

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

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BA (Hons, Psychology)**

This thesis is presented for the degree of Doctor of Philosophy
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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.

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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.

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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