Pasternak, 1996). See p 115 for more information regarding naltrexone and its use in the present research.

Importantly, the use of opioid antagonists led to the discovery of an nonopioid-mediated analgesic state both in animals and humans (Watkins et al., 1992). Although proving useful, opioid antagonists can have unexpected dose-response effects on neurochemical release. For instance, opioid antagonists, when

administered in large doses, may lead to agonistic effects (i.e., opioid-like activity) or to nonopioid-mediated effects such as the release of catecholamines (Kleber, 1985). Therefore, careful consideration must be given to dosage when using opioid antagonists to indirectly assess chemical mediation of SIA.

Cross-tolerance: Opioid or nonopioid mediation of analgesia has also been inferred by inducing cross-tolerance to opiates such as morphine. For example, cross-tolerance has been induced by administering morphine over a number of days, after which the opiate no longer has an analgesic effect (Amit & Galina, 1986). An environmental stimulus (known to activate SIA) is subsequently presented, and from the absence of analgesia it can be inferred that SIA under these conditions is opioid-mediated. On the other hand, if levels of analgesia are undisturbed, then nonopioid-mediated SIA can be presumed. One precaution with the use of morphine is that this exogenous opiate has been found to block opiate-mediated DNIC when administered in low doses (Le Bars et al., 1992; Willer & Le Bars, 1995).

Lesions: The source and route of analgesic substrates have been identified via surgical lesions of major peripheral and central sites of release, including the pituitary/adrenal glands and the CNS, respectively. Hypophysectomy, adrenalectomy, or removal of the adrenal medulla are used to determine whether analgesia is hormonally or neurally-mediated (Roper, 1988). Hormonally-mediated analgesia is implied if any of the above mentioned procedures results in the significant attenuation of analgesia in SIA-producing conditions (Amit & Galina, 1986). In cases of neurally-mediated analgesia, surgical lesions are confined to the dorsolateral funiculus of the spinal cord to determine whether intraspinal or centrifugal (descending from the brain to the spinal cord) pathways are involved in pain inhibition (Watkins et al., 1992). These procedures are used infrequently in animal research, as they are intrusive and often irreversible.

Animal Research

Data from animals suggests that various factors govern the induction of SIA, whether nonopioid- or opioid-mediated. Of particular relevance to the activation of SIA in humans is the controllability and predictability of aversive events. Therefore, the

effects of these variables on analgesia in animals will be presented in detail prior to a discussion of human literature. The reader is referred to Amit and Galina (1986) for a review of all other factors.

Control over stressors: The failure of classical stressors (e.g., ether vapours, horizontal oscillation) to increase pain thresholds (Hayes, Bennett, Newlon, & Mayer, 1976) indicated that physiological stress alone was not the essential factor in endogenous pain inhibition. Specifically, prolonged exposure to intermittent or uncontrollable noxious stimuli led to opioid-mediated naloxone-reversible analgesia that was cross-tolerant with morphine (Amir & Amit, 1978; Amir & Amit, 1979; Drugan & Maier, 1986; Galina, Rogan, & Amit, 1983; Girardot & Holloway, 1984a; Girardot & Holloway, 1984b; Grau, Hyson, Maier, Madden, & Barchas, 1981; Lewis, Cannon, & Liebeskind, 1980; Lewis, Sherman, & Liebeskind, 1981; Lewis, Termin, Nelson, & Liebeskind, 1984; Maier, Drugan, & Grau, 1982). In contrast, aversive events from which an organism could escape or avoid often resulted in little or no deficits in response-learning, producing naloxone-insensitive analgesia. Furthermore, exposure to uncontrollable shocks resulted in analgesia that was reinstated following brief re-exposure to uncontrollable conditions 24 hours later (Grau et al., 1981; Hemingway & Reigle, 1987; Jackson et al., 1979; Maier et al., 1983). Reinstated analgesia did not occur in animals submitted to controllable aversive events. After discovering that only inescapable shocks led to opiate analgesia, Maier (1986), concluded that it was not the *physical qualities of the stressor*, but *what an organism learnt about a stressor* that determined the type of analgesia.

Since this discovery, it has been widely demonstrated that *inescapable* or *unavoidable* aversive events lead to opioid-mediated SIA, and that this form of analgesia is often accompanied by a deficit in escape/avoidance learning (in the same or different environment) (e.g., Akil, Madden, Patrick, & Barchas, 1976; Maier, 1986; Maier et al., 1982). This behavioural correlate resembled characteristics of Seligman's concept of *learned helplessness* (LH) triggering speculation as to whether psychogenic and environmental factors producing helplessness might also activate opioid analgesia (Maier, 1986; Maier et al., 1982; Maier et al., 1983). The cataleptic effects of opiates (Mineka & Hendersen, 1985), and the prevention of

opioid-mediated SIA and LH with a high dose of naloxone or naltrexone (Hemingway & Reigle, 1987; Hunziker, 1992; Teixeira, Pereira, & Hermini, 1997; Whitehouse, Walker, Margules, & Bersh, 1983) or anti-anxiety agents (Maier, 1990) suggests that endogenous opioids may underlie the learning deficits and immobilisation observed in animals displaying LH. Nonetheless, a causal relationship between opioid-mediated SIA and LH is difficult to determine from this data.

Predictability of stressors: An aversive event is *predictable* if a conditioned stimulus predicts the occurrence or non-occurrence of the unconditioned stimulus (Seligman, Maier, & Solomon, 1971). In an extensive review of the animal literature, Abbott, Schoen and Badia (1984) concluded that predictable (or signalled) shocks were less physiologically aversive than unpredictable shocks, leading to fewer stomach lesions, less weight loss and lower secretions of gastric acid. Moreover, predictable shocks led to less distress vocalisations and were preferred over unpredictable shocks when the duration of the stress was brief and not intense (Abbott et al., 1984).

The variations in physiological and behavioural responses to predictable versus unpredictable aversive stimuli were originally attributed to the activation of SIA (Abbott et al., 1984). For example, analgesia was thought to reduce the intensity of a signalled shock, subsequently reducing distress vocalisations, gastric acid secretions and other ulcer forming substances, whilst increasing an organism's preference for predictable shocks (Abbott et al., 1984). There is some support for this interpretation. For instance, Fanselow (1979) found an opiate-mediated SIA biased preference towards predictable shocks. In this experiment rats were injected with either saline or naloxone subsequent to being trained for 90 minutes to recognise cues identifying the signalled condition. Only saline-injected rats indicated a significant preference (i.e., more time in the signalled compartment than their naloxone counterparts) for cues identifying predictable shocks (Fanselow, 1979). These results suggest that naloxone interfered with preferences for predictable shocks by blocking opioid-mediated SIA elicited by the signal. Fanselow and Baackes (1982) suggested that the activation of opioid-mediated pain inhibition in response to a signalled aversive event has survival value, in that analgesia diverts attention and energy from a (potential) wound, promoting defensive behaviour against the threat.

Evidence suggesting that signal preference is *not* primarily influenced by opioid-mediated SIA draws attention to the differing time course of both phenomena. For instance, opioid-mediated SIA habituates over time whereas preference strengthens and remains potent for a considerable number of shocks. Also, signal preference and SIA vary under different conditions (e.g., the strong stimulation required to activate opioid-mediated SIA is not necessary to influence signal preference) (Abbott et al., 1984). Therefore, it has been suggested that opioid-mediated SIA may increase the initial attraction to signalled aversive events, but that subsequent responses are nonopioid-mediated (Abbott et al., 1984).

Analgesic responses can also be automatically elicited following exposure to stimulus-related cues (Seligman et al., 1971). In demonstrating evidence of classically conditioned analgesia, MacLennan, Jackson, and Maier (1980) found that rats became analgesic when placed in the shock apparatus for 5 seconds, after experiencing 80 tail-shocks (one per 60 seconds) over 6 sessions in the same apparatus. Similarly, Chance and Rosecran (1979) identified conditioned analgesia (tested via tail flick latencies) in rats when administering grid-shocks. Hayes, Price, Bennett, Wilcox, and Mayer (1978) extended these findings when they discovered that conditioned analgesia was naloxone-reversible and cross-tolerant to morphine, and thus was mediated by endogenous opioids. Conversely, there is evidence suggesting that conditioned analgesia arising from predictable aversive events may not be mediated by endogenous opioids. For instance, Guile and McCutcheon (1984) found that the attenuation of vocalisations and ulceration in the signalled group was not affected by naltrexone. Other data shows that rats respond similarly to signalled and stronger unsignalled shocks (Miller, Greco, Vigorito, & Marlin, 1983).

Predictability regulates the release of ACTH from the anterior pituitary, suggesting a possible pathway by which hormonal opioids could be released (Davis & Levine, 1982). Nonetheless, the suggestion that conditioned SIA is mediated hormonally does not appear to be supported, as conditioned opioid analgesia is not attenuated by the removal of the pituitary or adrenal glands, and is therefore more likely to be mediated neurally (Watkins et al., 1982b; Watkins et al., 1992).

In conclusion, although evidence for signal preference and conditioned analgesia is strong, the neurochemical substrates mediating both effects are yet to be clarified in animals.

1.7 STRESS-INDUCED ANALGESIA (SIA) IN HUMANS

In comparison with animal literature, research exploring the activation of SIA in humans is sparse (Bandura et al., 1988). Moreover, the lack of control over an aversive event appears to be noxious in humans, leading to *more* pain not less. In instances where uncontrollable stressors do lead to analgesia in humans, the stressor seems to be more intense, threatening, longer in duration and entail a realistic manipulation of 'lack of control'.

In the following section, laboratory and clinical pain studies in which uncontrollable stressors increase pain, and the apparent contradictions between human and animal research will be addressed. Next, these findings will be contrasted with human data that is commensurate with SIA observed in animals, including findings from 'real-life' stressors. Finally, the impact of stressor predictability, and interactive influences of 'control' and 'predictability' on analgesia will be discussed.

1.7.1 Lack of control: Pain sensitisation

Laboratory-induced pain

Actual/perceived control: In an extensive review, Arntz and Schmidt (1989) defined numerous different types of control over aversive events, all of which were found to have varying effects on endogenous pain inhibition. Each type of control (shown in italics) is defined and the resulting effects on pain perception are briefly reviewed.

The *self-administration* of a painful stimulus was preferred to stimuli administered by an experimenter in a study conducted by Weisenberg, Wolf, Mittwoch, Mikulincur and Aviram (1985). The two techniques in this study did not vary in their effect on subjective pain reports; however, the manipulation of control was reportedly weak (Arntz & Schmidt, 1989). Others demonstrated a more positive

effect of self-administration on pain perception. For instance, Lepanto, Moroney and Zenhausern (1965) found that subjects who were unable to control the termination of an aversive heat stimulus reported lower heat pain thresholds.

An increase in pain tolerance was observed among subjects who had *instrumental control* over the noxious stimulus i.e., they could, or perceived they could avoid, escape from, reduce or alter the stimulus (Arntz & Schmidt, 1989; Geer & Maisel, 1972; Rosenbaum, 1980). Studies examining the effects of *locus of control* on pain tolerance echoed these findings, in that subjects who perceived that they could control their surroundings were able to tolerate painful stimuli longer than those attributing control to external sources (Davison & Valins, 1969; Kanfer & Seidner, 1973). Also, instrumental control either resulted in less subjective impact or did not differ from having no control (Arntz & Schmidt, 1989). Conversely Weisenberg et al. (1985) found that instrumental control over the painful stimulus was related to more pain. However, their manipulation of control over pain and definition of the controlling response lacked validity (Arntz & Schmidt, 1989).

Potential control over a noxious stimulus is where a subject has a controlling response available to them, but they do not use it. An example of potential control can be found in a CPT where a subject is told they can remove their hand from the water if they need to, but they do not. Research has found that when subjects are given the option to use a controlling response they tolerate more pain (Kilminster & Jones, 1986). However, the effects on pain tolerance and intensity become less clear when subjects are urged not to use the controlling response (Arntz & Schmidt, 1989). The impact of 'potential' control on noxious stimuli has been made salient in studies where a subject's control is removed. Staub, Tursky and Schwartz (1971) found that by removing a subject's control over shock intensity, they reported higher PI and tolerated less pain than subjects who never had control in the first place.

Despite the benefits on pain perception, actual or perceived control over a noxious stimulus has been found to have deleterious effects on physiological arousal and PI when a response becomes too difficult or the outcome of the response is no longer easy to predict (Houston, 1972; Litt, 1988). For example, Litt (1988) found that subjects with high levels of perceived control over the termination of a CPT

experienced greater PI than those with low perceived control when they could not end the task promptly. It was suggested that subjects high in internal locus of control altered their perceptions of control after not being able to control the aversive stimulus, thereby heightening levels of distress and perceived PI. Litt (1988) suggested that a subject's perceived ability to modify the painful stimulus was one factor that mediated the effect of perceived/actual control on the experience of the noxious stimulus.

In summary, it is clear that control over an aversive stimulus (whether *actual* or *perceived*) increases pain tolerance. However, this is only the case when there is a high chance that a subject will succeed in controlling the noxious event. Effects of control on subjective pain are less consistent.

Self-efficacy: As previously noted, a closely related cognitive variable that mediates pain tolerance and PI is *self-efficacy*. Bandura et al. (1987) defined perceived self-efficacy as "...a person's judgement of their capabilities to *execute* a given level of performance and to exercise control over events" (p 563). While *perceived control* refers to the availability of a controlling response over an event, *self-efficacy* refers to an individual's confidence in carrying out that response (Litt, 1988). Research into the general effects of self-efficacy on the experience of pain is limited, and even less is known about the neurochemical mechanisms (opioid or nonopioid) by which self-efficacy moderates pain.

Litt (1988) investigated how self-efficacy and perceived control interacted to impact upon experimental PI and tolerance. Perceptions of efficacy regarding the control of sensations arising from a perceivably controllable or uncontrollable stressor (i.e., CPT) were manipulated via performance-related feedback about tolerance of the cold water. Self-efficacious subjects tolerated the CPT for longer periods of time, indicating that self-efficacy mediated the coping behaviour executed by subjects. Furthermore, self-efficacy mediated the effects of perceived control on pain tolerance, in that self-efficacious subjects who perceived that they had control over termination of the aversive stimulus tolerated the CPT for the longest time. Surprisingly, it was perceived control and not self-efficacy that influenced subjective reports of pain, where subjects in 'controllable' conditions experienced greater

perceived pain (Litt, 1988). Litt explained that subjects in the perceived control condition may have become distressed at not being able to terminate the CPT at the time the first pain rating was made (30 seconds into the task). Self-efficacy typically influences pain tolerance but not PI (Baker & Kirsch, 1991; Dolce et al., 1986; Vallis & Bucher, 1986), as self-efficacy represents a measure of behavioural intention or active coping as reflected in pain tolerance.

A possible explanation as to why self-efficacy was not associated with subjective reports of pain is that self-efficacy ratings usually refer to expectations about *performance or pain tolerance*, and not the *regulation of PI* (Litt, 1988). Stevens (1992) and others (e.g., Ohlwein, Stevens, & Catanzaro, 1996) addressed this hypothesis by assessing the relationship between *self-efficacy for regulating PI* and finger pressure pain. Contrary to expectations, no relationship was found between these variables. However, the null finding was attributed to a poorly defined measure of self-efficacy, and a demand for pain endurance rather than pain regulation. After addressing these methodological shortcomings, Stevens (1993) found that self-efficacy for regulating PI did predict finger pressure pain. Similarly, Reese (1983) found that self-efficacy influenced both pain tolerance and ratings of pain in subjects trained in various pain coping techniques. Specifically, self-efficacious subjects experienced lower PI, higher pain thresholds and tolerated the CPT for longer than their self-inefficacious counterparts. In sum, these results suggest that whilst perceived self-efficacy leads to greater endurance and active coping with pain (i.e., pain tolerance), the effects on PI are unclear due to methodological shortcomings. Furthermore, PI appears to be confounded with pain tolerance in many of these studies.

In a unique study, Ohlwein et al. (1996) investigated how self-efficacy may interact with temporal context (fixed/set duration or open interval pain stimulus) to mediate pressure pain tolerance and intensity. Contrary to expectations, self-efficacy relating to pain endurance did not maximise performance during the open interval pain stimulus, and expectations regarding the regulation of PI did not affect pain reports during the fixed interval stimulus. A number of factors may have overridden the effect of self-efficacy on pain in both contexts, including incentive/experimenter demand to endure pain, tolerance ceiling for an insufficiently intense pain stimulus,

weak manipulations of the relationship between expected coping and pain in each context and/or a discrepancy between expectations and actual experience (and resulting emotional distress) (Ohlwein et al., 1996). Interestingly, subjects in the fixed interval context expected less pressure pain, suggesting that their coping efforts would be directed towards regulating instead of tolerating pain.

To date, Bandura and colleagues (1988; 1987) remain the only ones to have investigated the role of opioid and nonopioid substrates in the cognitive control of pain. In their first study, subjects were either trained in cognitive pain coping strategies (self-efficacious subjects), administered a so-called 'analgesic' drug which was actually a placebo (external pain relief) or they waited to complete repeated cold pressor pain tolerance tasks (control group) (Bandura et al., 1987). Prior to the CPT, subjects in each condition were administered an injection of either saline or naloxone. They rated their perceived ability to *withstand* and *reduce* cold pressor pain before and after each CPT. Perceived self-efficacy to *withstand pain* was positively associated with pain tolerance regardless of experimental condition, suggesting that the more a subject believed they could tolerate pain, the more they actually did. However, perceived ability to *alleviate pain* was only associated with longer pain tolerance in groups relying on internal coping skills (cognitive copers and controls). With regards to opioid activation, Bandura et al. (1987) found that saline 'cognitive copers' were significantly more able to tolerate the cold pressor stimulus than their naloxone counterparts. Similar effects were found for the placebo medication group; however, the effect of naloxone was less pronounced. Progressive increases in pain tolerance in 'cognitive copers' under an opioid blockade suggested that nonopioid mechanisms were also contributing to pain control.

In a related study, Bandura et al. (1988) investigated cognitive conditions that led to the activation of endogenous opioids. Importantly, this study did not confound the stressor (math task) with the measure of pain (CPT). Specifically, maths items were presented at a speed controlled by the subject or by the experimenter (whereby conditions strained or exceeded the cognitive capacity of each subject). Following completion of the mathematical problem-solving session, subjects received either a saline or naloxone injection, at which point pain tolerance was assessed during a number of CPTs. Bandura et al. (1988) found that subjects in the low control

condition who had received naloxone experienced more physiological arousal (heart rate), subjective stress, mental strain and lower pain tolerance than their saline counterparts. In contrast, pain tolerance in the perceived control condition was not affected by opioid blockade, indicating no evidence of opioid activation. Concurring with several lines of evidence (Holroyd, Penzien, Hursey, Tobin, Rogers, Holm, Marcille, Hall, & Chila, 1984; Reese, 1983), high control was associated with high pain tolerance.

At first glance, the lack of opioid activation in the high control condition in this study appears to contradict results found earlier by Bandura et al. (1987), where opioids were activated in efficacious 'pain copers'. On the contrary, Bandura suggested that in the event that pain could not be managed effectively (as is often the case with cold pressor pain), stronger pain control efficacy would eventually lead to more distress and opioid activation. A parallel can be drawn between opioid activation in Bandura's low control condition and opioid analgesia in animals exposed to inescapable stress.

Clinical pain

Acute clinical pain: Research exploring the inhibition of acute pain has primarily focussed on pain during childbirth and dental procedures.

As in laboratory studies, a perceived lack of control over childbirth was associated with aversive outcomes such as greater pain and heavier reliance on medication during labour. For instance, Brewin and Bradley (1982) found that women who had attended preparatory classes on childbirth tended to perceive that they and hospital staff members had control over labour-related discomfort and labour duration. These women also tended to experience less pain and discomfort during actual childbirth. Manning and Wright (1983) investigated the effects of self-efficacy on time in labour without medication and use of medication during childbirth. Perceived self-efficacy regarding pain control was found to be a strong predictor of the time spent in labour without medication (pain tolerance), and actual use of medication (Manning & Wright, 1983). In summary, perceptions of control over labour resulted in less pain and discomfort, less reliance on medication and more time in labour without

medication. Unfortunately, none of these studies investigated the substrates involved in endogenous pain control during childbirth.

Similarly, when dental patients possessed more control over surgical procedures they tended to experience less pain and discomfort. For instance, Thrash, Marr and Boone (1982) found lower levels of discomfort and pain in patients who could communicate their level of discomfort and control dental proceedings by illuminating a red light, than patients who could not. Thus, perceived control mediated pain control; however, the substrates involved were not investigated. Decreasing the uncertainty surrounding dental procedures can be just as effective in modulating the intensity of pain when compared to perceived control (Arntz & Schmidt, 1989). To illustrate, Wardle (1983) found that dental procedural information (including the kind of sensations to expect) was as effective in modulating pain as allowing patients to control proceedings by signalling the dentist to stop if they became distressed.

In contrast with other dental research, Chaves and Brown (1987) found that a lack of perceived control and catastrophisation, or exaggerating about the fearful aspects of dental procedures, led to increases in stress/anxiety but not pain. However, trends in their results suggested that the more confident a patient perceived themselves to be in controlling pain, the more predictable procedures and sensations were and the less pain and discomfort was experienced during dental surgery.

Although not directly manipulating control or predictability during painful dental surgery, Gracely, Dubner, Wolskee and Deeter (1983) found that naloxone significantly increased pain ratings following extraction of an impacted molar. Those who received a placebo analgesic also experienced an increase, but not a complete resurgence, of pain after naloxone. This suggested that placebo analgesia is both mediated by opioid and nonopioid mechanisms.

In conclusion, studies have found that perceived control, self-efficacy and predictability often lead to less discomfort and pain in acute clinical pain. However, very few studies have investigated the neurochemical mechanisms by which these factors modify pain. Hence, the substrates by which acute clinical pain is modulated remain unclear.

Chronic pain: Individuals suffering from intractable or chronic pain disorders often experience depression and anxiety resulting from perceptions that their pain is uncontrollable and unpredictable (Craig, 1989). According to the notion of LH, a perceived lack of control should activate endogenous pain inhibitory systems, thereby reducing pain in chronic pain patients. On the contrary, it has been demonstrated that in patients with low self-efficacy (relating to the capacity to reduce pain), the belief that pain is controlled by external influences and an ensuing display of helpless behaviour is related to *lowered* pain tolerance (McCracken, 1998) and *higher* reports of PI in chronic pain patients (Schiaffino & Revenson, 1995). Nonetheless, these relationships do not imply causality as high levels of pain may also lead to low self-efficacy regarding pain regulation.

Holroyd (1984) demonstrated the effects of self-efficacy on recurrent tension headache pain by providing bogus feedback to headache sufferers as to their success (high or low) in reducing pain with an electromyographic (EMG) biofeedback technique. Regardless of whether subjects decreased or increased EMG activity, subjects receiving high success feedback experienced increased perceived self-efficacy and locus of control, in addition to reductions in headache complaints and reliance on medication. Similarly, when cancer patients were granted control over morphine administration, they typically used 50% less morphine to achieve similar levels of pain relief, and developed a tolerance to exogenous opiates much more slowly than patients whose medication was controlled by hospital staff (Hill et al., 1990).

Contradiction between human and animal research

The majority of human studies reviewed herein suggest that higher levels of perceived control and self-efficacy are related to greater pain tolerance, and in cases of acute and/or chronic pain, less pain and distress. In contrast, animal research indicates that pain inhibitory systems are activated in the event that aversive conditions are uncontrollable. Although seemingly irreconcilable, these differences have been attributed to varying experimental paradigms, where 'control' is associated with different consequences for humans versus animals (Bandura et al., 1987).

In animal research 'control' means that the animal can terminate the stressor, or promptly escape from the situation. 'Control' in human studies may lead to extended exposure to the stimulus which increasingly tax the subject's ability to cope. For example, a self-efficacious individual may increase engagement in an activity, and in turn generate more pain and distress. It is possible that the stressor, or pain generated from sustained endurance may eventually overwhelm the individual's capacity to cope – at which time opioid-mediated pain inhibitory systems are activated.

Bandura et al. (1987) suggested that opioid mechanisms are activated if the response becomes too difficult, or the outcome is no longer easily predicted or controlled. Nonopioid mechanisms are presumed to be active until coping begins to fail, a time at which the endogenous opioid system is activated (Bandura et al., 1987). This explanation is consistent with the finding that losing control over a stressor is more physiologically taxing than never having had control in the first place (Staub et al., 1971).

In light of this argument, it is possible that self-efficacious subjects in Bandura et al. (1987) found their prolonged endurance and failing cognitive control over cold pressor pain more aversive and stressful than subjects in other conditions. Therefore, extended exposure to an aversive stimulus and heightened levels of physiological arousal may have contributed to opioid activation. In comparison, subjects completing a non-stressful, controllable mathematical task in Bandura et al. (1988) did not activate opioid mechanisms, whereas subjects experiencing failure of cognitive control over the task did. Therefore, the activation of opioid mechanisms in these two studies may be attributed to the lack of control over a stimulus, or the experience of failing control and self-efficacy.

Other inconsistencies between human and animal research could be attributed to the flawed definition of 'control' in studies on humans. For instance, many laboratory studies of pain tolerance have unwittingly confounded 'potential control' with 'instrumental control', as human subjects can withdraw at any time. In animal research, potential control is not available to the organism in a shock chamber, beaker of water or harness. Thus, differing manipulations of control between animal

and human research could explain why uncontrollable stressors do not lead to SIA in all human investigations.

Pain and stress have often been confounded in both animal and human research, whereby methods of pain induction (i.e., CPT) have been used to induce stress. Confounding pain and stress is problematic in human research for two reasons: first, control cannot be effectively manipulated in pain tolerance designs; second, pain, although often aversive, does not necessarily lead to the level of psychological stress required to induce SIA.

Finally, in humans the effects of actual or perceived control and self-efficacy on pain have often been evaluated using inadequate pain parameters. For instance, psychological effects have primarily been measured on pain tolerance, a behavioural component of pain that also measures factors unrelated to the pain experience (e.g., expectancy, motivation, experimental demand/instructions) (Blitz & Dinnerstein, 1968; Gelfand, 1964). In contrast, pain threshold and intensity are typically measured in animal research. Moreover, when the effects of psychological factors have been measured on PI in humans, results are unclear as this parameter is often assessed inadequately. For example, Litt (1988) only recorded one set of pain ratings after 30 seconds into a 5-minute CPT. As pain perceptions change over time, important fluctuations could have been overlooked. Finally, few studies have explored the neurochemical mechanisms by which control and self-efficacy modulate pain, limiting comparisons between animal and human literature.

1.7.2 Lack of control: Pain inhibition

Laboratory-induced pain

Opioid-mediated endogenous analgesia in the laboratory is more likely to occur when stressors are high intensity, noxious, novel, and threaten to overwhelm a subject's capacity to cope (Price, 1999; Rosenzweig et al., 1996). Buchsbaum, Davis, Naber and Pickar (1983) demonstrated a naloxone-reversible effect after delivering a large number of moderately painful shocks (n>690) to subjects. In this study, somatosensory evoked potential amplitudes decreased whereas pain ratings did not,

suggesting that evoked potentials provide a more sensitive measure, containing less inter-subject variability than subjective ratings. Physical stressors such as CPTs (Pickar, Cohen, Naber, & Cohen, 1982a), capsaicin-induced acute pain (Anderson, Sheth, Bencherif, Frost, & Campbell, 2002), and physical exercise (Lobstein, Rasmussen, Dunphy, & Dunphy, 1989; Pickar et al., 1982a) that exceed thresholds for pain or stress have also led to increased concentrations of plasma beta-endorphins and alterations in pain perception. Other human studies corroborate these findings using a variety of intense cognitive stressors in the laboratory. As mentioned previously, Bandura et al. (1988) found an opioid-mediated increase in cold pressor pain tolerance in subjects during a difficult mental arithmetic task, whilst subject who could cope with the demands of the task experienced no stress or opioid activation.

Fear also has an analgesic quality. Willer and colleagues (Willer & Albe-Fessard, 1980a; Willer, Dehen, & Cambier, 1981) found an opioid-mediated increase in thresholds of the RIII in subjects who were anticipating previously experienced intensely noxious foot-shocks (70 mA). In a related study (Willer & Ernst, 1986), this effect was reduced with diazepam (an anti-anxiety drug) suggesting a mediating effect of fear or intense anxiety on SIA. In support of a pain inhibitory role for fear, Pitman, van der Kolk, Orr and Greenberg (1990) found that Vietnam veterans suffering from post-traumatic stress disorder displayed analgesic responses (decrease in heat pain) after viewing a segment of the *Platoon* film depicting combat scenes during the Vietnam war. Controls demonstrated no analgesia in response to this segment of film, and neutral films had no analgesic effect on either group. Others have supported the notion that negative emotions such as fear inhibit human pain (Rhudy & Meagher, 2000; Rhudy & Meagher, 2001a; Rhudy & Meagher, 2001b) (see *1.8 Mood modulation of pain* for more discussion, p 61).

Clinical pain

In a study of a small number of patients undergoing laparotomies for the assessment of testicular or ovarian cancer, Dubois, Pickar, Cohen, Roth, Macnamara and Bunney (1981) found that surgical stress was associated with an increase in beta-endorphin plasma concentrations. Moreover, an inverse relationship between plasma beta-

endorphin levels prior to surgery and post-operative requests for morphine suggested that opioid levels not only reflected a patient's ability to cope with surgery (i.e., stress response), but were also related to decreased pain sensitivity. As with experimentally induced pain, negative mood or pre-operative anxiety has been found to mediate reports of pain and coping after surgery (de Bruin, Schaefer, Krohne, & Dreyer, 2001).

Other painful and stressful clinical procedures such as molar extraction (Levine, Gordon, & Fields, 1978), dental stimulation (Butler, Colpitts, Gagliardi, Chen, & Chapman, 1983), the later stages of labour and childbirth have also been associated with opioid-mediated SIA (Cohen, Pickar, & Dubois, 1983; Price, 1999). Finally, chronic pain has been associated with decreased lumbar CSF levels of beta-endorphins (Cohen et al., 1983).

Real-life stress

Painful stimuli used to induce stress in laboratory studies have been frequently criticised as artificial and lacking the 'danger' element that produces psychological trauma, such as in animal research where an animal may fear for its life. Researchers wanting to investigate the effects of real life aversive situations on pain have studied soldiers in military training, where stress involved fear of bodily harm and fear of failure (Rosenzweig et al., 1996). For instance, Yamaguchi, Toda and Hayashi (2003) investigated the effects of intensive ground training on the pain thresholds (skin and tooth pulp) of seven members of the Japanese defence force. Significant increases in pain thresholds were observed at both anatomical sites after forty days of training. Others have shown similar reactions to such training (Ursin, Baade, & Levine, 1978), including changes to neuroendocrine functioning (i.e., increased noradrenaline, adrenaline, growth hormone and cortisol secretions). Unfortunately, neurochemical mediators of pain inhibition were not investigated in either study.

A naloxone-reversible opioid-mediated analgesia was demonstrated in civilian parachute jumpers following their first jump (Janssen & Arntz, 2001). In comparison to naloxone recipients, the placebo group showed lower pain sensitivity and a sudden

large increase in plasma levels of beta-endorphins after the jump that was associated with reports of anxiety and loss of control during the jump.

As evident from the discussion above, few studies have investigated the effect of 'lack of control' in real-life situations on pain, and even fewer have delineated chemical mediators of this phenomena. Therefore, there is an obvious need for more human research in this area.

1.7.3 Pain perception in chronic pain

Paradoxically, chronic pain patients often demonstrate *higher* pain thresholds (e.g., Yang, Richlin, Brand, Wagner, & Clark, 1985) but *lower* tolerance to pain (e.g., Brands & Schmidt, 1987) when compared to pain free individuals. Two theories have attempted to explain the variations in psychophysiological responses to painful stimuli, including DNIC and the adaptation theory.

Proponents of DNIC hypothesised that 'pain inhibits pain', such that chronic pain would inhibit experimentally induced pain, thus increasing the threshold to experimental pain (e.g., Peters, Schmidt, Van den Hout, Koopmans, & Sluijter, 1992). This theory has gained little support as DNIC is mediated in part by endogenous opioids and naloxone has failed to alter the pain thresholds of chronic pain patients (Peters & Schmidt, 1991; Peters & Schmidt, 1992; Peters et al., 1992).

The adaptation theory appears to account better for the differences in chronic pain patients. This theory proposes that chronic and constant pain leads to the establishment of higher internal anchors, and thus higher pain thresholds (Peters & Schmidt, 1992; Peters et al., 1992). Chronic pain patients become less able to discriminate between levels of stimuli within a context of constant pain (Clark, Yang, & Janal, 1986), and often under-predict pain (Arntz & Peters, 1995). Poorer discrimination of pain intensities (Clark et al., 1986) and less physiological habituation to pain (Peters & Schmidt, 1991) provides pain patients with very little opportunity to learn preventative responses, resulting in overestimation of physical capabilities and exhaustion (Arntz & Peters, 1995). Furthermore, since chronic pain patients are used to experiencing no pain at lower intensities and have not habituated

to higher intensities, anything above threshold is likely to be experienced as overwhelming and intolerable (Arntz & Schmidt, 1989) - hence, the lower pain tolerance in chronic pain patients than pain free individuals (e.g., Brands & Schmidt, 1987). Moreover, chronic pain patients are likely to experience a loss of control over their pain, feel helpless, become fearful of future intensities and perceive pain as unpredictable. As mentioned previously, losing control is more psychologically and physiologically stressful than never having had control at all (Staub et al., 1971).

In searching for explanations as to why pain becomes intractable in some people, attention has been drawn to the higher levels of beta-endorphins being released tonically in chronic pain patients than in pain free controls (Clark et al., 1986). Higher tonic levels of opioids have been associated with higher levels of depression and helplessness in those suffering from chronic pain (Almay, Johansson, von Knorring, Terenius, & Wahlstrom, 1978). Drummond and Holroyd (2000) suggested that a perceived lack of control in chronic pain patients may lead to the release of endogenous opioids but that opioids only provide short-term relief, as once a tolerance develops, the analgesic quality of opioids are reduced significantly. Lindblom and Tegner (1979) provided strong evidence that endogenous opioids provided very little alleviation from pain, as naloxone had no effect on pain reports or heat pain thresholds in chronic pain patients. Thus, opioid activation has very little impact on a system that is already flooded (Arntz & Schmidt, 1989).

To conclude, it is possible that endogenous pain inhibitory systems are activated in chronic pain patients in the context of uncontrollable pain, but that chronic activation of these systems appears to be ineffective for long-term pain inhibition.

1.7.4 Predictability of stressors

Two types of predicability have been investigated in human research. *Descriptive predictability* is where subjects have been told what an event will be like. The more frequently explored *contingency predictability* is where subjects are informed of conditions under which an aversive event will occur (Miller, 1981). Since contingency predictability has been explored in the bulk of research and is

experimentally manipulated in this thesis, studies detailing this form of predictability will be reviewed.

Although the effects of predictability on pain perception have been less clear in humans than in animal subjects, trends in results suggest that predictability has a minimal effect on pain. For instance, in 15 of the 20 studies reviewed by Miller (1981), predictability had no effect on subjective reports of pain. Of the remaining five studies, four found that predictable shocks led to less pain, whereas only one found that they increased pain (Miller, 1981). In accordance with these findings, Klemp and Rodin (1976) demonstrated that shock predictability had no real effect on perceptions of stimulus intensity. Furthermore, Crombez, Baeyens and Eelen (1994) found that temporal predictability had no effect on subjective reports of intensity in an experiment where subjects were informed (or not) of when a heat stimulus would be applied.

By using a paradigm commensurate to those used in animal research, Willer and colleagues (1980a; 1981) induced naloxone-reversible conditioned SIA in humans by submitting subjects to predictable, foot-shock-related cues. More recently, Flor et al. (2002) conditioned naloxone-reversible SIA in humans, where auditory cues served as conditioned stimuli whilst a mental arithmetic stressor served as the unconditioned stimulus. Although conditioned analgesia was evident both in pain tolerance and pain threshold, only tolerance to pain was influenced by endogenous opioids. Aside from these three studies, the neurochemical (opioid/nonopioid) mechanisms that mediate the effects of stressor predictability on SIA are relatively unexplored in humans.

The preceding studies demonstrated that both predictable (or signalled/conditioned) and uncontrollable stimuli result in opioid-mediated analgesia, suggesting that different relationships exist between predictability and controllability in the activation of SIA (Abbott et al., 1984).

Interactions between controllability and predictability

Traditionally, predictability was viewed as impossible to disentangle from controllability, in that a controllable response would provide information about the

predictability of the event (Seligman et al., 1971). What's more, controllable responses that were not predictable were viewed as instances of uncontrollable responses (Nickels, Cramer, & Gural, 1992). Consequently, conditions whereby the response could be controlled but was unpredictable were ignored, and in many studies controllability and predictability were confounded (Miller, 1981).

More recently control has been disentangled from prediction, whereby a subject is permitted actual or perceived control over a response but cannot predict the likelihood of the outcome of their response (Nickels et al., 1992). An example of *predictionless control* given by Langlois, Cramer and Mohagen (2002) involved a TV remote control whose label is no longer visible – which when used will have some effect on the TV, but the user will have no idea of what the effect will be (e.g., channels may be changed or volume adjusted). Some have argued that under these conditions subjects may feel that they have no control (Langlois et al., 2002). Nickels et al. (1992) found this to be untrue in that subjects controlling their response reported more influence over the outcome than subjects without control, regardless of prediction.

Despite this advance, few studies have examined the relative contributions of stressor controllability and predictability on pain. After reviewing studies that had explored the impact of predictability on stimulus aversiveness whilst keeping control constant, Miller & Grant (1979) agreed that the available physiological and subjective evidence is inconclusive. For instance, only three out of eleven of the pain rating studies indicated lower pain following predictable noxious events, whilst the remaining studies showed no difference in pain perception with regards to stressor predictability. In four experimental conditions (resulting from crossing control with predictability), Nickels et al. (1992) found that, despite increasing the subject's estimate of influence over the aversive stimulus (noise), neither control nor predicability (alone or in combination) affected stimulus UP. The lack of effect of either psychological variable may be attributed to the relatively brief nature and low intensity of the stimulus (Nickels et al., 1992). In more limited designs where stressor predictability is controlled and perceived/actual control is varied, control *alone* has been found to have positive effects on pain tolerance and, less

conclusively, on subjective pain (Arntz & Schmidt, 1989) (see *1.7.1 Stress-induced analgesia in humans: Actual and perceived control*, p 45).

The preceding discussion illustrates the extraordinary complexity of the relationship between stressor predictability and controllability and the activation of SIA. Clearly, this relationship requires analysis at many different levels, including investigation of psychological and neurochemical mediators of endogenous pain inhibition.

1.8 MOOD MODULATION OF PAIN

Emotions have been viewed as both a cause and consequence of nociception, and are central to the experience and expression of pain (Craig, 1989). Common emotional concomitants of acute pain include anxiety and grief, which can escalate into fear and depression as the pain deteriorates into a chronic condition (Vlaeyen, 1991). Anxiety and fear are often the emotional result of not being able to predict the occurrence or absence of pain, whereas depression or feelings of hopelessness result from an individual's response having no impact on pain (i.e., does not reduce, produce, terminate or prevent pain) (Seligman et al., 1971). Emotional bi-products of anxiety and depression include anger and guilt (Craig, 1989).

It is generally accepted that negative emotions (particularly anxiety) modulate pain; however, despite much conjecture, the mechanisms by which emotions influence pain remain unclear (Janssen & Arntz, 1997). Several hypotheses have been formulated in an attempt to explain the interaction between pain perception and emotion. For instance, Fernandez (2002) proposed six different relationships between mood and pain, namely mood as a predisposing, precipitating, exacerbating, and perpetuating factor, as well as a correlate or a consequence of pain. Others have focussed on the facilitatory and inhibitory nature of mood on pain (Janssen, 2002). For instance, emotions such as anxiety have been hypothesised to heighten sensations of pain through the release of noradrenaline, which sensitise nociceptors in the periphery (Rosenzweig et al., 1996). Similarly, depression supposedly inhibits the release of serotonin, and enhances the release of noradrenaline, which in turn excites nociceptors and increases PI (Romano & Turner, 1985). Within their g*ate-*

control theory, Melzack and Wall (1965) proposed a mechanism by which psychological processes could regulate nociceptive signals travelling from the periphery to the brain. It was hypothesised that descending controls travelling from brain structures responsible for processing emotions would modulate peripheral pain by either 'closing' or 'opening' a hypothesised gating mechanism within the spinal dorsal horn.

Studies examining the effect of experimentally induced emotion on pain have generally found that *valence*, meaning the pleasant or unpleasant nature of the emotion (Rhudy & Meagher, 2001b), influenced pain perception. For instance, Hertel and Hekmat (1994), after inducing mood using pleasant, unpleasant or neutral imaginal scenes, found that pleasant mood led to an increase in cold pressor pain tolerance. In a number of related studies, Stevens and colleagues (Stevens, Heise, & Pfost, 1989; Stevens & Rogers, 1990) found that experimentally induced pleasant mood was associated with higher pain tolerance, whereas negative affect (i.e., anger) decreased tolerance to pressure pain. In a large study (N = 200) in which films were used to induce amused, negative and neutral mood, Weisenberg et al. (1998) found increased pain tolerance and reduced pain ratings following the humorous film. However, this occurred only after a waiting period of 30 minutes post-film, suggesting that positive emotional memories faded more slowly than negative memories. Difficult to explain was the finding that longer films (regardless of emotional valence) had a positive effect on pain tolerance after this same waiting period (Weisenberg et al., 1998).

Research demonstrating that negative emotion can inhibit as well as facilitate pain suggests that the emotional modulation of pain involves factors other than *valence*. Rhudy and Meagher (2001b) suggested that negative valence may interact with the *intensity* of emotional arousal to yield either hyperalgesia (negative valence and low arousal) or analgesia (negative valence and high arousal). Moreover, it would seem that situations invoking intense negative affect (e.g., fear) typically are those that are uncontrollable and extremely threatening.

Evidence regarding how the three most frequent negative emotional concomitants of pain i.e., anxiety, depression, and anger modulate experimentally induced acute and chronic clinical pain is reviewed below.

1.8.1 Anxiety and pain

Of the three emotions, the role of anxiety in pain modulation has been examined most extensively. Most studies induced anxiety with pain-related (e.g., threat of painful shocks) or pain-unrelated stimuli (e.g., cognitive stressors), and examined these effects on responses to a variety of pain induction techniques (i.e., CPT, hand-grip/ischemic procedures, and painful electro-cutaneous stimuli).

Research involving the induction of anxiety with pain-unrelated stimuli such as imaginal scenes (Hertel & Hekmat, 1994) demonstrated that anxiety reduced the subject's ability to tolerate pain. Similarly, Meagher, Arnau and Rhudy (2001) found that exposure to pain-unrelated fear-evoking slides (from the International Affective Picture System) resulted in reduced cold pressor pain tolerance, and reduced UP and PI thresholds, when compared to exposure to neutral slides. Conversely, intense anticipatory anxiety and fear relating to the noxious stimulus inhibited pain by decreasing pain ratings, and increasing pain thresholds and tolerance (Rhudy & Meagher, 2000; Schull, Kaplan, & O'Brien, 1981; Willer & Ernst, 1986). These results suggested that in order for anxiety to inhibit pain, it has to be related naturalistically to the pain experienced (Fernandez, 2002) or of high intensity (Rhudy & Meagher, 2001b).

In light of findings from studies where noxious, anxiety-provoking but pain-unrelated stimuli inhibited pain (stressful mental arithmetic task - Bandura et al., 1988; parachute jumps by novices - Janssen & Arntz, 2001; combat-related stimuli shown to Vietnam war veterans - Pitman et al., 1990; noise bursts - Rhudy & Meagher, 2001a), the relevance of anxiety to the painful stimulus does not appear to be the most important factor. Instead the *intensity* of emotional arousal appears to determine whether anxiety-fear facilitates or inhibits pain (Rhudy & Meagher, 2001b). Rhudy and Meagher (2000; 2001a; 2003b) concurred with this notion, finding that fear (whether it resulted from shock pain or intensely aversive noise

bursts) led to pain inhibition, whereas anticipatory anxiety (a less arousing version of fear) led to pain facilitation. Interestingly, other emotions such as humour, when experienced concurrently with fear, can inhibit the hypoalgesic response usually induced by fear alone (Rhudy & Meagher, 2003a). When surprise is experienced instead of fear, hyperalgesia results (Rhudy & Meagher, 2001a).

Similar results have been found in animal research (Maier, 1990; Takahashi, Tokuyama, & Kaneto, 1988). For instance, Maier (1990) found that diazepam (an anti-anxiety, benzodiazepine solution) blocked SIA if the animals had received 80 tail-shocks, but not if they had received 1-20 shocks. The effect was powerfully persistent as diazepam blocked endogenous analgesia even when the animals were removed from the shock environment. In a related study, Takahashi, Tokuyama, and Kaneto (1988) found that diazepam reduced the degree of analgesia induced in rats by traditional uncontrollable stress-paradigms (i.e., tail-pinch, foot-shock, swim-stress, tail-flick). These results suggested that anxiety or fear contributed significantly to the inhibition of pain in these animals. In an equivalent set of studies in humans, Willer et al. (1980a; 1981; 1986) examined the effect of anticipatory anxiety about extremely aversive foot-shocks on the RIII threshold and on subjective pain reports by administering diazepam. Since diazepam reduced the analgesic effect of the stressor on RIII and subjective pain responses, intense anxiety was deemed to have a moderating effect on SIA in humans.

The mediation of endogenous analgesia by fear has been replicated with a range of painful stressors. In a study where the aversiveness and anticipatory anxiety of two pain procedures were maximised, Schull et al. (1981) found increases in ischaemic pain tolerance and reductions in pain ratings, however, no analgesia was noted during a CPT. Reductions in tension-anxiety were reported after both procedures. Notably, the novelty of the ischaemic pain procedure had been maintained, whereas subjects had been exposed to a 'practice run' CPT prior to the experimental trials. Additionally, Schull et al. (1981) speculated that it may have been the deep, dull, worsening ache of the pressure pain that led subjects to experience it as uncontrollable and fear provoking, which in turn led to pain inhibition. Grevert and Goldstein (1978) found no effect of tension-anxiety on either ischemic or cold pressor pain. These null findings could be attributed to certain 'anxiety–reducing'

methodological factors such as the use of the dominant hand (which typically has a higher pain threshold), mildly painful stressors (CPT – 10°C for 5 minutes; ischemic pressure inflated to 250 mmHg for 10 minutes, whilst squeezing a ball 20 times) and contact with the experimenter. By comparison, Schull et al. (1981) used the non-dominant hand, more intense stimuli (CPT – 10°C for 7 minutes; ischemic pressure inflated to 250 mmHg for 20 minutes, whilst squeezing a ball 30 times), and minimised contact between the subject and experimenter (i.e., the subject was left alone whilst procedures were delivered from outside the testing cubicle). In another study where negative mood failed to play a role in mediating cold pressor pain (Palmer, 2000), it was suggested that cold pressor stimuli were not stressful enough and did not lead to high enough levels of arousal to activate endogenous pain inhibitory systems.

Clinically, elevated levels of anxiety and depression have been found to reduce a patient's threshold and tolerance to pain, and in some cases increase PI (McCracken, 1998). For instance, Gil, Ginsberg, Muir, Sykes and Williams (1990) found that following orthopaedic surgery those reporting higher anxiety also reported more pain and self-administered more analgesics. Although not measuring mood directly, Gracely et al. (1978) found that affective responses (degree of discomfort and UP) to handgrip and painful electro-cutaneous stimulation were significantly reduced by diazepam in subjects who were due to undergo oral surgery immediately after the experiment. In contrast, sensory ratings regarding PI were not affected at all by diazepam. In this case, diazepam decreased the affective responses to pain by reducing anticipatory anxiety relating to upcoming dental surgery.

In conclusion, most data supports the notion that strong anxiety-fear responses lead to pain inhibition, whereas low to moderately arousing anxiety leads to pain facilitation (Rhudy & Meagher, 2001b). However, it is clear from the review above that many studies have confounded stress with pain by inducing anxiety with a pain stimulus. Others have examined this effect in clinical populations, contrasting results with non-medicated clinical subjects instead of healthy controls (Pitman et al., 1990). Also, physiological measures such as heart rate have been used to represent stress and anxiety instead of subjective mood ratings (Bandura et al., 1988). This overview suggests that research should examine the relationship between subjectively rated

anxiety and experimental pain in healthy controls, employing designs that do not confound pain and stress.

1.8.2 Depression and pain

A number of studies using films (Weisenberg et al., 1998) or Velten (1968) emotive statements (Willoughby, 2000; Zelman, Howland, Nichols, & Cleeland, 1991) to induce mood found that depressive affect decreased motivational aspects of cold pressor pain perception (i.e., pain tolerance) without influencing sensory aspects, such as pain ratings. Furthermore, subjects experiencing depressed mood catastrophised more about painful cold pressor sensations than controls (Willoughby, 2000). Hyperalgesia may have been a result of depressed mood being induced passively in these contexts, unlike in animal research where anhedonia and helplessness was 'acquired' after the animals learnt that they no longer, or never, had control over an aversive event (e.g., Hemingway & Reigle, 1987; Jorum, 1988; McCubbin, Kizer, & Lipton, 1984).

Only one human study examining the effects of experimentally induced subjective helplessness (a concomitant of depression) on PI was located at the time of this literature review (Mueller & Netter, 2000). Using a 'yoked control' design, subjective helplessness was induced via 'uncontrollable' electric shocks, where shock delivery was not contingent on performance during a reaction time task. A strong positive association between experimentally induced helplessness and PI was demonstrated using a path analysis. Anxiety and anger, on the other hand, were not significantly correlated with PI. It is unclear whether helplessness and depressed mood was induced within the 'uncontrollable' condition as shocks were of low intensity (1 mA, 100 ms duration), and individual pain thresholds were not determined for shock stimuli. Furthermore, evidence of helplessness in both 'controllable' and 'uncontrollable' conditions raises the question as to whether the conditions were manipulated adequately. Finally, the subject sample consisted only of males, limiting the extent to which these results could be applied to females or clinical groups.

In sum, the lack of robust data calls for future research with humans to examine the effects of stress-induced depressed or discouraged mood on pain perception.

1.8.3 Anger and pain

Very few studies have examined the effects of anger on pain (Fernandez, 2002), and those that do have adopted heterogenous methodologies producing divergent results. For instance, experimentally induced anger has increased cold pressor pain sensitivity (Janssen, Spinhoven, & Brosschot, 2001) and decreased pressure pain tolerance in some studies (Stevens et al., 1989), whilst leading to increased tolerance to cold pressor pain in others (Westcott & Horan, 1977). However, Westcott and Horan (1977) acknowledged that female subjects in the anger imagery condition may have tolerated the cold pressor for significantly longer than those in the neutral or relaxation imagery conditions due to alterations in subject response criteria or questionable methodology (e.g., covert demand characteristics), and not the mobilisation of pain inhibitory mechanisms. Despite these inconsistencies, it would appear in general that anger-related dimensions are most readily associated with pain sensitivity.

Others have examined the effect of anger management styles (i.e., anger-in/suppressed anger, anger-out/expressed anger) on pain, finding that the expression *and* suppression of anger were significantly related to acute ischaemic and finger pressure pain responsiveness (Bruehl, Burns, Chung, Ward, & Johnson, 2002). Conversely, in other studies one style over the other was strongly correlated with increased cold pressure pain sensitivity (anger-in - Gelkopf, 1997; anger-out - Janssen et al., 2001). Only anger-out has been associated with opioid antinociceptive dysfunction (Bruehl et al., 2002).

Bruehl et al. (2002) speculated that anger management style may influence pain through different mechanisms, and that "anger-in may work in conjunction with depressed mood and its biochemical sequelae" (p 230) in activating opioid-mediated pain inhibitory mechanisms. Fernandez (2002) agreed that situations that produce fear and sadness often result in anger. Correspondingly, Burns, Bruehl and Caceres (2004) found that suppressed anger was associated with increased cold pressor pain

tolerance after anger provocation. However, the involvement of endogenous opioids was not explored in this study.

Anger represents the emotional component of an active, fight-flight response to a stimulus that is perceived as 'threatening'. It has been hypothesised that the frequent experience of anger and hostility may create a chronically stressful environment in which anti-nociceptive mechanisms are continually activated, and eventually impaired through exhaustion. In accordance with this notion, Bruehl et al. (2002) found that low anger-out and anger-in styles in healthy controls and chronic low back pain patients were associated with opioid-mediated endogenous analgesia (lower pressure PI), suggesting that the expression of anger may lead to the dysfunction of descending inhibitory influences, and eventually increase pain sensitivity. Janssen et al. (2001) also supported this hypothesis, finding that experimentally induced anger in healthy subjects increased ischemic pain sensitivity, especially in those inclined to express anger. More recently, it has been suggested that the deleterious effects of anger-out on acute pain sensitivity can be exacerbated by anger provocation (Burns et al., 2004) or ameliorated if behavioural anger expression is allowed to occur (Burns, Kubilus, & Bruehl, 2003).

Although this notion has gained support from recent data, the idea that anger expression exhausts opioid-mediated antinociceptive mechanisms remains speculative, as no study has measured the effects of anger resulting from an uncontrollable stressor on pain-related outcomes. Anger has been induced either retrospectively via imagery (Stevens et al., 1989; Westcott & Horan, 1977), or experimentally during harassment (Janssen et al., 2001). The effects of pre-existing anger on pain have also been evaluated (Bruehl et al., 2002). Studying the effects of anger induced during a stressful, uncontrollable task on pain could help clarify the effects of this mood on endogenous antinociceptive mechanisms.

In sum, negative emotions serve not just as correlates or consequences, but also as potent modulators of pain. In particular, the inhibitory influence of intense negative emotions on pain is adaptive and important for survival (see *1.6.3 Stress-induced analgesia: Function of SIA*, p 38).

1.8.4 Attributional and attentional mediators

In addition to emotional valence and intensity, attribution of arousal and attention can also influence how emotions modulate pain. According to the *attributional* theory, physiological arousal arising from pain-related emotions serves to indirectly increase PI when the increased arousal is labelled as pain. However, PI is more likely to be inhibited by negative emotions if the emotions are attributed to factors unrelated to the pain (Reisenzein, 1983).

According to the *attentional* model, mood modulation of pain is mediated by attentional, and not attributional factors (Arntz, Dreessen, & de Jong, 1994). Specifically, pain is facilitated by negative emotions if they are pain-related and if attention is focussed on the pain (Janssen & Arntz, 1997). In contrast, a negative emotion unrelated to pain would draw attention toward pain-irrelevant factors and away from the pain, hence, reducing painful sensations. The effects of attention on pain have been widely demonstrated in the literature. Whether it be pain reduction from distraction or pain facilitation from directing attention towards the painful sensation, attention modulates sensory-discriminative responses to pain in healthy (Hodes, Howland, Lightfoot, & Cleeland, 1990) and chronic pain samples (Eccleston, Crombez, Aldrich, & Stannard, 2001; Johnson & Petrie, 1997). McCaul, Monson and Maki (1992) found that affective-motivational elements of pain could only be inhibited by distraction if this technique did not lead to high levels of arousal and that the emotional arousal that did occur was positive.

In an attempt to test the validity of attributional and attentional models, Arntz et al. (1994) examined the influence of pain-relevant and pain-irrelevant anxiety, and attention on the perception of painful electrical stimulation in arachnophobic subjects. They found that attentional focus influenced pain ratings, whereas pain-relevant anxiety influenced autonomic pain responses (e.g., skin conductance). Thus, these results suggested that attention mediates the influence of anxiety on pain (Arntz et al., 1994). Others concur with these results, providing support for the attentional model in favour of the attributional model (Janssen & Arntz, 1996). Although some go as far to say that attention influences pain regardless of anxiety (Arntz & de Jong, 1993), the evidence is insufficient to draw such a conclusion.

1.9 GENERAL SUMMARY/CONCLUSIONS

In animal and human research, the cognitive evaluation of an aversive stressor has been associated with the activation of endogenous pain inhibitory systems. Within animal research, inescapable or uncontrollable aversive stimulation unequivocally leads to the activation of either an opioid- or nonopioid-mediated analgesia, termed SIA. Nonopioid-mediated analgesia occurs in response to constant stimuli of brief duration and low intensity, whereas opioid-mediated analgesia is activated after extended, intermittent exposure to a more noxious stimulus. Furthermore, SIA can be conditioned in animals. Conditioned analgesia often appears to be mediated by opioids, suggesting that the predictability of an aversive stimulus also influences the activation of endogenous opioids.

The activation of SIA in humans has been less extensively investigated and the mechanisms involved in endogenous pain inhibition are speculative at present. Laboratory investigations suggest that actual and perceived control, and perceived self-efficacy in executing control over a noxious event, have a positive effect on pain endurance. However, the effects on subjective pain are unclear. In contrast, loss or lack of control and low self-efficacy leads to the activation of opioid and nonopioid-mediated forms of analgesia. Research investigating the conditions that inhibit clinical (acute or chronic) pain states is limited, and the substrates mediating the inhibition of acute and chronic pain require further investigation. However, there is some suggestion that the psychological conditions and neurochemical substrates inhibiting experimentally induced pain are also responsible for the modulation of clinical pain. The impact of predictability on the activation of SIA in humans is uncertain, as many studies have confounded it with the controllability of a stressor.

It would appear that the valence (negative or positive) and intensity of mood interacts to modulate pain. In particular, intense negative emotions such as fear contribute significantly to pain inhibition in animals and humans, whereas moderately arousing negative emotions such as anxiety increase pain sensitivity. The effects of other emotional concomitants of pain (i.e., depression, anger) remain relatively unexplored. The studies that do exist suggest a hyperalgesic effect for depressed

mood and anger; however, the intensity of each mood has not been controlled in any study. Finally, there has been considerable suggestion that attention mediates the effect of negative mood (in particular, anxiety) on pain.

1.10 OVERVIEW OF THIS RESEARCH

This thesis investigates the effects of psychological factors on natural pain inhibitory mechanisms in four sequential experiments. The first three studies were conducted on university students, whilst the fourth study was carried out on participants from the community, including a sub-group diagnosed with major depression.

The purpose of Study 1 was to investigate the effects of the perceived control and predictability of a stressor (shocks during a timed math task) on PI and UP in an experimental design that systematically addressed the shortcomings of previous research with humans. Study 2 investigated the role of endogenous opioids in SIA, by administering an opiate antagonist (naltrexone) to one half of the subject sample and a placebo to the other half. The number of stressful events or shocks was altered in an additional experimental condition to ensure that the shocks themselves were not responsible for analgesic effects observed during the math task.

The primary aim of Study 3 was to examine the effect of negative mood (in particular, discouragement - a *state-like* depressive emotion) on pain modulatory systems, and to determine the opioid or nonopioid nature of these effects. Additionally, Study 3 aimed to investigate whether the activation of endogenous SIA could be replicated using a variety of pain response parameters, including pain tolerance and a nociceptive reflex (RIII). The concept of pain tolerance as a measure of *endurance of unpleasantness* was also investigated.

Due to the suggestion that opioid functioning and pain inhibitory mechanisms may be impaired in depression, Study 4 assessed a number of endogenous antinociceptive phenomena mediated by opioids (i.e., SIA, DNIC) in depressed and non-depressed participants. As in Study 3, analgesia was assessed in a variety of ways, including pain ratings, pain tolerance and the nociceptive component of the blink reflex (R2).

The role played by the cardiovascular system in endogenous anti-nociception is well established. However, the suggestion that endogenous opioids mediate blood pressure-related analgesia is relatively unexplored in normotensive human subjects. Therefore, the involvement of endogenous opioids in the interaction between cardiovascular and pain regulatory systems was explored under conditions of rest and stress in Studies 2, 3 and 4.

CHAPTER TWO

2. STUDY 1

2.1 INTRODUCTION

2.1.1 Rationale/Purpose of this study

Stressor controllability and predictability

It has long been recognised that endogenous analgesia is activated not only in response to noxious environmental conditions, but is also powerfully triggered by psychological factors such as the controllability and predictability of an aversive event. These findings have been based mainly on experimentation with animals (e.g., Maier, 1986; Maier et al., 1982; Maier et al., 1983), whereas laboratory studies with humans have been less definitive (Bandura et al., 1988). For instance, some lines of evidence suggest that perceived control over an aversive event (often pain) leads to an increase in pain tolerance (Dolce et al., 1986; Litt, 1988; Ohlwein et al., 1996; Vallis & Bucher, 1986), whilst the effects on PI remain unclear (Ohlwein et al., 1996; Stevens, 1992). Acute and chronic pain studies concur with laboratory findings, whereas studies involving real life stress reflect findings from animal research, which may be attributed to more stressful, realistic manipulations of control (e.g., Janssen & Arntz, 2001).

It has generally been acknowledged that when the stressor is brief and not intense, animals prefer aversive events that are predictable, rather than unpredictable (Abbott et al., 1984). Endogenous analgesia has been conditioned by signalled aversive events in both animals (MacLennan et al., 1980) and humans (Flor et al., 2002; Willer & Albe-Fessard, 1980a; Willer et al., 1981); however, poorly designed methodologies have meant that the effects of stressor predictability on pain remain uncertain. This is especially relevant to experimentally induced pain in humans

(Miller, 1981). In consideration of these points, the effect of stressor controllability and predictability on pain needs to be examined in a well-controlled study.

Cognitive-affective mediators of pain

In addition to having a direct effect on pain, the controllability and predictability of an aversive event indirectly influences pain perception by inducing changes in self-efficacy and negative emotions common in clinical pain such as anxiety, depression and anger (Fernandez, 2002) . Although it is agreed that mood and self-efficacy modulate pain, the literature is unclear as to conditions under which these mediating factors may facilitate or inhibit pain. Therefore, well-controlled research needs to be conducted to examine the effects of mood and self-efficacy on pain.

2.1.2 Aims of Study 1

The **first aim** was to develop a cognitive stressor that could activate SIA.

The **second aim** was to investigate the impact of perceived control over a cognitive stressor (i.e., mental arithmetic task) on a painful stimulus (i.e., CPT). To rectify the shortcomings of pain measures in previous research, a 4-minute fixed interval cold pressor paradigm was adopted. In a fixed interval paradigm pain intensity (PI) and unpleasantness (UP) ratings were made frequently throughout the task, rather than when the pain stimulus was terminated, to avoid confounding PI and UP with pain tolerance (Ohlwein et al., 1996). To ensure that 'control' during the math task was believable and not beyond the capacity of the subject, mental arithmetic questions were chosen so that the majority of subjects could answer them. Conversely, the difficulty of questions in 'uncontrollable' conditions was beyond the ability of most subjects but not so difficult that subjects gave up straight away. *Perceived* instead of *actual* control was adopted as the effects are equally potent when it comes to influencing pain-related outcomes (Arntz & Schmidt, 1989).

Many studies have confounded control and prediction – or viewed the separation of both concepts and the creation of 'predictionless control' as logically impossible (Seligman et al., 1971). As indicated by Nickels, Cramer and Gural (Nickels et al.,

1992), predictionless control is possible by permitting a subject actual or perceived control over a response without allowing them to predict the likelihood of the outcome of their response. Moreover, very few studies have *systematically* studied the relative effects of control and stimulus certainty. Hence, the **third aim** of this study was to investigate the interaction between control and predictability by creating four conditions (i.e., controllable–predictable shocks; controllable–unpredictable shocks; uncontrollable–predictable shocks; uncontrollable–unpredictable shocks). *Predictionless control* was achieved by using an easy, controllable task in the context of shocks delivered at a random, pre-determined schedule set by the experimenter.

Most studies examining the effect of psychological variables on endogenous analgesia have utilised a pain stimulus to induce stress, thereby confounding pain with the experimental stressor. Confounding pain with stress also prevents the induction of negative affect that is not simply a result of the pain (Janssen, 2002). Therefore, the **fourth aim** was to remove this confound by manipulating pain and stress separately. This aim was addressed by studying the effects of a cognitive stressor (math task) on a commonly utilised method of pain induction, the CPT.

To summarise, the first study aimed to identify psychological variables (i.e., perceived control) and environmental conditions (i.e., predictability) that lead to the activation of SIA in humans, and systematically address the shortcomings of previous research in doing so.

2.1.3 Hypotheses for Study 1

In light of the previous review of relevant research and aims of the first study, it was hypothesised that:

Lack of control over the cognitive stressor would lead to stress and the activation of endogenous antinociceptive mechanisms. This would be evident by lower ratings of PI and UP during the CPT after the math task, in comparison to pre-math task cold pressor ratings. Since subjects in ‘controllable’ conditions were expected not to experience stress, endogenous pain inhibitory systems would not be activated and cold pressor pain ratings would not differ before and after the math task. To sum up,

it was hypothesised that subjects in uncontrollable conditions would experience greater decreases in PI and UP than those in controllable conditions.

The effects of predictability on SIA are uncertain; therefore, no specific hypotheses could be formulated. Rather, by controlling for predictability it would be possible to determine whether stimulus certainty contributed any unique element, and whether it interacted with perceived control to influence endogenous analgesia. If not, then this factor would be omitted from subsequent studies.

2.2 METHOD

2.2.1 Subjects

Fifty-six subjects aged between 17 and 50 years [28 males: M = 23.11 years, SD = 7.28; 28 females: M = 25.18 years, SD = 7.82] participated in Study 1. Subjects suffering from any previous/current injury to their non-dominant arm (used during the CPT), chronic pain conditions (including headaches/migraines), and/or medical or psychiatric conditions necessitating the use of any form of analgesic, antidepressant/anti-anxiety or BP medication were excluded from the present experiment. As previous research has demonstrated clear sex differences in pain sensitivity (Giles & Walker, 2000; Stevens, 1993; Westcott, Huesz, Boswell, & Herold, 1977) and age-related decline in endogenous analgesia (Washington, Gibson, & Helme, 2000), equal numbers of young male and female subjects were included in this sample. Three subjects were excluded from the study due to the failure of equipment during testing. An additional three subjects withdrew prematurely either due to the noxious nature of the cold pressor (N = 2), or 'uncontrollable-predictable' condition of the math task (N = 1). Subjects were recruited from Murdoch University undergraduate psychology classes and the general university population via posters advertising the study on campus. Subjects were remunerated $10 for their participation. All subjects were right-handed as established by Bryden's Handedness Questionnaire (1977) (Appendix 2, p 320).

2.2.2 Experimental design/Overview

As shown in Figure 2.1, subjects completed mood/self-efficacy ratings using visual analogue scales (VAS), and a CPT before and after a timed mental arithmetic task. Electric shocks were delivered randomly throughout the math task and subjects completed PI and UP ratings after each electrical shock. Mood and self-efficacy ratings were also completed during the math task. Prior to the math task, subjects were randomly assigned to one of four experimental conditions balanced for age ($F(3,52) = 1.46$; $p = .24$) and sex (Table 2.1).

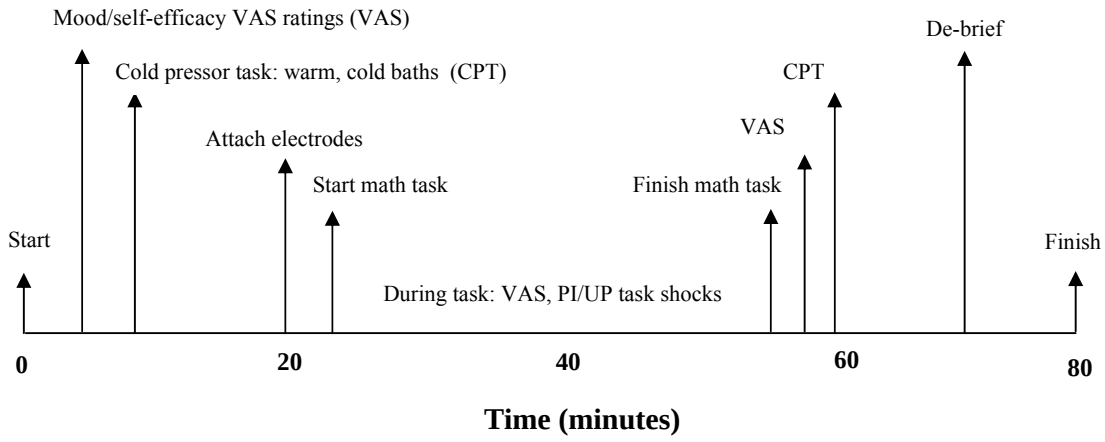


Figure 2.1: Experimental timeline for Study 1.

Table 2.1: Subject age and sex in each experimental condition.

	Experimental conditions			
	C-U	**C-P**	**UC-U**	**UC-P**
Mean	26.64	24.36	24.71	20.86
SD	9.72	7.52	8.05	2.66
N	7F, 7M	7F, 7M	7F, 7M	7F, 7M

Note. C-U = controllable-unpredictable; C-P = controllable-predictable; UC-U = uncontrollable-unpredictable; UC-P = uncontrollable-predictable; F = females; M = males.

2.2.3 Procedure/Materials

The subject was seated at a desk inside one of two air-conditioned cubicles maintained at 22 ± 2°C (Cubicle A) and given a consent form to read (Appendix 3, p 321). Once all queries about the experiment had been addressed, informed consent was obtained from the subject in writing and the experiment commenced. The Murdoch University Human Research Ethics Committee approved these and all other procedures in the present thesis. Each subject was tested individually, and the same two cubicles were used for all subjects.

Mood and self-efficacy ratings

Moods (anxiety, confusion, discouragement, anger, sluggishness and liveliness) and perceived self-efficacy with regards to avoiding electric shocks during the math task were rated before and after the math task in Cubicle A. Subjects marked how they felt *right at that moment* on separate 0-100 point VAS grouped together on a single sheet of paper. As shown in Figure 2.2, each scale consisted of a horizontal line 10 cm in length, with endpoints 'Not (mood) at all' and 'Extremely (mood)', or 'No ability to prevent shocks' and 'Complete ability to prevent shocks', for mood and self-efficacy respectively. The two-anchor, horizontal format of each VAS was adopted to reduce clustering around particular labels (Scott & Huskisson, 1976). Ratings were scored to the nearest millimetre (on a 100-point scale) as this has been found to be the most convenient, appropriate and sufficiently sensitive scoring technique (Aitken, 1969).

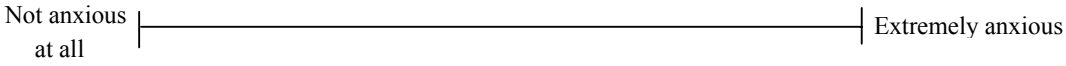


Figure 2.2: Example of a visual analogue scale.

The use of VAS to reliably (test-retest with short intervals, inter-rater reliability), validly (concurrent) and efficiently assess mood states such as depression and

anxiety has been established recently when compared to well-established, standardised instruments such as the Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory and the Profile of Mood States (Bond, Shine, & Bruce, 1995; Cella & Perry, 1986; McCormack, Horne, & Sheather, 1988). However, Cella & Perry (1986) recommend the use of supporting instruments with clinical groups as VAS alone may not be as reliable or sensitive when assessing mood disorders.

The same dependent variables were rated at irregular intervals during the math task (1:30, 7:39, 15:20 minutes) in Cubicle B using computer-generated VAS, where ratings were made by shifting a cursor from the mid-point either left (less so) or right (more so) according to how the subject felt *right at that moment*. To minimise the time taken to make ratings and prevent subjects from disengaging from the task, they were instructed to complete their ratings within 15 seconds, "or risk increasing their chance of getting an electric shock" while completing the rating. If subjects exceeded the time limit they did not receive any shocks; however, an aversive loud siren sounded until the rating was completed and the subject returned to the task. Computer generated VAS retain the same construct validity established for paper and pencil VAS (Maruff, Wood, Currie, McArthur-Jackson, Malone, & Benson, 1994).

Cold pressor tasks

The CPT stimulates pain fibres peripherally and centrally, exciting neurones entering the spinal cord and travelling to the thalamus (to the somatosensory cortex), the medulla (to the reticular formation) and limbic system (Lovallo, 1975). The extensive representation of cold pain throughout cortical and limbic structures supports the selection of the CPT as one of the most valid methods of pain induction (Wolff, 1978). Furthermore, the CPT meets stringent criteria for laboratory-evoked pain by achieving stimulus controllability, reliability and sensitivity throughout the range of the stimulus, and by being non-hazardous and convenient by design (Hardy, Wolff, & Goodell, 1952).

As illustrated in Figure 2.1, a CPT was completed in Cubicle A before and after the math task. Two insulated containers measuring 21 cm (width) x 33 cm (length) x 25 cm (height) housed approximately 15 litres of warm or cold water. The temperature

of each bath was monitored with a mercury thermometer (range = -5°C to +50°C). Temperatures of both baths changed slightly throughout each CPT (warm: -1.95°C; cold: +1.5°C); however, changes were consistent across groups.

During each CPT subjects first placed their left, non-dominant hand into a 37°C warm water bath for 3 minutes up to their wrist crease to standardise hand temperature. This temperature approximated normal body and hand temperature (Kenshalo & Nafe, 1963; Wolff, 1978), and has been used previously to equalise initial hand temperature (Bandura et al., 1987). Subjects then immediately placed the same hand into a nearby 7°C water bath for 4 minutes. To prevent pockets of warm water from developing near the subject's hand, an aquarium pump submerged and secured at the bottom of the bath continuously circulated the cold water. Preliminary piloting indicated that 7°C was extremely noxious but could be tolerated by subjects for the entire 4 minutes. Furthermore, when using hand temperature as a physiological indicator of distress, previous research has shown that 7°C, after an initial vasoconstriction, causes considerable vasodilation (Ahles et al., 1983). The duration of 4 minutes was chosen to capture the time at which distress peaks (2 to 2.5 minutes in Ahles et al., 1983), but avoid the point at which the hand becomes so numb that the CPT no longer retains noxious qualities (5 minutes according to Williams & Thorn, 1986).

The CPT was a fixed interval task with the option of withdrawal if necessary (Appendix 4, p 322). However, all subjects kept their hand in the water for the entire time. A fixed-interval paradigm was chosen because the *sensory* and *affective*, and not behavioural components (i.e., tolerance time) of pain were of interest with regards to testing experimental hypotheses. Pain tolerance, although a central facet of the pain experience, measures an individual's belief in their ability to endure different types of pain (Hirsch & Liebert, 1998). The sensory dimension refers to the location, quality and - of particular interest in this study - intensity of pain, whereas an individual's emotional reaction to pain comprises the affective, or UP dimension (Hirsch & Liebert, 1998). Although both dimensions are often closely related, contextual factors (e.g., labelling of cold pressor stimuli - Hirsch & Liebert, 1998) and psychological factors (e.g., fearful expectations - Ahles et al., 1983) have been

shown to influence the affective component. In some cases, different nociceptive stimulus response functions (or regression lines) have resulted from ratings of sensory and affective dimensions of pain (Price et al., 1994; Price et al., 1983), highlighting the importance of assessing PI *and* UP.

In right-handed subjects, previous researchers have established a greater sensitivity to cold pressor pain in the left, non-dominant hand (Ferracuti, Seri, Mattia, Cruccu, Schiff, & Gagliese, 1994b; Westcott et al., 1977; Wolff & Jarvik, 1964; Wolff et al., 1965). Conversely, other researchers have found either no difference in thermal pain sensitivity of the right and left hands (Long, 1994), or that cold pressor pain threshold and tolerance is greater for the right, than left hand *despite handedness* (Murray & Safferstone, 1970). However, results from the latter study also suggest that the non-dominant hand (or left hand in most of their subjects) was more sensitive to pain than the dominant, right hand as their sample consisted mostly (88%) of right-handed subjects. Haslam (1970) assessed pressure pain thresholds for non-dominant and dominant hands in left and right-handed subjects. Hand dominance only made a difference to pain thresholds in right-handed subjects; however, left-handed subjects only made up 20% of the sample.

Greater sensitivity in the left hand has been attributed to lateralization in the brain, where the right cerebral hemisphere dominates processing of negative affect (Long, 1994; Schiff & Gagliese, 1994), and physiological differences in neural origins of the left arm, where neural connections with the heart and neck exist in the left but not in the right arm (Murray & Safferstone, 1970). To date, no research has comprehensively compared cold pressor pain threshold and tolerance for the left and right hand of left-handed subjects. Therefore, considering that right-handed subjects were more abundant and that previous research has demonstrated the activation of emotional components of pain and greater sensitivity for the left, non-dominant hand – the left hand was tested during the CPT.

Subjects were prompted at 30-second intervals to rate the PI and UP of the cold water by using their right hand to slide a guide along a 0-100 point, mechanical visual analogue scale (M-VAS) with anchors 0 = 'No Pain'/'Not unpleasant at all' (left side) and 100 = 'Pain as bad as it could get'/'As unpleasant as it could get'

(right side). According to Price, McGrath, Rafii and Buckingham (1983) ratings from VAS reliably and validly represent the intensity and unpleasantness of the experimental pain experience. Furthermore, VAS demonstrate true ratio properties, allowing meaningful comparisons of both aspects of pain across occasions, conditions or subjects (Price et al., 1983). Ratio properties of VAS also apply to M-VAS (Price et al., 1994).

Previous researchers have demonstrated that cold pressor pain ratings vary according to the frequency of pain reports (Loftin, Zeichner, & Given, 1998), and that ratings 'commit' subjects to certain levels of pain, affecting future ratings (Hirsch & Liebert, 1998). Nonetheless, since relative changes in pain rather than absolute levels of pain were of interest in this study, frequent ratings were deemed appropriate. Furthermore, frequent ratings interrupt the use of cognitive coping strategies (i.e., distraction), drawing attention to and potentially increasing the pain (Loftin et al., 1998). Since the use of coping strategies was not monitored nor manipulated in this study, the interruption of their use by ratings was advantageous. Adding further comfort to this, Spanos, Hodgins, Stam and Gwynn (1984) demonstrated that when not explicitly instructed to do so, subjects would not use available coping strategies to reduce pain. Finally, to prevent subjects from using rating intervals as 'markers' to help them withstand the pain, the timing device was not visible to subjects and no cues were given as to when the next rating was due.

Math task

Subjects completed a computer programmed 20-minute[2] mental arithmetic task in Cubicle B. The math task was completed in a different cubicle to heighten the novelty and anticipatory anxiety with regards to the task. The experimenter entered a code into the computer, randomly allocating subjects to one of four conditions of which the experimenter was unaware. Identifying information was entered into the computer and saved with each subject's performance record on completion of the task. The experimenter left the room and delivered initial instructions (Appendix 4,

[2] Subjects took approximately 23-26 minutes to complete the task as the task was suspended each time subjective ratings were completed.

p 322) from outside Cubicle B using a two-way headset system. A closed-circuit television screen and speaker relaying performance-indicated sounds (see description below) enabled the progress of subjects to be monitored. Equipment used solely by the experimenter (i.e., stimulator, constant current unit, TV, speaker) was kept outside both Cubicle A and B.

Once the headset was turned off subjects read the remaining computer generated instructions and began a brief set of practice trials (2-3 minutes), during which subjects were reminded no shocks would be delivered. On completion of the practice trials, the task was suspended and subjects rated their ability to avoid shocks (self-efficacy) on a pen and paper VAS located on the desk. Subjects initiated the 'real' task by a keystroke and continued solving problems at the same level of difficulty seen at the end of the practice trials. On initiating the task subjects were reminded that shocks could be delivered after this point.

Each question appeared in yellow 2 cm high numbers in the middle of a black computer screen. When solving questions, subjects were instructed to use their left hand and the row of numbers at the top of a computer keyboard (and not the number-pad) to increase the difficulty and aversive nature of the task. When each problem was completed, feedback such as 'CORRECT' (green), 'INCORRECT' (red) or 'TOO SLOW' (purple) appeared on the computer screen, and either a pleasant 3-note jingle (correct responses) or an aversive loud beep (too slow or incorrect responses) sounded for one second.

Each question involved addition and subtraction and varied according to five levels of difficulty beginning at the easiest, level 1 [(1 + 3) – 2], level 2 [(56 + 4) – 6], level 3 [(77 + 19) – 2], level 4 [(245 + 63) – 4], and the most difficult level 5 [(771 + 195) – 2]. A different time limit was set for questions at each level on the basis of preliminary piloting[3].

[3] Pilot: Twenty-four subjects were asked to complete as many questions as possible within 2 minutes, at each level. The average time taken to complete items at each level was calculated. In the present experiment, time limits were either set slightly above the mean for easier questions (Level 1 and 2), at

At the outset of the task subjects were instructed that the number of shocks received depended on their mathematical performance, i.e., poor or slow performers were led to believe that they had a greater chance of being shocked. However, so that the number of shocks did not confound results, no such contingency existed and subjects received an identical number of shocks at approximately similar stages throughout the task. In order to deliver shocks at similar stages during the task subjects were 'forced' to make an error or respond too slowly by 'shifting' subjects into a higher level of difficulty (only if at ≤ Level 4), and simultaneously providing a shorter time-limit. Shocks were delivered at irregular intervals to prevent subjects from anticipating their occurrence. When queried after the task, all subjects reported being unaware of the 'contingency' of shock delivery.

Conditions in the math task were designed to create a combination of either high or low ability to *predict* shocks, and either high or low perceptions of self-efficacy regarding arithmetic problems and *control* over electrical shocks. This resulted in four experimental conditions: 'Controllable – Predictable', 'Controllable – Unpredictable', 'Uncontrollable – Predictable', 'Uncontrollable – Unpredictable'.

Starting from the practice trials, subjects in the 'controllable' condition were presented with arithmetic problems from Level 1 and 'shifted' to the next level of difficulty if ≥ 7 out of 8 consecutive questions were answered correctly. When reaching an error rate of 25% (2 wrong in 8 questions) subjects were maintained at the same level for the next 8 questions. If their error rate was >25% (>2 wrong in 8 questions), subjects were dropped down a level (if at ≥ Level 2) making the task relatively easy. Subjects in the 'uncontrollable' condition were presented problems from Level 3 at the outset of the practice trials, and were maintained at this level if their error rate was 75% (6 wrong in the first 8 questions). If >75% errors were being made, subjects were shifted down a level. However, if less than 75% of questions were incorrect subjects were shifted up a level, making this task much harder.

---

the mean (Level 3), or slightly below the mean for harder questions (Level 4 and 5) to increase the challenge of the task, but not make it so difficult that subjects gave up trying.

Subjects in the 'predictable' condition witnessed the computer screen intermittently change from black to blue, and were warned that they were in increased danger of receiving an electric shock during this time. Subjects were not told that the presentation of a blue screen was pre-programmed to standardise the experience of each subject, and that shocks would not be presented during every blue screen. Shocks were only delivered during the blue screens that coincided with pre-programmed timing of shocks set for all subjects (see *Task Shocks* below), and never during black screens. In the 'unpredictable' condition the computer screen remained black and no such instructions were given.

Task shocks

Stimulation consisted of three 15 mA ± 1.10 (SEM) rectangular pulses of 25 milliseconds duration. The delivery of repeated shocks throughout the task led to minor fluctuations in skin conductance and variations in shock intensity. Each pulse was delivered via 1 cm^2 Grass silver/silver chloride surface electrodes. Electrodes were attached with double-sided adhesive washers and secured with 3M surgical tape. They were positioned 2 cm apart on the ventral surface of the forearm, 10 cm from the elbow towards the wrist, along the cutaneous branch of the ulnar nerve. The ulnar nerve was stimulated due to the aversive nature of this stimulation as demonstrated in a small pilot[4]. The skin was slightly abraded with a pumice stone and degreased with an alcohol swab to achieve skin impedance lower than 5 K ohms [M = 3.5 K ohms ± 0.7 (SEM); measured by a PA300 impedance meter]. Furthermore, silver/silver chloride electrodes and water-soluble, saline electrode gel were used to decrease skin impedance.

Each pulse was delivered 3, 10 and 17 minutes into the task using an SD9 Grass Square Pulse stimulator and constant current unit. A custom-built digital current meter monitored current intensity (mA) delivered from the constant current unit to

[4] Pilot: Twenty-four subjects had electrical pulses delivered to the ulnar and median nerve in the non-dominant forearm in 1 mA steps (via the staircase method) to compare aversion to the sensation. In general, pain threshold and tolerance of the ulnar nerve was lower, and led to an unpleasant burning sensation not apparent when stimulating the median nerve.

the subject. A 'trigger box' connected to the computer was programmed to turn the stimulator on and off at the times when shocks were to be delivered during the task.

The task was suspended whilst subjects gave PI and UP ratings after each shock using a computer-generated 0-100 point VAS, where 0 = 'No pain'/'Not unpleasant at all' and 100 = 'Pain as bad as it could get'/'As unpleasant as it could get'. As with mood and self-efficacy ratings, subjects were instructed to complete their ratings within 15 seconds or risk receiving an electric shock whilst making their rating.

Debriefing

The purpose of the experiment was explained and subjects were remunerated at the end of the experimental session. Details regarding the math program were not revealed as the task was to be used in subsequent studies.

2.3 RESULTS

2.3.1 General data considerations

Cell sizes were insufficient to investigate sex differences in each condition; therefore, all analyses were performed on data collapsed across males and females. To ensure that sex was not a confounding factor within the analyses, and that results could be generalised to the general population, equal numbers of males and females were recruited for each condition. Multivariate solutions for repeated measures factors with more than two levels are reported to minimise the likelihood of Type 1 errors. These practices were adopted across all studies.

2.3.2 Mood and self-efficacy

Data considerations

Mood and perceived self-efficacy with regards to avoiding electric shocks during the math task were rated on a 0-100 point VAS prior to, during and after the math task. Only results for anxiety, discouragement and anger are presented as these moods

most often accompany pain (Zelman et al., 1991). Ratings of confusion, sluggishness and liveliness were included as filler items and thus were not analysed. Moods were analysed separately to facilitate interpretation of findings. These procedures were adopted in all studies.

Randomisation check

Separate 2 (controllable, uncontrollable shocks) x 2 (predictable, unpredictable shocks) univariate ANOVAs were carried out on pre-math task mood and self-efficacy ratings. As indicated in Tables 2.2 and 2.3, groups did not differ on mood or self-efficacy prior to the math task.

Table 2.2: Mood and self-efficacy ratings before, during and after the math task in each experimental condition.

		Controllable				Uncontrollable			
		Predictable		Unpredictable		Predictable		Unpredictable	
Mood	**Time**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Ax.	**Pre**	36.39	24.54	40.83	22.95	42.18	23.03	52.80	22.78
	1	55.29	12.98	59.93	22.55	68.29	11.68	54.29	29.45
	2	61.93	20.62	61.86	21.69	65.07	15.54	60.71	27.11
	3	57.00	26.10	61.64	26.76	57.79	18.96	61.07	29.81
	Post	41.51	29.95	47.37	29.55	47.20	27.93	54.82	32.60
Ds.	**Pre**	14.09	12.90	20.85	22.28	23.84	27.02	23.00	24.19
	1	36.14	20.52	36.64	23.40	59.86	28.36	59.86	22.76
	2	36.64	14.26	40.43	29.85	54.57	21.30	59.36	19.92
	3	41.43	24.06	41.07	32.28	63.43	18.64	62.36	30.31
	Post	32.04	26.13	31.76	27.49	58.88	28.39	60.71	32.21
Ag.	**Pre**	6.11	5.78	8.13	10.45	6.30	14.03	11.84	20.21
	1	22.00	21.01	21.64	20.62	39.71	25.14	30.71	31.05
	2	32.86	23.51	28.21	29.10	37.93	23.73	38.64	29.18
	3	33.50	28.02	29.00	27.47	45.29	27.05	44.00	33.60
	Post	29.98	28.95	25.84	26.09	41.35	30.84	43.89	36.34
Sf.	**Pre**	54.19	18.52	46.76	24.81	52.13	26.12	41.62	24.95
	Prac	53.00	20.79	50.47	25.06	22.95	20.22	19.14	18.06
	1	53.21	20.28	50.14	26.92	28.29	22.90	21.93	13.20
	2	50.36	20.02	50.64	27.74	30.86	24.07	26.71	20.12
	3	57.50	17.72	42.93	28.54	29.29	21.73	29.14	24.63
	Post	61.47	15.92	44.95	27.93	28.85	30.67	15.62	12.93

Note. N = 14 subjects in each condition; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; Pre = prior to practice trials and math task; Prac = following practice trials, prior to math task; 1-3 = 1:30, 7:40, and 15:20 minutes into math task, respectively; Post = after math task.

Table 2.3: F ratios of pre-task mood and self-efficacy ratings across conditions.

Source	Anxiety	Discouragement	Anger	Self-efficacy
Controllable (C)	2.03	1.00	0.28	0.32
Predictable (P)	1.46	0.25	1.07	1.99
C x P	0.24	0.41	0.23	0.06

Note. Degrees of freedom = 3,52.

Effects of the math task on mood and self-efficacy

Effects of the math task on mood ratings were investigated with separate 5 (Time: pre-task, during task at 1:30", 7:40", 15:20", post-task) x 2 (controllable, uncontrollable shocks) x 2 (predictable, unpredictable shocks) repeated measures ANOVA. Similar analyses were carried out on self-efficacy ratings, except that ratings made after the practice trials were deemed a more relevant point of comparison than those made before the practice trials and math task i.e., 'pre-task' in *Time* factor in mood analyses (Table 2.2 and 2.4).

Subjects experiencing difficult math questions and who perceived shocks to be uncontrollable experienced significantly greater levels of discouragement (M = 52.59) than those who believed they could control the shocks (M = 33.11). Shock predictability failed to affect mood during or after the math task.

The exploration of Time main effects with simple contrasts (where pre-task ratings were the point of comparison) revealed that significantly higher levels of anxiety, discouragement, and anger were reported during the math task, than beforehand. Subjects remained significantly more discouraged and angry following the math task; however, anxiety returned to pre-task levels.

The Controllable main effect for self-efficacy indicated that subjects experiencing difficult math questions and 'uncontrollable' shocks perceived that they were significantly less able to prevent electric shocks after the practice trials and beyond, compared to their counterparts in controllable conditions. As expected, the predictability of shocks did not influence self-efficacy as "…perceived self-efficacy

is concerned with people's judgements of their capabilities to execute given levels of performance and to *exercise control over events*" (Bandura et al., 1987, p 563). No other interactions were found.

Table 2.4: F ratios for mood and self-efficacy before, during and after the math task.

Source	Anxiety	Discouragement	Anger	Self-efficacy[a]
		Between subjects		
Controllable (C)	0.69	15.52***	3.11	25.26***
Predictable (P)	0.22	0.09	0.05	1.51
C x P	0.11	0.01	0.03	0.03
		Within subjects		
Time[†] (T)	11.13***	19.07***	17.17***	0.47
T x C[†]	0.46	2.10	1.49	1.35
T x P[†]	1.52	0.35	0.51	2.15
T x C x P[†]	1.26	0.09	0.74	1.84

Note. [a] Self-efficacy ratings after the practice trial = first level of *Time* factor in self-efficacy analyses; [†] Pillai's Trace F ratio; degrees of freedom: between S's = 1,52; within S's = 4,49. ***p≤.001.

2.3.3 Electro-cutaneous task shocks

Subjects received three 15 mA shocks during the math task and gave PI and UP ratings after each shock, using a computer-generated 0-100 point VAS. Separate 2 (controllable, uncontrollable shocks) x 2 (predictable, unpredictable shocks) x 3 (Trials: first, second, third shock) repeated measures ANOVAs were carried out on PI and UP ratings (Tables 2.5 and 2.6).

Cell means suggested that subjects perceived the shocks to be moderately to somewhat severely painful and unpleasant (i.e., M = 45.43 – 66.71). A Trial main effect indicated that PI and UP ratings increased with shock repetition. Neither 'controllability' nor 'predictability' affected either shock-related PI or UP.

Table 2.5: Pain intensity and unpleasantness ratings for shocks during the math task.

	Controllable				Uncontrollable			
	Predictable		Unpredictable		Predictable		Unpredictable	
Trial	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				Pain intensity				
1	48.36	21.13	45.43	20.16	54.93	20.89	55.50	23.05
2	53.29	21.28	48.64	21.84	62.00	21.12	61.86	17.13
3	54.86	25.35	57.29	26.35	59.14	21.21	63.64	21.06
				Unpleasantness				
1	52.57	20.01	53.07	17.93	59.36	19.94	54.29	27.29
2	53.79	21.45	55.43	20.41	66.36	16.54	62.29	21.65
3	60.93	20.94	61.50	22.69	66.71	16.63	66.14	26.83

Note. N = 14 subjects in each condition.

Table 2.6: F ratios for shock pain and unpleasantness ratings during the math task.

Source	**Pain Intensity**	**Unpleasantness**
	Between subjects	
Controllable (C)	2.29	1.44
Predictable (P)	0.00	0.05
C x P	0.10	0.16
	Within subjects	
Trial†(T)	7.53***	11.31***
T x C†	1.35	1.24
T x P†	1.26	0.18
T x C x P†	0.06	0.22

Note. †Pillai's Trace F ratio; degrees of freedom: between S's = 1,52; within S's = 2,51.

***p≤.001.

Effect of mood and self-efficacy on task shock sensitivity

The degree to which mood and self-efficacy impacted upon task shock ratings was explored with Pearson product correlations (Table 2.7). Since mood and self-efficacy *per se* were of interest in relation to perception of the shocks (and not what contributed to a subject's affective state i.e., experimental condition), correlations were carried out on results collapsed across experimental conditions.

As shown in Table 2.7, anxiety, discouragement, and anger were positively associated with task shock ratings, in that the more negative a subject felt the more PI and UP they reported for each shock. Being the only positive 'cognitive mediator' of pain, self-efficacy was inversely associated with task shock sensitivity.

Table 2.7: Pearson product correlations between mood, self-efficacy and pain intensity and unpleasantness of task shocks during the math task[5].

Mean task mood/	**Mean shock pain index**	
self-efficacy	**Pain intensity**	**Unpleasantness**
Anxiety	.51**	.58**
Discouragement	.50**	.58**
Anger	.44**	.47**
Self-efficacy	-.44**	-.54**

Note. **p<.01.

[5] Correlations were calculated between mood and individual shock ratings; however, results corresponded with the analyses of mean ratings. For brevity, results for mean ratings are presented.

2.3.4 Cold pressor pain perception

Data considerations

PI and UP were rated using a 0-100 point M-VAS at 30-second intervals spanning 4 minutes of the CPT. M-VAS ratings were averaged and analysed minute by minute to simplify statistical analyses and, importantly, identify analgesic effects likely to develop over the course of the CPT. As shown in Table 2.8 (shaded areas), sensory (PI) and affective (UP) M-VAS ratings during the CPT were only moderately related, giving credence to separate analyses of each aspect of the cold pressor pain experience.

Table 2.8: Pearson product correlations between cold pressor pain intensity and unpleasantness ratings before and after the math task.

	Pain intensity							
	Pre-maths task CPT				**Post-maths task CPT**			
Unpleasantness	**1st min**	**2nd min**	**3rd min**	**4th min**	**1st min**	**2nd min**	**3rd min**	**4th min**
1st minute	.52**				.83**			
2nd minute	.36**	.67**			.44**	.79**		
3rd minute	.30*	.56**	.75**		.14	.55**	.87**	
4th minute	.20	.49**	.74**	.84**	.06	.39**	.75**	.87**

Note. CPT = cold pressor task.

*p<.05; **p<.01

Randomisation/Methodological check

Separate 2 (controllable, uncontrollable shocks) x 2 (predictable, unpredictable shocks) univariate ANOVAs were carried out on pre-math task mean PI and UP ratings that were averaged over the duration of the CPT. As indicated in Tables 2.9 (shaded areas) and 2.10, groups did not differ on cold pressor ratings prior to the math task. According to Collins, Moore and McQuay (1997), the CPT in this experiment was a valid pain induction method, as PI and UP did not drop below moderate levels at any time.

Table 2.9: Cold pressor pain intensity and unpleasantness ratings before and after the math task.

Pain Intensity

	Controllable				Uncontrollable			
CPT	**Predictable**		**Unpredictable**		**Predictable**		**Unpredictable**	
Minute	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				Pre-math task				
1	62.68	17.48	56.79	22.87	53.75	21.94	57.18	22.44
2	57.07	20.16	54.68	22.37	60.32	15.34	54.39	22.61
3	44.61	21.04	42.07	27.02	51.30	18.00	39.11	18.19
4	31.57	20.66	28.79	25.26	34.71	18.33	32.29	18.31
Mean	48.98	16.77	45.58	20.20	50.02	14.72	45.74	18.30
				Post-math task				
1	61.93	20.63	60.21	22.98	56.57	19.08	60.71	15.41
2	61.25	20.94	56.14	20.83	56.21	15.49	62.04	11.69
3	41.18	20.81	39.32	26.05	42.39	18.92	42.80	14.12
4	27.39	20.58	29.68	26.27	30.46	18.00	21.11	15.13
Mean	47.94	16.32	46.34	20.16	46.41	15.04	46.66	11.27

Unpleasantness

	Controllable				Uncontrollable			
CPT	**Predictable**		**Unpredictable**		**Predictable**		**Unpredictable**	
Minute	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				Pre-math task				
1	64.89	19.42	65.46	15.65	51.64	21.89	64.04	19.98
2	58.71	20.26	55.71	21.52	55.50	20.42	55.68	18.41
3	47.36	20.83	39.82	22.76	46.20	19.42	40.32	18.30
4	31.04	19.59	30.75	24.88	30.64	19.91	29.64	17.64
Mean	50.50	15.81	47.94	19.27	45.99	17.61	47.42	14.15
				Post-math task				
1	61.96	21.98	64.54	22.30	54.93	20.93	68.71	12.94
2	55.96	19.70	53.32	21.24	53.64	18.19	64.21	17.32
3	36.21	18.53	38.57	25.84	38.18	20.30	43.41	17.53
4	25.43	20.19	28.64	24.22	26.64	16.81	26.36	21.72
Mean	44.89	15.72	46.27	20.14	43.35	16.49	50.67	14.12

Note. CPT = cold pressor task.

Table 2.10: F ratios of cold pressor pain intensity and unpleasantness ratings in each condition, before the math task.

Source	Pain Intensity	Unpleasantness
Controllable (C)	0.02	0.31
Predictable (P)	0.67	0.02
C x P	0.01	0.20

Note. Degrees of freedom = 3,52.

Effects of the math task on cold pressor pain perception

Effects of the math task on cold pressor PI and UP ratings were investigated in separate 2 (Time: pre- and post-math task) x 4 (Minute: 1", 2", 3", 4") x 2 (controllable, uncontrollable shocks) x 2 (predictable, unpredictable shocks) repeated measures ANOVAs (Table 2.11).

Main effects of Minute were found for PI and UP ratings. Repeated pair-wise comparisons (where the rating during the previous minute was the point of comparison) indicated that cold pressor UP decreased significantly after each minute in the cold water, whereas cold pressor intensity only became less painful from the second minute onwards. However, the Time x Minute, Time x Minute x Controllable and Time x Minute x Controllable x Predictable effects suggested that changes in PI were not equivalent across experimental conditions or occasions.

Since the four-way interaction subsumes the two- and three-way, only the four-way interaction will be discussed. To locate the source of significance, change scores were calculated by subtracting pre- from post-task ratings, and repeated pair-wise comparisons were carried out within each experimental condition. As indicated in Table 2.12 and Figure 2.3, subjects in the 'Uncontrollable-Predictable' condition found the CPT to be less painful after the math task than beforehand, from one minute onwards ($F(1,13) = 5.34$; $p = .04$). Similarly, subjects in the 'Uncontrollable-Unpredictable' condition found the CPT to be less painful after the math task than

beforehand, during the final minute of the CPT (F (1,13) = 19.45; p = .001). Subjects in 'controllable' conditions experienced no change in cold pressor PI or UP after the math task.

Table 2.11: F ratios for cold pressor pain and unpleasantness ratings before and after the math task.

Source	Pain Intensity	Unpleasantness
	Between subjects	
Controllable (C)	0.00	0.02
Predictable (P)	0.30	0.21
C x P	0.00	0.36
	Within subjects	
Time†(T)	0.18	0.86
T x C†	0.11	1.20
T x P†	0.80	1.87
T x C x P †	0.15	0.07
Minute† (M)	66.16***	62.40***
M x C†	0.69	1.44
M x P†	0.51	1.78
M x C x P†	0.59	0.52
T x M†	3.32*	1.37
T x M x C†	4.08*	0.53
T x M x P†	2.25	2.19
T x M x C x P†	4.81**	0.96

Note. †Pillai's Trace F ratio; degrees of freedom: within S's 'Minute' factor = 3,50, and 1,52 for remaining analyses.

*p<.05; **p<.01; ***p≤.001.

Table 2.12: Repeated pair-wise comparisons[a] of change in cold pressor pain intensity ratings from before to after the math task.

Experimental	Post-maths cold pressor minute			
Condition	**1**	**2**	**3**	**4**
C-P	-0.75	4.18	-3.43	-4.18
C-U	3.43	1.46	-2.75	0.89
UC-P	2.82	-4.11*	-8.91	-4.25
UC-U	3.54	7.64	3.70	-11.18***

Note. [a] minute 2 was compared with minute 1, minute 3 was compared with minute 2 and minute 4 was compared with minute 3; C-P = controllable-predictable shocks; C-U = controllable-unpredictable shocks; UC-P = uncontrollable-predictable shocks; UC-U = uncontrollable-unpredictable shocks; degrees of freedom for comparisons within each group = 1, 13.

*p<.05; ***p≤.001.

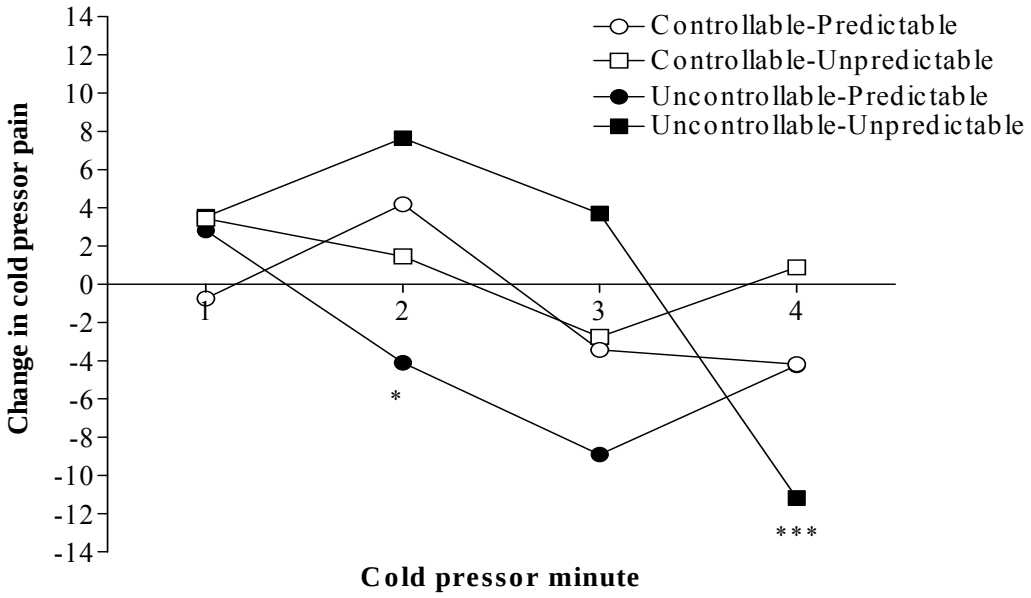


Figure 2.3: Change in cold pressor pain intensity in each group, following the math task. Note. *p<.05; ***p≤.001 for within group, minute-by-minute comparisons.

Effect of mood and self-efficacy on cold pressor pain perception

Change scores

The effects of (task-induced) change in mood and self-efficacy on cold pressor pain perception were of primary interest, and explored with Pearson product correlations. Since change in mood and self-efficacy per se was of interest in relation to changes in cold pressor perception (and not what caused these changes i.e., experimental condition), results were collapsed across conditions. 'Change scores' were calculated by subtracting pre-math task ratings from corresponding ratings after the task. In self-efficacy analyses, post-practice trial ratings were used to calculate change after the math task.

As shown in Table 2.13, greater increases in anxiety, anger, and to a lesser extent discouragement were associated with smaller increases in cold pressor PI and UP after the math task. When examined minute-by-minute, these associations appear to be strongest for PI ratings towards the end of the CPT. Changes in self-efficacy were not related to cold pressor pain perception after the math task.

Table 2.13: Pearson product correlations between change in mood, self-efficacy and change in cold pressor pain intensity and unpleasantness after the math task.

	Cg in cold pressor pain perception									
Cg in	**Pain intensity**					**Unpleasantness**				
mood	**1**	**2**	**3**	**4**	**M**	**1**	**2**	**3**	**4**	**M**
Ax.	-.10	-.07	-.34*	-.32*	-.26*	-.12	-.24	-.23	-.19	-.26[a]
Ds.	-.11	-.01	-.17	-.28*	-.18	.15	.23	-.05	-.07	.08
Ag.	-.04	-.00	-.18	-.37**	-.18	-.04	-.07	-.38**	-.38**	-.29*
Sf.	-.12	-.11	-.11	-.02	-.12	.08	.12	-.11	-.00	.02

Note. Cg = change; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; 1-4 = cold pressor minute; M = mean changes in mood/cold pressor pain perception.

[a] p = .055; *p<.05; **p<.01.

Absolute scores

In an alternate analysis, the effects of mood and self-efficacy on cold pressor pain were explored with Pearson correlations at each time-point. As illustrated in Table 2.14, no association was found between absolute mood and mean cold pressor PI and UP ratings. Since self-efficacy ratings related to performance during the math task, the relationship between self-efficacy and cold pressor responses were only explored *after* the math task. Self-efficacy for preventing shocks during the math task was negatively related to cold pressor UP and (less so) PI, where self-efficacious subjects reported less PI and UP after psychological stress.

Table 2.14: Pearson product correlations between mood, self-efficacy and cold pressor pain intensity and unpleasantness before and after the math task.

	Cold pressor pain perception									
	Pain intensity					**Unpleasantness**				
Mood	**1**	**2**	**3**	**4**	**M**	**1**	**2**	**3**	**4**	**M**
					Pre-math task					
Ax.	.09	-.02	-.08	.02	-.16	-.08	-.27*	-.16	-.03	.00
Ds.	-.01	-.03	-.06	.02	-.04	.04	-.03	-.12	-.01	-.02
Ag.	-.01	.05	.03	.15	-.11	-.15	-.12	-.16	-.05	-.07
					Post-math task					
Ax.	.15	.24	.11	.10	.16	.15	.15	.11	.11	.18
Ds.	-.14	-.00	-.05	-.14	.03	-.04	.08	.05	.02	-.11
Ag.	.25	.21	.00	-.10	-.01	.20	.02	-.11	-.12	.10
Sf.	-.00	-.25	-.27*	-.14	-.20	-.17	-.30*	-.34*	-.19	-.30*

Note. Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; Mood was measured just prior to each CPT (see Figure 2.1: Experimental Timeline, p 77).

*p<.05.

2.4 DISCUSSION

2.4.1 Summary of major findings

The key findings to emerge from the present study were:

- Lack of control over an aversive stimulus (i.e., shocks during a stressful math task) led to an analgesic response to sustained cold pressor pain. Analgesia did not occur with shocks during the math task presumably due to their brief, infrequent, and moderately intense nature.
- Stressor predictability alone had no effect on the perception of painful stimuli; however, when interacting with stressor controllability, this variable influenced the onset and degree of analgesia.

Other findings of interest were that negative mood was associated with heightened pain to brief electrical stimuli during the task, whereas negative mood apparently inhibited sustained cold pressor pain after the task. Interestingly, low self-efficacy in terms of avoiding the shocks was associated with high pain ratings both for shocks and the CPT.

2.4.2 Effects of stressor controllability and predictability on pain

Inhibition of sustained cold pressor pain

As hypothesised, subjects who perceived that they had very little control over shocks during the math task experienced significantly greater decreases in cold pressor pain when compared to their counterparts in 'controllable' (less difficult/ stressful) conditions. Significant decreases in self-efficacy after the practice trials for subjects in 'uncontrollable' conditions confirmed that stressor controllability was successfully manipulated in the math task. Studies have shown that exposure to an aversive event – over which the subject is not permitted to alter or exert control – produces strong analgesic reactions in humans (Gracely et al., 1983; Janssen & Arntz, 2001) and animals (Maier, 1986; Maier et al., 1982; Maier et al., 1983) that persists for some

time after the termination of the stressful stimulus. Thus, the present findings of SIA in humans concur with results demonstrated previously in the literature.

With regards to the effect of stressor predictability on pain perception, no hypotheses could be formulated due to largely inconclusive effects in recent literature. Instead, stressor predictability was controlled in each condition to clarify the effects (alone and in conjunction with stressor controllability) on cold pressor PI and UP. Alone, the predictability of task shocks seemed to have very little impact on cold pressor pain sensitivity, self-efficacy, mood, or the mediation of mood on pain. These results appear to be in contrast with evidence of conditioned analgesia in humans (Flor et al., 2002; Willer & Albe-Fessard, 1980a; Willer et al., 1981). However, pain tolerance and threshold rather than PI were assessed in conditioning studies – measures which are affected by factors other than pain sensitivity (e.g., instructions, motivation - Gelfand, 1964; Wolff et al., 1965). Moreover, Willer et al. (1980a; 1981) failed to separate pain from stress (using noxious foot-shocks as a stressor), and measured the nociceptive flexion reflex as a pain-related outcome instead of subjective reports of pain. Therefore, divergent methodologies make it difficult to compare these findings with the current results.

Despite having relatively little effect on its own, stressor certainty interacted with stressor controllability, resulting in pain insensitivity in 'uncontrollable-unpredictable' and 'uncontrollable-predictable' conditions at different times during the CPT. A slight hyperalgesic effect noted early on in the 'uncontrollable-unpredictable' condition appeared to mask an analgesic response observed in the 'uncontrollable-predictable' condition. Previous research has established that unpredictable events are more aversive than predictable events (Seligman et al., 1971), leading to higher secretions of gastric acid, more stomach lesions, greater weight loss in response to stress, and more distress vocalisations (Abbott et al., 1984). Furthermore, predictable shocks are preferred over unpredictable shocks when the duration of the stress is brief and not intense (Abbott et al., 1984). In accordance with these findings, distress associated with unpredictable shocks may have initially overridden endogenous analgesic effects that developed towards the end of the CPT.

Hyperalgesia in response to brief electrical stimuli

The controllability of electric shocks did not influence shock PI or UP. Moreover, ratings increased throughout the math task. These findings diverge from animal studies (Akil et al., 1976; Hayes et al., 1976; Hyson, Ashcraft, Drugan, Grau, & Maier, 1982; Jackson et al., 1979; Lewis et al., 1980; Lewis et al., 1981; Lewis et al., 1984; Maier et al., 1982) and human studies (Flor et al., 2002; Willer & Albe-Fessard, 1980a; Willer et al., 1981) that demonstrated immediate SIA with inescapable shocks. The difference between this study and findings with animals could be attributed to the number and duration of shocks delivered. To illustrate, shocks in animal research were considerably longer in duration (i.e., 5-180 seconds versus 25 milliseconds), and delivered more frequently during experimentation (i.e., 60-80 shocks versus 3 shocks). In animals, it has been established that many (at least 5) prolonged shocks (>60 seconds - Maier et al., 1983), over an extended period of time (20-30 minutes) are necessary for the animal to learn that it has no control over these events, and subsequently activate descending pain inhibitory influences (Hyson et al., 1982). Similarly, shocks used in other human studies were considerably more intense and frequently delivered (e.g., 70 mA, 19-20 times during three 90 minute sessions - Willer et al., 1981) than those used in the present study (i.e., 15 mA, 3 times during a 20 minute math task). Therefore, although subjects in uncontrollable conditions learnt that the electrical shocks were inescapable, the frequency, duration and intensity of shocks may have been insufficient for SIA to inhibit shock PI and UP.

Similarly, shock predictability failed to influence reports of shock PI or UP. In a large number of studies reviewed by Miller (1981), there was very little effect of stressor certainty on subjective reports of pain. Thus, the unremarkable effects of predictability on cold pressor and electrical pain stimuli concurs with this extensive review and recent laboratory studies (Crombez et al., 1994; Klemp & Rodin, 1976; Lejuez, Eifert, Zvolensky, & Richards, 2000).

2.4.3 Cognitive-affective mediators of pain

The current study examined the effects of experimentally induced anxiety, discouragement, anger and perceived self-efficacy on pain perception. The math task proved to be a powerful cognitive stressor as subjects from each experimental condition experienced significant increases in negative emotion during the task. Some moods, such as discouragement and anger, remained elevated even after the task had been completed. As expected, 'control' over shocks influenced feelings of discouragement and self-efficacy both during and after the task, where subjects who perceived shocks to be uncontrollable reported significantly greater levels of discouragement and lower self-efficacy than those who perceived the shocks to be controllable.

Previous research with animals has established that predictable events are less aversive than unpredictable events (Abbott et al., 1984). Therefore, it is not surprising to find that anxiety in humans is lower for predictable than unpredictable aversive events (Crombez et al., 1994). In the present study, subjects in predictable and unpredictable conditions experienced similar levels of anxiety. This may be attributed to a number of factors. First, anxiety was not measured during the warning period, when the screen changed from black to blue, only periodically throughout the task and anxiety was averaged at the end. Therefore, the measurement of anxiety may not have been sensitive enough to detect differences during times in which shocks were predictable. Second, the task required that subjects perform well in between blue screens, meaning that times signalling no aversive event (i.e., black screen) were not times to relax, unlike in other experiments. Furthermore, the math task was a powerful stressor causing persistent negative mood (including anxiety), and it may be that effects of the stressor itself outweighed the benefits of warning periods. Finally, the lack of difference between conditions could be attributed to the fact that shocks were not delivered during every warning period, possibly weakening the manipulation of predictability in this study.

The manipulation of predictability failed to influence mood and had little effect on pain perception, therefore, appearing not to be a promising technique. Thus, stressor predictability was not adopted in subsequent studies. Methodological limitations of

the present study and possible implications of assessing predictability in future studies will be addressed in the general discussion.

Negative mood and inhibition of cold pressor pain

Increases in anxiety, discouragement and anger during the math task were associated with a reduction in cold pressor pain after the math task. Emotional inhibition of cold pressor PI and UP following the cognitive stressor concurs with the majority of animal and human studies in which subjects were exposed to uncontrollable, aversive, and intensely arousing stimuli. For instance, SIA experienced by animals exposed to uncontrollable stressors was reversed by diazepam, an anti-anxiety agent (Maier, 1990; Takahashi et al., 1988). These results have been replicated in humans in situations where intense anticipation (Willer & Ernst, 1986) or fear of actual electrical stimuli (Rhudy & Meagher, 2000) led to analgesic responses that could be reduced or reversed by diazepam.

Rhudy and Meagher (2001b) suggested that the *valence* (negative/positive) and *intensity* of emotions interact to influence pain. According to this notion, pain is facilitated by negative emotion of low to moderate intensity, but inhibited by negative emotions that lead to high levels of arousal. Therefore, the association between intense negative emotions and a reduction in cold pressor pain in the present study provides support for Rhudy and Meagher's (2001b) notion that highly arousing negative emotions inhibit pain. These results also demonstrate that negative mood mediated analgesic effects for some time after the math task.

No relationship was detected between absolute mood and cold pressor pain ratings before or after the math task. At first glance, these results seem puzzling and at odds with those of change scores (discussed above). However, one possible explanation is that inter-subject variability in absolute mood ratings diluted the relationship between mood and cold pressor pain perception. To explain, absolute ratings reflect rating biases and socially desirable reporting, and would thus be highly subject to individual differences. Change in mood, on the other hand, would probably be rated according to 'similar rules' across participants, thus reducing the error variance and 'unmasking' the effects of mood on pain.

There was no relationship between changes in self-efficacy and changes in cold pressor PI and UP after the math task; hence, self-efficacy failed to mediate SIA persisting beyond the stressor. The present findings concur with studies demonstrating a lack of relationship between self-efficacy and PI (Litt, 1988; Ohlwein et al., 1996; Stevens, 1992). Absolute ratings of self-efficacy were negatively related to cold pressor pain sensitivity after the math task, perhaps for the same reasons mentioned for electro-cutaneous stimuli (i.e., positive mood associated with high self-efficacy leading to pain reduction; see next paragraph).

Negative mood and sensitisation to brief electrical pain

Correlational analyses identified a positive association between mood and the perception of electric shocks. For instance, the more anxious, discouraged and angry a subject was, the more UP and/or PI they experienced during the shocks. Although pain sensitisation by negative affect has been corroborated by a large body of human research (Bandura, Taylor, Williams, Mefford, & Barchas, 1985; Cornwall & Donderi, 1988; Drolet et al., 2001), these findings are at odds with those found for the cold pressor stimulus.

It has been proposed that emotions such as anxiety and depression heighten sensations of pain through the increased release of noradrenaline - a neurotransmitter known to sensitise nociceptors in the periphery, thereby increasing PI (Romano & Turner, 1985). Furthermore, there is some suggestion that a reduction in parasympathetic tone during stress may also deactivate other pain inhibitory systems (Pinerua-Shuhaibar, Prieto-Rincon, Ferrer, Bonilla, Maixner, & Suarez-Roca, 1999). Others explain negative mood-induced acute pain sensitivity with theories of attention (Arntz et al., 1994) and, less convincingly, attribution of arousal (Janssen, 2002). Neither theory adequately accounts for mood sensitisation of pain, as negative mood should be attributed to the math task (away from the pain), hence *decreasing* perceived intensity of the shocks.

In the context of cold pressor findings, the most credible explanation for these results is that the hyperalgesic effects of negative mood masked pain inhibitory mechanisms for *brief, intermittent* electrical pain but not *prolonged* cold pressor pain. In other

words pain facilitatory effects of negative mood were evident for less arousing pain stimuli, namely electric shocks. This explanation is in keeping with Rhudy and Meagher's (2001b) notion that low to moderate emotional arousal facilitates pain, whilst high levels of arousal inhibits pain. It is possible that negative mood and arousal during the math task intensified during the highly noxious cold pressor stimulus, unmasking pain inhibitory influences.

Perceived self-efficacy to control shock frequency was negatively related to shock sensitivity, in that self-efficacious subjects reported less shock PI and UP. Although self-efficacy has been identified as a strong predictor of pain threshold and tolerance (Baker & Kirsch, 1991; Bandura et al., 1988; Bandura et al., 1987; Reese, 1983; Vallis & Bucher, 1986), the effect of self-efficacy on PI or UP is less clear (Holroyd et al., 1984; Litt, 1988; Ohlwein et al., 1996; Stevens, 1992; Stevens, 1993). Moreover, in the only known study in which an association was identified, self-efficacy and PI were *positively* related (Stevens, 1993). The divergent results of the present study may be explained by the type of self-efficacy measured, which related to performance on the math task rather than PI/UP regulation (in contrast to Stevens, 1993). According to Bandura and colleagues (1987), self-efficacy can bring relief from pain in two ways: firstly, by reducing negative anticipations which heighten physiological arousal and bodily tension that exacerbates perceived pain; secondly, by diverting attention to the challenge at hand, rather than towards painful sensations. Positive mood has been associated with reductions in pain (Rhudy & Meagher, 2001b) and since self-efficacy was inversely associated with anxiety, discouragement and anger in the present study[6], it is possible that high self-efficacy may have indirectly reduced shock PI and UP via positive mood. This explanation is corroborated by the positive relationship found between negative mood and shock PI and UP.

In summary, negative mood and self-efficacy mediated the effects of stressor controllability on the perception of both electrical and cold pressor pain stimuli. Specifically, more intense anxiety, discouragement, anger, and low self-efficacy were associated with high ratings of electrical PI and UP during the math task.

[6] See Appendix 1, p 319.

Conversely, negative mood persisting beyond the math task appeared to inhibit cold pressor pain perception. The action of these mediators could be partially explained by the nature of each pain stimulus. To clarify, although subjects were strongly encouraged to persist with each pain stimulus, the CPT was prolonged, and intensely painful which may have encouraged the activation of endogenous pain inhibitory mechanisms. However, since cold pressor analgesia was only found in the 'uncontrollable' conditions, the stress of the math task in conjunction with the CPT appeared to be necessary to activate pain inhibitory systems. Electrical shocks, on the other hand, were brief and intermittent, and were more likely to be affected by pain facilitatory effects of moderately arousing negative emotions during the math task.

CHAPTER THREE

3. STUDY 2

3.1 INTRODUCTION

3.1.1 Rationale/Purpose of this study

Opioid and nonopioid mediators of stress-induced analgesia (SIA)

The previous study provided preliminary support for the notion that the controllability of an aversive event and intense, experimentally induced anxiety, discouragement and anger were associated with endogenous pain inhibition – at least with cold pressor pain stimuli.

Studies have shown that endogenous opioids mediate a late-analgesic response in animals exposed to prolonged inescapable stressors (Grau et al., 1981; Jackson et al., 1979; Lewis et al., 1980; Lewis et al., 1981; Maier et al., 1982), and similarly in humans exposed to uncontrollable stress that is induced experimentally (Bandura et al., 1988; Clark et al., 1986; Flor et al., 2002; Pitman et al., 1990; Willer et al., 1981; Willer & Ernst, 1986) and in real-life (Janssen & Arntz, 2001; van der Kolk et al., 1985). Nonopioid forms of SIA, on the other hand, are induced after exposure to escapable stressors and dissipate more rapidly than opioid-mediated analgesia (Maier et al., 1982; Maier et al., 1983). Also, opioids are present in neural pathways that mediate both mood and pain in humans (Janssen, 2002). Therefore, mood-mediated and stress-induced decreases in pain after the psychological stressor in Study 1 may have been due to the release of endogenous opioids. Thus, the administration of naltrexone, an opioid antagonist, would help assess whether opioid or nonopioid substrates mediated the analgesic effect observed in Study 1.

Separation of pain and stress

Pain and stress have often been confounded in studies examining SIA. To ensure that pain (from the electric shocks) was not confounded with the stress of the math task, an additional 'uncontrollable' condition with double the number of shocks was included in the experimental design. Therefore, any difference in pain perception between the 'hard task-many shocks' and 'hard task-few shocks' conditions would suggest that the pain stimulus, and not the psychological stressor alone, may be at least partly accountable for analgesic effects. Shocks were increased from three to seven, as this was the maximum number of shocks that could be delivered throughout the math task whilst still maintaining the 'random' delivery sequence.

Physiological measures of stress – BP/pulse rate

Challenging mental activities such as timed mental arithmetic questions, and stressful tasks requiring active coping can lead to increases in BP and heart rate (Andreassi, 1989). Hence, measures of systolic and diastolic BP and pulse rate were included as general physiological indices of mental stress in the present study.

Interaction between cardiovascular and pain inhibitory systems

The cardiovascular system - via the stimulation of baroreceptors or centrally-mediated analgesic mechanisms - plays an important role in endogenous antinociceptive responses to acute pain in normotensive humans (Bruehl et al., 1992; McCubbin & Bruehl, 1994). Recent investigations have suggested that opioids may mediate the blood pressure-hypoalgesia relationship that occurs within the normotensive humans (Bragdon et al., 2002; McCubbin & Bruehl, 1994). Nonetheless, few studies have convincingly identified the physiological substrates underlying this relationship within the normotensive range of BP. Examining the relationship between cardiovascular and acute pain responses in normotensive subjects under opioid blockade could shed light on the role of opioids in the cardiovascular-pain regulatory relationship.

3.1.2 Aims of Study 2

Primary aims

The **first aim** was to replicate the finding from Study 1 that an uncontrollable psychological stressor (math task) decreased pain.

The **second aim** was to determine whether analgesia induced by the math task was mediated by opioid or nonopioid substrates. To test whether the opioid system was activated, one half of the subjects received a capsule containing naltrexone, an opioid antagonist. The other half were given an identical capsule of sugar (i.e., placebo).

The **third aim** was to investigate whether the number of noxious electrical shocks during the math task, or the task itself, inhibited pain.

Secondary aim

The **fourth aim** was to investigate the effect of cardiovascular activity on pain sensitivity in normotensive subjects, both during the psychological stressor and at times of rest. Opioid mediation of the cardiovascular-pain relationship was examined by comparing responses in subjects under opioid blockade with those who were not.

3.1.3 Hypotheses for Study 2

In light of aims of the second study, it was hypothesised that:

Lack of control over shocks during the math task should lead to stress and the activation of endogenous opioids. Therefore, placebo recipients in 'uncontrollable' conditions should give lower ratings of cold pressor PI and UP after the math task, compared to ratings beforehand. Conversely, subjects under opioid blockade should demonstrate increased cold pressor pain sensitivity. Subjects in the 'controllable' condition were expected not to experience stress, nor the activation of endogenous opioids. Hence, cold pressor pain perception was expected not to change in either placebo or naltrexone groups before or after the math task in the 'controllable' condition.

As the inclusion of more shocks in the 'hard task-many shocks' condition was purely exploratory, it was unclear what effects this would have on the inhibition of pain. Thus, no hypotheses could be generated.

Based on results of previous normotensive research, it was hypothesised that cardiovascular activity would be negatively related to PI and UP ratings for electrical and cold pressor stimuli in placebo participants. However, there should be no evidence of a relationship between cardiovascular activity and pain sensitivity following opioid blockade with naltrexone.

3.2 METHOD

3.2.1 Subjects

Seventy subjects aged between 17 and 55 years [34 males: M = 24.88 years, SD = 8.49; 36 females: M = 23.61 years, SD = 8.77] participated in Study 2. Criteria used to exclude subjects were identical to criteria described in Study 1. Additional exclusion criteria included digestive problems, as naltrexone produces 'gastric distress' in 20% of healthy subjects (Meyer, Straughn, Lo, Schary, & Whitney, 1984), and medication that alters liver metabolism, as these drugs alter the concentration of naltrexone (Kleber, 1985). Four subjects withdrew prematurely due to the noxious nature of the CPT (N = 1) or 'hard task-few or many shocks' conditions of the math task (N = 3). Although attrition from the math task was non-random, numbers were minimal and deemed not to impact upon the overall results. Subjects were recruited from Murdoch University undergraduate psychology classes and the general university population. Subjects were remunerated $15 for their participation. Sixty-eight subjects were right-handed and two were left-handed as established by Bryden's Handedness Questionnaire (1977) (Appendix 2, p 320).

Subjects refrained from eating and smoking two hours prior to the experiment, as an empty stomach would facilitate drug absorption. As naltrexone interacts with alcohol (Kleber, 1985), subjects abstained from consuming alcohol 12 hours prior to, and at least 24 hours after ingesting the drug. Subjects abstained from consuming

caffeinated beverages 12 hours before being tested so that reproducible cardiovascular measures could be obtained (Shapiro, Jamner, Lane, Light, Myrtek, Sawada, & Steptoe, 1996).

3.2.2 Experimental design/Overview

As shown in Figure 3.1, subjects completed mood/self-efficacy ratings, CPTs and had their BP and pulse rate measured before the drug, approximately 50-60 minutes after the drug, and on completion of the math task. Prior to the math task, subjects were randomly assigned to the placebo or naltrexone group in one of three experimental conditions ('easy task-few shocks', 'hard task-few shocks', and 'hard task-many shocks') balanced for age ($F(5,64) = 1.28$; $p = .28$) and sex (Table 3.1). Mood/ self-efficacy ratings, cardiovascular measurements, and PI/UP shock ratings were completed during the task. Subjects were tested individually.

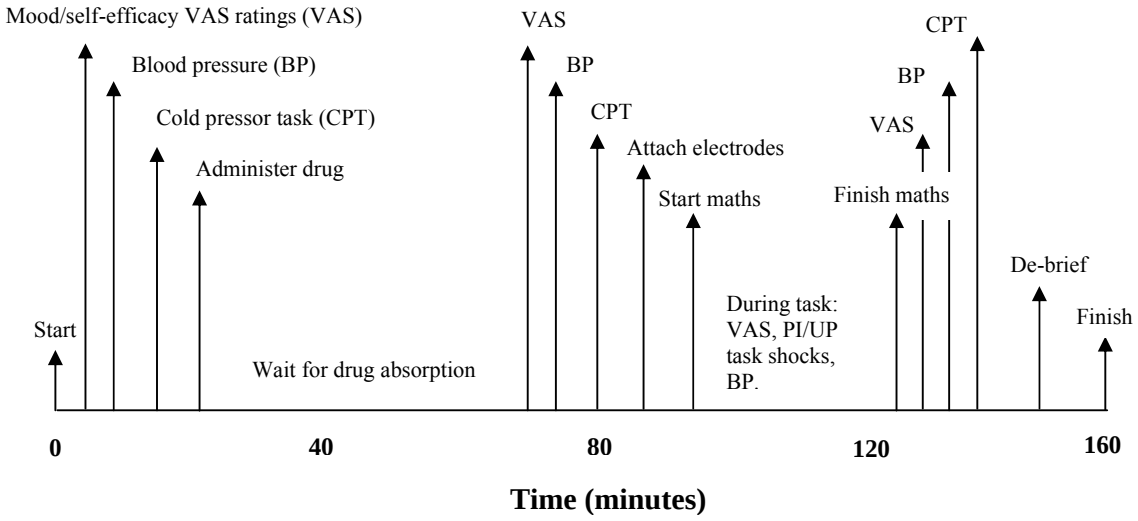


Figure 3.1: Experimental timeline for Study 2.

3.2.3 Procedure/Materials

As in Study 1, the subject was seated at a desk inside one of two air-conditioned cubicles maintained at 22 ± 2°C (Cubicle A) and given a consent form to read (Appendix 5, p 325). Informed consent was obtained from each subject in writing, and a medical checklist (Appendix 6, p 326) was completed.

Table 3.1: Subject age and sex in each experimental condition.

	EFS		HFS		HMS	
	Naltrexone	**Placebo**	**Naltrexone**	**Placebo**	**Naltrexone**	**Placebo**
Mean	24.45	22.90	21.00	29.17	23.23	24.82
SD	6.79	4.82	4.58	12.86	7.96	10.65
N	6F, 5M	5F, 5M	6F, 7M	6F, 6M	7F, 6M	6F, 5M

Note. EFS = easy task-few shocks; HFS = hard task-few shocks; HMS = hard task-many shocks; F = females; M = males.

Mood and self-efficacy ratings

As described in Study 1, mood (anxiety, confusion, discouragement, anger, sluggishness and liveliness) and self-efficacy (with regards to avoiding electric shocks during the math task) were rated on separate 0-100 point VAS. Paper and pen ratings were made pre-drug, post-drug, and after the math task, and ratings were made using computer-generated VAS at irregular intervals during the math task, as described in Study 1.

Cardiovascular responses

BP and heart rate were measured as they serve to indicate mental load and task difficulty (Andreassi, 1989). Resting measures were compared with those taken during the math task, to assess the effect of a cognitive stressor on cardiovascular activity.

Systolic and diastolic blood pressure (SBP, DBP) and pulse rate were measured pre-drug, post-drug, during and after the math task with an M4 Omron automatic digital BP monitor. The automatic monitor measured BP within ± 3 mmHg (or 2 %), and pulse rate within ± 5 % of the actual reading (manufacturer's guarantee)[7]. Initial

[7] Prior to use, the accuracy of the electronic monitor was calibrated with a mercury manometer by connecting a cuff to both. Three measures were taken from eight subjects and averaged. During the manual method, SBP was indicated by the first appearance (Phase 1) and DBP by the disappearance (Phase 5) of the Korotkoff sounds (Shapiro et al., 1996). Measuring DBP at Phase 5 rather than at

measures were taken after the subject had been resting in excess of five minutes (Shapiro et al., 1996). A medium 140 mm (width) x 480 mm (length) BP cuff was applied to the (clothing free) dominant forearm, with the bottom edge of the cuff 2 cm above the bend of the elbow covering the brachial artery. Although the right arm can lead to BP measures 2-10 mmHg higher than the left, BP is usually measured from this arm (O'Brien & O'Malley, 1981). The cuff automatically inflated to 170 mmHg, deflating 5 mmHg/sec until the DBP range was reached, after which the pressure was released and the cuff was fully deflated.

During all measurements, subjects were seated with their forearm resting horizontally on a desk, at the level of the heart. Placing the cuff at heart level reduced the hydrostatic effects on BP (Shapiro et al., 1996). Hydrostatic effects alter BP by 0.7 mmHg per centimetre that the cuff is placed above or below the level of the heart. Subjects were instructed to not speak and remain as relaxed and still as possible when the cuff was inflating, as movement or muscle tension often resulted in an error. This was stressed to subjects prior to the math task, and a sock was placed over the subject's dominant hand to prevent him or her from using this hand to answer math questions during the task.

Although automatic devices have been deemed highly convenient (Shapiro et al., 1996), it is their susceptibility to artifactual readings that highlights the importance of identifying such errors (Clark, Denby, Pregibon, Harshfield, Pickering, Blank, & Laragh, 1987). According to Shapiro et al. (1996), a measurement ± 30 mmHg in the context of adjacent readings could be classified as an artefact or outlier. Since BP varies at most ± 10 % over a 24-hour period (Parati, Mutti, Omboni, & Mancia, 1992), Shapiro's criterion appeared to be justified. Therefore, any SBP, DBP or pulse reading ± 30 mmHg from adjacent readings was substituted with an average of nearby readings. Similarly, a missing measurement (resulting from an error) was

---

Phase 4 when Korotkoff sounds have become muffled is the preferred method (O'Brien & O'Malley, 1981). SBP and DBP obtained from the electronic monitor correlated closely with measures from the manual method (SBP: r=.88, p=.004; DBP: r=.92; p=.001). Similar relationships were found when calibrating the unit (averaging three measures from six subjects) at the end of the study (i.e., SBP: r=.99, p<.001; DBP: r=.69, p=.13), as recommended by Shapiro et al. (1996).

substituted with an average of values temporally closest to the missing value (e.g., readings taken before and after). The presence of a camera inside Cubicle B assisted in ascertaining the reason for erroneous readings.

On each occasion, resting measures were taken five times at 2-minute intervals. To avoid the effect of startle (Shapiro et al., 1996), the first two measures were discarded, and the following three measures were averaged. Throughout the math task measures were taken every two minutes until task-completion, resulting in a maximum of 17 measures. The cuff was inflated at 2-minute intervals to allow re-circulation of blood, and to minimise discomfort during prolonged, repeated measures (O'Brien & O'Malley, 1981). Realistically, the rate of inflation/deflation only allowed for this rate of measurement.

Cold pressor tasks

As detailed in the previous study, subjects completed a 4-minute CPT in Cubicle A before and after the drug, and immediately after the math task. The equipment and procedures used during each CPT were identical to those used in Study 1 (Appendix 7, p 327 for standardised instructions). Slight changes in water temperatures during each CPT (warm -1.90°C; cold +1.5°C) were consistent across groups.

Naltrexone intervention

Naltrexone is known to competitively bind to opioid receptors, thereby counteracting analgesic effects of opiates and endogenous opioid activity (Gonzalez & Brogden, 1988). To investigate endogenous opioid activation during the current experiment, half the subjects in each experimental condition were administered a flour-packed opaque gel capsule containing a 50 ml caplet of naltrexone, and the other half received an identical capsule containing a same-sized sugar pellet, or placebo. A 50 ml dose of naltrexone can block the powerful subjective and objective effects of intravenously-administered heroin (25 ml) in opiate-dependent individuals (Gonzalez & Brogden, 1988). Therefore, this dose was deemed adequate to produce complete blockade of endogenous opioids. Using a double-blind design, each drug condition

was assigned a code by someone other than the experimenter, and the experimenter randomly assigned subjects to either code.

When compared to another commonly investigated opioid-antagonist, naloxone, naltrexone possesses minimal agonistic properties (Gonzalez & Brogden, 1988) and is longer-lasting with a half-life of approximately four hours (Meyer et al., 1984). Naltrexone is administered easily (orally) and demonstrates excellent systemic availability in proportion to the administered dose - with a reported 60% reaching systemic circulation (Gonzalez & Brogden, 1988). Naltrexone reaches peak plasma levels within one hour when taken on an empty stomach; hence, testing was suspended for approximately 60 minutes after drug administration to achieve maximum absorption.

In a small proportion of healthy subjects (4-20%) a 50 ml dose of naltrexone is associated with side effects such as lethargy (King, Volpicelli, Frazer, & O'Brien, 1997), mild malaise (Hollister, Johnson, Boukhabza, & Gillespie, 1981; Mendelson, Ellingboe, Keuhnle, & Mello, 1978; Meyer et al., 1984), decreased mental acuity (King et al., 1997), anxiety (Malcolm, O'Neil, Von, & Dickerson, 1987), constipation, light-headedness, nausea, lack of appetite, body aches and headaches (Meyer et al., 1984). However, these studies have been criticised for serious methodological flaws such as inadequate sampling, reliance on anecdotal reports and lack of valid assessment instruments (Malcolm et al., 1987). In the treatment of alcohol and opiate addiction, Miotto, McCann, Basch, Rawson, and Ling (2002) reported that dysphoria was not a serious side-effect stemming from the long-term use of naltrexone. Similar results have been found in non-addicted healthy individuals taking naltrexone for two months (Malcolm et al., 1987). In light of these results, a one-off dose of naltrexone was deemed unlikely to cause serious malaise. In fact, only 14% of subjects taking naltrexone in the present study reported mild side effects (i.e., nausea, fatigue or decreased mental acuity) – none of which prevented subjects from completing the experiment.

Math task

Subjects completed a timed, computer programmed 30-minute[8] mental arithmetic task in Cubicle B. Aside from the parameters of each experimental condition (described in the next paragraph), the instruments and procedures were identical to those used in Study 1.

Specifically, the 'easy task-few shocks' (EFS) and the 'hard task-few shocks' (HFS) conditions were identical to the 'controllable' and 'uncontrollable' experimental conditions, respectively, in Study 1. The 'hard task-many shocks' (HMS) condition also resembled the 'uncontrollable' condition in the first study; however, the number of shocks was increased from three to seven. Task duration was extended from 20 to 30 minutes to accommodate the increase in number of shocks. Consequently, shocks were scheduled at different times across conditions (EFS and HFS: 3, 14, 27 minutes into the task; HMS: 3, 6, 12, 14, 16:30, 19, 27 minutes into the task). As in Study 1, shocks were delivered at irregular intervals to prevent subjects from guessing the schedule of shocks, and to add validity to the cover story of the 'performance-shock' contingency during the math task.

Task shocks

Stimulation consisted of either three or seven 15 mA ± 0.95 (SEM) rectangular pulses of 25 milliseconds duration. Minor variations in shock intensity may be attributed to slight fluctuations in skin impedance (M = 4.2 K ohms ± 0.5 SEM) induced by the repeated delivery of shocks. The instruments and procedures used to deliver the shocks and record the PI and UP ratings of each pulse were identical to those described in Study 1.

[8] Subjects took approximately 32-34 minutes to complete the task as the task was suspended each time subjective ratings were completed.

Debriefing

The purpose of the study was explained and subjects were remunerated after all tasks were completed. Details of the math program were concealed as the task was to be used in Study 3. Subjects were not told which drug they had taken to preserve the double-blind nature of the design. Instead, subjects were instructed to contact the experimenter if they experienced any adverse effects, and that the code could be 'broken' if necessary. After being 'broken', the code was re-set according to procedures mentioned above (see *Naltrexone intervention*, p 115). Due to the double-blind nature of the design, all subjects were warned against consuming alcohol within 24 hours after the experiment.

3.3 RESULTS

3.3.1 General data outline

Dependent variables were explored at three time points during the experiment: prior to drug administration; post-drug administration/prior to the math task; and post-math task. Initial ratings helped identify pre-existing, chance differences among groups. Post-drug ratings served a dual purpose: first, to detect the effects of naltrexone on the dependent variables, and second, to act as baseline ratings from which change during and after the math task could be calculated.

Pearson product correlations and hierarchical linear multiple regression analyses were both computed as they each provided a unique insight into the data. In particular, correlations provided an overview of relationships between continuous dependent variables, whilst multiple regression analyses allowed for the simultaneous analysis of continuous and categorical data - from which definitive conclusions regarding group differences could be drawn. Results of regression analyses are summarised as *t* values due to the large number of analyses. The issue of *multicollinearity,* whereby variables (including the interaction term) are correlated, is usually addressed by *centering* continuous variables (Jaccard, Turrisi, & Wan, 1990). Centering is the process by which the grand mean is subtracted from each subject's

raw score, resulting in a deviation score (Cohen & Cohen, 1983). In the present study, the data satisfied the criterion of $r \leq .85$ within the matrix of independent variables (Pedhazur & Kerlinger, 1982), thus departing from singularity. Therefore, centering was deemed unnecessary.

Identical practices were adopted in Study 3 and 4.

3.3.2 Randomisation check

Separate 2 (Drug: naltrexone, placebo) x 3 (Condition: EFS, HFS, HMS) univariate ANOVAs were carried out on each pre-drug mood, self-efficacy, resting BP and pulse rate, and mean PI and UP ratings on the CPT. As indicated in Tables 3.2 and 3.3, groups did not differ on any dependent variable at the outset of the experiment. Cardiovascular measures were within normotensive ranges (Lobstein et al., 1989; O'Brien & O'Malley, 1981).

Table 3.2: Pre-drug measures in each experimental condition.

	Placebo						Naltrexone					
	EFS (N = 10)		HFS (N = 11)		HMS (N = 11)		EFS (N = 11)		HFS (N = 14)		HMS (N = 13)	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Mood												
Ax.	29.5	19.3	27.0	22.1	38.0	23.1	33.2	19.0	24.1	19.7	35.8	21.0
Ds.	12.4	10.3	16.7	17.7	29.4	28.3	27.8	22.5	10.2	12.3	17.5	22.9
Ag.	3.2	3.2	2.7	4.2	10.4	11.3	8.6	13.7	6.1	8.8	10.6	17.4
Sf.	53.6	30.1	44.2	27.4	39.9	18.9	52.1	22.7	56.7	17.3	48.3	17.2
Cardiovascular measure												
SBP	119	12.5	118	8.8	121	12.6	116	18.6	118	12.2	113	12.8
DBP	74.0	11.0	73.1	10.8	72.5	12.8	72.8	11.3	71.6	8.8	67.1	6.7
Pulse	79.5	15.1	84.4	12.6	81.3	11.9	81.7	12.2	77.0	7.0	74.6	12.6
Cold pressor pain index												
PI	46.5	10.2	39.5	13.3	46.4	19.0	44.1	21.1	45.6	12.7	46.4	14.5
UP	47.8	8.3	43.2	16.3	48.1	21.2	40.5	24.6	45.4	14.1	40.8	17.2

Note. M = mean; SD = standard deviation; Conditions: EFS = easy task-few shocks; HFS = hard task-few shocks; HMS = hard task-many shocks; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute; PI = pain intensity; UP = unpleasantness.

Table 3.3: F ratios for pre-drug measures across conditions.

	Mood				Cardiovascular			Cold pressor	
Source	**Ax.**	**Ds.**	**Ag.**	**Sf.**	**SBP**	**DBP**	**Pulse**	**PI**	**UP**
Condition (C)	1.79	1.56	1.92	0.94	0.09	0.75	0.41	0.40	0.00
Drug (D)	0.01	0.04	1.24	1.45	1.31	1.22	1.91	0.12	0.94
C x D	0.17	2.87	0.31	0.57	0.55	0.31	1.11	0.46	0.58

Note. Degrees of freedom = 5, 64; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute; PI = pain intensity; UP = unpleasantness.

3.3.3 Mood and self-efficacy

Effects of the drug on mood and self-efficacy

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on each mood rating (Table 3.4 and 3.5). Apart from being examined in an initial randomisation check, self-efficacy ratings were not analysed before the math task as they related to performance *during* the task. Similarly, analyses were collapsed across experimental conditions, as this factor was not expected to influence mood ratings before the math task. As indicated by results in Table 3.5, anxiety (M = 31.25 versus M = 25.83) and discouragement (M = 18.99 versus M = 13.79) decreased after subjects had remained in the experimental environment for over an hour. Mood was not affected by drug, and no interactions were found.

Table 3.4: Pre-and post-drug mood ratings (collapsed across experimental condition).

	Placebo (N = 32)				**Naltrexone (N = 38)**			
	Pre-drug		**Post-drug**		**Pre-drug**		**Post-drug**	
Mood	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Anxiety	31.54	21.47	27.15	22.47	30.73	20.10	24.75	24.45
Discouragement	19.72	21.08	13.38	18.21	17.78	20.27	13.83	17.65
Anger	5.51	7.93	4.81	11.43	8.38	13.42	5.54	9.48

Table 3.5: F ratios of pre- and post-drug mood ratings (collapsed across condition).

Source	**Anxiety**	**Discouragement**	**Anger**
Time† (T)	4.20*	5.32*	2.27
Drug (D)	0.12	0.03	0.60
T x D†	0.10	0.29	0.83

Note. † Pillai's Trace F ratio; degrees of freedom = 1,68.

*p<.05.

Effects of the math task on mood and self-efficacy

Separate 2 (Drug: naltrexone, placebo) x 3 (Condition: EFS, HFS, HMS) x 5 (Time: pre-task, during task at 1:30", 7:40", 15:20", post-task) repeated measures ANOVAs were carried out on mood and self-efficacy ratings (Table 3.6 and 3.7). In self-efficacy analyses, post-practice trial ratings were used instead of pre-task ratings.

The exploration of Time effects with planned simple comparisons (where pre-task ratings were the point of comparison) indicated that all moods worsened during the task (Table 3.8). Discouragement and anger remained elevated once the task was completed, whereas anxiety returned to pre-task levels.

Post-hoc multiple comparisons (with Bonferroni corrections) were used to explore Condition main effects. Anxiety was influenced by the number of shocks delivered during the task, as subjects in the HMS condition reported significantly higher anxiety (M = 54.08) compared to those in the EFS (M = 38.99) and the HFS condition (M = 41.24). Task difficulty (and control over shocks) influenced how discouraged and inefficacious a subject became, as subjects in the HFS and HMS conditions were significantly more discouraged (HMS: M = 47.08, HFS: M = 39.46) and less self-efficacious (HMS: M = 24.52; HFS: M = 22.76) than their counterparts in the EFS condition (M discouragement = 26.63; M self-efficacy = 51.33). Anger increased with the number of shocks and task difficulty.

Time x Condition effects were found for discouragement and self-efficacy. Between-group comparisons at each time-point indicated that subjects in the EFS condition became significantly less discouraged, and more self-efficacious throughout the math task than subjects in the difficult conditions (Figure 3.2 and 3.3).

Table 3.6: Mood and self-efficacy before, during, and after the math task.

		Placebo						Naltrexone					
		EFS (N = 10)		HFS (N = 11)		HMS (N = 11)		EFS (N = 11)		HFS (N = 13[a])		HMS (N = 13)	
Mood	**Time**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Ax.	**Pre**	22.7	20.5	17.9	14.1	40.4	26.0	19.4	22.7	19.6	25.7	35.7	23.2
	1	57.9	14.8	46.6	27.2	66.4	16.3	52.1	25.4	61.3	17.0	67.1	27.7
	2	50.9	21.7	50.2	22.4	55.8	20.0	44.8	23.8	56.1	15.4	64.3	21.4
	3	49.1	19.4	46.7	16.9	56.2	26.8	41.6	20.1	56.0	19.7	64.8	26.3
	Post	29.6	23.0	25.8	18.7	37.8	29.0	23.1	15.9	28.7	23.5	49.9	32.3
Ds.	**Pre**	11.3	10.5	9.5	11.2	19.2	27.3	19.6	20.5	9.6	14.5	14.2	18.2
	1	42.0	26.1	38.4	20.3	60.7	16.4	34.8	26.8	51.7	22.0	56.0	31.0
	2	39.4	20.7	38.6	20.6	51.3	19.5	24.1	23.7	58.4	21.8	57.8	24.6
	3	32.6	23.9	46.0	13.7	56.5	25.0	23.3	22.3	59.1	17.5	57.7	28.2
	Post	25.7	27.3	28.2	23.6	44.0	16.6	13.1	13.9	40.6	35.2	52.8	29.0
Ag.	**Pre**	2.8	4.8	2.3	3.1	9.2	18.5	1.7	1.7	4.1	5.6	10.2	14.3
	1	17.5	19.7	9.0	9.9	28.6	21.9	16.4	21.7	36.4	23.7	29.5	28.4
	2	16.2	20.7	10.9	11.3	25.7	22.0	13.1	17.4	39.9	21.6	37.8	24.6
	3	10.6	15.7	15.3	13.5	31.2	29.0	20.5	23.8	42.8	25.3	45.2	30.5
	Post	4.9	8.0	4.4	4.3	15.7	23.0	11.3	18.4	29.6	29.4	34.3	28.2
Sf.	**Prac**	50.5	24.5	19.4	18.0	32.0	23.7	43.9	32.0	16.4	17.4	14.6	13.4
	1	49.0	23.8	27.5	17.6	32.5	22.4	47.5	28.8	23.5	19.8	21.6	22.1
	2	51.6	21.8	22.6	16.2	33.1	16.5	55.3	20.2	27.1	16.9	18.9	16.8
	3	43.6	21.2	21.9	22.2	34.6	16.4	55.2	22.6	28.6	17.6	15.2	13.7
	Post	54.1	27.6	21.1	20.9	26.5	20.3	62.5	25.6	19.3	15.7	16.1	15.7

Note. [a] N = 1 missing data; M = mean; SD = standard deviation; Conditions: EFS = easy task-few shocks; HFS = hard task-few shocks; HMS = hard task-many shocks; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; Pre = prior to practice trials and math task; Prac = following practice trials, prior to math task; 1-3 = 1:30, 7:40, and 15:20 minutes into math task, respectively; Post = after math task.

Table 3.7: F ratios for mood and self-efficacy before, during and after the math task.

Source	Anxiety	Discouragement	Anger	Self-efficacy
		Between subjects		
Condition (C)	6.74**	8.45***	5.15**	19.31***
Drug (D)	0.32	0.24	8.57**	0.58
C x D	1.16	1.83	2.31	1.93
		Within subjects		
Time† (T)	24.84***	29.36***	18.42***	2.36
T x C†	0.40	2.77**	0.62	2.14*
T x D†	0.16	0.12	2.44[a]	1.29
T x C x D†	0.53	1.13	1.43	1.40

Note. † Pillai's Trace F ratio; degrees of freedom: C, C x D = 2,63; D = 1,63; T, T x D = 4,60; T x C, T x C x D = 8,122.

[a]p=.056; *p<.05; **p<.01; ***p≤.001.

Table 3.8: Simple pair-wise comparisons[a] of mood and self-efficacy before, during and after the math task.

		Math Task			
Mood	**Pre**	**1**	**2**	**3**	**Post**
Anxiety	25.98	58.59***	53.68***	52.41***	32.48
Discouragement	13.90	47.27***	44.93***	45.88***	34.08***
Anger	5.05	22.89***	23.95***	27.60***	16.70***
Self-efficacy	29.42	33.56**	34.83*	33.29	33.25

Note. [a] Each rating was compared to pre-math task (mood) or post-practice trial ratings (self-efficacy); 1-3 = 1:30, 7:40, and 15:20 minutes into math task, respectively; Post = after math task.

*p<.05; **p<.01; ***p≤.001.

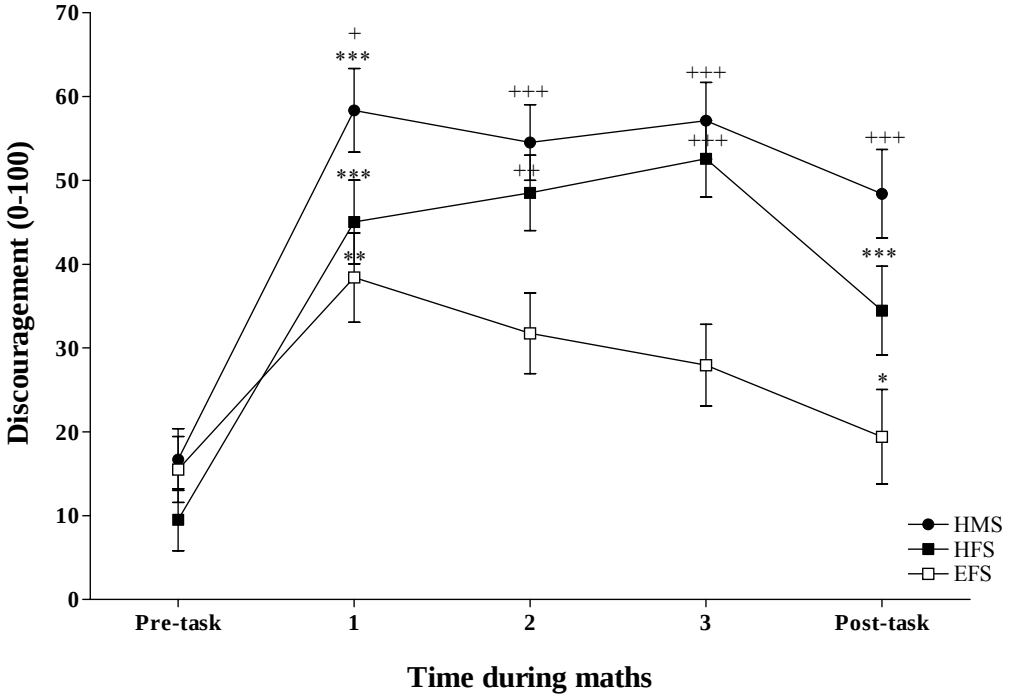


Figure 3.2: Discouragement before, during and after the math task in each experimental condition. Note. EFS = easy task-few shocks, HFS = hard task-few shocks, HMS = hard task-many shocks; *p<.05, **p<.01, ***p<.001 within-group, repeated pair-wise contrasts comparing ratings to the previous point; +p<.05, ++p<.01, +++p≤.001 t-test comparisons between EFS and each difficult condition at each time-point (i.e., no differences were found between HFS and HMS).

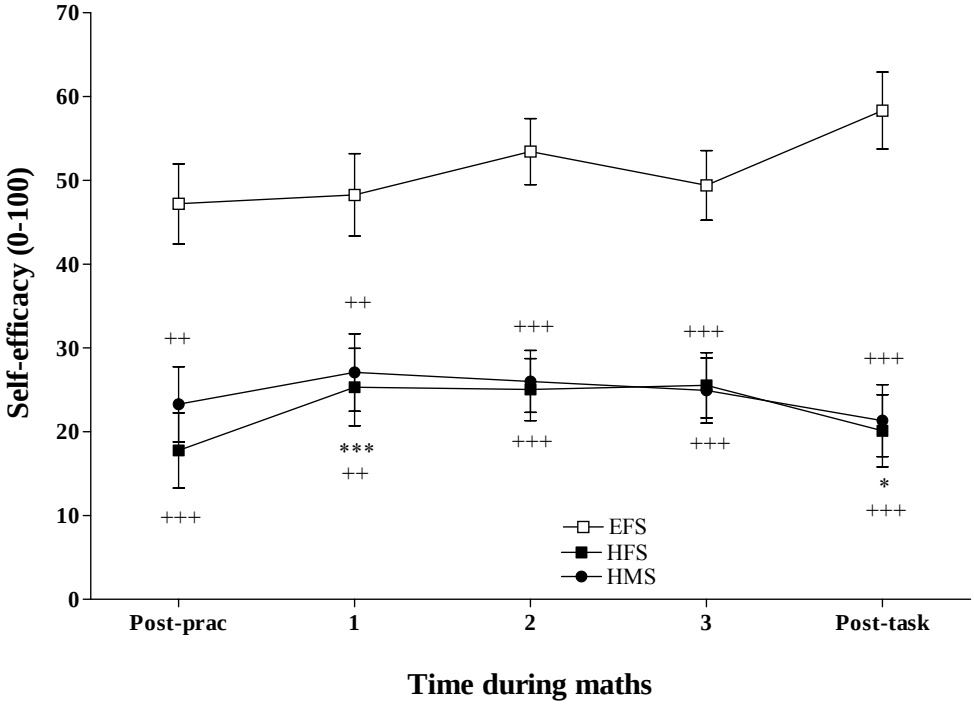


Figure 3.3: Self-efficacy before, during and after the math task in each experimental condition. Note. *p<.05, ***p≤.001 within-group, repeated pair-wise contrasts between successive points; ++p<.01, +++p≤.001 t-test comparisons between EFS and each difficult condition at each time-point (i.e., no differences were found between HFS and HMS).

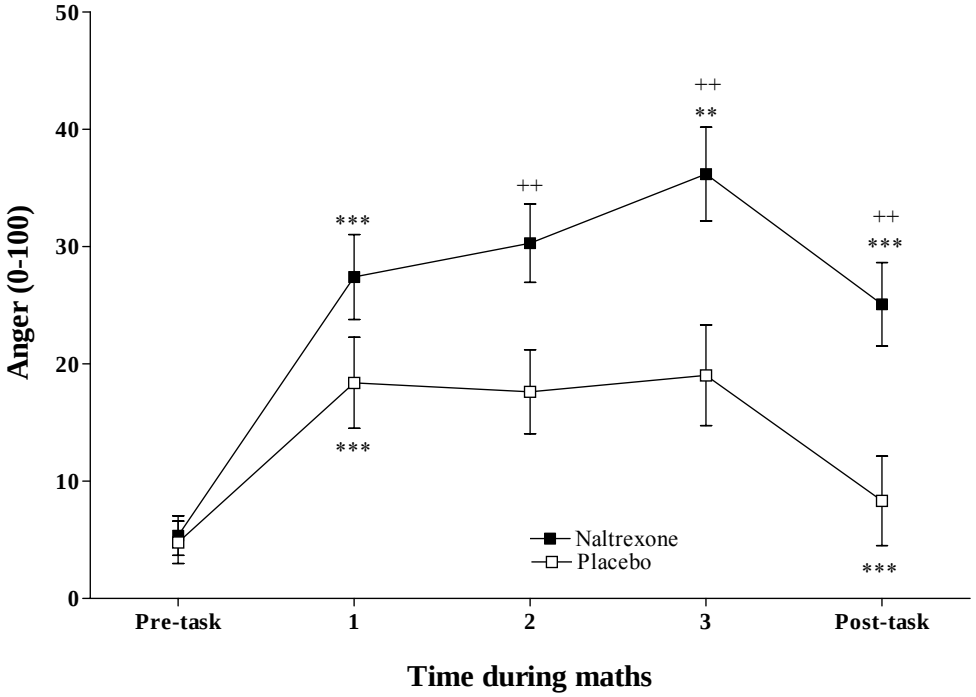


Figure 3.4: Anger before, during and after the math task for placebo and naltrexone recipients. Note. **p<.01 ***p≤.001 within-group, repeated pair-wise contrasts between successive points; ++p<.01 between group t-test comparisons at each time-point.

As shown in Figure 3.4, a Drug and marginal (p = .054) Time x Drug effect for anger indicated that endogenous opioids served to inhibit rising anger in subjects taking the placebo. Drug did not affect any other mood, self-efficacy, nor interact with any other factor.

3.3.4 Electro-cutaneous task shocks

Subjects received three 15 mA shocks in the EFS and HFS conditions, and seven shocks during the HMS condition. Ratings were averaged across all shocks and separate 2 (Drug: naltrexone, placebo) x 3 (Condition: EFS, HFS, HMS) univariate ANOVAs were carried out on mean PI and UP ratings (Tables 3.9 and 3.10).

Table 3.9: Pain intensity and unpleasantness ratings for shocks during the math task.

	Placebo						Naltrexone					
	EFS		HFS		HMS		EFS		HFS		HMS	
Shock	(N = 10)		(N = 11)		(N = 11)		(N = 11)		(N = 14)		(N = 13)	
rating	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
PI	34.9	16.2	45.8	16.7	45.5	24.9	29.1	17.2	48.4	21.7	46.9	24.7
UP	36.4	17.4	52.4	17.2	48.5	25.3	34.4	18.3	49.9	23.0	56.3	24.8

Note. Mean = mean; SD = standard deviation; PI = pain intensity; UP = unpleasantness.

Table 3.10: F ratios of pain intensity and unpleasantness ratings for shocks during the math task.

Source	Pain intensity	Unpleasantness
Condition (C)	3.65*	4.24*
Drug (D)	0.01	0.05
C x D	0.26	0.43

Note. Degrees of freedom = 5,64.

*p<.05.

Overall means suggested that subjects perceived the shocks to be moderately painful and unpleasant. The Condition main effect was explored with multiple comparisons corrected with the Bonferroni method. The difficulty of the task, and not the number of shocks influenced shock perception, as subjects in the EFS condition reported significantly lower PI and UP compared to subjects in HFS and HMS conditions. Shock ratings did not differ between HFS and HMS conditions. Drug failed to influence shock pain sensitivity.

Effects of mood, self-efficacy and the drug on task shock sensitivity

Hierarchical multiple linear regression analyses were used to explore the effect of mood and self-efficacy on shock PI and UP in each drug condition. Since the intensity of mood and self-efficacy (and not the experimental condition leading to these states) were of primary interest, results were entered into the regression analyses collapsed across condition. In each regression model, drug was the categorical independent variable, whilst mood and self-efficacy were considered moderator variables on shock PI and UP. The interaction term consisted of the product of drug and mood, or drug and self-efficacy variables. Drug and mood (or self-efficacy) were entered first, followed by the drug x mood (or drug x self-efficacy) interaction. As with earlier analyses, each mood and self-efficacy were investigated separately to help identify *qualitatively* different effects on shock responses. Pearson product correlations between these variables provided a context in which to interpret these results (Tables 3.11 and 3.12).

Table 3.11: Pearson correlations between mood, self-efficacy, shock pain and unpleasantness during the math task.

	Task shock pain index			
	Placebo (N = 33)		**Naltrexone (N = 37)**	
Mood during task	**PI**	**UP**	**PI**	**UP**
Anxiety	.50**	.52**	.46**	.31
Discouragement	.43*	.32	.45**	.37*
Anger	.39*	.32	.43**	.34*
Self-efficacy	-.12	-.30	-.16	-.13

Note. PI = pain intensity; UP = unpleasantness.

*p<.05; **p<01.

Table 3.12: Summary of t-values from hierarchical regression analyses illustrating the effects of mood, self-efficacy and drug on shock pain intensity and unpleasantness during the math task.

		Task shock pain index							
		Pain intensity				**Unpleasantness**			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Sf.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
1	**Drug (D)**	-0.46	-0.44	-1.17	-0.18	0.03	0.05	-0.53	0.19
	Mood (M)	4.44***	4.02**	3.76***	-1.18	3.56***	3.08**	2.88**	-1.65
2	**D x M**	0.93	0.81	0.11	-0.18	-0.85	-0.05	0.05	0.71

Note. Step 1 = main effects model (degrees of freedom = 2,67); Step 2 = full model (df = 3,66); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

**p<.01; *** p≤.001.

Anxiety, discouragement and anger were positively associated with shock PI and UP, indicating that the more negative a subject was feeling, the more PI and UP they experienced during each shock, regardless of drug (Table 3.12). Self-efficacy did not affect task shock sensitivity.

3.3.5 Cold pressor pain perception

A 4-minute CPT was completed at the beginning of the experiment, after absorption of the drug 60 minutes later, and after the math task. As in Study 1, participants rated PI and UP at 30-second intervals using a M-VAS. In order to simplify statistical analyses, M-VAS ratings were averaged across each minute. As indicated in Table 3.13 (shaded areas), sensory (PI) and affective (UP) cold pressor ratings were moderately to strongly related on each occasion. Nonetheless, these variables were analysed separately for exploratory purposes.

Table 3.13: Pearson product correlations between pain intensity and unpleasantness ratings on pre-drug, post-drug and post-math task cold pressor tasks.

	Unpleasantness											
Pain	**Pre-drug**				**Post-drug**				**Post-math task**			
Min.	**1 "**	**2"**	**3"**	**4"**	**1 "**	**2"**	**3"**	**4"**	**1 "**	**2"**	**3"**	**4"**
1"	.66				.86				.93			
2"	.57	.69			.80	.89			.87	.96		
3"	.34[b]	.49	.84		.64	.74	.92		.74	.85	.94	
4"	.22[a]	.33 [b]	.77	.92	.40	.50	.78	.93	.49	.60	.80	.95

Note. [a]p<.05; [b]p<.01; remaining correlations are significant at p≤.001.

Effects of the drug on cold pressor pain perception

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on mean cold pressor PI and UP ratings (Tables 3.14 and 3.15). To maintain consistency between Study 1 and 2, analyses were initially carried out on minute-by-minute cold pressor PI and UP ratings. However, since analyses of mean versus minute-by-minute cold pressor ratings did not differ, mean ratings were reported for brevity. Once again, analyses were collapsed across experimental condition, as this factor was not expected to influence pain before the math task. Subjects found the second CPT marginally more painful than the first (M = 46.76 versus M = 44.81; p = .10); however this was not due to drug absorption.

Table 3.14: Cold pressor pain intensity and unpleasantness ratings before and after the drug (collapsed across experimental condition).

	Placebo (N = 32)				**Naltrexone (N = 38)**			
	Pre-drug		**Post-drug**		**Pre-drug**		**Post-drug**	
CPT pain index	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Pain intensity	44.24	14.47	47.46	16.85	45.38	15.92	46.06	17.90
Unpleasantness	46.26	15.75	46.75	18.06	42.36	18.55	42.93	19.23

Note. CPT = cold pressor task.

Table 3.15: F ratios of cold pressor pain intensity and unpleasantness ratings before and after the drug (collapsed across experimental condition).

Source	Pain intensity	Unpleasantness
Time† (T)	2.83	0.17
Drug (D)	0.00	0.88
T x D†	1.21	0.00

Note. † Pillai's Trace F ratio; degrees of freedom = 1,68.

Effect of the math task on cold pressor pain perception

Separate 2 (Drug: naltrexone, placebo) x 3 (Condition: EFS, HFS, HMS) x 2 (Time: pre- and post-math task) repeated measures ANOVAs were carried out on mean PI and UP ratings (Tables 3.16 and 3.17). Experimental condition did not affect cold pressor PI and UP ratings after the math task. However, exploratory 2 (Drug: naltrexone, placebo) x 2 (Time: pre- and post-math task) repeated measures ANOVAs on difficult conditions alone (HFS, HMS) indicated that UP decreased after the task in the placebo group (pre-task M = 46.4 to post-task M = 42.3), but increased in the naltrexone group (pre-task M = 44.3 to post-task M = 46.3) ($F(1,46) = 3.89$; $p = .05$). A similar, although non-significant, trend existed for PI.

Table 3.16: Cold pressor pain intensity and unpleasantness ratings before and after the math task.

	Placebo						Naltrexone					
	EFS		HFS		HMS		EFS		HFS		HMS	
Pain	(N = 10)		(N = 12)		(N = 11)		(N = 11)		(N = 13[a])		(N = 13)	
index	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
						Post-drug/Pre math task						
PI	49.3	9.8	42.4	18.0	50.4	21.3	44.0	23.0	47.6	15.4	46.7	16.2
UP	47.5	10.4	42.7	20.1	49.9	22.6	39.3	22.6	46.6	17.6	42.5	18.0
						Post-math task						
PI	49.8	15.0	39.6	19.3	46.4	23.7	43.4	21.7	47.8	22.4	46.2	21.1
UP	49.3	14.7	39.0	20.4	45.4	24.0	41.6	23.4	48.1	23.0	44.3	21.9

Note. [a] N = 1 missing data; M = mean; SD = standard deviation; PI = pain intensity; UP = unpleasantness.

Table 3.17: F ratios for cold pressor pain intensity and unpleasantness ratings before and after the math task.

	Pain intensity	Unpleasantness
	Between subjects	
Condition (C)	0.18	0.04
Drug (D)	0.01	0.16
C x D	0.64	0.82
	Within subjects	
Time[†] (T)	0.90	0.01
T x C[†]	0.29	0.60
T x D[†]	0.65	2.17
T x C x D[†]	0.41	0.41

Note. [†] Pillai's Trace F ratio; degrees of freedom: any effect including Condition = 2,63; any effect including Drug = 1,63.

Effects of mood, self-efficacy and the drug on cold pressor pain perception

Pearson product correlations (Table 3.18) and hierarchical multiple linear regression analyses (Table 3.19) were used to explore the effects of mood on cold pressor PI and UP in each drug condition. For reasons mentioned earlier, effects of self-efficacy were only examined after the math task. Given that the intensity of mood and self-efficacy, and not the condition that led to these states, was of primary interest in relation to cold pressor pain perception, absolute and change scores were analysed collapsed across experimental conditions.

Absolute scores

As shown in Tables 3.18 and 3.19, higher levels of anxiety were associated with higher reports of PI and UP after drug absorption. A similar relationship existed for anger in the correlations, but did not reach significance in regression analyses. Neither anxiety nor anger was associated with cold pressor pain perception at any other time.

High levels of discouragement were associated with high reports of PI prior to the drug (PI: $r = .25$, $p = .03$). A Drug x Mood effect (Figure 3.5) indicated a similar relationship between discouragement and cold pressor pain for placebo, but not naltrexone recipients after drug absorption. A similar trend existed for cold pressor UP, but failed to reach significance. It is interesting to note that naltrexone recipients who experienced high levels of discouragement after the math task reported more UP than discouraged placebo recipients (Table 3.18); however, this effect was not strong enough to achieve statistical significance in regression analyses (Table 3.19). Self-efficacy did not influence cold pressor PI or UP.

Table 3.18: Pearson product correlations between mood, self-efficacy and cold pressor pain intensity and unpleasantness ratings.

	Placebo (N = 33)						Naltrexone (N = 37)					
	Pre-drug		Post-drug		Post-task		Pre-drug		Post-drug		Post-task[a]	
Mood	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**
Ax.	.05	.00	.37*	.45**	.17	.08	.00	.16	.20	.24	.17	.15
Ds.	.36*	.23	.50**	.43**	.10	.02	.17	.15	-.03	.04	.32[b]	.38*
Ag.	.27	.08	.37*	.38*	.19	.14	.13	.10	-.04	-.08	.17	.23
Sf.					.13	.15					-.02	-.03

Note. [a] N = 36 due to missing data; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

[b]p=.055; *p<.05; **p<.01.

Table 3.19: Summary of t-values from hierarchical regression analyses illustrating effects of mood, self-efficacy, and drug on cold pressor pain intensity and unpleasantness ratings.

		Mood on cold pressor pain perception									
		Pre-drug			Post-drug			Post-task			
	Variable	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
						Pain intensity					
1	**Drug (D)**	0.32	0.51	0.22	-0.18	-0.34	-0.36	0.11	0.10	-0.32	0.15
	Mood (M)	0.21	2.19*	1.46	2.32*	1.79	1.36	1.16	1.99[a]	1.43	0.37
2	**D x M**	-0.16	-0.59	-0.78	-0.79	-2.19*	-1.58	-0.24	0.76	-0.33	-0.58
						Unpleasantness					
1	**Drug (D)**	-0.98	-0.81	-.98	-0.69	-0.87	-0.87	0.06	0.05	-0.43	0.10
	Mood (M)	-0.69	1.52	0.76	2.85**	1.83	1.23	1.02	2.03*	1.66	0.38
2	**D x M**	-0.74	-0.14	0.00	-0.98	-1.56	-1.75	0.29	1.39	1.55	-0.71

Note. Step 1 = main effects model (degrees of freedom = 2,66); Step 2 = full model (df = 3,65); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

[a]p=.051; *p<.05; **p<.01.

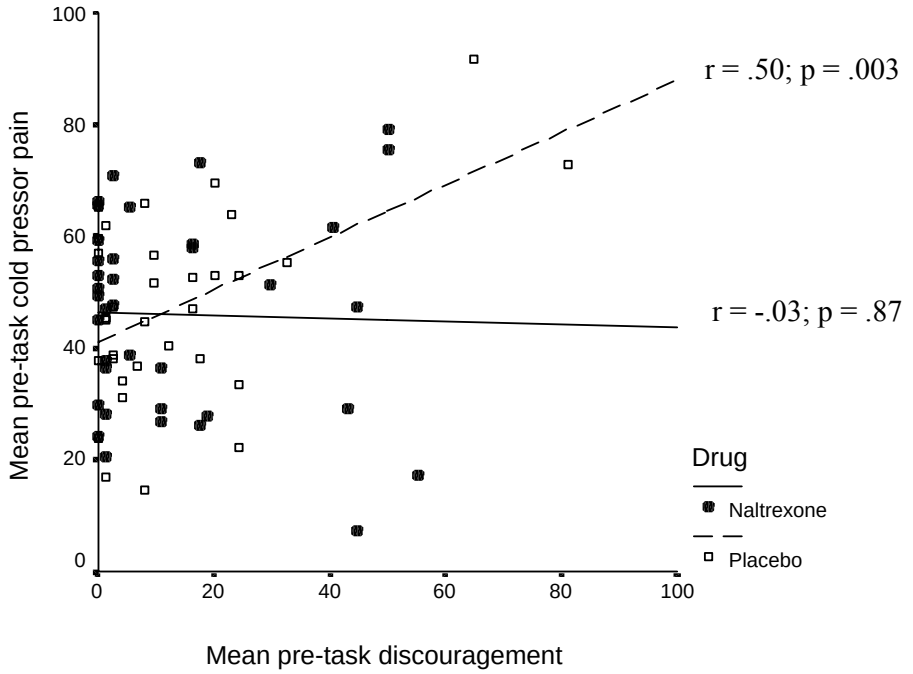


Figure 3.5: Scattergram indicating a positive relationship between discouragement and cold pressor pain for placebo, but not naltrexone recipients after the drug.

Change scores

Analyses regressing change in mood and self-efficacy on changes in cold pressor pain indices (in each drug condition) investigated the effects of negative emotional reactivity on pain perception.

A 'moving' baseline was used to calculate change in cold pressor pain indices during subsequent CPTs. To explain, pain indices reported during the pre-drug CPT were subtracted from ratings during the second, post-drug CPT to illustrate 'pure' effects of the drug on pain. Ratings during the post-drug CPT were subtracted from the third, post-math task CPT ratings to illustrate effects of the math task (in conjunction with the drug) on pain perception. Changes in mood were calculated in the same way. For reasons mentioned above, changes in self-efficacy were only calculated after the task (using post-practice trial ratings as the baseline). Although mood and self-efficacy were also rated *during* the math task, the effects of changes in mood during compared to after the math task on cold pressor pain were similar. To avoid

repetition, only effects of cumulative change in mood (as reflected by ratings *after* the task) on cold pressor pain, will be presented.

Post-drug: As shown in Tables 3.20 and 3.21, neither mood, drug, nor self-efficacy influenced cold pressor pain perception after drug absorption.

Post-math task: Increases in anxiety after the task were associated with *increased* ratings of UP for subjects taking the placebo (Figure 3.6, Tables 3.20 and 3.21). Changes in self-efficacy after the task did not affect changes in cold pressor responses. However, correlational analyses suggest that increases in self-efficacy were associated with decreases in cold pressor responses in the placebo group only.

Table 3.20: Pearson product correlations between change in mood and self-efficacy and cold pressor pain intensity and unpleasantness.

	Placebo (N = 33)				**Naltrexone (N = 37)**			
Cg in	**Cg after drug**		**Cg after maths**		**Cg after drug**		**Cg after maths[a]**	
Mood	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**
Ax.	.12	.11	.31	.42*	.25	.18	-.07	-.17
Ds.	.15	.10	.02	.09	-.06	-.14	.03	-.13
Ag.	-.00	.04	.01	.20	-.03	.03	.22	.07
Sf.			-.41*	-.43*			.04	.05

Note. Cg = change; [a] N = 36 due to missing data; PI = cold pressor pain intensity; UP = cold pressor unpleasantness; Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.
*p<.05.

Table 3.21: Summary of t-values from hierarchical regression analyses illustrating effects of change in mood and self-efficacy on change in cold pressor pain intensity and unpleasantness in each drug condition.

		Mood on cold pressor pain perception						
		Cg after drug			**Cg after maths**			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
				Pain intensity				
1	**Drug (D)**	-1.04	-1.10	-1.06	1.02	0.99	0.59	1.26
	Mood (M)	1.50	0.42	-0.14	0.92	0.23	1.11	-1.80
2	**D x M**	0.82	-0.80	-0.13	-1.50	0.04	0.69	1.60
				Unpleasantness				
1	**Drug (D)**	0.05	0.04	0.04	1.24	1.65	1.24	1.95
	Mood (M)	1.18	-0.12	0.25	1.56	-0.30	1.01	-1.98
2	**D x M**	0.56	-1.05	-0.01	2.50*	-0.85	-0.77	1.77

Note. Step 1 = main effects model (df = 2,66); Step 2 = full model (df = 3,65); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

*p<.05.

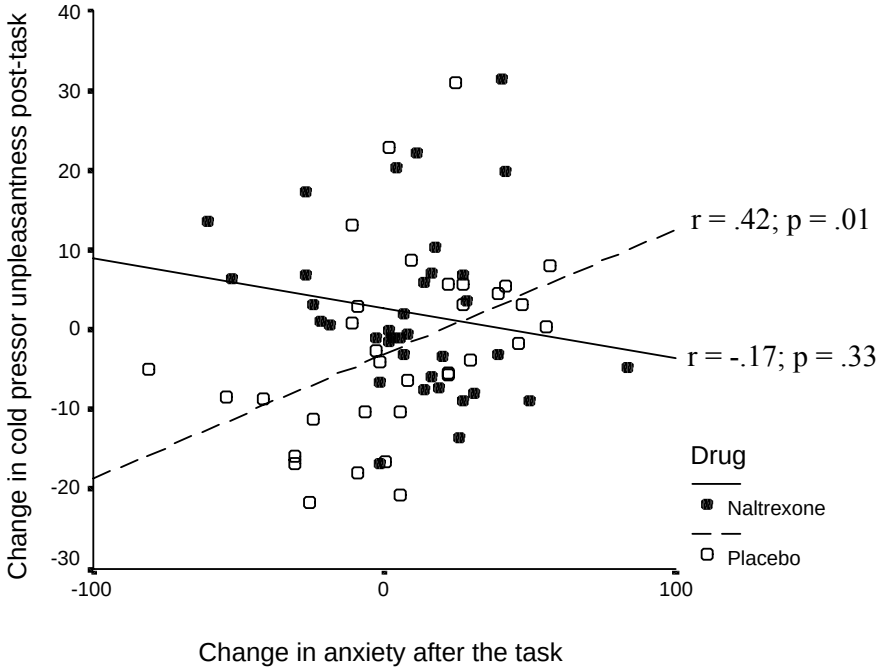


Figure 3.6: Scattergram indicating a positive relationship between anxiety and cold pressor unpleasantness for placebo, but not naltrexone recipients after the math task.

3.3.6 Cardiovascular activity

Effects of the drug on cardiovascular activity

SBP, DBP and pulse rate were taken on entering the experimental environment, and 60 minutes later following absorption of the drug. Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on mean SBP, DBP and pulse rate (Tables 3.22 and 3.23). Once again, analyses were collapsed across experimental condition, as this factor was not expected to influence pain before the math task.

As indicated in Table 3.23, SBP (pre-drug M = 117.68 versus post-drug M = 115.39) and pulse rate (pre-drug M = 79.65 versus post-drug M = 74.08) were significantly lower after the drug. Since the drug did not affect cardiovascular responses, decreases in SBP and heart rate may be attributed to subjects' familiarity with experimental procedures and setting, and a prolonged time at rest. The lack of effect of naltrexone on cardiovascular responses at rest meant that influences of the math task could be clearly determined without prior contamination from this opioid antagonist (McCubbin et al., 1996).

Table 3.22: Blood pressure and pulse rate before and after the drug (collapsed across experimental condition).

	Placebo (N = 33)				**Naltrexone (N = 37)**			
Cardiovascular	**Pre-drug**		**Post-drug**		**Pre-drug**		**Post-drug**	
response	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
SBP	119.24	11.04	117.15	9.88	116.12	14.47	113.63	11.53
DBP	72.79	11.31	71.53	10.46	70.67	9.03	69.72	9.25
Pulse	82.02	12.77	75.96	10.15	77.27	10.81	72.20	8.81

Note. SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg);
Pulse = heart beats per minute.

Table 3.23: F ratios of blood pressure and pulse rate before and after the drug (collapsed across experimental condition).

Source	SBP	DBP	Pulse
Time† (T)	5.90*	1.57	24.93***
Drug (D)	1.51	0.78	3.42
T x D†	0.04	0.03	0.19

Note. † Pillai's Trace F ratio; degrees of freedom = 1, 68; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
*p<.05; ***p<.001.

Effects of the math task on cardiovascular activity

SBP, DBP and pulse rate were measured at 2-minute intervals throughout the math task spanning approximately 28 minutes. To simplify interpretation, measures were averaged across two intervals (of 14 minutes each). Separate 2 (Drug: naltrexone, placebo) x 3 (Condition: EFS, HFS, HMS) x 4 (Time: pre-task, task interval 1-14 minutes and 15-28 minutes, post-task) repeated measures ANOVAs were carried out on SBP, DBP and pulse rate (Tables 3.24 and 3.25). Absolute scores were followed over time as they provided a more representative, and conceptually clearer picture of cardiovascular activity than change scores.

Time main effects for DBP and pulse rate were explored with planned simple comparisons, where each measure was compared to measures taken before the task. As indicated in Table 3.26, DBP was significantly higher during and after the math task compared to pre-task levels. Conversely, pulse rates remained at pre-task levels during the task and dropped off significantly after the math task. No general time effect was found for SBP; however, simple contrasts indicated that SBP rose significantly during the first 14 minutes of the task, but returned to pre-task levels from this time onwards. Neither naltrexone nor experimental condition influenced changes in cardiovascular activity.

Table 3.24: Blood pressure and pulse rate prior to, during and after the math task.

		Placebo (N = 32)				Naltrexone (N = 37)			
			Math task				Math task		
CVR		Pre	1	2	Post	Pre	1	2	Post
Easy task-few shocks									
SBP	**M**	118.24	118.09	115.98	119.19	112.76	117.33	117.16	114.68
	SD	10.56	12.73	19.41	13.46	13.12	11.61	9.64	11.14
DBP	**M**	74.45	77.56	77.99	74.48	72.65	75.81	74.84	75.49
	SD	9.64	12.54	15.47	10.86	9.21	8.18	9.13	10.13
Pulse	**M**	75.92	76.77	75.22	74.82	74.68	79.03	77.39	73.77
	SD	10.81	11.69	10.08	9.77	10.79	8.52	10.37	8.84
Hard task-few shocks									
SBP	**M**	118.54	117.82	117.98	114.65	115.86	118.94	114.52	117.85
	SD	8.00	12.79	11.91	14.18	13.24	10.65	9.50	9.32
DBP	**M**	71.85	76.91	76.58	75.18	71.33	74.81	72.77	73.26
	SD	10.69	11.77	11.40	12.87	10.35	8.88	8.19	9.11
Pulse	**M**	74.45	76.24	73.84	69.15	71.99	70.92	69.06	68.47
	SD	10.89	9.85	8.49	12.01	8.89	5.88	6.85	5.96
Hard task-many shocks									
SBP	**M**	115.89	121.24	124.62	117.78	111.28	114.12	113.81	113.18
	SD	11.30	8.96	15.17	13.20	8.60	5.31	7.52	13.25
DBP	**M**	69.51	75.18	78.44	72.48	65.32	70.49	70.62	69.49
	SD	11.30	9.94	15.99	9.24	7.21	8.26	11.16	9.55
Pulse	**M**	77.26	78.50	79.17	72.39	70.49	70.44	68.55	67.63
	SD	10.02	7.70	8.72	9.16	7.07	7.97	7.58	6.40

Note. M = mean; SD = standard deviation; Pre = prior to practice trials and math task; Math task: 1 = 1-14 mins, 2 = 15-28 mins; Post = after math task; CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 3.25: F ratios of blood pressure and pulse rate before, during and after the math task.

Source	SBP	DBP	Pulse
		Between subjects	
Condition (C)	0.02	1.04	1.74
Drug (D)	1.77	1.51	3.48
C x D	0.63	0.22	1.57
		Within subjects	
Time† (T)	1.97	9.83***	6.89***
T x C†	0.92	0.70	0.51
T x D†	0.81	0.86	0.49
T x C x D†	1.12	0.24	0.96

Note. † Pillai's Trace F ratio; degrees of freedom: C, C x D = 2,63; D = 1,63; T, T x D = 3,61; T x C, T x C x D = 6,124; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
***p<.001.

Table 3.26: Simple pair-wise comparisons[a] of blood pressure and pulse rate before, during and after the math task.

		Blood pressure across time		
		Math task		
CVR	**Pre-task**	**1-14 mins**	**15-28 mins**	**Post-task**
SBP	115.43	117.91*	117.34	116.22
DBP	70.85	75.13***	75.21***	73.40**
Pulse	74.13	75.32	73.87	71.04**

Note. [a] Pre-math task is the point of comparison; CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
*p<.05; **p<.01; ***p<.001.

Association between cardiovascular activity and task shock sensitivity

Task shock sensitivity was regressed onto cardiovascular activity during the math task using hierarchical linear regression analyses. Pearson product correlations demonstrated the relationship between these variables. As shown in Tables 3.27 and 3.28, cardiovascular activity was not related to shock PI or UP during the task.

Table 3.27: Pearson correlations between blood pressure, pulse rate, pain intensity and unpleasantness ratings for shocks during the math task.

	Task shock pain index			
	Placebo (N = 33)		**Naltrexone (N = 37)**	
CVR	**PI**	**UP**	**PI**	**UP**
SBP	-.06	-.02	-.06	-.21
DBP	.11	.02	.05	.03
Pulse	-.18	-.04	-.21	-.27

Note. PI = pain intensity; UP = unpleasantness ratings; CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 3.28: Summary of t-values from hierarchical regression analyses illustrating the effects of drug, blood pressure and pulse rate on task shock pain and unpleasantness during the math task.

		Task shock pain index					
		Pain intensity			**Unpleasantness**		
Step	**Variable**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**
1	**Drug (D)**	-0.18	-0.03	-0.60	0.18	0.26	0.15
	CVR	-0.47	0.65	-1.16	-0.67	-0.03	-1.40
2	**D x CVR**	-0.13	-0.09	-0.31	-1.16	-0.25	-1.07

Note. Step 1 = main effects model (df = 2,67); Step 2 = full model (df = 3,66); CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Association between cardiovascular activity and cold pressor pain perception

Pearson correlation coefficients (Table 3.29) and hierarchical linear regression analyses (Table 3.30) were used to explore the relationship between resting cardiovascular activity and cold pressor pain perception. These analyses were conducted on CPT data collected after the drug and after the math task, but not on data collected at the outset of the experiment (before the drug), as opioid involvement in this relationship was of interest.

Neither blood pressure nor pulse rate was associated with cold pressor pain perception either after drug absorption or the math task. Although correlations suggested differences amongst naltrexone and placebo groups at the end of the experiment, group differences failed to emerge in regression analyses.

Table 3.29: Pearson product correlations between cold pressor pain intensity and unpleasantness, blood pressure and pulse rate before and after the math task.

	Post-drug				**Post-math task**			
	Placebo		**Naltrexone**		**Placebo**		**Naltrexone**	
CVR	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**
SBP	-.15	-.14	-.21	-.26	.00	-.06	-.29	-.31
DBP	.01	.00	-.02	-.12	-.03	-.07	-.24	-.21
Pulse	-.21	-.21	-.06	-.06	-.06	-.14	-.13	-.13

Note. Placebo N = 33; Naltrexone N = 37; CVR = cardiovascular response; PI = pain intensity; UP = unpleasantness; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 3.30: Summary of t-values from hierarchical linear regression analyses illustrating the effects of drug, blood pressure and pulse rate on cold pressor pain intensity and unpleasantness.

		Cold pressor pain index					
		Pain intensity			**Unpleasantness**		
Step	**Variable**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**
				Post-drug			
1	**Drug (D)**	-0.58	-0.34	-0.55	-1.14	-0.89	-1.05
	CVR	-1.51	-0.05	-1.10	-1.76	-0.50	-1.09
2	**D x CVR**	-0.17	-0.10	0.53	-0.44	-0.57	0.50
				Post-math task			
1	**Drug (D)**	0.07	0.08	0.02	0.00	0.03	-0.08
	CVR	-1.19	-1.15	-0.72	-1.54	-1.16	-1.10
2	**D x CVR**	-1.34	-0.97	-0.45	-1.25	-0.70	-0.22

Note. Step 1 = main effects model (pre-/post-drug df = 2,67; post-task df = 2,66); Step 2 = full model (pre-/post-drug df = 3,66; post-task df = 3,65; CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart-beat per minute.

3.4 DISCUSSION

3.4.1 Summary of major findings

The key findings to emerge from the present study were:

- The *difficulty* or *uncontrollable* nature of the math task, and not the *shock stimulus* itself, was responsible for hyperalgesia, increased discouragement, and lower self-efficacy during the task, and opioid-mediated SIA after the math task. Anxiety increased with shock frequency, whereas anger increased with both shock frequency and task difficulty.
- Negative mood was associated with pain sensitisation to electrical stimuli during the math task, whilst (unexpectedly) anxiety was associated with opioid-mediated increases in cold pressor UP after the task. Discouraged subjects under opioid blockade reported more cold pressor UP after the task. However, these results failed to reach significance in regression analyses. Self-efficacy was not associated with pain sensitivity.
- No relationship existed between cardiovascular activity and pain during times of stress (shocks) or rest (CPTs before and after the math task).

3.4.2 Success of experimental manipulations

Subjective mood ratings and physiological indicators of stress (DBP) indicated that the math task induced the desired emotional state. For instance, anxiety, discouragement and anger worsened in all conditions during the task, but (as explained below) more so in some conditions than others. Interestingly, increases in anger were dampened by the release of opioids midway through the task. Furthermore, DBP increased and remained elevated throughout the task. Increases in SBP were transient, however, and heart rate did not change during the math task. Opioids typically dampen cardiovascular activity; however, heart rate was higher in placebo recipients than in subjects under opioid blockade during the task. Group differences in heart rate may have been due to paradoxical effects of opioids observed when minimal amounts of opioids are released (Le Bars et al., 1992).

Alternatively, group differences may not have been due to the task but to random differences noted at the outset of the experiment. Finally, effects of the math task persisted as subjects remained discouraged and angry, and DBP remained elevated after the math task had been completed.

As expected, the difficulty of the task in HMS and HFS conditions intensified discouragement and reduced perceived self-efficacy to answer questions correctly and avoid shocks. Whilst subjects in the difficult conditions were greatly discouraged and inefficacious, subjects in the EFS condition grew more self-efficacious and less discouraged as the task progressed. Therefore, *perceived lack of control* over the shocks, and not the *number of shocks* per se, influenced discouragement and self-efficacy.

Anxiety and fear have commonly been associated with the threat and actual delivery of painful or noxious events (Rhudy & Meagher, 2000; Willer & Albe-Fessard, 1980a). In accordance with these findings, anxiety was linked to the frequency of shocks rather than the difficulty of the math questions. Specifically, subjects in the HMS condition reported significantly higher anxiety than subjects in the HFS and EFS conditions. No difference was noted between the latter two conditions. The number of shocks and task difficulty operated in an additive fashion to heighten anger, with subjects in the HMS condition reporting the most anger.

For unknown reasons, electric shocks were perceived as less painful and unpleasant in the present study (M = 29.1 – 56.3), than in Study 1 (M = 45.43 – 66.71). However, perceptions of the cold pressor pain stimulus in the present study (M = 39.5 – 48.1) mirrored those in Study 1 (M = 45.58 – 50.02), suggesting that moderate PI and UP were experienced.

Naltrexone did not interfere with mood or any other dependent variable at rest, making this a useful method by which to study stress-induced opioid activation after the math task.

3.4.3 Separating pain from stress: Evidence of opioid-mediated stress-induced analgesia?

This experiment aimed to investigate whether the shocks delivered during the math task, or the math task *per se* was responsible for triggering analgesia by including an additional 'uncontrollable' condition with seven instead of the usual three shocks.

Hyperalgesia to brief electrical stimuli in difficult conditions

Shock pain perception was influenced by the difficulty of the task and not the number of shocks per se, as subjects in HMS and HFS conditions reported greater PI and UP than subjects in the EFS condition. Therefore, in contrast with previous research (Flor et al., 2002; Maier, 1986; Seligman et al., 1971), a perceived lack of control over the shocks during the math task led to pain facilitation rather than inhibition. Furthermore, this relationship was not mediated by endogenous opioids, as group differences were evident despite opioid blockade.

As suggested by Rhudy and Meagher (2001b), pain can be facilitated by negative emotions that lead to low to moderate levels of arousal. Moreover, the relationship between moderately arousing negative emotions and hyperalgesia is adaptive, leading to heightened environmental scanning and increased preparedness to deal with threat (Mueller & Netter, 2000). Therefore, it is possible that a 'lack of control', through factors such as low to moderately arousing negative mood, may have indirectly been associated with increased shock PI and UP.

Decreased sensitivity to sustained cold pressor stimuli in difficult conditions

Cold pressor pain perception did not differ among the experimental conditions after the math task. However, exploratory analyses of the difficult conditions (i.e., HFS, HMS) demonstrated an opioid-mediated stress-induced decrease in cold pressor UP after the math task that resembled SIA in Study 1.

3.4.4 Modulation of pain by negative mood

Sensitisation to electrical pain

The present study revealed a substantial relationship between negative mood and electrical pain sensitivity, where anxiety, discouragement and anger were positively associated with shock PI and UP during the math task. As mentioned above, pain can be facilitated by negative mood of low to moderate arousal through nonopioid-mediated mechanisms such as autonomic arousal, muscular reactivity to pain and hyper-vigilance (Janssen, 2002; Mueller & Netter, 2000; Rhudy & Meagher, 2001b). On the other hand, highly arousing negative emotions inhibit pain (Rhudy & Meagher, 2001b) through a number of mechanisms including endogenous opioid release, baroreceptor stimulation (via increases in BP) and attentional factors (Janssen, 2002). In light of this literature, negative mood during the math task may have been moderately arousing, increasing shock pain sensitivity and masking the inhibitory influences of the endogenous opioid system. In other words, the pain induced by brief and intermittent stimuli such as task shocks was more likely to be enhanced than inhibited in subjects who were distressed during the math task.

The relationship between perceived self-efficacy and shock sensitivity, although trending in the same direction as Study 1, failed to reach significance. For unknown reasons the PI and UP of shocks was considerably lower for subjects in the present study than in Study 1. Therefore, shocks may not have been aversive enough to be affected by perceptions of self-efficacy.

Inhibition of cold pressor pain

At the beginning of the experiment, discouragement was positively associated with pain during the CPT. Neither anxiety, nor anger influenced cold pressor pain perception at this stage of the experiment. As mentioned above, low to moderate levels of discouragement may have been responsible for the facilitation of cold pressor pain (Rhudy & Meagher, 2001b).

During the second CPT discouragement appeared to sensitise placebo recipients to cold pressor PI and, to a lesser degree, UP. Opioid-mediated mood *facilitation* of pain seems to contradict theories discussed earlier (e.g., Janssen, 2002); however, the present results could be attributed to paradoxical effects of opioids when released in small concentrations (Le Bars et al., 1992). For instance, Le Bars, Willer and De Broucker (1992) found that at a low dose, morphine blocked endogenous spinal controls usually triggered by heterosegmentally-applied noxious stimuli (see *Diffuse noxious inhibitory controls*, p 34). In animal research, others have demonstrated facilitatory effects of low dose systemic morphine on innate pain reflexes such as licking and guarding behaviour in response to thermal pain (Vierck, Acosta-Rua, Nelligan, Tester, & Mauderli, 2002). Since opioids usually serve as 'stress markers' (Beutler, Daldrup, Engle, Oro'-Beutler, Meredith, & Boyer, 1987), it is possible that only a small release of opioids occurred in response to the cold pressor stimulus itself. The cold pressor alone has served as a physical stressor leading to opioid-mediated increases in pain thresholds (Jungkunz, Engel, King, & Kuss, 1983), but only when the CPT lasts longer than one minute (Bullinger, Naber, Pickar, Cohen, Kalin, Pert, & Bunney, 1984). At this stage of the experiment, anxiety appeared to facilitate cold pressor PI and UP, regardless of opioid blockade.

After the math task, a positive association between discouragement and cold pressor UP, and to a lesser extent, PI emerged again. However, correlations indicated that this effect reached statistical significance in naltrexone recipients only. Thus, discouragement appeared to be associated with opioid release that *inhibited* further increases in cold pressor PI and UP. The present results support human studies associating opioid-mediated analgesia with subjective helplessness (which is akin to 'discouragement') after highly arousing (Janssen & Arntz, 2001) or noxious stimuli (Willer & Albe-Fessard, 1980a).

Surprisingly, the effects of change in mood on change in cold pressor PI and UP failed to mirror results with absolute scores (mentioned above). For instance, changes in discouragement were not associated with changes in pain perception after the drug, or after the math task. Similarly, changes in anxiety were not associated with changes in PI or UP after the drug; however, an opioid-mediated association was found between anxiety and UP after the math task. This association indicates that

naltrexone antagonised decreases in pain (consistent with SIA) in less anxious subjects after the math task. Why this effect is linked to this subgroup is unclear.

Perceived self-efficacy was not associated with cold pressor pain perception at any stage of the experiment. Furthermore, outcomes of absolute and change scores were identical. The present results are in accordance with other studies finding that the effect of self-efficacy on pain ratings is less clear than the effects on pain tolerance. Reasons for this finding will be clarified in the following study.

3.4.5 Cardiovascular–pain relationship

Cardiovascular activity has been associated with acute pain sensitivity in hypertensive-prone (Caceres & Burns, 1997; France, 1999) and normotensive humans (Bruehl et al., 1992; Randich & Maixner, 1984). Analgesia is thought to originate either from stress-induced increases in cardiovascular activity, which in turn stimulates baroreceptors that synapse in pain regulatory centres in the brainstem, or hyperactive centrally-mediated analgesic mechanisms in subjects with elevated resting blood pressure (France, 1999). The effects of cardiovascular activity on painful stimuli at rest (CPTs conducted after the drug and the math task) and during stress (math task shocks) were assessed in the present study. Since opioid involvement in the cardiovascular-pain relationship was also of interest, the association between the above-mentioned variables was assessed from drug absorption onwards.

Surprisingly, there was no association between cardiovascular activity and pain in the present study. The reason for this is unclear. However, the cardiovascular-pain relationship will be investigated further in the following study.

CHAPTER FOUR

4. STUDY 3

4.1 INTRODUCTION

4.1.1 Rationale/Purpose of this study

Adoption of 'Hard task-many shocks' condition only

In the previous study, there was some evidence that a perceived lack of control over shocks and discouragement inhibited UP via opioid release after the math task. However, these findings were based on correlational and exploratory analyses. The effect of negative mood on pain may have been disguised in Study 2 by the inclusion of subjects in the EFS condition who reported relatively low levels of discouragement and no change in pain perception. Additionally, the numbers in each cell (approximately 10) may not have been sufficient to detect differences among groups. Thus, to enable a more powerful examination of the effect of 'no control' and negative mood on pain, only the most stressful condition (HMS) was examined in Study 3.

Multi-dimensional assessment of pain

The opioid system appears to influence *pain tolerance* after stress (Abraham & Joseph, 1986; al'Absi, Wittmers, Ellestad, Nordehn, Kim, Kirschbaum, & Grant, 2004; Bragdon et al., 2002; Flor et al., 2002; Jungkunz et al., 1983). For instance, Bandura et al. (1988; 1987) found that endogenous opioids influenced how long subjects tolerated a painful cold pressor stimuli after a timed math stressor. Since cold pressor pain in Study 2 was assessed via *PI and UP ratings*, it is possible that analgesic effects of stress may have been overlooked due to the type of pain response parameter chosen. Thus, in addition to PI and UP, the present study aimed to examine the effect of an uncontrollable stressor and negative mood on pain tolerance.

Pain tolerance can be influenced by a number of factors unrelated to pain perception *per se*; therefore, it is uncertain as to whether Bandura's (1988) results reflect tolerance for pain or tolerance to some other factor such as discomfort. Moreover, endogenous opioids may influence mood (e.g., anger in Study 2), which may be the important factor governing endurance of pain. To examine the concept of pain tolerance, tolerance to non-painful but unpleasant/boring cognitive (Letter Symbol Matching Task[9], LSMT) and physical stimuli (Valsalva manoeuvre, VM) was compared with pain tolerance in the present study.

Negative mood modulation of pain

The effect of discouragement on pain in Study 2 is consistent with effects noted in animals (Maier et al., 1983), but not humans. For instance, Mueller and Netter (2000) found that subjective helplessness (akin to discouragement) *increased* pain sensitivity after a stressful reaction time task. Others inducing discouragement via Velten (1968) mood statements found a reduction in tolerance to cold pressor pain and increased pain catastrophisation (Willoughby, 2000; Willoughby, Hailey, Mulkana, & Rowe, 2002). As proposed by Rhudy and Meagher (2000; 2001a), pain perception may differ according to the intensity of negative emotion induced in subjects, where less intense discouragement may lead to pain sensitisation rather than analgesia. In support of their notion, fear (a high threat/high arousal mood) has resulted in hypoalgesia in a number of studies (Rhudy & Meagher, 2000; Rhudy & Meagher, 2001a; Willer & Albe-Fessard, 1980a; Willer et al., 1981), whilst anxiety (a moderately arousing emotion) led to hyperalgesia in Study 2. Anger, on the other hand has led to both pain facilitation or inhibition depending on its expression (anger-out) or suppression (anger-in), respectively (Janssen et al., 2001). Anger may have failed to influence pain perception after the math task in Study 2 because of divergent psychological states evoked across the three experimental conditions. Therefore, this study aimed to clarify the effects of discouragement, anxiety and anger on pain, by adopting one experimental condition known to induce marked evidence of each emotion.

[9] Adapted from the Naylor-Harwood Adult Intelligence Scale (A.C.E.R., 1972).

Nociception flexion reflex (RIII)

The effects of stressor controllability and mood on pain are usually assessed via subjective responses (i.e., pain ratings, pain tolerance, pain thresholds). These effects are less commonly measured via objective means such as the nociceptive biceps femoris flexion reflex, or RIII. The RIII involves spinal and supraspinal pain pathways that connect to hypothalamic and limbic structures, thereby providing an objective method by which to assess the emotional modulation of pain. Furthermore, stress and negative mood are known to alter spinal excitability, activating endogenous opioids that in turn exert a depressive effect on the RIII (Willer & Albe-Fessard, 1980a). Therefore, the RIII would offer a complementary and objective method by which to assess opioid involvement in the effects of uncontrollable shocks and mood on endogenous pain modulation.

4.1.2 Aims of Study 3

Primary aims

The **first aim** was to examine the effect of an uncontrollable stressor (math task) and negative mood on endogenous pain inhibition, in relation to PI, UP *and* pain tolerance.

The **second aim** was to explore the concept of pain tolerance by comparing endurance to non-painful (but unpleasant) stimuli with endurance to pain.

The **third aim** was to clarify the effects of uncontrollable shocks and negative mood on pain by adopting an experimental procedure known to induce a *strong* state of stress (i.e., HMS condition in Study 2).

To complement subjective pain parameters, the **fourth aim** was to assess pain objectively via the nociceptive flexion reflex (RIII).

The **fifth aim** was to determine whether analgesia induced by the math task was mediated by opioid or nonopioid substrates. As in Study 2, naltrexone (an opioid

antagonist) was administered to one half of the subjects and an identical placebo capsule was given to remaining subjects to assess involvement of the opioid system.

Secondary aim

The **sixth aim,** as in Study 2, was to investigate the cardiovascular-pain relationship in normotensive subjects during stress and at rest. Opioid mediation of this relationship was explored by comparing responses in the naltrexone group with those from the placebo group.

4.1.3 Hypotheses for Study 3

In light of aims of the third study, it was hypothesised that:

Lack of control over the math task would lead to the release of endogenous opioids. Therefore, placebo recipients should show evidence of lower PI, UP and greater tolerance of cold pressor pain after the math task, than beforehand. Similarly, the placebo group should show evidence of RIII suppression after the task. Conversely, subjects under opioid blockade should demonstrate increased sensitivity to the CPT in all dimensions of pain and RIII facilitation.

Increases in discouragement induced by an uncontrollable cognitive stressor would be associated with reductions in cold pressor PI and UP ratings and increased pain tolerance, in placebo recipients after the math task. Conversely, subjects under opioid blockade should demonstrate increased sensitivity to the CPT in all dimensions. Similar results should be observed with anxiety, assuming that the math task induces a high level of arousal. If low to moderate levels of anxiety were evoked, hyperalgesic effects would be expected regardless of opioid blockade. As anger can facilitate *or* inhibit pain depending on anger management style (Bruehl et al., 2002), and research in this area is limited (Fernandez, 2002), no specific hypotheses with regards to the effects of stress-induced anger on pain were generated.

As in Study 2, it was hypothesised that placebo recipients would show an inverse relationship between cardiovascular responses and PI/UP ratings, and a positive

relationship with pain tolerance, for electrical and cold pressor stimuli. However, there should be no evidence of a relationship between cardiovascular activity and acute pain sensitivity in the naltrexone group.

4.2 METHOD

4.2.1 Subjects

Forty-three subjects aged between 18 and 41 years [21 males: M = 20.86 years, SD = 3.24; 22 females: M = 20.36 years, SD = 4.84] participated in Study 3. An additional subject withdrew prematurely due to the noxious nature of the CPT. Criteria used to exclude subjects were identical to criteria described in Study 2. As in previous studies, subjects were recruited from Murdoch University undergraduate psychology classes and the general university population. Subjects were asked to refrain from consuming alcoholic or caffeinated beverages 12 hours before, and food or tobacco two hours before the experiment to improve the reliability of cardiovascular recordings (Shapiro et al., 1996). Subjects were remunerated $15 for their participation. Bryden's Handedness Questionnaire (1977) was used to confirm that all subjects were right-handed (Appendix 2, p 320).

4.2.2 Experimental design/Overview

As in previous studies, subjects completed mood/self-efficacy ratings, CPTs, persistence tasks (LSMT, VM) and had their BP and pulse rate measured before the drug, approximately 50-60 minutes after the drug, and after completion of the math task (Figure 4.1). Similarly, RIII procedures were completed three times: 10 minutes and then 60-70 minutes after drug administration, and after the math task. During the math task, subjects rated the PI and UP of each electric shock, rated mood and self-efficacy at a number of intervals, and had their BP and pulse rate measured frequently. Subjects were tested individually.

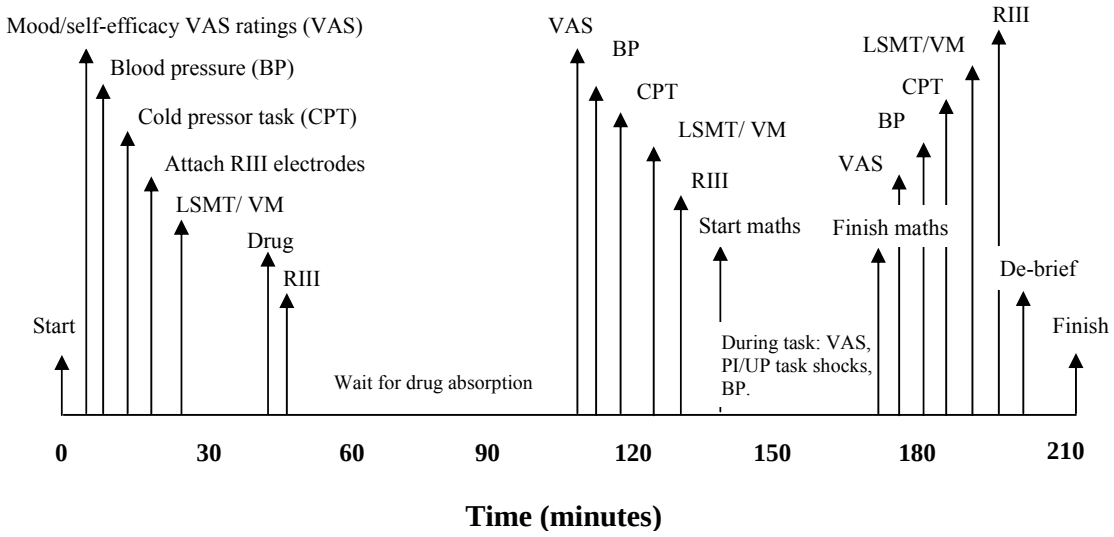


Figure 4.1: Experimental timeline for Study 3. Note: The drug was administered shortly before RIII measurement to maximise time efficiency.

Before starting the experimental session, subjects were randomly assigned to the naltrexone or placebo drug condition. Each condition was balanced for age ($F(1,41) = 3.37$; $p = .07$) and sex (Table 4.1).

Table 4.1: Subject age and sex in each drug condition.

	Naltrexone	**Placebo**
Mean	21.80	19.57
SD	5.56	1.70
N	12F, 11M	10F, 10M

Note. F = females; M = males.

4.2.3 Procedure/Materials

Once seated inside one of two cubicles maintained at 22 ± 2°C, written consent was obtained from each subject (Appendix 8, p 330), and a medical checklist was completed (Appendix 6, p 326).

Mood and self-efficacy ratings

Subjects rated six mood states (anxiety, confusion, discouragement, anger, sluggishness and liveliness) and perceived self-efficacy (with regards to avoiding electric shocks during the math task) on separate 0-100 point paper and pen VAS, as described in the previous studies. Mood and self-efficacy VAS ratings were completed pre-drug, post-drug, five times during the math task (using computer-generated VAS) and after the math task.

Cardiovascular responses

SBP, DBP and pulse rate were measured before and after the drug, during and after the math task. The equipment and procedures used to measure cardiovascular activity were identical to those used in Study 2[10].

Cold pressor tasks

Subjects completed a CPT in Cubicle A before and after the drug, and immediately after the math task. The equipment used for each CPT was identical to that used in Study 2. In each CPT, the non-dominant, left hand was immersed up to the wrist-crease into a 37°C warm water bath for three minutes to standardise hand temperature, and then into a 2°C ice water bath until subjects felt that the pain was

[10] As in Study 2, the M4 Omron electronic monitor was calibrated with a mercury manometer for five subjects. Once again, SBP and DBP obtained from both methods were closely associated (SBP: r=.85; p=.006; DBP: r=.87; p=.004). A high association between electronic and manual methods was also detected at the end of the study, when calibrated on six subjects (SBP: r=.81, p=.01; DBP: r=.79, p=.01).

too unpleasant to continue[11]. At this point they were asked to say: "Stop!" and pull their hand out of the water (Appendix 9, p 331). The experimenter used a stopwatch to measure time spent in the ice water. Subjects rated PI and UP every 30 seconds until they withdrew their hand from the water using the same 0-100 point M-VAS as described in Study 2. A final rating was made when they withdrew their hand from the ice water. A ceiling of four minutes was set but not explicitly stated to subjects.

Letter Symbol Matching Task (LSMT) and Valsalva manoeuvre (VM)

Each subject's ability or willingness to persist with an unattractive cognitive (LSMT) and physical task (VM) was assessed before and after the drug, and after the math task. The LSMT is a paper and pencil code substitution test where eight letters are paired with symbols (e.g., ⊥), and subjects substitute the appropriate symbol for each letter. After briefly practicing the task, subjects substituted as many symbols as they could on the page of letters for three minutes. A key was printed above the blank spaces for referral. A new set of matched symbols and letters was presented at each stage of the experiment. During the VM, subjects expelled air into a narrow tube as hard, and for as long as they could. To ensure that the task was brief, subjects were not permitted to 'fill' their lungs with air before beginning.

Nociceptive flexion reflex (RIII)

The close correlation between RIII and pain thresholds (Hugon, 1973; Sandrini, Alfonsi, Bono, Facchinetti, Montalbetti, & Nappi, 1986; Willer, 1977), and the reliability of this relationship (Sandrini et al., 1986) supports the notion that the RIII reflex can provide a valid, reliable and – most importantly - objective measure of spinal nociceptive processes. Also, basic patterns of the RIII are influenced by negative mood (Craig, 1989; Willer, Boureau, & Albe-Fessard, 1979) and stress-induced inhibition of the RIII has proven to be opioid-mediated (Willer et al., 1979;

[11] Although temperatures of both baths changed slightly throughout each CPT (warm: -1.90°C; cold: +0.10°C), changes were consistent across groups.

Willer et al., 1981). For these reasons, the RIII can provide insight into the effects of mood on pain, and whether these influences are mediated by endogenous opioids.

General procedure

RIII and pain thresholds, and RIII at empirically established threshold and supra-thresholds levels were measured shortly after drug administration, an hour later, and after the math task. Standard methods of stimulation and recording were used in both procedures (see description below).

Stimulation: The RIII was evoked by electro-cutaneously stimulating the right lateral sural nerve (behind the lateral malleolus) using silver/silver chloride surface electrodes taped 2 cm apart at the ankle. Stimulation consisted of a 6-pulse train (1 msec pulse duration, 263 Hz pulse frequency, 20 msec train duration) that was delivered at random inter-stimulus intervals (ISI) ranging between 20-40 seconds. Longer ISI were adopted to prevent habituation of RIII (Chabal, Jacobson, & Little, 1989; Dimitrijevic, Faganel, Gregoric, Nathan, & Trontelj, 1972). An S88 Grass Square Pulse stimulator and constant current unit were used to deliver pulses. The intensity of pulses was monitored via a custom-built digital current meter.

Recording: Electromyographic (EMG) data was measured from the ipsilateral biceps femoris (capitis longus) muscle because this muscle generates reflex activity earliest in the lower limb (Willer, 1977). Bipolar 8 mm shielded silver/silver chloride cup electrodes were placed 3 cm apart on the skin, parallel to the belly of the muscle fibre close to the tendon. The correct site was identified by a standardised palpitation procedure. A disposable pre-gelled, adhesive ground electrode was placed on a right lateral bony structure (the outer femural condyle). EMG data was amplified 20,000x and low and high pass filtered (active range 20-1000 Hz) using an MP100 Biopac amplifier in conjunction with an EMG multi-channel amplifier module. Results were sampled at rate of 1000 samples/sec (highest sampling rate permitted by the capacity of the computer), digitised and stored for off-line analysis using commercially available software (Acq*Knowledge®* version 3.7.1. ©1992-2001 Biopac Systems, Inc.; Goleta, CA).

The same equipment and procedures as described in Study 2 were used to achieve skin impedance of less than 10 K ohms [Mean K ohms = ankle - 8.09 ± 1.18 (SEM); biceps femoris - 6.53 ± 0.49 (SEM)], as recommended by Fridlund and Cacioppo (1986). The right foot was positioned in a foot-rest to achieve a 90° angle at the knee (France & Suchowiecki, 1999), and a neck-brace was placed on each subject to avoid unrelated vestibular input during assessment (Young, 1973).

RIII and pain thresholds

A staircase limits method was used to assess electro-cutaneous pain threshold. Specifically, pulse intensity (starting at 10 mA) was reduced by steps of 1 mA when it was painful, and increased in steps of 1 mA when no longer painful. Once six ascending and descending steps were completed, the exercise was terminated. RIII thresholds were determined from the resulting EMG recordings.

Subjects rated the pain of pulses using a 0-10 point horizontal verbal rating scale (VRS) that was taped to the wall in front of them. The VRS consisted of numerical markers spaced evenly between anchors 0 = 'No pain' and 10 = 'Pain as bad as it could get'. A rating of '3' indicated the point at which the pulse first became painful. This type of scale was deemed more practical than a VAS as subjects could not look down, and were to remain still throughout these exercises. Although VRS do not possess ratio scale characteristics (Price et al., 1994), responses from VRS and VAS are highly correlated (Littman, Walker, & Schneider, 1985) and response curves are indistinguishable (Duncan, Bushnell, & Lavigne, 1989).

Pain and unpleasantness ratings

To measure RIII at empirically established threshold (10 mA) and supra-threshold levels (15 mA) (Willer, 1977), shocks were delivered three times at each intensity in a random order. Subjects rated the perceived PI and UP of each shock using the same 0-10 point VRS used in thresholds detection exercises.

Naltrexone intervention

As in Study 2, naltrexone (50 ml) was administered to half of the subjects, and a placebo was administered to the other half of the sample to assess activation of the endogenous opioid system. Subjects were randomly assigned to either drug condition using the same double-blind procedure adopted in Study 2. The capsule was administered 10 minutes prior to RIII measurement to maximise time efficiency, as the likelihood of naltrexone affecting the results at that stage was deemed to be low. Thereafter, testing was suspended for approximately 50-60 minutes to achieve maximum drug absorption. Subjects were directed back to Cubicle A, where they sat quietly and read until the time had elapsed. Although 13% of subjects taking naltrexone reported mild nausea, decreased mental acuity or fatigue, symptoms did not prevent subjects from completing the experiment.

Math task

Subjects completed a 25-minute[12] computer programmed mental arithmetic task in Cubicle B. The math task resembled the HMS condition in Study 2; however, it was shortened by 5 minutes to maintain subject-engagement with the task and the frequency of mood/self-efficacy ratings was increased to 'capture' the subjective state of each subject more accurately. As a consequence, the schedule of shocks and subjective ratings was different to the schedule Study 2. Nonetheless, all 'events' were still delivered at irregular intervals to prevent them from becoming predictable. As in previous studies, subjects completed the math task in a different cubicle to increase the novelty and anticipatory anxiety associated with the task.

Task shocks

Stimulation consisted of seven 15.45 mA ± 0.04 (SEM) rectangular pulses of 25 milliseconds duration. The pulses were delivered to the ankle via the same electrodes used to elicit the RIII. Hence, equipment used to deliver shocks was identical to that

[12] The task took approximately 28-30 minutes, including completion of subjective ratings.

used during RIII measurement. As described in Study 2, subjects rated the PI and UP of each pulse using a computer-generated 0-100 point VAS.

Debriefing

At the end of the session, the purpose of the experiment was explained and subjects were remunerated. Details of the math program were not discussed as this task was to be used in Study 4. Subjects were told that the coding system for drug conditions would be 'broken' if required; however, this was not necessary. Subjects were informed (via email) as to which drug they had been given after data collection had been finalised. As in Study 2, subjects were reminded not to consume alcohol for at least one day after the experiment.

4.3 RESULTS

4.3.1 General data outline

Dependent variables were explored at three time points during the experiment: prior to the drug, after drug absorption/prior to the math task, and after the math task. This helped to disentangle drug effects from effects of the math task. As in Study 2, correlations *and* regression analyses were conducted as correlations provided an insight into the relationship between continuous dependent variables, and regression analyses help detect significant group differences within these relationships.

4.3.2 Mood and self-efficacy

Randomisation check

Independent t-test comparisons indicated that groups did not differ in anxiety ($t(41) = -.34$; $p = .74$), discouragement ($t(41) = -.27$; $p = .79$), or anger ($t(41) = .71$; $p = .48$) at the start of the experiment. However, the placebo group reported higher levels of self-efficacy than the naltrexone group ($t(41) = -2.55$; $p = .01$) (Table 4.2). Since subjects were randomly assigned to each drug condition this difference is difficult to explain, but is best dealt with by focusing on upcoming changes in self-efficacy.

Table 4.2: Mood and self-efficacy ratings before and after drug absorption.

	Mood							
	Anxiety		Discouragement		Anger		Self-efficacy	
Drug	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				Pre-drug				
Placebo	35.77	22.98	16.51	17.36	5.60	7.10	60.69	17.37
Naltrexone	33.53	19.90	15.00	19.75	8.42	17.29	44.73	23.49
				Post-drug				
Placebo	22.72	18.17	13.16	15.35	6.75	8.23		
Naltrexone	25.94	29.12	17.09	20.85	5.14	7.91		

Note. Placebo N = 23; Naltrexone N = 20.

Effects of the drug on mood and self-efficacy

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on each mood (Table 4.2 and 4.3). Aside from checking the randomisation of groups, self-efficacy was not assessed prior to the math task as ratings related to performance during the task.

Table 4.3: F ratios for mood before and after the drug.

Source	**Anxiety**	**Discouragement**	**Anger**
Time† (T)	8.84**	0.05	0.49
Drug (D)	0.00	0.06	0.04
T x D†	0.62	1.00	2.10

Note: †Pillai's Trace F ratio; degrees of freedom = 1, 41.

**p<.01.

As shown in Table 4.3, subjects in both conditions experienced a significant drop in anxiety (M = 34.65 to 24.33) after having spent over 90 minutes in the experimental setting. Presumably anxiety decreased as the novelty of the setting and procedures decreased with repetition and time. Discouragement and anger did not change after the drug.

Effects of the math task on mood and self-efficacy

Separate 2 (Drug: naltrexone, placebo) x 7 (Time: pre-task, during task at 1:30", 7:39", 13:20", 19:40", 24:00", post-math task) repeated measures ANOVAs were carried out on each mood and self-efficacy rating (Tables 4.4 and 4.5). 'Pre-task' level of *Time* referred to post-practice trial ratings in self-efficacy analyses.

Low self-efficacy scores after the practice trials and throughout the task suggested that subjects found the questions difficult and expected to have little control over performance-related shocks. Despite differences in self-efficacy at the outset of the experiment, changes in perceived self-efficacy were similar across conditions.

Time main effects were explored with simple pair-wise comparisons, where each rating was compared to pre-task ratings. As indicated in Table 4.6, subjects experienced a significant increase in anxiety, discouragement, and anger throughout the math task. Significant worsening of mood persisted after the task was completed.

Naltrexone did not influence changes in mood or self-efficacy. No interactions were noted.

Table 4.4: Mood and self-efficacy ratings before, during, and after the math task.

Time	Anxiety		Discouragement		Anger		Self-efficacy	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				Placebo (N = 22[a])				
Pre-task	23.15	18.48	12.84	15.63	6.04	7.67	29.98	23.55
1	57.41	22.72	47.41	23.67	23.50	22.62	35.73	22.77
2	61.04	17.83	51.95	23.88	26.50	22.46	39.59	27.33
3	61.27	23.81	54.86	23.72	28.04	24.18	31.45	24.91
4	60.78	26.09	58.86	24.36	32.59	27.26	27.68	21.67
5	59.23	27.77	56.09	25.84	34.45	28.56	25.32	19.93
Post-task	43.95	26.88	47.74[13]	28.90	24.75	23.73	24.67	18.89
				Naltrexone (N = 20)				
Pre-task	25.94	29.12	17.09	20.85	5.14	7.91	15.80	17.79
1	63.40	24.90	50.60	22.66	24.20	21.26	25.25	21.41
2	55.00	23.55	54.50	25.97	32.35	25.87	22.80	18.79
3	61.70	24.90	48.40	29.06	34.30	24.21	23.60	19.64
4	60.45	29.12	57.80	31.74	38.25	28.53	21.60	24.58
5	59.35	30.09	60.45	30.79	37.65	30.25	22.60	25.14
Post-task	48.45	31.96	60.13	31.48	26.64	27.54	19.20	21.95

Note. [a] N=1 missing data; Pre = prior to practice trials and math task in mood analyses, and post-practice trials in self-efficacy analyses; 1-5 = 1:30, 7:39, 13:20, 19:40 and 24:00 minutes into math task, respectively; Post = after math task.

[13] An exploratory 2 (Drug: naltrexone, placebo) x 2 (Time: last rating during task, post-math task) repeated measures ANOVA was carried out to see whether discouragement decreased after the task in the placebo group to a greater degree than in the naltrexone group. Group differences failed to reach statistical significance.

Table 4.5: F ratios for mood and self-efficacy before, during, and after the math task.

Source	Anxiety	Discouragement	Anger	Self-efficacy
Time† (T)	15.20***	22.14***	8.60***	1.86
Drug (D)	0.03	0.19	0.27	2.70
T x D†	0.56	1.24	0.35	0.87

Note: †Pillai's Trace F ratio; degrees of freedom: T, T x D = 6,35; D = 1,40.

***p≤ .001.

Table 4.6: Simple pair-wise comparisons[a] of mood before, during and after the math task.

		Math Task					
Mood	**Pre**	**1**	**2**	**3**	**4**	**5**	**Post**
Anxiety	24	60***	58***	61***	61***	59***	46***
Discouragement	15	49***	53***	52***	58***	58***	54***
Anger	6	24***	29***	31***	35***	36***	26***

Note. [a] Each rating was compared to pre-practice trials/ math task ratings.

***p≤.001.

4.3.3 Electro-cutaneous task shocks

Subjects received seven 15 mA shocks during the math task. PI and UP ratings were averaged across all shocks. Independent t-tests indicated no difference in shock PI (t (41) = -.47; p = .64) or UP (t (41) = -.29; p = .77) between drug conditions. On average, subjects perceived the shocks to be moderately to somewhat severely painful and unpleasant (M range = 54 – 58) (Table 4.7).

Table 4.7: Shock pain intensity and unpleasantness ratings during the math task.

	Placebo (N = 23)		Naltrexone (N = 20)	
Shock rating	**Mean**	**SD**	**Mean**	**SD**
Pain Intensity	57.74	20.54	54.50	24.36
Unpleasantness	55.76	23.58	53.59	25.93

Effects of mood, self-efficacy and the drug on task shock sensitivity

As shown in Pearson product correlations (Table 4.8) and regression analyses (Table 4.9), anxiety, discouragement, and anger were positively associated with shock PI and UP, irrespective of whether naltrexone or placebo was administered. A Drug x Self-efficacy effect was found for shock PI. As shown in Figure 4.2, naltrexone appeared to antagonise opioid-mediated pain inhibitory influences in self-efficacious subjects.

Table 4.8: Pearson correlations between mood, self-efficacy and shock pain intensity and unpleasantness ratings during the math task.

	Task shock pain index			
	Placebo (N = 23)		Naltrexone (N = 20)	
Task mood	**PI**	**UP**	**PI**	**UP**
Anxiety	.40[a]	.53**	.42	.47*
Discouragement	.47*	.34	.61**	.67***
Anger	.31	.45*	.38	.36
Self-efficacy	-.44*	-.27	.22	.14

Note. PI = pain intensity; UP = unpleasantness.

[a] p=.057; *p<.05; **p<01; ***p<.001.

Table 4.9: Summary of t-values from hierarchical regression analyses illustrating the effects of mood, self-efficacy and drug on shock pain intensity and unpleasantness, during the math task.

		Task shock pain index							
		Pain intensity				**Unpleasantness**			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Sf.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
1	**Drug (D)**	0.51	0.59	0.66	0.60	0.32	0.36	0.51	0.37
	Mood (M)	2.87**	4.18***	2.31*	-0.62	3.66***	3.80***	2.82**	-0.41
2	**D x M**	0.01	-0.49	-0.42	-2.16*	0.46	-1.06	0.17	-1.30

Note. Step 1 = main effects model (degrees of freedom = 2,40); Step 2 = full model (df = 3,39); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

*p<.05; **p<.01; *** p≤.001.

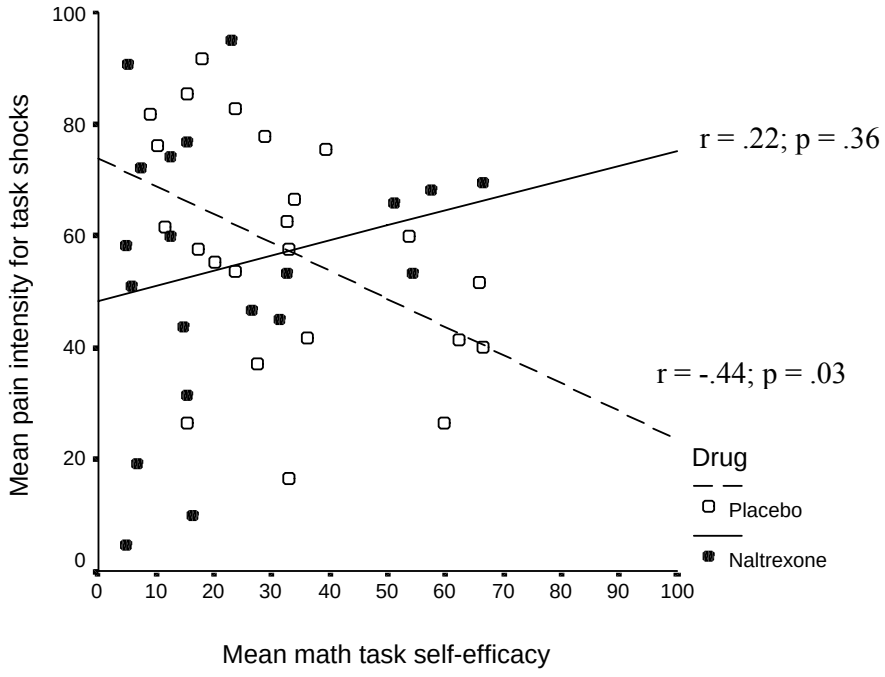


Figure 4.2: Scatter-plot showing the negative association between mean self-efficacy and pain ratings for shocks during the math task in placebo recipients only.

4.3.4 Cold pressor pain perception

Data considerations

Subjects rated the level of PI and UP during each CPT on a 0-100 point M-VAS at 30-second intervals, until they could no longer keep their hand in the water. Time in the water was averaged for each subject.

The number of subjects reaching the maximum time (i.e., four minutes) did not differ between groups at the beginning of the experiment (20% placebo, 20% naltrexone: χ^2 (1) = 0.05; p= .83), post-drug (10% placebo, 8.7% naltrexone: χ^2 (1) = 0.02; p=.88), or after the math task (20% placebo, 13% naltrexone: χ^2 (1) = 0.38; p=.54). Transformation of these outliers was deemed unnecessary due to their small number and equal distribution across groups. Pain tolerance in this sample exceeded mean tolerance times found in research using similar paradigms (Hirsch & Liebert, 1998). Many researchers have found significant sex differences in pain tolerance to experimentally induced pain, where males tend to tolerate cold water for longer (Berkley, 1997). Hence, the higher-than-average tolerance to cold pressor pain could be attributed to the inclusion of males in the group.

PI and UP ratings for each CPT were moderately related (pre-drug r = .37; post-drug r = .46; post-maths r = .55), suggesting that each variable was measuring qualitatively different aspects of the cold pressor experience. Thus, each rating was analysed separately.

Randomisation check

Groups did not differ on any pain parameter during the first CPT (PI: t (41) = -.49; p = .62; UP: t (41) = .11; p = .91; pain tolerance: t (41) = -.29; p = .77) (Table 4.10). Subjects perceived the initial CPT to be more painful than unpleasant; however, high ratings in both dimensions suggested that the CPT was a sufficiently noxious stimulus.

Table 4.10: Cold pressor pain tolerance, pain intensity and unpleasantness before and after the drug, and after the math task.

	Placebo (N = 23)						Naltrexone (N = 20)					
Pain	**Pre-drug**		**Post-drug**		**Post-math**		**Pre-drug**		**Post-drug**		**Post-math**	
index	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Tol.	105	79.4	76	67.8	85	76.6	98	80.2	80	74.2	87	84.9
PI	74.6	17.4	72.3	18.9	71.5	17.1	72.1	15.2	71.9	15.6	77.0	15.9
UP	64.1	24.7	74.1	18.3	72.9	15.3	64.9	21.0	65.6	19.5	71.9	20.3

Note. M = mean; SD = standard deviation; Tol. = pain tolerance (seconds); PI = pain intensity; UP = unpleasantness.

Effects of the drug on cold pressor pain perception

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on cold pressor pain tolerance, PI and UP ratings (Table 4.10 and 4.11).

Table 4.11: F ratios for cold pressor pain tolerance, pain intensity and unpleasantness before and after the drug, and after the math task.

	Tolerance Time		Pain intensity		Unpleasantness	
Source	**Post drug**	**Post task**	**Post drug**	**Post task**	**Post drug**	**Post task**
Time† (T)	9.26**	1.35	0.27	1.52	5.51*	1.98
Drug (D)	0.00	0.02	0.10	0.26	0.41	0.81
T x D†	0.60	0.04	0.17	2.87	4.25*	4.08*

Note. †Pillai's Trace F ratio; degrees of freedom = 1,41.

*p≤.05; **p<.01.

Pain and unpleasantness

Discussion of the Time main effect in the context of a Time x Drug interaction for UP ratings is redundant; hence only the latter is discussed. Paired t-test comparisons revealed significantly higher UP ratings following drug absorption in the placebo group ($t(22) = -2.73$; $p = .01$), but not in the naltrexone group ($t(19) = -0.26$; $p = .79$) (Figure 4.3). The CPT remained comparatively painful during the second occasion, regardless of drug condition.

Pain tolerance

A main effect of Time indicated that subjects tolerated the cold water for significantly less time after the drug; however, the decrease in pain tolerance was not due to absorption of naltrexone.

Effect of the math task on cold pressor pain perception

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre- and post-math task) repeated measures ANOVAs were carried out on pain tolerance, PI and UP ratings (Table 4.10 and 4.11).

Pain and unpleasantness

A Time x Drug interaction for cold pressor UP was explored with paired t-tests. Paired comparisons revealed marginal increases in cold pressor UP for subjects in the naltrexone group after the math task ($t(19) = -1.89$; $p = .07$), but not in the placebo group ($t(22) = 0.61$; $p = .55$) (Figure 4.3).

Pain tolerance

Pain tolerance did not change significantly after the math task, and was not affected by naltrexone.

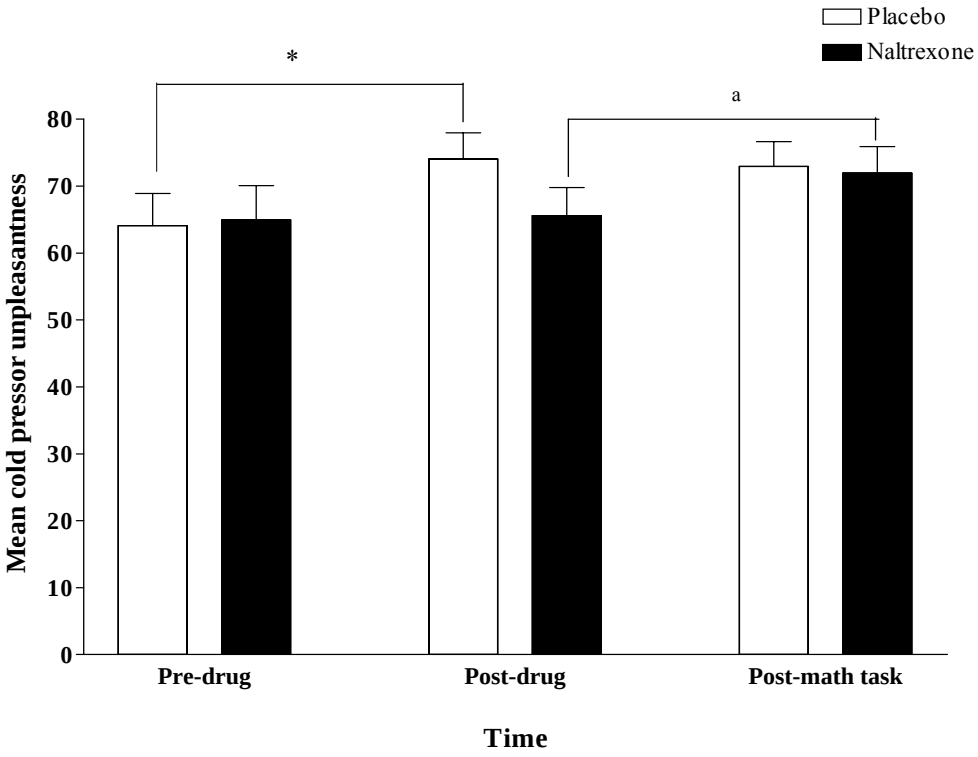


Figure 4.3: Cold pressor unpleasantness for placebo and naltrexone recipients throughout the experiment. Note. *p<.05; [a] p=.07.

Effects of mood, self-efficacy and the drug on cold pressor pain perception

Mood and self-efficacy ratings made before each CPT were analysed in regression models as they temporally coincided with cold pressor ratings. Self-efficacy prior to the math task was not analysed as ratings related to performance on the math task. Pearson product correlations provided a context within which regression analyses could be interpreted.

Absolute scores

To investigate the intensity of mood and self-efficacy on pain in each drug condition, absolute ratings were regressed on absolute cold pressor pain indices. Pearson correlations illustrated the relationship between these variables (Tables 4.12 and 4.13).

Pain intensity and unpleasantness: Regression analyses indicated that anxiety sensitised subjects to cold pressor PI after the drug. A similar trend, although non-significant, was found for discouragement. Regression analyses failed to identify differences amongst drug conditions after the math task. However, correlations indicated that discouragement was positively associated with cold pressor PI in the naltrexone group, but not in the placebo group. Presumably, when drug conditions were analysed together individual group effects were weakened via summation. Neither mood nor drug affected cold pressor UP. Self-efficacy did not influence cold pressor PI or UP.

Pain tolerance: Anger was associated with greater pain tolerance in the placebo group before the math task (Figure 4.4). No other mood or self-efficacy rating influenced pain tolerance during the experiment.

Table 4.12: Pearson product correlations between mood, self-efficacy and cold pressor pain intensity, unpleasantness and pain tolerance.

Pain	Post-drug/Pre-math			Post-math task			
index	Ax.	Ds.	Ag.	Ax.	Ds.	Ag.	Sf.
			Placebo (N = 23)				
Tol.	.03	.22	.58**	.30	.04	.25	.06
PI	.24	.00	-.12	-.10	.05	.13	-.15
UP	-.00	.00	-.28	.03	.13	.18	.06
			Naltrexone (N = 20)				
Tol.	.06	.15	-.30	.15	-.36	-.35	-.29
PI	.51*	.59**	-.23	.03	.47*	.04	-.16
UP	-.03	.30	.07	-.38	.22	-.29	-.24

Note. Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy; Tol. = pain tolerance (seconds), PI = pain intensity, UP = unpleasantness.

*p<.05; **p<.01.

Table 4.13: Summary of t-values from hierarchical regression analyses illustrating effects of mood, self-efficacy, and drug on cold pressor pain intensity, unpleasantness and pain tolerance.

		Mood on cold pressor pain perception						
		Post-drug/Pre-math			Post-math task			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
					Pain intensity			
1	**Drug (D)**	0.27	0.30	0.20	-1.08	-0.78	-1.06	-0.94
	Mood (M)	2.47*	1.87	-1.05	-0.25	1.60	0.55	-0.97
2	**D x M**	-0.11	-1.49	0.27	-0.44	-1.26	0.34	-0.08
					Unpleasantness			
1	**Drug (D)**	1.45	1.59	1.54	0.11	0.40	0.18	0.28
	Mood (M)	-0.11	1.09	-0.76	-1.35	1.14	-0.54	-0.72
2	**D x M**	0.06	-0.83	-1.08	1.41	-0.38	1.54	1.00
					Pain Tolerance			
1	**Drug (D)**	-0.20	-0.09	-0.32	0.01	-0.28	-0.08	0.02
	Mood (M)	0.28	1.16	1.03	1.43	-1.06	-0.39	-0.80
2	**D x M**	-0.04	0.33	3.06**	0.51	1.31	1.96[a]	1.07

Note. Step 1 = main effects model (df = 2, 40); Step 2 = full model (df = 3,39); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

[a]p=.058; *p<.05; **p<.01.

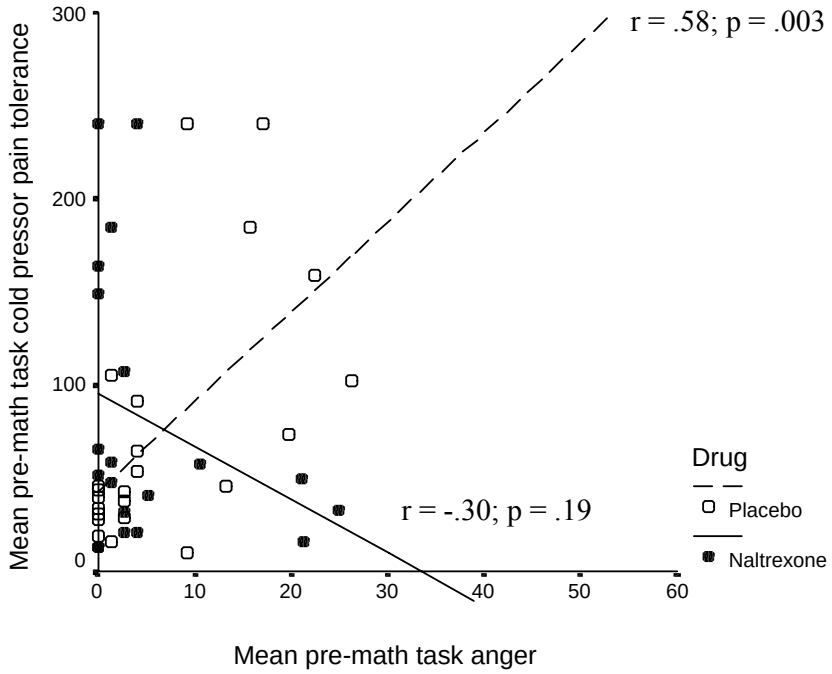


Figure 4.4: Scattergram depicting the positive relationship between anger and cold pressor pain tolerance after drug absorption in the placebo group, but not in the naltrexone group.

Change scores

As in Study 2, a 'moving' baseline (see p 136) was used to calculate change in cold pressor pain indices during subsequent CPT. Changes in self-efficacy were only calculated after the task (using post-practice trial ratings as a baseline) for reasons mentioned previously.

Post-drug: As shown in Tables 4.14 and 4.15, change in mood did not affect changes in pain tolerance, PI or UP after the drug.

Table 4.14: Pearson product correlations between change in mood, self-efficacy and cold pressor pain intensity, unpleasantness and pain tolerance after the drug.

	Change in cold pressor pain index					
	Placebo (N = 23)			Naltrexone (N = 20)		
Change in mood	**PI**	**UP**	**Tol.**	**PI**	**UP**	**Tol.**
Anxiety	.12	-.15	.05	-.11	-.26	.25
Discouragement	.03	-.07	-.09	.12	-.08	.16
Anger	.07	-.16	-.10	.11	-.08	-.05

Note. PI = pain intensity; UP = unpleasantness; Tol. = pain tolerance (seconds).

Table 4.15: Summary of t-values from hierarchical regression analyses illustrating the effects of change in mood and self-efficacy and drug on changes in cold pressor pain indices after drug absorption.

		Change in mood on Change in cold pressor index								
		Pain intensity			Unpleasantness			Pain tolerance		
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**
1	**Drug (D)**	-0.38	-0.35	-0.50	1.91[a]	1.95[a]	2.15[a]	-0.66	-0.75	-0.65
	Mood (M)	0.22	0.33	0.45	-1.18	-0.46	-0.67	0.89	0.01	-0.42
2	**D x M**	0.73	-0.11	0.24	-0.14	-0.04	-0.66	-0.37	-0.75	-0.38

Note. Step 1 = main effects model (df = 2,40); Step 2 = full model (df = 3,39); Ax. = anxiety; Ds. = discouragement; Ag. = anger.

[a] (see Figure 4.3).

Post-math task: After the math task, a Discouragement x Drug effect was identified for cold pressor PI and UP ratings (Tables 4.16 and 4.17). As shown in Figure 4.5 and 4.6, increases in discouragement were positively related to increases in cold pressor PI and UP in the naltrexone group, but not in the placebo group. No other factor influenced cold pressor responses after the math task.

Table 4.16: Pearson product correlations between change in mood, self-efficacy and cold pressor pain intensity, unpleasantness and pain tolerance after the math task

	Change in cold pressor pain index					
	Placebo (N = 23)			Naltrexone (N = 20)		
Change in mood	**PI**	**UP**	**Tol.**	**PI**	**UP**	**Tol.**
Anxiety	-.12	-.11	-.04	-.01	-.08	.29
Discouragement	-.28	-.05	-.02	.53*	.50*	-.20
Anger	-.25	-.10	-.15	.18	.25	-.12
Self-efficacy	-.25	-.10	.06	.08	.13	-.15

Note. PI = pain intensity; UP = unpleasantness; Tol. = pain tolerance (seconds).

*p<.05.

Table 4.17: Summary of t-values from hierarchical regression analyses illustrating the effects of change in mood and self-efficacy, and drug on changes in cold pressor pain indices after the math task.

		'Change in mood' on 'Change in post-task cold pressor index'											
		Pain intensity				Unpleasantness				Pain tolerance			
	Variable	**Ax**	**Ds**	**Ag**	**Sf**	**Ax**	**Ds**	**Ag**	**Sf**	**Ax**	**Ds**	**Ag**	**Sf**
1	**Drug (D)**	-1.68	-1.52	-1.66	-1.66	2.01[a]	-1.83[a]	-1.97[a]	-1.78	0.19	0.10	0.15	0.06
	Mood (M)	0.35	1.45	0.17	-0.28	-0.55	1.97	0.81	0.25	0.66	-0.73	-0.85	-0.33
2	**D x M**	-0.22	-2.91**	-1.32	-0.95	0.10	-2.08*	-1.10	-0.71	-1.16	0.51	-0.19	0.65

Note. Step 1 = main effects model (df = 2,40); Step 2 = full model (df = 3,39); Ax = anxiety; Ds = discouragement; Ag = anger; Sf = self-efficacy.

[a] (see Figure 4.3); *p<.05; **p<.01.

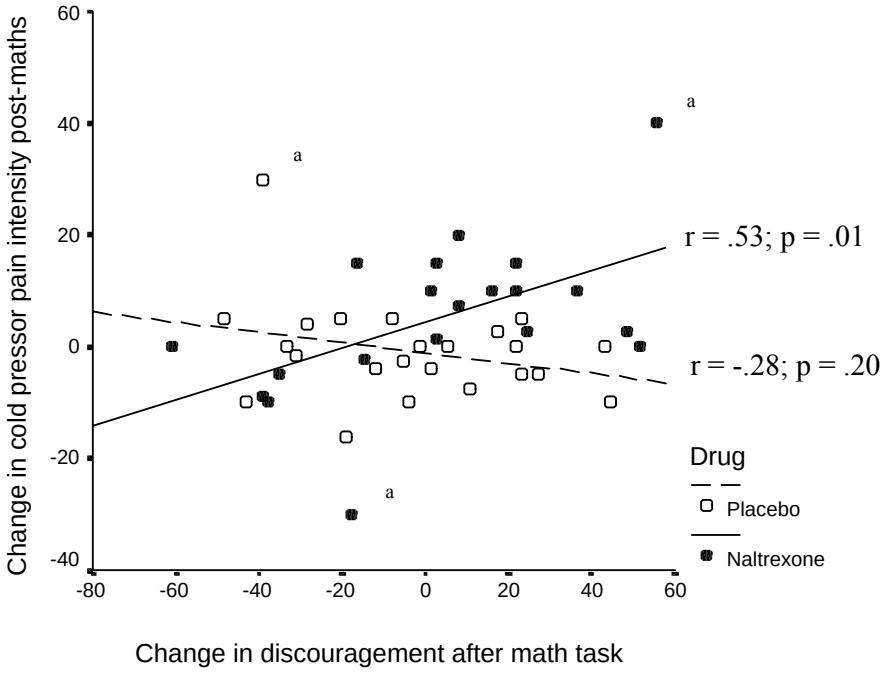


Figure 4.5: Scattergram depicting the positive relationship between increases in discouragement and cold pressor pain after the math task for recipients of naltrexone, but not the placebo. [a] Removal of outliers did not alter the significance of this effect.

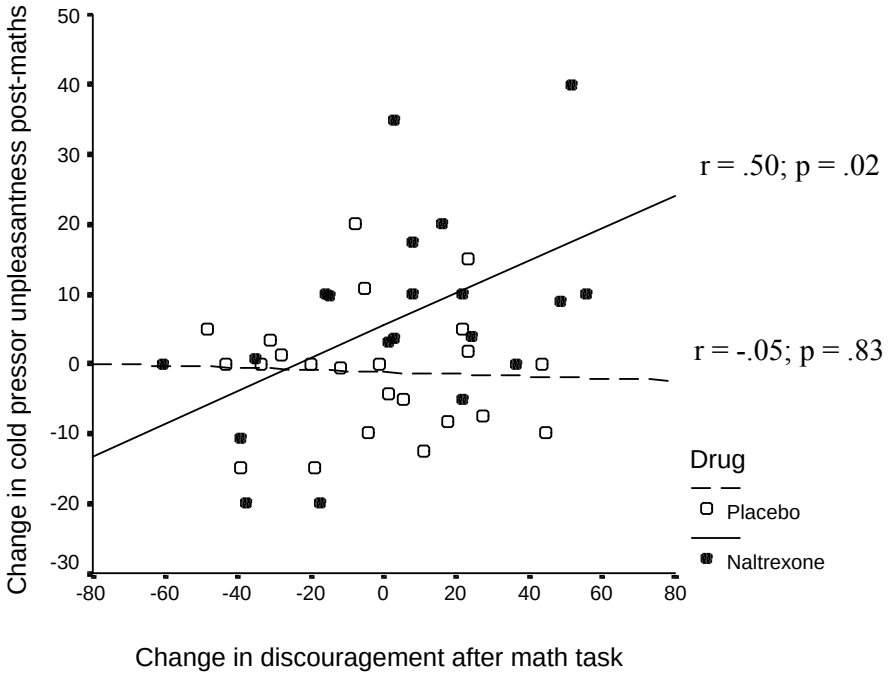


Figure 4.6: Scattergram depicting the positive relationship between increases in discouragement and increases in cold pressor unpleasantness after the math task for recipients of naltrexone, but not the placebo.

4.3.5 RIII nociceptive flexion reflex

RIII onset latency

Data considerations

Stimuli to elicit the RIII were set at threshold (10 mA) and supra-threshold levels (15 mA) (Willer, 1977). As expected, the nociceptive flexion reflex was elicited by 10 mA shocks on an average of 45.5% of occasions throughout the experiment. One explanation for <50% response rates could be the time at which participants were tested, and circadian variations in RIII threshold (Sandrini et al., 1986). Most participants were tested mid-morning through to the afternoon when RIII thresholds are generally on the rise, and 10 mA may not have been intense enough to elicit RIII responses 50% of the time. RIII was elicited more reliably by 15 mA shocks, as the flexion reflex was present on an average of 64.5% of occasions. RIII became less reliable with repeated stimulation, which may once again be due to rising thresholds throughout the course of the experiment (Sandrini et al., 1986).

Latency of an RIII response was taken as the point beyond 90 msec post-stimulus that could clearly be distinguished from preceding RII responses. Latencies that could not clearly be determined were excluded from analyses. For this reason, cell sizes were not large enough to proceed with repeated measures analyses. Therefore, group differences among RIII latencies were explored at three time points throughout the experiment using independent t-tests (Table 4.18).

Although exploratory analyses were conducted on area under the curve of the RIII response, no clear or interesting effects were found. Since this parameter is considered to be less reliable than onset latencies and requires many repetitions to attain reliable values (van Vliet, Vein, le Cessie, Ferrari, & van Dijk, 2002), area under the curve is not reported.

Randomisation/Methodological check

RIII latencies did not differ between groups at the beginning of the experiment in response to 10 mA (t (30) = -1.55; p = .13) or 15 mA shocks (t (35) = -0.69; p = .49) (Table 4.18). Latency of RIII responses were consistent with those identified previously (e.g., Garcia-Larrea, Charles, Sindou, & Mauguiere, 1993 = 80 - 130 msecs; Hugon, 1973 = 80 - 120 msecs). Furthermore, RIII were long enough to be distinct from RII responses, and short enough to avoid contamination by voluntary or startle responses occurring beyond 250 msecs (Le Bars et al., 1992). Neither RIII (t (19) = -1.3; p = .21) nor pain thresholds (t (41) = -0.36; p = .72) differed significantly between groups at the beginning of the experiment (Table 4.18).

Table 4.18: RIII onset latencies to 10 mA and 15 mA stimuli.

		Placebo			Naltrexone		
Time	**mA**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Pre-drug	**10**	18	103.64	18.77	14	95.28	8.43
	15	19	100.59	15.75	18	96.99	15.74
Post-drug	**10**	10	101.92	12.89	9	94.45	8.56
	15	15	104.69	15.57	15	102.31	15.33
Post-task	**10**	8	96.07	13.25	7	107.90	16.18
	15	9	93.93	10.65	10	101.97	11.01

Note. mA = milliamps.

Effects of the math task and drug on RIII onset latencies

RIII latencies did not differ between placebo and naltrexone groups after the drug in response to 10 mA shocks (t (17) = -1.47; p = .16) or 15 mA shocks (t (28) = -0.42; p = .68). Similarly, RIII did not differ between groups at either intensity (10 mA shocks: t (13) = 1.56; p = .14; 15 mA shocks: t (17) = 1.62; p = .12) after the math task.

Effect of mood, self-efficacy and the drug on RIII onset latencies

Exploratory analyses investigating the effects of mood and self-efficacy (absolute and change scores) on RIII onset in each drug condition were completed using two-step, hierarchical linear regression models. No major findings emerged, suggesting that these variables did not affect RIII onset. Alternatively, cell sizes may have been too small to detect any effects.

RIII and subjective pain thresholds

As found previously (Sandrini et al., 1986; Willer, 1977), subjective pain thresholds (detected using the staircase limits method) and RIII thresholds were positively related at all time points during the experiment (Table 4.19). An RIII threshold was defined as the intensity eliciting a response approximately 75-80% of the time (Willer, 1977). A response was polyphasic in shape, with an onset between 90-180 msec (post-stimulus).

Table 4.19: Pearson product correlations between RIII and subjective pain thresholds.

		Mean subjective pain thresholds - mA		
		Pre-drug	**Post-drug**	**Post-math**
Mean RIII thresholds - mA		3.52 (2.7)	5.69 (3.3)	5.39 (3.0)
Pre-drug	7.33 (2.1)	.56**	.61**	.41
Post-drug	8.25 (2.6)	.46	.71**	.43
Post-math	8.21 (1.7)	.45	.68*	.65*

Note. mA = milliamps; Numbers of subjects demonstrating clear RIII responses varied at each time point i.e., pre-drug N = 21, post-drug N = 18, and post-math task N = 12.
*p<.05; **p <.01.

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on subjective pain thresholds to explore differences after the drug. Similar 2 (Drug: naltrexone, placebo) x 2 (Time: pre- and

post-math task) repeated measures ANOVAs were carried out after the math task. As shown in Tables 4.20 and 4.21, pain thresholds increased significantly after drug absorption; however, this effect occurred regardless of opioid blockade. Pain thresholds did not change significantly after the math task.

Cell numbers were too small to carry out repeated measures analyses on RIII thresholds. Therefore, independent t-tests comparisons were computed between groups at each time point. RIII thresholds did not differ significantly between groups after drug absorption ($t(16) = .48$; $p = .63$) or the math task ($t(10) = -.84$; $p = .42$).

Table 4.20: Subjective pain thresholds for RIII-eliciting stimuli.

	Placebo (N = 23)			**Naltrexone (N = 20)**		
mA	**Pre-drug**	**Post-drug**	**Post-maths**	**Pre-drug**	**Post-drug**	**Post-maths**
Mean	4.30	4.91	5.54	4.65	5.89	6.35
SD	3.08	3.14	3.73	3.31	3.27	4.29

Note. mA = milliamps.

Table 4.21: F ratios comparing subjective pain thresholds (for RIII-eliciting stimuli) between conditions, after the drug and after the math task.

Source	**Post-drug**	**Post-math task**
Time† (T)	7.74**	2.25
Drug (D)	0.53	0.74
T x D†	0.92	0.06

Note. †Pillai's Trace F ratio; degrees of freedom = 1,41.

**p<.01.

4.3.6 Association between painful and non-painful stimuli[14]

Pearson product correlations were carried out between painful and non-painful stimuli i.e., LSMT, VM (Table 4.22). Whilst cold pressor PI and UP were moderately related to each other, neither pain rating was related to pain tolerance before or after the math task. Instead, pain tolerance was positively related to non-painful tasks of persistence (i.e., LSMT, VM) - particularly in the placebo group. Finally, cold pressor PI was inversely associated with RIII pain thresholds before and after the math task. That is, higher reports of cold-induced pain were related to lower electrical pain thresholds.

Table 4.22: Pearson product correlations between painful and non-painful stimuli after the drug and math task.

	Placebo (N = 23)						**Naltrexone (N = 20)**					
	1.	**2.**	**3.**	**4.**	**5.**	**6.**	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**
						Post-drug/Pre-math task						
1. Tol.	-						-					
2. PI	-.00	-					.21	-				
3. UP	-.15	.52*	-				.19	.41	-			
4. LSMT	.40	.13	-.03	-			-.01	.24	-.27	-		
5. VM	.52*	.16	.04	.16	-		.34	.08	-.02	-.14	-	
6. PTh.	.23	-.57**	-.10	.04	.14	-	.27	-.40	-.02	-.31	.21	-
						Post -math task						
1. Tol.	-						-					
2. PI	-.04	-					-.15	-				
3. UP	-.10	.67**	-				-.00	.47*	-			
4. LSMT	.48*	-.29	-.30	-			-.21	.13	-.09	-		
5. VM	.43*	.05	.15	.11	-		.39	.11	-.04	-.26	-	
6. PTh.	-.02	-.66**	-.29	.39	.28	-	.25	-.39	-.04	-.43	.08	-

Note. Tol. = tolerance time (seconds), PI = pain intensity; UP = unpleasantness; LSMT = Letter Symbol Matching Task; VM = Valsalva manoeuvre; PTh. = pain thresholds to RIII-eliciting stimuli. *p<.05; **p<.01.

[14] Since statistical analyses indicated that neither the LSMT nor the VM were affected by mood, time or any other experimental manipulation, these findings were not reported.

4.3.7 Cardiovascular activity

SBP, DBP and pulse rate were measured on entering the experimental environment, 90 minutes later after drug absorption, and during and after the math task. Absolute values reflected the relationship between hypertensive responses and endogenous opioid release most clearly. Hence, absolute cardiovascular responses were analysed rather than change scores.

Randomisation check

Independent t-tests indicated that cardiovascular responses did not differ among groups at the start of the experiment (SBP: t (40) = -1.13; p = .27; DBP: t (40) = -.50; p = .62; Pulse: t (40) = .13; p = .89) (Table 4.23). Cardiovascular responses were within normotensive levels (Lobstein et al., 1989; O'Brien & O'Malley, 1981).

Effects of the drug on cardiovascular activity

Separate 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were carried out on SBP, DBP and pulse rate (Tables 4.23 and 4.24). Cardiovascular measures decreased regardless of opioid blockade, suggesting that sympatho-inhibition was due to an extended period at rest and familiarisation with the experimental setting and procedures (Table 4.24). The lack of effect of naltrexone on cardiovascular responses at rest supported the use of this opioid antagonist when studying cardiovascular responses to the math task (McCubbin et al., 1996).

Table 4.23: Blood pressure and pulse rate before and after the drug.

	Placebo (N = 22[a])				Naltrexone (N = 20)			
Blood	**Pre-drug**		**Post-drug**		**Pre-drug**		**Post-drug**	
Pressure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
SBP	116.32	15.53	110.65	13.31	110.87	15.79	104.78	15.56
DBP	70.15	10.35	67.83	8.54	68.72	8.09	66.07	7.61
Pulse	80.66	13.42	73.04	11.64	81.17	10.72	72.58	9.27

Note. [a] N=1 missing data; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 4.24: F ratios of blood pressure and pulse rate before and after the drug.

Source	SBP	DBP	Pulse
Time[†] (T)	23.54***	10.15**	42.34***
Drug (D)	1.59	0.38	0.00
T x D[†]	0.03	0.04	0.15

Note. [†]Pillai's Trace F ratio; degrees of freedom = 1,40; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
**p<.01; ***p<.001.

Effects of the math task on cardiovascular activity

BP and pulse rate were measured at 2-minute intervals during the math task (28 minutes duration). As in Study 2, measures were averaged across two intervals (of 14 minutes each). Separate 2 (Drug: naltrexone, placebo) x 4 (Time: pre-task, task interval 1-14 minutes and 15-28 minutes, post-task) repeated measures ANOVAs were carried out on SBP, DBP and pulse rate (Tables 4.25 and 4.26).

Table 4.25: Blood pressure and pulse rate prior to, during and after the math task.

		Placebo (N = 20[a])				Naltrexone (N = 20)			
Blood			**Math task**				**Math task**		
Pressure		**Pre**	**1**	**2**	**Post**	**Pre**	**1**	**2**	**Post**
SBP	**M**	109.46	119.48	115.97	116.66	104.78	114.04	109.64	106.17
	SD	13.26	15.44	14.44	14.51	15.56	14.26	15.02	13.19
DBP	**M**	66.74	77.66	76.73	73.89	66.07	75.36	73.78	69.59
	SD	8.11	11.02	9.02	8.70	7.61	9.68	11.49	6.71
Pulse	**M**	70.90	71.39	71.09	68.84	72.58	72.23	72.59	69.95
	SD	9.59	11.49	10.35	11.64	9.27	11.75	10.16	8.57

Note. [a] N = 3 missing data; M = mean; SD = standard deviation; Pre = pre-math task; Math task 1 = 1-14 mins; Math task 2 = 15-28 mins; Post = post-math task; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 4.26: F ratios comparing blood pressure and pulse rate prior to, during and after the math task.

Source	**SBP**	**DBP**	**Pulse**
Time[†] (T)	17.90***	36.29***	2.17
Drug (D)	2.44	0.98	0.18
T x D[†]	1.81	1.39	0.05

Note. [†]Pillai's Trace F ratio; degrees of freedom: T, T x D = 2,37; D = 1,38; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
***p<.001.

Time main effects for SBP and DBP were explored with planned simple contrasts, where each rating was compared to pre-task ratings. As shown in Table 4.27, SBP and DBP were significantly higher during and after the task, than beforehand. Pulse rates remained at pre-task levels during the task, but were marginally lower once the task was completed. Naltrexone did not influence BP or pulse rate during or after the math task.

Table 4.27: Simple pair-wise comparisons[a] of blood pressure and pulse rate before, during and after the math task.

	Blood pressure across time			
Blood		**Math task**		
Pressure	**Pre-task**	**1-14 mins**	**15-28 mins**	**Post-task**
SBP	107.12	116.76***	112.80***	111.41**
DBP	66.40	76.51***	75.26***	71.74***
Pulse	71.74	71.81	71.84	69.40[b]

Note. [a] pre-task is the point of comparison; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

[b]p=.054; **p<.01; ***p<.001.

Association between cardiovascular activity and task shock sensitivity

Correlational analyses demonstrated an inverse relationship between task shock sensitivity and BP in the placebo group, but not in the naltrexone group (Table 4.28). There was evidence of a similar relationship in regression analyses, although group differences failed to reach significance (Table 4.29). No relationship existed between pulse rate and pain perception during task shocks.

Table 4.28: Pearson correlations between blood pressure, pulse rate and task shock pain intensity and unpleasantness ratings.

	Task shock pain index			
	Placebo (N = 21[a])		**Naltrexone (N = 20)**	
Task CVR	**PI**	**UP**	**PI**	**UP**
SBP	-.52*	-.41	.04	.00
DBP	-.51*	-.43[b]	.07	.01
Pulse	-.36	-.12	-.04	.16

Note. [a] N=2 missing data; CVR = cardiovascular response; PI = pain intensity; UP = unpleasantness; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

[b]p=.052; *p<.05.

Table 4.29: Summary of t-values from hierarchical regression analyses illustrating the effects of drug, blood pressure and pulse rate on task shock pain and unpleasantness during the math task.

		Task shock pain index					
		Pain intensity			Unpleasantness		
Step	**Variable**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**
1	**Drug (D)**	0.79	0.75	0.50	0.38	0.36	0.11
	CVR	0.46	-1.44	-1.23	-1.27	-1.39	0.14
2	**D x CVR**	-1.70	-1.68	-0.93	-1.26	-1.28	-0.88

Note. Step 1 = main effects model (df = 2,40); Step 2 = full model (df = 3,39); CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Association between cardiovascular activity and cold pressor pain perception

Pearson product correlations (Table 4.30) and regression analyses (Table 4.31) were carried out between cold pressor PI, UP and pain tolerance and cardiovascular activity measured just prior to each CPT.

SBP was positively associated with cold pressor pain tolerance after the math task. There was evidence of a similar relationship before the math task, although this did not achieve statistical significance. Correlational analyses suggested that this relationship was stronger for placebo than naltrexone recipients. However, group differences were not detected in regression analyses.

DBP was positively associated with cold pressor UP before the math task in the naltrexone group (Figure 4.7). This relationship disappeared after the math task. Instead, there was a general inverse association between blood pressure and cold pressor UP. This effect was not affected by the drug. Pulse rate was not associated with cold pressor pain perception.

Table 4.30: Pearson product correlations between cold pressor pain indices, blood pressure and pulse rate.

	Placebo (N = 22[a])			Naltrexone (N = 20)		
	PI	**UP**	**Tolerance**	**PI**	**UP**	**Tolerance**
			Post-drug/Pre-math task			
SBP	-.03	-.14	.42[b]	.25	.26	.18
DBP	-.15	-.35	.30	.34	.46*	.03
Pulse	-.06	-.12	.31	.11	.07	.03
			Post-math task			
SBP	-.07	-.29	.51*	-.06	-.44[c]	.21
DBP	-.09	-.55**	.28	.15	-.16	.06
Pulse	.02	.04	.14	.06	-.11	-.20

Note. [a] N=1 missing data; PI = pain intensity, UP = unpleasantness, Tolerance = pain tolerance (seconds); SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

[b]p=.051; [c]p=.052; *p<.05; **p<.01.

Table 4.31: Summary of t-values from hierarchical linear regression analyses illustrating the effects of drug, blood pressure and pulse on cold pressor pain, unpleasantness and tolerance.

		Pain intensity			Unpleasantness			Tolerance		
Step	**Variable**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**
					Post-drug/Pre-math task					
1	**Drug (D)**	-0.16	-0.07	-0.04	1.17	1.26	1.29	-0.64	-0.37	-0.28
	CVR	0.60	0.26	0.01	0.44	0.15	-0.22	1.90	1.13	1.19
2	**D x CVR**	-0.76	-1.52	-0.53	-1.25	2.76**	-0.58	0.88	0.74	0.70
					Post-math task					
1	**Drug (D)**	-1.00	-1.18	-1.25	0.93	0.63	0.00	-1.03	-0.41	-0.09
	CVR	-0.41	-0.05	0.22	-2.43*	-2.29*	-0.17	2.46*	1.17	0.03
2	**D x CVR**	-0.05	-0.62	-0.16	0.98	-0.62	0.56	0.78	0.50	1.10

Note. Step 1 = main effects model (df = 2,40); Step 2 = full model (df = 3,39); Tolerance = pain tolerance (seconds); CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

*p<.05; **p<.01.

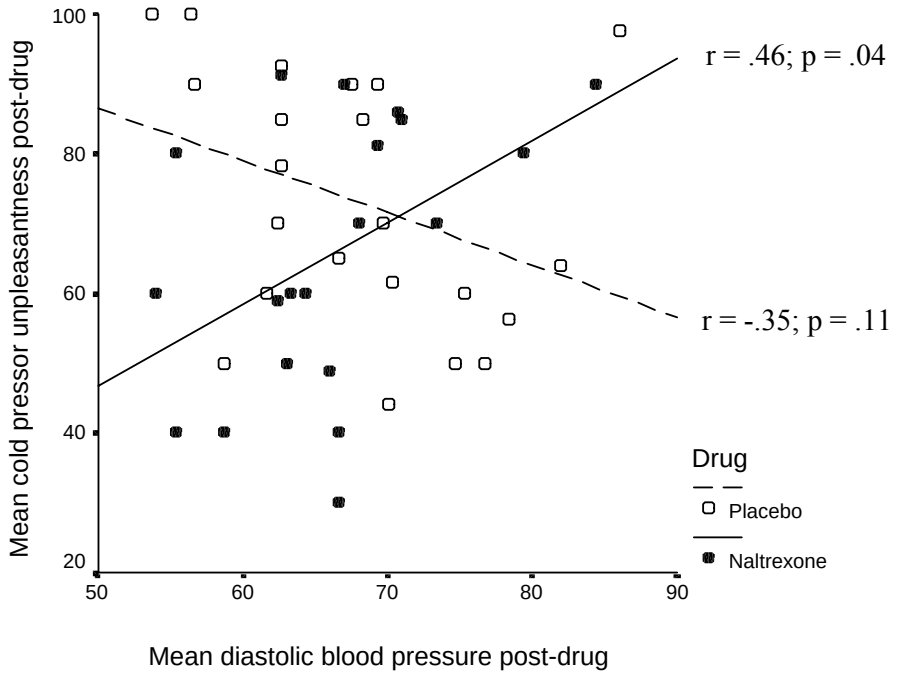


Figure 4.7: Scattergram depicting a positive association between cold pressor unpleasantness and diastolic blood pressure for naltrexone but not placebo recipients after the drug.

4.4 DISCUSSION

4.4.1 Summary of major findings

Two key findings emerged from the present study. First, opioid blockade increased the affective component of pain after psychological stress. Second, experimentally induced discouragement was associated with increased cold pressor PI and UP in the naltrexone group, whilst anxiety and anger failed to modulate pain. Since discouragement preceded the CPT, it is likely that discouragement had a direct inhibitory effect on pain. Conversely, negative mood was associated with pain sensitivity to brief electrical stimulation.

Other findings of interest included:

- Insensitivity of RIII responses to psychological stress, negative mood, or opioid release, despite being related to subjective pain thresholds.
- Pain tolerance reflected the ability to endure discomfort.
- An opioid-mediated inverse association between BP and pain during and after psychological stress.

4.4.2 Success of experimental manipulations

Significant increases in anxiety, discouragement, and anger and low self-efficacy characterised subjects' experience during and shortly after the math task. A significant decrease in self-efficacy after the practice trials confirmed that task controllability was manipulated effectively. Furthermore, the math task provoked sizable elevations in BP, presumably due to the constant threat and *actual* delivery of noxious electric shocks - an element not present in other studies (McCubbin et al., 1996). An increase in BP often leads to a slowing of the heart by reflex signals sent from the vasomotor centre (i.e., the 'baroreceptor reflex' - Steptoe, 1980). In normotensive individuals this reflex plays an important role in regulating arterial pressure and maintaining cardiovascular homeostasis (Andreassi, 1989). Thus, it is possible that baroreceptors responded to elevations in arterial pressure by slowing heart rate throughout and after the math task.

Naltrexone failed to influence mood or cardiovascular activity at rest, meaning that opioidergic effects observed after the math task could be attributed to psychological stress and not naltrexone.

Electric shocks during the math task and CPTs were valid pain stimuli as subjects reported 'moderate' to 'somewhat severe' PI and UP during each stimulus. Prior to the math task, anxiety was associated with high reports of cold pressor PI, particularly in the naltrexone group. Also, anger was positively associated with pain tolerance in the placebo group. These results suggest that opioids may have been released prior to the math task due to the stress of repeated CPTs. Placebo and naltrexone group differences in cold pressor UP before the math task support this idea (see *4.4.5 Multi-dimensional pain experience*, p 196).

4.4.3 Opioid involvement in stress-induced analgesia (SIA)

Sensitivity to brief electrical stimuli

Pain sensitivity to shocks did not differ between the placebo and naltrexone groups during the math task. Therefore, the results of the present study diverged from those demonstrating opioid-mediated SIA to electric shock stimuli in animals (e.g., Hyson et al., 1982) and humans (e.g. Willer & Albe-Fessard, 1980a; Willer et al., 1981). Shocks adopted in other studies were typically longer in duration, delivered at a higher frequency and were more intense than those delivered during the math task. According to Rhudy and Meagher (2001b), the negative affect and high levels of arousal resulting from the intensity of these stimuli may have activated the endogenous opioid system, leading to pain inhibition. Conversely, lower levels of negative arousal tend to facilitate pain in subjects who are exposed to aversive, uncontrollable events (Rhudy & Meagher, 2001b). In light of this, it is possible that the math task (in conjunction with the brief and intermittent nature of the shocks) led to low to moderate levels of negative arousal, which in turn enhanced shock PI and UP.

Decreased sensitivity to sustained cold pressor stimuli

Subjects under opioid blockade reported more cold pressor UP after the math task, than beforehand. UP remained the same in the placebo group demonstrating a 'relative analgesia' when compared to their counterparts in the naltrexone group. Neither PI nor pain tolerance differed in either the placebo or naltrexone group after the math task. Therefore, increasing the power of the present study by including only one stressful condition did not strengthen the analgesic effect observed in Study 2. It is possible that 'stimulus controllability' is less directly related to SIA than mediating variables such as negative mood. In demonstrating this, Mueller and Netter (2000) found a strong independent effect of 'subjective helplessness' on pain perception, whereas objective stimulus controllability was only indirectly related to perceived PI. Alternatively, the intensity of the cold pressor stimulus may have induced ceiling effects in perceived PI and UP, so that opioid-mediated SIA was unable to counteract nociceptive input in the placebo group.

RIII onset

The results of the present study do not support the hypothesis that RIII onset would be facilitated in the naltrexone group after the math task. The current findings diverge from those of Willer and colleagues (Willer & Albe-Fessard, 1980a; Willer et al., 1981), who demonstrated an opioid-mediated effect of anticipatory anxiety on RIII thresholds, whereby RIII responses were strongly facilitated (thresholds decreased) by naloxone in healthy humans. Opioid inhibition of the RIII at the spinal level has also been replicated in animal research (e.g., Goldfarb & Hu, 1976) and in patients suffering from chronic back and hip pain (Chabal et al., 1989). Divergent results in the present study may be explained by methodological differences such as stressor intensity on RIII indices. In comparison to the present study, Willer delivered much higher intensity shocks (70-80 mA versus 15 mA shocks) that may have led to a stronger opioid-mediated inhibitory effect on RIII responses. Alternatively, RIII thresholds may be a more sensitive measure of opioid involvement than onset latency. This explanation does not seem adequate as RIII thresholds measured in the present study were not influenced by opioid release either before or after the math task. In summary, the present findings indicate that the opioid system did not influence RIII, possibly owing to the nature of the stressor (math task + brief shocks) or other methodological limitations such as small cell sizes or limited precision in RIII measurement.

4.4.4 Negative mood and pain modulation

Facilitation of electrical pain

Negative mood was positively associated with shock PI and UP in both the placebo and naltrexone groups. Rhudy and Meagher (2001b) suggested that negative emotions can facilitate pain via the same neural circuitry that modulates startle. Thus, negative mood may 'prime' subjects to experience more PI and UP during each shock. The way in which a stimulus is interpreted can also influence the way it is perceived. For instance, an interpretation of shock stimuli as 'harmful' often leads to anxiety and hyper-vigilance to the stimulus that increases autonomic arousal,

attention towards pain, muscle tension and pain itself. Similar processes, of which do not involve opioids, may be responsible for the present findings.

An inverse association between self-efficacy and shock PI in the placebo group indicated that opioids were released in a subgroup of subjects with high self-efficacy. These results are at odds with those of Bandura et al. (1988), who found that self-efficacious subjects differed from their inefficacious counterparts in that they were not stressed and there was no evidence of opioid activation during a timed math task. However, they did state that in the event that a task exceeded a subject's capabilities it would become highly stressful - especially for self-efficacious subjects - resulting in opioid activation (Bandura et al., 1987). Thus, it is possible that the math task posed a difficult cognitive challenge even for self-efficacious subjects, who may have become stressed by their failure to perform well during the task, which in turn led to a release of opioids.

Inhibition of cold pressor pain

As hypothesised, naltrexone recipients who became more discouraged after the math task reported greater cold pressor PI and UP. Discouraged subjects in the placebo group experienced no change in cold pressor pain perception, suggesting that endogenous opioids were only partially effective in mediating pain inhibitory effects in discouraged subjects. This may be due to the intensity of the cold pressor stimulus and ceiling effects in PI and UP ratings. Although the relationship between discouragement and cold pressor pain perception failed to reach statistical significance in analyses of absolute scores, data trends agreed with those found with change scores. Discouragement in this experiment is akin to LH in animal research, which has been associated with opioid activation and endogenous analgesia. Therefore, a type of helplessness may have been induced during that math task, resulting in opioid activation and a 'capping' of pain sensations in the placebo group and pain sensitisation in subjects under opioid blockade.

Contrary to expectations, neither anxiety nor anger modulated cold pressor pain perception after the math task. Thus, anxiety and anger were not associated with opioid activation, or SIA. These results fail to support the results of others who

demonstrated pain inhibition by experimentally induced intense anxiety (Willer & Albe-Fessard, 1980a). Rhudy and Meagher (2000; 2001a; 2001b; 2003a) postulated that *fear* induced by uncontrollable stressors inhibits pain. Therefore, subjects may have experienced anxiety instead of fear during the math task. Very few studies have been carried out on the effects of stress-induced anger on pain, hence specific hypotheses could not be generated. However, it may be that anger is not related to SIA. Alternatively, the math task may have failed to induce anger that was intense enough to activate endogenous antinociceptive systems.

4.4.5 Multi-dimensional pain experience

Pain thresholds to electrical stimuli used to elicit the RIII were inversely associated with ratings of cold pressor PI. This convergent association indicates that ratings of PI accurately reflected the subject's pain experience across different stimulus modalities.

The lack of opioid involvement in pain tolerance at most stages of the experiment suggests that this measure of pain also reflects factors unrelated to nociceptive processes. Specifically, a positive association between pain tolerance and non-painful, unpleasant tasks (LSMT, VM) but not other pain-related measures (PI/UP ratings) suggests that pain tolerance reflects the ability to endure an unpleasant task, whether painful or not.

Repetition of the CPT influenced both pain UP and pain tolerance whilst the sensory domain of pain, or PI remained unaffected. Affective components of the pain experience such as UP and tolerance are most influenced by factors such as contextual cues, emotions, memory, attention and cognitive expectancies about the pain stimulus (Hirsch & Liebert, 1998; Zelman et al., 1991). Therefore, having already experienced the noxious nature of the cold water and having to complete more than one CPT, negative expectations regarding the experience may have increased over the course of the experiment reducing pain tolerance and increasing UP. The present results support those of Hirsch and Liebert (1998), who demonstrated that contextual factors can powerfully influence affective responses to pain, whilst sensory aspects remain relatively unchanged.

Interestingly, opioids influenced UP, but not PI or pain tolerance, both before and after the math task. Before the task (after drug absorption), greater UP was reported in the placebo group, whereas UP remained unchanged with naltrexone. This result is difficult to explain because *naltrexone*, once absorbed, was expected to lead to more PI and UP during the CPT. One explanation may be that at low doses endogenous opioids may paradoxically increase affective components of pain. In particular, low levels of exogenous opiates such as morphine can excite nociceptors and facilitate the transmission of pain signals in humans (Le Bars et al., 1992) and animals (Vierck et al., 2002). Thus, noxious cold pressor stimuli may have led to minor opioid release before the math task.

Endogenous opioids inhibited cold pressor UP after the math task, whereas PI and tolerance remained unchanged. This result is in accordance with both animal (e.g., Amir & Amit, 1978) and human research (Drolet et al., 2001), which demonstrated opioid modulation of affective elements of pain, without any change to pain sensation.

4.4.6 Opioid involvement in the cardiovascular-pain relationship

The widely researched relationship between cardiovascular and pain regulatory systems (Randich & Maixner, 1984) was explored in normotensive subjects in the present study. Specifically, the association between resting and stress-induced cardiovascular activity and pain was assessed prior to, during and after the math task. Mediation of this relationship by endogenous opioids was also of interest. Hence, the association between the above-mentioned variables was assessed after absorption of naltrexone.

Shock sensitivity and stress-induced cardiovascular activity

As hypothesised, according to correlational data subjects in the placebo group with high blood pressure reported less PI and UP for shocks during the math task. This relationship appeared to be weakened by naltrexone. Group differences suggest that stress-induced increases in BP were associated with opioid-mediated anti-nociception. Cardiovascular and pain regulatory systems are interrelated whereby

primary afferents from the heart and lungs synapse in brainstem structures also responsible for anti-nociception (Randich & Maixner, 1984). Therefore, decreased shock pain sensitivity could be attributed to baroreceptor activated opioid-mediated pain-dampening mechanisms. The present findings are consistent with previous normotensive research examining this relationship during laboratory-induced stress (Rosa et al., 1988).

Heart rate was not associated with shock pain perception. This may be explained by the different roles that BP and heart rate play in evoking baroreceptor-stimulated analgesia. BP plays a primary role in the stimulation of this form of analgesia as alterations in arterial pressure directly stimulate baroreceptors. Heart rate, on the other hand, *indirectly* influences the cardiovascular-pain relationship by influencing BP via a feedback regulatory mechanism known as the 'baroreceptor reflex'. An indirect involvement in this relationship may explain why heart rate failed to influence shock pain perception.

Cold pressor sensitivity and resting cardiovascular activity

A *positive* relationship between DBP and cold pressor UP was found in the naltrexone group before the math task. It would appear that baroreceptor-mediated analgesia failed to operate in subjects under opioid blockade at this time. These results, although only found for DBP, support the idea that the endogenous opioids modulate the relationship between resting BP and pain in normotensive subjects (McCubbin & Bruehl, 1994). A similar relationship existed between SBP and cold pressor UP before the math task. However, no difference was found between the placebo and naltrexone groups. It is unclear why opioids appear to have mediated the relationship between DBP, but not SBP, and cold pressor UP.

An inverse relationship between blood pressure and cold pressor UP was found in *both* naltrexone and placebo recipients after the math task. This suggested that the relationship between cardiovascular activity and pain was mediated (at least in part) by nonopioid mechanisms after the math task. It is not surprising that the association identified before the task disappeared afterwards because the stress-induced

activation of opioids during the math task could independently affect pain and blood pressure.

Resting SBP was positively associated with cold pressor pain tolerance after the math task. Evidence of this relationship also existed before the task, but failed to reach statistical significance. Unlike UP, the relationship between SBP and pain tolerance did not appear to be mediated by opioid mechanisms. The reason for this discrepancy is uncertain. However, the association between cardiovascular activity and pain will be investigated further in the following study.

CHAPTER FIVE

5. DEPRESSION AND PAIN

Negative mood, and discouragement in particular, was found to mediate stress-induced analgesic responses in healthy subjects in Studies 1-3. Furthermore, the inhibitory effect of negative mood on pain appeared to be mediated by endogenous opioids in Study 2 and 3. In the context of these and other findings, it has generally been accepted that negative mood modulates pain; however, the effects of *mood disorders* on pain are not clearly defined. Therefore, the aim of Study 4 was to investigate whether these results could be generalised to a mood disorder, namely *major depression*.

The following two chapters aim to provide an overview of the literature examining 1) the link between depression and pain and 2) opioid involvement in depression before presenting the rationale for the fourth study. Also, literature regarding the interaction of cardiovascular and pain regulatory systems in depression will be reviewed briefly.

5.1 CHAPTER OVERVIEW

The relationship between depression and pain is well established and has been discussed extensively. However, only a few controlled studies have been conducted. Furthermore, theoretical models that specify the way the two conditions interact have undergone limited refinement (Romano & Turner, 1985). The relationship between depression and pain will be examined via a review of recent literature outlining:

- the prevalence of pain in depression and depression in pain.
- temporal relationships between depression and pain.
- neurochemical pathways common to both disorders.
- pain sensitivity in depressed patients compared to non-depressed subjects.

Depressive diagnostic criteria: The majority of research in this area assessed patients from one diagnostic category, namely major depressive disorder (as diagnosed by Diagnostic and Statistics Manual of Mental Disorders criteria, DSM-IV). Major depression is characterised by "[one] or more major depressive episodes (i.e., at least 2 weeks of depressed mood or loss of interest accompanied by at least four additional symptoms of depression)" (A.P.A., 1994, p 317). Additional symptoms include significant weight loss or gain, decreased or increased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, excessive or inappropriate guilt, diminished ability to concentrate, indecisiveness, recurrent thoughts of death or suicidal ideation with or without a plan, or a suicide attempt. Included less often in the research are subjects with minor depression (i.e., the equivalent of <five, but >2 depressive symptoms mentioned above) (Jain & Russ, 2003).

5.2 PREVALENCE STUDIES

5.2.1 Pain in depression

High rates of pain have been found in depressed patients. For instance, in a study of 1146 patients with major depressive disorder, pain was the primary complaint in 69% of the cases (von Korff & Simon, 1996). Similarly, using rigorous Research Diagnostic Criteria (RDC), Lindsay and Wyckoff (1981) found that 59% of depressed patients complained of pain. Some data has indicated that pain occurs at different rates in some subgroups of depression versus others. For example, Von Knorring et al. (1983) found that rates of pain in depressed patients varied from 56% to 100%, with higher rates evident in patients with reactive depression, or *adjustment disorder with depressed mood* (according to DSM-IV diagnostic criteria). Romano and Turner (1985) established that pain complaints were more common in depressed patients with anxiety than those without, as anxious depressives tended to experience more muscular tension. Although generally high (above 50%), rates of pain in depression also vary according to the source of recruitment (newspaper articles versus primary care clinics), patient population (out versus inpatients), and the method of diagnosis (von Knorring et al., 1983; Ward, Bloom, & Friedel, 1979; Worz, 2003).

5.2.2 Depression in pain

The prevalence of major depression in the general population ranges from 5-17% (Banks & Kerns, 1996). In contrast, the prevalence of depression in chronic pain patients ranges between 10% and 100%, depending on the type of measure or clinical diagnostic criteria adopted (Romano & Turner, 1985). When major depression is diagnosed using stringent RDC and DSM-IV diagnostic criteria, the rate of depression in chronic pain patients is far higher than in the general population, ranging between 30% - 54% (Banks & Kerns, 1996). Consistent with this, Gureje, Simon and von Korff (2001) found that patients with persistent pain were four times more likely to have an anxiety or depressive disorder than pain free individuals. Furthermore, depression is consistently more common in chronic pain patients than in any other chronic medical patient subgroup presenting with physical symptoms (Banks & Kerns, 1996; Fishbain, Cutler, Rosomoff, & Rosomoff, 1997).

5.3 TEMPORAL RELATIONSHIPS BETWEEN DEPRESSION AND PAIN

The literature examining temporal relationships between depression and pain indicates a two-way interaction between both conditions. Before a brief overview of this literature is presented, explanations for each directional relationship (i.e., *depression causing pain* and *pain causing depression*) will be given.

According to the notion that depression precedes pain, depressed patients are more likely to experience pain and report distress due to increases in muscle tension and an increased focus on somatic symptoms (Romano & Turner, 1985). For example, people who complain of fatigue, headaches, or gastrointestinal problems are more likely to have a co-morbid anxiety or depressive disorder, and it seems that the presence of these disorders increases the probability of physical complaints reaching reportable levels (Gallagher & Cariati, 2002). To illustrate, out of two groups experiencing the same symptoms of irritable bowel syndrome, the group experiencing more life stress and psychiatric conditions were the ones who sought medical assistance (Drossman, 1999). Kroenke and Mangelsdorff (1989) found that

the presence of physical complaints increased the probability of a mood disorder three-fold, but that physical complaints in these cases were linked to disease-related pathology only 16% of the time. Biochemical changes in depression such as the reduced release of serotonin and noradrenaline may also explain increased pain in depression as these biochemical changes influence nociceptive processing (Romano & Turner, 1985; Ward et al., 1979).

Depression that is secondary to pain may reflect a patient's psychological reaction to the physically and emotionally demanding nature of persistent pain. In a cross-sectional study, Rudy, Kerns and Turk (1988) provided support for this view as pain led to negative cognitive and behavioural effects, which eventually resulted in depression in their sample. Alternatively, pain may increase the turnover of serotonin, thereby causing depression (Fishbain et al., 1997).

Literature review

Fishbain et al. (1997) conducted an extensive search of the literature, assessing eighty-three studies that investigated the temporal relationship between depression and pain. Only three of thirteen studies supported the view that depression increases the risk of chronic pain. Conversely, fifteen studies found evidence of depression following the onset of pain. Despite the comprehensive nature of this review, the 'vote-counting' approach failed to account for the quality of findings, nor did it address the quality or strength of group differences.

In a number of self-report studies, 38% to 46% of chronic pain patients reported pain prior to the onset of major depression, 10% to 12% recounted having depression before pain, whilst the remaining patients reported the simultaneous onset of both conditions (Bradley, 1963; Lindsay & Wyckoff, 1981; Lipowski, 1990). Atkinson, Slater, Patterson, Grant and Garfin (1991) also provided (marginally) more support for the view that pain precedes depression as 58% of their sample recalled having pain before depression, whilst only 42% recalled that their depression began before their pain.

In a large longitudinal, prospective study, Brown (1990) used covariance structural equation modelling to permit causal inferences between pain and depression in 243

rheumatoid arthritis patients. Although the onset of depression was not specifically assessed, Brown (1990) found that depression was aggravated by pain, providing further support for the idea that depression is a consequence of pain.

In a prospective study examining the view that depression precedes pain, Von Korff, LeResche and Dworkin (1993) found that over a three year period depression increased the risk of onset of some pain conditions (i.e., headache, chest pain, temporomandibular disorder). Similarly, in a 10-year follow up study Leino and Magni (1993) found that depressive symptoms predicted musculoskeletal pain in metal workers, but not the other way around. In another prospective study, Kivioja, Sjalin and Lindgren (2004) concluded that depressive morbidity prior to a motor vehicle accident influenced the presence of chronic neck pain one year after the whiplash injury. Moreover, there was a higher lifetime or pre-accident prevalence of depression in chronic neck pain sufferers (58%) than in those who completely recovered, suffering no pain (29%). In another line of support for the view that depression precedes pain, Keefe, Wilkins, Cook, Crisson and Muhlbaier (1986) found that the number of depressive symptoms predicted subsequent pain complaints. These results may be explained by the fact that depressed subjects demonstrate a lower tolerance of clinical pain (Merskey, 1976), making them more susceptible to developing chronic pain than non-depressed subjects..

In the first study to assess depressed, pain-free individuals and non-depressed patients with musculoskeletal pain, Magni, Moreschi, Rigatti-Luchini and Merskey (1994) found that the temporal relationship in either direction was weak but that the odds ratio for pain predicting depression was stronger. However, this study contained diagnostic weaknesses as chronic pain was diagnosed as persisting for only 1 month and depression was diagnosed using rating scales. Finally, Gureje et al. (2001) found that chronic pain at baseline predicted the onset of an affective disorder at the same strength as an affective disorder at baseline predicted persistent pain.

Methodology

Although the pain-depression temporal debate has drawn much attention, empirical approaches have been limited, providing considerable room for further investigation (Banks & Kerns, 1996). For example the use of physician reports, rigorous diagnostic criteria (DSM-IV or RDC), appropriate control groups, and prospective experimental designs may improve the quality of conclusions (Romano & Turner, 1985). As the literature stands, there appears to be support for both the view that depression occurs primarily, and secondarily to pain – with slightly more evidence supporting the latter contention.

5.4 COMMON NEUROCHEMICAL PATHWAYS

Serotonin, noradrenaline and opioids are all implicated in the pathogenesis of depression and pain modulation (Jain & Russ, 2003). Considering that opioid involvement in pain and depression is the focus of the next chapter, opioids will not be discussed in this section.

Serotonin and noradrenaline pathways are present in areas such as the prefrontal cortex and limbic system, both of which are implicated in depression. These neurotransmitters also regulate peripheral and central pain circuitry running through the amygdala, periaqueductal gray, dorsolateral pontine tegmentum and rostroventral medulla (Gallagher & Cariati, 2002). Preventing the release of serotonin and noradrenaline has led to an increase in depressive symptoms in patients taking antidepressants, and to a hyperalgesic response in animals and humans (Biegon & Samuel, 1980; Gallagher & Cariati, 2002). Conversely, inhibiting the uptake of both neurotransmitters with dual re-uptake inhibiting antidepressants (e.g., duloxetine) leads to the reduction in painful and depressive symptoms in patients afflicted with both disorders (Detke, Lu, Goldstein, Hayes, & Demitrack, 2002). Thus, this evidence and the efficacy of tricyclic antidepressants in pain conditions such as peripheral neuropathic pain, headache, migraine, facial pain, fibrositis and rheumatic pain, provides support for the contention that pain and depression share neurochemical pathways (Ruoff, 1996).

Some researchers argue that analgesia related to antidepressants is a secondary effect that can be attributed to the alleviation of depression and increased tolerance to pain (Onghena & Van Houdenhove, 1992). However, evidence of antidepressant-induced analgesia in both organic and psychogenic pain, and in both depressed and non-depressed subjects fails to support this explanation. Alternatively, antidepressant-induced analgesia may involve the inhibition of synaptic serotonin and noradrenaline re-uptake, both of which appear necessary for analgesia (Onghena & Van Houdenhove, 1992).

In summary, disruptions in descending pain inhibitory pathways, or any other brain structure mediated by serotonergic or adrenergic mechanisms, could influence pain or depression, and in turn influence the other (Manning, 2002). The overlap of neurochemical circuitry led Manning (2002) to speculate that these common factors could account for high rates of depression in chronic pain, or a depressive predisposition increasing an individual's vulnerability to chronic pain. Whether changes in these neurotransmitters precede or follow each disorder, and the extent to which these and other neurochemical mediators overlap in depression and pain, is yet to be fully investigated (Romano & Turner, 1985).

5.5 PAIN SENSITIVITY IN DEPRESSION

5.5.1 Experimental pain

In an extensive number of laboratory studies, depressed subjects have been reported to experience less pain than non-depressed subjects. Using a sensory detection paradigm, Davis, Buchsbaum and Bunney (1979) randomly delivered 93 shocks ranging from 1-31 mA to 76 affectively ill patients. They concluded that depressed patients were less sensitive to shocks, and rated fewer stimuli as 'unpleasant' and 'very unpleasant', than controls. In the same group of depressed patients, Davis et al. (1979) observed lower slope amplitude and intensity in somatosensory evoked potentials to four stimulus levels ranging from 2-23 mA indicated, in comparison to controls. Although Davis et al. (1979) tested both unipolar and bipolar subjects, pain insensitivity was comparable in both groups. In another signal detection paradigm

(Dworkin, Clark, & Lipsitz, 1995), patients with major depression were less able to discriminate between painful thermal stimuli, and demonstrated a higher response criterion (or more stoicism) to painful stimuli, when compared to controls. In contrast, sensory discrimination of thermal stimuli at lower intensities did not differ between the groups.

Increased pain thresholds to other pain stimuli such as contact heat have also been demonstrated in depressed patients (Bar, Greiner, Letsch, Kobele, & Sauer, 2003; Lautenbacher, Roscher, Strian, Fassbender, Krumrey, & Krieg, 1994). For example, Launtenbacher et al. (1994) found higher contact heat pain thresholds in 20 patients with major depression compared with the same number of healthy controls. However, the severity of depressive symptoms was not related to pain thresholds. Bar et al. (2003) compared the heat pain thresholds and tolerance of 20 depressed patients, who had begun taking antidepressants, with 20 age- and sex-matched controls. Increased heat pain thresholds and tolerance were observed in depressed patients at the outset of treatment (on or off medication) and during recovery, when compared to controls.

In a recent meta-analysis examining the impact of depression on the perception of experimental pain stimuli in six methodologically rigorous studies, Dickens, McGowan and Dale (2003) reported that pain thresholds were significantly higher in depressed subjects compared to non-depressed controls. Experimental pain insensitivity in depression was attributed to decreased attention to pain in depressed subjects, and not to alterations in pain inhibitory mechanisms. Others such as Marazziti, Castrogiovanni, Rossi, Rosa, Ghione, Di Muro, Panattoni and Cassano (1998) have related elevated pain thresholds in depressed patients to hyper-functioning of the endogenous opioid system, which they attribute to the dysregulation of neurotransmitters involved in pain transmission (e.g., serotonin). However, the lack of effect of naloxone on heat pain insensitivity in depression (Lautenbacher et al., 1994) fails to support this view.

Pinerua-Shuhaibar, Prieto-Rincon, Ferrer, Bonilla, Maixner and Suarez-Roca (1999) found that PI, UP and pain thresholds in response to sustained ischemic pain produced by a maximal effort tourniquet procedure did not differ between 11 patients

with minor depression and 32 controls. However, pressure pain led to lower pain tolerance in depressed subjects compared to controls. Results of this study were difficult to compare with others for a number of reasons. First, the depressed group was mostly comprised of females, who often report more pain and display lower tolerance to pain than males (Giles & Walker, 2000; Stevens, 1993; Westcott et al., 1977). Second, depression was diagnosed using the Zung scale rather than rigorous DSM-IV diagnostic criteria. Furthermore, the patients had only been diagnosed with *minor depression*.

5.5.2 Clinical pain

Paradoxically, in the context of decreased sensitivity to experimental pain, a higher prevalence and intensity of clinical pain has been found in depressed patients (Lautenbacher, Spernal, Schreiber, & Krieg, 1999). Kudoh, Katagai and Takazawa (2002) explored post-operative pain and experimental pain thresholds to electrical stimuli in 30 patients with major depression (taking antidepressants) and 30 controls - all of whom underwent major abdominal surgery. The depressed patients complained of significantly more pain following surgery, and clinical pain was related to the degree of pre-operative depressive symptomatology (as measured by scores on the Hamilton Depression Rating Scale). However, depressed patients did not differ from controls in their perception of electrical stimuli.

These results suggest that depressed patients are more distressed by clinical than experimental pain, perhaps because of the greater intensity, longer duration, and unpredictable/uncontrollable nature of clinical pain. Depressed patients may tolerate experimental pain better than control subjects, as it is perceived to be below personal distress thresholds or is not intense enough to mobilise/reflect impaired pain inhibitory mechanisms (Lautenbacher et al., 1999). Clinical pain, on the other hand, may lead to an exaggerated affective response, catastrophic cognitions and fears relating to one's own body, thus increasing the likelihood of clinical pain exceeding personal distress thresholds (Kudoh et al., 2002). A similar relationship was established in controls by Willoughby (Willoughby, 2000; Willoughby et al., 2002),

where experimentally induced depressed mood led to lower pain tolerance and an increase in catastrophising about pain.

In other words, the discrepancy between experimental and clinical pain sensitivity in individuals with major depression may be due not only to nociceptive processes, but also to affective-evaluative responses to pain. This assumption was corroborated by Lautenbacher et al. (1999), who failed to find a substantial relationship between clinical pain and experimentally induced pain thresholds. Lautenbacher and Krieg (1994) also speculate that hyperalgesic reactions to clinical pain in depression can be attributed to the insufficient activation of pain inhibitory mechanisms.

5.6 SUMMARY/CONCLUSIONS

In summary, the prevalence of pain in depression appears to be higher than the prevalence of depression in pain. Specifically, when rigorous diagnostic criteria have been used, approximately two-thirds of depressed patients complain of (mostly muscular, headache and back) pain, whereas approximately one-third to one-half of patients with persistent pain also present with depression. With regards to the temporal relationship between depression and pain, there seems to be support for both the notion that depression precedes pain and that pain precedes depression, with slightly more evidence in favour of the latter idea. Neurochemicals such as serotonin, noradrenaline and endogenous opioids regulate both mood and pain circuitry, suggesting that depression and pain share common neurochemical pathology. Depressed patients report higher pain thresholds and lower sensitivity to a variety of experimentally induced pain (contact heat, electrical stimuli) than controls. Explanations include attentional mediators of mood (i.e., towards negative mood, away from pain) and hyper-functioning of the opioid system, neither of which have been adequately assessed. Greater sensitivity to clinical pain in depressed subjects compared to controls has been attributed to the intensity and meaning attached to clinical pain, factors which are aggravated by the degree of depressive symptomatology. Others speculate as to the role of impaired pain inhibitory mechanisms in clinical pain hypersensitivity experienced by depressed patients. The impairment of endogenous pain inhibitory mechanisms in depression will be examined in the following chapter.

CHAPTER SIX

6. OPIOIDS IN DEPRESSION

The effects of exogenous and endogenous opioids on mood, behaviour and pain led to speculation regarding a relationship between depression and alterations in the endogenous opioid system. Additional lines of evidence connecting abnormal opioid activity with depression point specifically to high concentrations of opioid receptors in limbic and hypothalamic regions associated with mood (Extein, Pottash, & Gold, 1982). Furthermore, the involvement of opioids in pain regulation has prompted speculation that pain insensitivity and the increased prevalence of clinical pain in depression may be mediated by impaired endogenous opioid mechanisms.

The role of opioid peptides in depression has been examined by measuring opioids from various biological fluids (i.e., blood plasma, cerebrospinal fluid), and by assessing the effects of exogenous opioids and opioid antagonists on mood. More recently, physiological systems known to be mediated by opioids i.e., pain and cardiovascular regulatory systems and the hypothalamic-pituitary-adrenal (HPA) axis, have been compared between depressed and non-depressed subjects (Davis, Buchsbaum, & Bunney, 1981). The aim of this chapter is to provide a representative, although not comprehensive, summary of this research. Studies examining SIA in animal models of depression will also be discussed.

6.1 OPIOIDS IN BIOLOGICAL FLUIDS

Because of the location of opioid receptors in the brain, alterations in the opioidergic system are difficult to measure directly. Therefore, the functioning of the endogenous opioid system in depression has been assessed indirectly by measuring opioid levels from biological fluids including blood plasma, blood mononuclear cells and cerebrospinal fluid (CSF). However, some have criticised the relevance of opioid levels to central mechanisms (Agren, Terenius, & Wahlstrom, 1982). One

measurement technique termed the *radio-receptor assay* (RRA) method addressed this criticism by measuring stereo-specific binding at opiate receptors as an indicator of 'functioning' of the opioid system (Pickar, Naber, Post, van Kammen, Kaye, Rubinow, Ballenger, & Bunney, 1982b). A second related technique termed the *radioimmunoassay* (RIA) method has a distinct advantage over RRA in that the level of each opioid type can be detected. Nonetheless, antibodies that are commonly used in this technique cross-react with peptide molecules, masking results with a multitude of other substances (Pickar et al., 1982b).

6.1.1 Blood plasma

Recent results suggest that in depressed and non-depressed subjects concentrations of beta-endorphin in blood plasma reflect anxiety, fear and stress, more so than depression. For instance, Darko et al. (1992) found that plasma beta-endorphin concentrations were related to anxiety sequelae, in particular somatic anxiety, panic attacks, and phobias in depressed and control subjects, and with obsessive-compulsive tendencies in depressed patients only. Beta-endorphin levels were not related to measures of anger or depression in patients or controls. Correspondingly, Daly, Duggan, Bracken, Doonan and Kelleher (1987) found no difference in the plasma beta-endorphin levels of patients with (non-organic) pain and those without pain, despite pain patients scoring higher on the Beck Depression Inventory. In support of the view above, beta-endorphin levels decreased in the brain and pituitary, and increased in the blood plasma of rats in response to acute stress (i.e., 5 mins of acute foot-shock - Millan, Przewlocki, Jerlicz, Gramsch, Hollt, & Herz, 1981).

Others found that beta-endorphin levels in blood plasma were positively related to the occurrence of a psychosocial stressor in depressed patients (Goodwin et al., 1993). For example, plasma beta-endorphin levels were lower in patients with what used to be termed endogenous depression (i.e., no environmental precipitant) than in patients with reactive depression (i.e., obvious stressful precipitant) (Galard, Gallart, Arguello, Schwartz, Castellanos, & Catalan, 1988).

Transient increases in plasma concentrations of beta-endorphins have been found after a small number (≤ 6) of electroconvulsive therapy sessions in depressed patients

(Alexopoulos, Inturrisi, Lipman, Frances, Haycox, Dougherty, & Rossier, 1983; Ghadirian, Gianoulakis, & Nair, 1988; Inturrisi, Alexopoulos, Lipman, Foley, & Rossier, 1982; Misiaszek, Cork, Hameroff, Finley, & Weiss, 1984; Weizman, Gil-Ad, Grupper, Tyano, & Laron, 1987). It has been speculated that beta-endorphin release represents markers of stress or CNS arousal (Jackson & Nutt, 1990). However, others suggest that increases in plasma levels of beta-endorphins are associated with the therapeutic effects of electroconvulsive therapy (Cohen, Pickar, Dubois, Nurnberger, Roth, Cohen, Gershon, & Bunney, 1982).

In contrast, others have linked beta-endorphin release to depressive symptomatology. For instance, Bastuerk, Muhtaroglu, Karaaslan, Oguz, Simsek and Reyhancan (2000) found that higher morning concentrations of beta-endorphins in depressed patients, than controls, were related to the severity of depressive symptoms. Bastuerk et al. (2000) attributed higher plasma beta-endorphin levels to a central limbic disturbance characteristic of depressive episodes in patients prone to depression. Similarly, Darko et al. (1992) and Goodwin et al. (1993) found higher daytime plasma beta-endorphin concentrations in depressed versus control subjects. However, beta-endorphin levels were *negatively* related to symptom severity (Goodwin et al., 1993), suggesting that beta-endorphin release may decrease as depression worsens. Cohen et al. (1984) failed to support this view, finding lower plasma beta-endorphin levels in minor versus major depression. However, the severity and duration of major depression was not stated in either study, making it difficult to compare findings. Moreover, these studies failed to measure anxiety or stress. Hence, higher concentrations of beta-endorphins in blood plasma may represent a greater stress response in depressed patients versus healthy controls.

Together, these results suggest that plasma concentrations of beta-endorphin reflect anxiety and stress-related symptoms in depressed and non-depressed subjects, and that beta-endorphin levels may be higher in depressed subjects than controls because of a greater and more persistent stress response.

6.1.2 Blood mononuclear cells

Using the RIA technique, Panerai, Vecchiet, Panzeri, Meroni, Scarone, Pizzigallo, Giamberardino and Sacerdote (2002) found significantly higher levels of beta-endorphin in peripheral blood mononuclear cells in depressed patients than controls. However, similar levels of beta -endorphins have been found in older (aged 24-73) depressed patients and controls (Brambilla, Maggioni, Panerai, Sacerdote, & Cenacchi, 1996). In light of the potential for the beta-endorphin response to be reduced over the course of depression (Goodwin et al., 1993), the lack of difference between older depressed patients and non-depressed controls could be attributed to opioid dysfunction in ageing patients. However, the non-equivalent age of patients and duration of depressive illnesses make comparisons across these studies difficult.

6.1.3 Cerebrospinal fluid (CSF)

In comparison to plasma concentrations, levels of beta-endorphins in CSF give a better indication of central activation and metabolism of these opioids. Furthermore, CSF levels of beta-endorphins reflect opioids synthesised in the brain, as individuals suffering from hypopituitarism (i.e., malfunctioning pituitary) often show traces of beta-endorphins in CSF but not in blood plasma (Gerner & Sharp, 1982).

There is some suggestion that CSF opioid activity may be related to central noradrenergic systems and the biologic response to stress, rather than the pathophysiology of depression (Naber & Pickar, 1983). In support of this notion, Pickar et al. (1982b) reported an association between nurses' ratings of anxiety and CSF opioid activity in patients with major depressive disorder. In another study, CSF concentrations of beta-endorphins *decreased* after an extended therapeutic course of electroconvulsive therapy (i.e., up to 12 sessions) (Nemeroff, Bissette, Akil, & Fink, 1991). Nemeroff et al. (1991) stated that CSF endorphins at the time of therapy "represent state markers of depression" (p 62) and that clinical improvement was associated with *reductions* in beta-endorphin levels, providing support for the view that levels of beta-endorphins in CSF represent a marker of stress.

While some studies have found evidence of abnormal CSF opioid activity in sub-groups of depression, most research found similar opioid levels in the CSF of depressed patients and controls. Using rigorous RIA methodology, Gerner and Sharp (1982) failed to find abnormal levels of endorphin the CSF of subjects with unipolar or bipolar depression. Moreover, ratings of depression were not associated with levels of beta-endorphins in CSF, and no differences between subgroup were noted. France and Urban (1991) examined beta-endorphin concentrations in the CSF of 9 depressed and 19 non-depressed sufferers of chronic neuralgic low back pain. CSF concentrations of beta-endorphins were similar in both groups regardless of depression, and the decrease in depressive symptomatology following 3 weeks of multi-modal inpatient pain treatment failed to influence CSF concentrations of beta-endorphins. Similarly, Davis, Buchsbaum, Naber, Pickar, Post, van Kammen and Bunney (1982), Catlin et al. (1982), and Pickar et al. (1982b) failed to identify differences between depressed and normal subjects when using RIA and RRA methodology to measure levels of beta-endorphins in CSF.

On the other hand, Agren et al. (1982), via the RRA method, found that unipolar patients had higher concentrations of beta-endorphins in CSF than bipolar patients, suggesting that unipolar depression may be characterised by beta-endorphin dysfunction. Similarly, Terenius, Wahlstroem and Agren (1977) reported elevated opiate-binding material in the CSF of a small group (female N = 5) of depressed patients. Also, subjects suffering from psychogenic pain syndromes (i.e., pain without an obvious somatic lesion) were found to have significantly higher beta-endorphin levels in CSF than those with organic pain syndromes (Almay et al., 1978). Nonetheless, the level of depressive symptomatology was related to beta-endorphin levels in CSF in all pain patients. No relationship was found between anxiety and CSF endorphin levels (Almay et al., 1978). Aside from these studies, evidence of abnormal CSF opioid activity in depression is limited.

In another line of research, opiate-binding in CSF is associated with urinary free cortisol (UFC) in depressed but not control subjects (Pickar et al., 1982b). UFC is linked with abnormalities in the HPA axis (see *6.4 Hypothalamic-pituitary-adrenal axis dysfunction in depression*, p 218). These findings suggest that CSF opioid

activity in depression may play a role in the abnormalities of the HPA axis commonly identified in depressive disorders.

In light of the data discussed above, it is unlikely that a simple notion of abnormally high or low levels of centrally circulating beta-endorphins can explain the underlying mechanisms of major depression. These results suggest that in depression there may not be an abnormality in the endogenous opioid system *per se*, but that alterations in CSF opioid activity may be related to biological mechanisms of anxiety and stress, which in turn may contribute to abnormalities in the HPA axis. However, as mentioned earlier, one fundamental flaw in studies of opioid levels (whether from blood plasma, blood mononuclear cells or CSF) is that these levels do not indicate *opioid system function*. Studies in which opioid antagonists have been used *do* allow conclusions to be drawn about opioid activity i.e., the availability of endogenous opioid ligands and opioid receptor sensitivity. These studies are presented in the following section.

6.2 EFFECTS OF OPIOID AGONISTS AND ANTAGONISTS IN DEPRESSION

6.2.1 Opioid agonists

Results are mixed with regards to the effect of beta-endorphins on mood in depressed patients, with some finding transient improvements (e.g., Catlin et al., 1982; Kline, Li, Lehmann, Lajtha, Laski, & Cooper, 1977), and others reporting no change or a worsening of mood (Angst, Autenrieth, Brem, Kovkkov, Meyer, Stassen, & Storck, 1979). For instance, depressed patients reported notable improvements in psychiatric symptoms 2-4 hours after beta-endorphin administration in a double blind, placebo controlled study (Gerner, Catlin, Gorelick, Hui, & Li, 1980). Similar results were found in other double blind (Catlin et al., 1982) and single blind, low dose (1.5–9 mg) studies (Kline et al., 1977), suggesting that depressed patients may suffer from a deficit in endogenous BE. Contrary to these results, Pickar et al. (1981) found no change in behaviour or psychiatric symptoms (as measured by scores on the Brief Psychiatric Rating Scale) in the majority of depressed subjects, and a worsening of mood in two patients after intravenously administering 4-10 mg of beta-endorphins

(using a placebo-controlled, double blind design). Also, in a non-placebo controlled study, patients with unipolar and bipolar depression reported a worsening of mood (hypomania or mania) (Angst et al., 1979). Similarly, Extein, Pickar, Gold, Gold, Pottash, Sweeney, Ross, Rebard, Martin and Goodwin (1981) found no antidepressant effect at all when administering exogenous opiates to those with depression.

Another group of studies has indirectly measured opioid receptor functioning in depression by measuring the release of prolactin, adrenocorticotrophin hormone (ACTH) and cortisol in response to an opioid agonist (usually morphine). An increase in prolactin is mediated through opioid receptor stimulation (by morphine), whereby opioid receptor activation inhibits dopaminergic inhibition of prolactin secretion, allowing the release of prolactin. Cortisol, on the other hand, is released in response to ACTH. Since ACTH and beta-endorphins derive from the same peptide precursor, cortisol release in response to an opioid agonist or antagonist reflects alterations in beta-endorphin release in depression (Extein et al., 1982; Rosenzweig et al., 1996).

In a controlled study, Extein et al. (1982) found a blunted prolactin response to morphine in depressed subjects, suggesting possible deficits in opioid receptor functioning or the down-regulation of receptors to compensate for excessive endorphin levels. Alternatively, a blunted prolactin response may have been due to irregular increases in prolactin, decreased sensitivity of the prolactin system, or abnormalities in dopamine, serotonin or other neuroregulatory systems (e.g., thyroid, corticosteroid axes) in depressed subjects. Although previously demonstrated to be a strategy effective in detecting endorphin deficit (Rosenzweig et al., 1996), the release of cortisol did not change in response to naloxone (Extein et al., 1982). These results uncover a possible role for the endogenous opioid system in abnormal functioning of the HPA axis (see *6.4 HPA axis dysfunction in depression*, p 218*).*

6.2.2 Opioid antagonists

Evidence of opioid antagonists (i.e., naltrexone) producing dysphoria in a number of non-depressed patients (Hollister et al., 1981) has led to speculation as to the role of

opioids in the aetiology of depression. Nonetheless, recent data disconfirms the relationship between naltrexone and dysphoria since chronic use in non-depressed healthy subjects (Malcolm et al., 1987) and addicted patients (Miotto et al., 2002) failed to cause serious depressive side-effects. Additionally, recent results suggest that the inhibition of opioids may actually *benefit* some subjects under psychological stress. For instance, gradual improvements in mood have been noted in depressed patients after the administration of an opioid antagonist (Davis et al., 1981). Also, after 1-3 weeks of 3 x daily administration, cessation of the opioid antagonist naloxone led to an abrupt worsening of mood in a small number of patients (Terenius et al., 1977). Similarly, in a single-blind saline/naloxone cross-over design, morning and afternoon dysphoria occurred after cessation of naloxone (Martin del Campo, Dowson, Herbert, & Paykel, 2000). Other opioid antagonists (i.e., cyclazocine) have demonstrated antidepressant effects in depressed subjects (Fink, Simeon, Itil, & Freedman, 1970), providing further support for the hypothesis that endogenous opioids may worsen mood in depressed subjects.

6.2.3 Miscellaneous substrates

Other chemical substrates have been found to have anti-manic and depressive properties, for example, the cholinesterase inhibitor physostigmine (Berger & Barchas, 1982). In a study with healthy subjects, physostigmine-induced increases in depression, hostility and confusion were related to increases in plasma beta-endorphin levels (Risch, Cohen, Janowsky, Kalin, & Murphy, 1980), suggesting that endorphin activity could be mediated cholinergically, and an increase in beta-endorphin activity could exacerbate depressive symptoms.

6.3 OPIOIDS AND PAIN SENSITIVITY IN DEPRESSION

Acute pain insensitivity has been demonstrated widely in depressed patients in comparison to healthy subjects (Bar et al., 2003; Davis et al., 1979; Dworkin et al., 1995; Lautenbacher et al., 1994). Amongst other psychobiological explanations, the possibility that central or peripheral opioids may be responsible for pain insensitivity in depression has been examined. Opioid involvement in pain insensitivity in

depression has been investigated with the use of opioid antagonists and by measuring opioids from biological fluids (blood plasma, CSF). Evidence pertaining to this hypothesis will be discussed.

Levels of beta-endorphins in CSF have been related to pain insensitivity; however, this relationship has not been restricted to depressed patients. For instance, higher levels of CSF endorphins were associated with greater pain insensitivity in both normal and depressed subjects (Davis et al., 1982). Levels of plasma beta-endorphins, on the other hand, have not as readily been related to the degree of pain insensitivity in depression. For example, Daly et al. (1987) failed to find a difference in plasma levels of beta-endorphins between depressed patients with and without non-organic pain. Furthermore, depressed patients suffering from pain recorded the highest outlying values of beta-endorphins in blood plasma.

In searching through this literature, only one study administered an opioid antagonist to investigate opioid involvement in pain insensitivity in depression. Lautenbacher et al. (1994) demonstrated that decreases in pain sensitivity in 20 depressed patients were not mediated by endogenous opioids as naloxone failed to alter elevated contact heat pain thresholds. Moreover, increased pain thresholds were not related to any particular depressive symptom.

These findings suggest that pain insensitivity in depressed patients may not be associated with excessive or abnormal beta-endorphin activity, but may involve the normal recruitment of central opioid- or nonopioid-mediated neural mechanisms in patients experiencing distress.

6.4 HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS DYSFUNCTION IN DEPRESSION

The HPA axis is a complex system involving multiple hormones (e.g., beta-endorphins, ACTH and cortisol) and feedback regulatory loops. Specifically, in healthy subjects the release of beta-endorphins and ACTH from the anterior lobe of the pituitary gland is regulated by the hypothalamic release of corticotrophin

releasing factors (CRF), which are in turn affected by limbic and other brain structures. Cortisol released from the adrenal cortex is influenced by beta-endorphin and ACTH release (Meador-Woodruff, Haskett, Grunhaus, Akil, Watson, & Greden, 1987).

Overactivity of the HPA axis has being widely established in major depression (Burnett, Scott, Weaver, Medbak, & Dinan, 1999; Zis, Haskett, Albala, Carroll, & Lohr, 1985), and stressors early in life have been identified as precipitants of depressive symptomatology and subsequent HPA dysfunction (Burnett et al., 1999). Nonetheless, it is still relatively unclear at which level the dysfunction occurs (Meador-Woodruff et al., 1987). One mechanism thought to mediate overactivity of the HPA axis in depressed patients is an abnormal excitatory drive from the limbic system to the hypothalamus. This results in chronic release of ACTH, the reduction of cellular corticosteroid receptors and, consequently, faulty feedback regulatory loops (Rosenzweig et al., 1996). Another mechanism involves the failure of opioid-mediated inhibitory influences on the HPA axis. Normally, endogenous opioids inhibit the HPA axis by influencing the release of hypothalamic CRF, including noradrenergic pathways that control ACTH releasing factors. Naloxone-induced increases in ACTH and cortisol provide evidence of opioid inhibition of the HPA axis in normal subjects. Therefore, opioid inhibition of the HPA response to stress is though to be adaptive, in that the organism is protected from chronic arousal and hypersecretion of ACTH.

To examine the role of opioids in the regulation of the HPA axis in depression, Zis et al. (1985) administered morphine to 24 depressed inpatients, 18 affectively ill control patients and 14 healthy controls. They found an early secretion of cortisol following morphine administration in those suffering from depression, suggesting that the HPA axis is non-responsive to opioid inhibition in this illness.

To investigate opioid tone in depressed patients and controls, Burnett et al. (1999) measured ACTH and cortisol responses to administration of naloxone. Levels of cortisol and ACTH released in response to naloxone were smaller in depressed patients, than in controls; however, basal levels of cortisol and ACTH didn't differ between groups. Nonetheless, the higher the basal levels in depressed subjects, the

smaller the ACTH and cortisol release in response to naloxone. A similar trend existed for controls, but did not reach significance. Martin del Campo et al. (2000) found higher basal levels of cortisol in the morning and evening, and a smaller cortisol release in response to naloxone in the evening in a small group of depressed patients compared to healthy controls. In other evidence of opioid dysfunction in depression, a positive association was found between CSF opioid activity and UFC (linked with HPA axis abnormalities) in depressed but not control subjects (Pickar et al., 1982b).

In summary, these results suggested a reduction in opioid tone and the possible involvement of the endogenous opioid system in alterations to the HPA axis in depression. Others failed to find reduced opioid tone in depressed patients (Extein et al., 1982; Judd, Janowsky, Zettner, Huey, & Takahashi, 1981). However, the opioid effect could have been masked by an exaggerated ACTH response (Burnett et al., 1999).

The Dexamethasone Suppression Test (DST) has been used to demonstrate abnormal suppression of BE, plasma cortisol, and ACTH in the HPA axis of depressed patients. Dexamethasone is a synthetic corticosteroid that powerfully suppresses the rise in ACTH typically observed in the morning. When given late at night in normal healthy subjects, dexamethasone artificially conditions the hypothalamus to function as if high levels of cortisol are circulating, resulting in the suppression of cortisol (Rosenzweig et al., 1996). Depression is most commonly characterised by the non-suppression of plasma cortisol by dexamethasone (Ball, Howlett, Silverstone, & Rees, 1987; Cohen et al., 1984; Meador-Woodruff et al., 1987; Risch, Janowsky, Judd, Gillin, & McClure, 1983). This results in high levels of cortisol in patients.

The degree of beta-endorphin non-suppression following the DST has been positively related to cortisol non-suppression (Risch et al., 1983; Rupprecht, Barocka, Beck, Schrell, & Pichl, 1988), and depressive symptomatology. For instance, high scorers on the Hamilton Rating Scale for Depression were likely to suppress plasma levels of beta-endorphins to a lesser degree than low scorers (Meador-Woodruff et al., 1987). However, others have found cortisol non-suppression in the presence of low levels of ACTH and beta-endorphins (Ball et al.,

1987). Ball et al. (1987) attributed these findings to dysregulation at all levels of the HPA axis in severe depression. For instance, dysregulation may occur centrally with the hypersecretion then hyposecretion of ACTH secondary to chronic high levels of CRF, whilst peripheral dysregulation may involve excessive cortisol release in response to low ACTH and beta-endorphin levels. Alternatively, the severity of depression may lead to the secretion of differing forms of ACTH and BE, resulting in abnormal cortisol responses (Ball et al., 1987).

Taken together, these results suggest that overactivity of the HPA axis in depressed patients may be, in part, attributed to a reduction in endogenous opioid tone and/or the failure of opioid inhibition of the axis. The association of central opioid activity with abnormalities in other HPA axis hormones, such as cortisol, provides tentative support for the role of the endogenous opioid system in the dysfunction of the HPA axis in depression.

6.5 OPIOID MEDIATION IN ANIMAL MODELS OF DEPRESSION

A large number of animal models of depression have been generated to examine psychobiological elements of this illness. Models using stress to induce depression make up the largest group. Two that have been extensively studied are Seligman's *learned helplessness* (LH) model and the *chronic mild stress* (CMS) model. An overview of these models and a discussion of supporting evidence is reviewed below.

Seligman's LH model of depression boasts high predictive and construct validity with major depression in humans (Norman & McGrath, 2000; Tejedor-Real, Mico, Maldonado, Roques, & Gibert-Rahola, 1995). Although not modelling all aspects of major depression (e.g., guilt, worthlessness), the LH model enables the examination of psychobiological elements of depressive disorders (Norman & McGrath, 2000) and stress and coping (Maier, 1984). In this model the degree to which an organism can control an aversive event, and not the event *per se*, impacts heavily upon behavioural (locomotor activity), motivational (appetite and weight), emotional (aggression), cognitive and physiological responses (corticosterone release and cholinergic, noradrenergic, dopaminergic and GABAergic activity) (Norman &

McGrath, 2000). Most prominently, exposure to uncontrollable aversive events impairs the ability to escape from noxious events in the future both in animals and humans.

In early studies, the effect of inescapable electric shocks produced opioid-mediated performance deficits characteristic of LH during one-way shuttle-box training. Inescapable shocks also produced analgesia that could be reversed by opioid antagonists such as naloxone and naltrexone (e.g., Hemingway & Reigle, 1987; McCubbin et al., 1984; Whitehouse et al., 1983). Paradoxically, subsequent studies suggested that endogenous opioids and opioid agonists reduce or reverse these behavioural deficits (Besson, Privat, Eschalier, & Fialip, 1996; Natan, Chaillet, Lecomte, Marcais, Uchida, & Costentin, 1984; Tejedor-Real, Mico, Maldonado, Roques, & Gibert-Rahola, 1993; Tejedor-Real et al., 1995). Besson et al. (1996) attributed the benefits of opioids and opioid agonists to motivational and antidepressant rather than analgesic effects, as opioids are distributed in brain structures associated with emotion and motivation. Specifically, opioids activate reinforcement pathways, facilitate learning and memory, and reduce stress-induced helplessness by decreasing fear or anxiety (Drolet et al., 2001). Thus, opioid-induced reversal of LH may result from direct or indirect activation of these mechanisms. It is well known that serotonergic and noradrenergic systems (implicated in depression) are located in brain structures with mu-opioid receptors (Tejedor-Real et al., 1995). Therefore, an interaction between these systems may also account for these effects.

Another popular animal model of depression is the CMS model, in which animals reportedly demonstrate depressive behaviours after being exposed to a series of stressors such as change in cage mates, food and water deprivation, and temperature changes (Norman & McGrath, 2000). Depressive behaviours include reduced responsivity to rewards (e.g., sucrose solutions) reflecting anhedonia, alterations in locomotor behaviour, adrenal hypertrophy and corticosterone hypersecretion, and reduction in aggressiveness, sexual behaviour, body weight, and rapid eye movement (REM) sleep. In a recent study, rats exposed previously to CMS showed a reduction in sucrose preference following restraint for 90 minutes, freezing behaviour in response to a single shock, and anxious behaviour in a maze task (Zurita, Martijena, Cuadra, Brandao, & Molina, 2000). All responses were reversed with naltrexone,

whilst a low dose of morphine potentiated locomotor activity (Molina et al., 1994), thus demonstrating the complexity of opioid effects on depressive behaviour in animals.

In conclusion, the activation of endogenous opioids in animal models of depression appears to result in either a recuperative response characterised by LH and/or SIA or in paradoxical motivational effects (i.e., decreased immobility and reduced escape/avoidance failures). Discordant results, although difficult to reconcile, can be attributed to the differing roles of opioids in the stress response and divergent methodologies. Nonetheless, evidence of opioid involvement in both LH and CMS animal models of depression suggests that pathogenic opioidergic functioning may link stress and depression in humans (Algarabel, 1985). Research extending these findings to humans is needed.

6.6 OPIOID MEDIATION OF CARDIOVASCULAR RESPONSES IN DEPRESSION

Whilst *opioid hyper-function* (i.e., the overproduction/excessive responsivity to opioids) can lead to immobility, behavioural freezing and other performance deficits (e.g., escape failure), *opioid hypofunction* (i.e., the underproduction/ underresponsivity to opioids) can disinhibit the cardiovascular response to stress. Autonomic disturbances found in depression, i.e., a decreased blood pressure (BP) response to pain in contrast to the increase observed in normal healthy subjects (Pickar et al., 1982a), has led to speculation about the role endogenous opioids may play in cardiovascular regulation in depression. In a double-blind, placebo-controlled study of a small group of depressed subjects, Catlin et al. (1982) found that infusion of beta-endorphins led to decreases in SBP and increases in heart rate. These results support the notion that endogenous opioids may regulate BP in depression; however, this was only achieved with the administration of exogenous opioids. In other evidence of pathological cardiovascular events in depression, Pinerua-Shuhaibar et al. (1999) found a significant increase in systolic and mean arterial BP in controls in response to ischemic pain, compared to no change in patients with minor depression.

Administration of an opioid antagonist would help to elucidate the role that endogenous opioids play in regulating cardiovascular activity in depression.

Recent research has used animal models of depression to explore the relationship between associated behavioural and cardiovascular changes. In a study using the CMS model of depression, rats displayed elevated heart rate, reduced heart rate variability and increased sympathetic nervous system reactivity (Grippo, Beltz, & Johnson, 2003). Although the behavioural responses in rats returned to baseline levels, cardiovascular changes persisted four weeks after exposure to the stressors. When generalised to humans, the chronicity of these changes could lead to deleterious cardiac events and increased mortality in depressed patients.

In an extensive review and meta-analysis, Rugulies (2002) concluded that clinical depression was a strong, consistent predictor of coronary heart disease (CHD). Physiological factors thought to underlie the association between depression and CHD include anomalies in cardiovascular functioning (e.g., reduced heart rate variability), the dysregulation of the ANS and HPA axis, and depressed patients being at higher risk for hypertension (possibly brought on by environmental stressors) (Grippo & Johnson, 2002). Additionally, psychological stressors involving the loss of control increase the incidence both of depression and CHD. However, the relationship between depression and CHD is independent of more traditional coronary risk factors such as poor health behaviours (e.g., smoking, poor diet, lack of exercise) and increased body mass (Grippo & Johnson, 2002).

More recently, additional physiological mechanisms have been implicated in the relationship between depression and cardiovascular dysregulation (Grippo & Johnson, 2002). These factors include impaired baroreflex sensitivity, reduced immune function, an exaggerated stress response and co-morbid psychological conditions in particular, anxiety. Despite the burgeoning interest, the patho-physiology underlying this relationship remains unclear (Grippo & Johnson, 2002).

6.7 SUMMARY/CONCLUSIONS

The previous review suggested that anxiety, fear, and stressful events are associated with higher circulating levels of beta-endorphins in blood plasma and, in some instances, in CSF. Although this relationship did not differ between depressed and non-depressed subjects there was some suggestion that, after persistent stress, beta-endorphin release as evidence in blood plasma may decrease throughout the course of depression (Darko et al., 1992; Lobstein et al., 1989). In contrast, levels of beta-endorphins in CSF were not reliably associated with the severity of depressive symptomatology. Transient improvement in mood following the inhibition of endogenous opioids (using opioid antagonists) suggests that opioids may worsen mood in depressed patients. However, the mixed results from opioid agonists failed to provide support for this hypothesis. Nonetheless, the use of opioid agonists (e.g., morphine) to indirectly investigate receptor functioning suggested possible opioid receptor dysfunction or down-regulation in depression.

Helplessness and anhedonic behaviours in animals are facilitated or reversed by endogenous opioids depending on the methodology adopted (i.e., species tested, dosage of opioid antagonist, experimental conditions). These findings are yet to be extended to depressed patients.

Dysregulation of the HPA axis in depression may be attributed, in part, to the failure of opioid inhibitory mechanisms in depressed patients. Similarly, disturbed cardiovascular responses to pain in depressed individuals suggest that the regulatory role opioids can play in autonomic responses to stress and pain, may be impaired.

CHAPTER SEVEN

7. STUDY 4

7.1 INTRODUCTION

7.1.1 Rationale/Purpose of this study

Opioid-mediated stress-induced analgesia in depression

The previous study supported a role for opioids in depressed affect, which in turn reduced sensitivity to pain. Specifically, opioid blockade increased cold pressor PI and UP in discouraged subjects. The influence of discouragement, although only a *state-like* depressive emotion, on opioid-mediated anti-nociception may resemble processes occurring in the early stages of major depression. People suffering from an ongoing psychiatric illness such as major depression are likely to experience chronic stress (Clark et al., 1986). Chronic activation of opioids in major depression in response to stress may lead to abnormalities in the opioid system with regards to opioid release and/or dysregulated receptor functioning. Moreover, the ability to inhibit pain in a persistent negative affective state such as depression may be compromised (Beutler, Engle, Oro'-Beutler, Daldrup, & Meredith, 1986). Importantly, impaired opioid functioning in depression may contribute to the onset of chronic pain (Bruehl et al., 1999).

As evident from the literature review presented in the previous two chapters, the endogenous opioid system may be impaired in major depression. While no study has directly addressed this issue, empirical evidence indirectly supports this hypothesis. For instance, an inverse relationship between the severity of depressive symptomatology and plasma levels of beta-endorphins suggests that the response to opioids may initially be increased, but then down-regulated throughout the course of depression (Goodwin et al., 1993). Moreover, studies examining the functioning of

the HPA axis in depression have found a reduction in opioid tone (Burnett et al., 1999; Martin del Campo et al., 2000) and ineffective opioid inhibitory mechanisms in depressed patients consistent with endogenous opioid dysfunction (Zis et al., 1985). High rates of pain complaints (Gallagher & Cariati, 2002) and higher demands of opiates for post-operative pain relief in major depression (Kudoh et al., 2002; Lautenbacher et al., 1999) also concurs with the notion that the endogenous opioid system may be compromised in depression. Other studies have demonstrated higher resting concentrations of beta-endorphins in plasma and CSF in depressed subjects, presumably due to increased perceptions of stress (Cohen et al., 1984; Darko et al., 1992; Galard et al., 1988). Despite this data, there has been no empirical test of the relationship between major depression and opioid activation in the context of experimentally induced pain and stress.

The role of opioids in cardiovascular-pain regulatory systems in depression

Cardiovascular and pain regulatory systems are interrelated in healthy normotensive subjects due to the convergence of primary cardiac and pain afferents in the brainstem (Randich & Maixner, 1984). It has been suggested recently that this interaction can be opioid-mediated in healthy subjects (Bragdon et al., 2002; McCubbin & Bruehl, 1994) and that opioid hypofunction can result in the disinhibition of the cardiovascular response to stress increasing the risk of cardiovascular-related diseases (McCubbin, 1993). In depressive disorders, autonomic disturbances in response to pain (Pickar et al., 1982a; Pinerua-Shuhaibar et al., 1999), cardiovascular regulation with exogenous opiate agonists (Catlin et al., 1982), chronic cardiovascular changes following persistent stress (Grippo et al., 2003), increased risk of hypertension (Rugulies, 2002) and increased incidence of CHD (Grippo & Johnson, 2002) may be attributed to the failure of opioid regulatory mechanisms. However, no study has specifically addressed the relationship between cardiovascular and pain regulatory systems in major depression.

7.1.2 Aims of Study 4

Primary aims

The **first aim** of Study 4 was to investigate the role of endogenous opioids in major depression in the context of an uncontrollable cognitive stressor (math task). Functioning of the opioid system was assessed indirectly by measuring the reaction of depressed subjects to acute pain stimulation (i.e., electrical stimulation, CPT) whilst under opioid blockade. All responses were compared with those of psychiatrically and medically healthy age- and sex-matched controls.

The **second aim** of Study 4 was to examine opioid involvement in another endogenous pain inhibitory mechanism, termed *diffuse noxious inhibitory controls* (DNIC), in depressed and non-depressed subjects. This mechanism involves the powerful inhibition of wide dynamic range neurones by heterosegmentally-applied noxious stimuli within the spinal cord and trigeminal system (Ellrich & Treede, 1998). In this study, the impact of a noxious CPT applied to the hand was observed on the nociceptive, or R2, component of the blink reflex. A number of studies in healthy controls have demonstrated the inhibition of R2 by the remote application of painful stimuli such as heat, ice water and electrical pulses (Ellrich & Treede, 1998; Willer et al., 1982a; Willer et al., 1982b). Furthermore, suppression of the R2 by a remotely applied noxious stimulus has been reversed by opioid blockade in several investigations (Boureau, Willer, & Dauthier, 1978; Boureau, Willer, & Yamaguchi, 1979; Pomeranz & Warma, 1988; Willer et al., 1982b). These results suggest that in healthy controls the mechanism involved in DNIC is opioid-mediated. Thus, the role of opioids in DNIC was investigated indirectly by observing the response of the blink reflex to naltrexone.

Secondary aim

The **third aim** of Study 4 was to examine the relationship between cardiovascular activity and endogenous opioid-mediated analgesia to electrical and cold pressor stimulation in depressed and non-depressed subjects.

7.1.3 Hypotheses of Study 4

Due to limited research in this area, no clear predictions could be generated. Instead hypotheses were exploratory and generalised from Study 3:

Based on Study 3, it was hypothesised that discouraged controls administered naltrexone would show evidence of increased cold pressor pain sensitivity after the math task. Similarly, controls would show evidence of decreased cold pressor-induced R2 suppression (DNIC) following opioid blockade. If the opioid system is compromised in depression, then opioid blockade should have little impact on cold pressor pain or R2 in depressed subjects.

Based on previous research with normotensive subjects and the findings of Study 3, it was hypothesised that cardiovascular responses would vary inversely with PI and UP ratings to electrical and cold pressor stimuli, and directly with cold pressor pain tolerance in controls taking the placebo. However, there should be no evidence of a relationship between cardiovascular response and pain following opioid blockade. Finally, it was hypothesised that there would be no relationship between cardiovascular response and pain sensitivity in depressed subjects, regardless of opioid blockade.

7.2 METHOD

7.2.1 Subjects

General overview

Sixty-one subjects (28 = depressed; 33 = non-depressed) aged between 17 and 57 years [29 males: M = 35.77 years, SD = 11.19; 32 females: M = 35.36 years, SD = 13.79] participated in Study 4. Exclusion criteria were identical to those described in Study 2. All participants were deemed medically healthy by participant self-reports. Two depressed subjects withdrew from the experiment prematurely due to the noxious nature of the math task or blink reflex procedure. One control subject did not

complete the experiment due to an adverse reaction to naltrexone. Data from one subject was discarded due to equipment malfunction.

Subjects were asked not to consume alcoholic or caffeinated beverages 12 hours before, and not to eat or smoke for two hours before the experiment to improve the reliability of cardiovascular recordings (Shapiro et al., 1996). A longer period of abstinence was required for subjects who consumed any of these substances moderately on a daily basis (see *Psychiatric Diagnoses*, p 230). Subjects were remunerated $20 for their participation, and were given a chocolate bar at the end of the experimental session. According to Bryden's Handedness Questionnaire (1977) (Appendix 2, p 320), 59 subjects were right-handed whilst two subjects were left-handed.

Recruitment

Non-depressed and depressed subjects were recruited through advertisements in local community and metropolitan newspapers and advertisements on community radio. Depressed participants were recruited via advertisements and flyers placed in the waiting rooms of general practitioners, privately practicing psychologists and psychiatrists, and articles in newsletters produced by local divisions of General Practice in Western Australia and mental health oriented non-governmental organizations (Appendix 10, p 336).

Psychiatric Diagnoses

All depressed participants were given a primary diagnosis of Major Depressive Disorder (recurrent episode) using the Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version (First, Spitzer, Gibbon, & Williams, 1997) (Appendix 11, p 338). However, 71% of this group were also given a secondary diagnosis, consisting of Axis I anxiety or other mood disorders such as dysthymia (Figure 7.1). Controls had no personal or familial history of psychiatric illness.

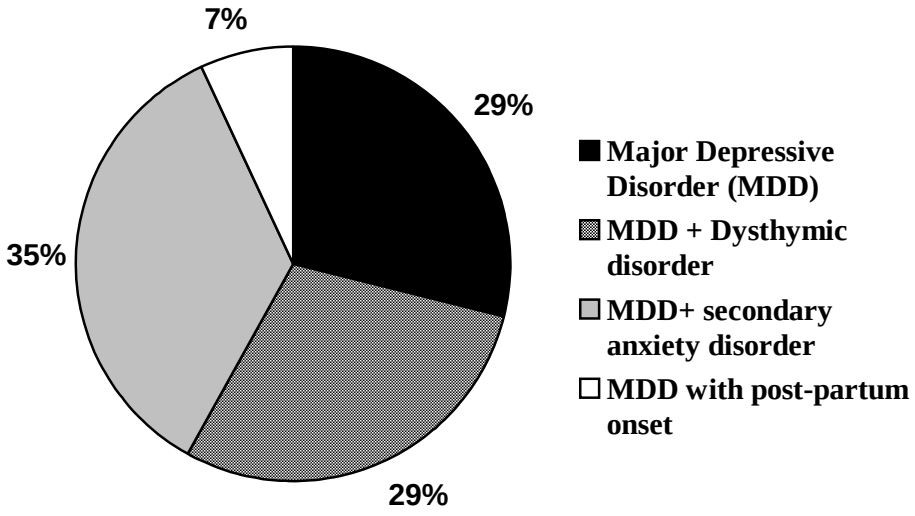


Figure 7.1: Psychiatric diagnoses for depressed participants. Note: Secondary anxiety disorders included post-traumatic stress disorder (11%), generalised anxiety disorder (7%), obsessive-compulsive disorder (7%), panic disorder without agoraphobia (7%), and social phobia (3%).

Psychiatric exclusion criteria included psychotic disorders, alcohol and/or other substance use disorders, and DSM-IV Axis II disorders (i.e., personality disorders, mental retardation). Two depressed participants who used marijuana and alcohol moderately on a daily basis agreed to abstain from both substances for one week before, and two days after testing. Two depressed and one control participant who used tobacco moderately on a daily basis (i.e., 10-20 cigarettes per day) also agreed to abstain for one day before testing.

Pre-existing anxiety, stress and depression

While waiting for the drug to be absorbed, subjects completed the Depression, Anxiety, Stress Scales (DASS - Lovibond & Lovibond, 1995b), State-Trait Anxiety Inventory, Form Y (STAI - Spielberger, 1983) and the Beck Depression Inventory – Second Edition (BDI-II - Beck, Steer, & Brown, 1996) (see *7.2.2 Psychometric tests*, p 234).

As indicated by independent t-test comparisons in Table 7.1, depressed subjects reported significantly higher levels of anxiety (STAI- State/Trait Anxiety, DASS Anxiety scale), stress (DASS Stress scale) and depression (DASS Depression scale, BDI-II) than non-depressed controls. In comparison to the general population of adults aged 19-39 years, controls reported lower than average levels of state anxiety (percentile ranks, PR: females-39%, males-44%) and trait anxiety (PR: females-42%, males-43%). In comparison to normal adults (Spielberger, 1983), depressed subjects reported state and trait anxiety commensurate with the top 2%-5% of this population. In comparison to psychiatric samples (Spielberger, 1983), depressed participants reported state anxiety commensurate with the top 18%(male)-25%(female) of this population. Reports of trait anxiety were similar (i.e., top 17% male-19% female of the psychiatric group). Controls fell within normal ranges of depression, anxiety and stress on the DASS. Not surprisingly, depressed subjects gained a 'severe' rating for depression, and a 'moderate to severe' rating for anxiety and stress on the DASS. According to assessment categories for the BDI-II, controls fell within the minimal/normal range and depressed subjects fell between moderate to severe ranges of depression.

In summary, when compared to the general population, depressed subjects reported high levels of anxiety, and moderate to severe levels of depression and stress. Controls on the other hand appeared to be less anxious than the general population, and reported almost negligible levels of depression and stress.

Table 7.1: Pre-existing anxiety, depression and stress in depressed and non-depressed subjects.

	Experimental group				
	Depressed (N = 28)		Controls (N = 33)		
Measure	**Mean**	**SD**	**Mean**	**SD**	***t***
STAI					
State anxiety	57.89	12.77	32.15	7.95	9.60**
Trait anxiety	58.61	10.31	32.06	8.26	11.16**
DASS					
Depression scale	24.89	10.93	3.24	4.78	10.29**
Anxiety scale	14.00	10.60	2.00	2.37	6.33**
Stress scale	25.43	10.13	6.55	5.21	9.35**
BDI-II	28.57	12.38	3.88	3.66	10.92**

Note. **p<.01

Medication

Six of the 28 depressed participants who had taken anti-depressant medication in the past had ceased at least five weeks prior to testing. The use of hypericum perforatum (St John's Wort) was also prohibited, as randomised controlled studies indicated drug-efficacy comparable to prescription anti-depressants (Whiskey, Werneke, & Taylor, 2001). Two depressed participants used benzodiazepine medication (e.g., temazepam) approximately once a week, but agreed to abstain for one week prior to testing. Two controls regularly took pseudoephedrine hydrochloride for ongoing sinus problems but agreed to abstain for a week before testing. Three controls and four depressed participants were taking daily dietary supplements (e.g., vitamin C, B, iron, zinc, magnesium), and two participants in each group were taking a contraceptive pill at the time of testing.

Two controls and five depressed participants had used codeine (30 ml) and/or paracetamol (500 ml) at least one week prior to testing to manage temporary pain (e.g., tension headache, fever). However, no subject used opiates regularly or had taken naltrexone in the past. All participants were opiate-free at the time of testing.

Demographics

As indicated in Table 7.2, minor demographic differences existed between groups. For instance, controls were able to achieve higher levels of education than depressed participants. Differences in educational attainment may be attributed to motivation, energy levels, self-confidence/efficacy, and the ability to concentrate – characteristics that are depleted in depression. Occupationally, controls were drawn to similar types of jobs as depressed participants. Approximately 18% of depressed subjects were unable to work and received a disability pension. Conversely, no controls were prevented from working due to disability. Equivalent numbers of control and depressed subjects were living as single, divorced, separated and in de-facto relationships. However, controls sustained marital relationships at a higher rate than depressed participants (controls – 30.3%; depressed – 7.1%). These demographic differences may have been contributing factors or outcomes of depression. Considering that subjects within the clinical group rated themselves as moderately to severely depressed, these demographic differences are not surprising.

7.2.2 Psychometric tests

Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version (SCID-CV)

Prior to the experiment, participants were interviewed by a psychologist (experimenter) using the SCID-CV (First et al., 1997). Each interview was conducted over the phone, taking approximately 45-90 minutes to complete. Information was transcribed into an interview booklet (Appendix 11, p 338) and participants were each assigned a code for confidentiality purposes. A structured interview was used to increase diagnostic reliability (Segal, Hersen, & Van Hasselt, 1994). Additionally, the use of DSM-IV diagnostic criteria (now used widely to describe participants in psychological research) increased the validity of diagnoses made in this experiment. The Clinician Version was used instead of the Research Version, as this was shorter (no subtypes/specifiers) and more convenient to use.

Table 7.2: Demographic variables for depressed and control subjects.

Demographic Variable	Proportion (% within group)		χ^2
	Depressed (N=28)	Controls (N=33)	
Education			
≤ 10 years	8 (28.6%)	3 (9.1%)	3.89*
≤ 12 years	5 (17.9%)	2 (6.1%)	2.08
Adv. diploma (12+ years)	9 (32.1%)	6 (18.2%)	1.59
Undergraduate (12-15 years)	6 (21.4%)	20 (60.6%)	9.51**
Postgraduate (15-17+ years)	0 (0%)	2 (6.1%)	1.75
Occupation			
Unemployed	8 (28.6%)	5 (15.2%)	1.63
Pension	5 (17.9%)	0 (0%)	6.42*
Retired	0 (0%)	1 (3%)	0.86
Student	0 (0%)	4 (12.1%)	3.63
Homemaker	0 (0%)	2 (6.1%)	1.75
Un/Semi-skilled	11 (39.3%)	9 (27.3%)	0.99
Skilled	2 (7.1%)	6 (18.2%)	1.62
Professional	2 (7.1%)	6 (18.2%)	1.62
Marital Status			
Single	14 (50%)	14 (42.4%)	0.35
Married	2 (7.1%)	10 (30.3%)	5.14*
Defacto	1 (3.6%)	3 (9.1%)	0.75
Divorced	9 (32.1%)	6 (18.2%)	1.59
Separated	2 (7.1%)	0 (0%)	2.44

Note**. '***Education*-Adv. diploma (12+ years)' includes equivalent qualifications such as an advanced certificate attained at college/TAFE; '*Occupation*-Un/semi-skilled' refers to service staff, labourers, administrative support personnel etc; '*Occupation*-Skilled' refers to trades people.

*p<.05 **p<.01.

Beck Depression Inventory – Second Edition (BDI-II)

The BDI-II (Beck et al., 1996) is a 21-item self-report questionnaire that measures symptoms that correspond with DSM-IV criteria. Moreover, the BDI-II was developed and normed using a clinical population (Beck et al., 1996), deeming it appropriate to use with this research group. Importantly, the BDI-II complimented SCID-CV-assisted diagnoses by quantifying the severity of depression in each participant. However, as instructed by Beck et al. (1996), the BDI-II was not used as a diagnostic instrument. The time period of 'the past 2 weeks, including today' that subjects were asked to reflect upon assessed a subject's recent past and not trait depressive characteristics. Participants rated each item on a 4-point scale (0-3 in terms of severity).

The psychometric properties of the BDI-II will not be discussed here as this questionnaire has been widely used and is well validated amongst adult psychiatric (Beck et al., 1996; Kumar, Steer, Teitelman, & Villacis, 2002) and normal groups in western and eastern cultures (Al-Musawi, 2001; Arnau, Meagher, Norris, & Bramson, 2001; Beck et al., 1996; Dozois, Dobson, & Ahnberg, 1998; Kojima, Furukawa, Takahashi, Kawai, Nagaya, & Tokudome, 2002).

State-Trait Anxiety Inventory (STAI)

The self-report STAI (Spielberger, 1983) was chosen to quantify subject anxiety in their recent past (STAI-State: 20 'state' items) and in general (STAI-Trait: 20 'trait' items). The STAI is a brief, convenient instrument whose manual provides normative data for clinical groups of both sexes. Participants rated each item on a 4-point scale ('not at all' to 'very much so'). Psychometric properties of the STAI have been well-documented in studies of psychiatric (Kabacoff, Segal, Hersen, & Van Hasselt, 1997; Spielberger, 1983) and normal groups (Spielberger, 1983), and will not be reported here.

Recent criticisms of the STAI have emerged highlighting that, when compared to other measures of psychiatric disorders (such as depression), the STAI (especially the STAI-State) does not adequately differentiate between those suffering from anxiety and depressive disorders (Andrade, Gorenstein, Vieira Filho, Tung, & Artes, 2001; Kabacoff et al., 1997; Kennedy, Schwab, Morris, & Beldia, 2001). Spielberger (1983) admitted there needed to be more research into the ability of the STAI to distinguish anxiety from depression, but pointed out that most depressed individuals suffer from high levels of anxiety making it difficult to separate the two. In recognition of this, Kennedy et al. (2001) suggested using multiple tests to evaluate the two disorders, which is the approach adopted in this study.

Depression, Anxiety, Stress Scales (DASS)

The 42-item DASS (Lovibond & Lovibond, 1995b) was chosen to compliment results from the BDI-II and STAI-State. Lovibond et al. (1995b) view depression as not primarily being characterised by sadness of mood (as in BDI-II), but by the loss of self-esteem and the perception that personal goals will not be attained in the future. Also, the DASS Anxiety scale measures symptoms of autonomic arousal, skeletal muscle effects, and situational anxiety – none of which are measured in the primarily cognitive STAI-State. Participants rated each item on a 4-point (0-3) scale of severity. Since the DASS is less utilised than the previous instruments, psychometric properties will be briefly described.

Correlational data confirms the unique contributions that the DASS makes to this battery of tests (Lovibond & Lovibond, 1995a). For instance, scores from psychology students on the DASS Depression scale correlated highly, but not spuriously with the BDI-II ($r = .74$). Additionally, factor analyses and correlations established that all three scales were moderately related but distinct from one another (DASS Depression and Anxiety $r = .54$; DASS Depression and Stress $r = .56$; DASS Anxiety and Stress $r = .65$). Separation between the three scales has been corroborated by other researchers (e.g., Antony, Bieling, Cox, Enns, & Swinson, 1998).

When comparing DASS Depression scale symptoms with items in well validated self-report measures of depression (as compiled by Levitt & Lubin, 1975), the content validity of the DASS has been firmly established (i.e., an average of 67% of DASS items were represented in these other measures). Moreover, outstanding items i.e., items not found in the DASS, were not confined to individuals diagnosed with depression. The DASS Anxiety and Stress scales overlap less with other scales. However, Lovibond et al. (1995b) found that most other anxiety scales contained items narrow in content, and no scale was strictly comparable to the DASS Stress scale.

Alpha values quoted in the manual suggest excellent internal reliability of items within each scale (DASS Depression r = .91; DASS Anxiety r = .84; DASS Stress r = .90). No test-retest reliability data was provided in the manual; however, Lovibond (1998) provided compelling evidence, reporting strong test-retest statistics for each scale *3-8 years later*.

One limitation of the DASS is that it was developed using normal, non-clinical respondents. The authors justified this by stating that clinical and non-clinical samples do not differ *qualitatively*, just in the *severity* of their symptoms (Lovibond & Lovibond, 1995b). Despite this, other research has confirmed the concurrent validity of the DASS, in that this instrument can effectively distinguish between depressed and anxious psychiatric groups in English and non-English speaking cultures (Antony et al., 1998; Brown, Chorpita, Korotitsch, & Barlow, 1997; Daza, Novy, Stanley, & Averill, 2002).

To be consistent across all tests, subjects were required to rate DASS and STAI-S items in accordance with how they felt *over the past 2 weeks*, instead of the time periods specified on each of these tests. This alteration meant that scores reflected how a participant felt in their recent past, not the past week. Spielberger (1983) stated that in a research context, altering instructions for the STAI-S is acceptable.

7.2.3 Experimental design/Overview

Mood/self-efficacy ratings, and BP/pulse rate measurements were completed before, and approximately 50-60 minutes after drug administration, and after the math task was completed. The blink reflex was elicited alone and simultaneously with a noxious hand cold pressor stimulus shortly after drug administration and after drug absorption, and then alone after the math task. Finally, a foot cold pressor task (fCPT) was completed before and after the math task. As in previous studies, subjects rated their perceived mood, self-efficacy, PI and UP for each electric shock, and experienced frequent BP and pulse rate measurements throughout the math task (Figure 7.2). Subjects were tested individually.

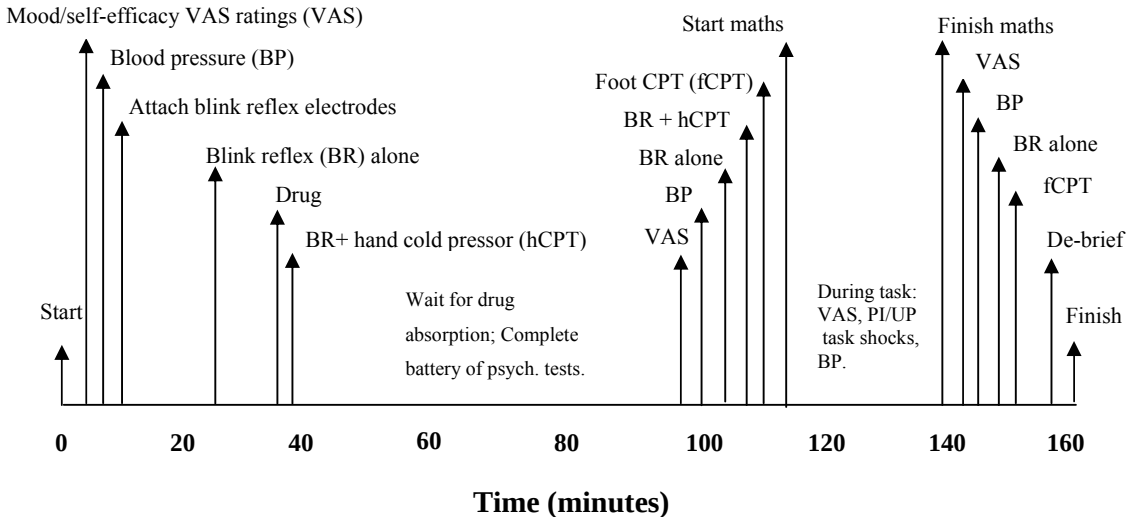


Figure 7.2: Experimental timeline for Study 4. Note: The drug was administered shortly before BR measurement to maximise time efficiency.

Depressed and non-depressed subjects were randomly assigned to either the naltrexone or placebo condition, which were balanced by sex and age ($F(1,57) = 0.09$; $p = 0.77$) (Table 7.3).

Table 7.3: Subject age and sex in each experimental condition.

	Depressed (N = 28)		Controls (N = 33)	
	Naltrexone	**Placebo**	**Naltrexone**	**Placebo**
Mean	36.68	35.05	35.17	35.49
SD	11.51	12.36	14.31	12.68
N	7F, 6M	8F, 7M	8F, 8M	9F, 8M

Note. F = females; M = males.

7.2.4 Procedure/Materials

Two cubicles maintained at 22 ± 2° Celsius were used to test subjects in Study 4. Subjects were seated in a communal area where they were given a consent form (Appendix 12, p 344) to read and sign and a medical checklist to complete (Appendix 6, p 326).

Mood/ self-efficacy and cardiovascular measures

Subjects began the experiment by completing mood and self-efficacy ratings and having their BP and pulse rate measured. The instruments, procedures and schedule of mood/self-efficacy ratings and cardiovascular measures[15] were the same as those described in Study 3 (Appendix 13, p 346).

[15] The M4 Omron electronic monitor was calibrated with a mercury manometer on five subjects. Measures from both methods were strongly related at the beginning (SBP: r=.88, p=.05; DBP: r=.87; p=.053) and end of the current study (SBP: r =.98, p=.002; DBP: r=.98; p=.003).

Blink reflex – R2 component

General procedure

R2 and R3 have been identified as the nociceptive components of the blink reflex (BR); however, since the neural circuitry for the R3 is currently still under debate, the R2 provided a model of pain transmission and inhibition in this study.

Test stimuli: To date, electrical stimuli have provided the most reliable and convenient way by which to elicit the R2 component of the blink reflex (Sarno, Blumenthal, & Boelhouwer, 1997), because unlike mechanical stimuli, electrical stimuli bypass receptors to directly excite afferent nerve endings (Ferracuti, Leardi, Cruccu, Fabbri, & Itil, 1994a). The supraorbital nerve on the non-dominant side was stimulated directly over the supraorbital notch using silver/silver chloride surface electrodes taped 2 cm apart (cathode over notch; anode above cathode). Stimulation consisted of single square wave pulses (0.3 msec duration - Kaube, Katsarava, Kaufer, Diener, & Ellrich, 2000) delivered by an SD9 Grass Square Pulse stimulator in series with a constant current unit. To minimise modulation of R2 by anticipatory behaviour (Cruccu, Ferracuti, Leardi, Fabbri, & Manfredi, 1991), habituation (Esteban, 1999) and an R3 component (Ellrich & Treede, 1998), pulses were delivered manually using random inter-stimulus intervals ranging between 10-20 seconds. Current intensity was monitored via a custom-built digital current meter. A disposable pre-gelled, adhesive ground electrode was placed directly in the middle of the forehead.

Recording: Electromyographic (EMG) signals from the ipsilateral and contralateral orbicularis oculi muscles were recorded by means of 8 mm shielded silver/silver chloride cup electrodes placed over the muscle below (mid-lower lid) and lateral to the eye (on the outer portion of the eyelid). EMG data was amplified and low and high pass filtered (active range 10 to 2,500 Hz) using a Biopac MP100 and EMG multi-channel amplifier modules. Responses were digitally sampled by the Biopac MP100 interface at a rate of 1000 samples/sec (highest sampling rate permitted by computer capacity) for the duration of the task. Data was stored for off-line analysis

using commercially available software (Acq*Knowledge®* version 3.7.1. ©1992-2001 Biopac Systems, Inc.; Goleta, CA).

The skin at each electrode site was slightly scratched with abrasive paste and degreased with an alcohol swab. Electrodes were coated with saline conductance gel to achieve skin impedance of less than 10 K ohms [supraorbital notch = 7.09 ± 0.69 (SEM); below non-dominant eye = 8. 62 ± 0.84 (SEM); below dominant eye = 9.42 ± 1.03 (SEM)]. See Appendix 13 (p 346) for standardised instructions and a diagram of electrode placement.

Hetero-segmental pain inhibition

The status of descending pain inhibitory influences (Esteban, 1999) was explored in depressed and non-depressed subjects via activation of DNIC, whereby wide dynamic range neurones within the spinal cord and trigeminal system (responsible for the R2) are powerfully inhibited by hetero-segmentally-applied noxious stimuli. As inhibition of the R2 via DNIC is mediated by endogenous opioids (Boureau et al., 1978; Boureau et al., 1979; Pomeranz & Warma, 1988; Willer et al., 1982b), noxious stimuli were applied hetero-segmentally both before and after absorption of the drug. On each occasion subjects were seated in Cubicle A, and fitted with a two-way headset system. During stimulation, subjects' eyes remained open and focussed on a cross in front of them which led to a slightly downward gaze (Esteban, 1999).

In a random sequence, three 2 mA, 6 mA, and 10 mA test stimuli (TS) were delivered alone, and then during a noxious hand CPT (or conditioning stimulus, CS). Intensities of 2 mA, 6 mA and 10 mA were chosen to investigate the effects of low intensity stimuli, stimuli at pain threshold[16], and high intensity stimuli (respectively) on the nociceptive component of the blink reflex (R2).

During each CS the non-dominant hand was immersed up to the wrist-crease into a 37°C warm water bath for 3 minutes to standardise hand temperature, and then into a

[16] 6mA was identified as the pain threshold (i.e., point at which the stimulus has just begun to get painful) in an informal pilot (N=10) completed by a colleague.

noxious 7°C cold-water bath for the time it took to deliver nine TS (approximately 2 minutes). However, delivery of TS commenced after 30 seconds of cold-water immersion - the point at which cold pressor pain often peaks[17]. To check that the cold water remained noxious, subjects were required to rate perceived PI and UP after 30 seconds and then upon termination of the CS, using two 0-9 point verbal rating scales (VRS) described in Study 3. Small fluctuations occurred in water temperature; however, changes were consistent across groups. The cold pressor apparatus was identical to that used in Study 3.

Subjects use the same 0-9 point VRS to rate the TS (CS or no CS) As expected, 2 mA shocks were rated within the non-nociceptive range (0), and 6 mA and 10 mA shocks were rated within nociceptive ranges (above 2 and 3).

Stress-induced analgesia

In brief, subjects rated perceived PI and UP of nine TS (2 mA, 6 mA, 10 mA) before and after the math task, using two 0-9 point VRS as described in Study 3. Representation of the nociceptive blink reflex in the brainstem highlights the utility of this reflex when investigating suprasegmental influences on pain transmission and inhibition. Therefore, R2 responses were compared before and after the math task to assess the impact of a stressful task on an objective pain reflex.

<u>R2 data notes:</u>

- Although R2 occurs bilaterally and was measured from both sides, contralateral responses did not differ significantly from those measured ipsilaterally to the stimulation. For the sake of brevity, contralateral results were not reported.
- With regards to TS, subjects appeared to have difficulty assigning a rating to such a brief stimulus; therefore this data was not considered to be an adequate representation of the pain experience and was not explored in detail.

[17] As established in previous pilot studies conducted by the experimenter.

Naltrexone intervention

Using the same double-blind procedure as described in Study 3, depressed and non-depressed subjects were randomly assigned to either the naltrexone (50 mg) or placebo condition. As in Study 3, to maximise time efficiency the capsule was administered 10 minutes prior to initial blink reflex procedures. During the time set aside for drug absorption, subjects completed a battery of psychometric tests (see *7.2.2 Psychometric tests*, p 234) and read light material provided by the experimenter until testing resumed. A slightly smaller percentage of subjects than in previous studies (6-10% versus 13-14%) complained of naltrexone-induced symptoms such as nausea, decreased mental acuity and fatigue. However, one subject reacted adversely to naltrexone and could not complete the experiment.

Foot cold pressor task (fCPT)

Subjects completed a fCPT in Cubicle A immediately before and after the math task. Subjects immersed their non-dominant foot to the top of the lateral malleolus (ankle) firstly into a 37°C warm water bath for 3 minutes (to standardise foot temperature), and then into a 2°C ice water bath. Each bath measured 21 cm (height) x 19 cm (width) x 34 cm (depth), and was insulated to minimise changes in water temperature. Also, a small aquarium pump was submerged in the ice water bath to prevent warm pockets of water from developing around the foot. Although water temperatures altered slightly throughout each task, temperature fluctuations were equivalent across groups. The foot was used instead of the hand to avoid carry-over effects from previous cold-water tasks. Given that lateral dominance has been observed for pain perception in the foot (Weinstein & Sersen, 1961), the non-dominant foot was deemed more sensitive and chosen for immersion.

Subjects were instructed to say, "Stop!" and withdraw their foot from the water when they felt that the pain was too unpleasant to continue (Appendix 13, p 346 for standardised instructions). At 30-second intervals, and after pain tolerance was reached, subjects rated the PI and UP of the ice water using two 0-9 point VRS described in Study 3. A ceiling of 4 minutes was set but not divulged to subjects.

Math task

The math task was identical to that used in Study 3. As in Study 3, subjects completed the math task in Cubicle B to heighten the novelty and anticipatory anxiety with regards to the task.

Task shocks

As in Study 3, stimulation consisted of seven 15 ± 1 mA (SEM) rectangular pulses of 25 milliseconds duration. Mean skin impedance (as measured by a PA300 impedance meter) at the site of electrodes was 3.38 K ohms ± 0.68 (SEM). Apart from an SD9 Grass Square Pulse stimulator used to deliver shocks, equipment and procedures were identical to those used in Study 3.

Debriefing

At the end of the study, the purpose of the experiment was explained and subjects were given a chocolate bar and remunerated $20. Furthermore, subjects were promised written notification of the results. Information about counselling services was given to depressed subjects on request. If concerned by unusual symptoms after testing, subjects were told that the drug code could be 'broken' and they would be informed of which drug they were administered. The code was broken for one anxious subject, who had actually been given the placebo. Due to the potential for naltrexone to interact with alcohol, at least one alcohol-free day was recommended after the experiment.

7.3 RESULTS

7.3.1 Mood and self-efficacy

Data considerations

For reasons mentioned in Study 1, anxiety, discouragement, and anger were the only moods analysed. As in previous studies, apart from being examined in an initial randomisation check, self-efficacy was not assessed before the math task since this variable related to performance *during* the task.

Randomisation check

Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) univariate ANOVAs were calculated on pre-drug mood and self-efficacy ratings (Tables 7.4 and 7.5). As expected, at the beginning of the experiment depressed subjects reported significantly higher anxiety (M = 38.07 versus M = 22.93), discouragement (M = 24.75 versus M = 4.49) and anger (M = 13.05 versus M = 2.68) than non-depressed subjects. Difficult to explain was the Drug x Group interaction found for self-efficacy. Independent t-tests indicated that depressed subjects in the naltrexone condition reported significantly lower levels of self-efficacy than controls in the same condition (M = 31.27 versus M = 52.66; t (27) = -2.46; p = .02). No other interactions were found.

Table 7.4: Mood and self-efficacy ratings at the beginning of the experiment.

	Controls				Depressed			
	Naltrexone (N = 16)		Placebo (N = 17)		Naltrexone (N = 13)		Placebo (N = 15)	
Mood	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Anxiety	23.62	13.56	22.23	19.24	40.00	22.24	36.13	27.87
Discouragement	5.22	6.69	3.75	5.68	29.76	22.69	19.73	22.81
Anger	2.06	3.22	3.29	5.30	9.81	16.47	16.30	20.34
Self-efficacy	52.66	21.89	42.32	21.34	31.27	24.65	45.07	16.55

Table 7.5: F ratios for mood and self-efficacy ratings at the start of the experiment.

Source	Anxiety	Discouragement	Anger	Self-efficacy
Group (G)	7.74*	24.12***	9.60**	2.91
Drug (D)	0.23	1.94	1.33	0.10
G x D	0.05	1.08	0.62	4.87*

Note. Degrees of freedom = 1,57.

*p<.05; **p<.01; ***p<.001.

Effects of the drug on mood and self-efficacy

Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) x 2 (Time: pre-drug, post-drug) repeated measures ANOVAs were calculated on each mood rating (Tables 7.4, 7.6 and 7.7).

Subjects reported significantly less anxiety (M = 30.50 versus 22.03) after being in the experimental environment for over 90 minutes. All other moods remained stable over time and were not affected by naltrexone. As expected, when collapsed over pre- and post-drug measures depressed subjects reported significantly higher anxiety (M = 33.88 versus M = 18.65), discouragement (M = 24.05 versus M = 5.46), and anger (M = 13.84 versus M = 3.34) than non-depressed subjects.

Table 7.6: F ratios for mood ratings before and after drug absorption.

Source	Anxiety	Discouragement	Anger
		Between Subjects	
Group (G)	9.97**	19.60***	10.60***
Drug (D)	1.13	1.41	0.42
G x D	0.31	0.55	0.22
		Within Subjects	
Time† (T)	10.53**	0.02	0.79
T x G†	0.00	0.92	0.01
T x D†	0.92	0.19	1.17
T x D x G†	0.31	0.45	0.47

Note. †Pillai's Trace F ratio; degrees of freedom = 1,57.

*p<.05; **p<.01; ***p<.001.

Effects of the math task on mood and self-efficacy

The effect of the math task on mood was explored with separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) x 7 (Time: pre-task, during task at 1:30", 7:39", 13:20", 19:40", 24:00", post-math task) repeated measures ANOVAs (Tables 7.7 and 7.8). As described in previous studies, similar analyses were carried out on self-efficacy ratings, except that ratings made after the practice trials were deemed a more relevant point of comparison than those made prior to the practice trials (Tables 7.7 and 7.8).

As expected, depressed subjects reported significantly higher levels of discouragement (M = 50.80 versus M = 29.79), and anger (M = 40.66 versus M = 20.30) and marginally higher levels of anxiety (M = 52.20 versus M = 41.23) than controls before, during and after the math task. Furthermore, depressed subjects reported significantly lower self-efficacy ratings (M = 18.77 versus M = 30.78) throughout this time.

Exploration of Time main effects with planned simple pair-wise comparisons (where each point was compared to pre-task ratings) suggested that subjects experienced a

significant increase in anxiety, discouragement, and anger during the math task (Table 7.9). Self-efficacy ratings did not differ after the practice trials and during the task; however, low ratings (20-28 on a 0-100 point scale) suggested that the math items were difficult and that subjects perceived themselves to have little control over the shocks. Finally, the deterioration in mood and low self-efficacy persisted even after the task had been completed.

A Time x Drug effect for anxiety suggested that changes in anxiety were not equivalent in subjects taking either the placebo or naltrexone. When explored with repeated pair-wise comparisons, the Time x Drug effect indicated that mid-way through the task anxiety began to decrease in placebo recipients ($F(1,29) = 10.36$; $p = .003$), but persisted at a high level in naltrexone recipients to the end of the task ($F(1,26) = 14.75$; $p = .001$) (Figure 7.3).

Table 7.7: Mood and self-efficacy ratings before, during, and after the math task.

		Controls				Depressed			
		Naltrexone (N = 16)		Placebo (N = 17)		Naltrexone (N = 12)		Placebo (N = 14)	
Mood	**Time**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Ax.	**Pre**	16.12	16.88	12.62	15.10	35.25	30.68	23.14	24.62
	1	54.63	25.12	52.29	23.23	51.92	23.72	57.86	23.86
	2	54.44	25.25	45.00	26.69	56.75	20.25	67.14	21.89
	3	50.37	24.89	49.41	22.82	54.08	19.66	64.57	29.01
	4	54.50	26.10	37.82	27.67	61.67	16.52	53.29	33.35
	5	53.25	28.05	36.29	28.82	57.08	29.18	57.50	34.51
	Post	35.97	26.14	24.47	32.55	47.25	33.40	43.36	36.47
Ds.	**Pre**	8.02	9.44	5.29	9.03	27.64	29.73	21.00	25.24
	1	43.53	20.94	32.76	24.89	54.92	25.50	52.07	27.11
	2	42.13	28.46	33.29	29.74	58.33	25.74	52.57	36.86
	3	32.73	24.82	30.24	25.17	62.50	26.43	51.71	40.63
	4	36.40	27.67	26.35	28.95	62.75	24.84	52.21	38.68
	5	38.60	27.36	32.35	33.08	64.33	29.95	52.00	41.52
	Post	34.10	26.83	21.28	30.11	45.69	34.68	53.44	41.65
Ag.	**Pre**	4.03	6.78	3.97	5.67	15.46	21.88	6.07	21.43
	1	22.33	21.19	22.35	26.49	41.50	32.84	33.64	23.92
	2	22.27	20.76	26.59	28.15	51.08	30.05	44.21	32.78
	3	24.47	28.22	25.53	29.80	49.08	35.76	51.00	34.25
	4	28.87	26.61	23.53	29.92	45.67	38.92	49.29	33.43
	5	27.00	28.92	21.41	30.69	45.58	38.13	47.50	38.51
	Post	16.53	24.55	15.03	26.80	36.52	36.22	42.57	36.06
Sf.	**Prac**	23.10	26.98	28.59	23.14	10.65	9.68	19.06	26.44
	1	37.00	33.07	30.65	23.99	16.45	14.92	27.71	23.09
	2	34.38	32.68	30.00	20.45	23.36	15.82	25.43	22.99
	3	31.44	32.69	28.41	22.46	20.27	19.88	24.64	27.02
	4	32.75	32.12	29.41	24.47	17.64	20.65	16.71	19.97
	5	34.25	33.30	29.65	25.80	21.55	22.42	18.21	23.41
	Post	32.31	33.78	29.03	24.61	12.36	19.84	18.93	18.35

Note. Ax. = anxiety; Ds. = discouragement; Ag. = Anger; Sf. = self-efficacy; Pre = prior to math task and practice trials; Prac = after practice trials, prior to math task; 1-5 = 1:30, 7:39, 13:20, 19:40 and 24:00 minutes into math task, respectively; Post = after math task.

Table 7.8: F ratios for mood and self-efficacy ratings before, during and after the math task.

Source	Anxiety	Discouragement	Anger	Self-efficacy
		Between Subjects		
Group (G)	3.84[a]	10.69**	9.89**	4.38*
Drug (D)	0.56	1.12	0.01	0.06
G x D	0.67	0.02	0.01	0.52
		Within Subjects		
Time[†] (T)	21.32***	13.4***	8.69***	1.75
T x G[†]	1.17	1.12	0.61	0.89
T x D[†]	4.02**	0.25	0.27	1.11
T x D x G[†]	0.94	1.41	0.90	1.01

Note. [†] Pillai's Trace F ratio; degrees of freedom: within S's = 6,49; between S's = 1, 54.

[a] p=.055; *p<.05; **p<.01; ***p<.001.

Table 7.9: Simple pair-wise comparisons[a] of mood before, during and after the math task.

		Math Task					
Mood	**Pre**	**1**	**2**	**3**	**4**	**5**	**Post**
Anxiety	22	54***	56***	55***	52***	51***	38***
Discouragement	15	46***	46***	44***	44***	47***	39***
Anger	10	28***	36***	37***	37***	35***	28***

Note. [a]Each rating was compared to pre-math task ratings.

***p≤.001

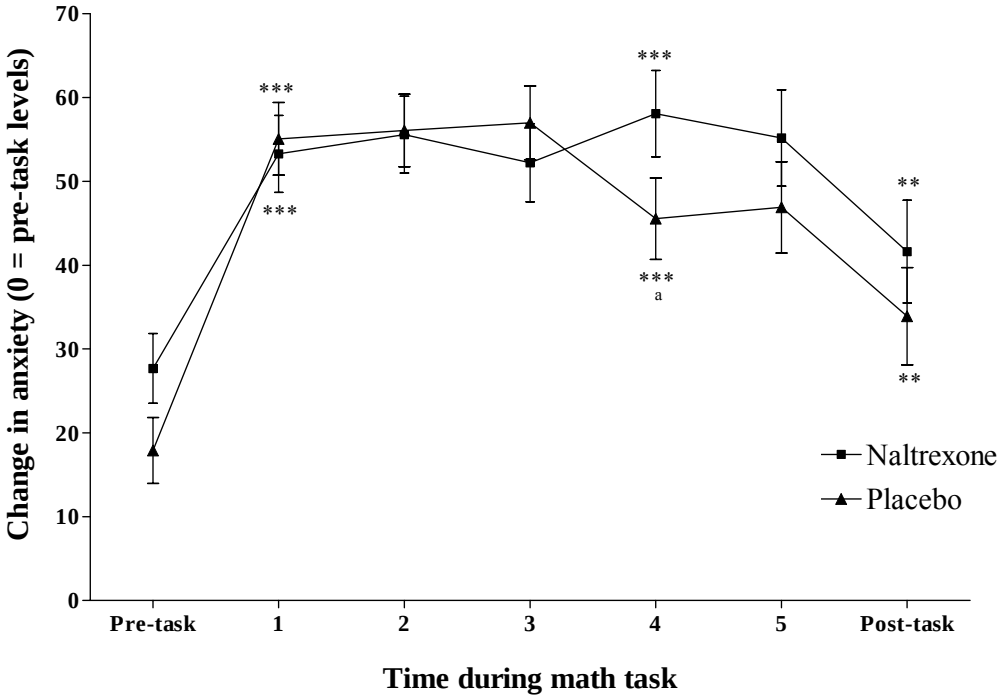


Figure 7.3: Anxiety before, during and after the math task in placebo and naltrexone conditions. Note. **p<.01, ***p≤.001 within group repeated pair-wise comparisons; [a]p=.08 independent t-test comparison.

7.3.2 Electro-cutaneous task shocks

Subjects rated the PI and UP of each shock using a computer-generated 0-100 point VAS. Ratings were averaged across shocks (N = 7). Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) univariate analyses were carried out on mean PI and UP ratings (Tables 7.10 and 7.11).

Table 7.10: Pain and unpleasantness ratings for task shocks.

		Depressed					Controls			
		PI		UP			PI		UP	
Drug	**N**	**M**	**SD**	**M**	**SD**	**N**	**M**	**SD**	**M**	**SD**
Naltrexone	12	57.68	25.31	61.86	25.44	16	54.19	21.85	51.53	23.10
Placebo	15	62.31	19.75	63.14	18.10	16	54.73	16.62	52.67	19.18

Note. M=mean; SD=standard deviation; PI=pain intensity; UP=unpleasantness.

Table 7.11: F ratios of pain and unpleasantness ratings for task shocks.

Source	Pain intensity	Unpleasantness
Group (G)	1.07	3.43
Drug (D)	0.24	0.05
G x D	0.16	0.00

Note. Degrees of freedom = 1,57.

Shocks were perceived as moderately to somewhat severely painful and unpleasant (i.e., M = 56.89 - 57.16). Depressed subjects gave higher ratings, although group differences failed to reach significance (PI: p = .31; UP: p = .07). Despite being fully absorbed during the math task, naltrexone did not alter how subjects perceived the shocks in comparison to the placebo. No interactions were found.

Effect of mood, self-efficacy and the drug on task shock sensitivity

Pearson correlations and hierarchical linear multiple regression models were used to explore the effects of depression, drug, mood and self-efficacy on PI and UP ratings for task shocks during the math task (Tables 7.12 and 7.13). Absolute mood and self-efficacy ratings were analysed as the intensity of these factors in relation to pain was of interest.

As indicated in Table 7.13 and Figures 7.4-7.6, greater anxiety and discouragement was associated with more PI and UP for each shock in naltrexone, but not placebo recipients. However, the opioid mediation of shock UP in highly anxious subjects was only detected in those with depression. Angrier subjects reported more PI (r = .31; p =.01) and UP (r = .38; p =.003) during the shocks irrespective of opioid blockade.

A marginally significant negative association was identified between shock UP and self-efficacy for naltrexone recipients (Table 7.13, Figure 7.7). The opioid release found in inefficacious stressed subjects reiterates the findings of Bandura et al. (1988), who found that perceived control over noxious stimuli inhibits the release of opioids.

Table 7.12: Pearson correlations between task shock pain and unpleasantness, and mood during the math task.

	Depressed				**Controls**			
	Placebo (N = 15)		**Naltrexone (N = 12)**		**Placebo (N = 16)**		**Naltrexone (N = 17)**	
Task mood	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**
Anxiety	.12	.21	.76**	.84**	.46[a]	.58*	.78***	.52*
Discouragement	.02	.18	.64*	.79**	.14	.30	.63**	.64**
Anger	.14	.25	.41	.59**	.34	.39	.30	.03
Self-efficacy	-.38	-.18	-.18	-.29	.10	.07	-.43	-.60*

Note. PI = pain intensity; UP = unpleasantness.

[a]p = .06; *p<.05; **p<.01; ***p ≤.001;

Table 7.13: Summary of t-values from hierarchical regression analyses illustrating effects of mood, self-efficacy, drug and depression on pain intensity and unpleasantness of shocks during the math task.

		Mood on task shock pain							
		Pain intensity				Unpleasantness			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Sf.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
1	**Group (G)**	-0.21	-0.06	-0.35	-0.76	-1.25	-0.59	-1.13	-1.61
	Drug (D)	0.78	0.78	0.53	0.45	0.35	0.55	0.17	0.09
	Mood (M)	4.69**	2.59*	2.23*	-1.81	4.55**	3.67**	2.56*	-2.12*
2	**G x D**	-0.35	-1.73	-0.81	-1.01	0.20	-1.45	0.41	-0.91
	G x M	-0.01	0.10	0.32	0.98	-0.27	0.08	-0.44	0.55
	D x M	-2.81**	-3.04**	-0.93	1.15	-1.58	-3.02**	-0.45	1.94[a]
3	**G x D x M**	1.33	0.41	0.34	0.73	2.18*	0.85	1.42	0.31

Note. Step 1 = main effects model (df = 3,56); Step 2 = two-way model (df = 6,53); Step 3 = full model (df = 7,52); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.
[a]p=.057; *p<.05; **p<.01.

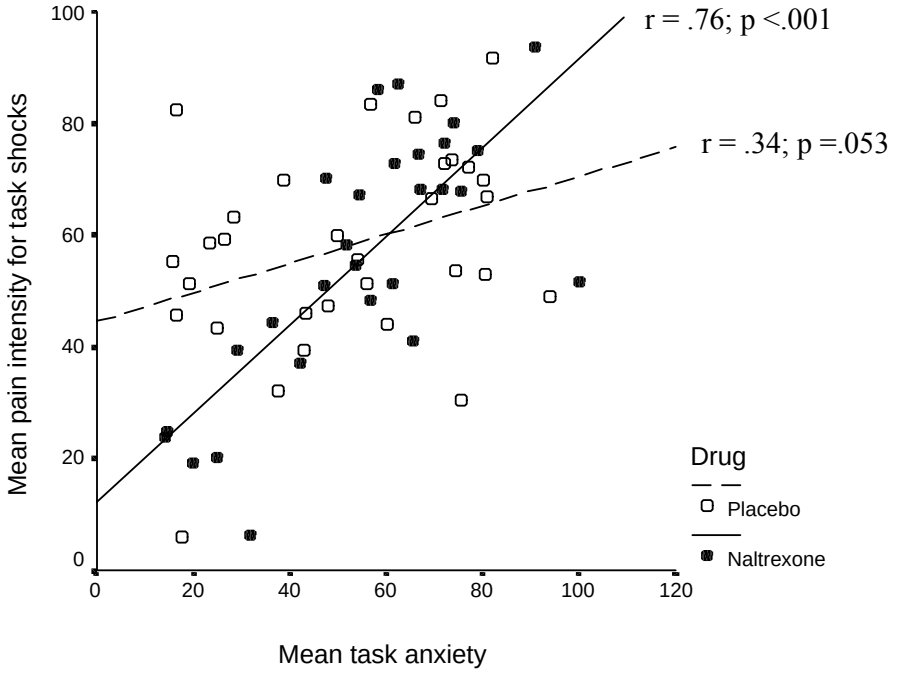


Figure 7.4: Scattergram depicting a positive relationship between anxiety and shock pain intensity for naltrexone recipients, and less so for placebo subjects.

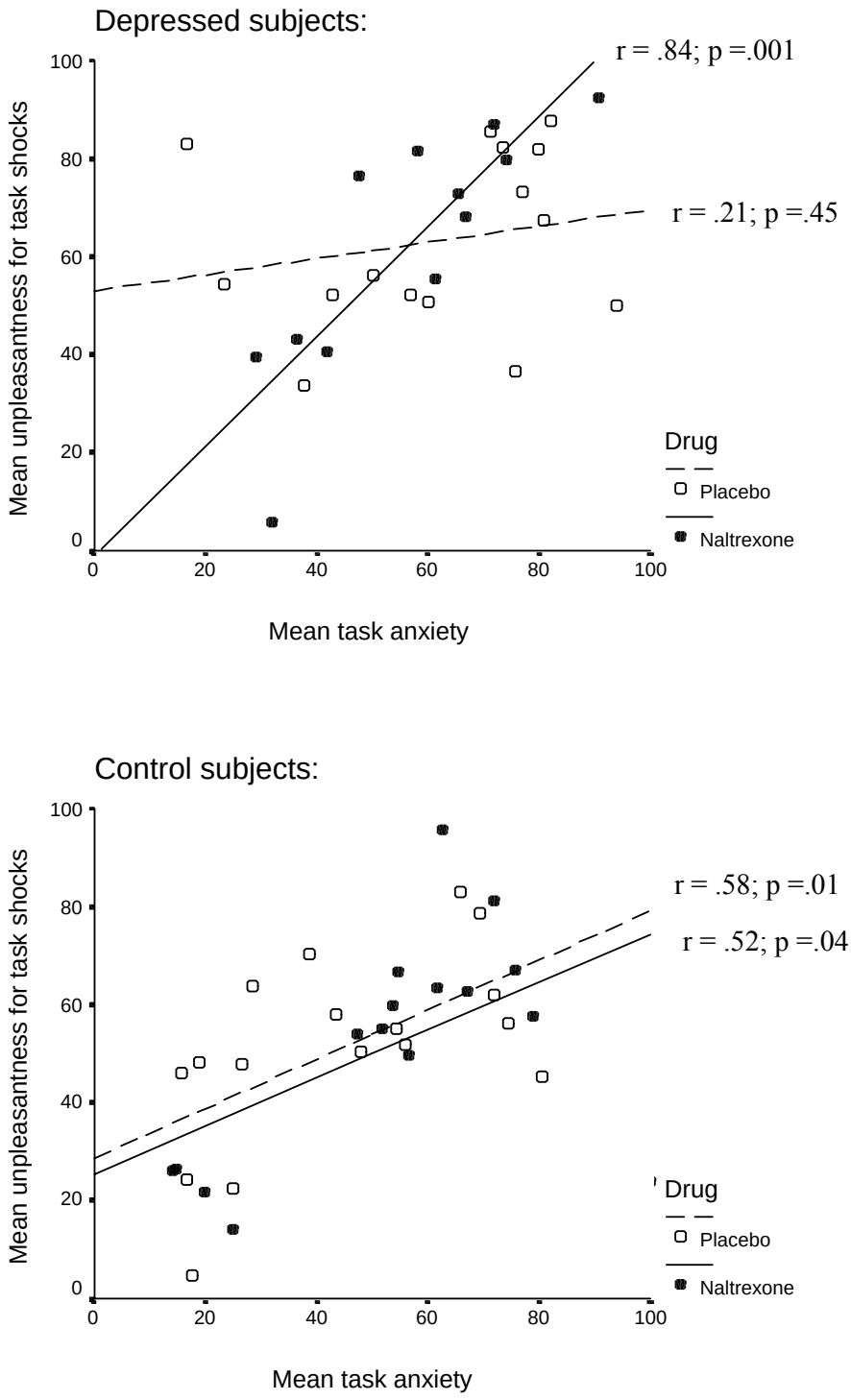
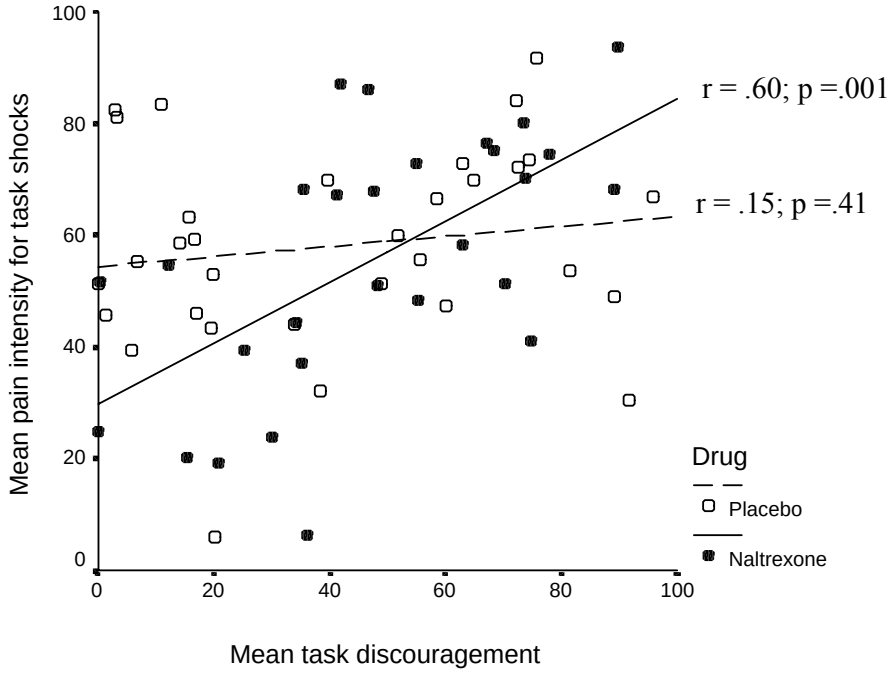


Figure 7.5: Scattergrams depicting the positive relationship between anxiety and shock unpleasantness for depressed naltrexone recipients and non-depressed subjects in taking either the placebo or naltrexone.

a)



b)

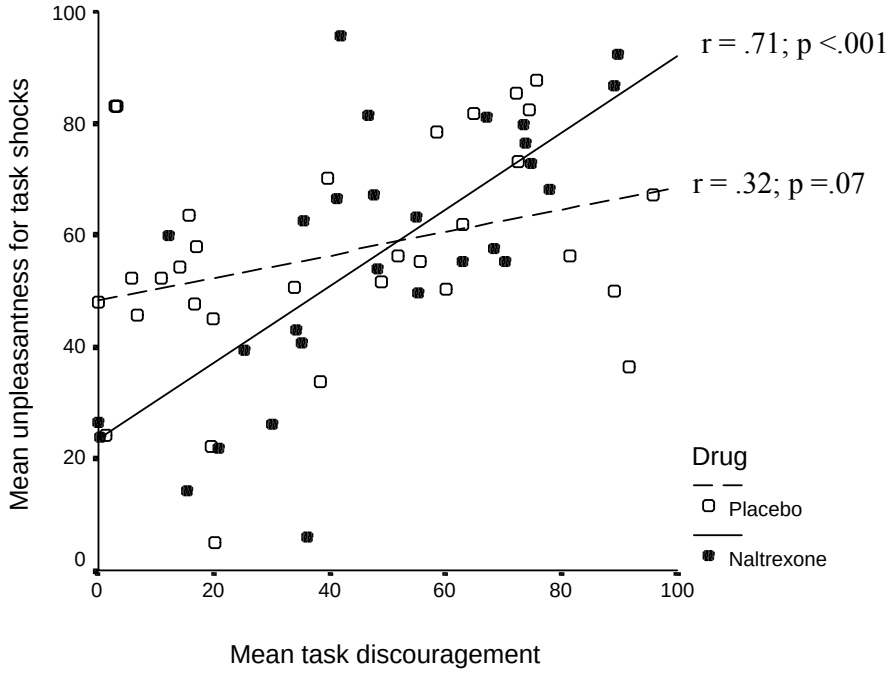


Figure 7.6: Scattergram depicting the positive relationship between discouragement and a) pain intensity b) unpleasantness of task shocks for naltrexone, but not for placebo recipients.

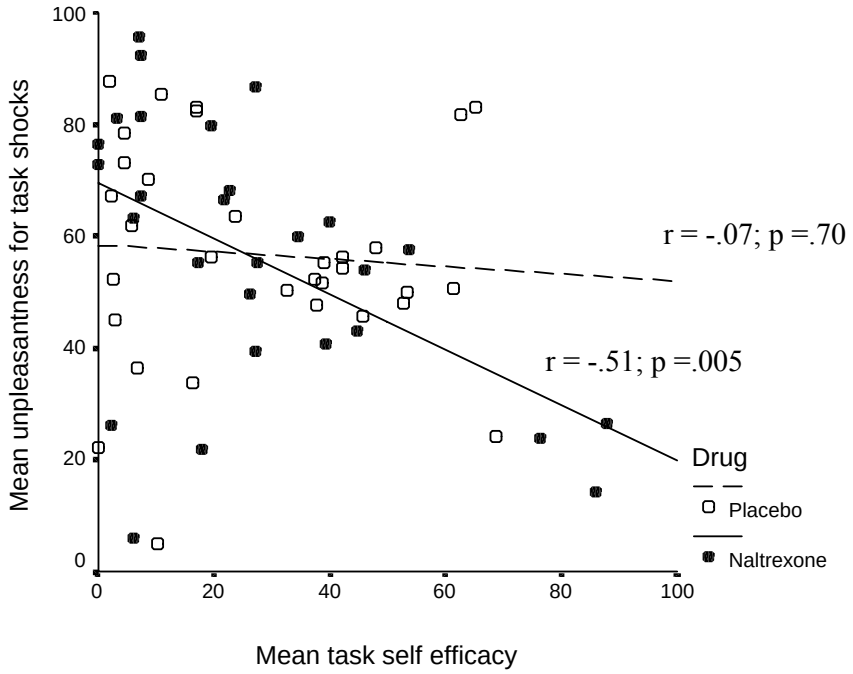


Figure 7.7: Scattergram depicting the negative relationship between self-efficacy and unpleasantness of task shocks for naltrexone, but not for placebo recipients.

7.3.3 Foot cold pressor task (fCPT)

Effect of the math task on foot cold pressor pain perception

Pain tolerance

A total of 23 subjects (37.7% of total sample) endured the water for the maximum time before and after the math task. The number of subjects reaching the maximum time did not differ between the groups (pre-maths: 35.7% depressed, 39.4% controls, χ^2 (1) = 0.09; p>.05; post-maths: 32.1% depressed, 42.4% controls, χ^2 (1) = 0.68; p>.05). Similarly, drug failed to influence whether subjects tolerated the cold water for the maximum time or not, either before or after the math task (pre-maths: 37.9% naltrexone, 37.5% placebo, χ^2 (1) = 0.00; p>.05; post-maths: 31% naltrexone, 43.8% placebo, χ^2 (1) = 1.05; p>.05). A log transformation was carried out on tolerance time to minimise the effect of these outliers on further analyses.

A 2 (Time: Pre- and post-math task) x 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) repeated measures ANOVA was carried out on transformed tolerance times (Tables 7.14 and 7.15). The math task did not affect tolerance to the ice water, as participants maintained their foot in the water for a similar duration before versus after the task. Neither depression nor naltrexone influenced pain tolerance.

Pain and unpleasantness ratings

Separate 2 (Time: Pre- and post-math task) x 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) repeated measures ANOVAs were carried out on mean PI and UP ratings (Tables 7.14 and 7.15). The ice water was significantly less painful (pre-maths M = 6.62 versus post -maths M = 6.40) and unpleasant (pre-maths M = 6.91 versus post-maths M= 6.66) after the math task. Although the drug main effect (PI: $p = .13$; UP: $p = .25$) and time x drug interaction did not reach significance (PI: $p = .08$; UP: $p = .10$), placebo recipients reported significantly less PI and UP following the math task (PI: $t(31) = 3.17$; $p = .003$; UP: $t(31) = 2.56$; $p = .01$). Conversely, their naltrexone counterparts reported no change (PI: $t(28) = 0.39$; $p = .70$; UP: $t(31) = 0.45$; $p = .65$). Depression, alone or with any other factor, did not affect foot cold pressor pain perception.

Table 7.14: Foot cold pressor pain tolerance[a], pain intensity and unpleasantness ratings before and after the math task.

	Naltrexone						Placebo					
	Tol.		PI		UP		Tol.		PI		UP	
fCPT	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
						Depressed (N = 28)						
Pre	126	97	7.16	1.10	7.63	1.32	142	85	6.46	2.50	6.88	2.57
Post	126	90	7.30	1.27	7.81	1.32	132	100	6.02	2.98	6.27	2.79
						Controls (N = 33)						
Pre	130	93	6.71	1.59	6.62	1.99	154	86	6.12	2.36	6.49	2.39
Post	131	91	6.48	1.99	6.34	2.01	152	87	5.74	2.46	6.18	2.61

Note. [a] untransformed data is presented for ease of interpretation; M = mean; SD = standard deviation; Tol. = pain tolerance (seconds); PI = pain intensity; UP = unpleasantness; fCPT = foot cold pressor; Pre and Post = fCPT before and after the math task, respectively.

Table 7.15: F ratios for foot cold pressor pain tolerance, pain intensity and unpleasantness ratings before and after the math task.

Source	**Tolerance**	**PI**	**UP**
		Between subjects	
Group (G)	0.66	0.76	1.74
Drug (D)	0.47	2.30	1.33
G x D	0.11	0.09	0.80
		Within subjects	
Time[†] (T)	1.01	4.96*	4.44*
T x G[†]	1.31	0.61	0.11
T x D[†]	0.56	3.27	2.83
T x G x D[†]	0.13	1.08	2.31

Note. [†] Pillai's Trace F ratio; degrees of freedom = 1,57.

*p<.05.

Effect of mood, self-efficacy and the drug on foot cold pressor pain perception

Pearson product correlations (Table 7.16) and hierarchical multiple linear regression analyses (Table 7.17) were used to explore the effects of mood, drug and depression on foot cold pressor PI, UP and tolerance before and after the math task. For reasons mentioned earlier, effects of self-efficacy were only examined after the math task. Absolute scores were preferred over change scores, as change scores would not accurately represent substantial pre-existing differences in mood between each group.

Pre-math task

When groups were analysed together in regression analyses, drug interacted with discouragement, and to a lesser extent anger and anxiety, to influence cold pressor pain perception prior to the math task (Table 7.16 and 7.17, Figure 7.8). However, inspection of Table 7.17 indicates that these effects were present only in the depressed group. Presumably, the group x mood x drug effect failed to reach significance due to an averaging effect, when both groups were combined. Therefore, a decision was made to analyse each group separately to explore differences between placebo and naltrexone conditions noted in the correlations (Table 7.18). Inhibitory effects of discouragement, anxiety and (less so) anger on cold pressor PI and UP were antagonised by naltrexone in depressed subjects (Figures 7.9 and 7.10). Results for pain tolerance were trending in the same direction, but failed to reach significance. However, neither mood nor drug influenced cold pressor PI or UP in controls before the math task.

Table 7.16: Pearson product correlations between mood and cold pressor pain tolerance, pain intensity and unpleasantness ratings before the math task.

	Depressed (N = 28)		Controls (N = 33)	
Mood	**Naltrexone**	**Placebo**	**Naltrexone**	**Placebo**
		Pain intensity		
Anxiety	.62*	-.41	-.12	.06
Discouragement	.57*	-.42	-.03	.06
Anger	.54[a]	-.35	-.01	.06
		Unpleasantness		
Anxiety	.55*	-.42	-.09	.04
Discouragement	.50	-.42	.07	.04
Anger	.44	-.36	-.07	.04
		Pain tolerance		
Anxiety	-.49	.03	.24	-.03
Discouragement	-.58*	.08	-.21	.31
Anger	-.55*	.04	-.19	.31

Note. [a]p=.055; *p≤.05.

Table 7.17: Summary of t-values from hierarchical regression analyses illustrating effects of mood, drug and depression on cold pressor pain intensity, unpleasantness and pain tolerance before the math task.

		Mood on foot cold pressor pain								
		Pain intensity			**Unpleasantness**			**Pain tolerance**		
	Variable	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**
1	**Group (G)**	-0.83	-0.88	-0.86	-1.26	-1.25	-1.34	0.10	-0.16	-0.07
	Drug (D)	-1.29	-1.29	-1.24	-0.79	-0.78	-0.74	0.73	0.74	0.89
	Mood (M)	-0.34	-0.46	-0.42	-0.30	-0.32	-0.54	-0.71	-1.21	-1.20
2	**G x D**	-0.36	-0.64	-0.48	0.04	-0.23	-0.02	0.61	1.16	0.82
	G x M	0.20	0.36	0.21	0.15	0.53	-0.01	1.21	0.70	0.75
	D x M	-1.60	-1.98[a]	-1.72	-1.63	-2.02*	-1.62	0.66	2.15*	2.00[b]
3	**G x D x M**	1.65	1.02	0.81	1.51	0.70	0.83	-1.33	0.77	0.87

Note. Step 1 = main effects model (df = 3,57); Step 2 = two-way model (df = 6,54); Step 3 = full model (df = 7,53); Ax. = anxiety; Ds. = discouragement; Ag. = anger.

[a]p=.053; [b]p=.051; *p<.05.

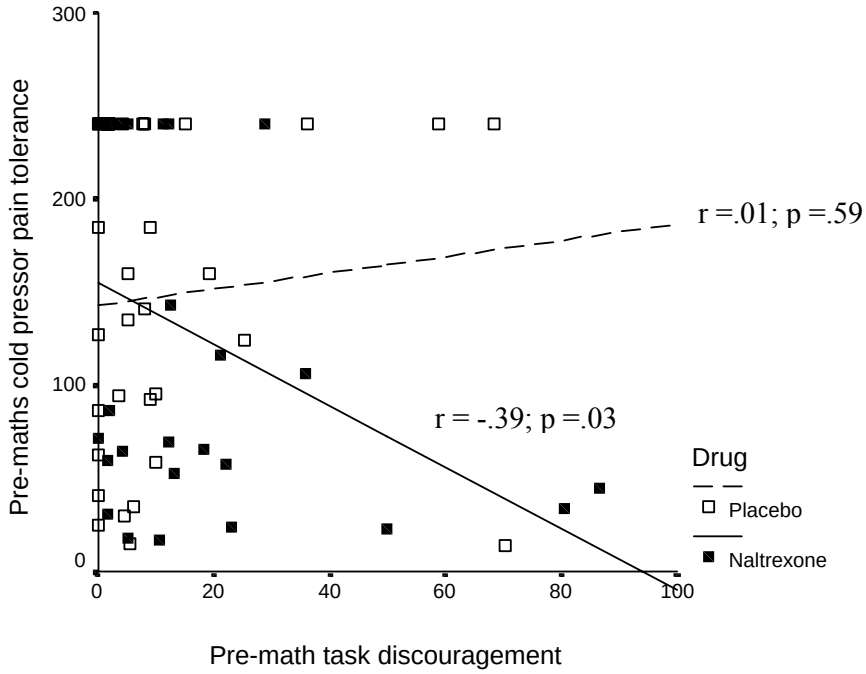


Figure 7.8: Scattergram depicting a negative relationship between discouragement and cold pressor pain tolerance in naltrexone recipients before the math task.

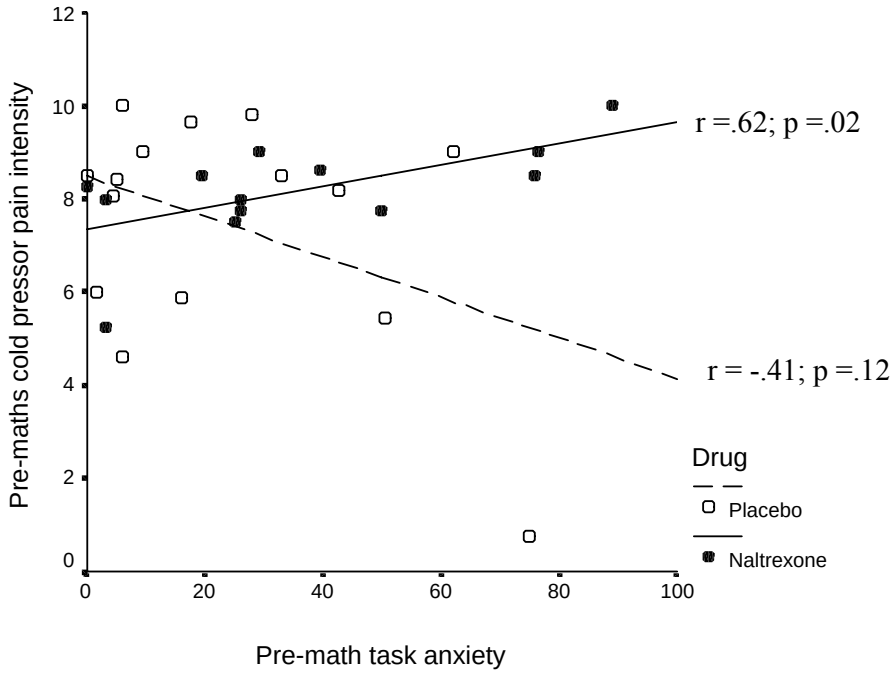
Table 7.18: Summary of t-values from *separate group* hierarchical regression analyses illustrating effects of mood and drug on cold pressor pain intensity, unpleasantness and pain tolerance before the math task.

		Mood on foot cold pressor pain								
		Pain intensity			**Unpleasantness**			**Pain tolerance**		
	Variable	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**
		Depressed subjects								
1	**Drug (D)**	-0.99	-0.99	-0.92	-1.00	-1.00	-0.93	0.17	0.30	0.49
	Mood (M)	-0.39	-0.54	-0.49	-0.37	-0.50	-0.54	-1.29	-1.40	-1.32
2	**D x M**	-2.43*	-2.38*	-1.99[a]	-2.43*	-2.33*	-1.92[b]	-1.30	1.77	1.66
		Control subjects								
1	**Drug (D)**	-0.81	-0.79	-0.81	-0.17	-0.12	-0.16	0.81	0.77	0.74
	Mood (M)	-0.06	0.12	0.16	-0.10	0.30	-0.08	0.63	0.27	0.22
2	**D x M**	0.46	0.24	0.24	0.33	-0.50	-0.29	-0.74	1.45	1.42

Note. Step 1 = main effects model (df =2,30); Step 2 = full model (df = 3,29); Ax. = anxiety; Ds. = discouragement; Ag. = anger.

[a]p=.06; [b]p=.07; *p<.05.

a)



b)

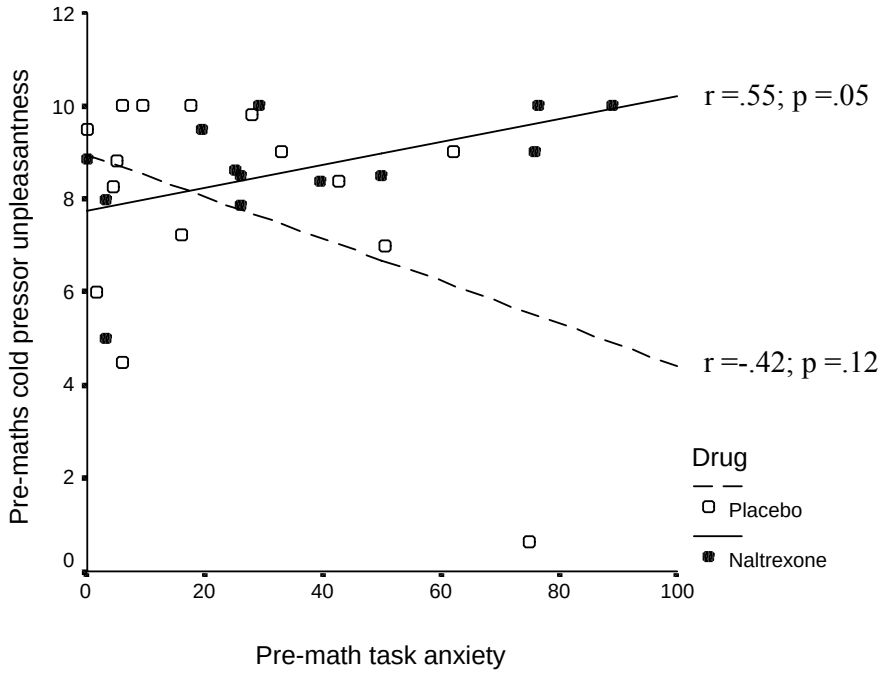


Figure 7.9: Scattergrams depicting a direct relationship between anxiety and cold pressor a) pain intensity and b) unpleasantness in *depressed subjects* taking naltrexone, before the math task.

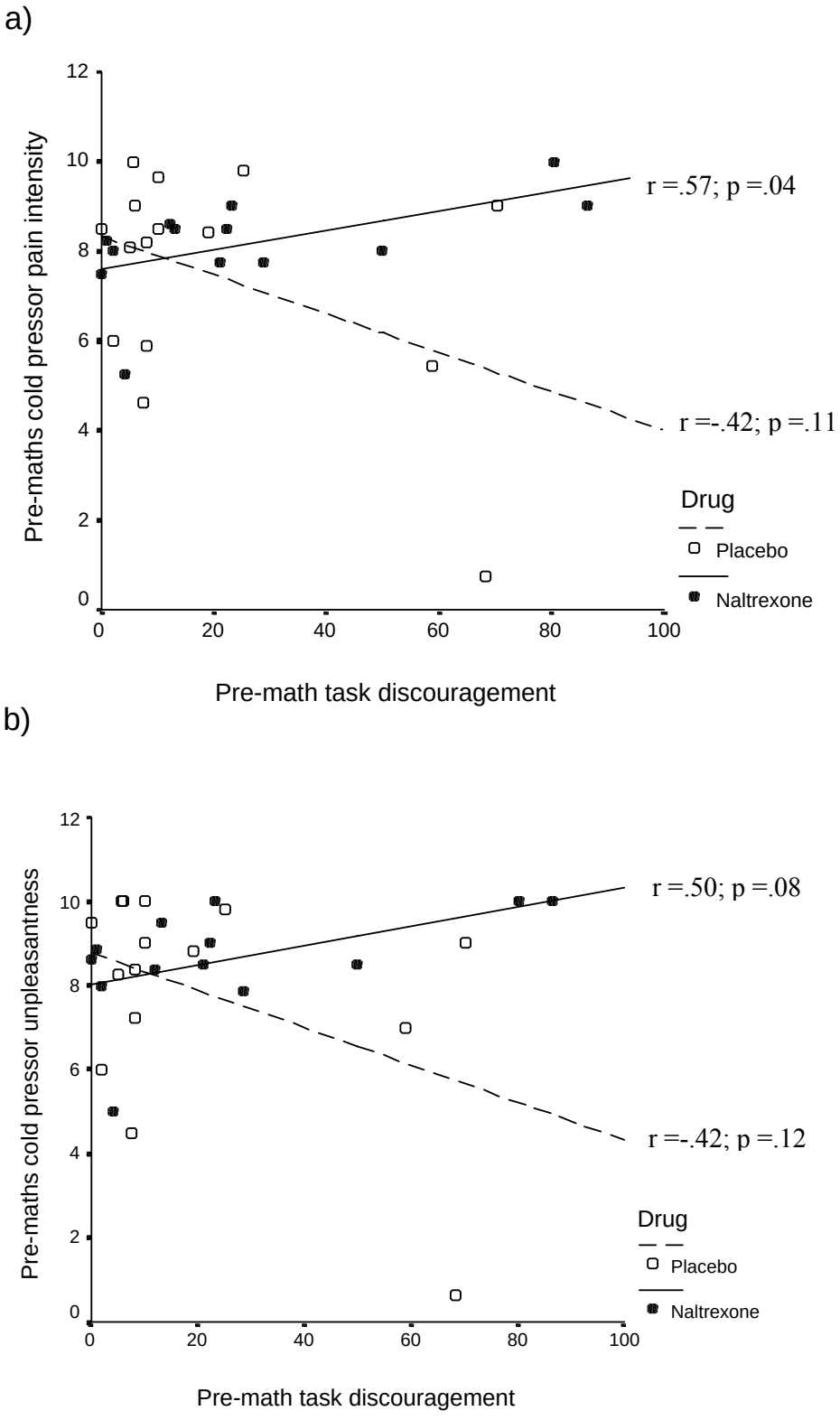


Figure 7.10: Scattergrams depicting a direct relationship between discouragement and cold pressor a) pain intensity and b) unpleasantness in *depressed subjects* taking naltrexone, before the math task.

Post-math task

The interactions involving Drug before the math task were no longer present after the math task (Tables 7.19 and 7.20). Greater levels of anxiety (r = -.31; p = .01), discouragement (r = -.28; p = .03), and anger (r = -.35; p = .006) were associated with lower cold pressor pain tolerance. Conversely, greater levels of self-efficacy were associated with extended cold pressor persistence after the math task (r = .27; p = .04). Neither drug nor depression influenced cold pressor pain tolerance after the math task. No interactions were found.

No main effects or interactions between mood, drug and/or depression were found for cold pressor PI and UP ratings. A Self-efficacy x Drug x Group effect qualified the main effect for UP ratings, indicating that naltrexone antagonised the inverse association between self-efficacy and cold pressor UP for controls, but not depressed subjects[18] (Figure 7.11).

Table 7.19: Pearson product correlations between mood, self-efficacy and cold pressor pain intensity, unpleasantness and pain tolerance after the math task.

	Depressed (N = 28)		**Controls (N = 33)**	
Mood	**Naltrexone**	**Placebo**	**Naltrexone**	**Placebo**
		Pain intensity		
Anxiety	.14	.04	.38	.04
Discouragement	.25	.06	.34	-.08
Anger	.40	.16	.21	-.16
Self-efficacy	-.69**	-.23	.18	-.52*
		Unpleasantness		
Anxiety	.25	-.03	.36	.17
Discouragement	.37	-.03	.32	.10
Anger	.48	.00	.25	.02
Self-efficacy	-.82**	-.18	-.05	-.68**
		Pain tolerance		
Anxiety	-.42	-.44	-.11	-.21
Discouragement	-.29	-.37	-.25	-.16
Anger	-.74**	-.41	-.08	-.11
Self-efficacy	.33	.03	.18	.55*

Note. *p<.05;**p<.01.

[18] The inverse relationship between UP and self-efficacy in depressed naltrexone recipients was due to an outlying value (see Figure 7.11, p 268).

Table 7.20: Summary of t-values from hierarchical regression analyses illustrating the effects of mood, drug and depression on cold pressor pain intensity, unpleasantness, and pain tolerance after the math task.

		Mood on foot cold pressor pain							
		Pain intensity				Unpleasantness			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Sf.**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
1	**Group (G)**	-0.70	-0.65	-0.59	-0.44	-0.99	-0.93	-0.89	-0.53
	Drug (D)	-1.60	-1.67	-1.71	-1.59	-1.25	-1.33	-1.37	-1.22
	Mood (M)	0.82	0.62	0.80	-1.73	0.96	0.72	0.84	-2.80**
2	**G x D**	0.42	0.27	0.27	0.55	1.15	0.98	0.82	1.22
	G x M	0.49	-0.00	-0.68	0.61	0.88	0.55	0.12	-0.03
	D x M	-0.66	-0.86	-0.64	-1.68	-0.68	-0.84	-0.90	-1.68
3	**G x D x M**	-0.61	-0.68	-0.74	-1.49	-0.04	-0.03	-0.02	-2.11*

		Pain tolerance			
Step	**Variable**	**Ax.**	**Ds.**	**Ag.**	**Sf.**
1	**Group (G)**	-0.03	-0.22	-0.44	-0.00
	Drug (D)	0.40	0.59	0.74	0.47
	Mood (M)	-2.39*	-2.18*	-2.80**	1.98[a]
2	**G x D**	0.12	-0.00	0.32	0.32
	G x M	0.92	0.32	1.41	0.47
	D x M	-0.18	0.11	0.60	0.66
3	**G x D x M**	-0.08	0.34	-0.51	1.41

Note. Step 1 = main effects model (df = 3,57); Step 2 = two-way model (df = 6,54); Step 3 = full model (df = 7,53); Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

[a]p=.053; *p<.05; **p<.01.

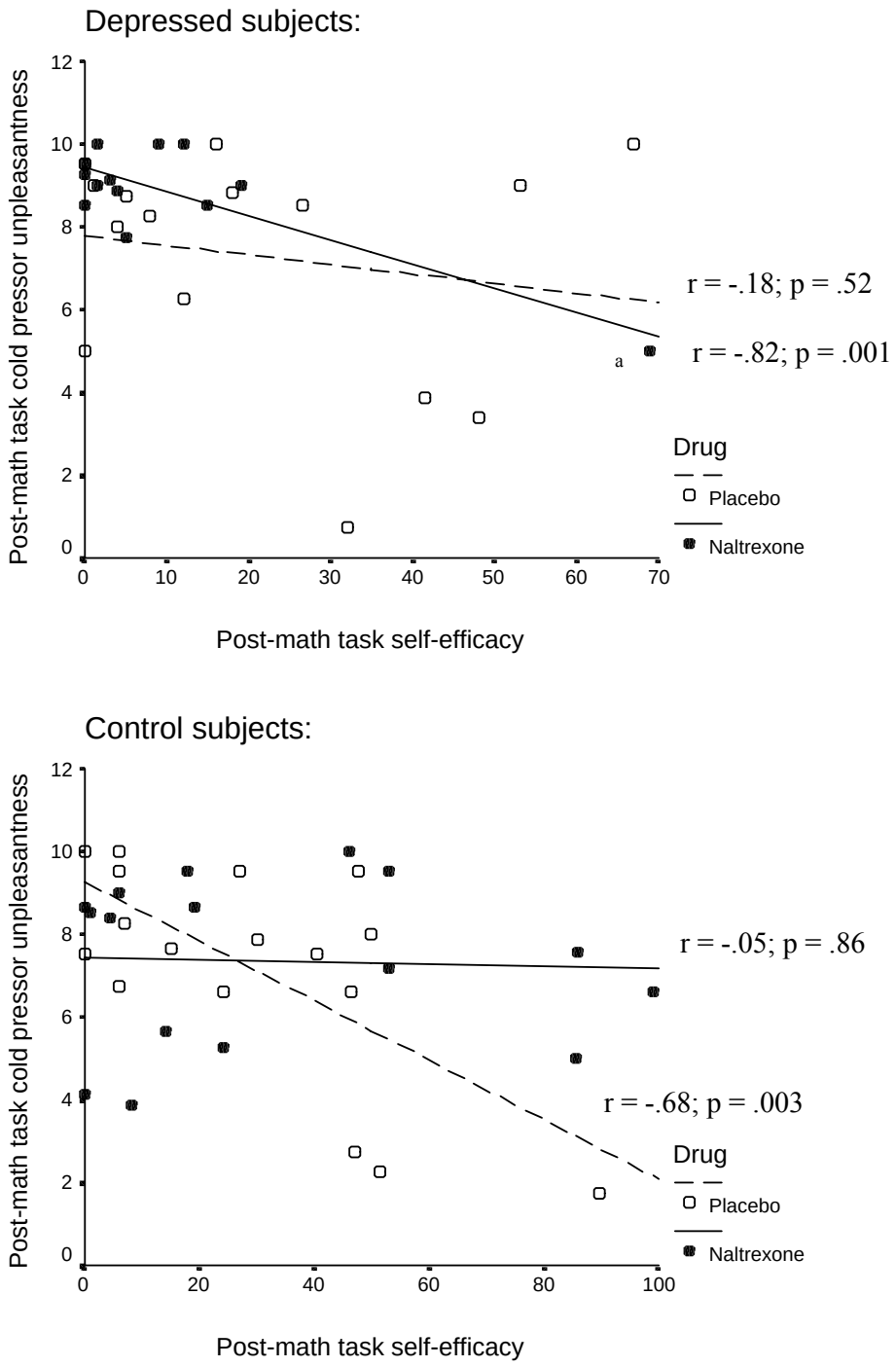


Figure 7.11: Scattergram depicting a negative relationship between self-efficacy and cold pressor unpleasantness for controls taking the placebo after the math task. [a] removal of this outlier eliminates the relationship in depressed subjects (r = .00; p = .99).

7.3.4 Blink reflex – R2 onset latency

Data considerations

Onset latency was identified as the first peak of EMG activity (after rectification) within a 27-87 msec window (Ellrich & Treede, 1998). Analyses were carried out on mean onset latencies for R2 responses ipsilateral to TS. R2 onset at the time of the first and the second CS was analysed separately to simplify interpretation of the results.

First conditioning stimulus

R2 onset was investigated in separate 2 (Group: depressed, controls) x 2 (Condition: TS, TS + CS) repeated measures ANOVAs for 2 mA, 6 mA and 10 mA shocks. Drug was not included as a factor as it was not expected to be fully absorbed at the time of the first CS. As demonstrated in Tables 7.21 and 7.22, R2 onset was delayed during the CS for shocks of all intensities. Depression did not affect R2onset at any stimulus intensity.

Table 7.21: R2 onset (msecs) during the first test and conditioning stimuli.

		Controls (N = 30[a])			Depressed (N = 27[a])		
Condition		**2mA[b]**	**6mA**	**10mA**	**2mA[b]**	**6mA**	**10mA**
TS	**M**	43.02	35.19	34.36	41.90	36.50	34.46
	SD	7.22	5.24	4.71	6.08	4.73	3.82
TS +CS	**M**	45.76	36.90	35.06	44.66	38.06	36.35
	SD	7.85	6.37	5.37	4.87	7.60	6.59

Note. M = mean; SD = standard deviation; [a] missing data; [b] The R2 component was less evident at 2 mA, hence cell numbers were smaller i.e., Controls N = 27; Depressed N = 24; TS = test stimuli (i.e, electric shocks to elicit blink reflex); CS = conditioning stimulus (i.e., hand cold pressor task).

Table 7.22: F ratios for R2 onset during the first test and conditioning stimuli.

	Test stimulus		
Source	**2mA**	**6mA**	**10mA**
Group (G)	0.48	0.67	0.29
Condition (C)	8.37**	8.49**	7.65**
C x G	0.00	0.02	1.59

Note. Degrees of freedom: 2 mA = 1,47; 6 mA and 10 mA = 1,53.

**p<.01.

Second conditioning stimulus

Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) x 2 (Condition: TS, TS + CS) repeated measures ANOVAs were calculated on mean onset latencies for 2 mA, 6 mA and 10 mA shocks. As indicated in Tables 7.23 and 7.24, inhibitory effects of the CS on R2 onset were greatly weakened at the time of the second CS. Neither group nor drug influenced R2 onset. A marginal Condition x Group x Drug effect for 6 mA shocks was explored with paired and independent t-tests (Table 7.25, Figure 7.12). R2 onset during the TS condition was significantly faster for non-depressed controls taking the placebo compared with depressed subjects taking the placebo.

Table 7.23: R2 onset during the second test and conditioning stimuli.

	Controls				Depressed			
	Naltrexone (N = 16)		Placebo (N = 17)		Naltrexone (N = 13)		Placebo (N = 15)	
Condition	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				2mA				
TS	43.64	8.14	40.75	8.39	41.71	5.70	41.11	6.41
TS +CS	43.73	8.81	42.96	9.86	42.19	6.65	43.55	7.61
				6mA				
TS	37.00	5.27	34.87	3.65	36.85	4.75	38.70	6.02
TS +CS	36.86	5.53	36.89	6.44	38.15	7.40	37.57	6.24
				10mA				
TS	34.91	5.48	35.02	5.09	35.68	4.45	35.24	4.29
TS +CS	35.05	5.02	35.31	5.84	35.63	7.20	35.77	3.98

Note. The R2 component was less evident at 2 mA, hence cell numbers were smaller i.e., Controls: naltrexone N = 13, placebo N = 16; Depressed: naltrexone N = 12, placebo N = 14; TS = test stimuli (i.e., electric shocks to elicit blink reflex); CS = conditioning stimulus (i.e., hand cold pressor task).

Table 7.24: F ratios for R2 onset during the second test and conditioning stimuli.

	Test stimulus		
Source	**2mA**	**6mA**	**10mA**
		Between subjects	
Group (G)	0.11	1.08	0.16
Drug (D)	0.14	0.02	0.00
G x D	0.33	0.39	0.02
		Within subjects	
Condition (C)	1.85	0.80	0.25
C x G	0.03	0.55	0.00
C x D	1.12	0.01	0.16
C x G x D	0.00	3.96[a]	0.05

Note. Degrees of freedom: 2 mA = 1,51; 6 mA = 1,57; 10 mA = 1,56.

[a]p=.051.

Table 7.25: T-test comparisons of R2 onset for 6 mA shocks in experimental conditions during the second test and conditioning stimuli.

	Depressed			Controls			Both	
Drug	**TS**	**TS + CS**	**t**	**TS**	**TS + CS**	**t**	**t^{TS}**	**t^{TS+CS}**
N	36.85	38.15	-0.91	37.00	36.86	0.16	-0.08	0.53
P	38.70	37.57	0.94	34.87	36.89	-1.77	2.20*	0.30
t	-0.89	0.22		1.35	-0.01			

Note. TS = test stimuli (i.e., electric shocks used to elicit the blink reflex); CS = conditioning stimulus (i.e., hand cold pressor task); N = naltrexone; P = placebo; t^{TS} and t^{TS+CS} refers to between drug/group comparisons for the TS and TS + CS conditions, respectively.

*p<.05.

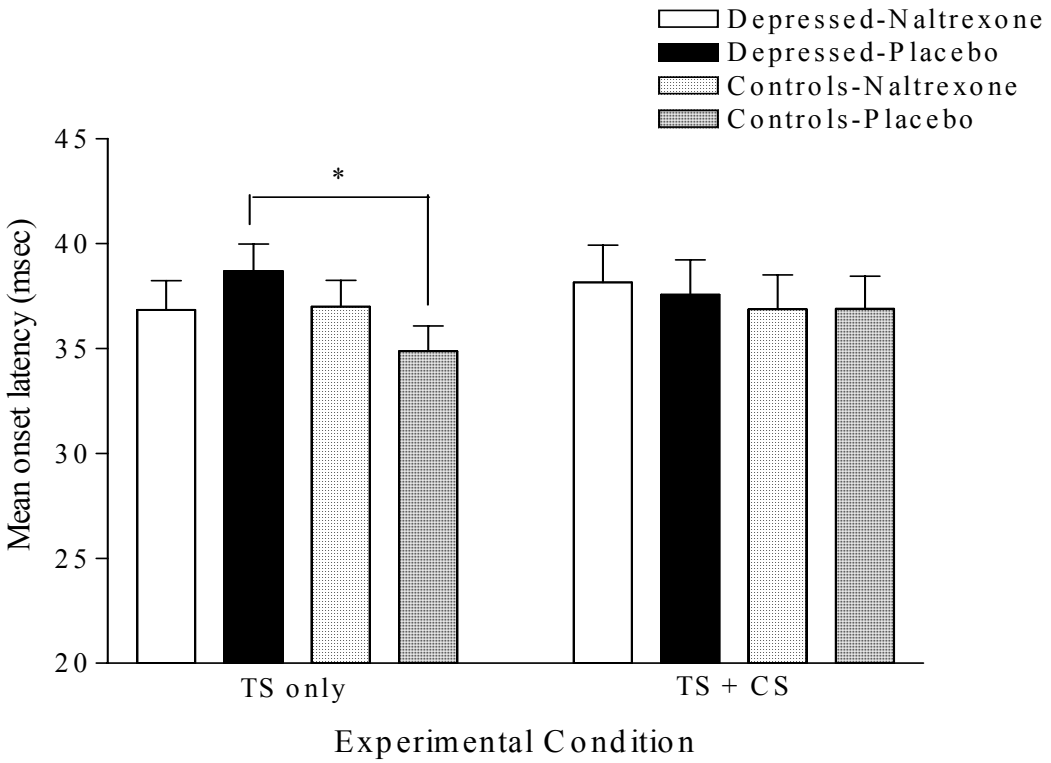


Figure 7.12: R2 onset latencies to 6mA shocks during the post-drug test and conditioning stimuli. Note. *p<.05, between group comparison.

Effect of the math task on R2 onset latencies

Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) x 2 (Time: TS conditions before and after math task) repeated measures ANOVAs were calculated for 2 mA, 6 mA and 10 mA shocks (Table 7.26 and 7.27). The onset of R2 to 10 mA shocks was facilitated after the math task (pre-maths M = 35.38 versus post-maths M = 34.56 msec), and trended in the same direction for 6 mA shocks. Neither drug nor depression influenced R2 onset.

Table 7.26: R2 onset before and after the math task.

	Controls				**Depressed**			
	Naltrexone		**Placebo**		**Naltrexone**		**Placebo**	
TS	**(N = 16)**		**(N = 17)**		**(N = 13)**		**(N = 15)**	
condition	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				2mA				
Pre-maths	44.81	8.96	40.75	8.39	41.65	5.46	40.61	6.39
Post-maths	44.24	7.48	42.10	6.45	42.55	8.95	42.13	7.31
				6mA				
Pre-maths	37.00	5.27	34.87	3.65	36.85	4.75	38.70	6.02
Post-maths	36.32	6.16	35.43	4.65	36.84	6.54	35.93	6.50
				10mA				
Pre-maths	34.91	5.48	35.02	5.09	36.35	4.89	35.24	4.29
Post-maths	34.44	5.55	34.66	4.28	34.32	5.46	34.83	4.72

Note. The R2 component was less evident at 2 mA, hence cell numbers were smaller i.e., Controls: naltrexone N = 14, placebo N = 16; Depressed: naltrexone/placebo N = 13; TS = test stimuli (i.e., electric shocks to elicit blink reflex).

Table 7.27: F ratios for R2 onset before and after the math task.

	Test stimulus		
Source	**2mA**	**6mA**	**10mA**
	Between subjects		
Group (G)	0.45	0.78	0.12
Drug (D)	1.07	0.15	0.00
G x D	0.41	0.56	0.03
	Within subjects		
Time† (T)	0.97	2.29	5.26*
T x G†	0.25	1.93	1.28
T x D†	0.61	0.63	1.47
T x G x D†	0.16	4.37*	1.12

Note. † Pillai's Trace F ratio; degrees of freedom: 2 mA = 1,52; 6 mA and 10 mA = 1,57.
*p<.05.

Once again, a Time x Group x Drug interaction was found for 6 mA shocks (Figure 7.13). Paired t-test comparisons indicated that R2 onset was facilitated in depressed placebo recipients after the math task, whereas R2 onset remained the same in all other groups (Table 7.28). The faster pre-task onset of R2 in controls taking the placebo, in comparison to their depressed counterparts, replicated the finding established in the previous section (see *Second conditioning stimulus*, p 270). No other interactions were detected.

Table 7.28: T-test comparisons of R2 onset for 6 mA shocks in experimental conditions before and after the math task.

	Condition							
	Depressed			**Controls**			**Both**	
Drug	**Pre**	**Post**	**t**	**Pre**	**Post**	**t**	**t^{Pre}**	**T^{Post}**
N	36.85	36.84	0.00	37.00	36.32	0.86	-0.08	0.22
P	38.70	35.93	2.96*	34.87	35.43	-0.65	2.20*	0.25
t	-0.89	0.37		1.35	0.47			

Note. N = naltrexone; P = placebo; Pre = before math task; Post = after math task; t^{Pre} and t^{Post} refers to between group/drug comparisons for R2 onset before and after the math task.
*p<.05.

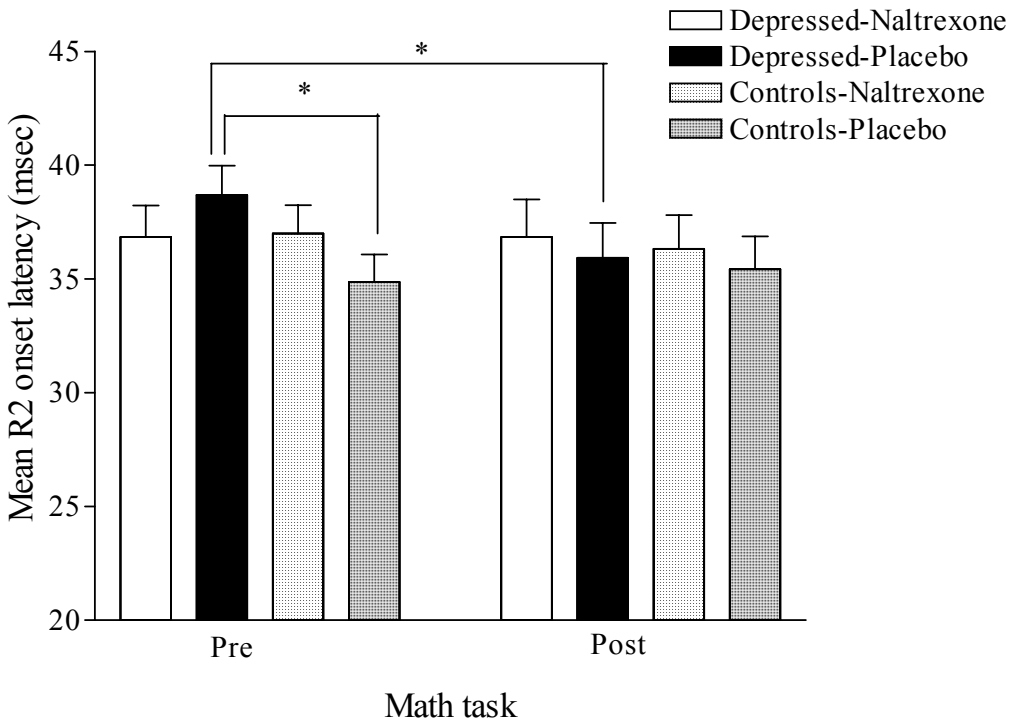


Figure 7.13: Drug and depression effects on R2 onset to 6mA shocks before and after the math task. Note. *p<.05.

7.3.5 Cardiovascular activity

Data considerations

Cardiovascular responses were measured using the same equipment and procedures at the same stage of the experiment as in Studies 2 and 3. Absolute rather than change scores were analysed for reasons mentioned in previous studies.

Randomisation check

Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) univariate ANOVAs established that equivalent SBP, DBP and pulse rates were recorded from groups at the beginning of the experiment (Table 7.29 and 7.30). Resting blood pressure and pulse rate were within normotensive ranges (Lobstein et al., 1989; McCubbin & Bruehl, 1994; O'Brien & O'Malley, 1981).

Table 7.29: Blood pressure and pulse rate before and after the drug.

	Depressed (N = 28)				Controls (N = 31)			
	Pre-drug		Post-drug		Pre-drug		Post-drug	
CVR	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				Naltrexone				
SBP	116.86	14.97	112.82	13.45	118.33	13.19	111.81	10.12
DBP	75.40	10.80	73.87	7.89	75.02	11.50	72.80	9.59
Pulse	63.83	11.61	63.18	7.81	68.36	9.18	67.94	8.51
				Placebo				
SBP	116.40	19.28	115.53	21.22	118.60	11.25	115.24	12.48
DBP	73.60	13.62	72.64	13.84	76.30	8.64	73.65	9.08
Pulse	68.26	9.33	65.18	7.86	70.42	9.92	66.45	9.05

Note. CVR = cardiovascular responses; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 7.30: F ratios for pre-drug blood pressure and pulse rate.

Source	**SBP**	**DBP**	**Pulse**
Group (G)	0.22	0.16	1.64
Drug (D)	0.00	0.01	1.54
G x D	0.01	0.27	0.20

Note. Degrees of freedom = 1,55; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Effect of the drug on cardiovascular activity

Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) x 2 (Time: pre- and post-drug) repeated measures ANOVAs were carried out on SBP, DBP and pulse rate (Table 7.29 and 7.31). BP and pulse rate had dropped significantly after 90 minutes in the experimental environment, as subjects relaxed and became more familiar with the setting and experimental procedures (SBP: pre-drug M = 117.55 versus post-drug M = 113.51; DBP: M = 75.08 versus M = 73.20; Pulse M = 67.72

versus M = 65.51). No main effect was found for drug, indicating that naltrexone did not influence cardiovascular activity at rest (McCubbin et al., 1996).

Table 7.31: F ratios for blood pressure and pulse rate before and after the drug.

Source	SBP	DBP	Pulse
		Between subjects	
Group (G)	0.01	0.04	1.78
Drug (D)	0.12	0.01	0.54
G x D	0.00	0.20	0.48
		Within subjects	
Time† (T)	19.42**	6.00*	6.34*
T x G†	2.99	0.70	0.15
T x D†	2.35	0.00	3.29
T x G x D†	0.04	0.18	0.18

Note. † Pillai's Trace F ratio; degrees of freedom = 1,55; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
*p<.05; ** p<.01.

Effect of the math task on cardiovascular activity

BP and pulse rate were measured at 2-minute intervals throughout the length of the task (28 minutes). To simplify interpretation, measures were averaged across two intervals (of 14 minutes each). Separate 2 (Group: depressed, controls) x 2 (Drug: naltrexone, placebo) x 4 (Time: pre-task, task interval 1-14 minutes and 15-28 minutes, post-task) repeated measures ANOVAs were carried out on SBP, DBP and pulse rate (Tables 7.32 and 7.33).

Planned simple contrasts were used to explore Time effects for blood pressure and pulse rate (Table 7.34). When compared to pre-task levels, SBP and DBP remained significantly higher during and after the task. Pulse rate increased significantly during the first 14 minutes of the math task, but returned to pre-task rates towards the end of the math task and after it was completed. Cardiovascular reactivity did not differ between groups.

Table 7.32: Blood pressure and pulse rate before, during and after the math task.

Blood pressure		Depressed (N = 27[a])				Controls (N = 33)			
			Maths task				Maths task		
		Pre	1	2	Post	Pre	1	2	Post
					Naltrexone (N = 29)				
SBP	**Mean**	112.82	121.57	121.11	119.96	113.67	122.57	121.30	117.38
	SD	13.4	15.6	16.5	17.2	8.2	16.0	15.0	15.2
DBP	**Mean**	73.87	81.02	80.61	78.96	74.17	79.96	77.60	75.66
	SD	7.9	10.4	10.2	9.7	6.8	12.8	10.8	10.8
Pulse	**Mean**	63.18	64.04	64.24	63.00	68.79	70.39	66.01	68.71
	SD	7.8	7.0	5.9	8.5	9.1	8.5	12.4	10.27
					Placebo (N = 31)				
SBP	**Mean**	118.33	122.51	122.34	115.78	116.35	128.78	125.47	120.53
	SD	21.4	16.8	16.4	19.4	12.0	13.0	14.9	12.21
DBP	**Mean**	73.74	80.73	77.57	73.51	73.85	83.15	82.06	78.27
	SD	14.6	12.9	13.9	13.95	9.3	7.0	8.9	10.72
Pulse	**Mean**	65.29	67.10	66.80	66.30	66.23	70.88	68.21	67.57
	SD	7.8	7.6	5.2	8.87	9.3	11.5	13.7	7.85

Note. [a]N=1 missing data; Math task 1 and 2 = 1-14 minutes and 15-28 minutes, respectively; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

Table 7.33: F ratios comparing blood pressure and pulse rate before, during and after the math task.

Source	SBP	DBP	Pulse
		Between subjects	
Group (G)	0.07	0.02	2.35
Drug (D)	0.50	0.01	0.44
G x M	0.18	0.87	0.43
		Within subjects	
Time† (T)	20.86***	26.15***	2.84*
T x G†	1.84	0.10	1.73
T x D†	1.03	0.78	0.29
T x G x D†	0.94	1.23	0.43

Note. † Pillai's Trace F ratio; degrees of freedom: within S's = 3,54; between S's = 1,56;
SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
*p<.05; ***p<.001.

Table 7.34: Simple contrasts[a] of blood pressure and pulse rate before, during and after the math task.

		Maths task		
Blood Pressure	**Pre-task**	**1**	**2**	**Post-task**
SBP	114.24	123.85***	122.55***	118.92***
DBP	73.32	81.22***	79.50***	76.85***
Pulse	65.71	68.10*	66.31	66.43

Note. [a] pre-task measure is the point of comparison; Math task 1 and 2 = 1-14 and 15-28 minutes, respectively; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute;
*p<.05; ***p<.001.

Association between cardiovascular activity and task shock sensitivity

Pearson product correlations (Table 7.35) and hierarchical multiple linear regression analyses (Table 7.36) were used to explore the association between cardiovascular response and task shock sensitivity.

DBP was negatively associated with shock PI (r = -.34; p = .008) and UP (r = -.40; p = .002), where higher DBP was related to lower shock sensitivity. The association between SBP and task shock sensitivity trended in the same direction, but did not reach statistical significance (PI: r = -.19, p = .15; UP: r = -.24, p = .07). A Drug x Pulse effect was found for task shock UP. Although these relationships were not significant (Figure 7.14), naltrexone appeared to antagonise an opioid-mediated inhibition of shock UP in subjects experiencing higher pulse rates during the math task.

Depressed subjects experienced the shocks as significantly more unpleasant than non-depressed subjects (M = 62.57 versus 51.26; t (58) = -2.06; p =.04). The difference between depressed and non-depressed subjects reached significance in this t-test analysis and not in the univariate ANOVA (Table 7.11) as a degree of freedom associated with the *Drug* factor was lost in the ANOVA.

Table 7.35: Pearson correlations between pulse rate, systolic and diastolic blood pressure and pain and unpleasantness ratings for task shocks.

	Depressed				**Controls**			
	Naltrexone (N = 12)		**Placebo (N = 15)**		**Naltrexone (N = 16)**		**Placebo (N = 17)**	
CVR	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**	**PI**	**UP**
SBP	.00	.00	-.38	-.53*	-.24	-.18	-.07	-.19
DBP	-.14	-.15	-.42	-.60*	-.48	-.48	-.22	-.35
Pulse	.29	.36	-.23	-.35	.22	.37	-.12	-.17

Note. PI = pain intensity; UP = unpleasantness; CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
*p<.05.

Table 7.36: Summary of t-values from hierarchical linear regression analyses illustrating the effects of depression, drug, blood pressure and pulse rate on task shock pain and unpleasantness ratings.

		Math task shocks					
		Pain intensity			Unpleasantness		
Step	**Variable**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**
1	**Group (G)**	-0.97	-1.06	-1.15	-1.84	-2.03*	-2.05*
	Drug (D)	0.56	0.65	0.39	0.22	0.31	0.03
	CVR	-1.37	-2.72**	0.21	-1.66	-3.26**	0.35
2	**G x D**	-0.32	-0.14	-0.14	0.04	0.26	0.30
	G x CVR	0.08	-0.43	0.07	0.07	-0.68	0.21
	D x CVR	-0.27	0.01	-1.46	-0.80	-0.53	-2.28*
3	**G x D x CVR**	0.98	0.64	0.87	0.77	0.45	0.91

Note. Step 1 = main effects model (df = 3,56); Step 2 = two-way model (df = 6,53); Step 3 = full model (df = 7,52); CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.
*p<.05; **p<.01.

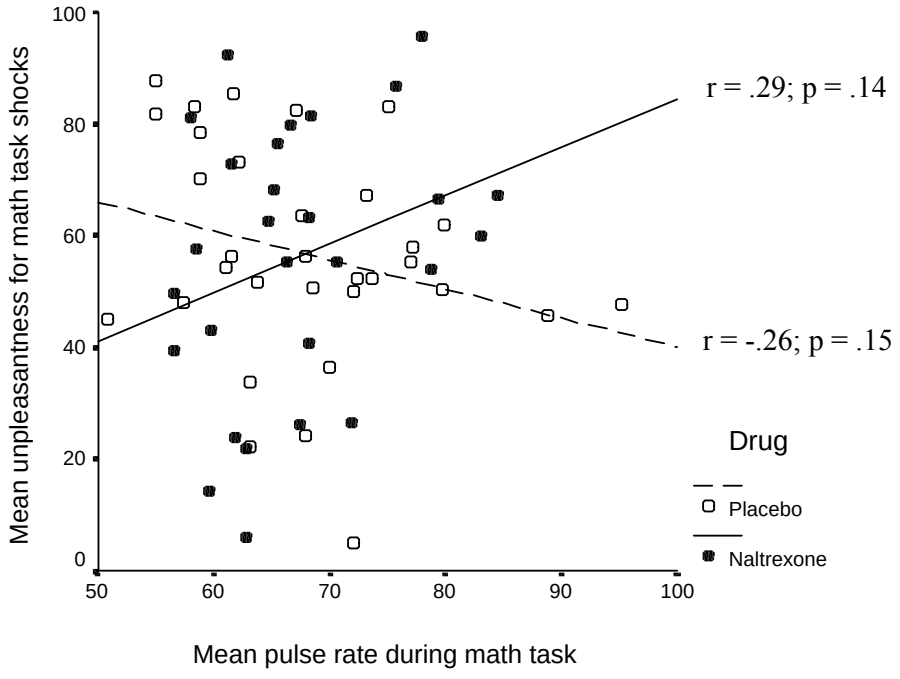


Figure 7.14: Scattergram depicting the relationship between diastolic blood pressure and task shock unpleasantness ratings for naltrexone and placebo recipients during the math task.

Association between cardiovascular activity and foot cold pressor pain perception

The association between resting cardiovascular activity and cold pressor pain perception (assessed immediately after cardiovascular measures) was explored with correlational and hierarchical regression analyses (Table 7.37 and 7.38). Before the math task, high SBP was associated with high pain tolerance and low pain sensitivity during the fCPT in controls taking the placebo (Figures 7.15 – 7.17). Endogenous opioids apparently inhibited pain in controls with high SBP, but not in depressed participants. A similar effect was detected for pain tolerance after the math task (Figure 7.18).

Table 7.37: Pearson correlations between pulse rate, systolic and diastolic blood pressure and foot cold pressor pain indices before and after the math task.

	Depressed						**Controls**					
	Naltrexone (N = 13)			**Placebo (N = 15)**			**Naltrexone (N = 16)**			**Placebo (N = 17)**		
fCPT	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**	**SBP**	**DBP**	**Pulse**
						Pre-math task						
Tol.	.41	.20	-.44	.29	.17	.07	-.18	.29	-.13	.53*	.27	-.17
PI	-.61*	-.15	-.18	-.19	-.09	.06	.32	-.03	.17	-.51*	-.21	.07
UP	-.63*	-.18	-.05	-.17	-.08	.10	.35	-.20	.25	-.35	-.04	.25
						Post-math task						
Tol.	.52	.39	-.34	-.01	-.09	.09	.15	.27	.06	.68*	.32	-.09
PI	-.40	-.45	-.05	-.16	-.02	.08	-.03	-.15	.05	-.57*	-.22	.12
UP	-.50	-.59*	.11	-.08	-.02	.10	.05	-.21	.10	-.47	.00	.24

Note. SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute; fCPT = foot cold pressor task; Tol. = pain tolerance (seconds); PI = pain intensity; UP = unpleasantness.

*p<.05.

Table 7.38: Summary of t-values from hierarchical linear regression analyses illustrating the effects of depression, drug, blood pressure and pulse rate on foot cold pressor pain indices before and after the math task.

		Foot cold pressor pain index								
		Pain tolerance			Pain intensity			Unpleasantness		
Step	Variable	SBP	DBP	Pulse	SBP	DBP	Pulse	SBP	DBP	Pulse
		Pre-math task								
1	Group (G)	0.42	0.37	0.58	-0.83	-0.77	-0.83	-1.28	-1.23	-1.44
	Drug (D)	0.66	0.89	0.88	-1.07	-1.26	-1.25	-0.61	-0.76	-0.77
	CVR	2.13*	1.72	-1.25	-1.89	-0.87	0.43	-1.36	-0.77	1.21
2	G x D	0.14	0.07	-0.14	0.16	0.15	0.12	0.52	0.60	0.60
	G x CVR	0.07	0.46	0.19	-0.42	-0.36	0.40	0.32	-0.03	0.68
	D x CVR	0.48	-0.31	0.82	-0.96	-0.42	0.16	-0.57	0.39	0.29
3	G x D x CVR	2.02*	0.23	-1.09	-2.24*	-0.47	-0.42	-2.05*	0.12	-0.25
		Post-math task								
1	Group (G)	0.45	0.47	0.59	-0.86	-0.88	-0.98	-1.21	-1.22	-1.39
	Drug (D)	0.63	0.67	0.61	-1.74	-1.74	-1.70	-1.36	-1.37	-1.38
	CVR	2.30*	1.46	-0.39	-1.85	-1.02	0.42	-1.36	-0.64	0.86
2	G x D	0.04	0.08	0.13	0.73	0.63	0.40	1.35	1.31	1.10
	G x CVR	0.97	0.71	0.39	-0.79	-0.28	0.21	-0.49	0.32	0.36
	D x CVR	-0.02	-0.79	0.42	-1.08	0.23	0.43	-0.69	1.01	0.55
3	G x D x CVR	2.28*	1.02	-1.07	-1.51	-0.68	-0.03	-1.71	-0.33	0.33

Note. Step 1 = main effects model (df = 3,56); Step 2 = two-way model (df = 6,53); Step 3 = full model (df = 7,52); CVR = cardiovascular response; SBP and DBP = systolic and diastolic blood pressure, respectively (scale = mmHg); Pulse = heart beats per minute.

*p<.05.

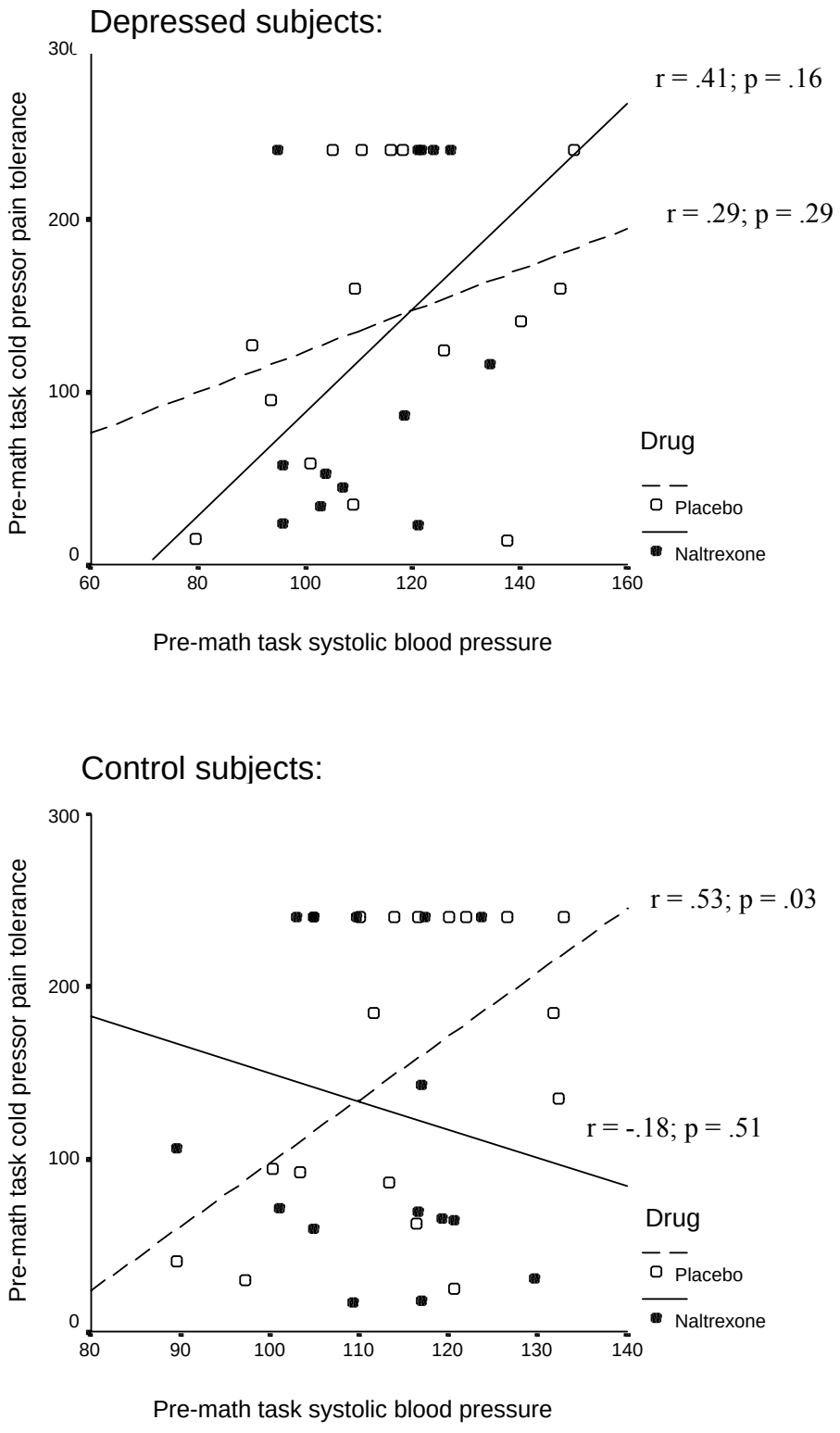


Figure 7.15: Scattergrams depicting a positive relationship between systolic blood pressure and cold pressor pain tolerance in non-depressed controls taking the placebo before the math task.

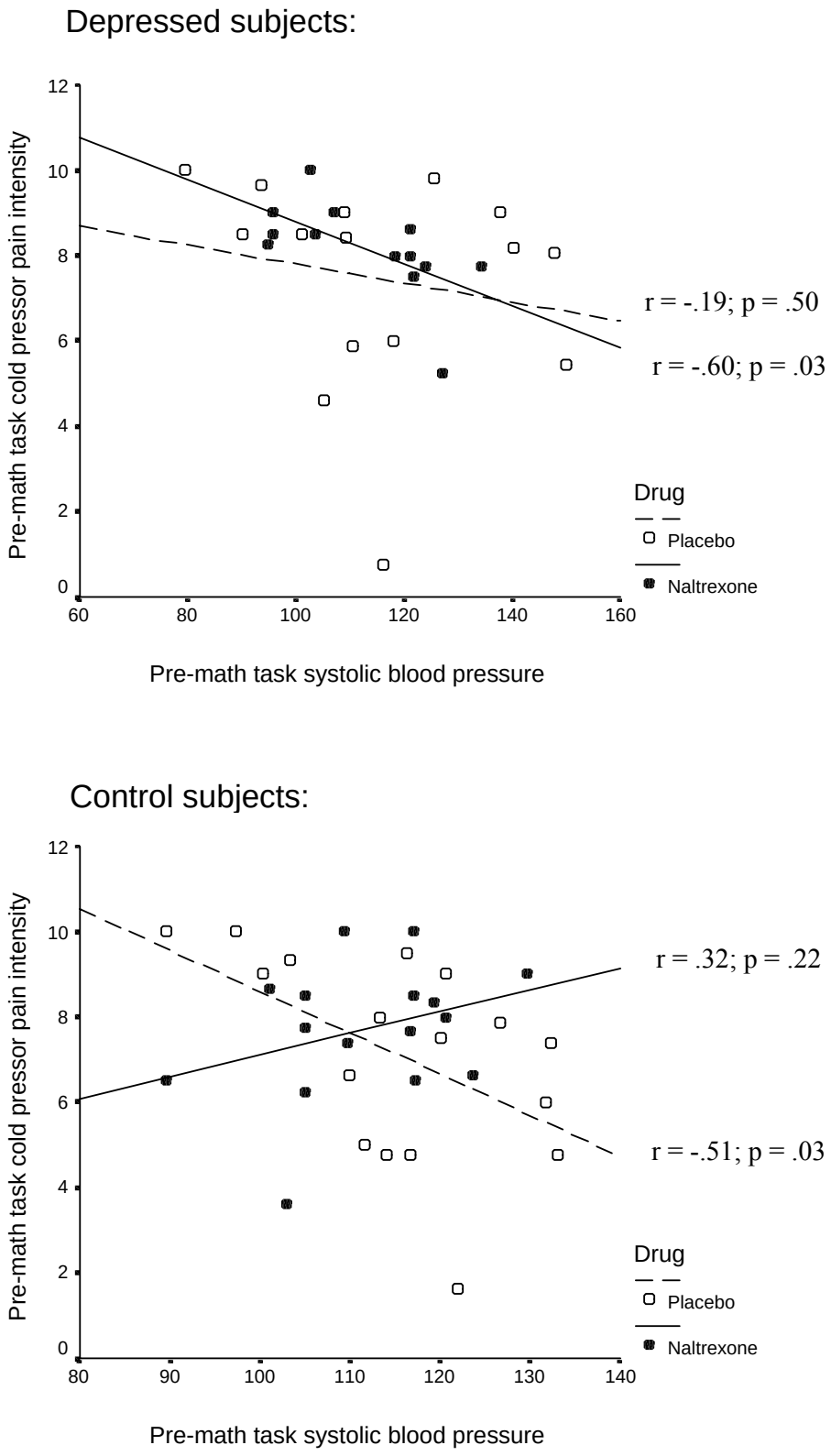


Figure 7.16: Scattergrams depicting a negative relationship between systolic blood pressure and cold pressor pain intensity in non-depressed controls taking the placebo and depressed naltrexone recipients before the math task.

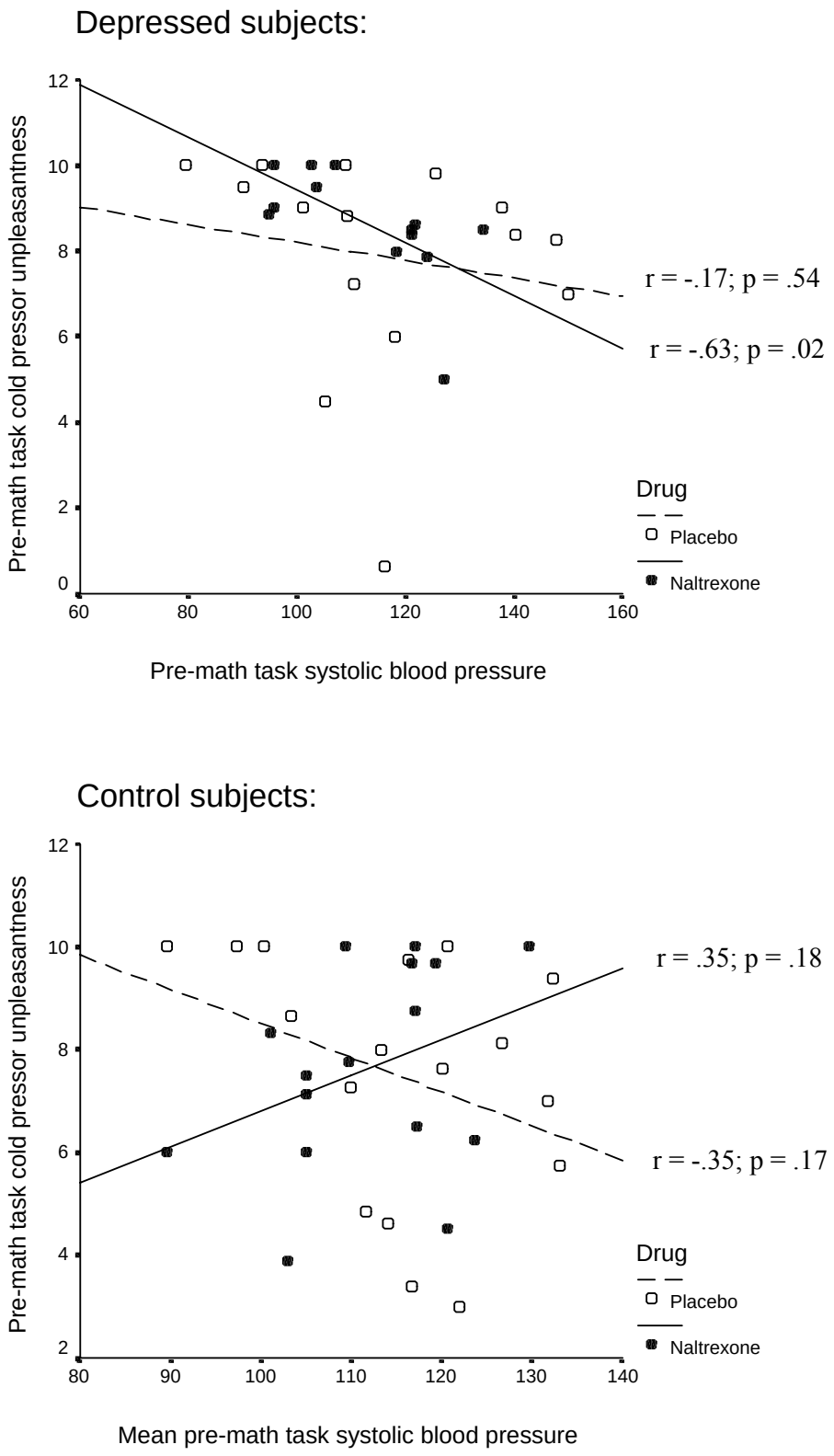


Figure 7.17: Scattergrams depicting a negative relationship between systolic blood pressure and cold pressor unpleasantness in depressed naltrexone recipients before the math task

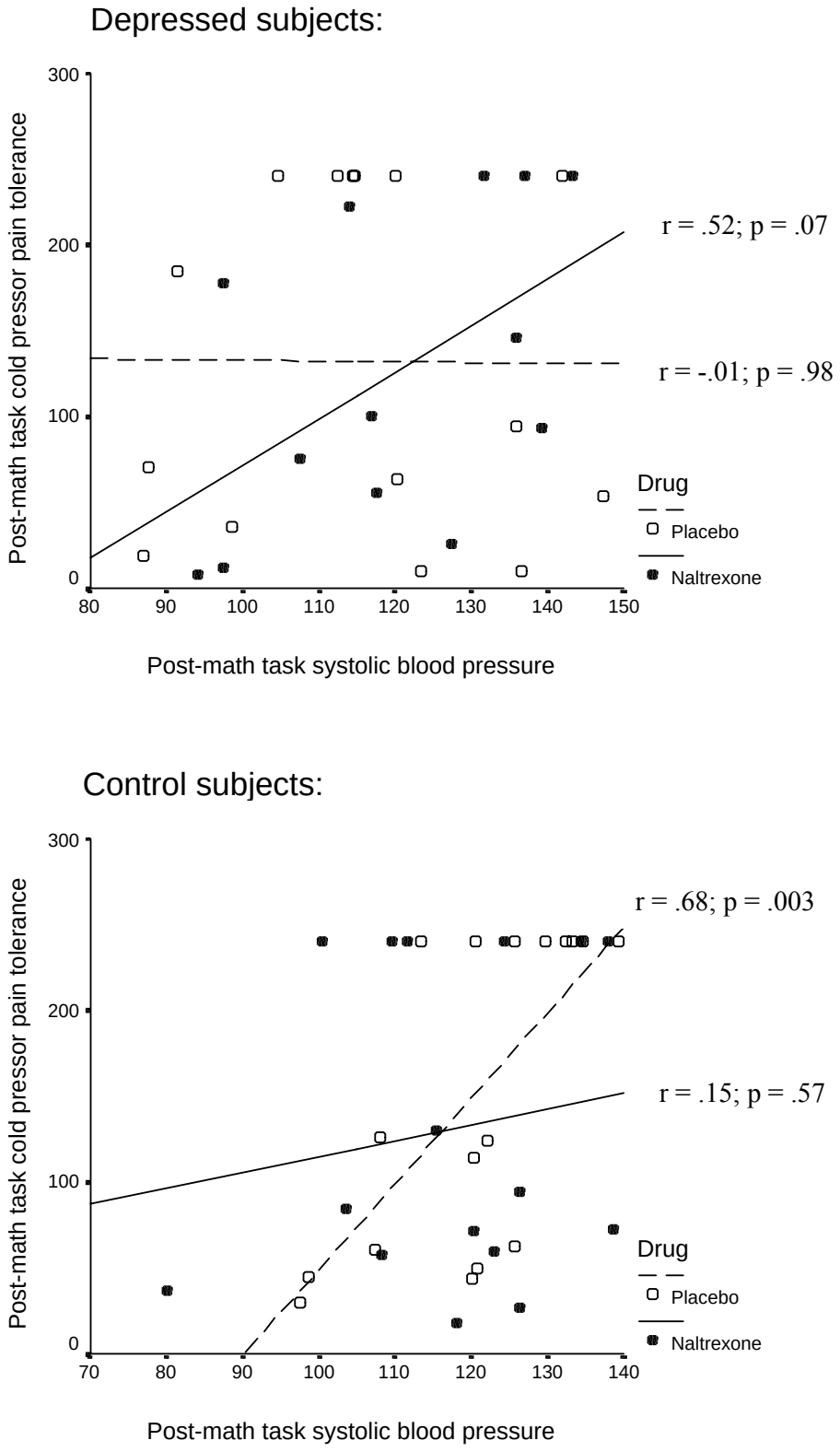


Figure 7.18: Scattergrams depicting a positive relationship between systolic blood pressure and cold pressor pain tolerance in non-depressed controls taking the placebo after the math task.

7.4 DISCUSSION

7.4.1 Summary of major findings

Salient points to emerge from the present study were:

- Acute pain sensitivity, opioid-mediated stress induced analgesia, and inhibition of the nociceptive component of the blink reflex (R2) were similar in depressed and non-depressed subjects.
- Opioidergic mechanisms mediated inhibitory effects of discouragement and anxiety on electrical and, to a lesser extent, cold-induced pain in both groups.
- High self-efficacy was associated with opioid release in both groups.
- A regulatory relationship between cardiovascular activity (during stress and at rest) and pain, appeared to be mediated by opioids more consistently in non-depressed than depressed subjects.

7.4.2 Subject selection

The process by which depressed and non-depressed control subjects were selected was effective in that depressed subjects reported significantly higher levels of (pre-experimental) anxiety, depression and stress than non-depressed controls on well-established psychological scales (State-Trait Anxiety Inventory, Depression, Anxiety, Stress Scales, BDI-II). In comparison to the general adult population, controls reported psychological symptomatology that reflected normal, and in some cases (i.e., state/trait anxiety), lower than normal levels of distress. Diagnoses of major depression (according to the SCID-CV - First et al., 1997) concurred with self–reported psychopathology. Responses to questionnaires demonstrated the presence of a severe depressive syndrome with co-morbid moderate to severe levels of anxiety and stress in depressed subjects. Groups were matched successfully for age and demographics. Similar numbers of males and females were included in each cell.

7.4.3 Success of experimental manipulations

The math task was a powerful cognitive stressor that led to significant increases in negative mood in both groups. Increases in anxiety were opposed by endogenous opioids mid-way through the task and, as mood was not affected by naltrexone per se, increasing anxiety in the naltrexone condition could be attributed to the math task. Moreover, the math task led to double the stress-induced cardiovascular reactivity of similar tasks used, despite being three times the duration (30 mins versus 10 mins in McCubbin et al., 1996). Sizable elevations in BP could have been due to the constant threat and actual delivery of noxious electric shocks, an element not present in the task employed by McCubbin et al. (1996). Pulse rate increased significantly during the first 14 minutes of the math task, but returned to pre-task rates towards the end of the task and experiment. Increases in heart rate represent mental effort or mental load, whereas increases in BP reflect both effort and lack of control (Ettema & Zielhuis, 1971; Peters, Godaert, Ballieux, van Vliet, Willemsen, Sweep, & Heijnen, 1998). Therefore, after 14 minutes the novelty of the math task may have worn off, and subjects may not have been expending as much effort. Alternatively, an increase in BP leads to a slowing of the heart by reflex signals from the vasomotor centre (i.e., the 'baroreceptor reflex' - Steptoe, 1980). This reflex plays an important role in the regulation of arterial pressure and maintenance of cardiovascular homeostasis (Andreassi, 1989). Therefore, in this task, baroreceptors may have responded to prolonged elevations in arterial pressure by slowing the heart during the second part of the task to prevent further increases in BP. Finally, increases in negative mood and blood pressure were strong enough to persist several minutes beyond the task.

A lack of control over aversive events was successfully manipulated during the math task, as perceived self-efficacy (to control shocks) decreased significantly after the practice trials. All methods of pain induction (CS i.e., hand CPT, task shocks, fCPT) proved to be valid, as they induced a ‘moderate’ to ‘somewhat severe’ level of PI and UP.

7.4.4 Pain sensitivity in depression

Depression is associated with higher pain thresholds (Adler & Gattaz, 1993; Bar et al., 2003; Lautenbacher et al., 1994; Marazziti et al., 1998), higher pain tolerance (Bar et al., 2003), lower acute pain sensitivity (Dworkin et al., 1995) and reduced somatosensory evoked potentials to painful stimuli (Davis et al., 1979). However, in the present study similar numbers of depressed and non-depressed subjects endured pre- and post-maths fCPT for the maximum time. Also, the average time in the water did not differ across these groups. Although seemingly divergent, the findings of the current study support those of others who have found that pain thresholds for ischemic (Pinerua-Shuhaibar et al., 1999) and electrical pain (Kudoh et al., 2002) do not differ between depressed and psychiatrically healthy participants.

A lack of difference in pain sensitivity in depressed and non-depressed subjects failed to support the notion of opioid hyperactivity in depression (Marazziti et al., 1998). Furthermore, the present results do not support the hypotheses that depressed individuals adopt a stoical approach to pain (Dworkin et al., 1995), or that depression lowers pain sensitivity through attentional mechanisms (Dickens et al., 2003). Perhaps the selection of control subjects (i.e., self-selection from the community) contributed to the lack of differences in PI between the groups. That is, controls may have been emotionally more robust than subjects in Studies 1-3, and thus more likely to display a similar level of stoicism to pain as depressed subjects.

Although depressed subjects responded similarly to controls to sensory aspects of pain, they reported marginally more UP during both types of pain stimuli (ANOVA results: task shocks $p = .07$; fCPT $p = .19$). Despite higher thresholds to experimentally induced pain, the unpleasantness of pain stimuli (Lautenbacher et al., 1999) and post-operative pain complaints (Kudoh et al., 2002) are often higher in depressed than non-depressed subjects. Similarly, in non-depressed subjects experimentally induced depressed mood can increase catastrophising about pain, whilst not influencing pain sensitivity or intensity (Willoughby, 2000; Willoughby et al., 2002). These findings have been attributed to the impact of depressed mood on affective components of pain appreciation (Jain & Russ, 2003). In accordance with

these findings, major depression may have affected the emotional response, and not sensitivity to or intensity of experimentally induced pain.

7.4.5 Opioid-mediated stress-induced analgesia (SIA) in depression

The mediation of SIA by endogenous opioids under certain circumstances, and the notion that the endogenous opioid system may be compromised in depression due to chronic activation (Besson, Privat, Eschalier, & Fialip, 1999) suggests that opioid-mediated pain inhibitory mechanisms may be weakened in depressed individuals. A similar hypothesis has been proposed and empirically assessed for chronic pain patients (Bruehl et al., 1999), but not in subjects with major depression. The current study aimed to investigate the role of endogenous opioids in major depression by subjecting depressed and non-depressed participants to an uncontrollable cognitive stressor that provoked opioid-mediated SIA. The first hypothesis that this study sought to test was that after psychological stress naltrexone would increase pain sensitivity in non-depressed subjects, but not in depressed subjects. Assessment of pain sensitivity to two types of noxious stimuli, i.e., electrical shocks during the math task and cold pressor stimuli before and after the math task, enabled measurement of an immediate and delayed analgesic response.

Electric shock sensitivity

In general, pain sensitivity to task shocks was not affected by opioid blockade in either non-depressed or depressed subjects. However, an exception to this general rule was detected in a subgroup of discouraged and anxious subjects (see *7.4.7 Modulation of pain by negative mood*, p 294).

Decreased sensitivity to sustained cold pressor stimuli

Although a drug x time interaction failed to reach significance, pair-wise comparisons indicated decreased cold pressor PI and UP after the math task in depressed *and* control subjects taking the placebo. No change was found in the naltrexone group. This finding did not support the hypothesis that effects of naltrexone would be greater in non-depressed than depressed subjects, implying that

the involvement of opioid mechanisms in SIA was not compromised in depression. Generally speaking, evidence of opioid-mediated SIA after an uncontrollable stressor in the current study is consistent with previous findings from animals (Maier, 1986; Maier et al., 1982; Watkins & Mayer, 1986) and psychiatrically-healthy humans (Flor et al., 2002; Janssen & Arntz, 2001).

Cold pressor pain tolerance was not affected by the math task, depression or opioid blockade. As previously established (Blitz & Dinnerstein, 1968; Gelfand, 1964; Wolff et al., 1965), non-permissive instructions and other methodological factors such as benign labelling of cold pressor sensations (Hirsch & Liebert, 1998) can significantly influence pain tolerance in healthy subjects (Neumann et al., 1997). Thus, the lack of change in pain tolerance across time may be attributed to methodological influences such as non-permissive instructions and demand characteristics during the fCPT. Furthermore, methodological elements may have overridden the influence of any other factor on endogenous analgesia. Therefore, when compared with subjective pain ratings, pain tolerance may have been influenced by methodological factors making this a less sensitive measure of pain transmission and inhibition.

7.4.6 Inhibition of the nociceptive blink reflex in depression

The R2 component of the blink reflex is mediated by wide dynamic range neurones, which are activated by both innocuous and noxious stimuli, and which are inhibited by remote noxious stimuli (Ellrich & Treede, 1998; Hu, 1990; Le Bars et al., 1979b). This pain inhibitory mechanism, termed DNIC, is believed to operate by suppressing the activity of wide dynamic range neurones located in the medial section of the dorsal horn, trigeminal nucleus in cervical spinal segments, and spinoreticular and spinothalamic tracts in the spinal cord (Le Bars et al., 1979a; Le Bars et al., 1979b). Since R2 inhibition is believed to be mediated by opioids (Boureau et al., 1978; Boureau et al., 1979; Pomeranz & Warma, 1988; Willer et al., 1982b), it was hypothesised that R2 onset would be facilitated under opioid blockade in non-depressed subjects, but not in depressed subjects due to deficits in the opioid system (Beutler et al., 1986).

R2 onset to innocuous (2 mA) and noxious intensities (6 mA, 10 mA) was delayed by the application of the first CS prior to drug administration. These effects were consistent with DNIC. Unexpectedly, however, this occurred in all subjects. Since the suppression of R2 occurs via brainstem reticular nuclei, and DNIC reveal the status of descending reticular brainstem pathways (Esteban, 1999), these results suggest that descending pain inhibitory mechanisms are fully functional in depressed subjects.

During the second CS after drug absorption, inhibition of R2 failed to reach significance at any intensity. Non-painful heterotopically applied stimuli have no effect on the R2; therefore, the second CS may have been perceived to be less noxious. This hypothesis seems unlikely since PI and UP ratings suggest that the second task was just as noxious as the first. The involvement of the cerebral cortex and medullary structures (i.e., lateral reticular formation) in R2 responses makes this component highly susceptible to suprasegmental influences. For example, Cruccu et al. (1991) found marked reductions in R2 with diazepam (an anti-anxiety drug), whilst Esteban (1999) found that the R2 was modulated when subjects were distracted with a cognitive task (e.g., mental arithmetic). Therefore, facilitatory effects of suprasegmental influences such as negative mood may have masked inhibitory influences such as DNIC on the R2.

Before the math task, R2 onset during the second round of TS (without the CS) was significantly delayed in depressed subjects taking the placebo, compared to their non-depressed counterparts. R2 in depressed subjects may have been inhibited by an early activation of the endogenous opioid system observed during other experimental stressors such as the pre-math task fCPT (see *7.4.7 Modulation of pain by negative mood*, p 294).

After the math task, R2 was facilitated during nociceptive shocks (10 mA; trending for 6mA). As mentioned, R2 is highly susceptible to suprasegmental influences such as anxiety (Cruccu et al., 1991). Hence, increases in negative affect induced by the math task could have facilitated R2. Finally, R2 onset to 6 mA shocks was facilitated in depressed subjects taking the placebo after the math task. Although opioid activation was expected to inhibit R2 after the math task, strong facilitatory effects of

negative affect on this nociceptive reflex appear to have overpowered the inhibitory action of opioids in depressed subjects. Nonetheless, this finding is curious and requires replication. Larger numbers in each cell may help to clarify this effect.

7.4.7 Modulation of pain by negative mood

Absolute mood scores were regressed onto cold pressor and task shock PI and UP ratings to investigate whether mood modulated experimentally induced pain in depressed and non-depressed subjects. Absolute mood was analysed (rather than change in mood) to accurately represent the substantial differences in negative mood between depressed and non-depressed subjects. For instance, a similar degree of change would not result in equivalent mood states between groups, making change scores difficult to interpret.

Electrical pain inhibition

In contrast to Studies 2 and 3, anxiety and discouragement was positively associated with shock PI in subjects taking naltrexone, but not the placebo. At a glance, this finding appears contradictory as similar mood ratings were found between Studies 2, 3 and 4. However, subjectively rated mood using VAS offers an approximation of how a subject is feeling, and may not accurately reflect their total experience. Moreover, similar VAS mood scores may not represent similar experiences across studies and subjects. Drawing subjects from different populations may have resulted in considerably different testing experiences. For instance, university students in Studies 2 and 3 would have been familiar with the university environment, and perhaps more confident with experimental procedures than subjects selected from the community. In contrast, subjects selected from the community may have been fearful about the novel setting and procedures, and more discouraged by their failure during the math task. Finally, opioid activation may be explained by considerably more noxious procedures in the final study, including three (not two) CPTs prior to the math task.

As found with PI ratings, discouragement was positively associated with shock UP in both groups receiving naltrexone. Anxiety, on the other hand, was associated with

higher shock UP in depressed, but *not* control, subjects under opioid blockade. In contrast, anxiety was positively associated with shock UP in controls regardless of naltrexone. Different interpretations of the meaning of 'anxiety' may account for group differences. For instance, anxiety, a moderately arousing emotion, facilitates pain UP (Ahles et al., 1983; Gracely et al., 1978; Rhudy & Meagher, 2000; Rhudy & Meagher, 2001a; Rhudy & Meagher, 2001b); whereas fear, although on the same continuum only more arousing, inhibits pain (Rhudy & Meagher, 2000; Rhudy & Meagher, 2001a; Willer et al., 1981). Hence, it is possible that depressed subjects were reporting fear and fearful expectations of shocks at the higher end of the 'anxiety' scale, which in turn resulted in an opioid-mediated reduction in shock UP. Controls, on the other hand, may have been rating anxiety, which heightened the UP of each shock. Alternatively, anxiety may lead to, or be associated with opioid release in depressed subjects but not controls. This explanation is consistent with the findings of Darko et al. (1992), who reported an association between symptoms of anxiety and plasma levels of beta-endorphins in depressed patients but not controls.

In accordance with Studies 2 and 3, anger was associated with higher electrical PI and UP despite naltrexone administration. These results support a number of other studies demonstrating a positive relationship between anger and a variety of pain induction measures (Gelkopf, 1997; Janssen et al., 2001). Bruehl et al. (2002) extended these findings to chronic pain patients, where a positive anger-pressure pain association was found both in patients and controls inclined to express their anger. This relationship was not influenced by naloxone administration (Bruehl et al., 2002).

In the current study, an inverse association was found between perceived self-efficacy and shock UP, where naltrexone antagonised the effect of opioids in subjects with low self-efficacy. These results resemble those of Bandura et al. (1988), who found that perceived self-inefficacy to exert control over an aversive event led to high levels of stress and autonomic arousal, and mobilisation of the endogenous opioid system. Conversely, there was no evidence of opioid release in their self-efficacious, non-stressed subjects (Bandura et al., 1988).

Cold pressor sensitivity

Prior to the math task, discouragement was associated with increased cold pressor PI and UP in depressed subjects under opioid blockade. A similar trend appeared for anxiety and anger. In contrast, negative mood was not associated with cold pressor sensitivity in controls before the math task, suggesting that pre-existing psychopathology in depressed subjects contributed to an early release of endogenous opioids not experienced by the psychologically healthy controls.

No association was found between negative mood and cold pressor pain perception after the math task. Perhaps the novelty of the fCPT contributed to negative mood and opioid release in depressed subjects during the first task, whereas the mood-pain relationship did not develop as strongly when the task was repeated some time later. Alternatively, lower statistical power in this study may account for the failure to replicate the pain inhibitory effect of negative mood on cold pressor pain found in Studies 1-3. For instance, the non-depressed sample was considerably smaller than in the previous three studies.

In self-efficacious controls, cold pressor UP was inhibited by opioids after the math task. Similar trends, although not significant, were found for the sensory aspect of cold pressor pain in both groups. These results support Bandura's (1987) notion that highly efficacious subjects, when experiencing failing control over an aversive event, will become distressed which in turn would lead to the release of opioids. Opioid activation in controls suggested that they responded with more distress to their lack of control over the task than depressed subjects. In their hopeless state, depressed subjects may have expected, or were familiar with their lack of control. Although these results seem to contradict findings with shocks, where naltrexone antagonised the effects of opioids in subjects low in self-efficacy, the prolonged cold pressor stimulus (over which subjects had no control) presented a particularly stressful experience to which self-efficacious subjects may have reacted adversely.

Prior to the math task, the most discouraged and (and to a lesser extent) angry subjects treated with naltrexone tolerated the fCPT for the least amount of time. Even though this relationship appeared strongest in depressed subjects, group differences

failed to reach significance. Nonetheless, these results show trends in depressed subjects that are consistent with subjective reports of cold pressor PI and UP. As mentioned above, small cell sizes may have contributed to these negative findings.

After the task, the most discouraged, anxious, angry and inefficacious subjects tolerated the foot cold pressor for the least amount of time. These findings may simply reflect waning levels of motivation and willingness to persist with a noxious stimulus after a gruelling experimental session, instead of pain modulatory mechanisms per se. As in many other studies (e.g., Vallis & Bucher, 1986), perceived self-efficacy predicted persistence with the fCPT.

7.4.8 Cardiovascular and pain regulatory systems in depression

The dysregulation of the normal relationship between cardiovascular and pain responses in depressed subjects (Pickar et al., 1982a; Pinerua-Shuhaibar et al., 1999) may be due to dysfunction of the opioid system in depression (Catlin et al., 1982). After an extensive review of the literature, it appeared that this hypothesis had not yet been empirically assessed. Therefore, the current study aimed to evaluate the role of opioids in the cardiovascular-pain relationship in depressed subjects, compared with non-depressed controls.

Task shock sensitivity

Diastolic blood pressure (DBP) was inversely associated with shock PI and UP during the math task. A similar trend, although non-significant, was found for SBP. Unexpectedly, this relationship was not mediated by endogenous opioids in either group. The present findings suggest that nonopioid mechanisms may mediate the BP–pain relationship both in depressed and non-depressed subjects, (see also Maixner & Randich, 1984; McCubbin & Bruehl, 1994). In contrast, the inverse association between heart rate and shock UP was mediated by opioids in both groups. The discrepancy between heart rate and BP emphasises the complexity of the cardiovascular-pain relationship.

In conclusion, the present findings demonstrate an association between pain suppression and cardiovascular activity both in depressed subjects and controls. Thus, the findings provide no support for the view that this mechanism is compromised in depression.

Cold pressor sensitivity

As hypothesised, prior to the math task an inverse relationship was found between resting SBP and cold pressor PI and UP in controls taking the placebo. Naltrexone eliminated this relationship. This study appears to be the first to provide strong evidence of an opioid-mediated inverse relationship between cold pressor pain sensitivity and resting SBP (Bragdon et al., 2002; McCubbin & Bruehl, 1994).

An inverse relationship was also found between SBP and cold pressor PI and UP in depressed subjects before the math task; however, this relationship existed for those under opioid blockade only. These results suggest that a nonopioid mechanism may mediate the relationship between acute cold pain sensitivity and SBP in depression. The fact that the BP-pain relationship was weakened or eliminated in the placebo condition suggests that erratic effects of opioids may mask nonopioid influences on BP. Therefore, a nonopioid baroreceptor-mediated analgesia appears to be more active in depressed, than in non-depressed, subjects.

After the math task, the relationship between resting BP and cold pressor PI and UP was weakened considerably in both groups. Opioid-mediated SIA after the task may have weakened traces of blood pressure-related analgesia via opposing influences on autonomic activity. To explain, stress-induced stimulation of the ventrolateral periaqueductal gray results in autonomic adjustments such as hypotension (reduced BP), and bradycardia (slowed rate of heart contractions) (Bandler & Shipley, 1994). Baroreceptor-mediated analgesia, on the other hand, is induced via an increase in venous and arterial pressure, which in turn activate baroreceptor afferents that terminate in brainstem structures responsible for anti-nociception (Randich & Maixner, 1984). Therefore, these two analgesic mechanisms may have resulted in opposing influences on the BP-pain relationship, eliminating effects observed prior to the stressor.

Prior to the math task, regression analyses revealed a positive relationship between SBP and cold pressor pain tolerance in controls taking the placebo. Unlike subjective ratings, this relationship persisted *after the task* in this group of subjects. As mentioned earlier, pain tolerance did not appear to be influenced by the math task in the current study. Therefore, it is possible that SIA did not mask baroreceptor-mediated analgesic influences on pain tolerance. A positive association between cold pressor pain tolerance and SBP approached significance in depressed subjects taking naltrexone before the math task. This link was strengthened after the math task in those under opioid blockade, suggesting once again that nonopioid baroreceptor-mediated analgesia were functioning more actively in depressed than control subjects.

Resting pulse rate was not associated with cold pressor PI, UP or pain tolerance before or after the math task. As already mentioned, BP directly stimulates baroreceptors, playing an important role in baroreceptor-mediated analgesia. Heart rate, however, is influenced by changes in BP and the baroreceptor reflex, thereby *indirectly* influencing the cardiovascular-pain relationship.

In summary, high resting SBP was associated with low cold pressor PI and UP and increased pain tolerance in controls not under opioid blockade. The existence of similar SBP-pain relationships in depressed subjects under opioid blockade suggests that dysregulation of the endogenous opioid system in depression may directly or indirectly interfere with the normal BP-pain relationship (McCubbin, 1993). Moreover, the current findings suggest that nonopioid substrates mediate a compensatory mechanism through which cardiovascular activity is regulated in depression. Other cardiovascular anomalies demonstrated in clinically depressed patients such as the dysregulation of the autonomic nervous system (ANS), baroreceptor insensitivity (Grippo & Johnson, 2002), and increased risk for CHD (Rugulies, 2002) may provide support for this view. Although seemingly contradictory, opioid mediation of the heart rate–shock UP relationship in depression suggests that opioid involvement in cardiovascular mechanisms other than baroreceptor-mediated analgesia may not be impaired. At this stage the mechanisms by which opioids interfere with the normal link between cardiovascular activity and pain are unclear.

Finally, the BP-pain relationship appeared to be determined by the type of noxious stimuli in the present study. This complexity has an adaptive purpose, as the organism can respond appropriately to all types of environmental stimuli (Randich & Maixner, 1984). However, it must be noted that cardiovascular responses were measured under different circumstances in the case of each pain stimulus (i.e., fCPT = resting BP/Pulse; shocks = BP/Pulse during the math task), which also may explain the different outcomes observed with each pain stimulus.

7.4.9 General summary/Conclusions

Experimental pain sensitivity failed to differ between depressed and non-depressed subjects. However, depressed subjects demonstrated a tendency to report marginally higher pain UP. Neither stress-induced opioid inhibition of pain after the math task, nor DNIC (as measured by R2 inhibition) were systematically compromised in depressed subjects. Negative mood (in particular discouragement, anxiety) and self-efficacy were associated with the release of endogenous opioids, which in turn led to lowered pain sensitivity both in depressed and non-depressed subjects. One notable group difference was that during the math task anxiety was associated with increased pain UP in depressed subjects taking naltrexone, but not the placebo. In contrast, anxiety was positively associated with pain UP in controls regardless of opioid blockade. A strong opioid-mediated SBP–cold pressor pain relationship existed for controls, whilst nonopioid mechanisms appeared to mediate the same relationship in depression. Generally speaking, in comparison to controls, pain transmission and inhibition, and opioid-mediated mood modulation of pain was not compromised in depressed subjects. However, opioid mediation of systems unrelated to mood (i.e., cardiovascular system) appears to operate differently in depressed, than in non-depressed, subjects.

CHAPTER EIGHT

8. GENERAL DISCUSSION

8.1 SUMMARY OF MAJOR FINDINGS

The key points to emerge from the four studies were:

- Dysphoric mood arising from an uncontrollable aversive event activated endogenous opioid-mediated antinociceptive mechanisms in depressed and non-depressed subjects. Conversely, anxiety and anger sensitised some subjects to pain. A strong belief that one can control an aversive event (i.e., high self-efficacy) in a context where control is not possible also activated the endogenous opioid system, perhaps via emotional responses (e.g., helplessness).
- The predictability of noxious events had little influence on negative mood or analgesia. However, this variable may not have been tested adequately.
- In university subjects, opioid-mediated SIA was more likely to be triggered during a sustained cold pain stimulus than brief electrical pain. Conversely, in the community sample negative mood was associated with opioid-mediated decreases in electrical shock-induced pain and, to a much lesser extent, cold-induced pain. This may be due to higher arousal (i.e., fear rather than anxiety) experienced by the community sample during the math task. In general, endogenous opioids blunted the UP, or affective component, of pain more consistently than the intensity of the sensation.
- Objective measures of pain such as nociceptive reflexes (RIII, R2 component of the blink reflex) were not altered by stress-induced opioid activation.
- Pain tolerance reflected a subject's ability to endure, not only pain, but also unpleasantness in general.
- High BP inhibited pain via opioid release in non-depressed subjects. However, opioid release masked the association between BP and pain in depressed subjects. Dysregulation of the opioid system may contribute to cardiovascular disturbances in major depression.

In this chapter, the effects of stressor controllability/predictability, negative mood and self-efficacy on SIA are examined in depressed and non-depressed subjects. This is followed by a discussion of the role of endogenous opioids in stress regulation and pain inhibition. Opioid involvement is then compared across various measures of pain, including subjective pain ratings, pain tolerance and nociceptive reflexes (RIII, R2 of the blink reflex). Following this, endogenous pain modulatory mechanisms in major depression, and the interaction between cardiovascular activity and pain is examined. Finally, conclusions and directions for future research are presented.

8.2 PSYCHOLOGICAL ACTIVATION OF STRESS-INDUCED ANALGESIA (SIA)

8.2.1 Stressor controllability

In the present series of experiments, an aversive event (so-called 'performance-contingent' shocks during a difficult math task) perceived to be uncontrollable led to inhibition of cold pressor pain sensitivity after the math task. In fact, the perception of controllability was critical because shock delivery was preset and identical for subjects in controllable and uncontrollable conditions. Exploratory analyses in Study 2 highlighted the fact that the difficulty of math questions and perceived 'lack of control' over the shocks led to the activation of antinociceptive mechanisms, and not the shocks themselves. Thus, findings from animal laboratory research have been extended to humans in this project where the inescapable nature of an aversive event, and not the event itself, led to analgesia.

Pain was expected to decrease after stress in placebo recipients but to increase after stress in naltrexone recipients. This pattern of effects was found in Study 2 (using exploratory analyses), and evidence of *relative* analgesia was found in Studies 3 and 4. After psychological stress in Study 3, the placebo group showed no change in pain sensitivity whilst pain increased in naltrexone recipients. Conversely, in Study 4 hypoalgesia occurred in the placebo group whilst naltrexone recipients showed no change in pain. These results are in accordance with Pitman et al. (1990), who found that pain decreased in placebo-receiving traumatised Vietnam veterans after they had

a watched a combat-related videotaped segment. In contrast, veterans in the naloxone condition showed no change in PI after watching the video.

Opioid-mediated hypoalgesia and opioid antagonist-induced hyperalgesia have been noted in studies in which extremely aversive (Rhudy & Meagher, 2001a) or painful stressors (Rhudy & Meagher, 2000; Willer et al., 1981; Willer & Ernst, 1986) were used to induce fear and analgesia in humans. Therefore, it is possible that cognitive stressors (e.g., math task + shocks; Pitman's videotaped stressor) were not intense enough to induce fear and consistent hypoalgesic/hyperalgesic effects in the placebo and naltrexone groups, respectively. Since fear was not rated, this explanation is difficult to assess. Alternatively, nociceptive activity evoked by the cold-water stimulus may have been too intense, creating ceiling effects in the placebo group. A less intense (warmer, shorter) CPT may be useful to evaluate the role of endogenous opioids in SIA. Finally, SIA may have been weaker in this research than in other human studies because 'stressor controllability' is only indirectly related to pain perception. Using a path analysis, Mueller and Netter (2000) found that subjective helplessness (arising from stressor uncontrollability) was directly related, whereas control over the stressor was indirectly related, to the perception of electrical pain. Thus, the use of a path analysis may help to determine the relative contribution of stressor controllability, and other variables such as negative mood, in pain perception.

Although the shocks were included during the task primarily to induce stress, the effect of stress, negative mood/self-efficacy and opioid blockade on the pain induced by shocks was examined nonetheless. Interestingly, in Study 2 a perceived lack of control over the shocks was associated with heightened shock PI and UP, and in Study 1 shock pain sensitivity increased as the task progressed. Importantly, shock PI and UP was not influenced by opioid activation in Studies 2 or 3. The results of these studies diverge from those of previous research, where immediate opioid-mediated analgesia has been demonstrated in response to electrical stimuli (Rhudy & Meagher, 2000; Willer & Albe-Fessard, 1980a; Willer et al., 1981; Willer & Ernst, 1986). One crucial difference between these studies and the present research is that the electrical stimuli delivered during the math task were brief, less frequent and less intense than in other studies. In summary, university students may not have found the electrical

stimuli or the math task noxious enough to induce high levels of arousal or trigger analgesic mechanisms (see *8.2.3 Affective and cognitive mediators of pain*, p 304). Nonetheless, if the temporal factors of shocks were to be changed so that they were noxious, pain would be confounded with stress during the math task – a problem that was minimised in this research.

8.2.2 Stressor predictability

As discussed in Study 1, stressor predictability (on its own) failed to influence pain perception after the math task. These results suggest that stressor certainty plays no clear role in the activation of endogenous pain inhibitory systems (see also Miller, 1981). However, similar levels of anxiety in predictable and unpredictable conditions suggested that the manipulation of predictability might have been methodologically flawed.

In future, a number of methodological aspects should be addressed to assess the relative contribution of stressor certainty on opioid activation. First, anxiety and cardiovascular activity should be measured during the warning period (i.e., blue screen) to assess whether this manipulation impacted upon subjects as intended. Second, periods signalling no aversive event (i.e., black, normal screen) should have been times during which subjects could relax and not have to continue with the stressful math task. As it stood, the stress of having to perform well for the entire duration of the math task seemed to outweigh the benefits of warning periods for subjects in predictable conditions. Finally, shocks should have been delivered during every warning period to strengthen the manipulation of predictability in this study.

8.2.3 Affective and cognitive mediators of pain

After completion of the math task, the mood experienced by subjects that was most consistently associated with endogenous analgesia was discouragement. Feeling discouraged could be likened to subjective helplessness in animals (Maier, 1986) and humans (Mueller & Netter, 2000). These findings concur with Maier (e.g., Maier, 1986; Maier et al., 1982; Maier et al., 1983) and many other authors who have demonstrated analgesia in animals behaving helplessly after being exposed to

inescapable or uncontrollable aversive events. Conversely, helplessness in humans appears to facilitate pain sensitivity (Mueller & Netter, 2000). Although seemingly contradictory, various methodological differences in Mueller and Netter's (2000) study, such as the use of lower intensity, non-noxious shocks (1 mA, 100 ms versus 15 mA, 25 ms during the math task), and the familiarisation of subjects with shocks during a training session prior to the actual task, may account for the differences between their study and the present research.

Inhibitory effects of negative mood on cold pressor PI and UP after the math task, although mirroring effects noted Studies 1-3, failed to reach significance in Study 4. These results suggest that negative mood inhibited pain in some subjects but not others. The inclusion of non-depressed and depressed subjects in the same sample may have diluted effects seen in previous studies. For instance, the notably smaller non-depressed sample in Study 4 may have contributed to these negative findings. Alternatively, negative mood induced by the math task may have decreased more rapidly once the task was completed in community subjects, than in university students. According to Rhudy and Meagher (2001b), moderately arousing negative mood tends to facilitate pain and reduce pain coping. Rhudy and Meagher's notion that emotional valence and arousal interact to modulate pain, and the fact that negative mood was negatively associated with pain tolerance in the community sample, supports the idea that negative mood in community participants may have been associated with only moderate levels of arousal after the task.

Whilst discouragement was positively associated with PI and UP in the placebo group before the math task in Study 2, greater discouragement was associated with *less* pain in depressed subjects not under opioid blockade before the math task in Study 4. Both results suggest that a certain level of discouragement was experienced during experimental procedures prior to the math task, and that opioid release in psychiatrically healthy subjects led to a paradoxical increase in pain whereas opioid activation led to pain inhibition in depressed subjects. It is possible that the intensity of distress experienced, hence level of opioid release differed between these groups – resulting in differing outcomes for pain.

Anxiety and anger did not consistently influence pain perception after the math task in Studies 2-4. The evidence that did exist (i.e., Study 2 - anxiety leading to greater cold pressor UP in placebo recipients; Study 4 – anxiety/anger decreasing cold pressor pain tolerance), suggests a pain facilitatory effect for both of these emotions after psychological stress. Therefore, it seems that discouragement or helplessness induced during the math task was associated with analgesia, whilst anxiety and anger were associated with hyperalgesia. The pain facilitatory effect found for anxiety (Rhudy & Meagher, 2000; Rhudy & Meagher, 2001a; Willer & Albe-Fessard, 1980a; Willer et al., 1981) and anger (Bruehl et al., 2002; Burns et al., 2004; Janssen et al., 2001; Stevens et al., 1989) concurs with previous research.

The association between anxiety and shock pain inhibition in Study 4 may indicate that participants experienced fear during the math task (see discussion below), as this emotion *is* associated with analgesia (Rhudy & Meagher, 2000; Willer & Albe-Fessard, 1980a; Willer et al., 1981). Increasing the frequency, intensity and duration of shocks so that fear is induced in an additional experimental condition may help elucidate the effects of fear versus anxiety on pain.

In Studies 3 and 4, anger before the math task was associated with opioid-mediated increases in cold pressor pain tolerance, whereas facilitatory effects of anger appeared to mask the inhibitory effects of opioids after the task. Janssen (2001) has suggested that anger increases motivation to withstand pain. The intervening steps between increases in anger and pain tolerance are unknown; however, opioids appear to be involved in this process. It is unclear why this mechanism no longer influenced pain tolerance after the math task.

Self-efficacy relating to control over shocks during the math task was associated with opioid-mediated reductions in cold pressor PI and UP after the task in Studies 2 and 4. Perceived self-efficacy was also related to less shock PI and UP. This effect appeared to be mediated by endogenous opioids in some subjects but not in others. As stated by Bandura et al. (1987), perceived self-efficacy can result in considerable stress and opioid activation if the demands of the task exceed the coping capacity of the subject. The math task (although involving only subtraction/addition mental arithmetic questions) was designed to be challenging, and in some conditions near to

impossible to master. However, it was the time limit for each question that made this task difficult, not the questions themselves – which may explain why subjects who perceived themselves to be proficient at mental arithmetic may have become particularly distressed and discouraged, thus mobilising the opioid system.

In university samples (Studies 1-3), negative mood was associated with higher ratings of PI and UP to electrical stimuli during the math task. In Study 4 the association between negative emotions and sensitivity to electric shocks was generally detected in naltrexone but not placebo recipients, indicating that opioids antagonised the PI and UP of shocks in distressed subjects. Even though mood ratings during the math task were not notably different between studies, the community sample in Study 4 may have experienced more intense discouragement and anxiety (or even fear) regarding the novel experimental setting and procedures. Attributing these divergent results to the intensity of negative emotions is in line with Rhudy and Meagher's (2001b) notion that negative mood that is highly arousing serves to inhibit pain, whilst moderately arousing negative mood facilitates pain.

It is interesting to note that whilst anger was associated with shock PI in university students, anger did not affect electrical pain sensitivity in the community participants. Once again, the intensity of anger did not appear different, but perhaps the quality of the anger (i.e., suppressed/expressed, towards self or experimenter) differed between groups. A tendency to express anger (anger-out) is typically associated with increased pain sensitivity (Bruehl et al., 2002; Janssen et al., 2001), whilst the suppression of anger (anger-in) is sometimes associated with endogenous analgesia (Bruehl et al., 2002). Thus, divergent modes of anger management may have led to differing pain outcomes in both groups. As noted by Fernandez (2002), the effect of anger on pain requires further investigation.

Finally, as each negative mood was assessed with a single item scale, it would have been interesting to explore the effects of a multi-item assessment of each mood on results. For example, if anger had been assessed with more socially acceptable labels such as 'irritation' the above-mentioned results may have been different.

8.2.4 Summing up: Psychological activation of the endogenous opioid system

In the current project, the endogenous opioid system apparently was activated by a discouraged and possibly fearful response to a situation in which control over a threatening event was unavailable. A number of studies implicate the endogenous opioid system in stress regulation (Drolet et al., 2001), including modulation of endocrine activity (in the HPA axis), sympatho-inhibition (hypotension and bradycardia involving the ANS) and decreased behavioural responsivity to the environment (immobility, quiescence) (Bandler & Shipley, 1994). Endogenous opioids are also known to reduce distress associated with pain (Drolet et al., 2001). These effects facilitate 'passive coping', an adaptive emotional mode of coping with inescapable, threatening or stressful situations (Bandler, Price, & Keay, 2000). Passive coping is adaptive in that further injury is avoided through immobility (e.g., to reduce blood loss), the psychological impact of the threat is minimised (via opioids), and healing and recovery is facilitated once the threat has decreased.

Learned helplessness (LH), or passive emotional coping in animals has been widely linked to opioid analgesia; however, few studies have explicitly associated emotional concomitants with endogenous pain inhibition in humans. In the current project, discouragement, which is akin to LH in animals, activated the endogenous opioid system and apparently facilitated passive coping in humans. Moreover, opioid activation was observed in self-efficacious subjects perhaps due to the emotional consequences of their diminishing capacity to cope. Secondary opioid-mediated antinociceptive effects were noted with painful stimuli following psychological stress. These points serve to identify the endogenous opioid system as not just responsible for pain inhibition but as an important contributor to the regulation of emotional processing of stressful, threatening inescapable stimuli. In fact, the endogenous opioid system may primarily serve to regulate stress and secondarily pain which, if not regulated, can intensify distress.

Responses to stressors from which escape is possible are usually active, involving confrontation (fight) with, or flight from, the threat (Bandler et al., 2000). 'Active coping' is typically associated with sympatho-excitation (hypertension/tachycardia involving the ANS), increased environmental scanning, fear and nonopioid-mediated

analgesia. Pain inhibition is adaptive in that the dulling of distracting pain signals enables defensive reactions such as fleeing the scene or fighting. Fear has also been associated with opioid release, but opioid activation appears to occur in the face of inescapable stressors (Janssen & Arntz, 2001; Pitman et al., 1990; Willer & Albe-Fessard, 1980a). Therefore, fear arising from different classes of stressors may determine whether opioid (inescapable stress) or nonopioid (escapable stress) analgesia develops.

Apart from in Study 4[19], anxiety and anger did not activate the endogenous opioid system in response to psychological stress. Rhudy and Meagher (2000) differentiated anxiety from fear, stating that anxiety represents apprehension about a *future*, rather than an *actual* threat and that this emotion facilitates sensory processing, increasing attention towards and amplifying the intensity of pain. It is possible that anxiety only sensitised subjects to pain during the math task (when shocks were delivered) and not after the math task (during the CPT) as the threat of shock had ceased. A drop in anxiety as measured by the mood ratings after the task supports this explanation. Anger has generally been associated with pain sensitisation (Bruehl et al., 2002; Janssen et al., 2001); however, the fact that anger can motivate some subjects to withstand pain (Janssen, Spinhoven, & Arntz, 2004) confirms that more research into the modulation of pain by anger is required.

Among an emerging body of animal research, Bandler and colleagues (Bandler et al., 2000; Bandler & Shipley, 1994) have recently identified neural substrates in the periaqueductal gray (PAG) region of the midbrain that are responsible for coordinating distinctly different emotional responses to stress. Specifically, the longitudinal columns of neurones located ventrolaterally and laterally to the aqueduct play a role in passive and active coping, respectively. Although it is difficult to confirm that such circuitry exists in humans, the results from the present and other research suggests that emotional coping strategies and associated neural circuitry are as diverse and complex as the stimuli that trigger them.

[19] In Study 4, insensitivity to shock pain/unpleasantness was mediated by opioids in anxious subjects.

8.3 PAIN RESPONSE PARAMETERS

Another point of interest is the effect of endogenous pain modulatory mechanisms on different pain response parameters. Pain perception was assessed with subjective *PI* and *UP* ratings in all studies, whereas *pain tolerance* was measured in Study 3 and 4 only. Notably, the analgesic effects of endogenous opioids blunted pain UP most consistently across all four studies, whereas PI either showed similar (Study 1 and 4) or non-significant trends (Study 2), or was not affected by the math task at all (Study 3). Pain tolerance, on the other hand appeared to be influenced by motivational processes unrelated to nociception. Pain ratings will be discussed, followed by an analysis of pain tolerance.

Affective (UP) and sensory (PI) components of pain are encoded in different structures of the brain, and represent very different aspects of the pain experience (Melzack, 1986; Rainville et al., 1997). Although involving distinct emotions, pain-associated distress and the stress response involve overlapping neurophysiological pathways, of which are mediated by similar neurochemical substrates, including endogenous opioids. For instance, endogenous opioids help regulate the stress response by diminishing stress-related neuroendocrine and autonomic responses, in addition to possessing analgesic characteristics (Drolet et al., 2001). The large number of enkephalin receptor sites in the limbic system of the brain (implicated in emotional responses) is consistent with the notion that opioids mediate both the stress and distress associated with pain (Drolet et al., 2001). In relation to the analgesic properties of opioids, Drolet et al. (2001) suggested that a primary feature was to reduce the distress, but not the sensation, associated with pain. Therefore, endogenous opioids may have inhibited pain-related distress in the present research, explaining why, after the math task, pain UP was more consistently blunted than PI.

Conversely, SIA was not demonstrated with pain tolerance - an outcome measure that is heavily influenced by affective-motivational dimensions of the pain experience (Hirsch & Liebert, 1998). Pain tolerance was associated with endurance of non-painful but unpleasant tasks such as the Valsalva manoeuvre and the Letter Symbol Matching Task, but was not associated with PI or UP ratings in Study 3.

These observations suggest that pain tolerance measures resilience, not nociceptive processes per se. Furthermore, the relationship between endurance of painful and non-painful tasks reached significance in the placebo but not the naltrexone group in Study 3. In addition to providing relief from pain, endogenous opioids play an important role in promoting positive reinforcement or reward for instrumental behaviour (Kalat, 1995). Therefore, the demand characteristics in the tasks of endurance in Study 3 and 4 may have influenced the behaviour of subjects, particularly those who benefited from opioid release, as opioids may mediate the drive to endure unpleasantness and experience rewards (e.g., intrinsic satisfaction, experimenter approval).

The present findings differ from those of Bandura et al. (1988), who demonstrated a significant increase in pain tolerance in stressed and mathematically inefficacious subjects taking a placebo, in comparison to their naloxone counterparts who showed no change in tolerance to pain. No difference was found between drug conditions in non-stressed, self-efficacious subjects. In the context of the previous discussion, opioid-mediated SIA in Bandura's (1988) study may in fact represent a greater willingness to endure unpleasantness in the subjects who had performed poorly during their mathematical task and who were not under opioid blockade. In support of this notion, pain tolerance was strongly related to self-efficacy to *endure pain* but not to *reduce pain* in Bandura's (1988) study. Furthermore, the greater the reduction in mathematical self-efficacy, the greater the tolerance of pain during the CPTs.

8.4 NOCICEPTIVE REFLEXES (RIII-FLEXION REFLEX, R2-BLINK REFLEX)

8.4.1 Stress-induced analgesia

The effects of stressor controllability on objective measures of pain such as the RIII and R2 component of the blink reflex were examined in Study 3 and Study 4, respectively. Onset latencies of each reflex were quantified in favour of other measures such as area under the curve or amplitude, since latencies are reliable with repeated measurement, do not require extremely high intensity stimuli to produce

stable responses, and are not influenced by extraneous factors such as muscle potentials or stimulus artefacts (Esteban, 1999; van Vliet et al., 2002).

Supraspinal influences including chronic or acute states of fear, stress, anxiety or depression that are unrelated to pain were expected to influence nociceptive reflexes after the math task (Craig, 1989). Mood is known to change the excitability of spinal inter- and motor-neurones, hence altering basic patterns of the RIII (Willer, 1977) and the R2 component of the blink reflex (Kimura, 1973). Specifically, Willer and colleagues postulated that the arousal of limbic structures via negative emotion has an excitatory effect on nociceptive reflexes (Willer et al., 1979). In support of this, Willer et al. (1979) found that the anticipatory anxiety associated with an intensely noxious stimulus (70mA) to the sural nerve facilitated the RIII.

Facilitation of the onset of R2 but not RIII after the math task may be attributed to methodological limitations in Study 3. First, RIII was detected in an insufficient number of subjects to adequately assess the effect of the math task on this reflex. Even though RIII-eliciting stimuli were set to threshold and supra-threshold intensities established elsewhere (Willer, 1977), the current level may not have been strong enough to reliably evoke RIII. In hindsight, personal thresholds should have been determined to ensure reliable evidence of RIII in each subject. Second, fewer trials were delivered in Study 3 (N = 3 at each intensity) than in other studies (N = 10-50 at each intensity), which may have reduced the reliability of results. Although a similar number of trials were used to detect the blink reflex, this reflex appeared to be considerably more consistent amongst subjects. The methodology used by other authors, such as recruiting subjects who were relaxed and familiar with RIII-inducing procedures whilst excluding others showing no evidence of this reflex, implies that detection of RIII can be elusive and possible only in certain subjects.

RIII thresholds and subjective pain thresholds to RIII-eliciting stimuli were not significantly influenced by the math task. These findings diverge from those of Willer and colleagues (1980a; 1981), who found that intermittent and repetitive stress resulting from the anticipation and delivery of a noxious event (e.g., 70-80 mA foot-shock) led to increases in RIII thresholds. In Willer's studies stress-induced inhibition of RIII proved to be opioid-mediated, as naloxone led to dramatic

decreases in RIII thresholds (Willer & Albe-Fessard, 1980a; Willer et al., 1981). Neither RIII nor R2 responses after the math task were influenced consistently by endogenous opioids in the present research. Although the role of endogenous opioids in the blink reflex has not yet been supported in the literature (Cruccu et al., 1991; Ferracuti et al., 1994a), the involvement of the opioid system in RIII parameters has been widely demonstrated in humans (Willer & Albe-Fessard, 1980a; Willer et al., 1981). Therefore, the lack of differences between placebo and naltrexone groups in RIII responses may have been due to the difficulty in consistently eliciting the RIII response in either group.

8.4.2 Diffuse noxious inhibitory controls (DNIC)

In Study 4, a second endogenous pain modulatory mechanism termed DNIC was examined in depressed and non-depressed subjects. This was achieved by investigating the effects of a heterosegmentally-applied noxious CS on the R2 component of the blink reflex. The first CS (i.e., hand CPT) significantly inhibited R2 responses, demonstrating evidence of DNIC in all subjects. However, the disappearance of these effects during the second CPT suggested that the inhibitory effects (noted at the outset of the experiment) were perhaps masked by pain facilitatory effects of negative mood. Alternatively, effects observed at the beginning of the experiment might have been due to SIA brought about by the extremely noxious nature of cold pressor CS. Most subjects were extremely distressed by the aversive nature of the cold water as they had no previous experience of the CPT and underestimated how noxious it would be. Measures of BP and heart rate during the CS would have been useful in determining whether R2 inhibition was stress-induced.

Endogenous opioids have been shown to mediate the effects of DNIC on the R2 component of the blink reflex (Boureau et al., 1979; Lozza, Schoenen, & Delwaide, 1997; Willer et al., 1982b). However, in Study 4 strong nociceptive signals from the cold water may have overridden opioid-mediated inhibitory effects, creating ceiling effects. Therefore, a less aversive CS would help clarify the effect of mood and opioids on DNIC. Alternatively, opioid effects may have become apparent if larger numbers had been included in each cell.

Despite the lack of evidence in the current research of opioid involvement in either RIII or R2 nociceptive reflexes after stress or heterotopically-applied noxious stimuli, there is substantial documentation of these effects in the literature for RIII (Willer & Albe-Fessard, 1980a; Willer et al., 1979; Willer et al., 1981; Willer & Ernst, 1986; Willer et al., 1990), and to a lesser extent, the R2 component of the blink reflex (Boureau et al., 1979; Lozza et al., 1997; Willer et al., 1982b). Methodological limitations (e.g., shocks not noxious enough; CS too noxious, small cell sizes) may explain why stress induced by the math task failed to modify RIII in Study 3, and CS failed to inhibit R2 in Study 4, and why opioids did not influence either reflex.

8.5 ENDOGENOUS PAIN MODULATION IN MAJOR DEPRESSION

The aim of Study 4 was to investigate whether the link between chronic pain and depression could be attributed to impairment of endogenous pain modulatory mechanisms, in particular the opioid system. Opioid functioning in depression was examined under conditions known to activate endogenous opioids (i.e., psychological stress, heterotopically-applied noxious CS, and stress-induced increases in cardiovascular activity).

As highlighted in the summary, major depression was not associated with pain insensitivity or impaired opioid functioning. In fact, aside from a marginally stronger affective response to painful stimuli in depression, stress-induced analgesic and DNIC effects did not differ between subjects with or without depression. However, the opioid system was more readily activated in depressed than control subjects in response to painful stimuli before the math task. These findings concur with the notion that opioid activation represents a normal, adaptive reaction to stress and anxiety, and that pain insensitivity in depression may be indirectly related to increased levels of acute stress, but not opioid dysregulation.

Even though more frequent activation of endogenous opioids in depression does not seem to impair the ability of this system to respond to stress, chronic opioid release may impact negatively on other systems. For instance, opioids hindered the

regulatory relationship between cardiovascular activity and pain in depression (see *8.6 Interrelationships between cardiovascular and pain modulatory systems*, p 315). The abnormal effect of opioids on cardiovascular activity may increase the risk of cardiovascular disorders in depression, suggesting an important reason to target coping inefficacy and stress in depression. Chronic activation of endogenous opioids also compromises immune function. Therefore, treatment of depression should address 'stressful thinking', by encouraging patients to appraise life events as non-stressful, controllable, or non-threatening, and instilling in them that they are not helpless or powerless to control aversive events.

Furthermore, opioid release in depression has been related to abnormalities in the HPA axis – a regulatory system responsible for the control of hormones released during the stress response. Although not assessed in this research, functioning of the HPA axis appears, in part, to be reliant on normal responsivity to opioids. If released regularly in response to stress, a tolerance to opioids can develop, which could in turn contribute to pathogenic functioning of the HPA axis in depression – highlighting another reason to improve the coping capacity of depressed patients.

8.6 INTERRELATIONSHIPS BETWEEN CARDIOVASCULAR AND PAIN MODULATORY SYSTEMS

The interaction between cardiovascular and pain regulatory systems was assessed during stress and at rest in Studies 2, 3 and 4.

During the math task, elevated BP was related to decreased shock PI and UP in Study 3 and 4, but not in Study 2. Also, heart rate was inversely associated with shock UP in Study 4, but not in Study 2 or 3. Considering that subjects in Study 2 demonstrated the least autonomic arousal during the math task and gave lower than average PI/UP ratings for shocks, it is possible that stress levels were not high enough to activate baroreceptor-mediated analgesic mechanisms. Conversely, subjects in Study 4 demonstrated the greatest autonomic arousal during the math task and the highest PI/UP ratings for shocks, which may explain why heart rate in addition to BP influenced pain perception. Heart rate, being indirectly associated

with baroreceptor-stimulation mediated analgesia, is not as readily related to pain inhibition as BP (Caceres & Burns, 1997; Rosa et al., 1988), but is related nonetheless (de Jong, Petty, & Sitsen, 1983; McCubbin, 1993).

The relationship between BP and shock pain sensitivity in Study 3 and heart rate and shock UP in Study 4 were both mediated by endogenous opioids, concurring with recent evidence in normotensive (Rosa et al., 1988) and hypertensive humans (McCubbin et al., 1985). A similar opioid-mediated inverse relationship existed between resting BP and cold pressor sensitivity before the math task in Study 3, and in non-depressed subjects in Study 4. In the context of previous research, these results provide possibly the strongest evidence of an opioid link between cardiovascular and pain responses in normotensive humans (Bragdon et al., 2002; McCubbin & Bruehl, 1994). Interestingly, this relationship only existed *under opioid blockade* in subjects with depression, as endogenous opioids masked a nonopioid modulatory mechanism. Although the inverse (resting) BP-cold pressor pain relationship was maintained to some extent after the math task[20], the antagonistic effects of naltrexone were weakened in Study 3 and 4. Furthermore, the nonopioid-mediated relationship did not appear to be as strong in depressed subjects after the math task. Opioid analgesia induced by the math task may have reduced cardiovascular activity, thereby diluting baroreceptor- or centrally-mediated analgesic effects on cold pressor sensitivity, whether they are mediated by opioid or nonopioid substrates.

Resting SBP was positively related to cold pressor pain tolerance in Study 3 and 4, both before[21] and after the math task. Moreover, this relationship was mediated by endogenous opioids in non-depressed subjects[22], but not in those suffering from depression. In depressed subjects, endogenous opioids failed to modulate the pre-math task SBP-pain tolerance relationship, whilst completely masking a nonopioid-

---

[20] Group x Drug x BP effects no longer reached significance after the math task in Study 4 (PI: p=.14; UP: p=.09); however, results trended in the same direction as before the math task.

[21] This result was marginal in Study 3 (p=.06).

[22] Evidence of opioid-mediation came from correlations in Study 3 (see Table 4.30, p 190) and multiple regression analyses in Study 4 (see Tables 7.37 and 7.38, p 282-3).

mediated modulatory mechanism after the math task. Therefore, in these two studies opioids apparently played a pivotal role in the relationship between BP and pain sensitivity in non-depressed normotensive subjects; however, opioid activation appears to mask this relationship in major depression.

8.7 FUTURE DIRECTIONS

This research provides interesting insights into the psychological factors and stimuli leading to endogenous opioid activation and pain inhibition. Further investigation as to how other negative mood states such as fear impact upon the endogenous opioid system and other pain modulatory mechanisms would help clarify the role of negative emotion in pain modulation. For instance, fear could be induced during the math task by introducing extremely noxious shocks resembling those used in Willer (1980a; 1981) and Rhudy and Meagher (2000). The effects of subjective helplessness could be compared with discouragement to determine whether these emotional states lie on the same continuum. Furthermore, research examining the effects of anger management style (anger-out versus anger-in) on the mobilisation of endogenous opioids and other pain modulatory systems could also prove fruitful, as very little is known regarding the effects of stress-induced anger on pain.

To determine whether these results generalise across all types of pain, this methodology should be replicated using pain stimuli other than CPTs (e.g., heat, prolonged/intense electrical stimuli). Moreover, developing more reliable methods to elicit the RIII flexion reflex and the R2 component of the blink reflex could help determine whether the regulatory role of the endogenous opioid system extends to nociceptive reflexes.

The opioid-mediated cardiovascular-pain relationship observed in healthy normotensive subjects in this project was not detected in subjects with major depression. Since these findings were exploratory, further research examining the role of opioid impairment in the cardiovascular-pain relationship in major depression is required.

8.8 CONCLUDING COMMENTS

In the current project, an uncontrollable stressor and discouragement activated endogenous pain inhibitory mechanisms in humans, whether they were suffering from depression or not. Furthermore, the endogenous opioid system appeared to play a modulatory role in the stress response, modifying negative emotional responses, inhibiting prolonged strong pain (in particular affective responses to pain), and regulating autonomic (sympatho-excitatory) responses. Hence, the current results suggest that in order to regulate stress and/or pain and restore homeostasis, the endogenous opioid system mediates the 'passive coping' response that is triggered by negative (primarily dysphoric) affect.

The integrity of the opioid-mediated pain inhibitory system was not compromised in depressed subjects, when compared with healthy controls in the present research. Nonetheless, opioid activation in depression appeared to adversely influence other important homeostatic functions, such as the interaction between cardiovascular and pain regulatory systems. Therefore, it is possible that regular activation of the endogenous opioid system may not impair pain inhibitory processes, but may contribute to other pathogenic mechanisms such as cardiovascular disease and compromised immunity.

APPENDICES

Appendix 1: Pearson product correlations between mood and self-efficacy.

	Pre-math task			During math task			Post-math task		
Mood	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**
Study 1:									
Ax.	-			-			-		
Ds.	.30 [a]	-		.38 [b]	-		.36 [b]	-	
Ag.	.13	.59 [c]	-	.18	.51 [c]	-	.33 [a]	.68 [c]	-
Sf.	-.29 [a]	-.28 [a]	-.02	-.23	-.51 [c]	-.18	-.35 [b]	-.75 [c]	-.47 [c]

	Pre-drug			Post-drug			During task			Post-math task		
Mood	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**	**Ax.**	**Ds.**	**Ag.**
Study 2:												
Ax.	-			-			-					
Ds.	.42 [c]	-		.57 [c]	-		.70 [c]	-		.62 [c]	-	
Ag.	.35 [b]	.60 [c]	-	.36 [b]	.56 [c]	-	.47 [c]	.61 [c]	-	.34 [b]	.54 [c]	-
Sf.	-.17	-.08	-.12	-.21	-.13	-.09	-.44[c]	-.44[c]	-.31[b]	-.27[a]	-.47[c]	-.34[b]
Study 3:												
Ax.	-			-			-					
Ds.	.63 [c]	-		.47 [c]	-		.76 [c]	-		.43 [b]	-	
Ag.	.24	.40 [b]	-	.07	.35 [a]	-	.59 [c]	.45 [b]	-	.34 [a]	.52 [c]	-
Sf.	-.02	-.14	-.14	-.30	-.23	.04	-.35[a]	-.53[c]	-.20	-.38[a]	-.66[c]	-.30[b]
Study 4:												
Ax.	-			-			-					
Ds.	.58[c]	-		.75[c]	-		.68[c]	-		.72[c]	-	
Ag.	.50[c]	.69[c]	-	.72[c]	.86[c]	-	.62[c]	.67[c]	-	.64[c]	.68[c]	-
Sf.	-.20	-.15	.01	-.12	-.10	-.02	-.19[a]	-.44[c]	-.20	-.17	-.37[b]	-.22

Note Ax. = anxiety; Ds. = discouragement; Ag. = anger; Sf. = self-efficacy.

[a] $p<.05$; [b] $p<.01$; [c] $p<.001$.

Appendix 2: Bryden's Handedness Questionnaire.

Bryden's (1977) Simplified Hand Preference Questionnaire

Instructions:

For each of the activities listed below, indicate with a "✓" (tick) which hand you normally use to perform the activity. If you would only use the other hand when forced to, mark a "x" (cross). If you would use both hands equally often, place a "✓" (tick) in each column.

	LEFT	RIGHT
Writing a message	_____	_____
Drawing a picture	_____	_____
Using a toothbrush	_____	_____
Throwing a ball	_____	_____
Using a pair of scissors	_____	_____

** Are any of your immediate family members, mentioned below, left-handed? (Tick Yes or No)

	Yes	No
Father	____	____
Mother	____	____
Sister(s)	____	____
Brother(s)	____	____

Appendix 3: Consent form, Study 1.

Division of Social Sciences, Humanities and Education

School of Psychology

MURDOCH UNIVERSITY
PERTH, WESTERN AUSTRALIA

South Street, Murdoch
Western Australia 6150
Telephone: (61–8) 9360 2186
Facsimile: (61–8) 9360 6492
psycholo@socs.murdoch.edu.au
http://www.murdoch.edu.au/
Registered Provider Code: 00125J
A.B.N. 61 616 369 313

CONSENT FORM

The effect of stress on pain

You are invited to participate in a study exploring the effects of stress on pain. Previous research has found that stress can alter how painful some experiences actually are. Therefore, the purpose of this study is to investigate the effects of psychological distress on natural pain modulatory mechanisms. Importantly, the results of this study will facilitate the development of treatment for depression and chronic pain.

We will attempt to induce psychological stress during a math task. You will be required to solve mental arithmetic problems while under a time constraint. Your performance on the task may influence the frequency of electrical shocks administered via electrodes attached to your forearm. These shocks are mildly painful, but are harmless. Intermittently throughout the math task you will be asked to rate the pain intensity and unpleasantness of the shocks, and rate how your mood. You will also be asked to rate your mood before and after the math task.

Prior to, and following the math task I will ask you to place your hand in cold water and rate the intensity of pain and unpleasantness experienced. Most people experience a moderate amount of pain during this experience. Our aim is to find out whether the math stressor alters your experience of the cold water.

Your decision to participate will be greatly valued, however withdrawal of your consent and the desire to discontinue is acceptable at any time. Any questions regarding this study can be directed to Ashley Frew (Ph: 9361 0071) or Peter Drummond (Ph: 9360 2415).

Participant's Consent

I_____ have read the information above and have had any questions I have asked answered satisfactorily. I have agreed to participate in this study recognizing that I can withdraw my consent at any time without prejudicing my relationship with Murdoch University.

I agree that results from this research may be published, provided that my identifying information is withheld.

_____	_____
Participant	**Date**
_____	_____
Primary Investigator	**Date**
_____	_____
Supervisor	**Date**

Appendix 4: Instructions for subjects, Study 1.

INSTRUCTIONS FOR SUBJECTS

(Experiment 1)

General Instructions

Action: Give consent form to read and explain further what will be done.

"Firstly, I will get you to rate how you feel according to a number of mood descriptors. Secondly, you will complete a *cold pressor task* that involves placing your hand into a warm water bath, then into a cold-water bath. I will explain this task in more detail later on. Once the cold pressor test is completed, you will begin the computer-generated math task. On completion of the math task, you will repeat the mood ratings and cold pressor task".

Action: Ask subject (S) to sign consent form (*countersign form*). S begins experiment by completing mood ratings.

Cold Pressor Instructions

"The first task that we will begin with is a commonly used pain induction measure called a cold pressor task. This involves you immersing your hand into warm water above your wrist crease to standardise your hand temperature, then placing it into cold water. By doing this before the math task, I can gain a baseline measure of your perception of pain.

Specifically, I am going to ask you to place your left hand up to your wrist crease *(demonstrate)* into cold water for 4 minutes, but please let me know if you want to remove it sooner. I would prefer that you left your hand in the water until I tell you to take it out, but tell me if you have kept it in there for as long as you can possibly stand and want to remove it.

During the time that you have your hand in the cold water, I want you to do 2 things:

1. Rate ***pain intensity*** - or how strong the pain feels…
2. Rate ***unpleasantness*** - or how disturbing the pain is for you…

Although the cold water can feel equally as intense as it can feel unpleasant, it is important to rate these two aspects independently. One way of distinguishing between these two aspects of pain is to compare pain to sound. Imagine that you are listening to a radio – the volume is being turned up – you could probably rate how loud it is and how unpleasant it is to listen to. Pain intensity is like loudness – is the pain getting louder or softer? Unpleasantness doesn't only depend on intensity – it depends on other things that may affect you (e.g., the same pain intensity may be less

unpleasant for a deep sea diving instructor than for someone who has not had a lot of experience with cold water). Any questions? (*answer questions*).

In terms of making these ratings – I will ask you to move this pointer along this scale, where left side = 'No pain'/ 'Not unpleasant at all' and right side = 'Pain as bad as it could get'/ 'As unpleasant as it could get' *(demonstrate)*. So I will say 'pain' and 'unpleasantness' every 30 seconds, and you are to respond by moving the pointer to a spot on this scale that reflects your experience. Any questions? (*answer questions*).

Ok, lets start. Please place your left hand into the esky of warm water to standardise the temperature of your hand – I will tell you when the time is up. Then place your hand immediately into the esky filled with cold water and I will begin recording your pain and unpleasantness ratings".

Math Task

Action: Move S into Cubicle B to complete math task. Attach headset and electrodes to S's forearm and leave cubicle.

"Can you hear me clearly? Good. You may have noticed a camera in the corner of the room – it will be switched on during the math task to help me communicate with you, but none of this session will be recorded. Do you have any objections to that?

Action: If S objects - ask what the objection is about and deal with it.

"The math task is 20 minutes long – during which time you will be required to answer addition and subtraction type questions. Each question will appear in the middle of the screen, and you will use your **left hand only** to type in the answer using the number keys at the top of the keyboard. You will get feedback after each question that will either be 'Correct', 'Incorrect' or 'Too Slow'. Both 'Incorrect' and 'Too Slow' are considered wrong and you will hear a high pitch beep at the same time. At various intervals you will be asked to rate your mood. You will see a scale like the one above the keyboard (*refer to self-efficacy scale on sheet next to the computer*) with a blinking cursor in the middle – you are to shift the cursor left or right (according to how you feel at the time) with either of the arrow keys at the bottom of the keyboard. Press enter – this will move you onto the next mood rating. You will get a chance to practice – there will be no shocks delivered during the practice trials. After finishing these I would like you to rate your perceived ability to avoid the shocks during the task on the sheet of paper in front of you. Press a key and this will then take you onto the real task. When you are finished just knock on the door and I will come and get you. Any questions?"

Action: If not…turn headset off.

Action: Once math task is complete, direct S back to Cubicle A to repeat mood ratings and cold pressor task.

Debriefing/Finishing Up

"Any questions about the experiment that you have just participated in?".

Action: Answer any queries regarding the experiment. Explain that the math task is designed to be difficult, but do not disclose design. Prompt each S not to disclose details of experiment to prospective S's. Remunerate S for participation.

Appendix 5: Consent form, Study 2.

Division of Social Sciences, Humanities and Education

School of Psychology

MURDOCH UNIVERSITY
PERTH, WESTERN AUSTRALIA

South Street, Murdoch
Western Australia 6150
Telephone: (61–8) 9360 2186
Facsimile: (61–8) 9360 6492
psycholo@socs.murdoch.edu.au
http://www.murdoch.edu.au/
Registered Provider Code: 00125J
A.B.N. 61 616 369 313

CONSENT FORM

The effect of stress on pain

You are invited to participate in a study exploring the effects of stress on pain. Previous research has found that stress can lead to the release of naturally occurring substances in the body, which reduce how painful some experiences actually are. These substances are called opioids, and are released from the opioid system. Importantly, the results of this study will facilitate the development of treatment for depression and chronic pain.

We will attempt to induce psychological stress during a math task. You will be required to solve mental arithmetic problems while under a time constraint and your performance on the task may influence the frequency of electrical shocks administered via electrodes attached to your forearm. These shocks are mildly painful, but are harmless. Intermittently throughout the math task you will be asked to rate how painful and unpleasant the shocks are, and rate your mood. You will also be asked to rate your mood at various other stages during the experiment

We aim to investigate how the opioid system affects your responses and will do this by giving you either naltrexone or a placebo pill prior to the math task. Naltrexone blocks the effect of natural opioids and opiates (e.g., heroin, morphine, pethidine, codeine), and will produce withdrawal symptoms if narcotic substances are taken on a regular basis. The effects remain invisible for a large percentage of people although naltrexone can lead to mild side effects such as lethargy, nausea and headache in a few people.

In order to investigate any changes in your perception of pain before and after the math task, you will be asked to place your hand in cold water and rate the intensity of pain and unpleasantness experienced. Most people experience moderate amount of pain during this task.

Finally, you will have your blood pressure taken frequently throughout this study.

Your decision to participate will be greatly valued, however withdrawal of your consent and the desire to continue is acceptable at any time. Any questions regarding this study can be directed to Ashley Frew (Ph: 9368 0558) or Peter Drummond (Ph: 9360 2415).

Participant's Consent

I_____ have read the information above and have had any questions I have asked answered satisfactorily. I have agreed to participate in this study recognizing that I can withdraw my consent at any time without prejudicing my relationship with Murdoch University or with my doctor.

I agree that results from this research may be published, provided that my identifying information is withheld.

_____ _____
Participant **Date**

_____ /_____ _____
Primary Investigator **Supervisor** **Date**

Appendix 6: Medical checklist.

MEDICAL CHECKLIST

Please read the questions below and respond to each by placing a tick in the appropriate box indicating either **Yes**, **No** or that you are **Unsure.**

	Yes	No	Unsure
Have you ever taken naltrexone (Revia®)?	❒	❒	❒
If you have taken naltrexone, have you experienced any adverse reactions? *(Leave blank if you have **not** taken naltrexone before).*	❒	❒	❒
Do you use opiates regularly? (e.g., heroin, morphine, codeine, pethidine)	❒	❒	❒
Have you used opiates in the past 2 weeks?	❒	❒	❒
Are you in an acute stage of withdrawal from opiates?	❒	❒	❒
Do you need to use opiate analgesics in the next 24 hours?	❒	❒	❒
Do you plan to consume alcohol during the next 24 hours?	❒	❒	❒
Do you suffer from cardiac problems? (e.g., angina, dys-rhythmia, heart attacks)	❒	❒	❒
Do you have renal implants?	❒	❒	❒
Do you suffer from kidney problems?	❒	❒	❒
Have you ever experienced liver failure?	❒	❒	❒
Do you suffer from any type of diabetes?	❒	❒	❒
Are you suffering from acute hepatitis?	❒	❒	❒

Thank you
Ashley Frew.

Appendix 7: Instructions for subjects, Study 2.

INSTRUCTIONS FOR SUBJECTS

(Experiment 2)

Introduction

Action: Give subject (S) consent form to read and explain what will be done.

"Firstly, I want you to rate how you feel according to a number of mood descriptors. Secondly, you will have your blood pressure taken, and complete a *cold pressor task* that involves placing your hand into a warm water bath, then into a cold-water bath. I will explain this task in more detail later on. I will give you the drug, and you will wait approximately an hour before repeating these exercises. Once the exercises are completed, you will begin the computer-generated math task. On completion of the math task, you will repeat the mood ratings, cold pressor task and blood pressure measures. Any questions?".

Action: Ask S to sign consent form (*countersign form*). Begin experiment – S completes mood ratings.

Cold Pressor/Blood Pressure

"The first task that we will begin with is a commonly used pain induction measure called a cold pressor task. This involves you immersing your hand into warm water above your wrist crease to standardise your hand temperature, then placing it into the cold water.

Before we begin let's get you used to the BP unit by taking some measures. I will take your blood pressure (from the other arm) now and during the warm water to save some time. Please keep this arm still whilst the cuff is inflating, as the BP unit is very sensitive to movement. Whilst the cuff is inflating I will explain in more detail what I would like you to do during the cold pressor task….

Specifically, I am going to ask you to place your left hand up to your wrist crease *(demonstrate)* into cold water for 4 minutes, but please let me know if you want to remove it sooner. I would prefer that you left your hand in the water until I tell you to take it out, but tell me if you have kept it in there for as long as you can possibly stand and want to remove it.

During the time that you have your hand in the cold water, I want you to do 2 things:

1. Rate ***pain intensity*** - or how strong the pain feels…
2. Rate ***unpleasantness*** - or how disturbing the pain is for you…

Although the ice water can feel equally as intense as it can feel unpleasant, it is important to rate these two aspects independently. One way of distinguishing between these two aspects of pain is to compare pain to sound. Imagine that you are listening to a radio – the volume is being turned up – you could probably rate how loud it is and how unpleasant it is to listen to. Pain intensity is like loudness – is the pain getting louder or softer? Unpleasantness doesn't only depend on intensity – it depends on other things that may affect you (e.g., the same pain intensity may be less unpleasant for a deep sea diving instructor than for someone who has not had a lot of experience with cold water). Any questions? (*answer questions*).

In terms of making these ratings – I will ask you to move this pointer along this scale, where left side = 'No pain'/ 'Not unpleasant at all' and right side = 'Pain as bad as it could get'/ 'As unpleasant as it could get' *(demonstrate)*. So I will say 'pain' and 'unpleasantness' every 30 seconds, and you are to respond by moving the pointer to a spot on this scale that reflects your experience. Any questions? (*answer questions*).

Please place your left hand into the esky of warm water to standardise the temperature of your hand – I will tell you when the time is up. Then place your hand immediately into the esky filled with cold water and I will begin recording your pain and unpleasantness ratings".

Action: Once cold pressor task is completed, give S the drug. Instruct S's to read quietly for an hour whilst the drug is absorbed.

Math Task

Action: Move S into Cubicle B to complete math task. Attach headset and electrodes to S's forearm and leave cubicle.

"Can you hear me clearly? Good. You may have noticed a camera in the corner of the room – it will be switched on during the math task to help me communicate with you, but none of this session will be recorded. Do you have any objections to that?"

Action: If S objects - ask what the objection is about and deal with it.

"The math task is 30 minutes long – during which time you will be required to answer addition and subtraction type questions. Each question will appear in the middle of the screen, and you will use your **left hand only** to type in the answer using the number keys at the top of the keyboard. I would like you to keep your right arm as still as possible because I will be measuring your blood pressure at regular intervals from this arm, throughout the entire task. Please place the sock on your right hand…this sock will act as a reminder that you can't use this hand. You will get feedback after each question that will either be 'Correct', 'Incorrect' or 'Too Slow'. Both 'Incorrect' and 'Too Slow' are considered wrong and you will hear a high pitch beep at the same time. At various intervals you will be asked to rate your mood. You will see a scale like the one above the keyboard (*refer to self-efficacy scale on sheet next to the computer*) with a blinking cursor in the middle – you are to shift the cursor left or right (according to how you feel at the time) with either of the arrow

keys at the bottom of the keyboard. Press enter – this will move you onto the next mood rating. You will get a chance to practice – there will be no shocks delivered during the practice trials. After finishing these I would like you to rate your perceived ability to avoid the shocks during the task on the sheet of paper in front of you. Press a key and this will then take you onto the real task. When you are finished just knock on the door and I will come and get you. Any questions?".

Action: If not…turn headset off.

Action: Once math task is complete, direct S back to Cubicle A to repeat mood ratings, cold pressor task and blood pressure measures.

Debriefing/Finishing Up

"Any questions about the experiment that you have just participated in?"

Action: Answer any queries regarding the experiment. Explain that the math task is designed to be difficult, but do not disclose design. Prompt each S not to disclose details of experiment to prospective S's. Remunerate S for participation.

Appendix 8: Consent form, Study 3.

MURDOCH UNIVERSITY
PERTH, WESTERN AUSTRALIA

South Street, Murdoch
Western Australia 6150
Telephone: (61–8) 9360 2186
Facsimile: (61–8) 9360 6492
psycholo@socs.murdoch.edu.au
http://www.murdoch.edu.au/
Registered Provider Code: 00125J
A.B.N. 61 616 369 313

CONSENT FORM

The effect of mood on pain perception

You are invited to participate in a study exploring the effects of negative mood and stress on pain. Previous research has found that negative mood and stress can lead to the release of naturally occurring substances called opioids in the body, which reduce how painful some experiences actually are. Importantly, the results of this study will facilitate the development of treatment for depression and chronic pain.

We will attempt to induce psychological stress during a math task. You will be required to solve mental arithmetic problems while under a time constraint. Your performance on the task may influence the frequency of electrical shocks administered via electrodes attached to your ankle. These shocks are moderately painful, but are harmless. Intermittently throughout the math task you will be asked to rate how painful and unpleasant the shocks are, and rate your mood.

In order to investigate any changes in your perception of pain and discomfort before and after the math task, I will ask you to complete the following exercises:

- Place your hand into cold water for as long as you can and rate the intensity of pain and unpleasantness experienced (most people report a moderate amount of pain).
- Exhale forcefully into a tube for as long as possible.
- Complete a number of *Letter Symbol Matching Tasks*.
- Rate the pain intensity and unpleasantness of ankle shocks designed to elicit a pain reflex.
- Rate your mood.

We aim to investigate how the opioid system affects your responses and will do this by giving you either naltrexone or a placebo pill prior to the math task. Naltrexone has a very specific effect on the body, in that it blocks the action of natural opioids and opiates (e.g., heroin, morphine, pethidine, codeine) and will produce withdrawal symptoms if narcotic substances are taken on a regular basis. The effects remain invisible for a large percentage of non-opiate dependent people although it can lead to mild side-effects in some such as lethargy, nausea and headache.

You will also have your blood pressure taken frequently throughout this study.

Your decision to participate will be greatly valued, however withdrawal of your consent and the desire to discontinue is acceptable at any time. Any questions regarding this study can be directed to Ashley Frew (Ph: 9360 6735) or Peter Drummond (Ph: 9360 2415).

Participant's Consent

I_____ have read the information above and have had any questions I have asked answered satisfactorily. I have agreed to participate in this study recognizing that I can withdraw my consent at any time without prejudicing my relationship with Murdoch University.

I agree that results from this research may be published, provided that my identifying information is withheld.

_____ _____
Participant **Date**

_____ /_____ _____
Primary Investigator **Supervisor** **Date**

Appendix 9: Instructions for subjects, Study 3.

INSTRUCTIONS FOR SUBJECTS

(Experiment 3)

Introduction

"As you have read in the consent form, I am interested in exploring the effects of stress on pain perception. This experiment will take approximately 3 ¼ hours. I will ask you to complete the list of exercises and take the pill mentioned on the consent form at very the beginning of this experiment. You will have a 50-60 min break then we will complete the list of exercises again. Following this, you will do the math task and complete the list of exercises for the third and final time.

I will explain each exercise as we go but do you have any questions about the experiment before we begin?".

Action: If not… subject (S) completes the medical checklist and signs the consent form (*countersign form*); S begins experiment by completing mood ratings in Cubicle A.

Cold Pressor/Blood Pressure

"The first task that we will begin with is a commonly used pain induction measure called a cold pressor task. This involves you immersing your hand into warm water above your wrist (for 3 minutes) to standardise your hand temperature, then placing it into cold water. I will be taking your blood pressure from the other arm during this task, and I would like you to keep this arm still whilst the cuff is inflating, as the BP unit is very sensitive to movement.

Before we begin let's get you used to the BP unit by taking some measures. Whilst the cuff is inflating I will explain in more detail what I would like you to do during the cold pressor task….

After removing your hand from the warm water (at the end of 3 minutes), I want you to put your hand into the cold water and leave it there for as long as you possibly can, until you feel that the pain is too unpleasant to continue. While your arm is in the cold water I will ask you to rate two aspects of pain:

Pain intensity - or how strong the pain feels…
Unpleasantness - or how disturbing the pain is for you…

…at 30 second intervals on this scale (*hold up M-VAS*). Although the cold water can feel equally as intense as it can feel unpleasant, it is important to rate these two aspects independently. One way of distinguishing between these two aspects of pain

is to compare pain to sound. Imagine that you are listening to a radio – the volume is being turned up – you could probably rate how loud it is and how unpleasant it is to listen to. Pain intensity is like loudness – is the pain getting louder or softer? Unpleasantness doesn't only depend on intensity – it depends on other things that may affect you (e.g., the same pain intensity may be less unpleasant for a deep sea diving instructor than for someone who has not had a lot of experience with cold water). Any questions? (*answer questions*).

To rate pain intensity you will use the anchor points 'No pain'/'Pain as bad as it could get', and for unpleasantness ratings 'Not unpleasant at all'/'As unpleasant as it could get' to guide your ratings. You will slide the indicator with your right hand to a point reflecting each aspect of pain, one at a time (*demonstrate*).

Any questions? (*answer questions*).

I would like you now to place your hand into the warm water up to your wrist crease (*demonstrate*) for 3 minutes…"

(OR get them to do this during the instructions if the time taken to measure the first three BP readings has elapsed)

"The three minutes has elapsed. Could you now please place your hand into the cold water and leave it there for as long as you possibly can, until you feel that the pain is too unpleasant to continue. Please say 'Stop' when you want to remove your hand".

RIII Measurement

Attaching electrodes

"The next exercise involves the measurement of a pain reflex which leads to a movement of the leg resembling that of the knee-jerk when tapping the knee-cap – except the leg is pulled backwards. This reflex is elicited by electrical pulses delivered to the ankle, and is measured by recording muscle movement at the back of the thigh.

Come outside and I will get you to lie stomach-down on the mat so that I can place the electrodes on your thigh and ankle.

To help me locate the right muscle I want you to lift your right heel back towards your bottom. I would now like you to push your heel into the palm of my hand as if you are trying to touch your bottom with your heel. I will now have to get rid of the dead skin cells and hairs to ensure a good contact between your skin and the electrodes.

Now if you could roll onto your left side – so that you are facing the door of the lab, then I can attach the ground and the ankle electrodes".

Action: Move back into Cubicle A.

Measuring Skin Impedance

"Take a seat and I will now measure how much skin resistance there is at the thigh and ankle. If it is too high I may have to pumice and clean the skin a second time"

Action: If OK, attach electrodes to Biopac and S88 – if not, re-abrade the skin etc

Postural Position

"It is important that you remain as still and relaxed as possible when I am measuring this pain reflex so I want you to get into a comfortable position in the chair. I want you to now place your foot in this footrest (*demonstrate*). This will keep your leg still. In a moment I will place a neck-brace on you to keep the position of your head steady…but before we begin I want you to complete some other tasks. I would now like to place a headset on you and I will explain what I would like you to do".

Action: Attach headset to S and leave Cubicle A. Deliver instructions and complete Letter-Symbol Matching Task/Valsalva manoeuvre.

Action: Get subject to take capsule and THEN proceed with RIII measurement.

Measuring Pain Threshold

"When you turn the page over in your booklet you will see a scale ranging from 0-10 where 0 = No pain and 10 = Pain as bad as it could get. In a moment I will begin to deliver electric shocks to your ankle, one at a time. I would like you to rate the intensity of pain of each shock using this scale by calling out a number from 0-10. I want you to use '3' as the point at which the shock first becomes painful – this may feel like a pinprick. Thus you would reserve ratings of 1 or 2 for shocks that feel like a small tap or touch, and anything at '4' or above for shocks which become progressively more painful (e.g., stronger pinprick, sharp needle).

Shocks will be delivered relatively quickly so try to make your ratings fairly rapidly. Ok I want you to relax and remain as still as possible from now on… the first one will be delivered soon…."

Experimental Shocks (1.5 threshold)

"Now I will be giving you a small number of shocks of a higher intensity. I would like you to rate these shocks according to 0-10 pain intensity and unpleasantness scales over the page (*Explain that S is to differentiate their ratings like they did during the cold pressor task*).

Please stay as relaxed and still as you can…"

Action: Direct S to read quietly (whilst they wait for drug absorption).

<u>Letter Symbol Matching Task</u>

"Can you hear me clearly? Good. You may have noticed a camera in the corner of the room – it will be switched on for the following exercises to help me communicate with you, but none of this session will be recorded. Do you have any objections to that?".

Action: If S objects - ask what the objection is about and deal with it.

"In front of you is a booklet. Do not turn to the next page until I tell you to do so.

The front page includes instructions for the Letter Symbol Matching Task. There should be a row of boxes at the top of the page. In the upper part there is a letter, and beneath it is a symbol. Each letter has it's own symbol. Now look further down the page - there is another row of boxes. This time they have letters in the top but the boxes below are empty. I want you to practice filling these boxes in with the symbol that corresponds to each letter…go ahead. Tell me when you have finished.

In the first box you should have put a '+' to match the letter 'B', then a forward slash to match the letter 'A', then a circle with a line through it's center to match the letter 'I', and so on (*match these instructions whichever form is used*). Did you get them right – do you have any questions?

When I tell you to turn over the page I want you to fill in as many boxes as you can until I tell you to stop. Complete the boxes from left to right (across the page) and don't skip any as you do them. Work as fast and as accurately as you can. Ready? Turn the page now…"

Action: After 3 mins – "Stop".

Valsalva Manoeuvre

"Taped to the desk in front of you is a clear piece of tubing – unhook it from the tape and hold it to your mouth. I want you to blow into this tube as hard and for as long as you can when I tell you to start, but do not 'fill' your lungs with air before beginning. When you don't think you can continue any longer say: "STOP!" Any questions? Ok start now!

When they stop say: Thanks. Now I will come in and put the neck-brace on so that we can measure the pain reflex…."

Math Task

Action: Ask S to move into Cubicle B.

"The math task is 25 minutes long – during which time you will be required to answer addition and subtraction type questions. Each question will appear in the middle of the screen, and you will use your left hand only to type in the answer using the number keys at the top of the keyboard. I would like you to keep your right arm as still as possible because I will be measuring your blood pressure at regular

intervals from this arm, throughout the entire task. Please place the sock on your right hand…this sock will act as a reminder that you can't use this hand. You will get feedback after each question that will either be 'Correct', 'Incorrect' or 'Too Slow'. Both 'Incorrect' and 'Too Slow' are considered wrong and you will hear a high pitch beep at the same time. At various intervals you will be asked to rate your mood. You will see a scale like the one next to the keyboard (*refer to self-efficacy scale on sheet next to the computer*) with a blinking cursor in the middle – you are to shift the cursor left or right (according to how you feel at the time) with either of the arrow keys at the bottom of the keyboard. Press enter – this will move you onto the next mood rating. You will get a chance to practice – there will be no shocks delivered during the practice trials. After finishing these I would like you to rate your perceived ability to avoid the shocks during the task on the sheet of paper in front of you. Press a key and this will then take you onto the real task. When you are finished just knock on the door and I will come and get you. Any questions?"

Action: If not…turn headset off.

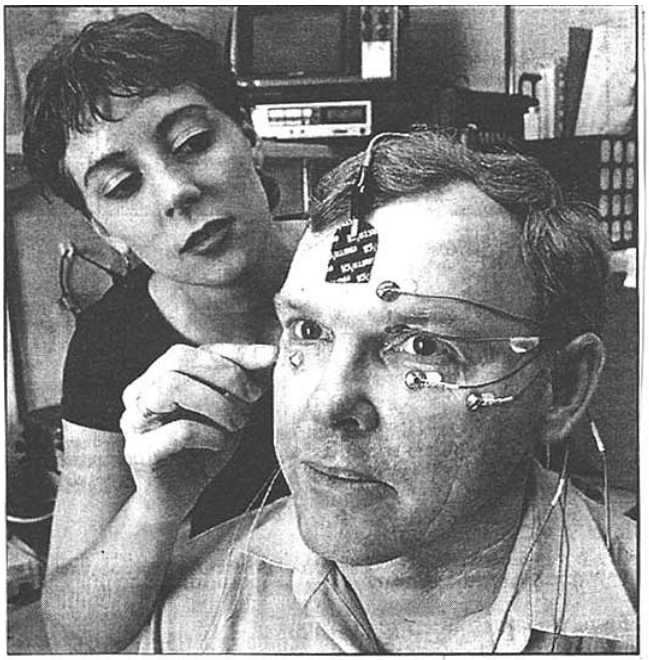
Debriefing/Finishing Up

"Any questions about the experiment that you have just participated in?"

Action: Answer any queries regarding the experiment. Explain that the math task is designed to be difficult, but do not disclose design. Prompt each S not to disclose details of experiment to prospective S's. Remunerate S for participation.

Appendix 10: Example of recruitment articles, Study 4.

Community newspaper articles:



Ashley Frew wires up PhD supervisor associate professor Peter Drummond.

Depressed? – read on

DEPRESSION and its affect on pain are under the spotlight in a study now being completed by Murdoch University student Ashley Frew.

Ms Frew, a PhD Psychology student, needs volunteers to help in the study of depression's affect on the body's release of endorphins, natural morphine-like substances.

"Endorphins can moderate an individual's mood and pain experience, enabling them to cope more effectively," she said.

"From the high rates of chronic pain suffered by individuals who are depressed, it is suspected that this system works in a different way for those who are depressed compared with those who are not depressed."

Volunteers who are depressed but not taking anti-depressants and those who are not depressed are needed for the study.

Volunteers will be paid $20 for participation in a two-and-a-half hour session.

Call 9360 6735 or 0407 476 441.

THE WEST AUSTRALIAN **HEALTH+MEDICINE** WEDNESDAY DECEMBER 12 2001

health news

Depressed volunteers sought

THE effects of endorphins released into the body during negative mood states are being examined by Ashley Frew, who is completing her PhD in psychology at Murdoch University.

The study is looking at how depression can affect a person's perception of pain.

Volunteers are needed and will be paid $20 each to take part in the study. Each participant will take part in a two-hour session where they will be exposed to mild amounts of discomfort.

"I am looking for volunteers who are somewhat depressed but not taking anti-depressant medication or currently suffering from physical pain," Ms Frew said.

"Also, I am looking for a control group who are not depressed or suffering from any physical pain and who have no history of mental illness."

For more information please contact her on 9360 6735 or 0407 476 441.

GP newsletter:

This is printed at the requrest of Murdoch University PhD candidate Ashley Frew

A new Look at the Link Between Depression and Pain...

Hello! My name is Ashley Frew and I am currently completing my PhD in Psychology at Murdoch University. I am in need of participants for my research investigating how depression affects pain inhibitory mechanisims in the body.

Needed are participants suffering from major depression (single or recurrent depressive episode) in addition to healthy individuals, ranging in age from 18-55. Participants must not suffer from any major medical condition, or have used antidepressants or any pain relief medication int he last 2-4 weeks.

Where: Murdoch University, School of Psychology (temporary parking permit and map will be provided).

Payment: $20 for a 2-3 hour session (one session only).

Contact: Ashley Frew - 9360 6735 **Mobile:** 0407 476 441.

Perth Division of General Practice News

WISH newsletter (non-governmental organization):

Coming Events....Coming Events....Coming Events

DEPRESSION Study

Did you know that depression can effect aspects of your functioning, even how we perceive pain?

Want to know more?

Better still - would you like to help contribute to our knowledge about depression by being part of a study to be conducted at Murdoch University?

Within the community depression has reached epidemic proportions and it is only through extensive research that the effects of this disabling disorder are becoming clearer.

Ashley Frew (a PhD student at Murdoch University) is investigating the effects of mood on pain. People who are currently suffering from depression, - and those who are not -, are invited to take part in a two hour study being conducted at Murdoch's School of Psychology. Participants will be reimbursed for their time.

For further information please contact Ashley on 9360 6735 or on her mobile 0407 476 441.

Appendix 11: Structured Clinical Interview for DSM-IV Axis I Disorders.

Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version
First, Spitzer, Gibbon, & Williams, 1997
(modified Nov, 2001 for Exp. 4)

INTERVIEW DATE:	PARTICIPANT:
Demographics What's your date of birth? Are you married, single, divorced? Do you have children?	
Educational How far did you get in school? - if failed to complete program enrolled in - Why didn't you finish?	
Occupational What kind of work do you do? Are you working now? - if yes - How long have you worked there? - if no - Why is that? How are you supporting yourself? Has there ever been a time when you were unable to work or go to school?	
Status Of Current/Past Treatment/s Have you received any kind of treatment in the past month? - if yes – When did you start coming to the clinic/ group/ office/ hospital? or When did you start taking ---- medication? - if no – Have you ever received treatment for emotional or psychiatric problems? What was that for? When was that? What treatments did you get? Have you ever been a patient in a psychiatric hospital?	

Chief Complaint What is the major problem you are having trouble with? (Tell me more about that… or What do you mean by…?) When did this begin? or When were you last feeling OK? Is this something new or a return of something you had before? After it started, what happened next? Did other things start to bother you?"	
Other Current Problems How has your physical health been? Do you take any other medications or vitamins (other than those you have already told me about?)? How much have you been drinking in the past month? Have you been taking any drugs in the past month (e.g. marijuana, cocaine, ecstasy)?	
Social Functioning How have you been spending your spare time? Whom do you spend time with?	
MAJOR DEPRESSIVE EPISODE… *5 or more of the following symptoms – where at least one symptom is either 1 or 2* Now I am going to ask you some more questions about your mood. In the past month …	
1. Has there been a period of time when you were feeling depressed or down most of the day, nearly every day? if yes – How long did that last? As long as 2 weeks? 2. What about losing interest or pleasure in things you usually	

enjoyed?
if yes – Was it nearly every day? How long did it last? As long as 2 weeks?

If neither in the past month...for differential diagnosis
Has there ever been a time like that?
Have you had more than one time like that?
Which one was the worst?

Did you lose or gain weight?
- if yes - How much? Were you trying to lose weight?
- if no – How was your appetite? What about compared with your usual appetite (more or less)? Did you have to force yourself to eat? Was that nearly every day?

How were you sleeping?
- trouble falling asleep
- waking frequently
- trouble staying asleep
- waking too early
- sleeping too much
- number of hours compared to normal

Were you so fidgety or restless that you were unable to sit still?
- if yes - Did other people notice?
- if no – what about the opposite – moving more slowly? Did other people notice?

What was you energy like?
- tired all the time? Was this nearly every day?

How did you feel about yourself?
- worthless? Was this nearly every day?

Did you have trouble concentrating?
- if yes - Did other people notice?

What kinds of things did this interfere with?
- if no – was it hard to make decisions about everyday things?

Were things so bad that you were thinking a lot about death or that you would be better off dead? What about thinking of hurting yourself?
- if yes - Did you do anything to hurt yourself?

Functioning During Depression
Symptoms cause clinical significant distress or impairment (social, occupational, other important areas of functioning)
Has the depression made it hard for you to do your own work, take care of things at home, or get along with other people?

Differential Diagnosis
Just before this began, were you physically ill?
Just before this began, were you taking any medications?
- if yes – any change in the amount that you were taking?

Just before this began, were you drinking or using any street drugs?

Expanding on substance use....

When the mood symptoms began were you already using the substance or had you just stopped or cut down your use?

Do you think your mood symptoms are in any way related to your substance use?
- Which came first the mood or the substance symptoms?
- Have you had a period of time when you stopped using – did the mood symptoms get better?
- Have you had any other episodes of

mood symptoms – were you using then? When you stopped did the mood symptoms get better? Does your drinking/ drugging cause problems for you or anyone else? Do they object to your drinking/ drugging? Did this begin soon after someone close to you died? How many separate times have you been depressed nearly every day for at least 2 weeks and had several of the symptoms that you just described, such as …? **MANIC EPISODE…** Have you ever had a period of time when you were feeling so good/ high/ excited or hyper that other people thought you were not your normal self or you got into trouble? - if yes - Did anyone say that you were manic? Was that more than just feeling good? How long did this last – *as long as 1 week*? - if no – What about a period of time when you were so irritable that you found yourself shouting at people or starting fights or arguments? *During period of mood disturbance, 3 (4 if irritable) or more of following symptoms…* How did you feel about yourself? – *inflated self esteem or grandiosity?* Did you need less sleep than usual? – *decreased need for sleep e.g. 3 hrs* Were you much more talkative than usual? - if yes - Did people have trouble stopping you talking? Were your thoughts racing through your head? Were you so easily distracted by things around you that you had trouble	

concentrating, or staying on one track? How did you spend your time? Were you so active that friends and family were concerned about you? – *increase in goal directed activity or psychomotor agitation* Did you do anything that could have caused trouble for you and/or your family? *Excessive involvement in pleasurable activities that have a high potential for negative consequences* Did you have serious problems at home, or work because you were (*symptoms*) or did you have to go into a hospital?	
DYSTHYMIA… For the past couple of years have you been bothered by depressed mood, most of the day more days than not? *more than half the time for at least 2 years; presence of 2 or more of the following symptoms* - if yes – What was that like? During these periods do you find that most of the time you - lose your appetite (or overeat)? Have trouble sleeping? Have little energy to do things or feel tired a lot? Feel down on yourself? Have trouble concentrating /making decisions? Feel hopeless? How long have you been feeling this way? What is the longest time during this period of long-lasting depression that you felt OK? - *Has never been without the symptoms for longer than 2 months* Did it begin gradually or did it start with a bad period of depression? *For differential diagnosis*	
PSYCHOSIS… Now I am going to ask you about unusual	

experiences that people sometimes have

Delusions- false personal beliefs based on incorrect inferences about external reality; not ordinarily accepted by other members of the person's culture
Has it ever seemed like people were talking about you or taking special notice of you?
Were you convinced they were talking about you or did you think it might have been you imagination?
What about anyone going out of his or her way to give you a hard time or trying to hurt you?
Did you ever feel that you were especially important in some way or that you had special powers to do things that other people couldn't do?
Did you ever feel that something was very wrong with you physically even though your doctor said nothing was wrong – like you had cancer or some other terrible disease?
Have you ever been convinced that something was very wrong with the way a part or parts of your body looked?
Did you ever have any unusual religious experience?
Did you ever feel that you had committed a crime or done something terrible for which you should be punished?
Did you ever feel that someone or something was controlling your thoughts or actions against your will?
Did you ever believe that someone could read your mind?
Did you ever feel that certain thoughts that were not your own were put into your head or taken out of your head?
Hallucinations – a sensory perception that ha the compelling sense of reality of a true perception but occurs without external stimulation of the relevant sensory organ.
Did you hear things that other people couldn't hear?
Did you ever have visions or see things that others couldn't?
What about strange sensations in your body or on your skin?
What about smelling or tasting things that other people couldn't smell or taste?
Disorganised speech
Grossly disorganised/ catatonic behaviour
Negative symptoms i.e. flat affect

ANXIETY DISORDERS…

PANIC DISORDER (W/OUT AGORAPHOBIA)
Recurrent unexpected panic attacks; reach a peak in less than 10 minutes; At least 4 symptoms.
Have you ever had a panic attack e.g. suddenly feeling frightened or anxious; suddenly developed a lot of physical symptoms (e.g. heart racing, sweating, shaking, breathlessness, choking, chest pain, nausea, dizzy, detached, fear losing control, afraid might die, numbness, flushes)?
- if yes – did these attacks ever come out of the blue? How many? How long did it take for symptoms to come on and get really bad?

At least one attack has been followed by 1 month (or more) of one of these worries/ change in behaviour…
Did you worry that there may be something terribly wrong with you e.g. heart attack, going crazy or that you may have another?
- if no – did you do anything differently because of the attacks e.g. avoid certain activities like exercise, shopping, make sure you are near an exit?

With agoraphobia…
Anxiety about being in a place where escape may be difficult
Are there situations that make you nervous because you are afraid that you might have

a panic attack? - if yes – Do you avoid these situations? *Agoraphobic situations are avoided.*	
OCD *Obsessions -Recurrent/ persistent thoughts that are inappropriate – causing marked distress.* Have you ever been bothered by thoughts that did not make any sense and kept coming back to you even when you tried not to have them (e.g. contaminated by dirt, wanting to hurt someone?) *Complusions – repetitive behaviours or mental acts that the person feels driven to do/ rules must be applied rigidly* Was there ever anything that you had to do over and over again and could not resist doing such as washing your hands again and again, counting up to a certain number, or checking something several times to make sure you had done it right? *Excessive obsession or compulsion*	
PTSD *Person experienced/ witnessed actual or threatened serious injury or death* Sometimes thing happen to people that are extremely upsetting – things such as being in a life-threatening situation (e.g. major disaster, accident, assaulted); seeing another person killed/dead, or badly hurt; or hearing about something horrible that has happened to someone you know. At any time during your life have any of these kinds of things happened? *Response involved fear, helplessness or horror* How did you react when trauma happened (with fear, helplessness or horror)? *Trauma is re-experienced in 1 or more ways lasting more than one month*	

Now I would like to ask a few questions about specific ways it may affect you - Do thoughts of the trauma come into your head when you didn't want them to? - What about having dreams of the trauma? - What about finding yourself acting as if you were back in the situation? - What about getting upset when something reminded you or the trauma? - What about having physical symptoms such as sweating, breathlessness, heart racing? - Have you avoided thinking or talking about what happened? - Have you stayed away from things/ people that reminded you of the trauma? - Have you been unable to remember one aspect? - Have you been much less interested in doing things that used to be important to you? - Have you felt distant or cut off from others? - Have you felt numb? - Have you changed your plans for the future? *Persistent symptoms of increased arousal* - Trouble sleeping? - Unusually irritable? - Trouble concentrating? - Watchful or on-guard even when there is not reason to be? - Been jumpy? *Significant distress or impairment in social, occupational or other important areas; Symptoms more than 1 month* **SOCIAL PHOBIA** *Marked interference with routine, socia/, occupational/relationship functioning.* Is there anything that you have been afraid	

to do or felt uncomfortable doing in front of other people such as speaking, eating or writing?	
SPECIFIC PHOBIA *Marked and persistent fear that is excessive and unreasonable – interferes with functioning* Are there any other things that you have been especially afraid of such a flying, seeing blood, getting a shot, heights, closed places, or certain kinds of animals?	
GAD *Excessive worry more days than not for at least 6 months* In the past 6 months have you been particularly nervous or anxious?	
SOMATOFORM DISORDERS Over the past several years, what has your physical health been like? How often have you had to go to a doctor because you weren't feeling well? Was the doctor able to find out what was wrong? Do you worry about your physical health? Does you doctor think you worry too much? Some people are very bothered by the way they look – does this bother you? **EATING DISORDERS** *Anorexia Nervosa* Have you ever had a time when you weighed much less than other people thought you ought to weigh? *Bulimia Nervosa* Have you often had times when your eating was out of control?	

ADJUSTMENT DISORDER *Emotional or behavioural symptoms in response to an identifiable stressor occurring within 3months of the stressor* Did anything happen to you just before the onset of current symptoms? Do you think that the stressor had anything to do with your symptoms? *Marked distress in excess of what would be expected* What effect have the symptoms had on your ability to do things? Have you had this reaction before? Were you having symptoms before the stressor happened? *Symptoms do not persist for more than 6 months once stressor (and consequences) have been terminated.* How long has it been since the stressor?	

Appendix 12: Consent form, Study 4.

Division of Social Sciences, Humanities and Education

School of Psychology

MURDOCH UNIVERSITY
PERTH, WESTERN AUSTRALIA

South Street, Murdoch
Western Australia 6150
Telephone: (61–8) 9360 2186
Facsimile: (61–8) 9360 6492
psycholo@socs.murdoch.edu.au
http://www.murdoch.edu.au/
Registered Provider Code: 00125J
A.B.N. 61 616 369 313

CONSENT FORM

The link between depression, pain and the opioid system.

You are invited to participate in a study exploring the effects of mood on pain perception. Previous research has found that negative mood and stress can lead to the release of naturally occurring substances in the body, which reduce how painful some experiences actually are. These substances are called opioids, and are released from the opioid system. It is suspected that depression may affect the release of opioids. The purpose of this study is to investigate how negative mood and depression affects natural pain inhibitory mechanisms. Importantly, these results will facilitate the development of treatment for depression and chronic pain.

We aim to investigate how the opioid system functions and will do this by giving you either naltrexone or a placebo pill. Naltrexone has a very specific effect on the body, that is it blocks the action of natural opioids, such as endorphins. The effects remain invisible for a large percentage of people although it can lead to mild side-effects such as lethargy, nausea and headache in a few people. Naltrexone should not be taken if you are currently using opiates such as heroin, morphine, codeine, or have problems with your liver or any other serious medical condition.

We will attempt to induce psychological stress during a math task. You will be required to solve mental arithmetic problems while under a time constraint. Your performance on the task may influence the frequency of electrical shocks administered via electrodes attached to your forearm. These shocks are moderately painful, but are harmless.

In order to investigate any changes in your perception of pain before and after the math task, the blink reflex, which is a physiological measure of pain, will be measured. Mild electrical pulses will be sent through electrodes attached to your forehead. These pulses are very brief and harmless, and are described by most to feel like a mild pin-prick.

It has been found that the application of a more intense pain tends to alter the experience of the less intense pain. We will investigate this phenomenon by asking you to place your hand in iced water whilst we measure the blink reflex. Most people report moderate burning or stinging during the cold-water task. However, these effects are temporary.

We will also ask you to place your foot in cold water for as long as you can tolerate just prior to, and after the math task. Our aim is to find out whether the math stressor alters your tolerance to pain.

You will have your blood pressure taken frequently and will be asked to rate your mood at various stages.

Your decision to participate will be greatly valued, however withdrawal of your consent and the desire to discontinue is acceptable at any time. Any questions regarding this study can be directed to Ashley Frew (Ph: 9360 6735; mob: 0407 476 441) or Peter Drummond (Ph: 9360 2415).

Participant's Consent

I_____ have read the information above and have had any questions I have asked answered satisfactorily. I have agreed to participate in this study recognizing that I can withdraw my consent at any time without prejudicing my relationship with Murdoch University.

I agree that results from this research may be published, provided that my identifying information is withheld.

_____	_____
Participant	**Date**
_____	_____
Primary Investigator	**Date**
_____	_____
Supervisor	**Date**

Appendix 13: Instructions for subjects, Study 4.

INSTRUCTIONS FOR SUBJECTS

(Experiment 4)

Introduction

Action: Seat subject (S) in the communal area and get them to read through the consent form when they initially arrive; Sit on stool and begin instructions…

"As you have read in the consent form, I am interested in investigating how mood (e.g., depression) and stress affects pain perception. This experiment will take approximately 2 1/2 hours. In order to gain a baseline reading of your perception of pain I will be using a physiological measure of pain called the blink reflex. I will deliver very brief mild electrical pulses just under your left eyebrow (*demonstrate*), and measure the muscle movement (or blink) from under both eyes. I will ask you to take a capsule containing either naltrexone or glucose (placebo), after which we will repeat the blink reflex procedure when your hand is immersed in cold water. You will have approximately 50-60 minutes break, during which I would like you to complete some questionnaires enquiring about your mood over the past 2 weeks. Finally, we will repeat the blink reflex procedure and a different cold-water task before and after you complete the math task. I will explain each exercise as we go but do you have any questions about the experiment before we begin?".

Action: If not… S completes consent form (*countersign form*), medical checklist and mood ratings. Begin experiment.

Blood Pressure

"In order to get an accurate picture of your resting blood pressure I will measure it a few times using this automatic device. I would like you to remain quiet, still and calm whilst the cuff is inflating as the BP unit is very sensitive to muscle tension and any movement".

Blink Reflex

"I would like you to move onto this stool so that I can attach the electrodes for the blink reflex procedure".

Action: After S is seated, place the head-band on…

"Firstly I will have to remove any dead skin from a number of places on your face with paste that that has an exfoliating effect. I'd like you to close your eyes while I do this…now I am going to clean the skin with alcohol. This should sting a little if I have gotten rid of the dead skin layer. It is really important that you keep your eyes shut during this and for a little while after until the stinging has stopped"

Action: Place the electrodes on ("Could you please look up, thanks").

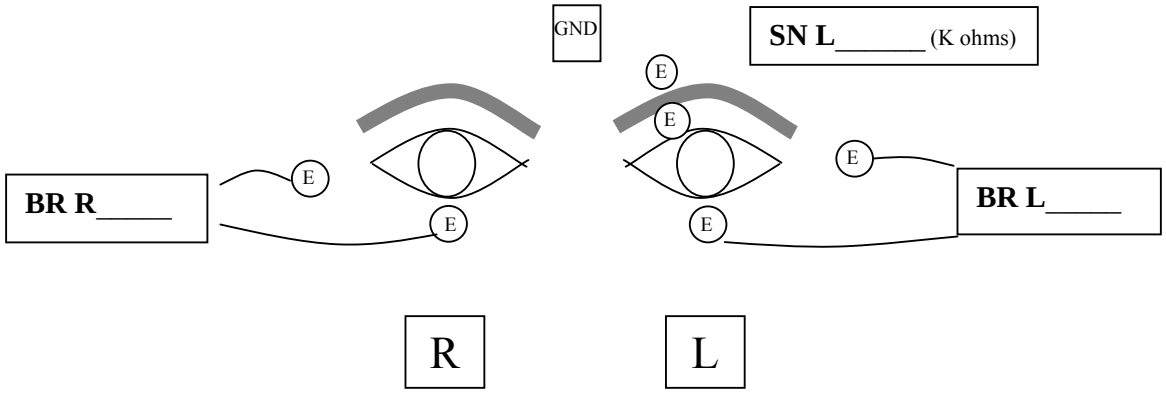


Figure 1: Diagrammatical depiction of electrode (E) placement during measurement of the blink reflex, and recording of skin impedance at each site. GND = ground electrode; SN = supraorbital notch; BR = blink reflex; R = right eye, L = left eye.

Action: Measure skin impedance for each set of electrodes…if sufficiently low, ask S to move into Cubicle A. Connect EMG electrodes, ground and stimulating electrodes.

Action: Place the headset/intercom on and leave Cubicle A.

"Can you hear me clearly? Good. You may have noticed a camera in the corner of the room – it will be switched on for the following exercises to help me communicate with you, but none of this session will be recorded. Do you have any objections to that?".

Action: If S objects - ask what the objection is about and deal with it.

"Beside you in the small foam esky is warm water. I would like you to place your left hand in up to your wrist crease whilst we complete the blink reflex procedure. This is to standardise your hand temperature before placing your hand into the cold water.

In a moment I will begin to deliver one brief shock at a time to elicit the blink reflex. I would like you to rate two aspects of pain after each shock:

Pain intensity - or how strong the pain feels…
Unpleasantness - or how disturbing the pain is for you…

I would like you to make these ratings using the scales taped to the wall in front of you by calling out a number from 0-9, where 0 = 'No pain' or 'Not unpleasant at all' and 9 = 'Pain as bad as it could get' or 'As unpleasant as it could get'.

Although the shocks can feel equally as intense as unpleasant, it is important to rate these two aspects independently. A way of distinguishing between these two aspects is to compare the electric shocks to sound. Imagine that you are listening to a radio – the volume is being turned up – you could probably rate how loud it is and how unpleasant it is to listen to. Pain intensity is like loudness – is the pain getting louder or softer? Unpleasantness doesn't only depend on intensity – it depends on other things that may affect you (e.g., the same pain intensity may be less unpleasant for an electrician than for someone who has not had a lot of experience with electric shocks). Any questions?

When making your ratings, I want you to use:
0 - when you feel no sensation.
1 - for shocks that are mildly painful and unpleasant
2 or **3** - for shocks that are moderately painful and unpleasant
4, **5** or **6** - for shocks that are somewhat severely painful and unpleasant
7 or **8** - for shocks that are severely painful and unpleasant
9 - for those that are the worst pain imaginable, or as unpleasant as they could get.

Each shock will be presented close together – so please make your ratings quickly. I want you to relax and remain as still as possible from now on and keep your eyes focussed on the cross positioned between both scales... the first shock will be delivered soon".

Action: Administer capsule to S.

Blink Reflex & Cold Pressor

"In a moment I would like you to remove your hand from the warm water and place it into the cold whilst we measure the blink reflex again. However, I would like you to keep your hand in the cold water for 30 seconds just before we start to measure the blink reflex, and keep it in there until we have finished. Are you ready? Please place your hand into the cold water now".

Psychometric Tests

"There will be approximately 50-60 minutes before we begin testing again. During that time I would like you to complete each of these questionnaires. They should take between 5-10 minutes each. Please read the instructions before completing them. Once these are done there are some magazines that you can read. I will inform you when it is time to begin testing again".

Action: Turn headset off and enter Cubicle A to deliver questionnaires.

Blood Pressure/Mood ratings

"It is time to start testing again, but before we begin I would like to measure your blood pressure again. I also want you to complete another set of mood ratings according to how you feel now".

Blink Reflex – Repeated

Action: Turn headset on.

"In a moment we will repeat the blink reflex procedure where you will rate each shock again. I would like you to place your left hand into the warm water bath as you did before. Now, I would like you to remain as relaxed and still as you can - in a moment I will deliver the first shock".

Blink Reflex & Cold Pressor – Repeated

"When I tell you to, I want you to place your left hand into the cold water for 30 seconds, prior to beginning the blink reflex procedure again, and then keep it there until we finish - just like you did before".

Foot Cold Pressor (2°C)

" OK now I would like you to complete a cold water task on it's own. This time the task will be a little different…I want you to place your left foot into the cold water and leave it there for as long as you possibly can, until you feel that the pain is too unpleasant to continue. While your foot is in the cold water I will ask you to rate *pain intensity* (how strong the pain feels) and *unpleasantness* (how disturbing the pain is for you) - at 30-second intervals using the scales that you used during the blink reflex procedure. Although the cold water can feel equally as intense as it is unpleasant, it is important to rate these two aspects independently. Just like you did with the blink reflex shocks".

Math Task

Action: Ask S to move into Cubicle B. Place headset on S.

"The math task is 25 minutes long – during which time you will be required to answer addition and subtraction type questions. Each question will appear in the middle of the screen, and you will use your **left hand only** to type in the answer using the number keys at the top of the keyboard. I would like you to keep your right arm as still as possible because I will be measuring your blood pressure at regular intervals from this arm, throughout the entire task. Please place the sock on your right hand…this sock will act as a reminder that you can't use this hand. You will get feedback after each question that will either be 'Correct', 'Incorrect' or 'Too Slow'. Both 'Incorrect' and 'Too Slow' are considered wrong and you will hear a high pitch beep at the same time. At various intervals you will be asked to rate your mood. You

will see a scale like the one in front of you (*indicating the self-efficacy scale on sheet next to the computer*) with a blinking cursor in the middle – you are to shift the cursor left or right (according to how you feel at the time) with either of the arrow keys at the bottom of the keyboard. Then press enter – this will move you onto the next mood rating. You will get a chance to practice – there will be no shocks delivered during the practice trials. After finishing these I would like you to rate your perceived ability to avoid the shocks during the task on the sheet of paper in front of you. Press a key and this will then take you onto the real task. When you are finished just knock on the door and I will come and get you. Any questions?"

Action: If not…turn headset off.

Mood Ratings

Action: Return to Cubicle A and place headset on.

"Now that the math task is finished, I would like you to complete another set of mood ratings according to how you feel now".

Blink Reflex – Repeated

"In a moment we will repeat the blink reflex procedure for the final time. Please remain as relaxed and still as you can - the first shock will be delivered soon".

Foot Cold Pressor & Blood Pressure

"The cold-water task is the final task to be completed. As before, I would like you to place your foot into the cold water and leave it there for as long as you possibly can, until you feel that the pain is too unpleasant to continue. Like before, I want you to rate *pain intensity* and *unpleasantness* of the cold water at 30-second intervals using the scales taped to the wall in front of you.

First off though, we must standardise the temperature of your foot in warm water. While we are doing this I will take one final set of BP measures".

Debriefing/Finishing Up

"Any questions about the experiment that you have just participated in?"

Action: Answer any queries regarding the experiment and explain what this experiment was investigating. Explain that the math task is designed to be difficult and induce stress. Note address details of each S, explaining that a letter regarding the findings will be sent when the study is completed. Remunerate S for their participation.

REFERENCES

A.C.E.R. (1972). The Naylor-Harwood Adult Intelligence Scale. Melbourne, Australia: Australian Council for Education Research.

A.P.A. (1994). Diagnostic and statistical manual of mental disorders (Fourth ed.). Washington, DC: American Psychiatric Association.

Abbott, B.B., Schoen, L.S., & Badia, P. (1984). Predictable and unpredictable shock: Behavioral measures of aversion and physiological measures of stress. Psychological Bulletin, 96(1), 45-71.

Abraham, H.D., & Joseph, A.B. (1986). Bulimic vomiting alters pain tolerance and mood. International Journal of Psychiatry in Medicine, 16(4), 311-6.

Adler, G., & Gattaz, W.F. (1993). Pain perception threshold in major depression. Biological Psychiatry, 34(10), 687-9.

Agren, H., Terenius, L., & Wahlstrom, A. (1982). Depressive phenomenology and levels of cerebrospinal fluid endorphins. Annals of the New York Academy of Sciences, 398, 388-98.

Ahles, T.A., Blanchard, E.B., & Leventhal, H. (1983). Cognitive control of pain: Attention to the sensory aspects of the cold pressor stimulus. Cognitive Therapy & Research, 7(2), 159-177.

Aitken, R.C. (1969). Measurement of feelings using visual analogue scales. Proceeding of the Royal Society of Medicine, 62(10), 989-93.

Akil, H., Madden, J., Patrick, R.L., & Barchas, J.D. (1976). Stress-induced increase in endogenous opiate peptides: Concurrent analgesia and its partial reversal by naloxone. In H. Kosterlitz (Ed.), Opiates and endogenous opioid peptides (pp. 63-70). Amsterdam: Elsevier.

al'Absi, M., Wittmers, L.E., Ellestad, D., Nordehn, G., Kim, S.W., Kirschbaum, C., & Grant, J.E. (2004). Sex differences in pain and hypothalamic-pituitary-adrenocortical responses to opioid blockade. Psychosomatic Medicine, 66(2), 198-206.

Alexopoulos, G.S., Inturrisi, C.E., Lipman, R., Frances, R., Haycox, J., Dougherty, J.H., Jr., & Rossier, J. (1983). Plasma immunoreactive beta-endorphin levels in depression. Effect of electroconvulsive therapy. Archives of General Psychiatry, 40(2), 181-3.

Algarabel, S. (1985). Learned helplessness, human depression, and perhaps endorphins? Behavioral & Brain Sciences, 8(2), 369.

Almay, B.G., Johansson, F., von Knorring, L., Terenius, L., & Wahlstrom, A. (1978). Endorphins in chronic pain. I. Differences in CSF endorphin levels between organic and psychogenic pain syndromes. Pain, 5(2), 153-62.

Al-Musawi, N.m.M. (2001). Psychometric properties of the Beck Depression Inventory-II with university students in Bahrain. Journal of Personality Assessment, 77(3), 568-579.

Amir, S., & Amit, Z. (1978). Endogenous opioid ligands may mediate stress-induced changes in the affective properties of pain related behavior in rats. Life Sciences, 23(11), 1143-51.

Amir, S., & Amit, Z. (1979). Enhanced analgesic effects of stress following chronic administration of naltrexone in rats. European Journal of Pharmacology, 59(1-2), 137-40.

Amit, Z., & Galina, Z.H. (1986). Stress-induced analgesia: Adaptive pain suppression. Physiological Reviews, 66(4), 1091-120.
Anderson, W.S., Sheth, R.N., Bencherif, B., Frost, J.J., & Campbell, J.N. (2002). Naloxone increases pain induced by topical capsaicin in healthy human volunteers. Pain, 99(1-2), 207-216.
Andrade, L., Gorenstein, C., Vieira Filho, A.H., Tung, T.C., & Artes, R. (2001). Psychometric properties of the Portuguese version of the State-Trait Anxiety Inventory applied to college students: Factor analysis and relation to the Beck Depression Inventory. Brazilian Journal of Medical and Biological Research, 34(3), 367-374.
Andreassi, J.L. (1989). Psychophysiology: Human behavior and physiological response. New Jersey: Lawrence Erlbaum Association.
Angst, J.V., Autenrieth, V., Brem, F., Kovkkov, M., Meyer, H., Stassen, H.H., & Storck, U. (1979). Preliminary results of treatment with beta-endorphin in depression. In E. Usdin, W.E. Bunney, Jr., & N.S. Kline (Eds.), Endorphins in mental health research (pp. 518-528). New York: Macmillan Press, Ltd.
Antony, M.M., Bieling, P.J., Cox, B.J., Enns, M.W., & Swinson, R.P. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. Psychological Assessment, 10(2), 176-181.
Arnau, R.C., Meagher, M.W., Norris, M.P., & Bramson, R. (2001). Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychology, 20(2), 112-9.
Arntz, A., & de Jong, P. (1993). Anxiety, attention and pain. Journal of Psychosomatic Research, 37(4), 423-31.
Arntz, A., Dreessen, L., & de Jong, P. (1994). The influence of anxiety on pain: Attentional and attributional mediators. Pain, 56(3), 307-14.
Arntz, A., & Peters, M. (1995). Chronic low back pain and inaccurate predictions of pain: Is being too tough a risk factor for the development and maintenance of chronic pain? Behaviour Research & Therapy, 33(1), 49-53.
Arntz, A., & Schmidt, A.J.M. (1989). Perceived control and the experience of pain. In A. Steptoe & A. Appels (Eds.), Stress, personal control and health (pp. 131-162). Chichester, UK: John Wiley & Sons.
Atkinson, J.H., Slater, M.A., Patterson, T.L., Grant, I., & Garfin, S.R. (1991). Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: A controlled study. Pain, 45(2), 111-21.
Baker, S.L., & Kirsch, I. (1991). Cognitive mediators of pain perception and tolerance. Journal of Personality & Social Psychology, 61(3), 504-510.
Ball, R., Howlett, T., Silverstone, T., & Rees, L. (1987). The interrelationship of beta endorphin, ACTH and cortisol in depressive illness: A controlled study. Psychological Medicine, 17(1), 31-7.
Bandler, R., Price, J.L., & Keay, K.A. (2000). Brain mediation of active and passive emotional coping. Progress in Brain Research, 122, 333-49.
Bandler, R., & Shipley, M.T. (1994). Columnar organization in the midbrain periaqueductal gray: Modules for emotional expression? Trends in Neurosciences, 17(9), 379-89.
Bandura, A., Cioffi, D., Taylor, C.B., & Brouillard, M.E. (1988). Perceived self-efficacy in coping with cognitive stressors and opioid activation. Journal of Personality and Social Psychology, 55(3), 479-88.

Bandura, A., O'Leary, A., Taylor, C.B., Gauthier, J., & Gossard, D. (1987). Perceived self-efficacy and pain control: Opioid and nonopioid mechanisms. Journal of Personality and Social Psychology, 53(3), 563-71.

Bandura, A., Taylor, C.B., Williams, S.L., Mefford, I.N., & Barchas, J.D. (1985). Catecholamine secretion as a function of perceived coping self-efficacy. Journal of Consulting and Clinical Psychology, 53(3), 406-14.

Banks, S.M., & Kerns, R.D. (1996). Explaining high rates of depression in chronic pain: A diathesis-stress framework. Psychological Bulletin, 119(1), 95-110.

Bar, K.J., Greiner, W., Letsch, A., Kobele, R., & Sauer, H. (2003). Influence of gender and hemispheric lateralization on heat pain perception in major depression. Journal of Psychiatric Research, 37(4), 345-53.

Bastuerk, M., Muhtaroglu, S., Karaaslan, M.F., Oguz, A., Simsek, A., & Reyhancan, M. (2000). The relationship between basal plasma beta-endorphin levels and the severity of major depressive disorders. Klinik Psikofarmakoloji Buelteni, 10(3), 117-120.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). Beck Depression Inventory - Second edition. New York: The Psychological Corporation/ Harcourt Brace & Company.

Berger, P.A., & Barchas, J.D. (1982). Studies of beta-endorphin in psychiatric patients. Annals of the New York Academy of Sciences, 398, 448-59.

Berkley, K.J. (1997). Sex differences in pain. Behavioral & Brain Sciences, 20(3), 371-380.

Besson, A., Privat, A.M., Eschalier, A., & Fialip, J. (1996). Effects of morphine, naloxone and their interaction in the learned-helplessness paradigm in rats. Psychopharmacology (Berl), 123(1), 71-8.

Besson, A., Privat, A.M., Eschalier, A., & Fialip, J. (1999). Dopaminergic and opioidergic mediations of tricyclic antidepressants in the learned helplessness paradigm. Pharmacology, Biochemistry & Behavior, 64(3), 541-8.

Beutler, L.E., Daldrup, R.J., Engle, D., Oro'-Beutler, M.E., Meredith, K., & Boyer, J.T. (1987). Effects of therapeutically induced affect arousal on depressive symptoms, pain and beta-endorphins among rheumatoid arthritis patients. Pain, 29(3), 325-34.

Beutler, L.E., Engle, D., Oro'-Beutler, M.E., Daldrup, R., & Meredith, K. (1986). Inability to express intense affect: A common link between depression and pain? Journal of Consulting and Clinical Psychology, 54(6), 752-9.

Biegon, A., & Samuel, D. (1980). Interaction of tricyclic antidepressants with opiate receptors. Biochemical Pharmacology, 29(3), 460-2.

Blitz, B., & Dinnerstein, A.J. (1968). Effects of different types of instructions on pain parameters. Journal of Abnormal Psychology, 73(3), 276-80.

Bond, A.J., Shine, P., & Bruce, M. (1995). Validation of visual analogue scales in anxiety. International Journal of Methods in Psychiatric Research, 5(1), 1-9.

Bouhassira, D., Bing, Z., & Le Bars, D. (1990). Studies of the brain structures involved in diffuse noxious inhibitory controls: The mesencephalon. Journal of Neurophysiology, 64(6), 1712-23.

Bouhassira, D., Bing, Z., & Le Bars, D. (1992a). Effects of lesions of locus coeruleus/subcoeruleus on diffuse noxious inhibitory controls in the rat. Brain Research, 571(1), 140-4.

Bouhassira, D., Bing, Z., & Le Bars, D. (1993). Studies of brain structures involved in diffuse noxious inhibitory controls in the rat: The rostral ventromedial medulla. Journal of Physiology, 463, 667-87.

Bouhassira, D., Chitour, D., Villaneuva, L., & Le Bars, D. (1995). The spinal transmission of nociceptive information: Modulation by the caudal medulla. Neuroscience, 69(3), 931-8.

Bouhassira, D., Villanueva, L., & Le Bars, D. (1992b). Effects of systemic morphine on diffuse noxious inhibitory controls: Role of the periaqueductal grey. European Journal of Pharmacology, 216(2), 149-56.

Boureau, F., Willer, J.C., & Dauthier, C. (1978). Study of naloxone in normal awake man: effects on spinal reflexes. Neuropharmacology, 17(8), 565-8.

Boureau, F., Willer, J.C., & Yamaguchi, Y. (1979). Abolition by naloxone of the inhibitory effect of peripheral electrical stimulation on the blink reflex. Electroencephalography and Clinical Neurophysiology, 47(3), 322-8.

Bradley, J.J. (1963). Severe localized pain associated with the depressive syndrome. British Journal of Psychiatry, 109, 741-5.

Bragdon, E.E., Light, K.C., Costello, N.L., Sigurdsson, A., Bunting, S., Bhalang, K., & Maixner, W. (2002). Group differences in pain modulation: Pain-free women compared to pain-free men and to women with TMD. Pain, 96(3), 227-237.

Brambilla, F., Maggioni, M., Panerai, A.E., Sacerdote, P., & Cenacchi, T. (1996). Beta-endorphin concentration in peripheral blood mononuclear cells of elderly depressed patients: Effects of phosphatidylserine therapy. Neuropsychobiology, 34(1), 18-21.

Brands, A.-M.E., & Schmidt, A.J. (1987). Learning processes in the persistence behavior of chronic low back pain patients with repeated acute pain stimulation. Pain, 30(3), 329-37.

Brewin, C., & Bradley, C. (1982). Perceived control and the experience of childbirth. British Journal of Clinical Psychology, 21(Pt 4), 263-9.

Brown, G.K. (1990). A causal analysis of chronic pain and depression. Journal of Abnormal Psychology, 99(2), 127-37.

Brown, T.A., Chorpita, B.F., Korotitsch, W., & Barlow, D.H. (1997). Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behaviour Research & Therapy, 35(1), 79-89.

Bruehl, S., Burns, J.W., Chung, O.Y., Ward, P., & Johnson, B. (2002). Anger and pain sensitivity in chronic low back pain patients and pain-free controls: The role of endogenous opioids. Pain, 99(1-2), 223-33.

Bruehl, S., Carlson, C.R., & McCubbin, J.A. (1992). The relationship between pain sensitivity and blood pressure in normotensives. Pain, 48(3), 463-7.

Bruehl, S., McCubbin, J.A., & Harden, R.N. (1999). Theoretical review: Altered pain regulatory systems in chronic pain. Neuroscience & Biobehavioral Reviews, 23(6), 877-90.

Bryden, M.P. (1977). Measuring handedness with questionnaires. Neuropsychologia, 15(4-5), 617-24.

Buchsbaum, M.S., Davis, G.C., Naber, D., & Pickar, D. (1983). Pain enhances naloxone-induced hyperalgesia in humans as assessed by somatosensory evoked potentials. Psychopharmacology (Berl), 79(2-3), 99-103.

Bullinger, M., Naber, D., Pickar, D., Cohen, R.M., Kalin, N.H., Pert, A., & Bunney, W.E., Jr. (1984). Endocrine effects of the cold pressor test: Relationships to subjective pain appraisal and coping. Psychiatry Research, 12(3), 227-33.

Burnett, F.E., Scott, L.V., Weaver, M.G., Medbak, S.H., & Dinan, T.G. (1999). The effect of naloxone on adrenocorticotropin and cortisol release: evidence for a reduced response in depression. Journal of Affective Disorders, 53(3), 263-8.

Burns, J.W., Bruehl, S., & Caceres, C. (2004). Anger management style, blood pressure reactivity, and acute pain sensitivity: Evidence for "Trait x Situation" models. Ann Behav Med, 27(3), 195-204.
Burns, J.W., Kubilus, A., & Bruehl, S. (2003). Emotion induction moderates effects of anger management style on acute pain sensitivity. Pain, 106(1-2), 109-18.
Butler, S.H., Colpitts, Y.H., Gagliardi, G.J., Chen, A.C., & Chapman, C.R. (1983). Opiate analgesia and its antagonism in dental event-related potentials: Evidence for placebo antagonism. Psychopharmacology (Berl), 79(4), 325-8.
Caceres, C., & Burns, J.W. (1997). Cardiovascular reactivity to psychological stress may enhance subsequent pain sensitivity. Pain, 69(3), 237-44.
Catlin, D.H., Gorelick, D.A., & Gerner, R.H. (1982). Clinical pharmacology of beta-endorphin in depression and schizophrenia. Annals of the New York Academy of Sciences, 398, 434-47.
Cella, D.F., & Perry, S.W. (1986). Reliability and concurrent validity of three visual analogue mood scales. Psychological Reports, 59(2), 827-833.
Chabal, C., Jacobson, L., & Little, J. (1989). Intrathecal fentanyl depresses nociceptive flexion reflexes in patients with chronic pain. Anesthesiology, 70(2), 226-9.
Chance, W.T., & Rosecrans, J.A. (1979). Lack of cross-tolerance between morphine and autoanalgesia. Pharmacology, Biochemistry & Behavior, 11(6), 639-42.
Chapman, C.R. (1995). The affective dimension of pain: A model. In B. Bromm & J.E. Desmedt (Eds.), Advances in pain research and therapy: Pain and the brain - from nociception to cognition. (Vol. 22, pp. 283-301). NY, USA: Raven Press.
Chaves, J.F., & Brown, J.M. (1987). Spontaneous cognitive strategies for the control of clinical pain and stress. Journal of Behavioral Medicine, 10(3), 263-276.
Chitour, D., Dickenson, A.H., & Le Bars, D. (1982). Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). Brain Research, 236(2), 329-37.
Clark, L.A., Denby, L., Pregibon, D., Harshfield, G.A., Pickering, T.G., Blank, S., & Laragh, J.H. (1987). A data-based method for bivariate outlier detection: Application to automatic blood pressure recording devices. Psychophysiology, 24(1), 119-25.
Clark, W.C., Yang, J.C., & Janal, M.N. (1986). Altered pain and visual sensitivity in humans: The effects of acute and chronic stress. Annals of the New York Academy of Sciences, 467, 116-129.
Coghill, R., Derbyshire, S.W., & Ploghaus, A. (2004). The individual in pain: Quantifying the factors that influence the experience of pain. Medscape Medical News [On-line]. Available: http://www.medscape.com/viewarticle/433599
Cohen, J., & Cohen, P. (1983). Applied multiple regression: Correlation analysis for the behavioral sciences (2nd. ed.). Hillsdale, New Jersey: Lawrence Erlbaum.
Cohen, M.R., Pickar, D., & Dubois, M. (1983). The role of the endogenous opioid system in the human stress response. Psychiatric Clinics of North America, 6(3), 457-471.
Cohen, M.R., Pickar, D., Dubois, M., Nurnberger, J., Roth, Y., Cohen, R.M., Gershon, E., & Bunney, W.E., Jr. (1982). Clinical and experimental studies of stress and the endogenous opioid system. Annals of the New York Academy of Sciences, 398, 424-32.

Cohen, M.R., Pickar, D., Extein, I., Gold, M.S., & Sweeney, D.R. (1984). Plasma cortisol and beta-endorphin immunoreactivity in nonmajor and major depression. American Journal of Psychiatry, 141(5), 628-32.

Collins, S.L., Moore, R.A., & McQuay, H.J. (1997). The visual analogue pain intensity scale: What is moderate pain in millimetres? Pain, 72(1-2), 95-97.

Cornwall, A., & Donderi, D.C. (1988). The effect of experimentally induced anxiety on the experience of pressure pain. Pain, 35(1), 105-13.

Craig, K.D. (1989). Emotional aspects of pain. In P.D. Wall & R. Melzack (Eds.), Textbook of Pain (2nd edition ed.) (pp. 220-30). Edinburgh: Churchill Livingstone.

Craig, K.D. (1995). From nociception to pain: The role of emotion. In B. Bromm & J.E. Desmedt (Eds.), Advances in pain research and therapy: Pain and the brain - from nociception and cognition (Vol. 22). New York: Raven Press Ltd.

Crombez, G., Baeyens, F., & Eelen, P. (1994). Sensory and temporal information about impending pain: The influence of predictability on pain. Behaviour Research & Therapy, 32(6), 611-622.

Cruccu, G., Ferracuti, S., Leardi, M.G., Fabbri, A., & Manfredi, M. (1991). Nociceptive quality of the orbicularis oculi reflexes as evaluated by distinct opiate- and benzodiazepine-induced changes in man. Brain Research, 556(2), 209-17.

Daly, R.J., Duggan, P.F., Bracken, P.J., Doonan, H.J., & Kelleher, N.J. (1987). Plasma levels of beta-endorphin in depressed patients with and without pain. British Journal of Psychiatry, 150, 224-7.

Darko, D.F., Risch, S.C., Gillin, J.C., & Golshan, S. (1992). Association of beta-endorphin with specific clinical symptoms of depression. American Journal of Psychiatry, 149(9), 1162-7.

Davis, G.C., Buchsbaum, M.S., & Bunney, W.E., Jr. (1979). Analgesia to painful stimuli in affective illness. American Journal of Psychiatry, 136(9), 1148-51.

Davis, G.C., Buchsbaum, M.S., & Bunney, W.E., Jr. (1981). Opiates, opioid peptides and psychiatry. Annals of the New York Academy of Sciences, 362, 67-75.

Davis, G.C., Buchsbaum, M.S., Naber, D., Pickar, D., Post, R., van Kammen, D., & Bunney, W.E., Jr. (1982). Altered pain perception and cerebrospinal endorphins in psychiatric illness. Annals of the New York Academy of Sciences, 398, 366-73.

Davis, H., & Levine, S. (1982). Predictability, control, and the pituitary-adrenal response in rats. Journal of Comparative and Physiological Psychology, 96(3), 393-404.

Davison, G.C., & Valins, S. (1969). Maintenance of self-attributed and drug-attributed behavior change. Journal of Personality and Social Psychology, 11(1), 25-33.

Daza, P., Novy, D.M., Stanley, M.A., & Averill, P. (2002). The Depression Anxiety Stress Scale-21: Spanish translation and validation with a Hispanic sample. Journal of Psychopathology & Behavioral Assessment, 24(3), 195-205.

de Broucker, T., Cesaro, P., Willer, J.C., & Le Bars, D. (1990). Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain, 113 (Pt 4), 1223-34.

de Bruin, J.T., Schaefer, M.K., Krohne, H.W., & Dreyer, A. (2001). Preoperative anxiety, coping, and intraoperative adjustment: Are there mediating effects of stress-induced analgesia? Psychology & Health, 16(3), 253-271.

de Jong, W., Petty, M.A., & Sitsen, J.M. (1983). Role of opioid peptides in brain mechanisms regulating blood pressure. Chest, 83(2 Suppl), 306-8.
Detke, M.J., Lu, Y., Goldstein, D.J., Hayes, J.R., & Demitrack, M.A. (2002). Duloxetine, 60 mg once daily, for major depressive disorder: A randomized double-blind placebo-controlled trial. Journal of Clinical Psychiatry, 63(4), 308-15.
Dickens, C., McGowan, L., & Dale, S. (2003). Impact of depression on experimental pain perception: A systematic review of the literature with meta-analysis. Psychosomatic Medicine, 65(3), 369-75.
Dimitrijevic, M.R., Faganel, J., Gregoric, M., Nathan, P.W., & Trontelj, J.K. (1972). Habituation: Effects of regular and stochastic stimulation. Journal of Neurology, Neurosurgery and Psychiatry, 35(2), 234-42.
Dolce, J.J., Doleys, D.M., Raczynski, J.M., Lossie, J., Poole, L., & Smith, M. (1986). The role of self-efficacy expectancies in the prediction of pain tolerance. Pain, 27(2), 261-72.
Dozois, D.J.A., Dobson, K.S., & Ahnberg, J.L. (1998). A psychometric evaluation of the Beck Depression Inventory-II. Psychological Assessment, 10(2), 83-89.
Drolet, G., Dumont, E.C., Gosselin, I., Kinkead, R., Laforest, S., & Trottier, J.F. (2001). Role of endogenous opioid system in the regulation of the stress response. Progress in Neuro-psychopharmacology & Biological Psychiatry, 25(4), 729-41.
Drossman, D.A. (1999). Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? American Journal of Medicine, 107(5A), 41S-50S.
Drugan, R.C., & Maier, S.F. (1986). Control vs. lack of control over aversive stimuli: Nonopioid-opioid analgesic consequences. In S.I. Szara (Ed.), Neurobiology of behavioral control in drug abuse. National Institute of Drug Abuse, Research Monograph 74. (pp. 71-89). Bethesda, MD: Public Health Services.
Drummond, P.D., & Holroyd, K.A. (2000). Psychological modulation of pain. In J. Olesen, P. Tfelt-Hansen, & K.M.A. Welch (Eds.), The Headaches (Second ed.) (pp. 217-221). Philadelphia: Lippincott Williams & Wilkins.
Dubois, M., Pickar, D., Cohen, M.R., Roth, Y.F., Macnamara, T., & Bunney, W.E., Jr. (1981). Surgical stress in humans is accompanied by an increase in plasma beta-endorphin immunoreactivity. Life Sciences, 29(12), 1249-54.
Duggan, A.W. (1985). Pharmacology of descending control systems. Philosophical Translations of the Royal Society of London. Series B, Biological Sciences, 308(1136), 375-91.
Duncan, G.H., Bushnell, M.C., & Lavigne, G.J. (1989). Comparison of verbal and visual analogue scales for measuring the intensity and unpleasantness of experimental pain. Pain, 37(3), 295-303.
Dworkin, R.H., Clark, W.C., & Lipsitz, J.D. (1995). Pain responsivity in major depression and bipolar disorder. Psychiatry Research, 56(2), 173-81.
Eccleston, C., Crombez, G., Aldrich, S., & Stannard, C. (2001). Worry and chronic pain patients: a description and analysis of individual differences. European Journal of Pain, 5(3), 309-18.
Ellrich, J., & Treede, R.D. (1998). Characterization of blink reflex interneurons by activation of diffuse noxious inhibitory controls in man. Brain Research, 803(1-2), 161-8.
Esteban, A. (1999). A neurophysiological approach to brainstem reflexes. Blink reflex. Neurophysiologie Clinique, 29(1), 7-38.

Ettema, J.H., & Zielhuis, R.L. (1971). Physiological parameters of mental load. Ergonomics, 14(1), 137-44.
Evers, A.W., Kraaimaat, F.W., Geenen, R., & Bijlsma, J.W. (1998). Psychosocial predictors of functional change in recently diagnosed rheumatoid arthritis patients. Behaviour Research & Therapy, 36(2), 179-93.
Extein, I., Pickar, D., Gold, M.S., Gold, P.W., Pottash, A.L., Sweeney, D.R., Ross, R.J., Rebard, R., Martin, D., & Goodwin, F.K. (1981). Methadone and morphine in depression [proceedings]. Psychopharmacology Bulletin, 17(1), 29-33.
Extein, I., Pottash, A.L., & Gold, M.S. (1982). A possible opioid receptor dysfunction in some depressive disorders. Annals of the New York Academy of Sciences, 398, 113-9.
Facchinetti, F., Sandrini, G., Petraglia, F., Alfonsi, E., Nappi, G., & Genazzani, A.R. (1984). Concomitant increase in nociceptive flexion reflex threshold and plasma opioids following transcutaneous nerve stimulation. Pain, 19(3), 295-303.
Fanselow, M.S. (1979). Naloxone attenuates rats preference for signaled shock. Physiological Psychology, 7, 70-74.
Fanselow, M.S. (1986). Conditioned fear-induced opiate analgesia: A competing motivational state theory of stress analgesia. Annals of the New York Academy of Sciences, 467, 40-54.
Fanselow, M.S., & Baackes, M.P. (1982). Conditioned fear-induced opiate analgesia on the formalin test: Evidence for two aversive motivational systems. Learning and Motivation, 13, 200-221.
Fernandez, E. (2002). Anxiety, depression, and anger in pain: Research findings and clinical options (First ed.). Dallas, Texas: Advanced Psychological Resources, Inc.
Ferracuti, S., Leardi, M.G., Cruccu, G., Fabbri, A., & Itil, T.M. (1994a). Analgesic-antiinflammatory drugs inhibit orbicularis oculi reflexes in humans via a central mode of action. Progress in Neuro-psychopharmacology & Biological Psychiatry, 18(1), 101-13.
Ferracuti, S., Seri, S., Mattia, D., Cruccu, G., Schiff, B.B., & Gagliese, L. (1994b). Quantitative EEG modifications during the cold water pressor test: Hemispheric and hand differences. International Journal of Psychophysiology, 17(3), 261-8.
Fink, M., Simeon, J., Itil, T.M., & Freedman, A.M. (1970). Clinical antidepressant activity of cyclazocine - a narcotic antagonist. Clinical Pharmacology and Therapeutics, 11(1), 41-8.
First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1997). Structured Clinical Interview for DSM-IV Axis I Disorders: Clinician Version. NY, USA: American Psychiatric Press.
Fishbain, D.A., Cutler, R., Rosomoff, H.L., & Rosomoff, R.S. (1997). Chronic pain-associated depression: Antecedent or consequence of chronic pain? A review. Clinical Journal of Pain, 13(2), 116-37.
Flor, H., Birbaumer, N., Schulz, R., Grusser, S.M., & Mucha, R.F. (2002). Pavlovian conditioning of opioid and nonopioid pain inhibitory mechanisms in humans. European Journal of Pain, 6(5), 395-402.
Fontana, F., Bernardi, P., Spampinato, S., Boschi, S., De Iasio, R., & Grossi, G. (1997). Pressor effects of endogenous opioid system during acute episodes of

blood pressure increases in hypertensive patients. Hypertension, 29(1 Pt 1), 105-10.
France, C.R. (1999). Decreased pain perception and risk for hypertension: Considering a common physiological mechanism. Psychophysiology, 36(6), 683-92.
France, C.R., & Suchowiecki, S. (1999). A comparison of diffuse noxious inhibitory controls in men and women. Pain, 81(1-2), 77-84.
France, R.D., & Urban, B.J. (1991). Cerebrospinal fluid concentrations of beta-endorphin in chronic low back pain patients. Influence of depression and treatment. Psychosomatics, 32(1), 72-7.
Freeman, T.B., Campbell, J.N., & Long, D.M. (1983). Naloxone does not affect pain relief induced by electrical stimulation in man. Pain, 17(2), 189-95.
Fridlund, A.J., & Cacioppo, J.T. (1986). Guidelines for human electromyographic research. Psychophysiology, 23(5), 567-89.
Galard, R., Gallart, J., Arguello, J.M., Schwartz, S., Castellanos, J.M., & Catalan, R. (1988). Plasma levels of beta-endorphin, cortisol, prolactin and growth hormone in depressed patients. Acta Psychiatrica Scandinavica, 78(2), 230-3.
Galina, Z.H., Rogan, F., & Amit, Z. (1983). Non-naltrexone reversible heat stress-induced analgesia. Sociological Neuroscience Abstracts, 13, 276.
Gallagher, R.M., & Cariati, S. (2002). The pain-depression conundrum: Bridging the body and mind. Medscape Medical News [On-line]. Available: http://www.medscape.com/viewprogram/2030
Garcia-Larrea, L., Charles, N., Sindou, M., & Mauguiere, F. (1993). Flexion reflexes following anterolateral cordotomy in man: Dissociation between pain sensation and nociceptive reflex RIII. Pain, 55(2), 139-49.
Gebhart, G.F. (1982). Opiate and opioid peptide effects on brain stem neurons: Relevance to nociception and antinociceptive mechanisms. Pain, 12(2), 93-140.
Geer, J.H., & Maisel, E. (1972). Evaluating the effects of the prediction-control confound. Journal of Personality & Social Psychology, 23(3), 314-319.
Gelfand, S. (1964). The relationship of experimental pain tolerance to pain threshold. Canadian Journal of Psychology, 18(1), 36-42.
Gelkopf, M. (1997). Laboratory pain and styles of coping with anger. Journal of Psychology, 131(1), 121-123.
Gerner, R.H., Catlin, D.H., Gorelick, D.A., Hui, K.K., & Li, C.H. (1980). Beta-endorphin. Intravenous infusion causes behavioral change in psychiatric inpatients. Archives of General Psychiatry, 37(6), 642-7.
Gerner, R.H., & Sharp, B. (1982). CSF beta-endorphin-immunoreactivity in normal, schizophrenic, depressed, manic and anorexic subjects. Brain Research, 237(1), 244-7.
Ghadirian, A.M., Gianoulakis, C., & Nair, N.P. (1988). The effect of electroconvulsive therapy on endorphins in depression. Biological Psychiatry, 23(5), 459-64.
Gil, K.M., Ginsberg, B., Muir, M., Sykes, D., & Williams, D.A. (1990). Patient-controlled analgesia in postoperative pain: The relation of psychological factors to pain and analgesic use. Clinical Journal of Pain, 6(2), 137-42.
Giles, B.E., & Walker, J.S. (2000). Sex differences in pain and analgesia. Pain Reviews, 7(3-4), 181-193.

Gillman, M.A., & Lichtigfeld, F.J. (1985). A pharmacological overview of opioid mechanisms mediating analgesia and hyperalgesia. Neurological Research, 7(3), 106-19.
Girardot, M.N., & Holloway, F.A. (1984a). Cold water stress analgesia in rats: Differential effects of naltrexone. Physiology & Behavior, 32(4), 547-55.
Girardot, M.N., & Holloway, F.A. (1984b). Intermittent cold water stress-analgesia in rats: Cross-tolerance to morphine. Pharmacology, Biochemistry & Behavior, 20(4), 631-3.
Goldfarb, J., & Hu, J.W. (1976). Enhancement of reflexes by naloxone in spinal cats. Neuropharmacology, 15(12), 785-92.
Gonzalez, J.P., & Brogden, R.N. (1988). Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs, 35(3), 192-213.
Goodwin, G.M., Austin, M.P., Curran, S.M., Ross, M., Murray, C., Prentice, N., Ebmeier, K.P., Bennie, J., Carroll, S., Dick, H., & et al. (1993). The elevation of plasma beta-endorphin levels in major depression. Journal of Affective Disorders, 29(4), 281-9.
Gracely, R.H., Dubner, R., Wolskee, P.J., & Deeter, W.R. (1983). Placebo and naloxone can alter post-surgical pain by separate mechanisms. Nature, 306(5940), 364-365.
Gracely, R.H., McGrath, P., & Dubner, R. (1978). Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: Manipulation of affect by diazepam. Pain, 5(1), 19-29.
Grau, J.W., Hyson, R.L., Maier, S.F., Madden, J.t., & Barchas, J.D. (1981). Long-term stress-induced analgesia and activation of the opiate system. Science, 213(4514), 1409-11.
Grevert, P., & Goldstein, A. (1978). Endorphins: Naloxone fails to alter experimental pain or mood in humans. Science, 199(4333), 1093-5.
Grippo, A.J., Beltz, T.G., & Johnson, A.K. (2003). Behavioral and cardiovascular changes in the chronic mild stress model of depression. Physiology & Behavior, 78(4-5), 703-10.
Grippo, A.J., & Johnson, A.K. (2002). Biological mechanisms in the relationship between depression and heart disease. Neuroscience & Biobehavioral Reviews, 26(8), 941-962.
Guile, M.N., & McCutcheon, N.B. (1984). Effects of naltrexone and signaling inescapable electric shock on nociception and gastric lesions in rats. Behavioral Neuroscience, 98(4), 695-702.
Gureje, O., Simon, G.E., & von Korff, M. (2001). A cross-national study of the course of persistent pain in primary care. Pain, 92(1-2), 195-200.
Haerkaepaeae, K., Jaervikoski, A., & Vakkari, T. (1996). Associations of locus of control beliefs with pain coping strategies and other pain-related cognitions in back pain patients. British Journal of Health Psychology, 1(Pt 1), 51-63.
Hardy, J.D., Wolff, H.G., & Goodell, H. (1952). Pain sensations and reactions. Baltimore, MD: Williams and Wilkins.
Haslam, D.R. (1970). Lateral dominance in the perception of size and of pain. Quarterly Journal of Experimental Psychology, 22(3), 503-7.
Hayes, J.D., Bennett, G.J., Newlon, P., & Mayer, D.J. (1976). Analgesic effects of certain noxious and stressful manipulations in the rat. Sociological Neuroscience Abstracts, 2, 1350.

Hayes, R.L., Price, D.D., Bennett, G.J., Wilcox, G.L., & Mayer, D.J. (1978). Differential effects of spinal cord lesions on narcotic and non-narcotic suppression of nociceptive reflexes: Further evidence for the physiologic multiplicity of pain modulation. Brain Research, 155(1), 91-101.

Hemingway, R.B., 3rd, & Reigle, T.G. (1987). The involvement of endogenous opiate systems in learned helplessness and stress-induced analgesia. Psychopharmacology (Berl), 93(3), 353-7.

Hertel, J.B., & Hekmat, H.M. (1994). Coping with cold-pressor pain: Effects of mood and covert imaginal modelling. Psychological Record, 44(2), 207-220.

Hill, H.F., Chapman, C.R., Kornell, J.A., Sullivan, K.M., Saeger, L.C., & Benedetti, C. (1990). Self-administration of morphine in bone marrow transplant patients reduces drug requirement. Pain, 40(2), 121-9.

Hirsch, M.S., & Liebert, R.M. (1998). The physical and psychological experience of pain: The effects of labelling and cold pressor temperature on three pain measures in college women. Pain, 77(1), 41-48.

Hodes, R.L., Howland, E.W., Lightfoot, N., & Cleeland, C.S. (1990). The effects of distraction on responses to cold pressor pain. Pain, 41(1), 109-14.

Hollister, L.E., Johnson, K., Boukhabza, D., & Gillespie, H.K. (1981). Aversive effects of naltrexone in subjects not dependent on opiates. Drug and Alcohol Dependence, 8(1), 37-41.

Holroyd, K.A., Penzien, D.B., Hursey, K.G., Tobin, D.L., Rogers, L., Holm, J.E., Marcille, P.J., Hall, J.R., & Chila, A.G. (1984). Change mechanisms in EMG biofeedback training: Cognitive changes underlying improvements in tension headache. Journal of Consulting & Clinical Psychology, 52(6), 1039-53.

Horn, S., & Munafo, M. (1997). Pain - Theory, research and intervention. Buckingham: Open University Press.

Houston, B.K. (1972). Control over stress, locus of control, and response to stress. Journal of Personality and Social Psychology, 21(2), 249-55.

Hu, J.W. (1990). Response properties of nociceptive and non-nociceptive neurons in the rat's trigeminal subnucleus caudalis (medullary dorsal horn) related to cutaneous and deep craniofacial afferent stimulation and modulation by diffuse noxious inhibitory controls. Pain, 41(3), 331-45.

Hugon, M. (1973). Exteroceptive reflexes to stimulation of the sural nerve in normal man. In J.E. Desmedt (Ed.), New developments in electromyography and clinical neurophysiology (Vol. 3, pp. 713-29). Basel: Karger.

Hunziker, M.H. (1992). Opioid nature of learned helplessness and stress induced analgesia observed without re-exposure to shock. Behavioral Pharmacology, 3(2), 117-121.

Hyson, R.L., Ashcraft, L.J., Drugan, R.C., Grau, J.W., & Maier, S.F. (1982). Extent and control of shock affects naltrexone sensitivity of stress-induced analgesia and reactivity to morphine. Pharmacology Biochemistry & Behavior, 17(5), 1019-25.

Inturrisi, C.E., Alexopoulos, G., Lipman, R., Foley, K., & Rossier, J. (1982). beta-Endorphin immunoreactivity in the plasma of psychiatric patients receiving electroconvulsive treatment. Annals of the New York Academy of Sciences, 398, 413-23.

Jaccard, J., Turrisi, R., & Wan, C.K. (1990). Interaction effects in multiple regression. Newbury Park, Calif: Sage Publications.

Jackson, H.C., & Nutt, D.J. (1990). Does electroconvulsive shock therapy work through opioid mechanisms? Human Psychopharmacology: Clinical & Experimental, 5(1), 3-23.
Jackson, R.L., Maier, S.F., & Coon, D.J. (1979). Long-term analgesic effects of inescapable shock and learned helplessness. Science, 206(4414), 91-3.
Jain, R., & Russ, N. (2003). Addressing both the emotional and physical symptoms in depression. Medscape Medical News [On-line]. Available: http://www.medscape.com/viewprogram/2240_pnt
Janssen, S.A. (2002). Negative affect and sensitization to pain. Scandinavian Journal of Psychology. Special Issue: Somatization, sensitization and subjective health complaints, 43(2), 131-138.
Janssen, S.A., & Arntz, A. (1996). Anxiety and pain: Attentional and endorphinergic influences. Pain, 66(2-3), 145-50.
Janssen, S.A., & Arntz, A. (1997). No evidence for opioid-mediated analgesia induced by phobic fear. Behaviour Research & Therapy, 35(9), 823-30.
Janssen, S.A., & Arntz, A. (2001). Real-life stress and opioid-mediated analgesia in novice parachute jumpers. Journal of Psychophysiology, 15(2), 106-113.
Janssen, S.A., Spinhoven, P., & Arntz, A. (2004). The effects of failing to control pain: An experimental investigation. Pain, 107(3), 227-33.
Janssen, S.A., Spinhoven, P., & Brosschot, J.F. (2001). Experimentally induced anger, cardiovascular reactivity, and pain sensitivity. Journal of Psychosomatic Research, 51(3), 479-485.
Johnson, M.H., & Petrie, S.M. (1997). The effects of distraction on exercise and cold pressor tolerance for chronic low back pain sufferers. Pain, 69(1-2), 43-8.
Jorum, E. (1988). Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. Pain, 32(3), 341-8.
Judd, L.L., Janowsky, D.S., Zettner, A., Huey, L.Y., & Takahashi, K.I. (1981). Effects of naloxone-HCl on cortisol levels in patients with affective disorder and normal controls. Psychiatry Research, 4(3), 277-83.
Jungkunz, G., Engel, R.R., King, U.G., & Kuss, H.J. (1983). Endogenous opiates increase pain tolerance after stress in humans. Psychiatry Research, 8(1), 13-18.
Kabacoff, R.I., Segal, D.L., Hersen, M., & Van Hasselt, V.B. (1997). Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. Journal of Anxiety Disorders, 11(1), 33-47.
Kakigi, R. (1994). Diffuse noxious inhibitory control. Reappraisal by pain-related somatosensory evoked potentials following CO2 laser stimulation. Journal of the Neurological Sciences, 125(2), 198-205.
Kalat, J.W. (1995). Biological psychology (5th ed.). Pacific Grove, Calif.: Brooks/Cole Pub. Co.
Kalra, A., Urban, M.O., & Sluka, K.A. (2001). Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). Journal of Pharmacology and Experimental Therapeutics, 298(1), 257-63.
Kanfer, F.H., & Seidner, M.L. (1973). Self-control: Factors enhancing tolerance of noxious stimulation. Journal of Personality and Social Psychology, 25(3), 381-9.

Kaube, H., Katsarava, Z., Kaufer, T., Diener, H., & Ellrich, J. (2000). A new method to increase nociception specificity of the human blink reflex. Clinical Neurophysiology, 111(3), 413-6.
Keefe, F.J., Wilkins, R.H., Cook, W.A., Jr., Crisson, J.E., & Muhlbaier, L.H. (1986). Depression, pain, and pain behavior. Journal of Consulting and Clinical Psychology, 54(5), 665-9.
Kennedy, B.L., Schwab, J.J., Morris, R.L., & Beldia, G. (2001). Assessment of state and trait anxiety in subjects with anxiety and depressive disorders. Psychiatric Quarterly, 72(3), 263-276.
Kenshalo, D.R., & Nafe, J.P. (1963). Cutaneous vascular system as a model temperature receptor. Perceptual & Motor Skills, 17, 257-8.
Kilminster, S.G., & Jones, D.M. (1986). Perceived control and the cold pressor test. Stress Medicine, 2, 73-77.
Kimura, J. (1973). The blink reflex as a test for brain-stem and higher central nervous function. In J.E. Desmedt (Ed.), New developments in electromyography and neurophysiology (Vol. 3, pp. 682-691). Basel: Karger.
King, A.C., Volpicelli, J.R., Frazer, A., & O'Brien, C.P. (1997). Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. Psychopharmacology, 129(1), 15-22.
Kivioja, J., Sjalin, M., & Lindgren, U. (2004). Psychiatric morbidity in patients with chronic whiplash-associated disorder. Spine, 29(11), 1235-9.
Kleber, H.D. (1985). Naltrexone. Journal of Substance Abuse Treatment, 2(2), 117-22.
Klemp, G.O., & Rodin, J. (1976). Effects of uncertainty, delay, and focus of attention on reactions to an aversive situation. Journal of Experimental Social Psychology, 12(5), 416-421.
Kline, N.S., Li, C.H., Lehmann, H.E., Lajtha, A., Laski, E., & Cooper, T. (1977). Beta-endorphin-induced changes in schizophrenic and depressed patients. Archives of General Psychiatry, 34(9), 1111-3.
Kohn, P.M., Cowles, M.P., & Dzinas, K. (1989). Arousability, need for approval, and situational context as factors in pain tolerance. Journal of Research in Personality, 23(2), 214-224.
Kojima, M., Furukawa, T.A., Takahashi, H., Kawai, M., Nagaya, T., & Tokudome, S. (2002). Cross-cultural validation of the Beck Depression Inventory-II in Japan. Psychiatry Research, 110(3), 291-9.
Kraus, E., Le Bars, D., & Besson, J.M. (1981). Behavioral confirmation of "diffuse noxious inhibitory controls" (DNIC) and evidence for a role of endogenous opiates. Brain Research, 206(2), 495-9.
Kroenke, K., & Mangelsdorff, A.D. (1989). Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. American Journal of Medicine, 86(3), 262-6.
Kudoh, A., Katagai, H., & Takazawa, T. (2002). Increased postoperative pain scores in chronic depression patients who take antidepressants. Journal of Clinical Anesthesia, 14(6), 421-5.
Kumar, G., Steer, R.A., Teitelman, K.B., & Villacis, L. (2002). Effectiveness of Beck Depression Inventory-II subscales in screening for major depressive disorders in adolescent psychiatric inpatients. Assessment, 9(2), 164-170.
Lackner, J.M., Carosella, A.M., & Feuerstein, M. (1996). Pain expectancies, pain, and functional self-efficacy expectancies as determinants of disability in

patients with chronic low back disorders. Journal of Consulting & Clinical Psychology, 64(1), 212-220.
Langlois, M.W., Cramer, K.M., & Mohagen, R.B. (2002). Isolating the effects of control, choice, and prediction. Current Research in Social Psychology, 7(10), 163-181.
Lautenbacher, S., & Krieg, J.C. (1994). Pain perception in psychiatric disorders: A review of the literature. Journal of Psychiatric Research, 28(2), 109-22.
Lautenbacher, S., Roscher, S., Strian, D., Fassbender, K., Krumrey, K., & Krieg, J.C. (1994). Pain perception in depression: Relationships to symptomatology and naloxone-sensitive mechanisms. Psychosomatic Medicine, 56(4), 345-52.
Lautenbacher, S., Spernal, J., Schreiber, W., & Krieg, J.C. (1999). Relationship between clinical pain complaints and pain sensitivity in patients with depression and panic disorder. Psychosomatic Medicine, 61(6), 822-7.
Le Bars, D., Bouhassira, D., & Villanueva, L. (1995). Opioids and diffuse noxious inhibitory control (DNIC) in the rat. In B. Bromm & J.E. Desmedt (Eds.), Advances in pain research and therapy: Pain and the brain - from nociception to cognition. (Vol. 22, pp. 517- 539). New York, USA: Raven Press.
Le Bars, D., Dickenson, A.H., & Besson, J.M. (1979a). Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain, 6(3), 283-304.
Le Bars, D., Dickenson, A.H., & Besson, J.M. (1979b). Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. Pain, 6(3), 305-27.
Le Bars, D., Willer, J.C., & de Broucker, T. (1992). Morphine blocks descending pain inhibitory controls in humans. Pain, 48(1), 13-20.
Leino, P., & Magni, G. (1993). Depressive and distress symptoms as predictors of low back pain, neck-shoulder pain, and other musculoskeletal morbidity: A 10-year follow-up of metal industry employees. Pain, 53(1), 89-94.
Lejuez, C.W., Eifert, G.H., Zvolensky, M.J., & Richards, J.B. (2000). Preference between onset predictable and unpredictable administrations of 20% carbon-dioxide-enriched air: Implications for better understanding the etiology and treatment of panic disorder. Journal of Experimental Psychology: Applied, 6(4), 349-358.
Leonard, B.E. (1990). Psychoneuroimmunology: An area of interest for the psychopharmacologist? Journal of Psychopharmacology, 4(1), 1-6.
Lepanto, R., Moroney, W., & Zenhausern, R. (1965). The contribution of anxiety to the laboratory investigation of pain. Psychonomic Science, 3, 475.
Levine, J.D., Gordon, N.C., & Fields, H.L. (1978). The mechanism of placebo analgesia. Lancet, 2(8091), 654-7.
Levitt, E.E., & Lubin, B. (1975). Depression: Concepts, controversies, and some new facts. New York: Springer.
Lewis, J.W., Cannon, J.T., & Liebeskind, J.C. (1980). Opioid and nonopioid mechanisms of stress analgesia. Science, 208(4444), 623-5.
Lewis, J.W., Sherman, J.E., & Liebeskind, J.C. (1981). Opioid and non-opioid stress analgesia: Assessment of tolerance and cross-tolerance with morphine. Journal of Neuroscience, 1(4), 358-63.
Lewis, J.W., Termin, G.W., Nelson, L.R., & Liebeskind, J.C. (1984). Opioid and non-opioid stress-induced analgesia. In M.D. Trickelbank & G. Curzon (Eds.), Mechanisms of stress-induced analgesia. Chichester: Wiley.

Lindblom, U., & Tegner, R. (1979). Are the endorphins active in clinical pain states? Narcotic antagonism in chronic pain patients. Pain, 7(1), 65-8.
Lindsay, P.G., & Wyckoff, M. (1981). The depression-pain syndrome and its response to antidepressants. Psychosomatics, 22(7), 571-3, 576-7.
Lipowski, Z.J. (1990). Chronic idiopathic pain syndrome. Annals of Medicine, 22(4), 213-7.
Litt, M.D. (1988). Self-efficacy and perceived control: Cognitive mediators of pain tolerance. Journal of Personality and Social Psychology, 54(1), 149-60.
Littman, G.S., Walker, B.R., & Schneider, B.E. (1985). Reassessment of verbal and visual analogue ratings in analgesic studies. Clinical Pharmacology and Therapeutics, 38(1), 16-23.
Lobstein, D.D., Rasmussen, C.L., Dunphy, G.E., & Dunphy, M.J. (1989). Beta-endorphin and components of depression as powerful discriminators between joggers and sedentary middle-aged men. Journal of Psychosomatic Research, 33(3), 293-305.
Loftin, M., Zeichner, A., & Given, M. (1998). Effects of frequency of pain report on subjective pain ratings of the cold pressor task. Perceptual & Motor Skills, 86(3 Pt 2), 1263-6.
Long, D.A. (1994). Hand differences and reported intensity of nociceptive stimuli. Perceptual & Motor Skills, 79(1 Pt 2), 411-7.
Lovallo, W. (1975). The cold pressor test and autonomic function: a review and integration. Psychophysiology, 12(3), 268-82.
Lovibond, P.F. (1998). Long-term stability of depression, anxiety, and stress syndromes. Journal of Abnormal Psychology, 107(3), 520-526.
Lovibond, P.F., & Lovibond, S.H. (1995a). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behaviour Research & Therapy, 33(3), 335-343.
Lovibond, S.H., & Lovibond, P.H. (1995b). Depression, Anxiety, Stress Scales. Sydney: Psychology Foundation Monograph.
Lozza, A., Schoenen, J., & Delwaide, P.J. (1997). Inhibition of the blink reflex R2 component after supraorbital and index finger stimulations is reduced in cluster headache: An indication for both segmental and suprasegmental dysfunction? Pain, 71(1), 81-8.
Luna, S.P., & Taylor, P.M. (2001). Cardiorespiratory and endocrine effects of endogenous opioid antagonism by naloxone in ponies anaesthetised with halothane. Research in Veterinary Science, 70(2), 95-100.
MacLennan, A.J., Jackson, R.L., & Maier, S.F. (1980). Conditioned analgesia in the rat. Bulletin of the Psychonomic Society, 15(6), 387-90.
Maes, M., De Meester, I., Scharpe, S., Desnyder, R., Ranjan, R., & Meltzer, H.Y. (1996). Alterations in plasma dipeptidyl peptidase IV enzyme activity in depression and schizophrenia: effects of antidepressants and antipsychotic drugs. Acta Psychiatrica Scandinavica, 93(1), 1-8.
Maes, M., Goossens, F., Scharpe, S., Meltzer, H.Y., D'Hondt, P., & Cosyns, P. (1994). Lower serum prolyl endopeptidase enzyme activity in major depression: Further evidence that peptidases play a role in the pathophysiology of depression. Biological Psychiatry, 35(8), 545-52.
Magni, G., Moreschi, C., Rigatti-Luchini, S., & Merskey, H. (1994). Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain, 56(3), 289-97.

Maier, S.F. (1984). Learned helplessness and animal models of depression. Progress in Neuro-psychopharmacology & Biological Psychiatry, 8(3), 435-46.
Maier, S.F. (1986). Stressor controllability and stress-induced analgesia. Annals of the New York Academy of Sciences, 467, 55-72.
Maier, S.F. (1990). Diazepam modulation of stress-induced analgesia depends on the type of analgesia. Behavioral Neuroscience, 104(2), 339-47.
Maier, S.F., Drugan, R.C., & Grau, J.W. (1982). Controllability, coping behavior, and stress-induced analgesia in the rat. Pain, 12(1), 47-56.
Maier, S.F., Sherman, J.E., Lewis, J.W., Terman, G.W., & Liebeskind, J.C. (1983). The opioid/nonopioid nature of stress-induced analgesia and learned helplessness. Journal of Experimental Psychology: Animal Behavior Processes, 9(1), 80-90.
Maixner, W., & Randich, A. (1984). Role of the right vagal nerve trunk in antinociception. Brain Research, 298(2), 374-7.
Malcolm, R., O'Neil, P.M., Von, J.M., & Dickerson, P.C. (1987). Naltrexone and dysphoria: A double-blind placebo controlled trial. Biological Psychiatry, 22(6), 710-716.
Manning, J.S. (2002). The brain-body connection and the relationship between depression and pain. Medscape Medical News [On-line]. Available: http://www.medscape.com/viewprogram/2166_pnt
Manning, M.M., & Wright, T.L. (1983). Self-efficacy expectancies, outcome expectancies, and the persistence of pain control in childbirth. Journal of Personality & Social Psychology, 45(2), 421-31.
Marazziti, D., Castrogiovanni, P., Rossi, A., Rosa, C., Ghione, S., Di Muro, A., Panattoni, E., & Cassano, G.B. (1998). Pain threshold is reduced in depression. International Journal of Neuropsychopharmcology, 1(1), 45-48.
Marchand, S., Sluka, K.A., Le Bars, D., & Rainville, P. (2004). Endogenous factors that modulate pain. Medscape Medical News [On-line]. Available: http://www.medscape.com/viewarticle/433600
Martin del Campo, A.F., Dowson, J.H., Herbert, J., & Paykel, E.S. (2000). Diurnal variations in endocrine and psychological responses to 0.2 mg/kg naloxone administration in patients with major depressive disorder and matched controls. Journal of Affective Disorders, 57(1-3), 37-47.
Martin, N.J., Holroyd, K.A., & Penzien, D.B. (1990). The headache-specific locus of control scale: Adaptation to recurrent headaches. Headache, 30(11), 729-34.
Maruff, P., Wood, S., Currie, J., McArthur-Jackson, C., Malone, V., & Benson, E. (1994). Computer-administered visual analogue mood scales: rapid and valid assessment of mood in HIV positive individuals. Psychological Reports, 74(1), 39-42.
Mayer, D.J., Price, D.D., & Rafii, A. (1977). Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Research, 121(2), 368-72.
McCaul, K.D., Monson, N., & Maki, R.H. (1992). Does distraction reduce pain-produced distress among college students? Health Psychology, 11(4), 1992.
McCormack, H.M., Horne, D.J.L., & Sheather, S. (1988). Clinical applications of visual analogue scales: A critical review. Psychological Medicine, 18(4), 1007-1019.
McCracken, L.M. (1998). Learning to live with pain: Acceptance of pain predicts adjustment in persons with chronic pain. Pain, 74(1), 21-7.
McCubbin, J.A. (1993). Stress and endogenous opioids: Behavioral and circulatory interactions. Biological Psychology, 35(2), 91-122.

McCubbin, J.A., & Bruehl, S. (1994). Do endogenous opioids mediate the relationship between blood pressure and pain sensitivity in normotensives? Pain, 57(1), 63-7.
McCubbin, J.A., Kizer, J.S., & Lipton, M.A. (1984). Naltrexone prevents footshock-induced performance deficit in rats. Life Sciences, 34(21), 2057-66.
McCubbin, J.A., Surwit, R.S., & Williams, R.B., Jr. (1985). Endogenous opiate peptides, stress reactivity, and risk for hypertension. Hypertension, 7(5), 808-11.
McCubbin, J.A., Surwit, R.S., & Williams, R.B., Jr. (1988). Opioid dysfunction and risk for hypertension: naloxone and blood pressure responses during different types of stress. Psychosomatic Medicine, 50(1), 8-14.
McCubbin, J.A., Wilson, J.F., Bruehl, S., Ibarra, P., Carlson, C.R., Norton, J.A., & Colclough, G.W. (1996). Relaxation training and opioid inhibition of blood pressure response to stress. Journal of Consulting & Clinical Psychology, 64(3), 593-601.
Meador-Woodruff, J.H., Haskett, R.F., Grunhaus, L., Akil, H., Watson, S.J., & Greden, J.F. (1987). Postdexamethasone plasma cortisol and beta-endorphin levels in depression: Relationship to severity of illness. Biological Psychiatry, 22(9), 1137-50.
Meagher, M.W., Arnau, R.C., & Rhudy, J.L. (2001). Pain and emotion: Effects of affective picture modulation. Psychosomatic Medicine, 63(1), 79-90.
Melzack, R. (1986). Neurophysiological foundations of pain. In R.A. Sternbach (Ed.), The psychology of pain. New York: Raven Press.
Melzack, R., & Wall, P.D. (1965). Pain mechanisms: A new theory. Science, 150(699), 971-9.
Melzack, R., & Wall, P.D. (1982). The challenge of pain. NY, USA: Penguin books.
Mendelson, J.H., Ellingboe, J., Keuhnle, J.C., & Mello, N.K. (1978). Effects of naltrexone on mood and neuroendocrine function in normal adult males. Psychoneuroendocrinology, 3(3-sup-4), 231-236.
Merskey, H. (1976). Psychiatric aspects of the control of pain. In J.J. Bonica & D. Albe-Fessard (Eds.), Advances in pain research and therapy (Vol. 1, pp. 711-716). New York: Raven Press.
Messing, R.B., & Wilcox, G.L. (1987). Non-opioid neurotransmitters in pain perception and analgesia. In G.D. Burrows, D. Elton, & G.V. Stanley (Eds.), Handbook of chronic pain management. Amsterdam: Elsevier Science Publishers.
Meyer, M.C., Straughn, A.B., Lo, M.W., Schary, W.L., & Whitney, C.C. (1984). Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. Journal of Clinical Psychiatry, 45(9 Pt 2), 15-9.
Millan, M.J., Przewlocki, R., Jerlicz, M., Gramsch, C., Hollt, V., & Herz, A. (1981). Stress-induced release of brain and pituitary beta-endorphin: Major role of endorphins in generation of hyperthermia, not analgesia. Brain Research, 208(2), 325-38.
Miller, R.R., Greco, C., Vigorito, M., & Marlin, N.A. (1983). Signaled tailshock is perceived as similar to a stronger unsignaled tailshock: Implications for a functional analysis of classical conditioning. Journal of Experimental Psychology. Animal Behavior Processes, 9(2), 105-131.
Miller, S.M. (1981). Predictability and human stress: Toward a clarification of evidence and theory. Advances in Experimental Social Psychology, 14, 201-256.

Miller, S.M., & Grant, R.P. (1979). The blunting hypothesis: A view of predictability and human stress. In P.O. Sjodon, S. Bates, & W.S. Dockens (Eds.), Trends in behavior therapy (pp. 135-151). New York: Academic Press.
Mineka, S., & Hendersen, R.W. (1985). Controllability and predictability in acquired motivation. Annual Review of Psychology, 36, 495-529.
Miotto, K., McCann, M., Basch, J., Rawson, R., & Ling, W. (2002). Naltrexone and dysphoria: Fact or myth? American Journal of Addiction, 11(2), 151-60.
Misiaszek, J., Cork, R.C., Hameroff, S.R., Finley, J., & Weiss, J.L. (1984). The effect of electroconvulsive therapy on plasma beta-endorphin. Biological Psychiatry, 19(3), 451-5.
Molina, V.A., Heyser, C.J., & Spear, L.P. (1994). Chronic variable stress enhances the stimulatory action of a low dose of morphine: Reversal by desipramine. European Journal of Pharmacology, 260(1), 57-64.
Mueller, M., & Netter, P. (2000). Relationship of subjective helplessness and pain perception after electric skin stimuli. Stress Medicine, 16(2), 109-115.
Murray, F.S., & Safferstone, J.F. (1970). Pain threshold and tolerance of right and left hands. Journal of Comparative and Physiological Psychology, 71(1), 83-6.
Naber, D., & Pickar, D. (1983). The measurement of endorphins in body fluids. The Psychiatric Clinics of North America, 6(3), 443-56.
Natan, L.B., Chaillet, P., Lecomte, J.M., Marcais, H., Uchida, G., & Costentin, J. (1984). Involvement of endogenous enkephalins in the mouse 'behavioral despair' test. European Journal of Pharmacology, 97(3-4), 301-4.
Nemeroff, C.B., Bissette, G., Akil, H., & Fink, M. (1991). Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. British Journal of Psychiatry, 158, 59-63.
Neumann, W., Kugler, J., Seelbach, H., & Krueskemper, G.M. (1997). Effects of nondirective suggestions on pain tolerance, pain threshold and pain intensity perception. Perceptual & Motor Skills, 84(3, Pt 1), 963-966.
Nickels, J.B., Cramer, K.M., & Gural, D.M. (1992). Toward unconfounding prediction and control: Predictionless control made possible. Canadian Journal of Behavioural Science. Special Issue: The psychology of control, 24(2), 156-170.
Norman, T.R., & McGrath, C. (2000). Stress induced animal models of depression. Stress Medicine, 16(4), 195-197.
O'Brien, E., & O'Malley, K. (1981). Essentials of blood pressure measurement. New York: Churchill Livingstone.
Ohlwein, A.L., Stevens, M.J., & Catanzaro, S.J. (1996). Self-efficacy, response expectancy, and temporal context: Moderators of pain tolerance and intensity. Imagination, Cognition & Personality, 16(1), 3-23.
Onghena, P., & Van Houdenhove, B. (1992). Antidepressant-induced analgesia in chronic non-malignant pain: A meta-analysis of 39 placebo-controlled studies. Pain, 49(2), 205-19.
Palmer, S.N. (2000). The role of affect and endogenous opioids in placebo analgesia. Dissertation Abstracts International: Section B: The Sciences & Engineering, 61(1-B), 581.
Panerai, A.E., Vecchiet, J., Panzeri, P., Meroni, P., Scarone, S., Pizzigallo, E., Giamberardino, M.A., & Sacerdote, P. (2002). Peripheral blood mononuclear cell beta-endorphin concentration is decreased in chronic fatigue syndrome

and fibromyalgia but not in depression: Preliminary report. Clinical Journal of Pain, 18(4), 270-3.
Parati, G., Mutti, E., Omboni, S., & Mancia, G. (1992). How to deal with blood pressure variability. In H. Brunner & B. Waeber (Eds.), Ambulatory blood pressure recording (pp. 71-99). New York: Raven Press, Ltd.
Pedhazur, E.J., & Kerlinger, F.N. (1982). Multiple regression in behavioral research (2nd ed.). New York: Holt Rinehart and Winston.
Pertovaara, A., Kemppainen, P., Johansson, G., & Karonen, S.L. (1982). Ischemic pain nonsegmentally produces a predominant reduction of pain and thermal sensitivity in man: A selective role for endogenous opioids. Brain Research, 251(1), 83-92.
Peters, M.L., Godaert, G.L., Ballieux, R.E., van Vliet, M., Willemsen, J.J., Sweep, F.C., & Heijnen, C.J. (1998). Cardiovascular and endocrine responses to experimental stress: Effects of mental effort and controllability. Psychoneuroendocrinology, 23(1), 1-17.
Peters, M.L., & Schmidt, A.J. (1991). Psychophysiological responses to repeated acute pain stimulation in chronic low back pain patients. Journal of Psychosomatic Research, 35(1), 59-74.
Peters, M.L., & Schmidt, A.J. (1992). Differences in pain perception and sensory discrimination between chronic low back pain patients and healthy controls. Journal of Psychosomatic Research, 36(1), 47-53.
Peters, M.L., Schmidt, A.J., Van den Hout, M.A., Koopmans, R., & Sluijter, M.E. (1992). Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls (DNIC). Pain, 50(2), 177-87.
Pfister, H.P., & Maffesoni, G. (1992). Stress induced activation of the endogenous opioid systems. In H.P. Pfister (Ed.), Stress effects on central and peripheral systems: A primer (pp. 81-95). Bowen Hills, Australia: Australian Academic Press.
Pickar, D., Cohen, M.R., Naber, D., & Cohen, R.M. (1982a). Clinical studies of the endogenous opioid system. Biological Psychiatry, 17(11), 1243-76.
Pickar, D., Davis, G.C., Schulz, S.C., Extein, I., Wagner, R., Naber, D., Gold, P.W., van Kammen, D.P., Goodwin, F.K., Wyatt, R.J., Li, C.H., & Bunney, W.E., Jr. (1981). Behavioral and biological effects of acute beta-endorphin injection in schizophrenic and depressed patients. American Journal of Psychiatry, 138(2), 160-6.
Pickar, D., Naber, D., Post, R.M., van Kammen, D.P., Kaye, W., Rubinow, D.R., Ballenger, J.C., & Bunney, W.E., Jr. (1982b). Endorphins in the cerebrospinal fluid of psychiatric patients. Annals of the New York Academy of Sciences, 398, 399-412.
Pinerua-Shuhaibar, L., Prieto-Rincon, D., Ferrer, A., Bonilla, E., Maixner, W., & Suarez-Roca, H. (1999). Reduced tolerance and cardiovascular response to ischemic pain in minor depression. Journal of Affective Disorders, 56(2-3), 119-26.
Pitman, R.K., van der Kolk, B.A., Orr, S.P., & Greenberg, M.S. (1990). Naloxone-reversible analgesic response to combat-related stimuli in posttraumatic stress disorder. A pilot study. Archives of General Psychiatry, 47(6), 541-4.
Plaghki, L., Delisle, D., & Godfraind, J.M. (1994). Heterotopic nociceptive conditioning stimuli and mental task modulate differently the perception and physiological correlates of short CO2 laser stimuli. Pain, 57(2), 181-92.

Pomeranz, B., & Warma, N. (1988). Electroacupuncture suppression of a nociceptive reflex is potentiated by two repeated electroacupuncture treatments: The first opioid effect potentiates a second non-opioid effect. Brain Research, 452(1-2), 232-6.
Price, D.D. (1999). Progress in pain research and management: Psychological mechanisms of pain and analgesia (Vol. 15). Seattle: IASP Press.
Price, D.D., Bush, F.M., Long, S., & Harkins, S.W. (1994). A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain, 56(2), 217-226.
Price, D.D., McGrath, P.A., Rafii, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain, 17(1), 45-56.
Price, D.D., & McHaffie, J.G. (1988). Effects of heterotopic conditioning stimuli on first and second pain: A psychophysical evaluation in humans. Pain, 34(3), 245-52.
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), 968-71.
Randich, A., & Maixner, W. (1984). Interactions between cardiovascular and pain regulatory systems. Neuroscience & Biobehavioral Reviews, 8(3), 343-67.
Reese, L.B. (1983). Coping with pain: The role of perceived self-efficacy. Dissertation Abstracts International, 44(5-B), 1641.
Reisenzein, R. (1983). The Schachter theory of emotion: Two decades later. Psychological Bulletin, 94(2), 239-64.
Reisine, T., & Pasternak, G. (1996). Opioid analgesics and antagonists. In L.S. Goodman, A. Gilman, J.G. Hardman, A.G. Gilman, & L.E. Limbird (Eds.), Goodman & Gilman's the pharmacological basis of therapeutics (9th / ed.) (pp. xxi, 1905). New York: McGraw-Hill Health Professions Division.
Rhudy, J.L., & Meagher, M.W. (2000). Fear and anxiety: Divergent effects on human pain thresholds. Pain, 84(1), 65-75.
Rhudy, J.L., & Meagher, M.W. (2001a). Noise stress and human pain thresholds: divergent effects in men and women. Journal of Pain, 2(1), 57-64.
Rhudy, J.L., & Meagher, M.W. (2001b). The role of emotion in pain modulation. Current Opinion in Psychiatry, 14(3), 241-245.
Rhudy, J.L., & Meagher, M.W. (2003a). Individual differences in the emotional reaction to shock determine whether hypoalgesia is observed. Pain Medicine, 4(3), 244-56.
Rhudy, J.L., & Meagher, M.W. (2003b). Negative affect: effects on an evaluative measure of human pain. Pain, 104(3), 617-26.
Risch, S.C., Cohen, R.M., Janowsky, D.S., Kalin, N.H., & Murphy, D.L. (1980). Mood and behavioral effects of physostigmine on humans are accompanied by elevations in plasma beta-endorphin and cortisol. Science, 209(4464), 1545-6.
Risch, S.C., Janowsky, D.S., Judd, L.L., Gillin, J.C., & McClure, S.F. (1983). The role of endogenous opioid systems in neuroendocrine regulation. The Psychiatric Clinics of North America, 6(3), 429-41.
Romano, J.M., & Turner, J.A. (1985). Chronic pain and depression: Does the evidence support a relationship? Psychological Bulletin, 97(1), 18-34.
Roper, N. (1988). Pocket medical dictionary (14th edition ed.). Edinburgh: Churchill Livingstone.

Rosa, C., Ghione, S., Mezzasalma, L., Pellegrini, M., Basile Fasolo, C., Giaconi, S., Gazzetti, P., & Ferdeghini, M. (1988). Relationship between pain sensitivity, cardiovascular reactivity to cold pressor test and indexes of activity of the adrenergic and opioid system. Clinical and Experimental Hypertension. Part A, Theory and Practice, 10(Suppl 1), 383-90.

Rosenbaum, M. (1980). Individual differences in self-control behaviors and tolerance of painful stimulation. Journal of Abnormal Psychology, 89(4), 581-90.

Rosenstiel, A.K., & Keefe, F.J. (1983). The use of coping strategies in chronic low back pain patients: Relationship to patient characteristics and current adjustment. Pain, 17(1), 33-44.

Rosenzweig, M.R., Leiman, A.L., & Breedlove, S.M. (1996). Biological psychology. Sunderland, Ma.: Sinauer Associates.

Rudy, T.E., Kerns, R.D., & Turk, D.C. (1988). Chronic pain and depression: Toward a cognitive-behavioral mediation model. Pain, 35(2), 129-40.

Rugulies, R. (2002). Depression as a predictor for coronary heart disease: A review and meta-analysis. American Journal of Preventive Medicine, 23(1), 51-61.

Ruoff, G.E. (1996). Depression in the patient with chronic pain. The Journal of Family Practice, 43(6 Suppl), S25-33; discussion S34.

Rupprecht, R., Barocka, A., Beck, G., Schrell, U., & Pichl, J. (1988). Pre- and postdexamethasone plasma ACTH and beta-endorphin levels in endogenous and nonendogenous depression. Biological Psychiatry, 23(5), 531-5.

Sandrini, G., Alfonsi, E., Bono, G., Facchinetti, F., Montalbetti, L., & Nappi, G. (1986). Circadian variations of human flexion reflex. Pain, 25(3), 403-10.

Sarno, A.J., Blumenthal, T.D., & Boelhouwer, A.J.W. (1997). Modification of the electrically elicited eyeblink by acoustic, visual, and vibrotactile pulses. Psychobiology, 25(3), 253-265.

Schermelleh-Engel, K., Eifert, G.H., Moosbrugger, H., & Frank, D. (1997). Perceived competence and trait anxiety as of pain coping strategies. Personality & Individual Differences, 22(1).

Schiaffino, K.M., & Revenson, T.A. (1995). Why me? The persistence of negative appraisals over the course of illness. Journal of Applied Social Psychology, 25(7).

Schiff, B.B., & Gagliese, L. (1994). The consequences of experimentally induced and chronic unilateral pain: Reflections of hemispheric lateralization of emotion. Cortex, 30(2), 255-67.

Schiffman, H.R. (1990). Sensation and perception: An integrated approach (Third ed.). New York, USA: John Wiley & Sons.

Schull, J., Kaplan, H., & O'Brien, C.P. (1981). Naloxone can alter experimental pain and mood in humans. Physiological Psychology, 9(3), 245-250.

Scott, J., & Huskisson, E.C. (1976). Graphic representation of pain. Pain, 2(2), 175-84.

Segal, D.L., Hersen, M., & Van Hasselt, V.B. (1994). Reliability of the Structured Clinical Interview for DSM-III-R: An evaluative review. Comprehensive Psychiatry, 35(4), 316-27.

Seligman, M.E.P., Maier, S.F., & Solomon, R.L. (1971). Unpredictable and uncontrollable aversive events. In F.R. Brush (Ed.), Aversive conditioning and learning (pp. 347-400). New York: Academic Press.

Shapiro, D., Jamner, L.D., Lane, J.D., Light, K.C., Myrtek, M., Sawada, Y., & Steptoe, A. (1996). Blood pressure publication guidelines. Society for Psychophysical Research. Psychophysiology, 33(1), 1-12.

Simonnet, G., & Rivat, C. (2003). Opioid-induced hyperalgesia: Abnormal or normal pain? Neuroreport, 14(1), 1-7.
Spanos, N.P., Hodgins, D.C., Stam, H.J., & Gwynn, M. (1984). Suffering for science: The effects of implicit social demands on response to experimentally induced pain. Journal of Personality and Social Psychology, 46(5), 1162-72.
Spielberger, C.D. (1983). State-Trait Anxiety Inventory. California: Consulting Psychologists Press, Inc.
Staub, E., Tursky, B., & Schwartz, G.E. (1971). Self-control and predictability: Their effects on reactions to aversive stimulation. Journal of Personality & Social Psychology, 18(2), 157-62.
Steptoe, A. (1980). Blood pressure. In I.Martin & P.Venables (Eds.), Techniques in psychophysiology (pp. 247-274). New York: Wiley.
Stevens, M.J. (1992). Does self-efficacy moderate intensity of pain? Perceptual & Motor Skills, 75(1), 320-322.
Stevens, M.J. (1993). Predictors of responses to acute pain. Imagination, Cognition & Personality, 13(4), 311-321.
Stevens, M.J., Heise, R.A., & Pfost, K.S. (1989). Consumption of attention versus affect elicited by cognitions in modifying acute pain. Psychological Reports, 64(1), 284-6.
Stevens, M.J., & Rogers, R.M. (1990). Intensity versus type of affect elicited by dissociative cognitions in moderating acute pain. Psychological Reports, 67(3 Pt 1), 747-51.
Sun, S.Y., Liu, Z., Li, P., & Ingenito, A.J. (1996). Central effects of opioid agonists and naloxone on blood pressure and heart rate in normotensive and hypertensive rats. General Pharmacology, 27(7), 1187-94.
Szilagyi, J.E. (1991). Psychosocial stress elevates blood pressure via an opioid dependent mechanism in normotensive rats. Clinical and Experimental Hypertension. Part A, Theory and Practice, 13(8), 1383-94.
Takahashi, M., Tokuyama, S., & Kaneto, H. (1988). Distinctive implication of emotional factors in various types of stress-induced analgesia. Japanese Journal of Pharmacology, 46(4), 418-20.
Talbot, J.D., Duncan, G.H., & Bushnell, M.C. (1989). Effects of diffuse noxious inhibitory controls (DNICs) on the sensory-discriminative dimension of pain perception. Pain, 36(2), 231-8.
Talbot, J.D., Duncan, G.H., Bushnell, M.C., & Boyer, M. (1987). Diffuse noxious inhibitory controls (DNICs): Psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. Pain, 30(2), 221-32.
Teixeira, N.A., Pereira, D.G., & Hermini, A.H. (1997). Effects of naltrexone and cross-tolerance to morphine in a learned helplessness paradigm. Brazilian Journal of Medical and Biological Research, 30(6), 775-82.
Tejedor-Real, P., Mico, J.A., Maldonado, R., Roques, B.P., & Gibert-Rahola, J. (1993). Effect of mixed (RB 38A) and selective (RB 38B) inhibitors of enkephalin degrading enzymes on a model of depression in the rat. Biological Psychiatry, 34(1-2), 100-7.
Tejedor-Real, P., Mico, J.A., Maldonado, R., Roques, B.P., & Gibert-Rahola, J. (1995). Implication of endogenous opioid system in the learned helplessness model of depression. Pharmacology, Biochemistry & Behavior, 52(1), 145-52.

Terenius, L., Wahlstroem, A., & Agren, H. (1977). Naloxone (Narcan) treatment in depression: Clinical observations and effects on CSF endorphins and monoamine metabolites. Psychopharmacology, 54(1), 31-33.
Thrash, W.J., Marr, J.N., & Boone, S.E. (1982). Continuous self-monitoring of discomfort in the dental chair and feedback to the dentist. Journal of Behavioral Assessment, 4(3), 273-284.
Ursin, H., Baade, E., & Levine, S. (1978). Psychobiology of stress: A study of coping men. NY: Academic Press.
Vallis, T.M., & Bucher, B. (1986). Self-efficacy as a predictor of behavior change: Interaction with type of training for pain tolerance. Cognitive Therapy & Research, 10(1), 79-94.
van der Kolk, B., Greenberg, M., Boyd, H., & Krystal, J. (1985). Inescapable shock, neurotransmitters, and addiction to trauma: Toward a psychobiology of post traumatic stress. Biological Psychiatry, 20(3), 314-25.
van Vliet, J.A., Vein, A.A., le Cessie, S., Ferrari, M.D., & van Dijk, J.G. (2002). Reproducibility and feasibility of neurophysiological assessment of the sensory trigeminal system for future application to paroxysmal headaches. Cephalalgia, 22(6), 474-81.
Velten, E., Jr. (1968). A laboratory task for induction of mood states. Behaviour Research & Therapy, 6(4), 473-82.
Vierck, C.J., Acosta-Rua, A., Nelligan, R., Tester, N., & Mauderli, A. (2002). Low dose systemic morphine attenuates operant escape but facilitates innate reflex responses to thermal stimulation. Journal of Pain, 3(4), 309-319.
Villanueva, L., & Le Bars, D. (1986). Indirect effects of intrathecal morphine upon diffuse noxious inhibitory controls (DNICs) in the rat. Pain, 26(2), 233-43.
Villanueva, L., & Le Bars, D. (1995). The activation of bulbo-spinal controls by peripheral nociceptive inputs: Diffuse noxious inhibitory controls. Biological Research, 28(1), 113-25.
Vlaeyen, J.W.S. (1991). IRV series in rehabilitation research: Chronic low back pain - assessment and treatment from a behavioral rehabilitation perspective (Vol. 1). Amsterdam, Netherlands: Swets & Zeitlinger.
Volavka, J., Anderson, B., & Koz, G. (1982). Naloxone and naltrexone in mental illness and tardive dyskinesia. Annals of the New York Academy of Sciences, 398, 97-102.
von Knorring, L., Perris, C., Eisemann, M., Eriksson, U., & Perris, H. (1983). Pain as a symptom in depressive disorders: I. Relationship to diagnostic subgroup and depressive symptomatology. Pain, 15(1), 19-26.
von Korff, M., LeResche, L., & Dworkin, S.F. (1993). First onset of common pain symptoms: A prospective study of depression as a risk factor. Pain, 55(2), 251-8.
von Korff, M., & Simon, G. (1996). The relationship between pain and depression. British Journal of Psychiatry Supplement(30), 101-8.
Ward, N.G., Bloom, V.L., & Friedel, R.O. (1979). The effectiveness of tricyclic antidepressants in the treatment of coexisting pain and depression. Pain, 7(3), 331-41.
Wardle, J. (1983). Psychological management of anxiety and pain during dental treatment. Journal of Psychosomatic Research, 27(5), 399-402.
Washington, L.L., Gibson, S.J., & Helme, R.D. (2000). Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. Pain, 89(1), 89-96.

Watkins, L.R., Cobelli, D.A., & Mayer, D.J. (1982a). Opiate vs non-opiate footshock induced analgesia (FSIA): Descending and intraspinal components. Brain Research, 245(1), 97-106.
Watkins, L.R., Cobelli, D.A., Newsome, H.H., & Mayer, D.J. (1982b). Footshock induced analgesia is dependent neither on pituitary nor sympathetic activation. Brain Research, 245(1), 81-96.
Watkins, L.R., & Mayer, D.J. (1982). Organization of endogenous opiate and nonopiate pain control systems. Science, 216(4551), 1185-92.
Watkins, L.R., & Mayer, D.J. (1986). Multiple endogenous opiate and non-opiate analgesia systems: Evidence of their existence and clinical implications. Annals of the New York Academy of Sciences, 467, 273-99.
Watkins, L.R., Wiertelak, E.P., Grisel, J.E., Silbert, L.H., & et al. (1992). Parallel activation of multiple spinal opiate systems appears to mediate "non-opiate" stress-induced analgesias. Brain Research, 594(1), 99-108.
Weinstein, S., & Sersen, E.A. (1961). Tactual sensitivity as a function of handedness and laterality. Journal of Comparative Physiological Psychology, 54, 665-9.
Weisenberg, M. (1989). Cognitive aspects of pain. In P.D. Wall & R. Melzack (Eds.), Textbook of pain (2nd edition ed.). Edinburgh: Chirchill Livingstone.
Weisenberg, M., Raz, T., & Hener, T. (1998). The influence of film-induced mood on pain perception. Pain, 76(3), 365-375.
Weisenberg, M., Wolf, Y., Mittwoch, T., Mikulincer, M., & Aviram, O. (1985). Subject versus experimenter control in the reaction to pain. Pain, 23(2), 187-200.
Weizman, A., Gil-Ad, I., Grupper, D., Tyano, S., & Laron, Z. (1987). The effect of acute and repeated electroconvulsive treatment on plasma beta-endorphin, growth hormone, prolactin and cortisol secretion in depressed patients. Psychopharmacology (Berl), 93(1), 122-6.
Westcott, T.B., & Horan, J.J. (1977). The effects of anger and relaxation forms of in vivo emotive imagery on pain tolerance. Canadian Journal of Behavioural Science, 9(3), 216-223.
Westcott, T.B., Huesz, L., Boswell, D., & Herold, P. (1977). Several variables of importance in the use of the cold pressor as a noxious stimulus in behavioral research. Perceptual & Motor Skills, 44(2), 401-2.
Whiskey, E., Werneke, U., & Taylor, D. (2001). A systematic review and meta-analysis of Hypericum perforatum in depression: A comprehensive clinical review. International Clinical Psychopharmacology, 16(5), 239-52.
Whitehouse, W.G., Walker, J., Margules, D.L., & Bersh, P.J. (1983). Opiate antagonists overcome the learned helplessness effect but impair competent escape performance. Physiology & Behavior, 30(5), 731-4.
Willer, J.C. (1977). Comparative study of perceived pain and nociceptive flexion reflex in man. Pain, 3(1), 69-80.
Willer, J.C., & Albe-Fessard, D. (1980a). Electrophysiological evidence for a release of endogenous opiates in stress-induced 'analgesia' in man. Brain Research, 198(2), 419-26.
Willer, J.C., Boureau, F., & Albe-Fessard, D. (1979). Supraspinal influences on nociceptive flexion reflex and pain sensation in man. Brain Research, 179(1), 61-8.
Willer, J.C., Dehen, H., & Cambier, J. (1981). Stress-induced analgesia in humans: Endogenous opioids and naloxone-reversible depression of pain reflexes. Science, 212(4495), 689-91.

Willer, J.C., & Ernst, M. (1986). Diazepam reduces stress-induced analgesia in humans. Brain Research, 362(2), 398-402.
Willer, J.C., & Le Bars, D. (1995). Electrophysiologic studies of morphine analgesia in humans. In B. Bromm & J.E. Desmedt (Eds.), Advances in pain research and therapy. Pain and the brain - from nociception to cognition. (Vol. 22, pp. 541-557). New York, USA: Raven Press.
Willer, J.C., Le Bars, D., & de Broucker, T. (1990). Diffuse noxious inhibitory controls in man: Involvement of an opioidergic link. European Journal of Pharmacology, 182(2), 347-55.
Willer, J.C., Roby, A., Boulu, P., & Albe-Fessard, D. (1982a). Depressive effect of high frequency peripheral conditioning stimulation upon the nociceptive component of the human blink reflex. Lack of naloxone effect. Brain Research, 239(1), 322-6.
Willer, J.C., Roby, A., Boulu, P., & Boureau, F. (1982b). Comparative effects of electroacupuncture and transcutaneous nerve stimulation on the human blink reflex. Pain, 14(3), 267-78.
Willer, J.C., Roby, A., & Le Bars, D. (1984). Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Brain, 107 (Pt 4), 1095-112.
Williams, D.A., & Thorn, B.E. (1986). Can research methodology affect treatment outcome? A comparison of two cold pressor test paradigms. Cognitive Therapy & Research, 10(5), 539-545.
Willis, W.D., Jr. (1995). From nociceptor to cortical activity. In B. Bromm & J.E. Desmedt (Eds.), Advances in pain research and therapy: Pain and the brain - from nociception to cognition. (Vol. 22, pp. 1-19). New York, USA: Raven Press.
Willoughby, S.G. (2000). The influence of depressed mood on behavioral, cognitive, and affective responses to cold pressor pain. Dissertation Abstracts International: Section B: The Sciences & Engineering, 61(2-B), 1101.
Willoughby, S.G., Hailey, B.J., Mulkana, S., & Rowe, J. (2002). The effect of laboratory-induced depressed mood state on responses to pain. Behavioral Medicine, 28(1), 23-31.
Witting, N., Svensson, P., Arendt-Nielsen, L., & Jensen, T.S. (1998). Differential effect of painful heterotopic stimulation on capsaicin-induced pain and allodynia. Brain Research, 801(1-2), 206-10.
Wolff, B.B. (1978). Behavioural measurement of human pain. In R.A. Sternbach (Ed.), The psychology of pain (pp. 129-168). New York: Raven Press.
Wolff, B.B., & Jarvik, M.E. (1964). Relationship between superficial and deep somatic thresholds of pain with a note on handedness. American Journal of Psychology, 77, 589-99.
Wolff, B.B., Krasnegor, N.A., & Farr, R.S. (1965). Effect of suggestion upon experimental pain response parameters. Perceptual & Motor Skills, 21(3), 675-683.
Woolf, C.J., Mitchell, D., & Barrett, G.D. (1980). Antinociceptive effect of peripheral segmental electrical stimulation in the rat. Pain, 8(2), 237-52.
Worz, R. (2003). Pain in depression - depression in pain. Pain - Clinical Updates, XI(5), 1-4.
Yaksh, T.L. (1985). Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacology, Biochemistry & Behavior, 22(5), 845-58.

Yamaguchi, K., Toda, K., & Hayashi, Y. (2003). Effects of stressful training on human pain threshold. Stress & Health: Journal of the International Society for the Investigation of Stress, 19(1), 9-15.

Yang, J.C., Richlin, D., Brand, L., Wagner, J., & Clark, W. (1985). Thermal sensory decision theory indices and pain threshold in chronic pain patients and healthy volunteers. Psychosomatic Medicine, 47(5), 461-8.

Young, R.R. (1973). The clinical significance of exteroceptive reflexes. In J.E. Desmedt (Ed.), New developments in electromyography and clinical neurophysiology (Vol. 3, pp. 697-712). Basel: Karger.

Zelman, D.C., Howland, E.W., Nichols, S.N., & Cleeland, C.S. (1991). The effects of induced mood on laboratory pain. Pain, 46(1), 105-11.

Zis, A.P., Haskett, R.F., Albala, A.A., Carroll, B.J., & Lohr, N.E. (1985). Opioid regulation of hypothalamic-pituitary-adrenal function in depression. Archives of General Psychiatry, 42(4), 383-6.

Zurita, A., Martijena, I., Cuadra, G., Brandao, M.L., & Molina, V. (2000). Early exposure to chronic variable stress facilitates the occurrence of anhedonia and enhanced emotional reactions to novel stressors: reversal by naltrexone pretreatment. Behavioral Brain Research, 117(1-2), 163-71.