

**FACTORS INFLUENCING THE
ANALGESIC EFFECTS AND
CLINICAL EFFICACY OF
TRANSCUTANEOUS
ELECTRICAL NERVE
STIMULATION (TENS).**

By

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Short Abstract

Factors influencing the analgesic effects and clinical efficacy of TENS have been examined in this thesis.

Clinical Studies: It was found that since the introduction of TENS into the Newcastle Pain Relief Clinic in 1979, 1582 patients have been given a trial of TENS to control chronic pain, of which 927 (58.6%) continue to use the therapy on a long-term basis. The clinical use of TENS by 179 of these patients was examined in-depth and it was found that any type of pain *may* respond to TENS although a lack of relationships between patient, stimulator and treatment outcome variables was observed. However, over half of the patients using TENS on a long-term basis achieve less than 50% relief of pain, therefore, an investigation to identify the optimal electrical characteristics of TENS on cold-pressor pain in healthy subjects was performed.

Electrical characteristics of TENS: Differential analgesic effects were observed between a range of pulse frequencies, pulse patterns and stimulating modes. It was suggested that continuous mode stimulation at 80Hz producing a 'strong but comfortable' electrical paraesthesia within the site of pain should be the primary choice when using TENS treatment in the clinic. However, acupuncture-like TENS produced powerful analgesic effects during and after TENS. A number of improvements in stimulator design are suggested.

EEG variables: Further studies, aimed at elucidating TENS mechanisms, showed that TENS altered electroencephalographic (EEG) variables in healthy subjects and pain patients. Moreover, chronic pain patients with small baseline peak-to-peak amplitudes of the somatosensory evoked potential (SEP) and low spontaneous EEG activity, showed poor response to TENS. It is suggested that an individual's intrinsic central response pattern to external stimuli may influence response to TENS.

The clinical implications of these findings are discussed.

Long Abstract

Transcutaneous electrical nerve stimulation (TENS) is a simple, non-invasive technique used in the control of chronic pain. Despite the success of TENS and its continued use for over twenty years, some patients either fail to respond or show only a partial response. Furthermore some patients respond initially to TENS but then become tolerant to its analgesic effects. The reasons for poor response to TENS are unknown; different clinics report widely differing success rates, and information on long-term efficacy is sparse. Furthermore, TENS is still administered on an empirical basis in which the patient determines by trial and error the most appropriate stimulator settings (i.e. electrical characteristics of TENS) to treat his or her particular pain. It is impossible to predict whether an individual patient will respond to TENS or which stimulator settings will be optimal. In an attempt to elucidate these problems, the clinical, electrophysiological, neuropharmacological, psychological and sociological factors that influence the analgesic effects and clinical efficacy of TENS have been examined in this thesis.

Three clinical studies were performed. The first (Study 2.1) reviewed the use of TENS since its introduction to Newcastle Pain Relief Clinic in 1979. It was found that 1582 patients have been given a trial of TENS of which 927 (58.6%) continue to use a stimulator on a long-term basis (Study 2.1). The clinical use of TENS by 179 of these patients was examined in-depth (Study 2.2). Although previous literature suggests that TENS is most efficacious for pains of neurogenic (neuropathic) origin, it was found that any type of pain *may* respond. No relationships were found to exist between the electrical characteristics of TENS (i.e. stimulator settings) used by patients during TENS treatment and the cause and site of pain. However, patients utilised specific pulse frequencies and patterns and consistently used these settings on subsequent treatment sessions (Study 2.3).

These clinical studies showed that in this population, 41.4% of patients failed to respond to TENS and half using TENS on a long-term basis achieved less than 50% relief of pain. Thus, a systematic investigation to determine optimal electrical characteristics of TENS was performed.

Three experiments were undertaken to examine separately the analgesic effects of different electrical characteristics of TENS (pulse frequency, pulse pattern and stimulation mode) on cold-pressor pain in healthy subjects. The effects of a range of

pulse frequencies (10Hz to 160Hz) applied to produce a 'strong but comfortable' electrical paraesthesia within the painful site were measured (Exp. 3.1). It was found that frequencies between 20-80Hz were most effective. However, no differential effects were observed between a range of pulse patterns (continuous, burst, modulation, random; Exp. 3.2). When TENS was applied in burst mode at an intensity sufficient to produce phasic muscle twitches at a site distant yet myotomally related to the site of pain (acupuncture-like TENS) a powerful analgesic effect was observed during and post-stimulation (Exp. 3.3). It is suggested that continuous mode stimulation at 80Hz, producing a 'strong but comfortable' electrical paraesthesia within the painful site, should be the primary TENS treatment choice in the clinic but that in selected cases AL-TENS may be more effective. A number of improvements in stimulator design are suggested.

Further experiments were aimed at elucidating the mechanism of TENS effects by investigating the influence of TENS on electrophysiological and neuropharmacological variables. It was found that TENS reduced peak-to-peak amplitudes of the late waveform components (N1P2) of somatosensory evoked potentials (Exp. 4.1) and increased alpha, beta and theta activity of spontaneous EEG in healthy subjects (Exp. 4.2) and/or pain patients (Exp. 4.3). As TENS produced changes in SEPs elicited from non-painful stimuli, and also changes in spontaneous EEG in pain-free subjects, it is suggested that the effects of TENS may be due in part to changes in sensory processing at several levels in the nervous system which may not specific for the perception of pain. The surprising finding that TENS increased peripheral circulating met-enkephalin in chronic pain patients was attributed to a stress-like release although this observation remains to be confirmed using a larger population sample (Exp. 5.1).

The results of these experiments suggest that baseline electrophysiological and neuropharmacological variables may be important determinants of individual response to TENS. Thus, a prospective investigation was undertaken on 29 patients who were undergoing a trial of TENS to control chronic pain, in an attempt to identify predictors of patient response. Patient response to TENS was related to baseline SEP amplitudes and spontaneous EEG but was not related to biochemical, psycho-social, personality or pain related factors (Exp. 6.1). Thus, patients with small peak-to-peak amplitudes of the SEP, and low power spectrum of spontaneous EEG showed poor response to TENS (Exp. 6.1). It is suggested that an individual's intrinsic central response pattern to external stimuli may influence response to TENS.

Publications

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Pain is one of the world's most costly health problems. It is financially expensive in terms of medical consultations, treatments and time lost from work, and immeasurably costly in terms of personal suffering and impaired quality of life. Nevertheless the medical management of pain, especially chronic pain, remains unsatisfactory and any potential improvement in pain control is worthy of serious study. The relatively recent technique of transcutaneous electrical nerve stimulation (TENS) appears to offer such promise in the control of chronic pain and is the subject of this investigation.

TENS is a simple, non-invasive technique, in which electrical currents, generated by a portable stimulating unit, are administered via conducting pads (electrodes) placed on the intact surface of the skin (Fig.1.1).



Fig.1.1 Nurse applying TENS to treat a patient with back pain. Electrodes are attached to surface of skin by adhesive tape. Electrical pulses from the TENS unit (next to the patient on the bed) are delivered to the electrodes via a lead to produce a *tingling sensation* (electrical paraesthesia).

In its simplest (conventional) form TENS produces a 'tingling' sensation (electrical paraesthesia) within the painful area. The intensity and quality of electrical paraesthesia can be varied and controlled by the patient according to his/her requirements. TENS has been shown to produce useful analgesic effects in patients with acute or chronic pain and has gained worldwide popularity. TENS has many advantages over conventional treatments for pain. It does not require surgical intervention and, unlike analgesic drugs, has no serious adverse effects. It can be used long-term and does not interfere with other analgesic treatments. However some patients fail to respond to TENS; others respond initially but then become tolerant; still others show only a partial response. The reasons for poor response to TENS are unknown; different clinics report widely differing success rates, and information on long-term efficacy is sparse.

Furthermore, there have been few detailed studies into the stimulator settings (electrical characteristics) utilised during TENS which may influence efficacy. In practice TENS is usually administered on an empirical basis where the patient determines by trial and error the most appropriate electrical characteristics of stimulation to control the pain condition. It is likely that TENS efficacy could be improved if the electrical characteristics of stimulation were optimised.

This investigation is aimed at elucidating some of the factors which determine the analgesic efficacy of TENS, with a view to predicting patient response to TENS and possible improvements in stimulator design.

PAIN

The working definition of pain as described by the Taxonomy Committee of The International Association of the Study of Pain (IASP) is :

"...an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

Some additional points of clarity accompany the definition:

"Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. It is unquestionably a sensation in a part of body but is also unpleasant and therefore an emotional experience."

A detailed explanation of this definition can be found in Merskey [1979] and IASP [1986].

Three aspects of pain perception arise from this definition:

- (i) The sensory components of pain, e.g. location, intensity and quality of pain.
- (ii) The affective components of pain, e.g. distress and anxiety associated with pain.
- (iii) The evaluative components of pain, e.g. significance and importance of pain.

Thus, the sensation of pain, like any other sensory modality, depends upon the activation of a discrete set of neural pathways, which in turn evoke a complex reflex and motivational-affective experience associated with emotional reactions such as suffering, anxiety, depression and an evaluation of what the pain means [Fields 1991]. Consequently inter-individual reactions to painful stimuli are variable.

ACUTE AND CHRONIC PAIN

Pain is most commonly produced by either (i) injury or (ii) stimuli that are intense enough to be potentially damaging (noxious). Along with the subjective experience of pain, noxious stimuli elicit a variety of behavioural responses which serve to protect uninjured tissues, i.e. withdrawal reflexes, escape, immobilisation of the injured part and avoiding future encounters with such stimuli. Thus in its acute state, pain serves as a warning signal or protective mechanism and is associated with acute disease or traumatic injury. If diagnosed and treated comprehensively acute pain can usually be resolved.

It is when a pain condition becomes chronic, persisting longer than the expected time after illness or injury, that the pain appears to lose its biological importance as a warning signal and the body may cease to react with appropriate protective reflexes. Four types of chronic pain have been described by Chapman and Bonica [1985]:

- (i) Pain persisting beyond the normal healing time for acute injury or disease.
- (ii) Pain related to chronic degenerative disease or a persisting neurological condition.
- (iii) Pain without any identifiable organic cause.
- (vi) Advanced cancer.

Often the diagnosis and treatment of chronic pain is difficult, and the failure of ineffective medication and surgery can leave patients seriously debilitated. Consequently chronic pain is often associated with severe depression since the patient may lose hope for prospects of relief.

To achieve adequate treatment of both acute and chronic pain, it is important to understand the basic neuroanatomical and neuropharmacological systems which lead to the sensation of pain.

NEUROANATOMY OF PAIN

Between the stimulus of tissue injury and the subjective experience of pain a series of complex electrical and chemical events take place. A schematic diagram of the major neural pathways that contribute to pain sensation is shown in Fig.1.2. There is no single pathway or brain centre devoted to pain transmission and processing but rather an elaborate neurobiological system in which many interacting processes convert the noxious stimulus into the subjective sensation of pain. These processes include, transduction, transmission, modulation and perception of nociceptive information.

Transduction: Refers to the process by which noxious stimuli is converted to electrical activity in the appropriate sensory nerve endings. This is achieved by nociceptors, which can be defined as:

"receptors preferentially sensitive to noxious or potentially noxious stimuli or to a stimulus which would become noxious if prolonged" [IASP 1986].

Two main classes of cutaneous nociceptors are known:

- (i) High threshold mechanoreceptors connected to myelinated A-delta fibres, which conduct at $5\text{-}10\text{ms}^{-1}$,
- (ii) Polymodal nociceptors connected to unmyelinated C-fibres, which conduct at $0.5\text{-}2\text{ms}^{-1}$.

Both groups of nociceptors begin to respond at stimulus intensities below those that evoke pain [Wall & McMahon 1986].

Transmission: Refers to the neural events subsequent to transduction. There are two major components of the nociceptive transmission system.

Peripheral: Small diameter A-delta and C-fibres ($2.0\text{-}5.0\mu\text{m}$ and $0.4\text{-}1.2\mu\text{m}$ respectively) transmit nociceptive information from nociceptors to the dorsal horn of the spinal cord (the majority via the dorsal root ganglia), where they branch profusely in the marginal zone and substantia gelatinosa, and form synapses with interneurons and second order neurones.

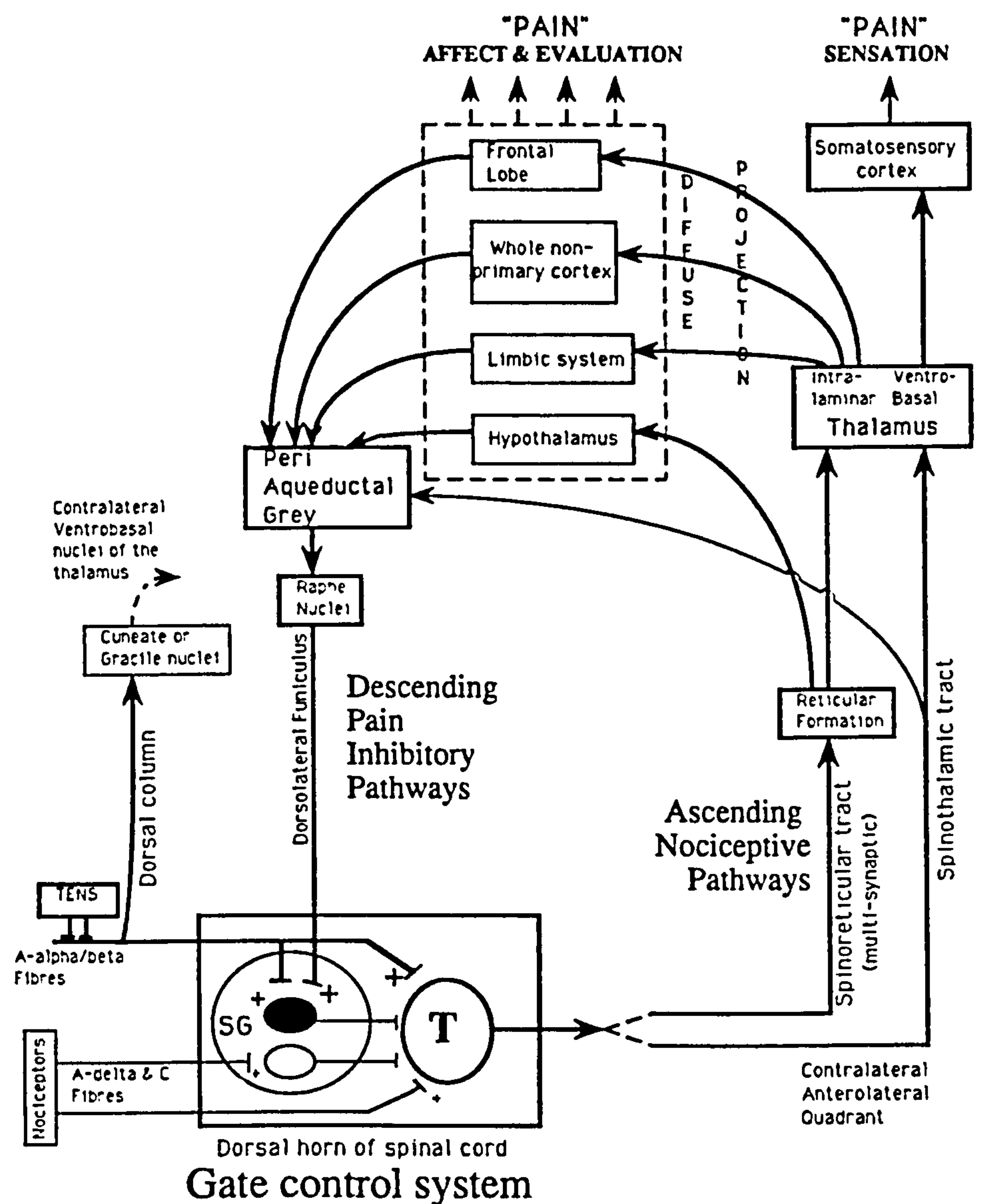


Fig. 1.2 Schematic diagram of the main nociceptive pathways. Non-noxious information is transmitted in large A-alpha/beta diameter fibres (thick line) which ascend ipsilateral via the dorsal column to synapse in the cuneate and gracile nuclei. Second order neurones originate here and cross the spinal cord to run in the contralateral medial lemniscus to the ventrobasal nuclei of the thalamus and the somatosensory cortex. Nociceptive information is transmitted from the periphery to the dorsal horn of the spinal cord via small diameter fibres (thin line) which synapse with second order transmission (T) cells either directly or via interneurons (white circle). The transmission cells are located in the deeper layers of the dorsal horn (lamina V) and project to the contralateral thalamus in spinothalamic and spinothalamic tracts. Diffuse projections to the whole cortex produce the affective - evaluative components of pain and projections to the specific (Areas SI & SII) somatosensory cortex produce the sensory - discriminatory components of pain. The transmission of nociceptive information is modulated by (i) a gate control system and (ii) descending pain inhibitory pathways. The gate control system modulates the firing of transmission cells via inhibitory interneurons (black circle) located in the Substantia Gelatinosa (SG). These inhibitory interneurons can be activated by either (i) collaterals from the large diameter fibres (activated by TENS) or (ii) descending pain inhibitory pathways. These descending pain inhibitory pathways originate in the periaqueductal grey matter of the brainstem and are activated by (i) collaterals from spinothalamic tract and (ii) higher centres of the brain. All synapses excitatory unless otherwise stated. (Adapted from Thompson [1984]; Bowsher [1988]; Fields [1987a]; Bonica [1990]).

Central: The most important pathways in the human spinal cord which relay nociceptive information to the brain and thalamus, ascend via second order neurones in the contralateral anterolateral white matter in the following nerve tracts:

- (i) Spinoreticular - a multi-synaptic tract which ascends to the medullary reticular formation and intralaminar nuclei of the thalamus.
- (ii) Spinothalamic - which ascends directly to the ventrobasal nuclear complex of the thalamus.

The spinothalamic tract has been subdivided into:

- (i) the neospinothalamic tract, responsible for pricking or localised sharp pain associated with A-delta fibre stimulation:
- (ii) the paleospinothalamic tract, responsible for slow burning pains associated with C-fibre stimulation.

Evidence suggests that the spinoreticular and the paleospinothalamic tracts serve as a single functional entity [Fields 1987b].

From its respective nuclei in the thalamus, the neospinothalamic tract projects to the somatosensory cortex (areas SI and SII) and sub-serves the sensory-discriminative aspects of pain. The spinoreticular pathway projects from the thalamus to widespread areas of the brain, and underlies the motivational-affective aspects of pain (Fig.1.2). Thus, diffuse projections from the thalamus to the hypothalamus, limbic system and cortex, account for the autonomic, emotional and cognitive processes associated with the perception of pain.

Modulation: Refers to the neural activity leading to control of the nociceptive transmission system. An antinociceptive system operates via (i) 'spinal gating mechanisms', where the further transmission of incoming nociceptive information is regulated by collaterals of primary afferent neurones (both large (primarily A-beta, 5-12µm) and small diameter) and interneurones, and (ii) supraspinal descending pain inhibitory pathways, extending from the periaqueductal grey to the spinal cord, where they impinge upon incoming nociceptive information.

Pain perception: Unfortunately knowledge is severely lacking in the understanding of the process of pain perception. A recent study by Jones et al. [1991] which used positron emission tomography (PET) to measure changes in regional blood flow during pain in healthy subjects, suggests that the cingulate cortex may play an important role in the perception of pain. However, pain is perceived in terms of injury in the context of the afferent barrage in fibres transmitting nociceptive and non-nociceptive information, and of analytical processes in the brain. Moreover, the peripheral and central nervous systems

change progressively with time, particularly after injury. Thus changes in neuronal connectivity and excitability resulting from injury may alter the way in which the nervous system responds to stimuli and may even evoke pain from innocuous stimuli.

NEUROPHARMACOLOGY OF PAIN

It is clear that many substances play a role in the transmission and modulation of nociceptive information. Endogenous algescic agents produced peripherally during noxious stimulation include serotonin (5-Hydroxytryptamine (5-HT)), histamine, and bradykinin. In addition prostaglandins play an important role in sensitising sensory nerve endings to nociceptive substances such as kinins. These peripherally acting substances will not be considered further. Neuropeptides (non-opioid and opioid), monoamines and amino acids appear to play important roles in the central transmission and modulation of nociceptive information, as shown in Fig.1.3. These central agents will now be discussed.

Non-opioid neuropeptides: Substance P has been shown to act as an excitatory neurotransmitter at primary nociceptive nerve endings in the dorsal horn [Hökfelt et al. 1975]. It may be co-released with other transmitters, possibly glutamate or ATP, and its release may be controlled by the pre-synaptic action of short enkephalinergic interneurons. In addition to substance P, other non-opioid polypeptides including somatostatin, neurotensin, angiotensin II and cholecystokinin (CCK) may be involved in pain modulation in the spinal cord and brain.

Opioid neuropeptides: Since the isolation of opioid peptides from the pig brain by Hughes et al. [1975], a wide distribution of multiple opioid peptides and opioid receptors have been found [for review see Mansour et al. 1988]. Many of these are closely associated with systems subserving pain modulation [for review see Clement-Jones & Besser 1983]. Three classes of endogenous opioid peptides appear to be of major physiological importance: dynorphin, endorphins and enkephalins. Enkephalins appear to control the response of dorsal horn neurones and modulate pain at higher sites in the central nervous system, although the analgesic effects of enkephalins are short lived due to their rapid degradation by enkephalinases.

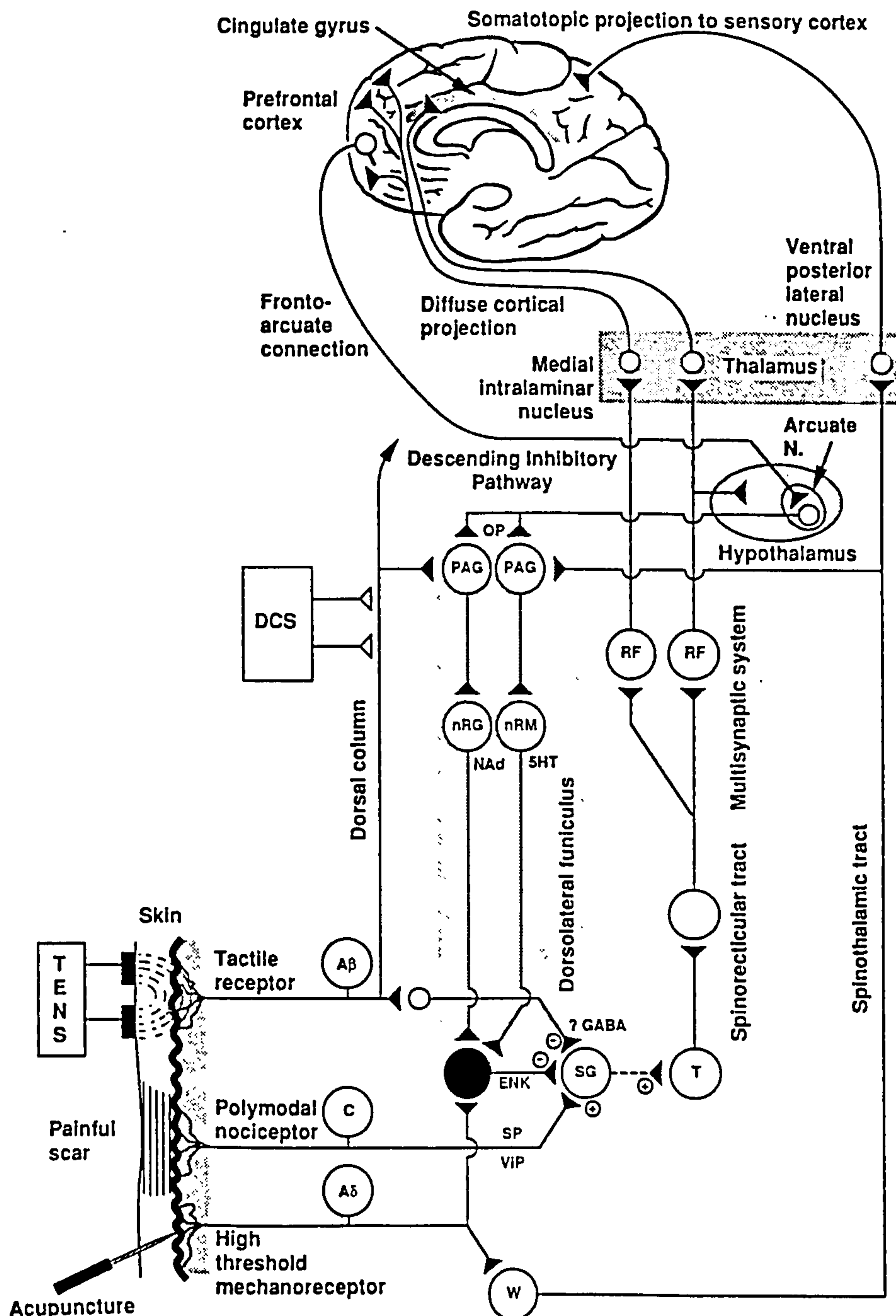


Fig.1.3 Simplified diagram of the neuropharmacology of antinociceptive pathways. Substance P (SP), and Vasoactive Intestinal Polypeptide (VIP) are released from primary afferent nociceptive neurones originating from the skin and viscera and terminate in the substantia gelatinosa (SG) of the dorsal horn. SG interneurons excite second order transmission cells (T) primarily in lamina V which ascend in multisynaptic spinoreticular tracts to the thalamus and produce the conscious sensation of 'slow aching' pain. Waldeyer cells (W) in lamina I of the dorsal horn can be excited by impulses generated in A-delta afferents and transmit noxious information conveying 'fast sharp' pain to consciousness via the spinothalamic tract and the somatosensory cortex. *Spinal antinociception:* Enkephalinergic interneurons (ENK, dark circle) operate on the borders of lamina I and II and inhibit onward transmission of noxious information generated by C-fibre activity. Low intensity TENS and dorsal column stimulation (DCS) inhibit SG, possibly by the release of GABA, to produce segmental inhibition of nociceptive transmission. *Supraspinal antinociception:* Descending pain inhibitory pathways are activated via collaterals of the spinothalamic tract by high intensity TENS or acupuncture, and originate in the periaqueductal grey (PAG). The PAG is rich in opioid peptides (OP) and receives input from a variety of sources including the hypothalamus. Neurones from the PAG project to the nucleus raphe magnus (nRM) and nucleus reticularis gigantocellularis (nRG). Serotonergic (5-HT) and noradrenergic (NAd) neurones arising from the nRM and nRG, project to ENK to inhibit onward transmission of nociceptive information. All synapses excitatory unless otherwise stated. From Thompson and Filshie [in press].

Endorphins are less rapidly degraded in the body and have longer lasting analgesic effects. A rise of concentration in cerebrospinal fluid (CSF) concentrations of beta-endorphin have been shown to occur during acupuncture [Clement-Jones et al. 1980b], electrical stimulation of the periaqueductal grey and associated nuclei [Akil et al. 1976], and during certain forms of TENS [Sjölund et al. 1977]. The role of dynorphin in pain modulation remains unclear.

Monoamines: Monoamine neurotransmitters appear to play a role in the modulation of nociceptive transmission via supraspinal descending pain inhibitory pathways terminating in the spinal cord [Akil & Liebeskind 1975]. Analgesia produced by electrical stimulation of the periaqueductal grey and raphe nuclei, is accompanied by the release of 5-HT and noradrenaline in the spinal cord in the cat [Belcher et al. 1978]. Histamine, acetylcholine, and dopamine, may also mediate pain suppression pathways [for review see Fitzgerald 1986].

Amino acids: Several amino acid transmitters have been shown to play a role in nociception. Glutamate is contained within three quarters of dorsal root ganglia cells and may be an excitatory neurotransmitter for primary afferent nociceptive afferents. Recently, the N-methyl d-aspartate (NMDA) receptor has been implicated in the amplification and prolongation of an ongoing nociceptive afferent barrage (C-fibre dependent facilitation, or 'wind-up') [Dickenson 1990]. Gamma-amino butyric acid (GABA) may be involved in central antinociceptive systems within the spinal cord and brainstem nuclei. Glycine, beta-alanine, and taurine, may also play a role.

MEASUREMENT OF PAIN IN MAN

One of the most difficult and critical aspects in the investigation of pain is its quantitative documentation. As pain is a subjective experience, the basic expression of pain in humans is the verbal report. Various methods on the scaling of subjective pain have been established.

Pain rating scales: Common approaches to the rating of pain sensation are category and analogue scales. The category scale is classified by a set of given descriptors to measure sensory (e.g. sharp, dull, burning, aching), affective (e.g. exhausting, sickening, gruelling, nagging), and evaluative (e.g. annoying, unbearable), components of pain as shown in the McGill Pain Questionnaire [Melzack 1975a]. The analogue scale translates different strengths or sensations into units of length, and although scales can vary in presentation, a 10 cm visual

analogue line labelled at ends with words and numbers (for example 'no pain' = 0 to 'worst pain imaginable' = 10) is commonly used in clinical research. The subject indicates the intensity of the pain by marking the line at the appropriate point. Despite problems with the reliability of the analogue scale in measuring inter-individual pain variables (i.e. intensity), and its ability to record only one component of the multi-dimensional pain sensation, it proves a most useful and simple means of comparing treatment effects within the laboratory setting.

Objective pain measures: To quantify objectively the verbal report of pain, physiological reactions accompanying pain can be recorded, such as peripheral nerve activity, withdrawal reflexes, skin resistance reactions, evoked potentials (EPs) and the electroencephalogram (EEG). It has been claimed that the cerebral evoked potential (the stimulus induced change in the electroencephalogram) can provide a stable and reliable correlate between brain activity and the subjective report of pain [for reviews see Chapman et al. 1979; Bromm 1985]. Many studies have utilised EPs to quantify pain and analgesic effects in man. With recent improvements in technology and methodology, it is also possible to monitor changes in spontaneous (ongoing) electroencephalographic activity during pain and analgesia, although few studies have been performed.

Experimental and clinical pain: Experimentally-induced pain in the laboratory differs from pain seen by the physician in the clinic because experimental pain can always be interrupted or stopped on request by the subject. Measurement of *experimental pain* is characterised by the sensory-discriminative rather than affective-evaluative components of pain, and is reflected by nocifensive motor reactions. By contrast, a *patient's pain* is characterised by aversive, emotional and vegetative components producing a feeling of illness, and ultimately causing the patient to visit the doctor.

TREATMENT OF PAIN

Until the 50's, many physicians had worked on the assumption that the brain had a hard-wired pain transmitting system, and that to stop pain one had to irreversibly block these transmitting pathways by either surgical (i.e. cordotomy) or chemical means (i.e. neurolytic block). Such treatment failed and at present analgesic medications are the mainstay of pain control as they have a proven efficacy, are widely available, and are convenient for patients to use and physicians to administer. Primary analgesic agents include antipyretics (non-steroidal anti-

inflammatory drugs), narcotics (opioids) and local and general anaesthetics. Secondary analgesic agents include anxiolytics, neuroleptics, antidepressants and anticonvulsants [Thompson 1984]. Nevertheless, patients and physicians are often dissatisfied with the long-term use of analgesic drugs for non-malignant pain as patients often report inadequate pain relief, experience intolerable side effects and/or are intimidated with the problems associated with long-term use .

Consequently a variety of non-drug treatment techniques have been developed and are gaining acceptance in the medical profession. These include cognitive behavioural methods (hypnotherapy, biofeedback, relaxation), ablative procedures (neurolytic blocks), neuroaugmentative surgery, acupuncture and transcutaneous electrical nerve stimulation (TENS). Unfortunately administration of most of these treatments requires specialised training and is labour intensive and thus expensive. TENS remains the exception to the rule, yet the value of the technique is still questioned due to contradictory reports on efficacy and the difficulty of designing good clinical studies [Deyo et al. 1990a; 1990b].

TENS came into widespread use following the prediction by Melzack and Wall in 1965 that stimulation of large diameter afferent fibres in a peripheral nerve would alleviate pain [Melzack & Wall 1965]. Over the last few decades TENS has been established as an efficacious therapeutic modality in the treatment of both acute and chronic pain, yet the technique is not really new.

HISTORY OF ELECTROANALGESIA

Long before the technology existed to generate electricity, man has used '*naturally occurring*' electricity for the treatment of ailments. Stone carvings dating from the Egyptian Fifth Dynasty (2500BC) indicate that *Malapterurus electricus*, a species of electric fish found in the Nile, was used to treat pain conditions [Kane & Taub 1975]. The earliest known reference to acupuncture was also reported at this time in the Yellow Emperor's Classic of Internal Medicine. Hippocrates (400BC) referred to the use of electric torpedo fish (*Torpedo marmorata*) for the treatment of headache and arthritis, and Scribonius Largus (46 AD), the Roman Physician, recorded the use of such fish to treat gout. The first english language book on medical electricity was published by Richard Lovett in 1756, following the classification of the phenomenon of electricity by William Gilbert (1544-1603).

2500 B.C.	Egyptian Fifth Dynasty	Stone carvings showing the use of electric fish to treat pain
400 B.C.	Hippocrates	Electric Fish used for headache and arthritis
A.D. 46	Scribonius Largus	Treated gout with electrical ray fish
1756	Richard Lovett	<i>Subtil Medium Proved</i> First textbook on medical electricity in English language
1759	Dr John Wesley	<i>"Electricity made plain and useful by a lover of mankind and common sense"</i> Sciatica hysteria headache kidney stone gout etc.
1772	John Birch	English surgeon who used electrotherapy extensively
1800+	Sarlandiere	Used electric discharge from Leyden bottles via acupuncture needles
1850's	W.J. Oliver	Electrical stimulation of muscle used to produce surgical and obstetric analgesia
1875	Rockwell et al.	<i>A practical treatise on the medical and surgical uses of electricity</i> 2nd ed.
c1900		'Electreat' apparatus sold direct to public with claims to cure many diseases including cancer. Banned by FDA in early 50's
1965	R. Melzack and P.W. Wall	Gate Control theory
1967	P.Wall and W. Sweet	High-frequency (50-100Hz) percutaneous electrical nerve stimulation for chronic neurogenic pain
1967	C.N.Shealy et al.	First dorsal column implantation
1969	D.V. Reynolds	Stimulation of periaqueductal grey produces surgical anaesthesia
1973-74	D.M. Long and C.N. Shealy	Report results of transcutaneous electrical nerve stimulation (TENS)
1977	L.E.Augustinsson et al.	Obstetric analgesia with TENS
1979	M.B.E. Eriksson et al	Increased analgesic efficacy of acupuncture-like TENS
1982	B.Kaada	High-intensity muscle stimulating TENS promotes healing of chronic ulceration

Table 1.1 History of electroanalgesia. From Thompson [1987a].

A multitude of reports, describing the use of electricity in medicine, termed *electrotherapy*, and for reducing pain, termed *electroanalgesia*, followed in the 1800's (Table 1.1). Of note was the finding of Berlioz (1816) that the effects of acupuncture were increased when administered in combination with electricity (electro-acupuncture). Nevertheless electrotherapy fell out of favour at the turn of the 20th century and, until recently, electroanalgesia has had little use in mainstream medicine.

The proposal of the gate control theory of pain mechanisms by Melzack and Wall re-awakened interest in pain treatment by electrical stimulation. The theory states "*A gate control system modulates sensory input from the skin before it evokes pain perception and response.*". Thus in short, the model suggests that *the action system* responsible for pain perception and response, is triggered after sensory information arriving from the periphery has been modulated in the spinal cord by sensory feedback and influences from the central nervous system. It was therefore inferred that activity in large diameter afferent nerve fibres, mediating non-noxious 'touch' messages, could block the transmission of nerve signals from small diameter afferent fibres, mediating noxious 'pain' messages, (Fig.1.4).

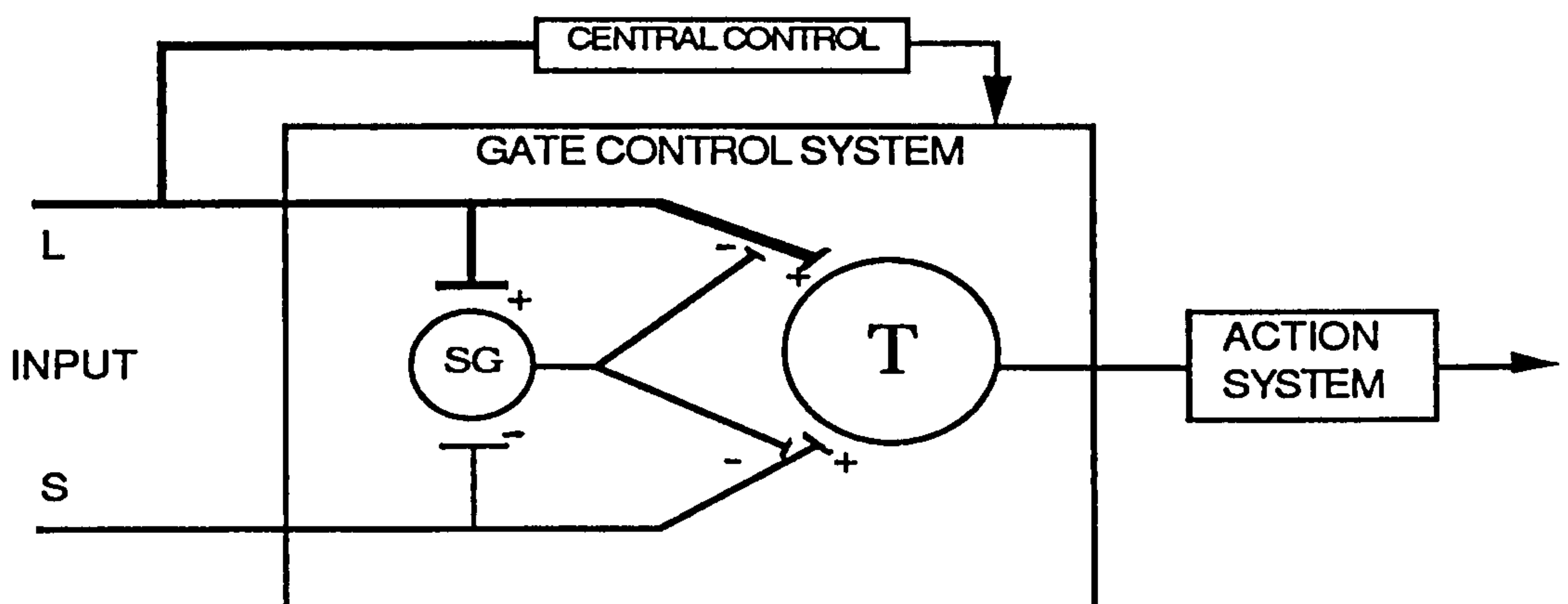


Fig.1.4 The original schematic diagram of the gate control theory of pain mechanisms as proposed by Melzack and Wall [1965]. Large (L) and small (S) diameter fibres project to the Substantia Gelatinosa (SG) and first Transmission cells (T) in the spinal cord. The inhibitory effect exerted by the SG on the T-cell is increased by activity in large diameter fibres and decreased by small diameter fibres. Thus, large diameter fibres reduce the increase in T-cell activity produced by the small diameter fibres. (+), excitation; (-), inhibition.

Consequently, generation of extra touch messages in the periphery, either naturally (i.e. rubbing) or artificially (i.e. electrical stimulation), would relieve pain. Although the experimental basis for the precise gating mechanism has been the subject of criticism [Nathan 1976], the concept of large fibre suppression of the transmission of nociceptive information by a spinal gating mechanism still remains largely intact, and has been amply verified experimentally [Wall 1978].

Wall and Sweet [1967] confirmed a prediction of the gate control theory when they showed that high-frequency (50-100Hz) percutaneous electrical nerve stimulation relieved chronic neurogenic pain. Shealy et al. [1966; 1967] reported the first clinical use of dorsal column stimulation to relieve pain via electrodes implanted into the spinal cord. Stimulation of the skin was used by Long [1974] and Shealy [1974] as a means to predict which patients would respond to dorsal column implantation. However they found that such skin stimulation proved successful as a free standing treatment. This finding coupled with the advent of solid state electronic devices resulted in the rapid development of portable battery powered stimulators for the relief of pain. Many reports followed which established the clinical use of TENS and this was followed by attempts to improve its efficacy. In 1976, Eriksson and Sjölund [1976] developed a form of stimulation which they termed "*Acupuncture-Like TENS*" (AL-TENS) because they felt it encompassed the mechanisms of both acupuncture and TENS. AL-TENS was found to reduce pain in patients who did not normally respond to conventional TENS.

To date, an overwhelming number of reports relating to the clinical use of TENS have been published, and it has been established that TENS can play a major role in the relief of a wide range of chronic pain conditions. However, its clinical efficacy is still questioned. This may be due in part to the difficulty in designing double blind controlled clinical trials, and thereby attributing TENS effects to placebo response [Deyo et al. 1990a].

MECHANISM OF TENS ACTION

It is generally accepted that TENS acts predominantly via segmental inhibition of nociceptive input in the spinal cord, as proposed in the gate control theory although, a number of interactive mechanisms may also play a role. During high-frequency (above 10Hz) electrical stimulation of cutaneous afferents, a sensation of electrical paraesthesia is produced, with a concurrent rise in the threshold for noxious and non-noxious stimuli and a reduction in clinical pain, which may persist

for hours post-stimulation. It has been suggested that these effects may be produced by peripheral, spinal and supraspinal mechanisms. These will now be discussed.

Peripheral: It has been claimed that the reduction in pain observed during TENS treatment is primarily due to changes in peripheral transmission of nociceptive information [Campbell & Taub 1973; Torebjork & Hallin 1974; Ignelzi & Nyquist 1979]. Ignelzi and Nyquist [1976] studied the effects of percutaneous neurostimulators used clinically on isolated peripheral nerve evoked activity in the cat. They found that electrical stimulation of the sural nerve altered nociceptive transmission in the same nerve by slowing conduction velocity or raising excitation threshold, thereby preventing nociceptive information from reaching the spinal cord. Strong stimulus intensities and the activation of both large and small diameter fibres, were required to achieve this effect, which was in contrast to the non-painful low intensity stimulation used by patients. Furthermore, Swett and Law [1983] in a study applying stimulation characteristics used by patients who were obtaining pain relief to the peripheral nerve of the cat, reported that the intensities used by patients were insufficient to activate small diameter fibres and found no evidence of small diameter nerve block.

Spinal: The bulk of experimental evidence supports a central mechanism of TENS action. It is possible that both spinal and supraspinal antinociceptive systems may operate during TENS, and the influence of each system may ultimately depend upon the mode of stimulation used. Conventional TENS, which activates large diameter fibres (predominantly A-alpha and A-beta, although activation of A-delta may also occur [Chung et al. 1984b]), is likely to inhibit incoming nociceptive information at a segmental level in the spinal cord, as suggested by the gate control theory. Electrophysiological studies have shown that segmental activation of cutaneous A fibres by peripheral conditioning stimuli, inhibits C-fibre and noxious-evoked activity in the dorsal horn of spinalised animals [Woolf et al. 1980; Woolf & Wall 1982; Chung et al. 1984a; Sjölund 1985]. Such stimulation has also been found to reduce noxious-induced flexion reflexes in man [Willer et al. 1982; Chan & Tsang 1987]. Both pre- and post-synaptic inhibition of nociceptive transmission has been shown to occur during TENS [Fitzgerald & Woolf 1981; Woolf & King 1987]. However the precise neuronal circuitry producing this inhibition is still largely unknown. The large density of enkephalinergic interneurons located in the substantia gelatinosa of the dorsal horn [Bennett et al. 1982], and the finding by Duggan and Foong [1985] that dorsal column stimulation in cats releases GABA within the cord, suggests important roles for these substances in the mechanism of

TENS action. The post-stimulation hypoaesthesia associated with conventional TENS has been attributed to a long-lasting depression of central synaptic transmission, possibly at the level of the cuneate nucleus [Macefield & Burke 1991].

Supraspinal: There is evidence that supraspinal descending pain inhibitory pathways originating in the brainstem, may also play a role in TENS analgesia. It is likely that these pathways are only activated by stimulus intensities greater than that achieved during conventional TENS. The concept of a supraspinal network modifying pain transmission was originally suggested by Reynolds et al. [1969], who found that electrical stimulation of the midbrain in rats selectively suppressed responses to painful stimuli. This '*Stimulation Produced Analgesia*' (SPA) was found to reduce clinical pain in humans with electrodes implanted into the periaqueductal grey (PAG) [Mayer & Liebeskind 1974]. It was confirmed that stimulation of a variety of midbrain, medullary, and pontine sites produced SPA, and that neurones originating from these areas projected spinally (via dorsolateral funiculus) to inhibit dorsal horn neurones in lamina I, II, and V, which contain terminals of nociceptive primary afferents [Bowie & Meyerson 1982].

Acupuncture-like TENS (AL-TENS) is a TENS technique originally developed by Eriksson and Sjölund [1976] to improve TENS efficacy by encompassing the mechanism of acupuncture and TENS. A requirement of AL-TENS is the production of phasic muscle contraction by high intensity stimulation, with concurrent activation of deep muscle afferents myotomally related to the pain. It has been suggested that stimulation of small diameter sensory and muscle afferents by acupuncture, activates descending pain inhibitory pathways via a supraspinal loop [for review see Bowsher 1987]. Thus, by implication, AL-TENS may activate supraspinal descending inhibitory pain control pathways with the release of opioid peptides and monoamines (see Fig.1.3). This is supported by the naloxone-reversibility (naloxone is an opiate receptor antagonist) of the pain reduction achieved during AL-TENS, but not conventional TENS [Sjölund & Eriksson 1979]. It seems unlikely that a pituitary and/or hypothalamic release of opioid peptides into the peripheral circulation would account for this naloxone-reversability [Facchinetti et al. 1984], but rather that segmental inhibition in the spinal cord is supplemented by the local release of opioid peptides activated by signals transmitted via the descending pain inhibitory pathways.

Further evidence for a central rather than peripheral mechanism of action of TENS has been provided by human studies using somatosensory evoked potentials (SEPs) [Golding et al. 1986; Nardone & Schieppati 1989]. These will be discussed in detail in Chapter 4.

Other actions of TENS, involving the activation of sympathetic reflexes, have been suggested. Thus, Kaada et al. [1982] reported an increase in blood flow during TENS in patients with Raynaud's syndrome, although Dean and Leijon [1990] found a decrease in blood flow during TENS in healthy subjects. Furthermore, Owens et al. [1979] and Abram et al. [1980] have observed increases in skin temperature during TENS in both healthy subjects and pain patients, although conflicting reports exist [Ebersold et al. 1977]. Abram et al. [1980] suggested that TENS may reduce sympathetic tone in certain patients and prove successful in treating chronic pain states associated with sympathetic hyperactivity. However, work in this field is still incomplete.

In summary, evidence suggests that the analgesic effects of TENS are produced by segmental inhibition in the spinal cord, and under certain stimulating conditions (i.e. AL-TENS) with the activation of descending pain inhibitory pathways and the release of opioid peptides.

PRINCIPLES OF USE

TENS has been used successfully in the treatment of a wide range of both acute and chronic pain conditions, although certain conditions are *less likely* to respond to TENS (Table 1.2a and 1.2b). In its conventional form, TENS is generally applied to produce a 'strong but comfortable' electrical paraesthesia within the site of pain. Electrical pulses generated from the stimulating unit are passed across the surface of the skin to activate underlying nerves via two electrodes (Fig.1.5). Conductive gel is used to decrease resistance across the skin-electrode interface, and the electrodes can be hidden or concealed under clothing if necessary. Patients can then administer stimulation as required and the electrical characteristics of stimulation varied via appropriate dials [Long & Hagfors 1975].

DISORDER	REFERENCE
PERIPHERAL NERVE DISORDERS	
Peripheral nerve injury	Wall & Sweet 1967 Bates & Nathan 1980
Traumatic neuromas	Richardson et al. 1980
Causalgia	Meyer & Fields 1972
Trigeminal nerve section	Bates & Nathan 1980
Amputation pain	Gyory et al. 1977
Phantom limb pain	Miles & Lipton 1978
Intercostal neuritis	Bates & Nathan 1980
Trigeminal neuralgia and	Eriksson et al. 1984
Atypical facial pain	Eriksson et al. 1979
Post-herpetic neuralgia	Nathan & Wall 1974
Mono and polyneuritis	Picaza et al. 1975
Nerve compression injury	Magora et al. 1978
SPINAL CORD AND SPINAL ROOT DISORDERS	
Dorsal root compression and spinal nerve compression	Andersson et al. 1976 Thorsteinsson et al. 1977 Eriksson et al. 1984
Brachial avulsion injury	Wynn-Parry 1980
Syringomyelia and postcordotomy	Picaza et al. 1975 Bates & Nathan 1980
Spinal cord injury	Hachen 1978 Richardson et al. 1980
Arachnoiditis	Picaza et al. 1975
PAIN ASSOCIATED WITH NEOPLASTIC LESIONS	
Metastatic bone pain	Magora et al. 1978
Neoplastic pain	Bates & Nathan 1980 Picaza et al. 1975
MUSCLE PAIN	
Secondary muscle spasm	Magora et al. 1978
Spastic torticollis	Ersek 1977
Musculoskeletal disorders	Wolf et al. 1981
JOINT PAIN	
Rheumatoid arthritis	Mannheimer & Carlsson 1979
Osteoarthritis	Taylor et al. 1981
ACUTE PAIN	
Obstetric pain	Augustinsson et al. 1977
Acute trauma	Nielzén et al. 1982
Acute orofacial pain	Hansson & Ekblom 1983
Post-operative pain	Hymes et al. 1974 Cooperman et al. 1977 Pike 1978 Solomon et al. 1980
MISCELLANEOUS CONDITIONS	
Itch	Augustinsson et al. 1976
Raynauds	Kaada et al. 1984
Angina	Mannheimer et al. 1982
Functional abdominal pain	Sylvester et al. 1986

Table 1.2a Clinical conditions successfully treated with TENS. Adapted from Woolf [1989].

DISORDER	REFERENCE
PERIPHERAL NERVE DISORDERS	
Metabolic peripheral neuropathies	<i>Long et al. 1979</i>
Post-herpetic intercostal neuralgia	<i>Cauthen & Renner 1975</i>
Occipital neuralgia	<i>Cauthen & Renner 1975</i>
Nerve injury and neuralgia	<i>Magora et al. 1978</i>
SPINAL CORD AND SPINAL ROOT DISORDERS	
Partial cord transection	<i>Cauthen & Renner 1975</i>
	<i>Richarson et al. 1980</i>
Myelodysplasia	<i>Picaza et al. 1975</i>
Spondyloarthrosis	<i>Picaza et al. 1975</i>
CENTRAL PAIN STATES	
Thalamic pain	<i>Bates & Nathan 1980</i>
	<i>Long & Hagfors 1975</i>
MISCELLANEOUS CONDITIONS	
Headache	<i>Loeser et al. 1975</i>
Vascular headache	<i>Picaza et al. 1975</i>
Atypical facial pain	<i>Cauthen & Renner 1975</i>
	<i>Bates & Nathan 1980</i>
Pain scars	<i>Bates & Nathan 1980</i>
Coccydynia	<i>Cathen & Renner 1975</i>
Visceral pain	<i>Eriksson et al. 1979</i>
Ischaemic pain	<i>Eriksson et al. 1979</i>
Industrial injury	<i>Long et al. 1979</i>
Psychogenic pain	<i>Long & Hagfors 1975</i>
	<i>Nielzén et al. 1982</i>
	<i>Johansson et al. 1980</i>

Table 1.2b Clinical conditions reported to be unsuccessfully treated with TENS. Adapted from Woolf [1989].

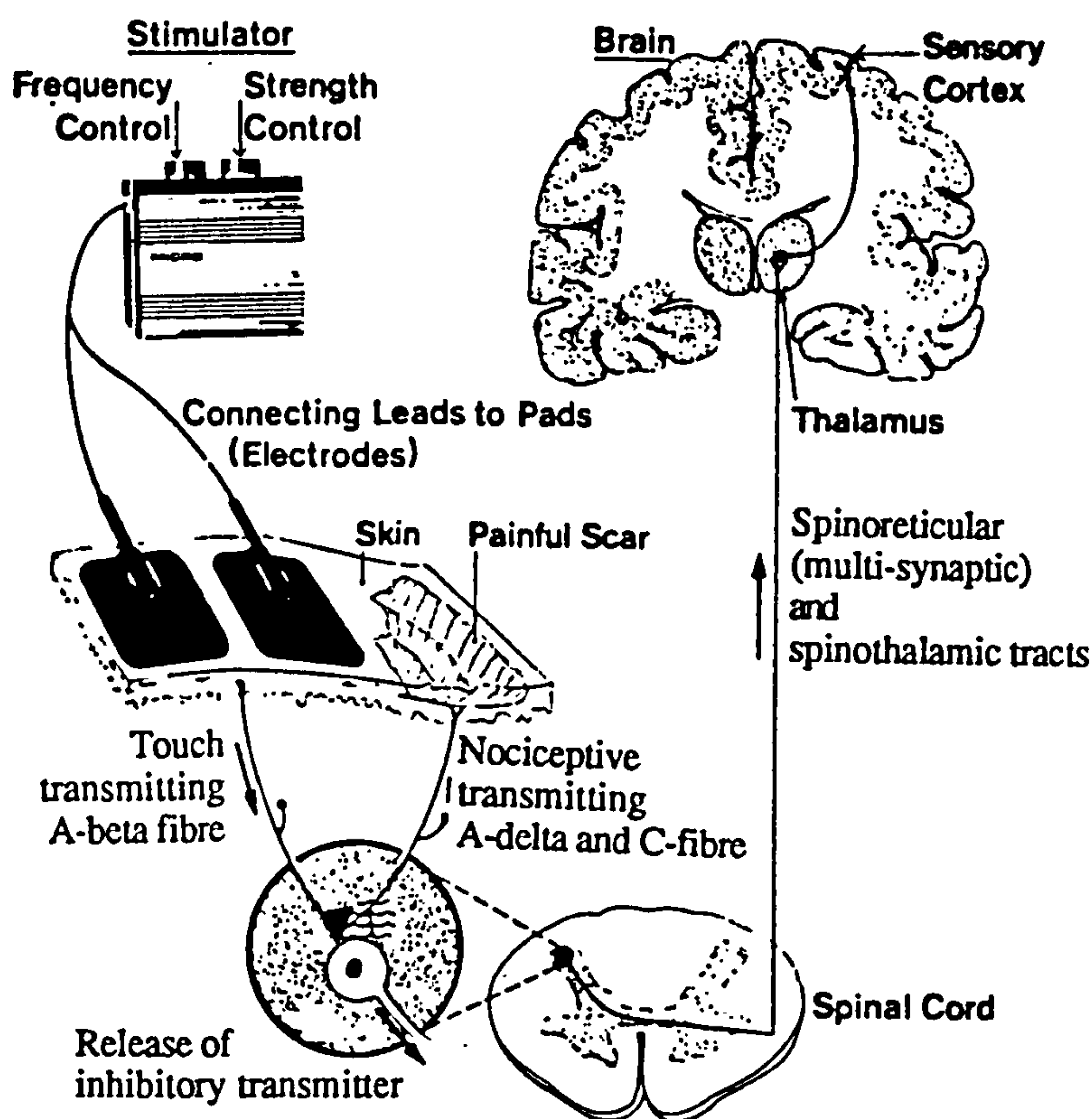


Fig.1.5 Simplified mechanism of TENS. Pulses of electrical current from the stimulator excite (via skin electrodes) touch receptors. These electrically-excited nerve impulses then pass to the spinal cord where they synaptically inhibit (by the release of transmitters) incoming nociceptive information which would normally be conveyed to the reticular formation, thalamus and cerebral cortex. From Thompson [1987b]

TENS units were designed on theoretical grounds to activate selectively large diameter fibres, without concurrent activation of small diameter nociceptive fibres. However, studies examining optimal stimulation characteristics for TENS remain sparse. Li and Bak [1976] examined the excitability of A- and C-fibres in cat saphenous nerves, by creating strength/duration curves for activation by electrical stimulation. They found that small unmyelinated 'nociceptive' axons were virtually unexcitable by pulse widths below $200\mu\text{s}$. Howson [1978] also created strength/duration curves during TENS to his own ulnar nerve on the forearm, and suggested that a good separation between motor responses, the perception of pain, and sensory detection was achieved at $100\mu\text{s}$. Pulse widths greater than $1000\mu\text{s}$ (1ms) were found to activate simultaneously all fibres even at low stimulation amplitudes. Thus pulse widths between $20\text{-}1000\mu\text{s}$ are ideal to selectively activate large (and not small) diameter afferents. Although the optimal frequency of electrical stimuli to produce maximal firing of large diameter fibres

(A-alpha/beta) in human nerve has not been defined, frequencies above 100Hz have been suggested to be no more effective [Buchthal & Rosenfalck 1966]. Consequently frequency ranges of 40-100Hz are generally suggested for clinical use of TENS [Woolf 1989].

Commercial stimulator specifications vary between companies, although stimulators used at Newcastle Pain Relief Clinic are similar (Table 1.3). In general, stimulators have facilities to vary pulse amplitude, pulse frequency, and pulse patterns (Fig.1.6).

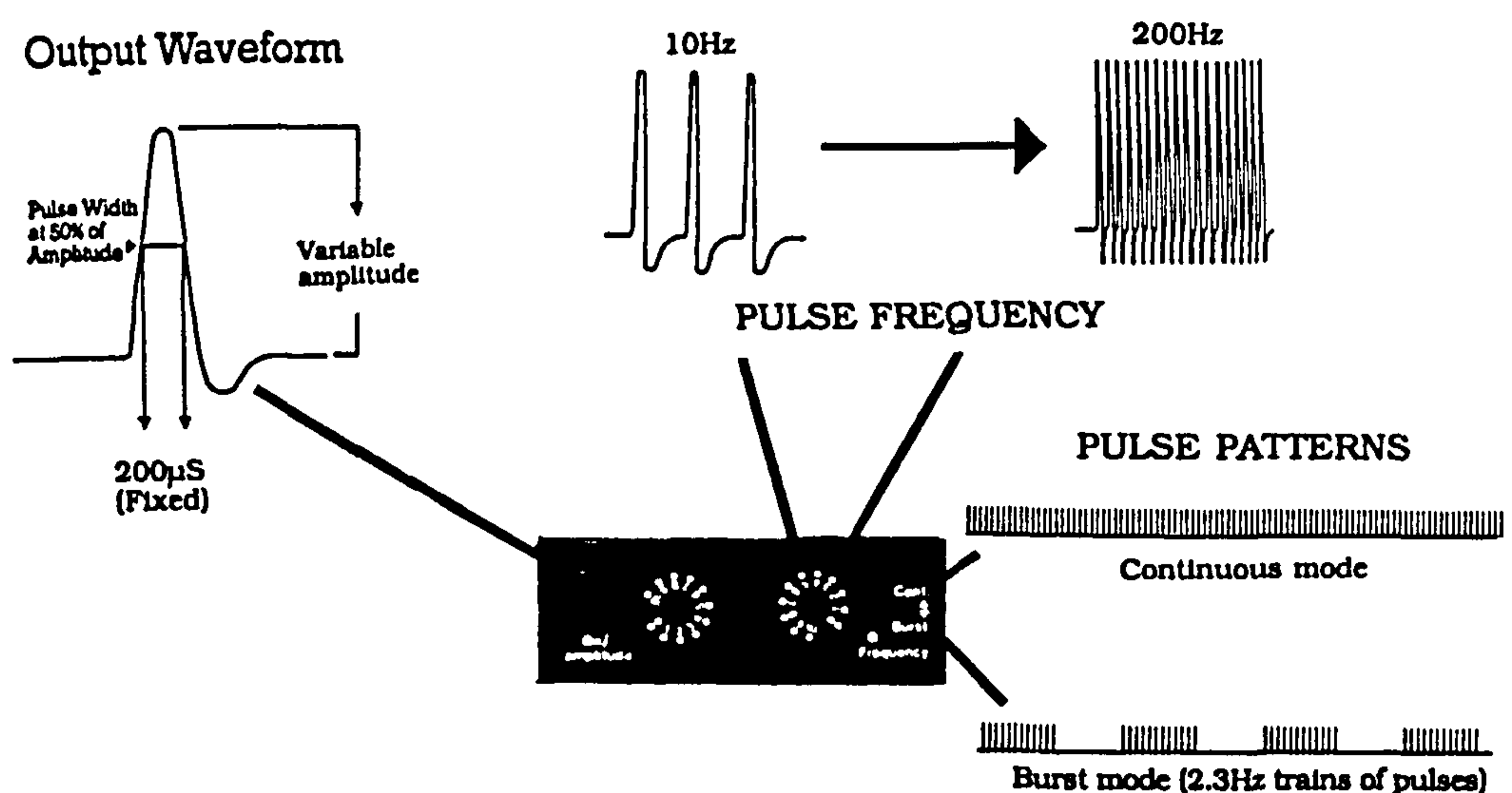


Fig.1.6 The control functions of a Microtens stimulator. The stimulator has facilities to control (i) pulse amplitude (intensity) - left hand dial, (ii) pulse frequency - right hand dial and (iii) pulse patterns (either continuous or burst) - right hand switch. The output waveform is biphasic with a fixed pulse width of 200µs.

Pulse frequency, ranges between 1-200Hz and a variety of pulse patterns are usually available (i.e. continuous, burst and random). A biphasic wave (where the area of the positive wave portion is equal to the the area of the negative) is most commonly used, since this reduces polarisation which may produce adverse skin reactions [Lampe & Mannheimer 1988]. The current amplitude (i.e. intensity or strength of stimulation) usually ranges between 0-50 volts, equating approximately to 0-50 mA across the skin (whose impedance range = 500-2000 ohms). This intensity range can produce sufficient current strength to twitch underlying musculature. Constant-current rather than constant-voltage design is preferred to compensate for variations in impedance at the electrode-skin interface. Variations in stimulator design (with pulse width control, dual channels, different pulse patterns and waveforms) have been introduced to optimise clinical efficacy, but have met with limited success.

MODEL	PULSE CHARACTERISTICS				CHANNEL	OTHER
	Amplitude	Width	Frequency	Pattern		
Microtens 7577 (NEEN)	0-50mA (Into a 1Kohm load)	200µs	15-175 Hz	Continuous Burst (2.3 bursts/s)	Single	Dial control Weight=75g
Tiger Pulse (RDG)	0-70 mA (Into a 1Kohm load)	150-200µs	1-140 Hz	Continuous	Single	Dial control (large) Polarity reverse switch Weight=115g
Tiger Burst (RDG)	0-70mA (Into a 1Kohm load)	150-200µs	1-140 Hz	Continuous Burst (2s on/1s off)	Single	Dial control (large) Weight=115g
Spembly 9000 (Spembly)	0-50 mA (Into a 1Kohm load)	200µs	15-200Hz	Continuous Burst (Pulsed' 2 bursts/s)	Single	Dial control Weight =120g
Xenos Xe/0150 (NEEN)	0-50mA (Into a 1Kohm load)	90-300µs (30µs incremental)	1-150 Hz (1 Hz incremental)	Continuous Burst (2 bursts/s) Multifrequency modulation (Random) (Upper limit set by freq. dial, lower limit = 8 Hz)	Single	Touch controls with autoscanner Weight =60g

Table 1.3 TENS specifications. Technical specifications of TENS units used by Newcastle Pain Relief Clinic. See Appendix D for company addresses.

AIM OF PROJECT

Although TENS has been used successfully for a variety of acute and chronic pain conditions, some patients either fail to respond, or respond initially and then develop tolerance to TENS analgesia. It has been estimated that over 70 % of patients initially respond to TENS, but only a third of these continue to obtain relief after two years [Bates & Nathan 1980]. The degree of pain relief obtained by patients responding to TENS proves variable; some patients report total relief of pain, whereas others, with a similar pain condition, report less than 20% relief (unpublished observations).

Despite its use for over twenty years, TENS is still administered on an empirical basis because it is impossible to determine whether a patient will respond prior to treatment. Prediction of response would not only be of value in the clinic, but may help understand treatment failure and the development of tolerance to TENS analgesia. The optimal electrical characteristics of TENS for various pain conditions remains unknown, and the patient is usually advised to experiment with stimulator settings until satisfactory relief is obtained. Few studies have systematically investigated the analgesic effects of different TENS characteristics. Therefore some patients may not be utilising the optimal electrical characteristics of TENS for their particular pain condition. Furthermore, information on the electrical settings used by patients successfully controlling pain is limited.

Hence, the aims of the project were to investigate:

- (i) The clinical factors which optimise TENS efficacy by studying, in depth, the use of TENS by patients successfully controlling chronic pain.
- (ii) The analgesic effects of different electrical characteristics of TENS in healthy subjects.
- (iv) The effect of TENS on electrophysiological and neuropharmacological variables.
- (v) The factors related to patient response to TENS.

It was hoped that the results of this work would improve TENS efficacy by:

- (i) optimising the electrical characteristics of TENS used by patients,
- (ii) elucidating the mechanisms of TENS analgesia and treatment failure,
- (iii) designing new and therapeutically more powerful electrical stimulators.

CHAPTER 2

THE CLINICAL USE OF TENS

INTRODUCTION

Despite the large number of clinical trials which confirm the effectiveness of TENS in the treatment of a wide range of acute and chronic pain conditions (Table 1.2a and b), information on the long-term clinical efficacy of TENS is limited (for summary see Table 2.1). Thus, uncertainty remains as to the number of patients who either fail to respond, or drop out of TENS treatment after a period of time.

Long-term efficacy of TENS

Bates and Nathan [1980] examined TENS efficacy in 235 patients with a variety of chronic pain conditions and found that approximately 30% of patients initially failed to respond to treatment. After 32 weeks, only one third of the patients who initially responded to treatment continued to use TENS, the proportion dropping to one fifth after 2 years. Similarly, Loeser et al. [1975] found that while 68% of patients (out of a total of 198) obtained short-term relief with TENS, this proportion fell to 12.5% after one year. Eriksson et al. [1979; 1984] found that patient response to TENS depended upon the type of pain, and that varying proportions of patients (18-82%) had effective relief after 2 months and 18-60% after a year. However, approximately 55% of patients obtained short-term relief of pain with TENS (2 month follow-up); 41% at the 1 year follow-up and 30% at the 2 year follow-up. These studies suggest that a significant proportion of patients drop out of TENS treatment between 2-12 months. Furthermore, Eriksson et al. [1979] found that acupuncture-like TENS (AL-TENS) produced analgesia in some patients who did not respond to conventional TENS.

The treatment of *acute* pain by TENS often takes place in a hospital ward (during labour or post-operative pain), where staff trained in TENS techniques are available to ensure correct TENS administration, and to monitor progress. For the treatment of a *chronic* pain condition the situation is different, as the patient needs to administer treatment away from the clinic [Sjölund et al.1990].

SOURCE	MODE	TYPE OF PAIN	NO. OF PATIENTS	% of Patients with pain relief at follow-up (months)				
				<1	2-6	7-12	13-24	25-36
Loeser et al. [1975]	Conv	Total	198	68%		12.5%		
		Low back	61	77%		13%		
		Cervical arthritis	18	83%		17%		
		Headache	13	23%		7%		
Wynn-Parry [1980]	Conv	Brachial plexus avulsion	98	30%	20%			
Bates & Nathan [1980]	Conv	Low back: peripheral nerve lesions: central pain	161			27%	16%	
		Post-herpetic	74	48%		20%	15%	
Sindou & Keravel [1980]	Conv	Radicular syndromes	28	60%				80%
		Peripheral nerve lesions	55	87%				
		Post herpetic neuralgia	34	67%		25%		
		Brachial plexus lesions	28	25%-30%				
		Central pain	22	0%-11%				
Bohm [1978]	Conv + AL-TENS	Peripheral nerve injury with sympathetic hyperactivity	24			42%		
Erksson et al. [1979]	Conv + AL-TENS	Facial neuralgia	11		82%	45%		
		Neuralgia (other locations)	32		56%	34%		
		Rhizalgia	22		64%	60%	34%	
		Central pain	18		67%	50%		
		Other organic etiology	23		52%	39%		
Erksson et al. [1984]	Conv + AL-TENS	Psychogenic pain	17		18%	18%		
		Facial pain	50		58%	51%	45%	

Table 1.2 Summary of studies on long-term efficacy of TENS for chronic pain.
From Sjölund et al. [1990]. Conv=Conventional TENS, AL-TENS = Acupuncture-like TENS.

Thus, after instruction on the principles of TENS use by a therapist in a clinic, patients must learn to master the TENS technique themselves, and administer the treatment as appropriate. Information on the treatment regimes used by patients controlling a chronic pain condition with TENS is limited.

Criteria for deciding to use TENS

Patients attending Newcastle Pain Relief Clinic (NPRC) have usually been referred by their general practitioner (GP), and many have tried a variety of treatments to control the pain condition. Two main criteria are used in deciding whether to administer TENS [Thompson personal communication]:

- (i) The patient's pain has failed to respond to other treatments, e.g. non-steroidal anti-inflammatory drugs (NSAIDS), weak opioids, antidepressants.
- (ii) The patient's pain is difficult to treat by other methods, e.g. deafferentation, post-herpetic neuralgia, phantom and stump pain.

Instruction to new patients

At Newcastle Pain Relief Clinic new TENS patients undergo an hour's trial of TENS in the clinic for three reasons:

- (i) to observe any immediate response to TENS,
- (ii) to observe any adverse reactions (including aggravation of the pain condition),
- (iii) to fully instruct the patient on stimulator use.

Nurses trained in TENS techniques instruct the patient on stimulator use as follows:

1. Apply electrodes to produce electrical paraesthesia ('tingling') within the painful area. Occasionally, for reasons of non-response, pain aggravation, or sensitive skin, this is not possible and electrodes are then applied:
 - (a) immediately proximal to the painful site,
 - (b) at the contralateral ('mirror image') site,
 - (c) straddling the spinal cord at the dermatome related to the painful region.
2. Initially use continuous mode TENS.
3. Set all controls (pulse amplitude (current intensity) and pulse frequency) to minimum setting.
4. Increase pulse amplitude (intensity) to a 'strong but comfortable' level.
5. Increase pulse frequency to maximal comfortable level.

6. If insufficient pain relief is obtained, try increasing pulse intensity, or use burst mode TENS.
7. Patients are encouraged to experiment with all stimulator settings and hunt for the most appropriate setting during each treatment session.

Under certain circumstances, burst mode TENS utilised as acupuncture-like TENS (AL-TENS) may be the first treatment choice (see Chapter 3 and Sjölund et al. [1990]). After this hour's trial, the patient administers TENS at home, prior to returning to the clinic (usually within two months) for further assessment. Patients not responding to TENS treatment return the stimulator, and a different treatment is tried. Those responding to TENS treatment are provided with a stimulator on loan from the clinic.

TENS variables related to treatment outcome

When TENS is used to treat a patient's pain, a number of important variables related to the patient, and to the stimulator, may influence treatment outcome. These include:

- (i) *Patient variables*: age, sex, cause and site of pain, personality, use of drugs and TENS treatment regime (i.e. how often TENS is administered).
- (ii) *Stimulator variables*: model of stimulator, site of electrodes, pulse waveform, pulse frequency (Hz), pulse pattern, pulse amplitude (current intensity) and pulse width (μ s).
- (iii) *Outcome variables*: TENS analgesic efficacy, onset of analgesia, post-TENS analgesia and adverse effects.

Although it has been well documented that TENS efficacy is dependent upon the electrical characteristics of stimulation (i.e. pulse frequency, pulse pattern, pulse width, stimulating mode and electrode placement; for review see Woolf [1989]), there have been few reports of the actual electrical characteristics of TENS used by patients. Linzer and Long [1976] were able to monitor the electrical characteristics of TENS in only 23 patients suffering from chronic pain who obtained satisfactory TENS analgesia. They found that 74% of patients utilised pulse frequencies below 60Hz, 74% of patients utilised pulse widths between 50-100 μ s and all patients who achieved relief produced a 'tingling' electrical paraesthesia within the area of pain. Thus the group concluded that the success rate with TENS could be improved by careful attention to electrode placement, stimulating variables and patient education. Mannheimer and Carlsson [1979] found that 'conventional' TENS delivered at a

frequency of 3 Hz, was less effective in suppressing pain than 'conventional' TENS at 70 Hz for patients with rheumatoid arthritis. However, the delivery of low frequency (3Hz) trains or 'bursts' of pulses at high intensity (acupuncture-like TENS), has been shown to be beneficial for patients not responding to conventional TENS [Eriksson et al. 1979] .

Wolf et al. [1981] attempted to determine optimal electrode placements and stimulating parameters while treating chronic pain patients with conventional TENS, administered at the clinic in 30-45 minute sessions. No clear correlations between electrode placements, stimulating parameters and pain relief were found, although TENS did reduce pain intensity scores. The group concluded that a patient's psychological profile may help to determine who would benefit from TENS. Johansson et al. [1980] found that the Eysenck Personality Questionnaire (EPQ) which records traits in personality (i.e. psychoticism, extroversion, neuroticism and an internal consistency 'lie' measure), may be predictive of outcome to TENS treatment. Recently Houlton et al. [1990] assessed the use of TENS in a population of chronic pain patients who had last attended the clinic over 3 years prior to the study. Of 189 questionnaires mailed, 68 were returned; of these, 57 patients had been given a trial of TENS and 29 (51% of those given a trial) were still using stimulators. Average daily use in these patients was 4.3 h/day. Although there appeared to be no comprehensive study of the electrical characteristics of TENS in these patients, pulse frequencies between 80-100 Hz were reported to be most beneficial.

To date, no comprehensive investigation has examined the electrical characteristics of TENS utilised by patients using the technique on a long-term basis to control chronic pain. Consequently TENS is administered on an empirical basis where the patient determines by trial and error the most appropriate electrical characteristics to control his or her pain.

Aims of Chapter 2

Because of the lack of information on the clinical use of TENS by both pain clinics, and patients successfully controlling chronic pain with TENS, it was decided to conduct a fact finding survey. Thus, the overall aim of Chapter 2 was to examine, in depth, the clinical use of TENS. This was achieved in three studies:

Study 2.1. Long-term use of TENS at Newcastle Pain Relief Clinic.

Study 2.2. An in-depth study of long-term users of TENS.

Study 2.3. The consistency of pulse frequencies and pulse patterns of TENS used by chronic pain patients.

THE STUDIES

Study 2.1

Long-term use of TENS at Newcastle Pain Relief Clinic.

The aim of this study was to assess long-term efficacy of TENS in a heterogeneous population of chronic pain patients, by examining administrative records of stimulators issued by Newcastle Pain Relief Clinic.

Patients and Procedure

Newcastle Pain Relief Clinic (NPRC) records containing names and addresses of patients, and the date of issue and return of stimulating units (up to 1st January 1991) were examined. All patients had attended NPRC for a follow-up appointment to assess TENS treatment. Although the records contain only sparse clinical information, it was possible to classify patients according to Anatomical Region, as described by the International Association for the Study of Pain Classification of Chronic pain conditions [for full description see IASP 1986].

Results of Study 2.1

The first stimulator, a Stimtech EP, was issued to a patient in October 1979. Since then, 1582 patients have received stimulators on loan, of which 655 (41.4%) have returned the stimulator and 927 (58.6%) continue to use TENS (Fig.2.1, pie chart). The clinic has progressively increased the use of TENS, and over the last five years approximately 180 stimulators were issued each year (3-4 stimulators/week), as shown in Fig.2.1. Although 655 stimulators were returned, the dates of return of 132 of these were not recorded. The majority of stimulators (368) were returned within the first 6 months, usually during the first follow-up appointment at the clinic. Only a small proportion of patients returned stimulators after the first year (Fig.2.2).

Of patients still in possession of stimulators, 28 have used TENS successfully for over 10 years (Fig.2.3). A wide range of pain conditions have been treated with TENS and the distribution of pain conditions treated reflect the distribution of complaints presenting at the clinic [Davies & Crombie 1990]. No particular pain condition responded better than another, and over 50% of patients continue to use stimulators in most groups (Fig.2.4). Of note is the large proportion of lower back problems, 67% of which were treated successfully with TENS.

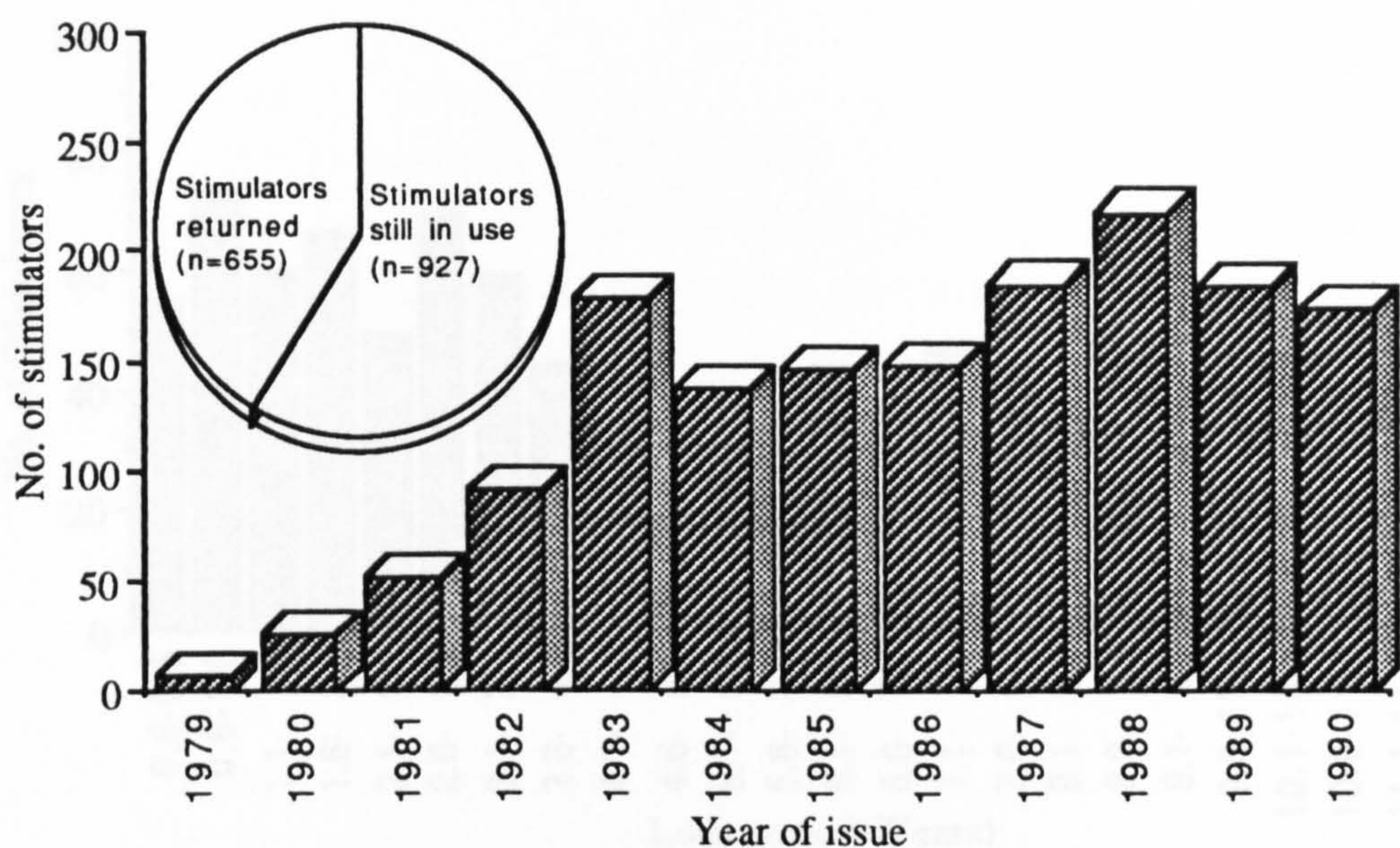


Fig.2.1 The number of stimulators issued by Newcastle Pain Relief Clinic per year (Study 2.1). Pie chart shows the number of patients still in possession of a stimulator.

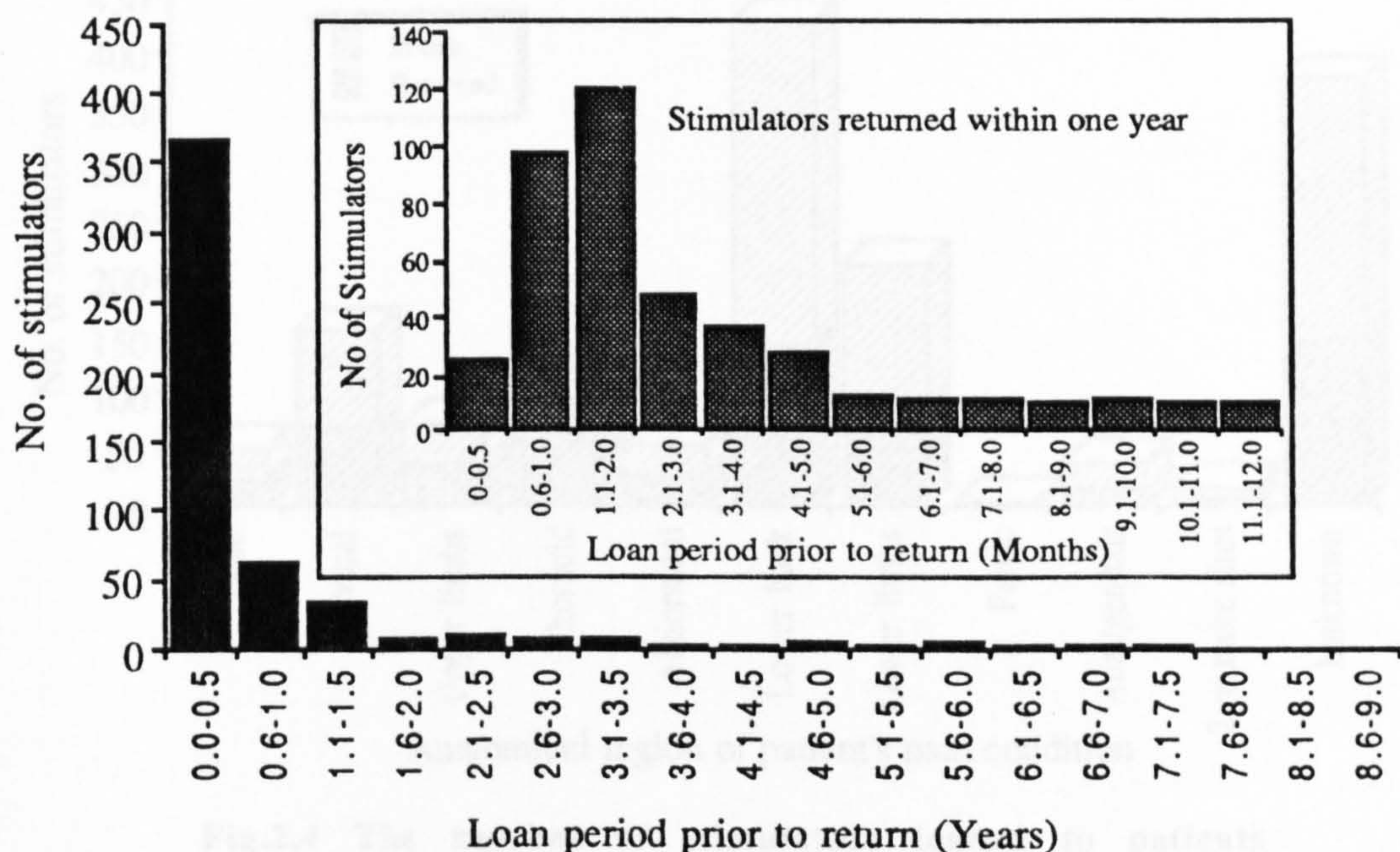


Fig.2.2 Duration of loan for stimulators returned to the clinic (Study 2.1, n=523). *Inset* breakdown of the duration of stimulator loan by patients returning stimulators within the first year.

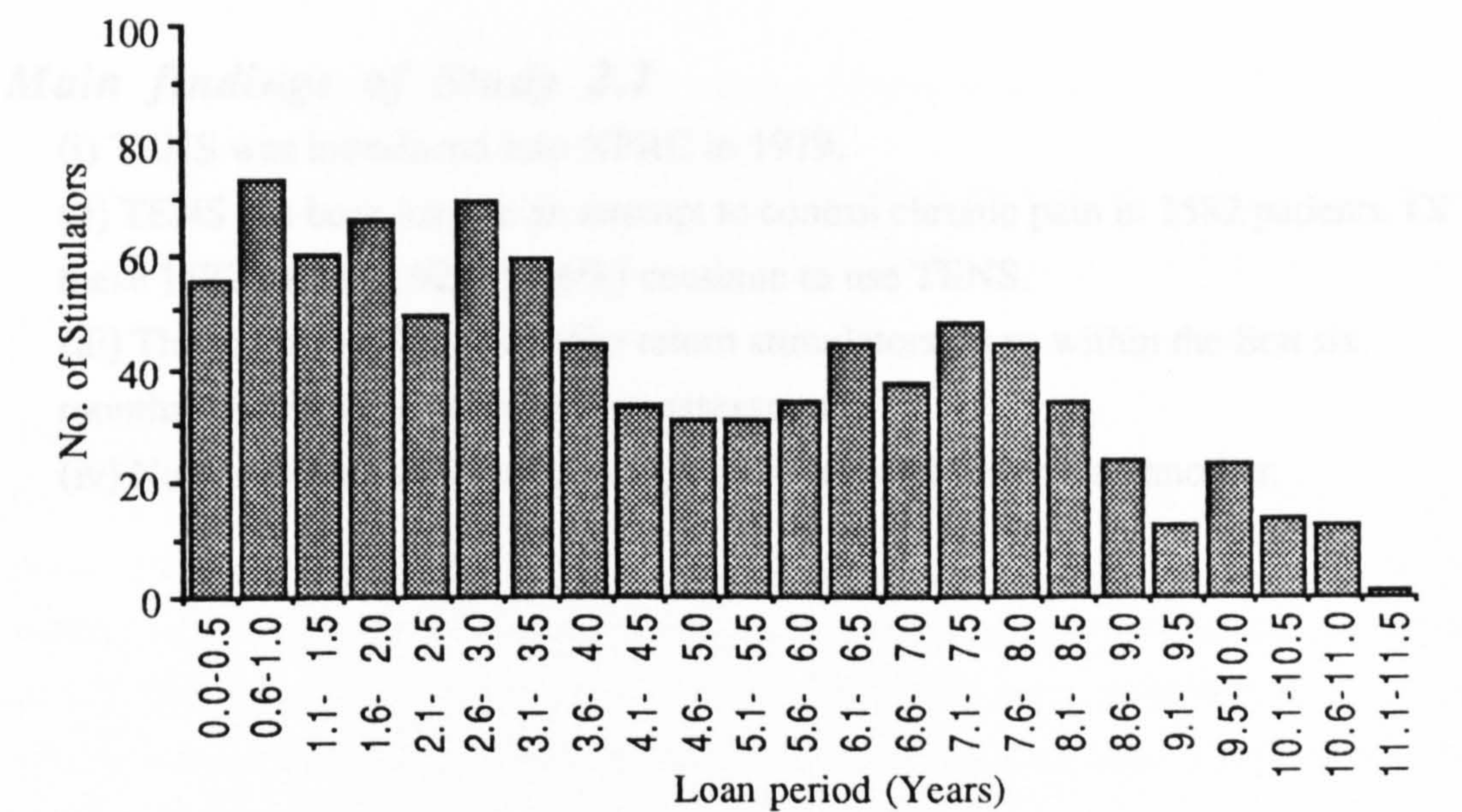


Fig.2.3 Duration of loan period amongst 927 patients still in possession of a stimulator (Study 2.1).

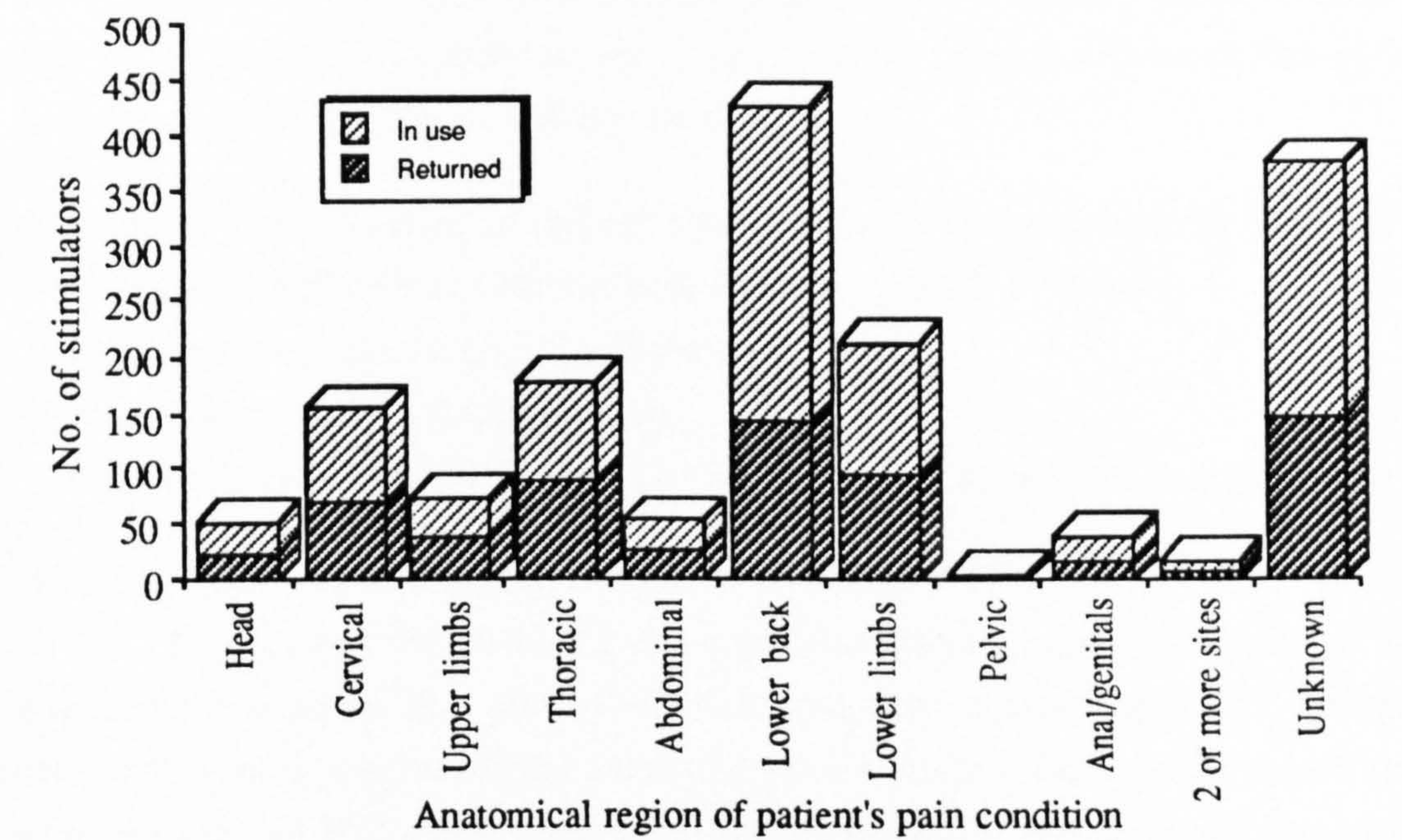


Fig.2.4 The number of stimulators loaned to patients classified according to the anatomical region of the patient's pain (Study 2.1, n=1582).

Main findings of Study 2.1

- (i) TENS was introduced into NPRC in 1979.
- (ii) TENS has been used in an attempt to control chronic pain in 1582 patients. Of these 1582 patients, 927 (58.6%) continue to use TENS.
- (iii) The majority of patients who return stimulators do so within the first six months (during the first follow-up assessment).
- (iv) No particular pain condition appears to respond better than another.

Study 2.2

An in-depth study of long-term users of TENS.

The aim of Study 2.2 was to examine the relationships between patient, stimulator, and outcome variables, in patients who were successfully using TENS on a long-term basis to control a chronic pain condition.

Patients and Procedure

One hundred and seventy nine patients drawn randomly from NPRC files (female $n=82$, male $n=97$; age range=24-85, mean \pm SD=55.2 \pm 12.9 years of age), and with a variety of chronic pain conditions participated in the study. All had been in possession of a TENS unit for at least three months (on loan from Newcastle Pain Relief Clinic after a successful trial session), although the majority had been using TENS for a number of years.

TENS Questionnaire

All patients completed a specially designed TENS Multiple Choice Questionnaire either: (i) by postal correspondence, or (ii) on attendance to the research unit (for TENS questionnaire see Appendix A). The questionnaire collected data regarding site and cause of pain, the model of stimulator, frequency of stimulator use and degree of pain relief. Personality variables were also measured using the Eysenck Personality Questionnaire (EPQ) [Eysenck & Eysenck 1975].

All patients were classified according to the International Association for the Study of Pain (IASP) classification of chronic pain conditions [IASP 1986] into:

- (i) anatomical region of pain (IASP Axis I),
- (ii) aetiology of pain, (IASP Axis V),
- (iii) a third group termed 'Diagnostic clusters' designed by Johnson et al. [1991a].

Determination of Electrical Characteristics of TENS

Of the 179 patients, 107 (female $n=58$, male $n=49$; age range=24-85 years of age) attended the research unit so that the electrical characteristics of TENS could be assessed. This was achieved by recording peak voltage (Volts), pulse width (μ s), pulse frequency (Hz), pulse amplitude (current intensity) and electrode impedance (Kohm), on a Frye Electronics Type 4000 TENS Analyser (Frye Analyser) supplied by RDG Electro-Medical (Fig.2.5a).

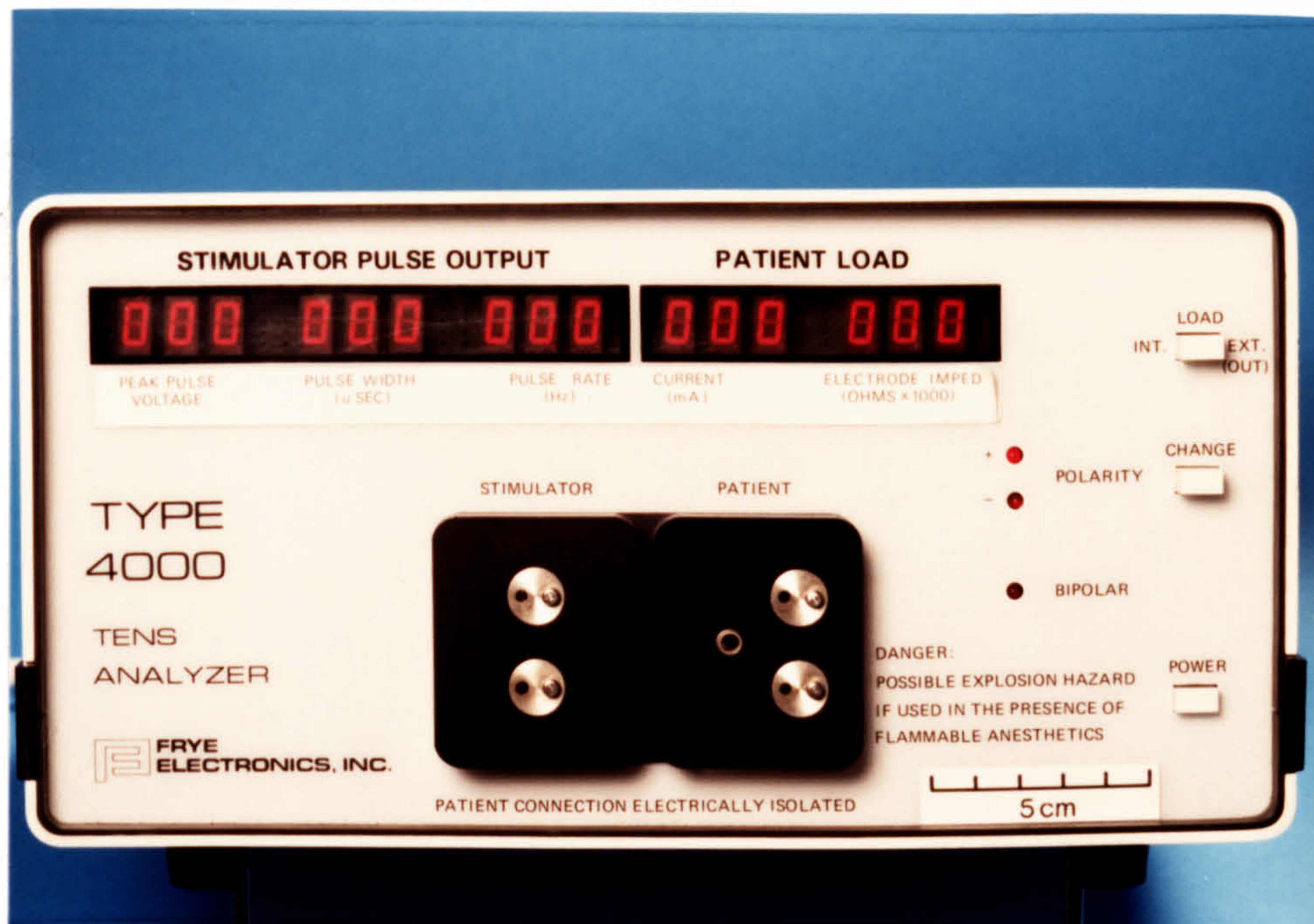


Fig.2.5a Frye Electronics Type 4000 TENS Analyser, *Frye Analyser*.

Patients applied TENS to the 'usual' anatomical site to achieve analgesia for their particular chronic pain condition. They were asked to adjust both pulse amplitude and pulse frequency (via the appropriate control dials) to the settings they routinely used to treat their pain. Patients free of pain during the visit ($n=10$ who rated <1 on a visual analogue scale where 0=no pain and 10=worst pain imaginable) were asked to adjust the stimulator to its 'normal therapy setting'.

Electrical characteristics were recorded at sensory threshold, therapy level and pain threshold to TENS electrical pulses at the site of electrode application (Fig.2.5b). Patients found their respective thresholds after a small amount of "hunting", and the mean of three repetitions was calculated. Pulse amplitude (current intensity) recordings were taken at the patient's preferred pulse frequency, and repeated at high frequency (100Hz) and low frequency (20Hz) stimulation. If stimulators possessed a burst mode facility, the entire procedure was repeated in burst mode.



Fig.2.5b Determination of the electrical characteristics of TENS.

Patients were in possession of one of the following types of stimulator (Fig.2.5c):

- 1.Tiger Pulse (Polarity reversal facility. RDG Medical)
- 2.Tiger Burst (Burst mode facility. RDG Medical)
- 3.Spembly 9000 (Burst mode facility. Spembly)
- 4.Microtens 7757 (Burst mode facility. NEEN Pain Management Systems)



Fig.2.5c Stimulators issued by Newcastle Pain Relief Clinic.

Follow-up

Twenty-four patients (female n=12, male n=12; age range=39-79, mean=54.2 years of age) returned for a follow-up assessment. A four month period elapsed between the two visits.

Statistical Analysis

Data was plotted to check for normal distribution prior to statistical analysis. Parametric statistical procedures were employed for continuous data (after logarithmic transformation for skewed distributions), and non-parametric procedures for categorical data. A detailed explanation of the statistical procedures used in this and future experiments is provided in Appendix B.

Results of Study 2.2

A wide range of chronic pain conditions, among which low back pain was predominant, was represented in the patient population (Fig.2.6a, b and c). The results of the 179 questionnaires are summarised in Table 2.2.

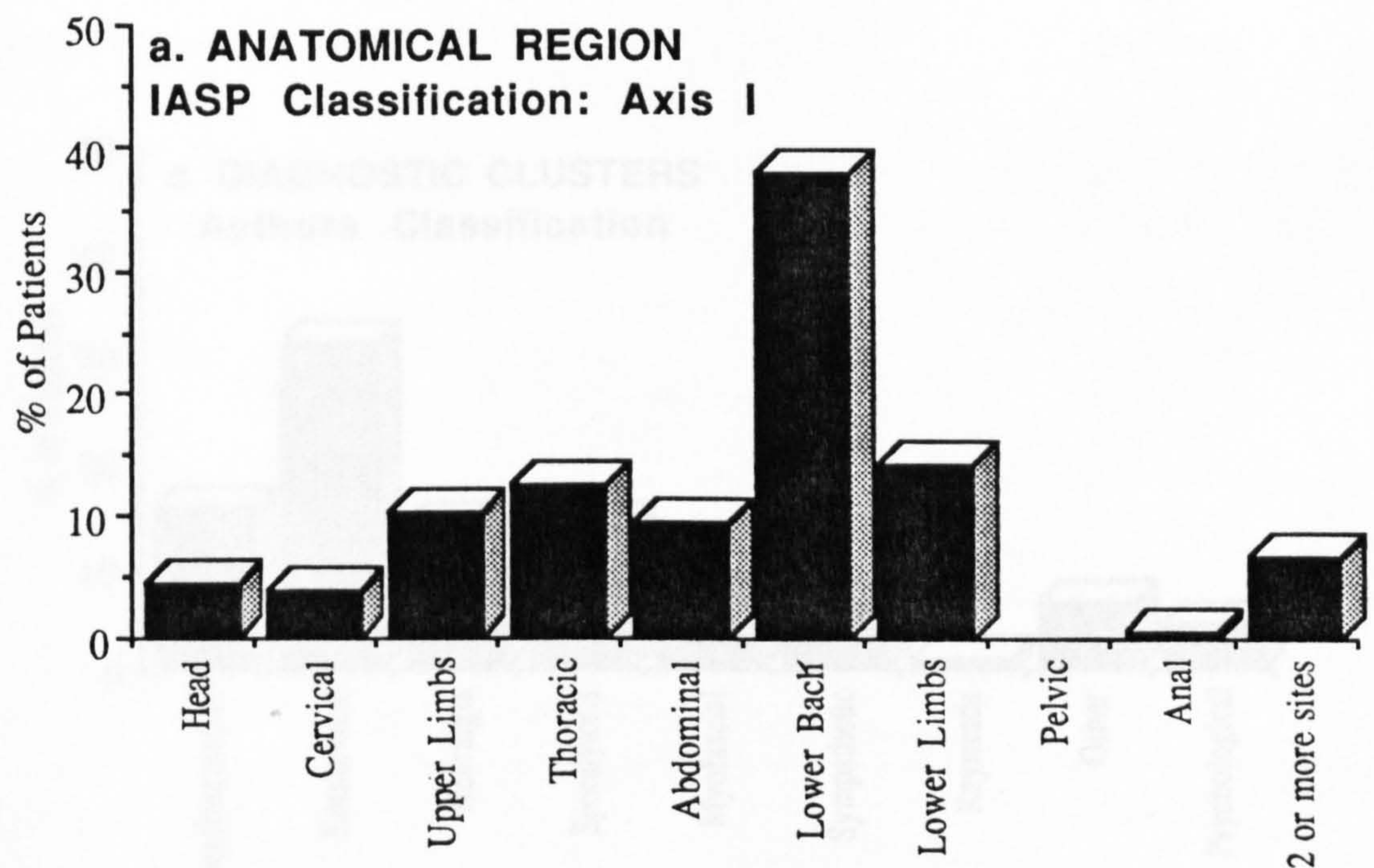


Fig.2.6a Long-term users of TENS classified according to Anatomical region (IASP Axis I, Study 2.2, n=179). For full details of terms see IASP [1986].

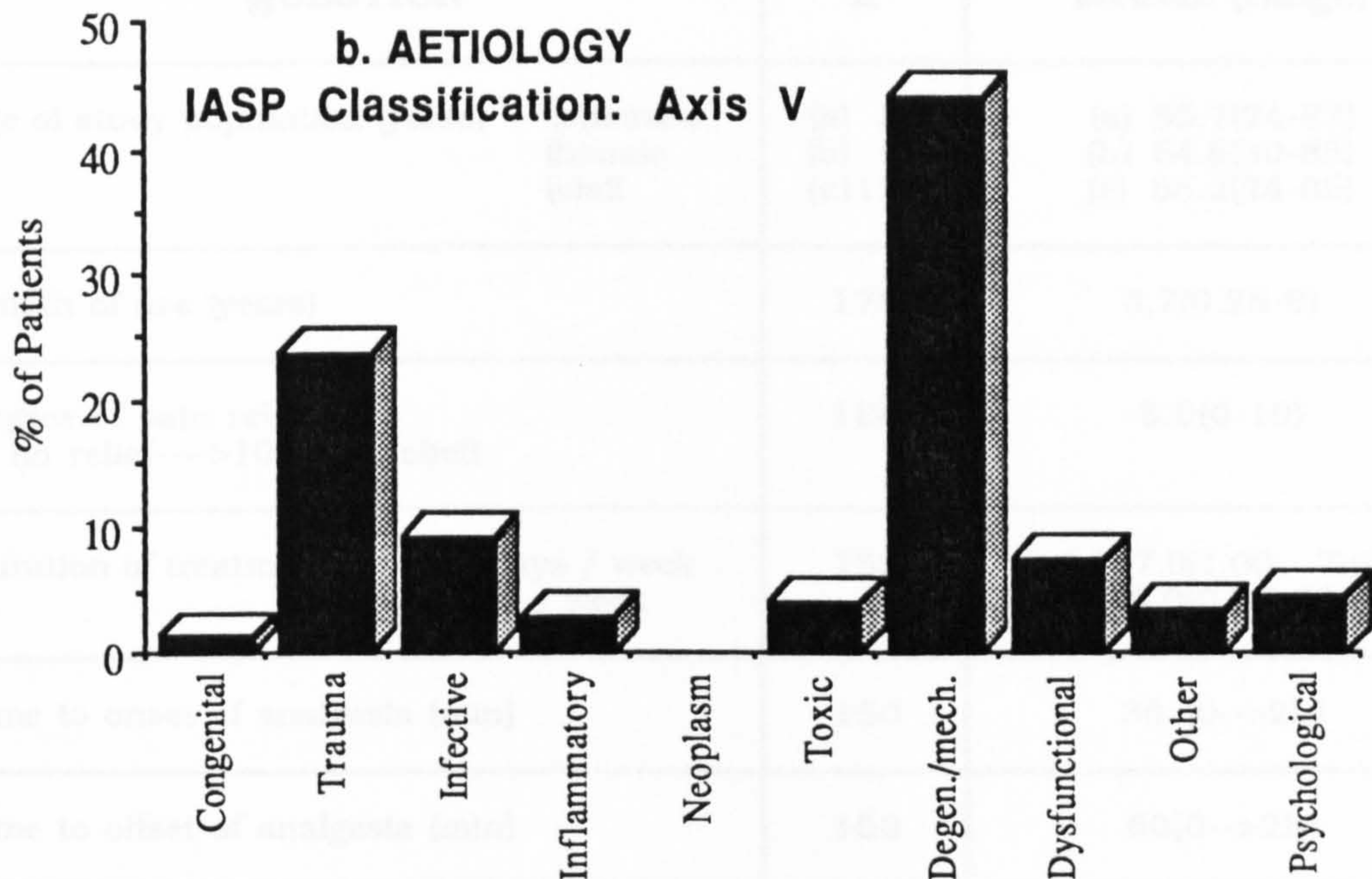


Fig.2.6b Long-term users of TENS classified according to Aetiology, (IASP Axis V, Study 2.2, n=179). For full details of terms see IASP [1986], degen/mech=degenerative/mechanical.

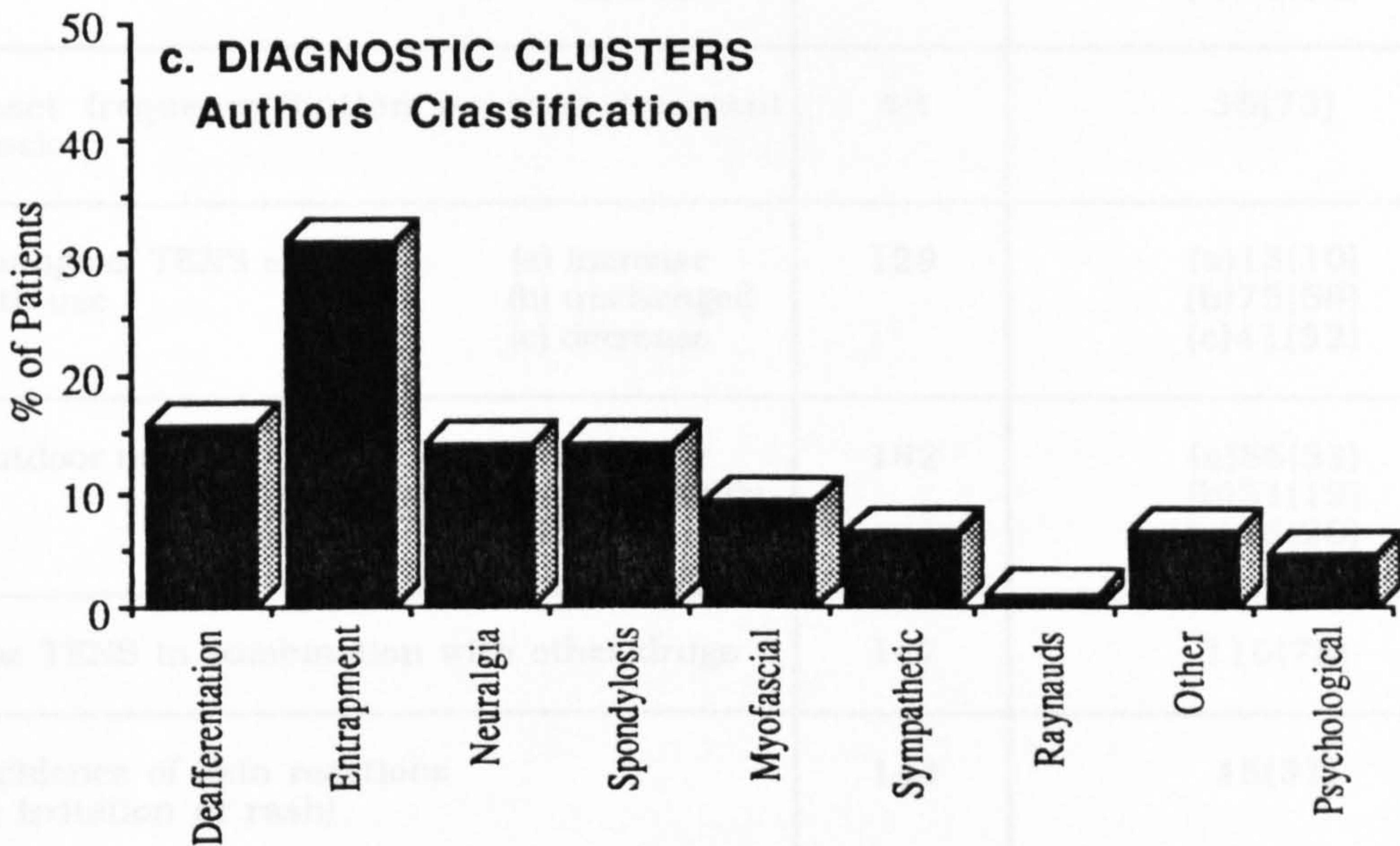


Fig.2.6c Long-term users of TENS classified according to Diagnostic clusters (Author's classification, Study 2.2, n=179). For full details of terms see Johnson et al. [1991a].

QUESTION	n	Median (range)
Age of study population (years) (a)female (b)male (c)all	(a) 82 (b) 97 (c)179	(a) 55.7(24-82) (b) 54.8(30-85) (c) 55.2(24-85)
Length of use (years)	179	3.7(0.25-9)
Degree of pain relief (0 no relief---->10 total relief)	168	5.0(0-10)
Duration of treatment (a)days / week (b)h / week	152	(a) 7.0(1.00- 7.0) (b)35.0(0.75-63.0)
Time to onset of analgesia (min)	150	30 (0-->2h)
Time to offset of analgesia (min)	150	60(0-->2h)
	n	No of patients (%)
Pulse pattern preference (a) fast (b) slow (c) none	128	(a)72(56) (b)29(23) (c)27(21)
Pulse frequency preference (a) fast (b) slow (c) none	48	(a)28(58) (b)15(31) (c) 5(11)
Reset frequency button on each treatment session	48	35(73)
Change of TENS efficacy with use (a) increase (b) unchanged (c) decrease	129	(a)13(10) (b)75(58) (c)41(32)
Outdoor use (a) regularly (b) occasionally (c) never	162	(a)85(53) (b)31(19) (c)46(28)
Use TENS in combination with other drugs	147	110(75)
Incidence of skin reactions (ie irritation or rash)	143	45(31)

Table 2.2 Summary of answers to TENS Questionnaire by long-term users of TENS. (See Appendix A for details of the questionnaire).

Questionnaires

As patients were instructed to omit any questions that they did not understand, the n values varied for different results. Sixty-seven (37%) patients were using a Microtens 7757, 49 (28%) a Tiger Burst, 44 (25%) a Tiger Pulse and 17 (10%) a Spemby 9000. The analgesic efficacy of TENS, assessed by a visual analogue scale (VAS; where 0 = no relief of pain and 10 = total relief of pain), is shown in Fig. 2.7. Seventy-nine (47%) patients reported that TENS reduced their pain by half or more; 23 (13.7%) of patients reported that TENS did not produce any relief (between 0-1 VAS) and 26 (15.5%) reported total relief of pain (between 9.1-10 VAS) whilst using TENS. A clustering effect was observed around the columns representing total relief of pain (VAS=10), no relief of pain (VAS=0), and relief of pain by half (VAS=5). This may be due in part to a psychological biasing of patient response to visual analogue scales.

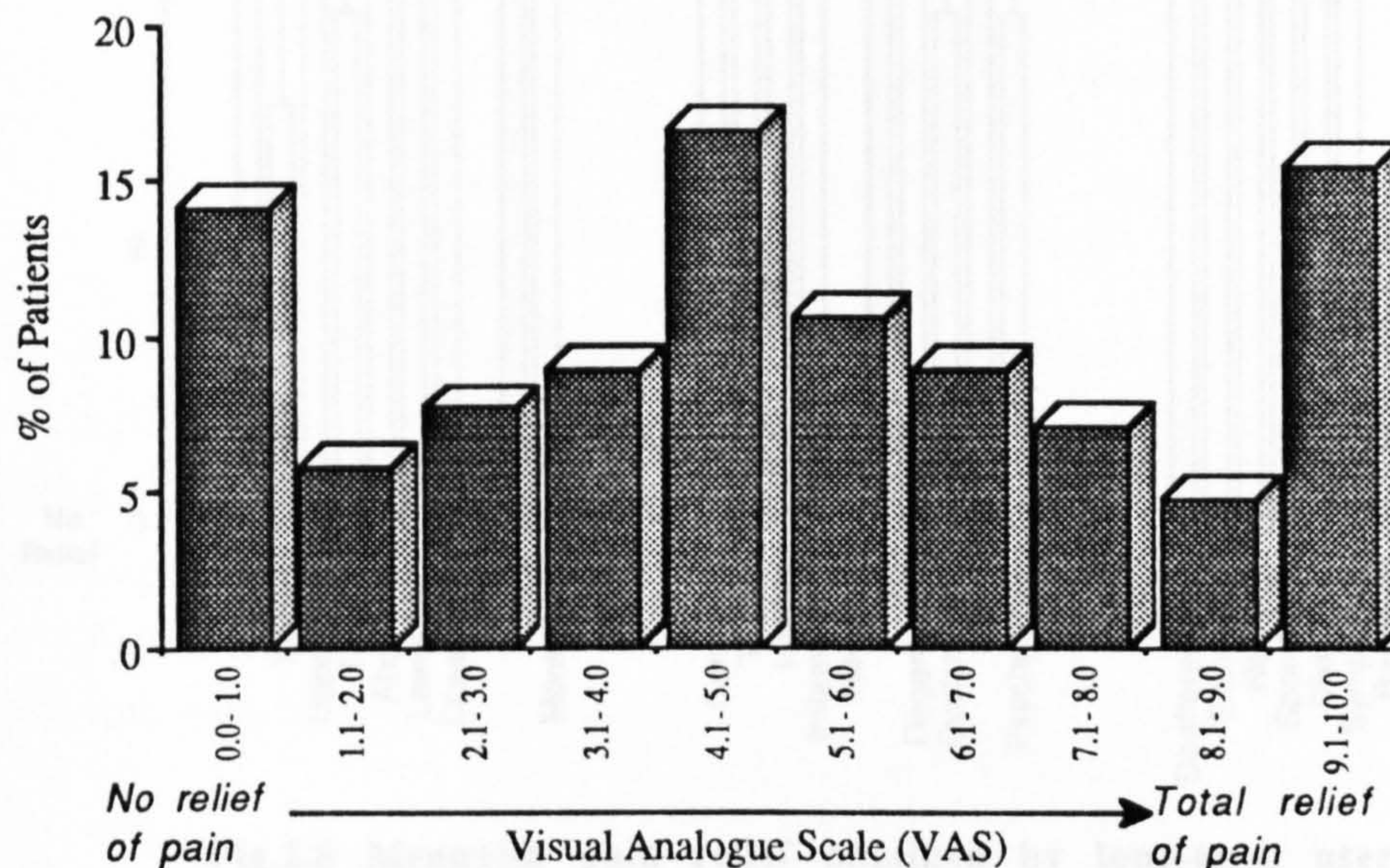


Fig. 2.7 Pain relief obtained by long-term users of TENS (Study 2.2, $n=168$). Patients marked with a cross a point on the visual analogue scale to represent the 'average' relief of pain obtained when using TENS.

All the patients who achieved no analgesic benefit from TENS (VAS < 1) nevertheless expressed a desire to continue TENS treatment. In fact, two thirds of the patients who reported complete failure of TENS analgesia continued to use the stimulator on a daily basis! No significant differences (one-way Analysis of Variance (one-way ANOVA)) were found between the degree of pain relief achieved with TENS when patients were classified according to anatomical region of pain, aetiology of pain or diagnostic clusters (Fig. 2.8).

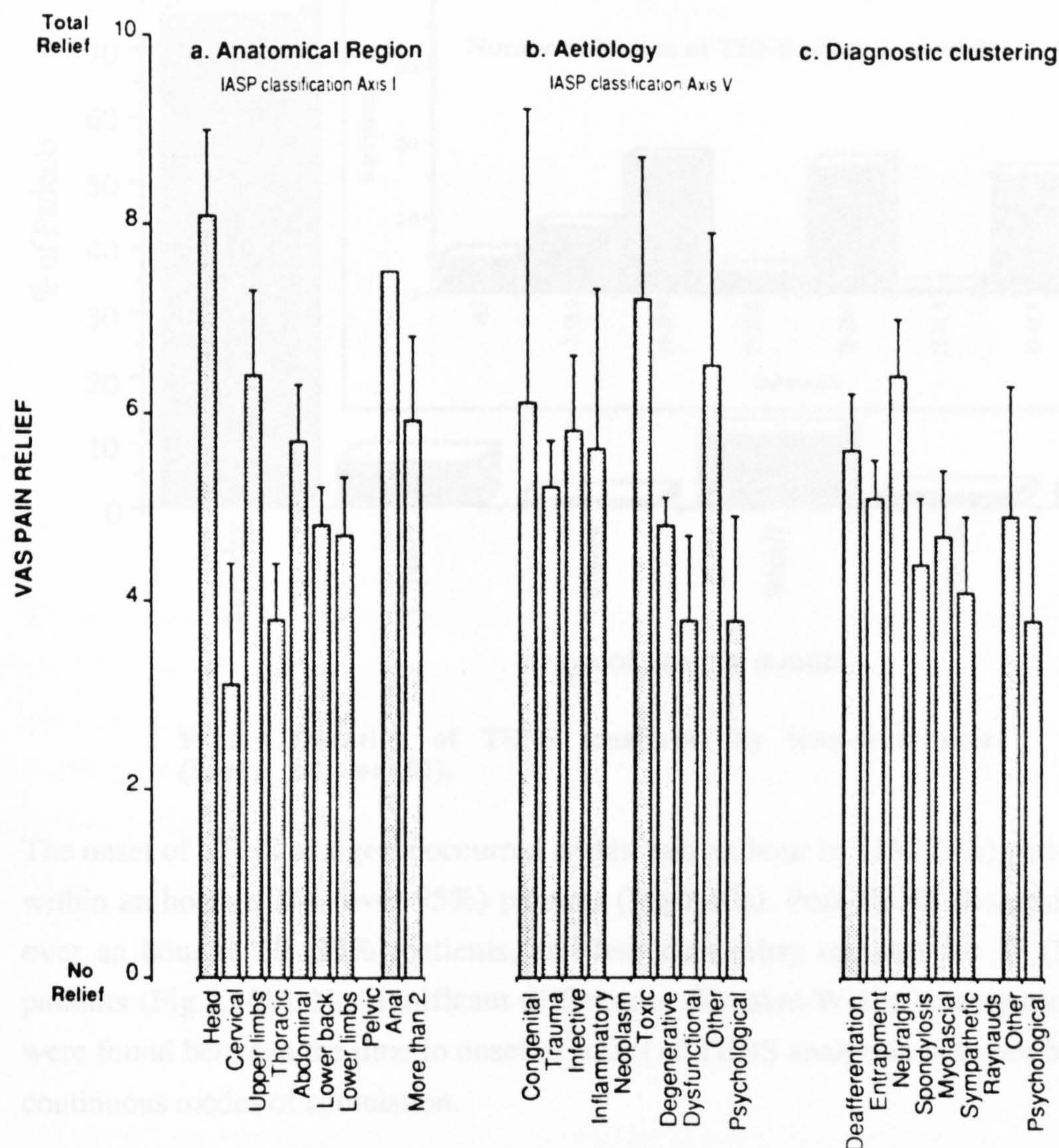


Fig.2.8 Mean±SE pain relief obtained by long-term users of TENS classified into: (a) Anatomical region, (b) Aetiology, (c) Diagnostic cluster (Study 2.2, n=168). See Fig.2.6 for respective n values for each group. For full details of terms see IASP [1986]

Although 117(75%) patients reported daily stimulator use (Fig.2.9), only 61 of these had used TENS on the previous day. This discrepancy may be due in part to an overestimate by certain patients of their daily use of TENS. Over 30% of patients used TENS for over 49 h/week (Fig.2.9 inset), calculated from the number of days used per week, and hours used per day.

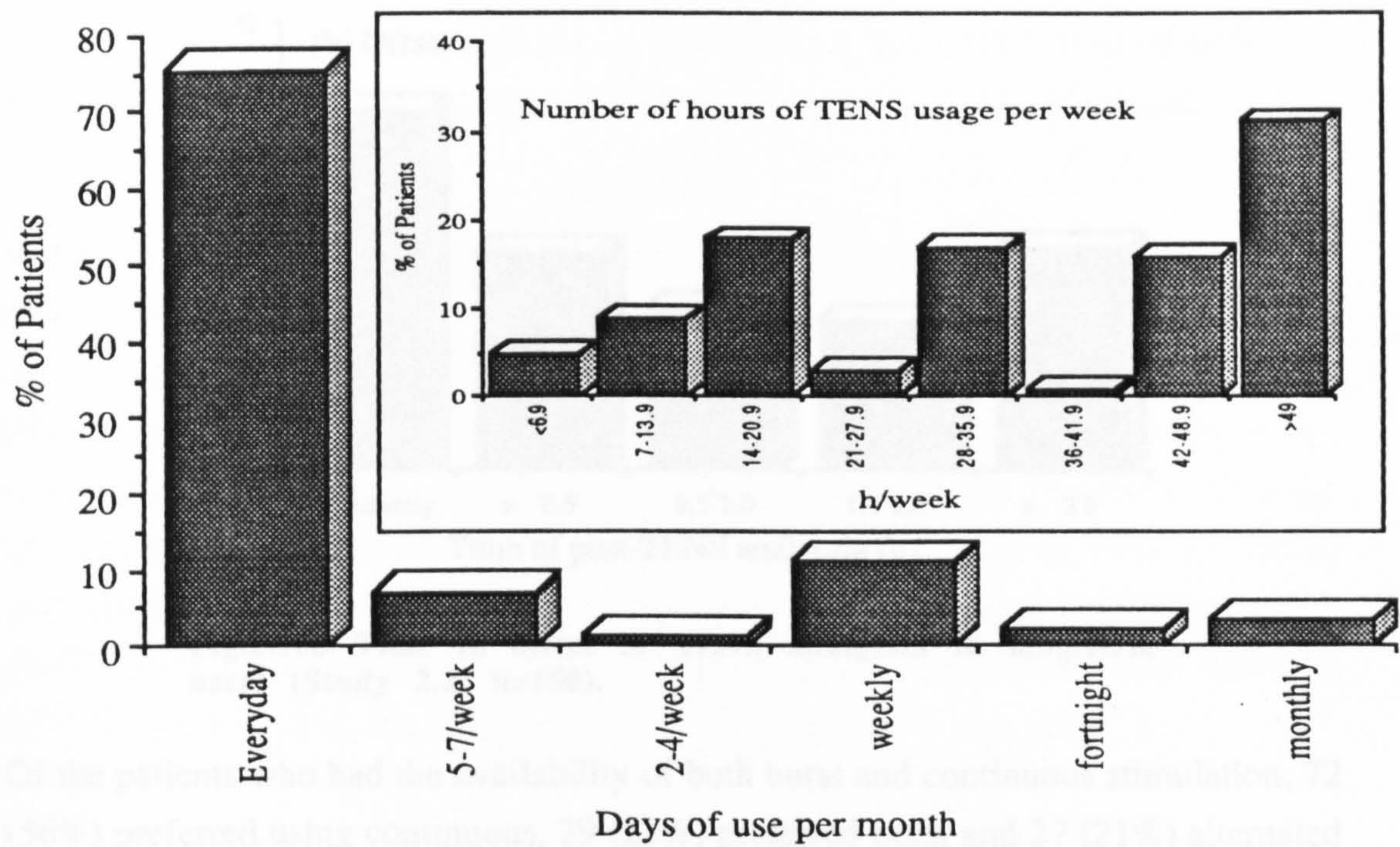


Fig.2.9 Duration of TENS treatment by long-term users (Study 2.2, n=152).

The onset of TENS analgesia occurred within half an hour in 115 (77%) patients and within an hour in 144 (over 95%) patients (Fig.2.10a). Post-TENS analgesia lasted over an hour in 50 (33%) patients, and less than thirty minutes for 77 (51%) of patients (Fig.2.10b). No significant differences (Kruskal-Wallis - categorical data) were found between the time to onset or offset of TENS analgesia between burst and continuous modes of stimulation.

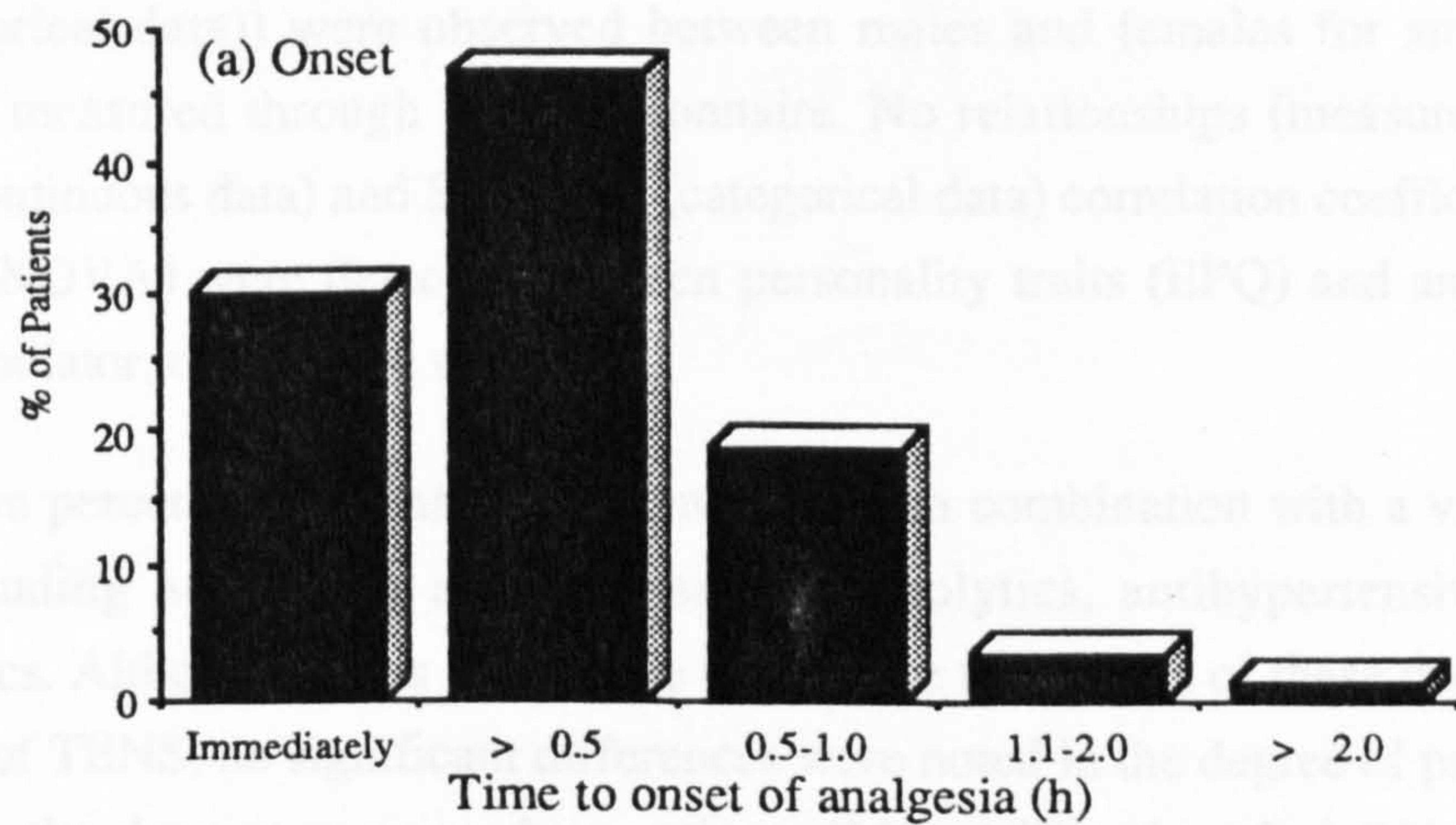


Fig.2.10a Time to onset of TENS analgesia in long-term users (Study 2.2, n=150).

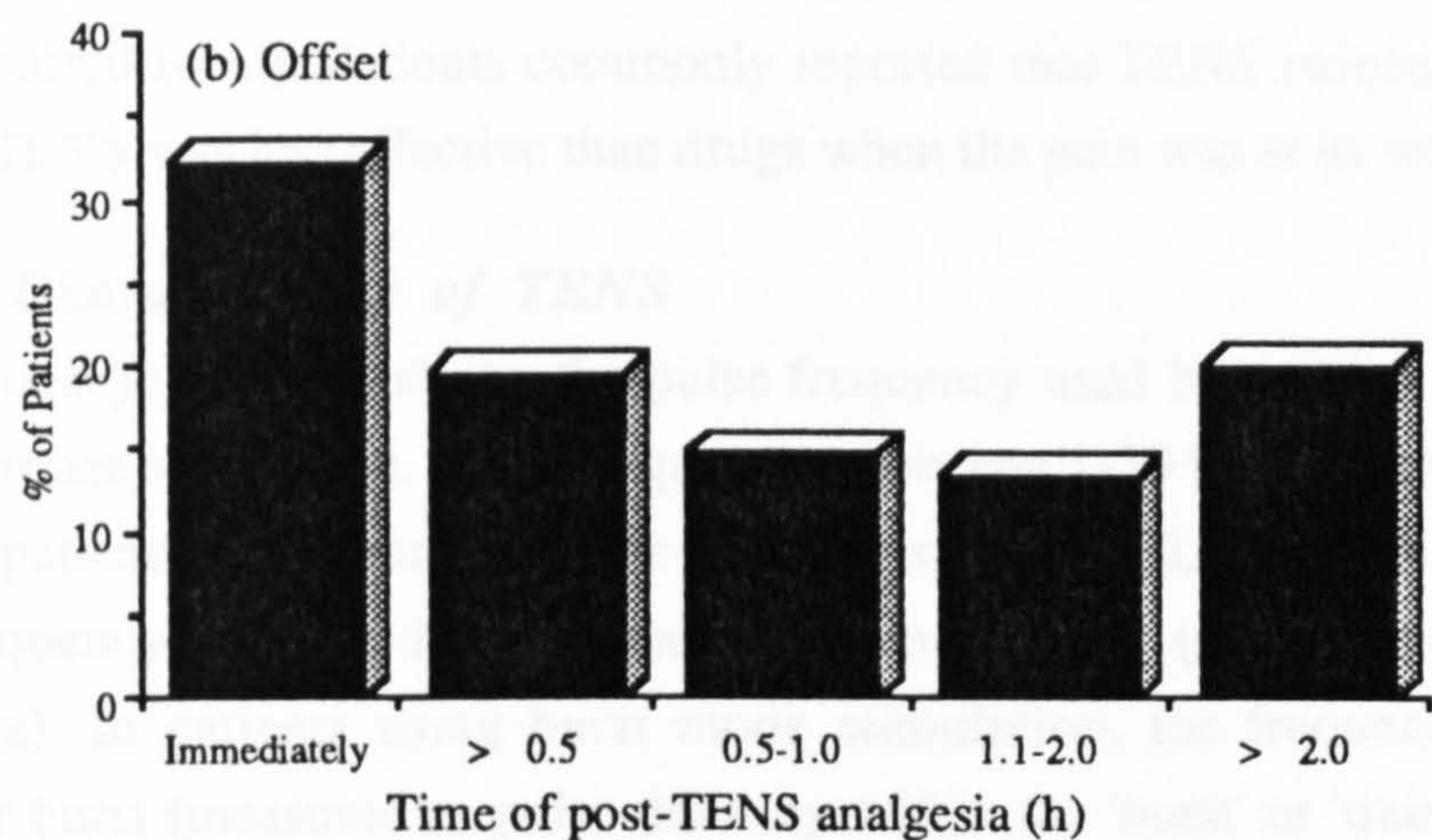


Fig.2.10b Time to offset of TENS analgesia in long-term users (Study 2.2, n=150).

Of the patients who had the availability of both burst and continuous stimulation, 72 (56%) preferred using continuous, 29 (23%) preferred burst and 27 (21%) alternated between the two. No significant differences (Kruskal-Wallis - categorical data) were found between the mode of stimulation and the anatomical region of pain, aetiology of pain or diagnostic clusters.

Forty-one (32%) patients reported a decline in TENS efficacy since the time of issue, although 75 (58%) continued to achieve the same degree of analgesia and 10 (13%) an increased effect. Forty-five (31%) patients had encountered skin reactions (i.e. rash or irritation) to either the tape, gel, or electrodes (Table 2.2).

No significant differences (unpaired t-tests (continuous data) and Mann-Whitney U-test (categorical data)) were observed between males and females for any of the parameters measured through the questionnaire. No relationships (measured using Pearson (continuous data) and Spearman (categorical data) correlation coefficient and one-way ANOVA) were detected between personality traits (EPQ) and any of the patient, stimulator, or outcome variables.

Seventy-five percent of patients were using TENS in combination with a variety of drugs, including analgesics, antidepressants, anxiolytics, antihypertensives, and antiepileptics. Although it was impossible to separate the effects of these drugs from the effects of TENS, no significant differences were noted in the degree of pain relief achieved in the drug versus non-drug patients (Mean±SD pain relief (VAS units); patients using drugs=5.0±3.2 (n=105), Patients not using drugs=4.5±2.4 (n=34),

P>0.05, unpaired t-test). Patients commonly reported that TENS reduced their drug intake, but TENS was less effective than drugs when the pain was at its worst.

Electrical Characteristics of TENS

Pulse Frequency: Fig.2.11 shows the pulse frequency used by patients when using continuous mode stimulation. Pulse frequencies between 1-70 Hz were utilised by 68 (75.5%) of patients, with a small cluster of patients, 12 (13%), choosing 111-140Hz. Median frequency of pulse delivery was found to be 32Hz (mean±SD=53±48 Hz; mode=24Hz). In patients using burst mode stimulation, the frequency of pulse delivery for burst (measured as pulse delivery within the 'burst' or 'train' of pulses) and continuous modes of stimulation were found to be highly correlated (r=+0.743, df=89, P<0.01, Pearson correlation coefficient) and not significantly different (P>0.01, paired t-test).

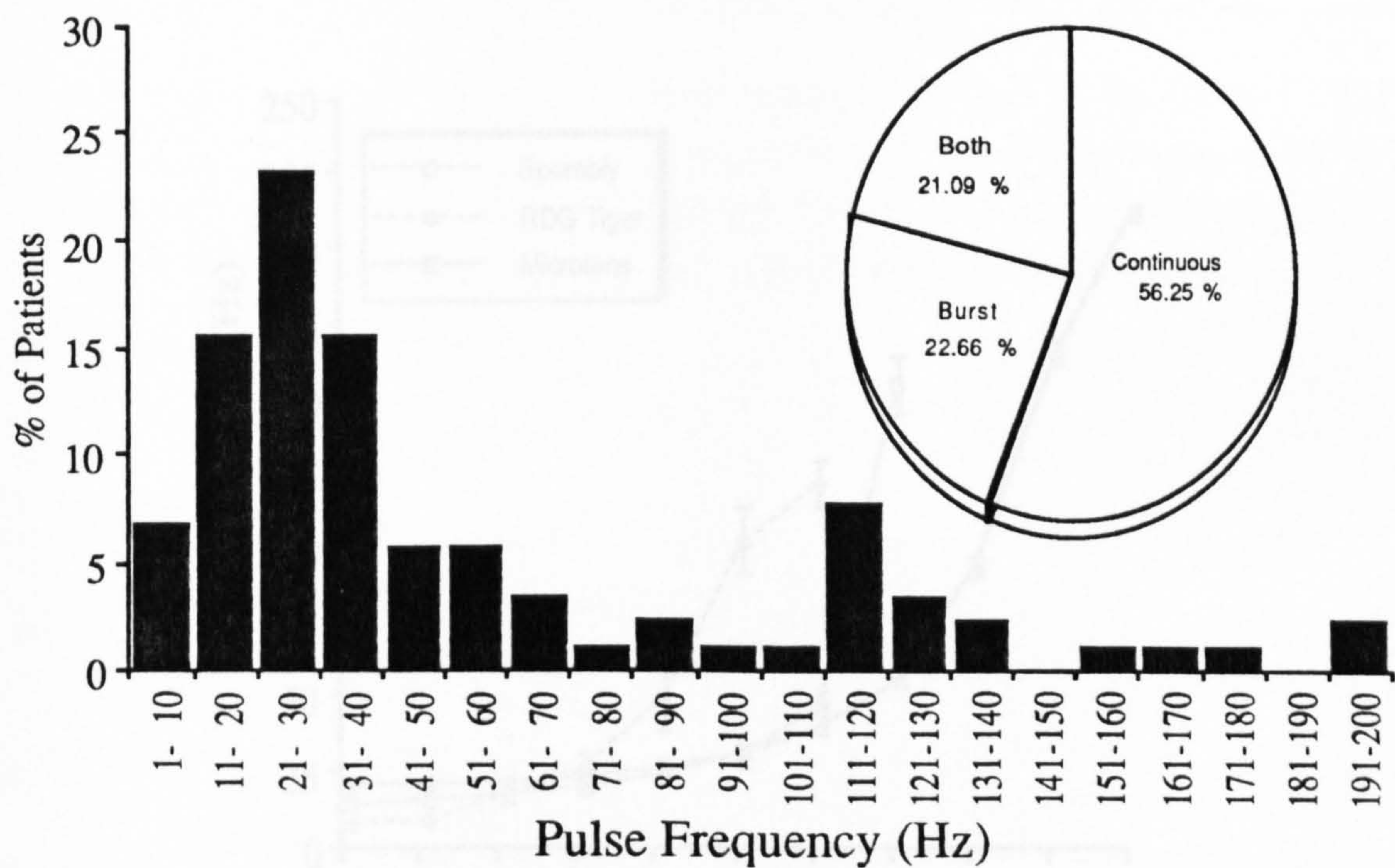


Fig.2.11 Pulse frequencies and pulse patterns used during stimulation by long-term users of TENS (Study 2.2). Pulse frequencies were recorded on a Frye Analyser when TENS was set to continuous mode (n=90). Pie chart shows preferred pulse patterns (n=128).

As all stimulators used by the patients were constructed with a frequency control dial with logarithmic characteristics, it is difficult for patients to adjust the instrument to specific pulse frequencies above 40Hz (Fig.2.12). Such frequencies lie on the steep

part of the frequency output curve, so that small turns of the frequency control dial result in large changes in frequency [Johnson et al. 1989]. As a consequence, the distribution of pulse frequencies used by patients may directly follow the characteristics of the frequency dial. All patients utilising pulse frequencies between 111-140 Hz were using Tiger Pulse or Tiger Burst stimulators, and had reached the maximum possible frequency available.

No significant differences in pulse frequency were found across anatomical region, aetiology and diagnostic clusters (one-way ANOVA). No correlations (Pearson correlation coefficients) were observed between pulse frequency (after log transformation to allow for the skew distribution) and (i) the present pain rating, (VAS; $r=+0.001$, $df=89$, $P>0.05$), (ii) the degree of pain relief achieved using TENS (VAS; $r=+0.132$, $df=89$, $P>0.05$), or (iii) any of the personality variables measured by the EPQ.

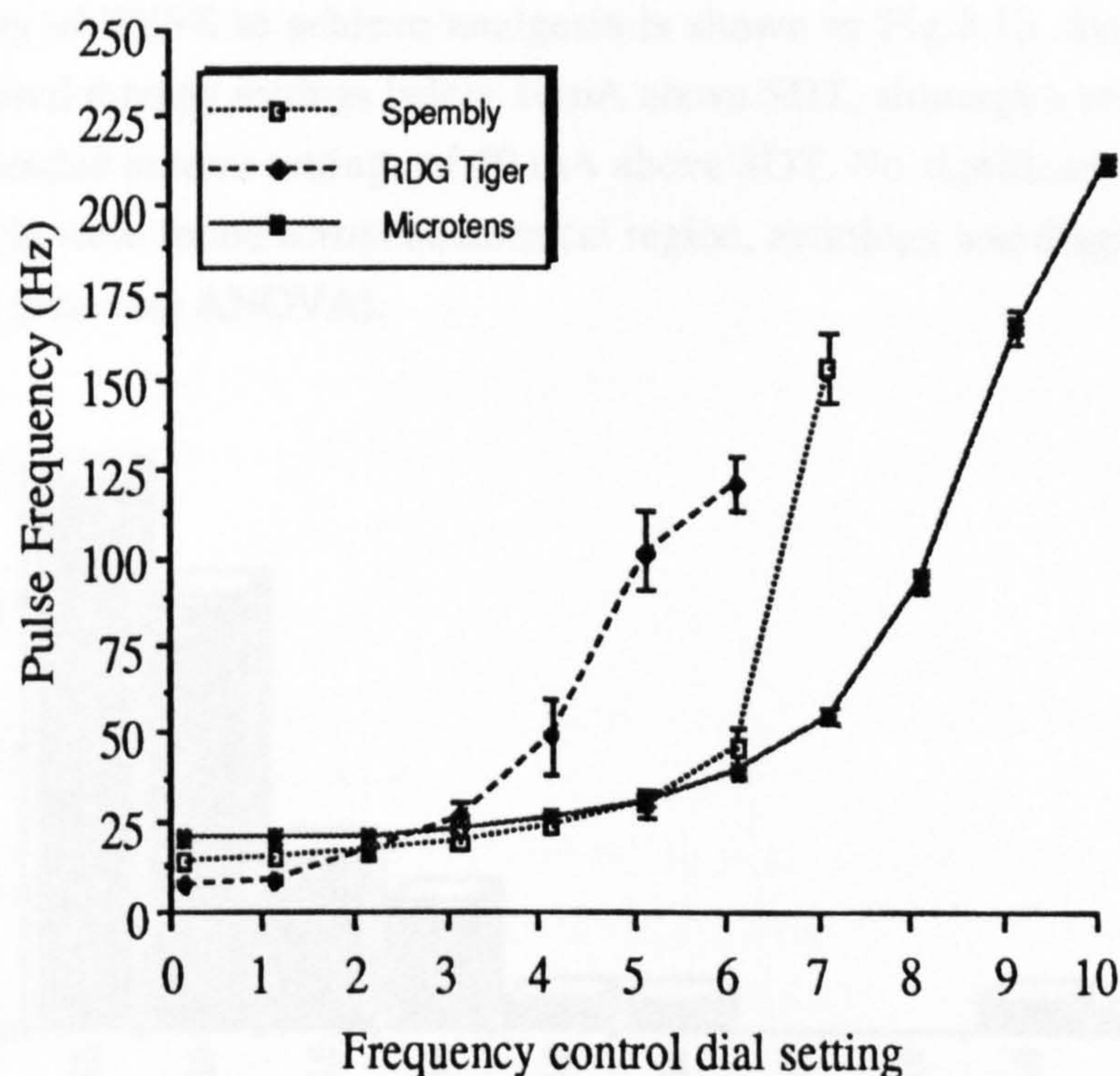


Fig.2.12 Calibration of the frequency control dial of stimulators issued by Newcastle Pain Relief Clinic. Corresponding pulse frequencies were recorded on a Frye TENS Analyser (1Kohm internal load) to incremental changes on the frequency control dial. Mean \pm SE (n=5).

Intensity of Stimulation

Sensory detection threshold: The mean \pm SD sensory detection threshold (SDT), measured at the site of application of TENS, was found to be 11.04 \pm 6.6mA (n=87) at the pulse frequency used by the patient. No relationship ($r=+0.2$, $df=86$, $P>0.05$, Pearson correlation coefficient) was found between sensory detection threshold and pulse frequency. Males were found to have a significantly higher sensory detection threshold than females (Mean \pm SD; female=9.2 \pm 5.9, male=12.9 \pm 6.9, $P<0.01$, unpaired t-test). No significant differences in sensory detection threshold (one-way ANOVA) were observed across regions, aetiology or diagnostic clusters.

Therapy level: The intensity of stimulation required to achieve the therapeutic analgesic effect, was corrected for individual variations in sensory detection threshold (SDT) by simple subtraction:

$$\text{Therapy Level (mA above SDT)} = \text{Absolute therapy level (mA)} - \text{SDT (mA)}$$

The intensity of TENS to achieve analgesia is shown in Fig.2.13. Sixty-one (71%) patients utilised therapy settings below 10mA above SDT, although a small number of patients exceeded current settings of 40 mA above SDT. No significant differences in therapy levels were found across anatomical region, aetiology and diagnostic clusters respectively (one-way ANOVA).

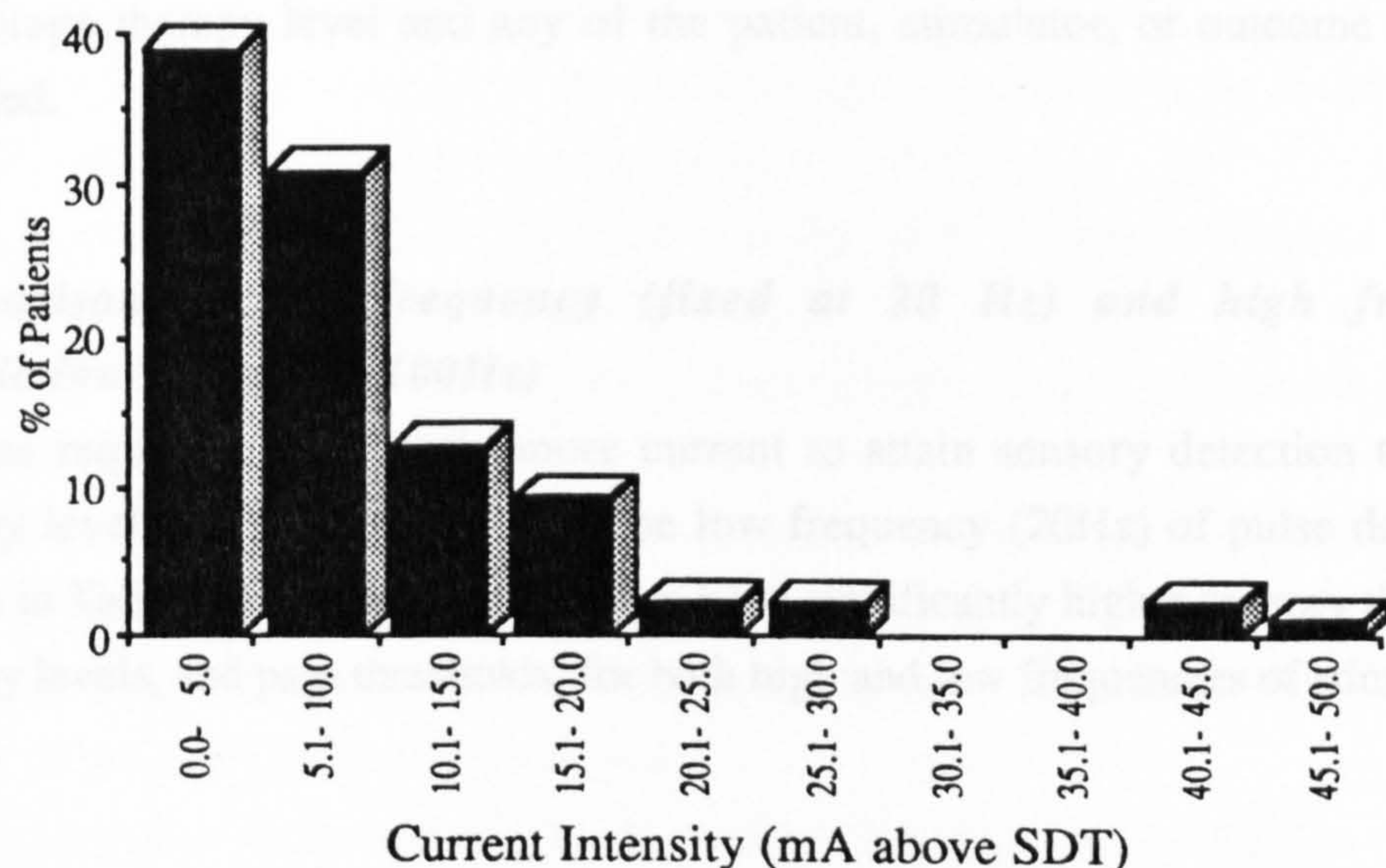


Fig.2.13 Current intensity of the therapy settings of stimulation utilised by long-term users of TENS (Study 2.2, n=87).

The mean±SD therapy level was found to be 9.1±9.1 mA above SDT (n=87). No relationship ($r=+0.2$, $df=86$, $P>0.05$, Pearson correlation coefficient) was found between therapy level and pulse frequency. Males utilised a significantly higher therapy level (Mean±SD (mA above SDT); female 7.0±6.4, male 11.4±11.1, $P<0.05$, unpaired t-test).

Pain threshold: Pain threshold measurements, taken at the site of TENS electrodes, were also corrected for sensory detection threshold in each individual. Mean±SD pain threshold for all patients was found to be 18.20±15.2 mA above SDT (n=87). No relationships ($r=+0.2$, $df=86$, $P>0.05$, Pearson correlation coefficient) were found between pain threshold and pulse frequency. Males showed significantly higher pain thresholds (Mean±SD (mA above SDT); females=14.4±11.6, males=22.5±17.6, $P<0.05$, unpaired t-test), and no significant differences in pain threshold were found across anatomical region, aetiology or diagnostic clusters (one-way ANOVA).

Percentage Therapy level: Therapy levels were re-calculated as a percentage falling within a window between sensory detection threshold and pain threshold. Thus:

$\% \text{Therapy level} = \frac{\text{Absolute Therapy level(mA)} - \text{SDT (mA)}}{\text{Pain threshold(mA)} - \text{SDT(mA)}} \times 100$

No relationships (examined by plotting data, Pearson and Spearman correlation coefficients, and ANOVA and Kruskal-Wallis tests) were found to exist between percentage therapy level and any of the patient, stimulator, or outcome variables recorded.

Comparison of low frequency (fixed at 20 Hz) and high frequency stimulation (fixed at 100Hz)

Patients required significantly more current to attain sensory detection threshold, therapy level and pain threshold at the low frequency (20Hz) of pulse delivery as shown in Table 2.3. Males were found to have significantly higher sensory thresholds, therapy levels, and pain thresholds, for both high and low frequencies of stimulation.

MEAN ± SD CURRENT INTENSITY (mA)	Low Frequency (20Hz)	High Frequency (100Hz)	Paired t-test
Sensory detection threshold [mA] (n=88)	11.6± 8.1	8.7± 5.4	p<0.001
Therapy level [mA above SDT] (n=87)	11.1±11.3	8.3± 9.9	p<0.001
Pain threshold [mA above SDT] (n=83)	21.6±16.9	16.7±16.3	p<0.001

Table 2.3 Comparison of current intensity achieved during TENS administered at low and high pulse frequencies (continuous mode) in long-term users of TENS. Recordings were taken at the site of pain. Data was logarithmically transformed prior to statistical analysis (SDT=sensory detection threshold).

Follow-up

Pulse frequency remained consistent over the 4 month follow-up period ($r = +0.66$, $df=23$, $P<0.01$, Pearson correlation coefficient; paired t-tests showed no significant differences between visits, $P=0.93$). Therapy settings declined between visit 1 and 2 (Mean±SD (mA above SDT); visit 1=10.2±10.6; visit 2=6.1±6.2, $P<0.01$, paired t-test) although no significant differences were observed for sensory detection threshold over the two visits (Mean±SD (mA); visit 1=12.7±6.5; visit 2=12.2±8.9, $P=0.55$, paired t-test: Pearson correlation coefficient: $r=+0.82$, $df=23$, $P<0.01$)

Main findings of Study 2.2

- (i) No relationships were observed between region, aetiology or the diagnosis of pain, with any patient, stimulator, or outcome variable.
- (ii) Patients applied TENS to produce a 'strong but comfortable' electrical paraesthesia within the painful area.
- (iii) In 47% of patients, TENS reduced (on average) the intensity of their chronic pain by more than half.
- (iv) The onset and offset of analgesia was reported to be rapid, within 30 minutes in the majority of patients.
- (v) Seventy-five per cent (75%) of patients reported to use TENS on a daily basis, and 30% use TENS for over 49 h/week.
- (vi) Forty-four per cent (44%) of patients benefitted from the availability of burst mode stimulation.
- (vii) Seventy-five per cent (75%) of patients used frequencies below 70 Hz, although this may be due in part to stimulator design.

Study 2.3.**The consistency of pulse frequencies and pulse patterns of TENS used by chronic pain patients.**

Study 2.2 found that 75% of patients utilised frequencies between 1-70 Hz and although no relationships were shown to exist between TENS pulse frequency and either the cause and site of pain, or TENS efficacy, the results implied that patients utilised specific pulse frequencies which were unique to the individual. Patients also expressed strong preferences for specific pulse patterns and 23% of patients reported burst mode TENS to be the most beneficial pulse pattern to reduce their pain. The aim of Study 2.3 was to investigate the consistency of TENS pulse frequencies and pulse patterns used by chronic pain patients over a one year period.

Patients and Procedure

Thirteen patients (female n=8, male n=5; age range=39-66, mean \pm SD=54.1 \pm 9.8 years of age) attended the research unit on three separate occasions (approximately 4 months apart over a one year period) to participate in the study. Of these 13 patients, 10 returned for a fourth visit. Patients were instructed to apply TENS as they would to treat their chronic pain condition. All patients applied electrodes directly over, or immediately proximal to, the site of pain. Patients set their stimulators to a 'strong but comfortable' intensity level and hunted for the most suitable pulse frequency. The electrical characteristics of TENS were recorded using the Frye Analyser as described in Study 2.2. Patients were in possession of one of four types of stimulator (i.e. Tiger Pulse, Tiger Burst, Microtens, or Spembly). Pulse width was fixed at 200 μ s in all stimulators, and electrode impedance was below 1.5 Kohms.

Patients were categorised according to the classification of chronic pain, prepared by the International Association for the Study of Pain [IASP 1986]. The patient population had a range of chronic pain conditions, including deafferentations (n=2), nerve entrapments (n=3), neuralgias (n=3), spondylosis (n=3), sympathetic (n=1) and 'other' (n=1). Five of these patients had low back pain of either 'traumatic' or 'degenerative/mechanical' aetiology.

All patients had been successfully controlling their pain condition with TENS for over one year prior to this study. Twelve of the 13 patients found that TENS generally reduced their pain by over half, as measured on a visual analogue scale.

Results of Study 2.3

The results of Study 2.3 are summarised in Table 2.4. Of the 13 patients, 4 were in possession of a Tiger Pulse stimulator (no burst mode option available), 3 a Tiger Burst, 3 a Spembly 9000 and 3 a Microtens 7577. Patients utilised pulse frequencies between 3-200 Hz (range=3-176Hz, mean=60Hz, median=47Hz, n=39; 3 visits per subject). All stimulators possess a frequency control dial with logarithmic output characteristics, therefore logarithmic transformation of pulse frequency data was performed before statistical analysis (see Appendix B).

PATIENT	PULSE FREQUENCY(Hz) [Pattern]							
	1 st visit		2 nd visit		3 rd visit		4 th visit	
(A)	12	[C]	28	[C]	12	[C]	35	[C]
B	140	[B]	136	[B]	176	[C]	200	[C]
(C)	124	[C]	72	[C]	124	[C]	[x]	[x]
D	47	[B]	56	[B]	56	[B]	60	[B]
(E)	8	[C]	17	[C]	3	[C]	[x]	[x]
F	92	[C]	100	[B]	26	[C]	112	[C]
G	16	[C]	16	[C]	16	[C]	18	[C]
H	104	[B]	29	[B]	29	[C]	26	[B]
I	24	[C]	32	[C]	33	[C]	29	[C]
J	58	[C]	43	[C]	50	[C]	16	[C]
(K)	10	[C]	18	[C]	23	[C]	16	[C]
L	55	[C]	92	[C]	80	[C]	32	[C]
M	136	[B]	112	[B]	124	[B]	[x]	[x]

Table 2.4 The consistency of pulse frequencies and pulse patterns of TENS in long-term users (Study 2.3). Pulse pattern; [B] = burst mode, [C] = continuous mode, [X] = patients not returning for 4th visit=[X]. Patients without the availability of burst mode stimulation = (A), (C), (E), (K).

One-way ANOVA for repeated measures showed no significant differences between the frequency of pulse delivery used between visits. Pulse frequencies used by individual patients were found to be highly correlated between visits (Visit 1 v 2, r=+0.84, df=12, P<0.01: Visit 1 v 3, r=+0.82, df=12, P<0.01: Visit 2 v 3, r=+0.81 df=12, P<0.01, Pearson Correlation coefficient, see Table 2.4). Analysis of the 10 patients who returned for a fourth visit also revealed no significant differences in pulse frequency between visits (one-way ANOVA).

Of the patients with the option of burst mode stimulation, 6 out of 9 patients utilised the same pattern of stimulation on 3 visits. Thus, 4 utilised continuous mode only, 2 patients utilised burst mode only, and 3 alternated between the two modes. All of the patients utilising either burst or continuous mode TENS alone, continued to do so if they returned for the fourth visit.

As in Study 2.2 no relationships were found between pulse frequency or pulse pattern, with the site or cause of pain. However, the patient sample was small in the present study.

Main findings of Study 2.3

- (i) Patients show individual preferences for pulse frequencies and patterns, and consistently turn to such settings on subsequent treatment sessions.

DISCUSSION

The clinical use of TENS in the treatment of chronic pain conditions has been examined in depth by three studies. Since the introduction of TENS to NPRC, 1582 patients with a wide variety of pain conditions have been given a trial of TENS, and 927 (58.6%) continue to use stimulators on a long-term basis (Study 2.1). No relationships between patient, stimulator and outcome variables were found in patients who successfully use TENS on a long-term basis to control a chronic pain condition (Study 2.2). However, patients prefer specific pulse frequencies and pulse patterns, and turn to such settings on subsequent TENS treatment sessions (Study 2.3). Furthermore, Study 2.2 revealed much information of importance to clinicians involved in pain control by means of TENS. These findings will now be discussed in detail.

Long-term use of TENS at Newcastle Pain Relief Clinic (Study 2.1)

The clinical importance of TENS as an analgesic technique in the treatment of chronic pain has been demonstrated. At present, approximately 180 stimulators are issued to patients by NPRC each year (3-4 per week), and since its introduction to the clinic in 1979, TENS has been issued on loan to 1582 patients. Of these 1582 patients, 927 (58.6%) continue to use stimulators. Although it was not possible to assess the degree of pain relief obtained by patients continuing with TENS treatment, nor to confirm that all were using stimulators regularly, the policy in the clinic was to stress that stimulators should be returned if not being used so that they could be issued to other patients. It may therefore be inferred that the majority of those not returning stimulators were obtaining some benefit from TENS. An investigation is planned to assess TENS use (by postal questionnaire) in all patients possessing stimulators.

Eriksson et al. [1979; 1984] found that varying proportions (18-60%) of patients continued to benefit from TENS after one year, depending upon the type of pain condition. Bates and Nathan [1980] reported 27% of patients to benefit after a year (Table 2.1). A wide range of chronic pain conditions (reflecting the distribution of pains presenting at NPRC [Davies & Crombie 1990]) were successfully treated with TENS, and no particular pain appeared to respond better than another. Thus, any type

of pain may benefit from TENS. This finding was confirmed by the results of Study 2.2 and by previous investigations [Loeser et al. 1975; Bates & Nathan 1980; Wolf et al. 1981]. However, it is clear that certain pain conditions are *less likely* to respond than others (see Table 1.2).

Most patients who returned their stimulators did so within the first six months, usually at the first follow-up appointment at NPRC. Such patients may be classified as non-responders, to TENS because:

- (i) it was ineffective,
- (ii) it aggravated the pain,
- (iii) it was too difficult or inconvenient to use.

Hence, patients responding to TENS for over 6 months usually continue with treatment, a finding consistent with Eriksson et al. [1984]. Reasons for patients returning stimulators after this time may include resolution of the pain problem, simple forgetfulness, and the development of tolerance to TENS analgesia [Pomeranz & Niznick 1987].

Long-term use of TENS by chronic pain patients (Study 2.2)

Study 2.2 is the first in-depth study of a large number of patients who successfully use TENS on a long-term basis for the relief of a variety of chronic pain conditions. Despite the wide range of conditions treated, no relationships were observed between patient (i.e. cause and site of pain), and stimulator variables (i.e. TENS settings used). This result is consistent with previous reports [Loeser et al. 1975; Bates & Nathan 1980; Wolf et al. 1981]. However, the patients examined in Study 2.2 were responding to TENS, and comparisons with TENS non-responders may provide more valuable information (see Chapter 6). Nevertheless, Study 2.2 revealed much information of importance to clinicians involved in pain control by means of TENS.

The following findings are of clinical relevance:

- (i) Patients applied TENS to produce a 'strong but comfortable' electrical paraesthesia within the painful site.
- (ii) Forty-seven per cent (47%) of patients found that TENS reduced their pain by more than half.

- (iii) The onset of TENS analgesia occurred immediately in 30% of patients, within less than 1/2 hour in 75% of patients, and within one hour in 95% of patients.
 - (iv) Post-TENS analgesia lasted less than 30 minutes in 51% of patients and more than an hour in over 30% of patients.
 - (v) Seventy-five per cent (75%) of patients reported to use TENS on a daily basis, 52% of patients used TENS for up to 28 hours per week, whilst 30% used it for over 49 hours per week.
 - (vi) Forty-four per cent (44%) of patients benefitted from the availability of burst mode stimulation.
 - (vii) Seventy-five per cent (75%) of patients utilised pulse frequencies between 1Hz-70Hz (median=32 Hz) although this may be in part due to stimulator design.
- Some of these points are discussed below.

TENS Questionnaires

In a study of patients with chronic facial pain, Eriksson et al. [1984] found that men attained greater benefit from TENS than women. By contrast, Johansson et al. [1980] found that neither age nor sex had predictive value. The latter finding is confirmed in the present investigation, in which there was no correlation between these factors and the degree of response to TENS across any of the chronic pain conditions. Moreover examination of the administrative records revealed no differences in the proportion of stimulators returned to the clinic by males and females.

Degree of analgesia: Long-term results of peripheral conditioning stimulation as reported by Eriksson et al. [1979], indicated that three-quarters of chronic pain patients who obtain successful analgesia reach over 50% pain relief (measured on a VAS). Approximately half of the patients in the present study reported over 50% relief of pain during TENS use. Surprisingly 11 of the 23 patients who reported no TENS analgesia continued to use the stimulator on a daily basis, thus posing an interesting anomaly. Patients who report no pain relief on a VAS may not necessarily represent failures of TENS treatment because some of them still receive benefit, evidenced by their statements that: "*TENS does not reduce my pain, but it distracts, or takes my mind off it*". Such patients may produce idiosyncratic VAS scores and reveals a deficiency in such ratings which record only one component of the pain sensation (i.e. pain intensity). Our patients utilised a wide range of treatment regimes. Some used TENS for over 7 hours daily, proclaiming the success of the "Wonderful black box"! However, despite the experience of long-term stimulator use, some patients still

showed anxiety on using TENS, possibly reducing efficacy, as suggested by Nathan and Wall [1974].

Onset of analgesia: The rapid onset of TENS analgesia (within 30 mins of stimulator 'switch on' for 75% of patients), and also rapid offset (within 30 minutes of stimulator 'switch off' for over 50% of patients), was noted by Hansson and Ekblom [1983]. This rapid 'on-off' analgesic effect accords with a neuronal gating mechanism as proposed by Melzack and Wall [1965]. However, Eriksson et al. [1979] using bursts mode TENS at an intensity sufficient to produce muscle contraction, as utilised in AL-TENS, found that the induction time of analgesia to be 20-30 minutes, and slower than the induction time of low intensity continuous mode TENS which was 2-10 minutes. In the present study, the time to onset of analgesia with burst or continuous mode did not differ. This may be due to the different intensities of burst stimulation used by the patients in Study 2.2 and those in the Eriksson et al. study. Thus the group of patients examined in Study 2.2 used burst mode TENS at intensities below that required to induce muscle contraction.

Post-TENS analgesia: In over 50% of patients, post-TENS analgesia lasted less than 30 minutes, as observed previously by Andersson et al. [1976]. However, a third of patients achieved post-TENS analgesia of over one hour, possibly as a result of activating descending pain inhibitory pathways and the release of opioid peptides. Nevertheless such patients were not observed to be using high intensity TENS or producing AL-TENS, which has been proposed to be a requirement to activate opioid release [Sjölund et al. 1977]. Over half of the patients preferred continuous mode TENS alone to treat their chronic pain, and a quarter used the burst facility alone. No significant differences were found between the duration of post-TENS analgesia obtained with burst or continuous stimulation.

TENS tolerance: The declining response to TENS with time, often termed tolerance to TENS analgesia, has remained a fundamental problem for clinicians and patients alike. Although the mechanism of this tolerance is far from understood, it may be due to an adaptative change by the nervous system to regular repetitive stimuli produced by TENS [Cheng & Pomeranz 1987]. In the present study, 32% of patients reported a decline in TENS efficacy from the time the stimulator was issued, although for the majority (58%) TENS efficacy remained unchanged. This finding is consistent with that of Study 2.1 in which few patients returned stimulators after one year. Attempts to

prevent or delay the occurrence of tolerance have led to the development of TENS units with 'random' pulse delivery facilities (i.e. Xenos), and a new generation of non-portable stimulators such as the Codetron [Pomeranz & Niznick 1987] and the Likon [Likon 1990]. Such devices remain to be fully validated.

Personality (EPQ): The possibility that personality might be correlated with response to TENS has been investigated by several workers. Nielzén et al. [1982] and Johansson et al. [1980] reported that psychiatric and personality assessments may have a predictive value for TENS outcome. However Andersson et al. [1976] found no relationships between the EPQ and patient response to TENS. Similarly in Study 2.2 no relationships were observed between EPQ ratings and any patient, stimulator, or outcome variables.

Adverse effects: The only common problem associated with TENS was skin irritation, and this was encountered by a third of patients, probably due to either, (i) drying out of electrode jelly [Mason & Mackay 1976; Yamamoto et al. 1986], or (ii) irritation from tape. Some patients reported using TENS for over 7 hours without replenishing electrode gel because of inconvenience. More severe *allergic* reactions to electrodes, gel or tape are occasionally encountered in the clinic, although the problem is usually overcome by changing the type of electrode used, for example, from carbon rubber with saline gel to a self-adhesive non-gel type.

Electrical characteristics of TENS

Site of stimulation: When patients were first issued with a stimulator, they were instructed to apply electrodes directly over, or immediately proximal to the site of pain [Wolf et al. 1981; Sjölund & Eriksson 1985]. Patients were also encouraged to experiment with electrode positions in order to find the optimal site for pain relief. Subsequently, most patients had carried out an exhaustive trial of different electrode positions, and were generally using sites to produce an electrical paraesthesia within the site of pain, rather than stimulating remote body sites. This finding is consistent with previous reports [Loeser et al. 1975; Linzer & Long 1976].

Pulse frequency: Andersson et al. [1976] found that the degree of pain relief was related to the frequency of stimulation, so that for example, 2 Hz was insufficient to produce analgesia. It is generally stated that frequencies between 40-100 Hz are the most beneficial for patients [Woolf 1989]. Linzer and Long [1976] reported that 74% of patients used frequencies between 1-60 Hz, although it is possible that this was due

to the logarithmic output characteristics of the frequency control dial on some stimulators.

The patients in Study 2.2 favoured frequencies between 1-70Hz, with an additional cluster at 111-140Hz. Unfortunately, specific frequencies above 40Hz are usually difficult to attain on commercially available stimulators, because these lie on the steep part of the frequency output curve, which has a logarithmic function. Hence a small turn of the control dial results in a big change in frequency (Fig.2.12). The distribution of pulse frequency used by patients in Study 2.2, reflected the characteristics of the frequency control dial. Different models of stimulators had different frequency output characteristics, and these probably influenced the patients choice of stimulation frequency. Thus, the cluster of patients using frequencies between 111-140 Hz were all using Tiger Pulse and Tiger Burst stimulators whose maximum frequency setting lies in this range. Moreover, analysis of the questionnaire indicates that patients prefer to use faster frequencies of stimulation. This fact, coupled with the lack of use of frequencies between 41-110 Hz, strongly suggests that patients were not always able to attain the maximal preferred frequency to achieve the largest analgesic effect. It is clear that there is considerable scope for improved design of commercially available stimulators.

The results of Study 2.2 suggest that each patient prefers a particular pulse frequency and pulse pattern to treat his or her pain condition because:

- (i) Patients inevitably returned to their preferred pulse frequency after completing the *Frye Analysis* recording session.
- (ii) Patients reported regularly resetting pulse frequency before use.
- (iii) Patients chose similar frequencies at the 4 month follow-up period.

These findings were confirmed in Study 2.3 where it was found that patients utilise specific pulse frequencies and pulse patterns (unique to the individual) to control their chronic pain condition. After experimenting with stimulator settings, patients find the most beneficial pulse frequency and pulse pattern and use these on subsequent treatment sessions.

The reason of why patients prefer certain pulse frequencies and patterns remains to be determined. Sjölund [1985] found that stimulation of peripheral nerves at a frequency of 80 Hz, produced the most profound suppression of the C-fibre-evoked reflex in rats. Theoretically, high frequency (often reported as between 40-100 Hz) low

intensity TENS should produce optimal conditions for selectively activating large diameter afferent fibres (A-beta), a prerequisite for closing 'pain gates' in the spinal cord.

In Study 2.2, 59 (65%) patients used frequencies below 50 Hz and in Study 2.3, 6 (46%) patients utilised frequencies below 50 Hz. The large variability in pulse frequencies used between individuals, and the lack of relationships between the pulse frequency and the cause and site of pain, or any of the many variables recorded, suggests that pulse frequency preference may be for reasons of comfort, unconnected with specific pain control mechanisms. Thus, it appears that patients experiment with frequency settings to 'tune in' to a favourite pulse frequency.

Pulse Pattern: Study 2.2 found that 72 (56%) patients used continuous TENS alone, 29 (23%) burst TENS alone, and 27 (21%) regularly alternated between the two. A similar distribution was observed in Study 2.3 where 4 out of 9 (44%) patients preferred to use continuous mode TENS alone, 2 (22%) preferred burst TENS alone, and 3 (33%) regularly alternated between burst and continuous. Furthermore, patients favoured pulse patterns on subsequent treatment sessions. All patients under study applied burst mode TENS at an intensity insufficient to activate deep muscle afferents which would be requirement to achieve AL-TENS. Therefore it seems probable that patients were utilising burst mode TENS in a similar manner to continuous mode TENS and for reasons of comfort [Mannheimer & Lampe 1988a]. Nevertheless some patients reported discomfort while using the burst mode, possibly due to the occurrence of phasic muscle contractions, and consequently preferred continuous mode stimulation.

Intensity of stimulation: Patients report stimulating at the highest possible 'strong but comfortable' (non-painful) level, without concurrent muscle contraction, during treatment. Wolf et al. [1981] reported a positive relationship between higher intensity TENS and increased analgesia, although this was not substantiated in the present investigation. In Study 2.2, males needed a higher current to achieve therapy level.

When pulse frequency was fixed by the experimenter, the lower frequency of pulse delivery (20Hz) required a higher intensity of current to achieve sensory threshold, therapy level, and pain threshold. No differences in sensory threshold, therapy level and pain threshold, whether measured at high or low fixed frequencies, were found over the different anatomical regions stimulated. It seems likely that the intensity of

therapeutic stimulation used during TENS is dependent upon a combination of both physiological (i.e. site and cause of pain) and psychological (i.e. personality) factors.

Clinical Implications

A number of findings from these investigations have direct clinical implication. Perhaps the most important is that clinicians cannot assume that any particular pain will not respond to TENS, because a wide range of chronic pain conditions have been treated successfully in the patient populations under study. As suggested previously TENS should be tried for a minimum of one hour in the clinic in order to:

- (i) observe any immediate response to TENS - some patients may take one hour to show a response,
- (ii) observe adverse reactions (i.e. skin irritation, or aggravation of pain by TENS),
- (iv) provide adequate instruction on stimulator use.

In most patients pain relief only occurs during stimulation and only 20% of patients will benefit from the bonus of post-TENS analgesia for more than 2 hours. Thus, patients may need to apply TENS over the entire day on a daily basis in order to control their pain condition successfully. Therefore, a two month home trial is necessary to fully assess response to treatment. Other patterns of stimulation (e.g. burst) should always be considered (and available), as some patients fail to respond to continuous mode TENS. Although patients need to determine their own optimal pulse frequency, it is possible that frequencies between 1-70Hz may be of benefit. Nevertheless, stimulator design may seriously hinder patient choice. The only common adverse effects of TENS is skin irritation in one third of patients, which could be reduced by careful instruction on electrode technique. The use of TENS outdoors by 72% of patients also implies that TENS may vastly improve patient mobility. It is important that attention be given to all these factors during the clinical use of TENS.

Summary

The importance of TENS as an analgesic technique especially in the control of chronic pain has been confirmed. Doubts about the clinical efficacy of TENS have been dismissed, as 58.6% of patients given a trial of TENS continue to use the technique to

control a wide range of chronic pain conditions. Approximately half of the patients using TENS successfully to control a chronic pain condition obtain over 50% reduction in their pain during treatment. For the majority of patients, the onset and offset of pain relief is rapid and only occurs during stimulation, thus to control the pain problem, patients use stimulators over the entire day. In general, patients apply TENS to produce a 'strong but comfortable' electrical paraesthesia within the painful area, and have specific preferences on pulse frequencies and pulse patterns, turning to these frequencies and patterns on subsequent treatment sessions. Nevertheless, these pulse frequencies and patterns were not related to the cause and site of pain, implying that patients turn to such frequencies and patterns for reasons of comfort, which may not be related to mechanisms specific to the pain system.

Despite the relative success of administering TENS on an empirical basis, in which the patient determines by trial and error the setting which best controls the pain condition, 41.4% of patients fail to respond to treatment, and half using TENS on a long-term basis achieve less than 50% relief of pain. It is therefore likely that improvements in TENS techniques can be made. Patients may not be utilising the most beneficial stimulator settings because of stimulator design. Furthermore, the electrical characteristics often suggested for TENS (high frequency 40-100Hz, low intensity 'strong but comfortable') are largely derived on theoretical grounds to selectively activate large diameter skin afferents. However, experimental evidence examining the effects of different electrical characteristics of TENS remains sparse. Thus a systematic investigation was performed to examine the analgesic effects of different electrical characteristics of TENS, as described in Chapter 3.

CHAPTER 3

THE ANALGESIC EFFECTS OF DIFFERENT ELECTRICAL CHARACTERISTICS OF TENS IN HEALTHY SUBJECTS

INTRODUCTION

Chapter 2 has shown that patients who successfully control a chronic pain condition with TENS, apply TENS to produce a 'strong but comfortable' electrical paraesthesia within the painful area. This paraesthesia is achieved using low intensity electrical pulses delivered at a range of pulse frequencies and pulse patterns dependent upon the patient's preference. In this *conventional* form of TENS, the electrodes are generally placed around the painful area, or over the same dermatome (i.e. the area of skin sending afferent nerve fibres to the same spinal nerve root) as the painful area. Stimulation in the contralateral dermatome at the same level may enhance the beneficial effect. Several variations in TENS techniques have been introduced in an attempt to increase efficacy, reduce the incidence of non-response and prevent the development of tolerance to TENS analgesia [for review see Mannheimer & Lampe 1988a]. However, these variations in TENS techniques have met with only modest success, and in practice the electrical characteristics of TENS used by individual patients are usually found by trial and error. Furthermore, the results presented in Chapter 2 have shown that this 'trial and error' method may not provide the most efficacious electrical characteristics of TENS as 41.4% of patients fail to respond, and half of the patients responding achieve less than 50% relief. Therefore, a systematic investigation was performed to examine the analgesic effects of different electrical characteristics of TENS in healthy subjects.

The electrical characteristics of TENS

In general, TENS units have dials to control:

- (i) pulse amplitude (current intensity),
- (ii) pulse frequency,
- (iii) pulse pattern,

as shown in Fig.1.5, although some stimulators have pulse width control. Few studies have systematically examined the effects of varying pulse frequency, pulse pattern or stimulation mode (i.e. 'conventional' or AL-TENS) on the degree of pain relief obtained with TENS.

Pulse Frequency

It has been well documented in clinical studies that TENS efficacy is dependent upon pulse frequency [Andersson et al. 1976; Linzer & Long 1976; Mannheimer & Carlsson 1979; Hansson & Ekblom 1983]. Animal studies performed by Sjölund [1985] found that within a range of stimulating frequencies between 10-160Hz, 80Hz produced the maximal suppression of the C-fibre evoked flexion response in lightly anaesthetised rats. Hansson and Ekblom [1983] reported significant relief of acute oro-facial pain in patients who were administered TENS at frequencies of 2Hz and 100Hz, although patients preferred to use the higher frequency. In contrast, an earlier study by Ashton et al. [1984a] carried out in this laboratory suggested that 8Hz rather than 100Hz was more effective in reducing experimental pain in healthy volunteers. However, many studies have been restricted to the investigation of only 2 stimulating frequencies.

The results of Study 2.2 and 2.3 have shown that patients have preferences toward specific pulse frequencies although such preferences do not appear to be related to the cause and site of pain [Johnson et al. 1991a; 1991b]. Furthermore, it is generally reported that pulse frequencies between 40-100Hz [Woolf 1989] are most beneficial. Nevertheless the majority of patients using TENS on a long-term basis administer pulse frequencies below 70Hz (Study 2.2). This has been attributed in part to the difficulty in obtaining specific frequencies above 40Hz because of the logarithmic output characteristics of the frequency control dial.

Pulse Pattern

The importance of the pattern of pulse delivery in TENS analgesia was shown in Chapter 2 (Studies 2.2 and 2.3) where 23% of patients required burst mode stimulation to reduce pain. A variety of pulse patterns have been incorporated into stimulator design in an attempt to improve efficacy (including burst, modulation and random), but few of these have been systematically investigated.

Eriksson et al. [1979] has shown that trains of pulses delivered in "bursts" at high intensity (sufficient to produce muscle twitch) and low frequency (AL-TENS) were sometimes more effective in pain relief than continuous (conventional) TENS. This

observation led to the incorporation of 'burst mode' on stimulators. Nevertheless, Study 2.2 revealed that many patients utilise burst mode stimulation at an intensity insufficient to produce muscle twitch. This low intensity burst mode TENS is thought to be similar to continuous TENS and is preferred by patients for reasons of comfort [Mannheimer & Lampe 1988a].

Preliminary observations in this laboratory showed that some patients found burst stimulation uncomfortable (even at low intensity) and disliked the 'stabbing' sensation it produced. Consequently a stimulator was developed by RDG Electro-Medical in which the amplitude of the pulses (current intensity) within each 'train' or 'burst' was gradually increased (or ramped) as shown in Fig.3.1. This ramping of output intensity has been termed 'modulation' stimulation and the subjective sensation it produces is similar to stroking. To date, no studies have investigated the effect of modulating current amplitude of TENS on humans. However, Ekström and Sjölund [1988] examined the effects of modulating both pulse frequency and pulse duration (width) on the C-fibre reflex in anaesthetised rats, and found that neither improved analgesic effect.

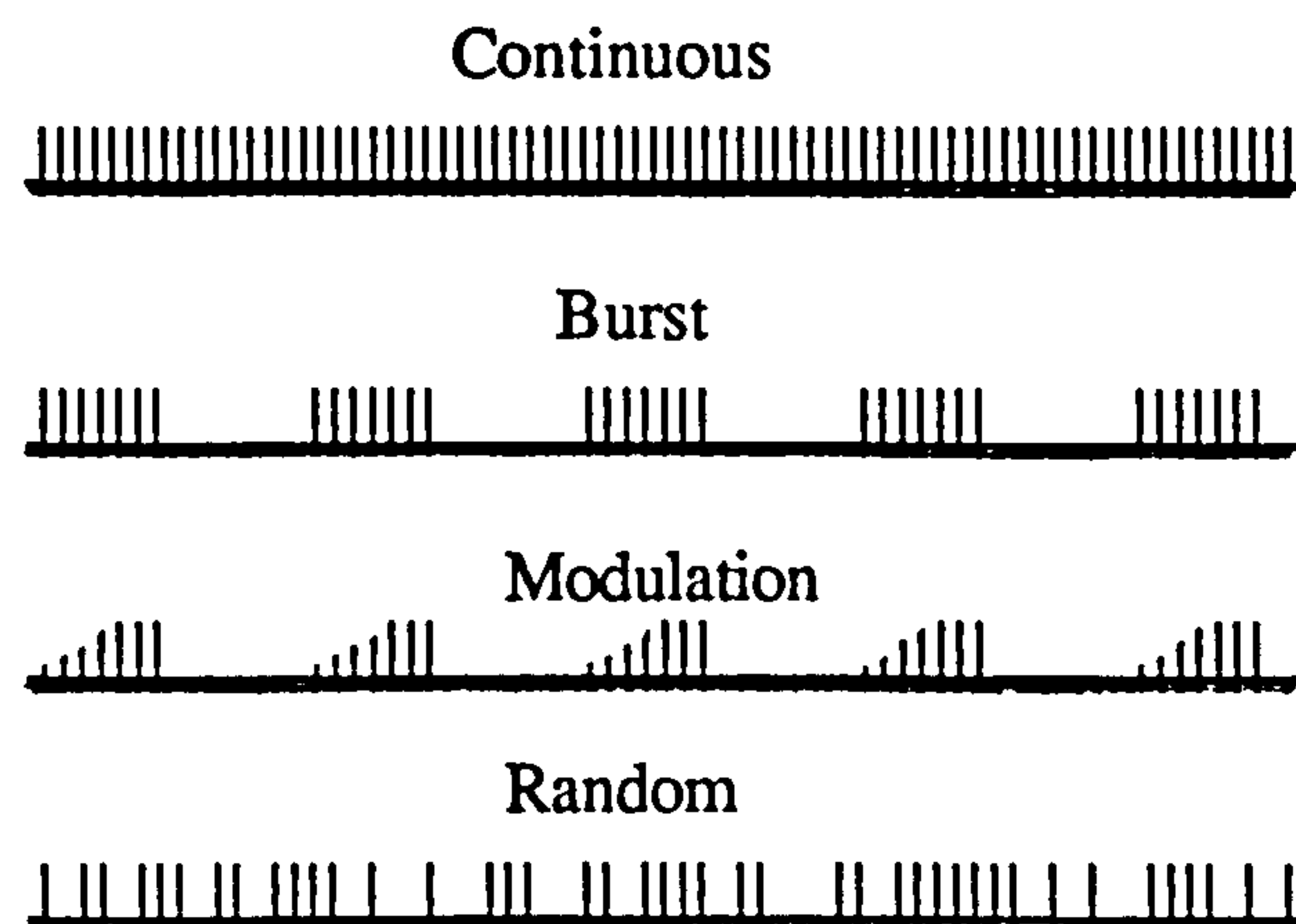


Fig.3.1 TENS pulse patterns (not drawn to scale). Continuous pulse pattern = free running delivery of regular pulses; the frequency of these pulses is regulated by the frequency control dial of the stimulator. Burst pulse pattern = regular *trains* or *bursts* of pulses, delivered at a fixed frequency of 2.3Hz. The frequency of pulses within the burst can be regulated by the frequency control dial. Modulation pulse pattern = similar to burst mode TENS except that pulse amplitude (current intensity) is increased to reach a plateau. Random pulse pattern = pulses delivered at a random frequency between 14-188Hz.

The development of tolerance to the analgesic effect of TENS may be in part the result of adaptation by the nervous system to regular, repetitive stimuli [Pomeranz & Niznick

1987]. The exact number of patients developing tolerance is not known. Bates and Nathan [1980] found that a significant number of patients dropped out of TENS treatment between the 1st and 2nd year (Table 2.1), suggesting the development of tolerance rather than placebo effects which are generally shorter lasting. In contrast, the findings of Study 2.1 that few patients return stimulators later than one year from issue, suggest that the proportion of patients developing tolerance may be small. Nevertheless, a prototype stimulator was specifically designed (by Neen Pain Management Systems) in an attempt to minimise TENS tolerance by delivering pulses in a random manner at frequencies between 14-188Hz.

Stimulation mode

Acupuncture-like TENS (AL-TENS), was developed by Eriksson and Sjölund [1976] and requires forceful phasic muscle contractions. Electrodes are placed over mixed nerves that supply muscles whose innervation arises from the same spinal root as the sensory nerves that innervate the area of pain (i.e. a related myotome, found using myotome tables). The delivery of single pulses at a low frequency and sufficient intensity to produce such phasic muscle twitches was found to be uncomfortable to patients, but this discomfort was reduced when pulses were delivered in low frequency 'trains' or 'bursts'. Consequently 'burst mode' was incorporated into stimulator design.

A major advantage of AL-TENS is that it can be applied at distant sites, but myotomally related to the site of pain, important in patients where electrical paraesthesia cannot be achieved in the painful area. Such cases include hyperaesthesia, in patients with highly sensitive skin (burns), projected pain (sciatica) and deep pain (myalgia) [Sjölund et al.1990]. Since acupuncture achieves a sustained post-treatment analgesia (sometimes up to several weeks) it has been suggested that AL-TENS could prolong the rather short post-TENS analgesia associated with conventional stimulation. Despite the clarity of Sjölund's and Eriksson's work, Chapter 2 has shown that the burst mode facility is usually utilised for reasons of comfort rather than the production of AL-TENS. As a consequence patients may not be obtaining the maximum benefit from their stimulator. Furthermore, patients who do not respond to conventional TENS may be lost as TENS failures, although a trial of AL-TENS (and other modes of stimulation) may prove successful.

Other modes of TENS have also been described [for review see Mannheimer & Lampe 1988a], including "Brief Intense" TENS [Melzack 1975b; Jeans 1979], where TENS

is administered as a continuous pulse pattern at the highest possible intensity tolerable to the patient. Such stimulation produces fasciculatory or tetanic muscle contraction and it has been suggested that the analgesic effects produced by intense TENS are due primarily to the peripheral blockade of ongoing nociceptive transmission in small diameter peripheral afferents [for review see Mannheimer & Lampe 1988b]. Although there are relatively few reports in the literature documenting clinical usage of intense TENS Strassburg et al. [1977] have used such stimulation to produce adequate analgesia for minor surgical procedures including muscle biopsies and median nerve decompressions. Thus it is apparent that there is a lack of controlled trials assessing the analgesic effects of AL-TENS (and other modes) in comparison to conventional TENS.

Finally, increasing electrode size might be expected to enhance TENS analgesia, since stimulation of a larger area of skin would activate a greater number of large diameter cutaneous afferents, and so lead to greater inhibition of nociceptive transmission in the spinal cord.

It was decided to examine the analgesic effects of different electrical characteristics of TENS on experimental pain in healthy subjects, rather than clinical pain in patients, because of difficulties in measuring clinical pain in heterogeneous patient populations (i.e. inter-individual variation in the intensity and quality of clinical pain in a group of patients, coupled with overlying psychological problems including depression, may reduce the reliability of recordings). Therefore it was necessary to produce a suitable experimental pain stimulus in order to investigate the analgesic effects of TENS.

Cold-Pressor Pain

The development of pain models capable of evaluating analgesic efficacy under standard conditions has proved to be one of the most challenging objectives in the study of pain. The important requirements of an experimental pain model in man include that the stimulus should:

- (i) be controllable, measurable and reproducible,
- (ii) provide a clear cut identification and perception of pain threshold,
- (iii) show a relation between stimulus and pain intensity,
- (iii) cause minimal tissue damage or lasting psychological or physical effects,
- (iv) be convenient to apply and rapidly terminated on demand by the subject.

For review see Gracely [1989].

Immersion of a limb in cold water has long been known to induce pain and the accompanying pressor response has been used as a stress test in the study of cardiac function. On immersion of the hand in cold water there is an initial sensation of cold, followed by pain which rapidly increases in intensity to reach a maximum within about one minute. This pain then plateaus or even subsides in a process known as adaptation, as described by Wolf and Hardy [1941]. Cold-pressor pain has been used extensively to study the effects of analgesics because it can allow for a variety of measurements relating to the pain response. Posner et al.[1985] measured pain intensity ratings on a visual analogue scale to immersion of the hand in 2°C water and found the technique a sensitive model for measuring opiate-induced analgesia in healthy volunteers. Hodes et al. [1990] allowed for two response measures, (i) the sensory-discriminative response to pain measured by ratings of pain intensity at fixed time intervals, and (ii) the affective-reactive response to pain measured by time to tolerance.

Ashton et al. [1984a] in an earlier study conducted in this laboratory, examined the effects of acupuncture, TENS and aspirin on pain threshold and pain tolerance to cold-pressor pain. They found that TENS at a frequency of 8Hz raised ice pain threshold in some normal subjects although this was accompanied by large inter-individual variation in response to TENS. TENS at 100Hz was ineffective.

Aim of Chapter 3

The aim of the present chapter was to examine the analgesic effects of different electrical characteristics of TENS by investigating the effects of:

- (i) pulse frequencies (Exp. 3.1),
- (ii) pulse patterns (Exp. 3.2),
- (iii) stimulation modes (Exp. 3.3).

on cold-pressor pain in healthy subjects.

Time to pain threshold and pain tolerance were used as measures of analgesic activity. However, because of the unreliability of pain tolerance in Exp. 3.1 and Exp. 3.2, pain intensity rating (recorded on a visual analogue scale) was recorded in Exp. 3.3.

THE EXPERIMENTS

General Methods

Subjects were recruited by advertising on departmental noticeboards and those taking part in the experiment were rewarded with a book token (value £3.50). Prior to the start of the experiment the nature of the experiment was explained to each subject, and in addition he or she was given a small printed protocol.

Pain Induction

Pain threshold and tolerance measurements were taken during 6 experimental cycles each lasting 15 minutes (see Fig.3.2). The non-dominant hand was immersed in warm water (37°C) for 5 minutes, and then plunged (up to the first wrist crease) into water maintained at 0°C in a cold water bath. Subjects silently observed sensations in the immersed hand until it became definitely painful, i.e. 'physically hurts', when they made the statement 'Pain'. The hand remained immersed until the sensation became 'unbearable', but not numb, at which point the statement 'Out' was made and the hand withdrawn. Pain threshold was recorded as the time from immersion in the cold water to the statement 'Pain' and pain tolerance as the time from 'Pain' to 'Out'.

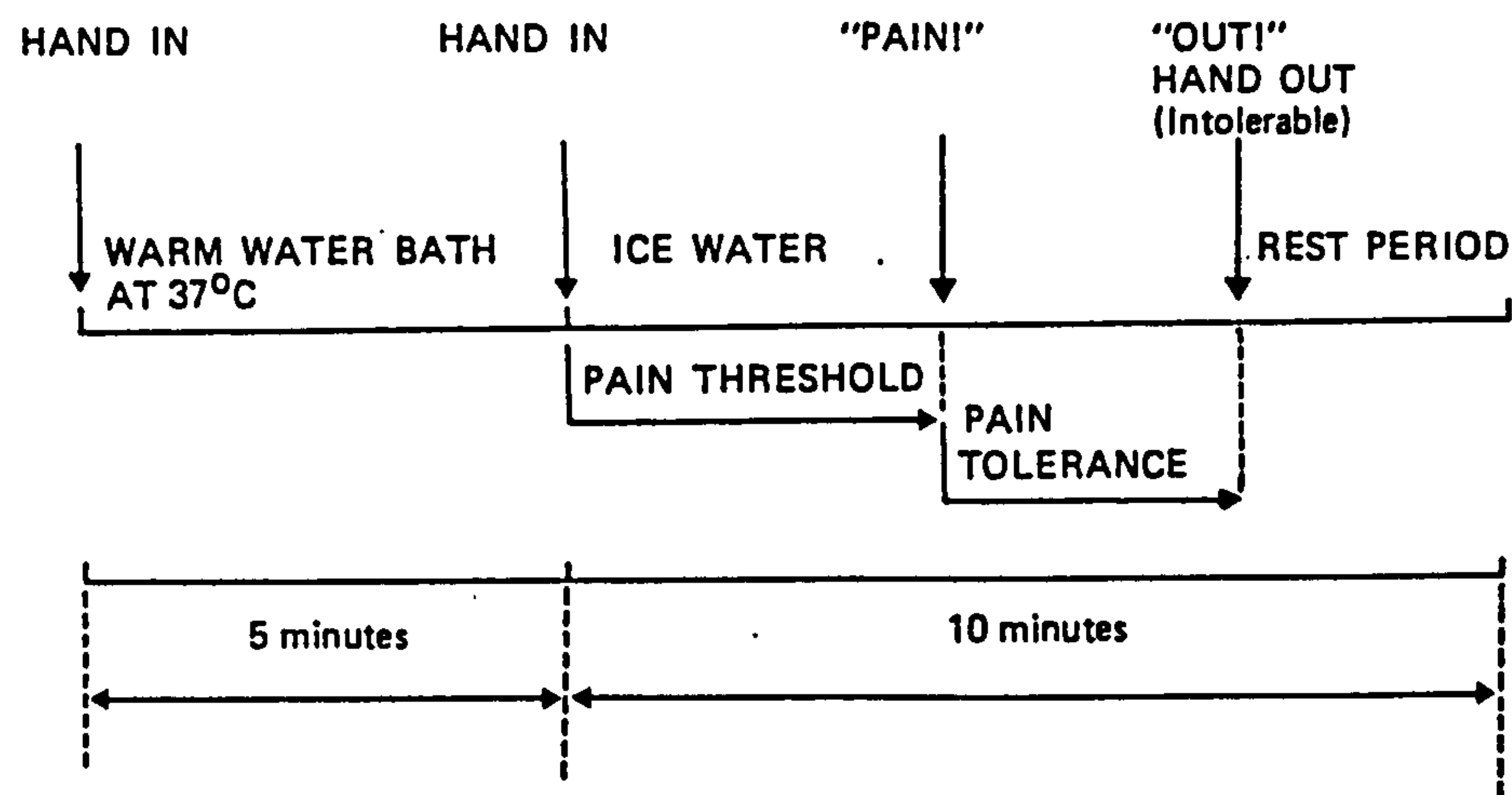


Fig.3.2 Cold-pressor pain (one cycle).

Subjects were requested to withdraw the hand if tolerance had not been reached by 5 minutes or the hand became numb. Subjects rested while filling in an Eysenck Personality Questionnaire (EPQ) or relaxed with light reading material until the start of the next cycle. Two pre-treatment cycles were followed by four treatment cycles. A familiarisation session was conducted prior to the start of the experiment.

TENS Treatment

A Microtens battery powered portable stimulator was used to produce TENS. Pulse width (fixed at 200 μ s), electrode impedance, current intensity and pulse frequency were monitored with a Frye Electronics Type 4000 TENS Analyser (Frye Analyser). TENS was delivered via two 2 cm² disposable electrodes, placed 1 cm apart (cathode proximal) on the ventral surface of the arm overlying the median nerve, 3 cm above the first wrist crease. Prior to immersion in warm water, the intensity of TENS was raised until the subject rated it as 'strong but comfortable', and appropriate adjustments to maintain this intensity level were made during the course of the experiment. A plateau of subjective sensation was usually reached by 20 minutes.

Sham TENS (no stimulation) was administered using a modified stimulator (no current output), with a flashing 'on' light and a coloured suggestion that

"The TENS unit is stimulating at a level that is expected to produce a response even though you may not feel it."

This was reinforced by a digital display on the Frye Analyser. Subjects rarely questioned this procedure. Control TENS subjects were aware that TENS was not switched on.

Statistical analysis

Data obtained from each experiment was analysed by calculating mean \pm SD for each cycle. As results showed marked heteroscedascity (i.e. increasing variance (SD) with increasing pain threshold/tolerance) data was logarithmically transformed prior to parametric statistical analysis [Matthews et al. 1990]. Differences between the two pre-treatment cycles were examined using a paired t-test. A mean pre-treatment baseline was calculated for each individual from the two pre-treatment measures. Differences in pre-treatment mean between groups were tested using one-way ANOVA. During-treatment changes were calculated by subtracting pre-treatment mean from each of the during-treatment cycles. Total change in ice pain threshold/tolerance was calculated for each group as the area under the curve (change in ice pain threshold/50minutes). Differences between active TENS (TENS) groups and sham TENS (sham) were examined using unpaired t-tests and differences between active TENS groups using one-way ANOVA (for further details see Appendix B).

Experiment 3.1.**Analgesic effects of different frequencies of TENS on cold-pressor pain in healthy subjects**

This investigation was undertaken to determine the effects of a range of frequencies of continuous mode TENS on cold-pressor pain.

Subjects and procedure

Eighty three TENS-naïve healthy subjects (female n=36, male n=47; age range 18-35 years of age), were randomly allocated to one of seven TENS treatment regimes (pulse pattern=continuous); 10Hz TENS, 20Hz TENS, 40Hz TENS, 80Hz TENS, 160Hz TENS, sham TENS and control TENS. Experimental procedures have been described previously (see Pain Induction). During TENS, subjects were requested to increase the intensity (pulse amplitude) of stimulation to produce a 'strong but comfortable' paraesthesia.

Mean \pm SD TENS intensity levels were:

10Hz=5.4 \pm 1.0mA above SDT
 20Hz=5.7 \pm 2.7mA above SDT
 40Hz=4.9 \pm 1.5mA above SDT
 80Hz=5.0 \pm 2.5mA above SDT
 160Hz=4.6 \pm 1.6mA above SDT

No significant differences in intensity were found across the treatment groups (one-way ANOVA). Because of equipment unavailability no intensity data was obtained for 22 subjects. Control and sham stimulators were not switched on.

Results of Experiment 3.1

The mean \pm SD results for ice pain threshold and ice pain tolerance are shown in Table 3.1.

Ice Pain Threshold: Marked heteroscedascity (increasing variance (SD) with increasing time to pain threshold and tolerance) was observed (Table 3.1), thus, data was logarithmically transformed prior to statistical analysis. No significant differences were found between the two pre-treatment observations (paired t-test), and mean pre-treatment threshold was calculated for each individual. One-way ANOVA showed no significant differences in pre-treatment mean across the treatment groups; thus, change in pain threshold during treatment for each cycle, and total change (area under curve), was calculated by subtracting pre-treatment mean for each individual from successive 'during treatment' observations.

Treatment		Pre treatment (-25 min)	Pre treatment (-10 min)	During treatment (+5 min)	During treatment (+20 min)	During treatment (+35 min)	During treatment (+50 min)
Pain threshold							
Control	(n = 12)	11.8 ± 5.4	12.6 ± 4.7	12.2 ± 4.0	13.3 ± 5.5	12.0 ± 3.7	13.4 ± 4.1
Sham	(n = 11)	14.2 ± 7.6	17.6 ± 9.5	18.2 ± 14.4	16.7 ± 6.1	16.7 ± 7.1	18.3 ± 8.2
10 Hz TENS	(n = 12)	16.3 ± 13.9	18.3 ± 13.6	23.6 ± 20.7	23.9 ± 19.6	25.1 ± 21.2	26.6 ± 25.5
20 Hz TENS	(n = 12)	22.2 ± 14.6	22.3 ± 19.8	32.7 ± 37.7	38.0 ± 57.5	35.1 ± 29.6	39.6 ± 39.2
40 Hz TENS	(n = 12)	22.0 ± 8.4	23.4 ± 9.1	33.0 ± 27.5	39.0 ± 41.5	45.6 ± 47.1	42.1 ± 37.5
80 Hz TENS	(n = 12)	24.7 ± 17.1	26.5 ± 14.6	33.0 ± 20.4	37.2 ± 25.6	46.2 ± 32.9	47.7 ± 33.2
160 Hz TENS	(n = 12)	20.7 ± 11.2	21.1 ± 16.9	23.4 ± 8.9	29.4 ± 27.1	27.0 ± 16.0	34.8 ± 31.1
Pain tolerance							
Control	(n = 12)	24.8 ± 11.6	23.8 ± 19.7	22.5 ± 20.3	21.3 ± 22.1	23.6 ± 25.6	24.3 ± 27.9
Sham	(n = 11)	38.3 ± 43.6	40.4 ± 47.3	44.0 ± 59.1	35.5 ± 33.9	37.4 ± 31.6	33.6 ± 30.8
10 Hz TENS	(n = 11)	44.0 ± 59.2	37.9 ± 32.1	34.1 ± 28.0	34.6 ± 22.8	42.1 ± 42.3	37.0 ± 24.0
20 Hz TENS	(n = 12)	94.0 ± 87.4	60.5 ± 46.8	70.5 ± 49.9	73.9 ± 53.7	62.8 ± 42.7	78.1 ± 61.3
40 Hz TENS	(n = 10)	57.5 ± 58.1	74.7 ± 84.4	72.0 ± 85.9	55.8 ± 66.6	57.2 ± 74.0	44.4 ± 43.2
80 Hz TENS	(n = 7)	70.9 ± 65.2	61.9 ± 43.9	65.0 ± 50.9	55.7 ± 31.5	70.9 ± 67.8	78.4 ± 77.5
160 Hz TENS	(n = 9)	44.4 ± 61.7	41.8 ± 67.1	32.1 ± 31.7	21.2 ± 10.9	23.8 ± 11.3	23.7 ± 10.5

Table 3.1 Mean±SD (s) ice pain threshold and ice pain tolerance by TENS treatment (continuous mode) and by time (6 successive observations at 15 minute intervals) for different pulse frequencies in healthy subjects (Exp.3.1).

TENS significantly increased ice pain threshold (Fig.3.3), with a rapid onset of analgesia occurring within 5 minutes of 'switch on'.

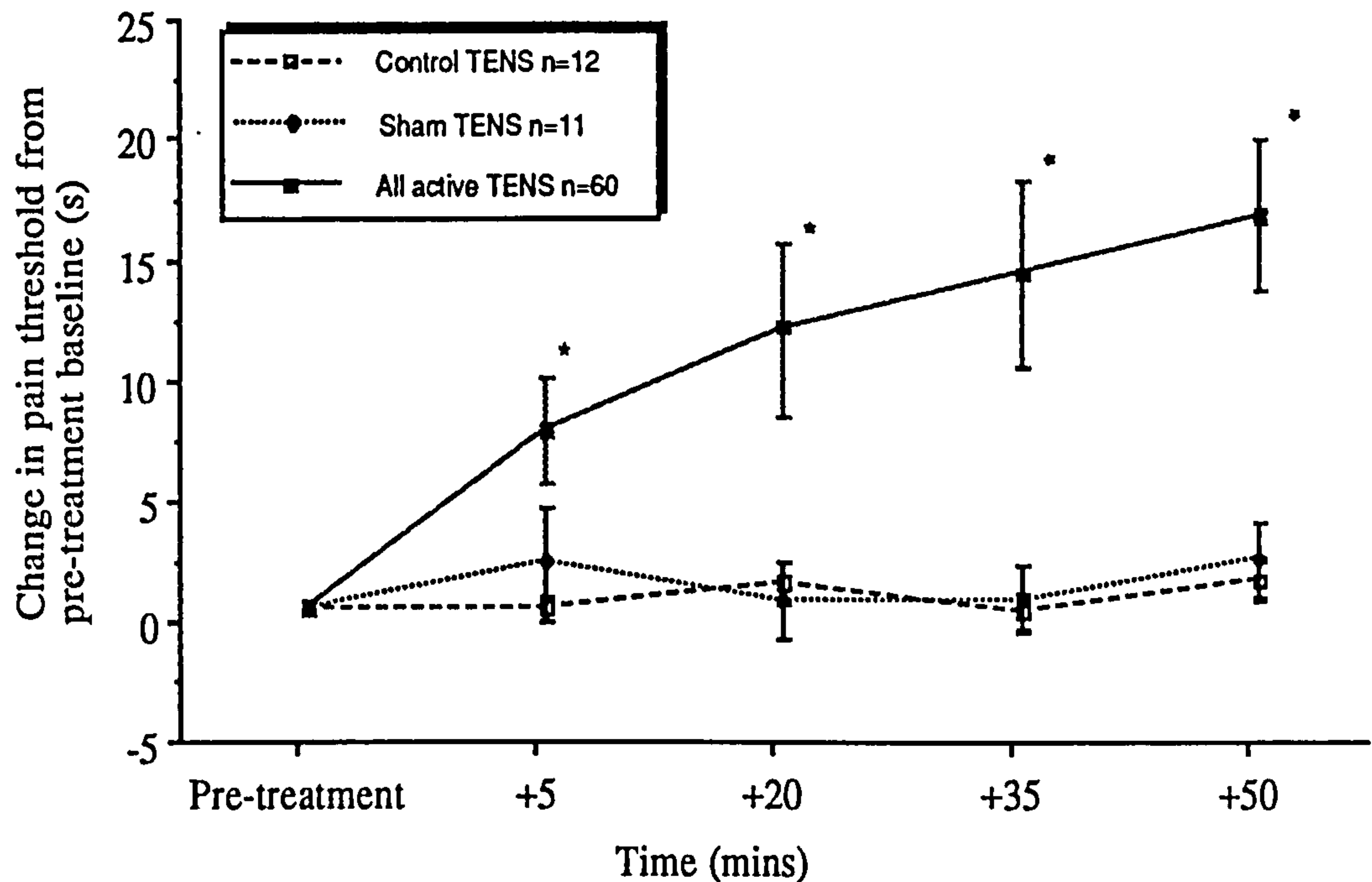


Fig.3.3 Mean \pm SE change in ice pain threshold during TENS in healthy subjects (Exp.3.1). (*= $P < 0.05$, unpaired t-test, TENS v sham).

Total increase in ice pain threshold across the 50 minute treatment session was calculated for each treatment group as the area under curve of change in pain threshold against the 50 minute session. No significant differences were found between the control and sham TENS (unpaired t-test).

A bell-shaped relationship was observed in which increased frequency (above 10Hz) produced greater analgesia up to a maximum between 20 and 80Hz, but analgesic effect declined at higher frequencies. A quadratic trend with log frequency across the actively treated groups (i.e. 10Hz, 20Hz, 40Hz, 80Hz, 160Hz) was found although just failing to reach significance ($F_{1:75} = 2.30$ $P = +0.1$, one-way ANOVA) due to the large increases in variance accompanying increases in threshold (Fig.3.4).

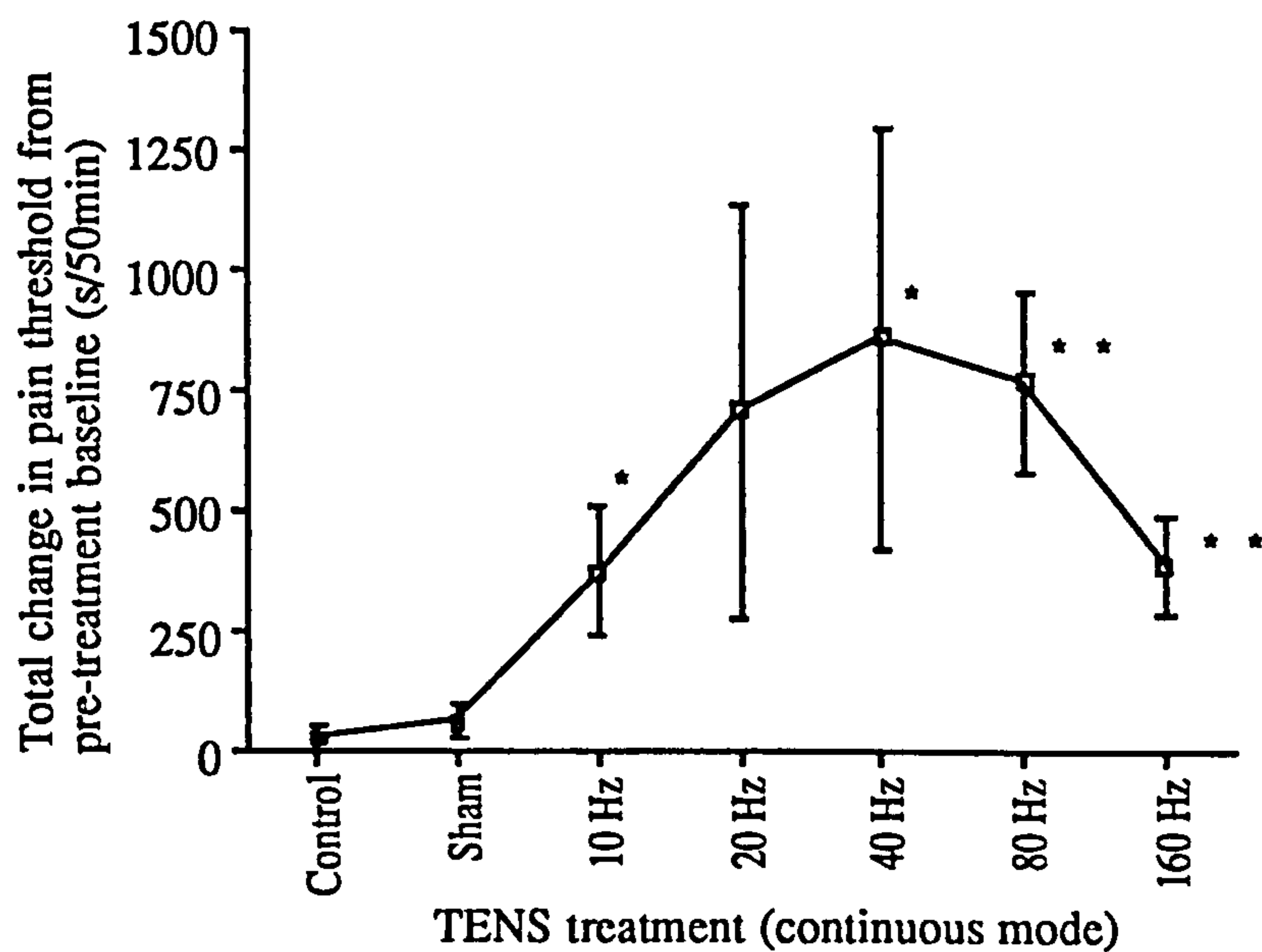


Fig.3.4 Mean±SE total change in ice pain threshold during a 50 minute treatment session for different TENS pulse frequencies in healthy subjects (Exp.3.1). Note the logarithmic scale for pulse frequency; (n=12 for each group except sham where n=11). Unpaired t-test total change TENS v sham, *=p<0.05, **=p<0.01.

Ice Pain Tolerance: Eleven subjects were excluded from the data as they tolerated cold immersion of the hand up to the 5 minute limit, making it impossible to assess the magnitude of subsequent changes. One-way ANOVA showed no significant difference across the treatment groups; thus change in ice pain tolerance during treatment and total change (area under curve), was calculated for each individual. No significant differences were found between the combined mean of the active TENS treatment and sham (unpaired t-test, Fig.3.5)

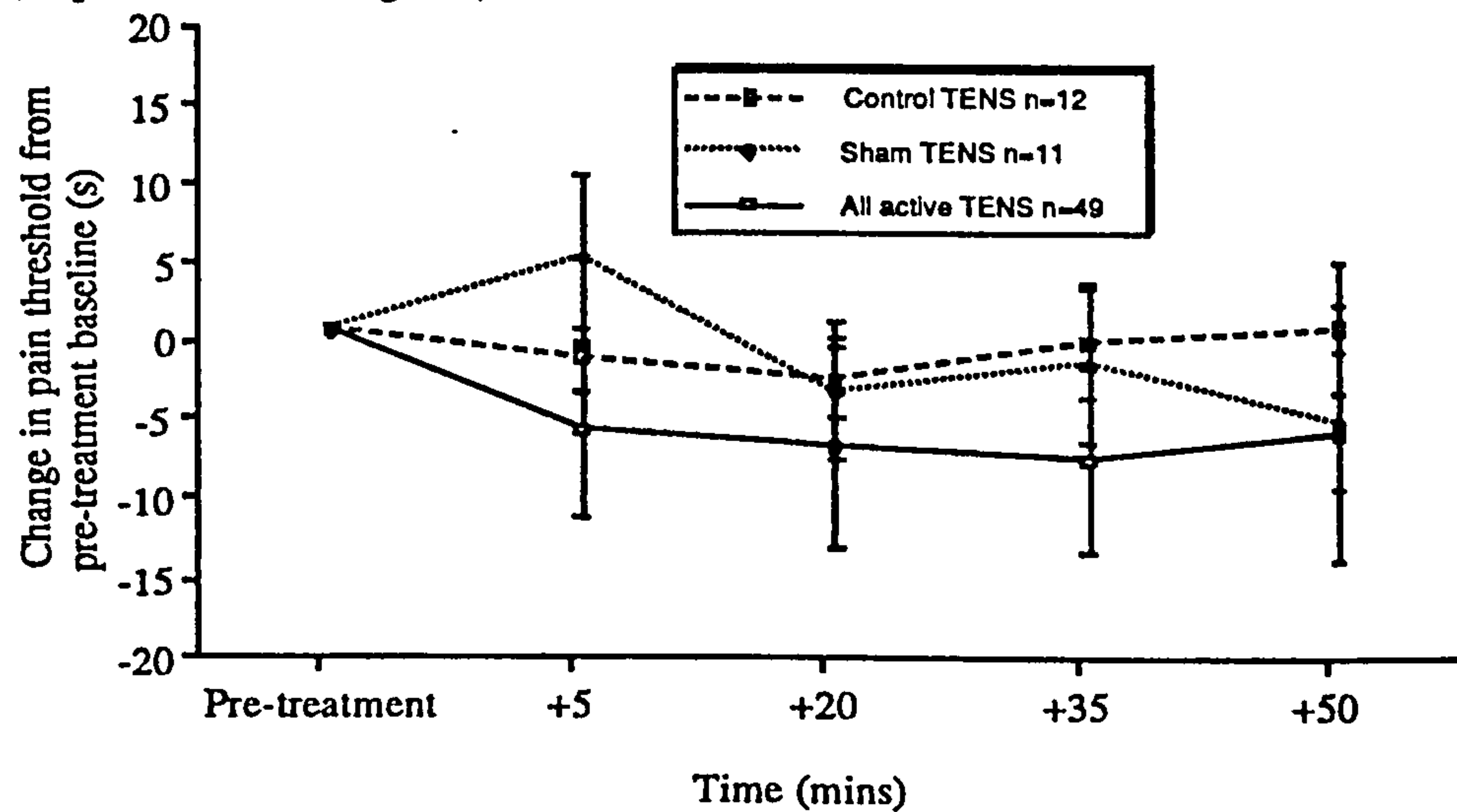


Fig.3.5 Mean±SE change in ice pain tolerance during a 50 minute treatment session in healthy subjects (Exp.3.1). The 'all active TENS' group consisted of the combined mean of the 10Hz, 20Hz, 40Hz, 80Hz and 160Hz groups.

No significant differences in the total change in ice pain tolerance were found between different active TENS groups (one-way ANOVA on total change in ice pain threshold across active TENS groups, Fig.3.6). Large variations in inter-individual response was observed.

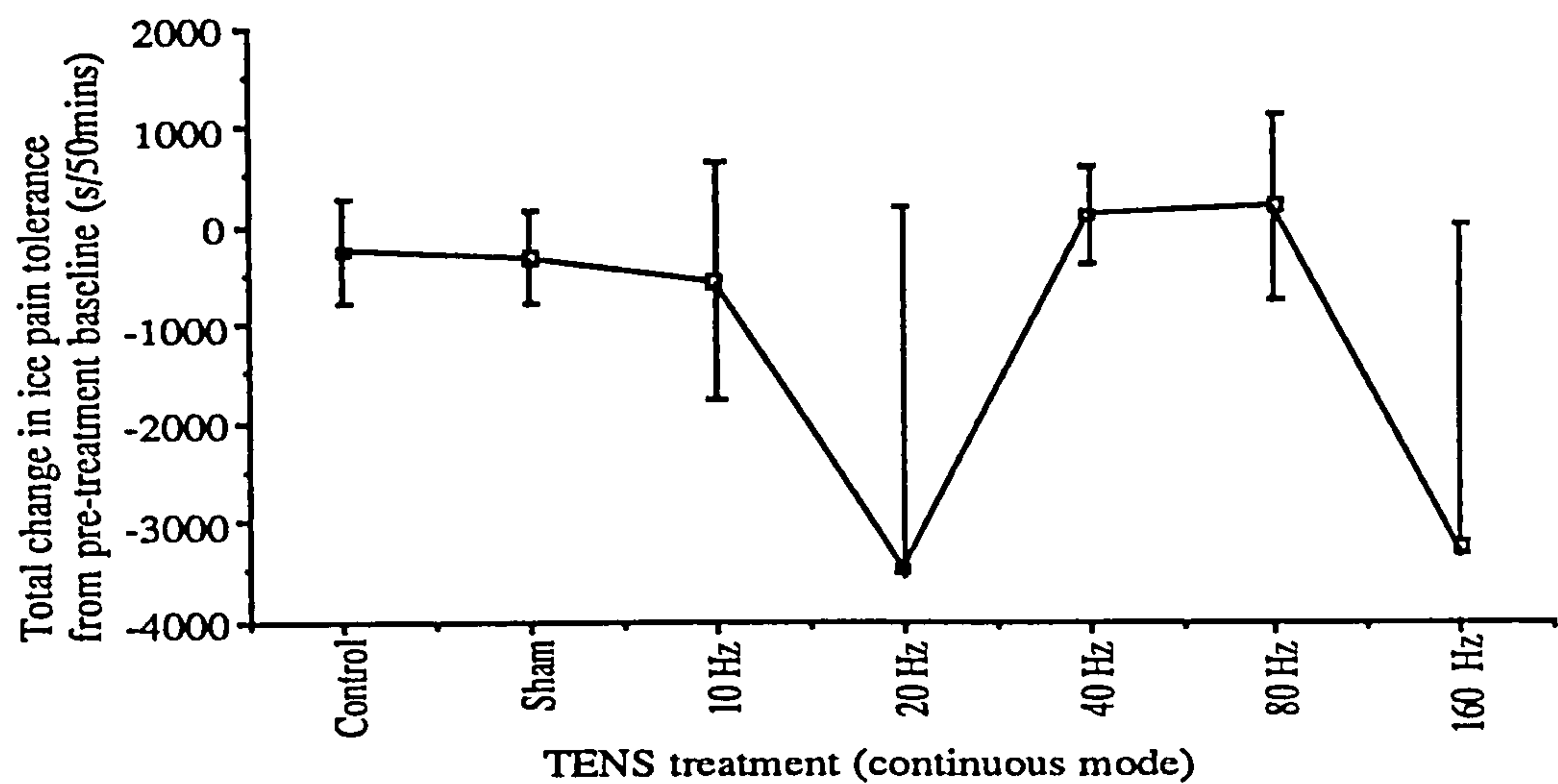


Fig.3.6 Mean±SE change in ice pain tolerance during a 50 minute treatment session for different TENS pulse frequencies in healthy subjects (Exp.3.1). Note the logarithmic scale for pulse frequency; (see Table 3.1 for respective n values)

Personality Variabilities: Mean±SD EPQ fell within the norms for students (Table 3.2). No significant differences were found between males and females. Relationships between personality variables and baseline threshold, tolerance and the magnitude of response to TENS were also small and non significant (Pearson correlation coefficient).

		P (Psychoticism)	E (Extroversion)	N (Neuroticism)	L (Lie)
Experimental results					
Female	(n = 36)	3.6 ± 2.8	14.3 ± 5.1	11.6 ± 5.1	6.0 ± 2.7
Male	(n = 47)	4.6 ± 3.1	14.7 ± 4.3	10.0 ± 5.7	6.1 ± 4.1
Both	(n = 83)	4.2 ± 3.0	14.5 ± 4.7	10.7 ± 5.4	6.0 ± 3.6
Medical student norms*					
Female	(n = 27)	3.4 ± 2.8	13.3 ± 4.7	9.7 ± 5.3	7.2 ± 3.8
Male	(n = 57)	4.8 ± 3.1	14.0 ± 4.0	9.1 ± 4.4	6.5 ± 3.8
Both	(n = 84)	4.1 ± 2.9	13.7 ± 4.4	9.4 ± 4.8	6.8 ± 3.8

All correlations between personality variables and baseline Ice Pain Threshold and Tolerance were small and non significant.

(*Values taken from Eysenck HJM Eysenck SBG, (1975). Manual of the Eysenck Personality Questionnaire (Junior and Adult). Essex: Hodder and Stoughton).

Table 3.2 Mean±SD Eysenck personality questionnaire scores (Exp.3.1).

Main findings of Experiment 3.1

- (i) TENS produced a rapid and significant increase in ice pain threshold, but not ice pain tolerance when compared to sham TENS and control TENS.
- (ii) Large inter-subject variability in response to TENS accompanied such changes.
- (iii) Pulse frequencies between 20-80Hz produced the greatest elevation of ice pain threshold, although frequencies above and below also produced significant increases in ice pain threshold but of lesser magnitude.
- (iv) A pulse frequency of 80Hz produced a large and reproducible (due to small inter-subject variability in response) increase in ice pain threshold.
- (v) No significant effects of TENS on ice pain tolerance were observed due to the large inter-subject variability in response.
- (vi) No relationships between EPQ and baseline threshold, tolerance or response to TENS were observed.

Experiment 3.2

Analgesic effects of different pulse patterns of TENS on cold-pressor pain in healthy subjects.

The aim of Experiment 3.2 was to compare the effects of burst, modulation, random, continuous and double-sized electrode TENS, delivered at a fixed pulse frequency (80Hz) and fixed intensity ('strong but comfortable') on cold-pressor pain in healthy subjects.

Subjects and procedure

Eighty four TENS-naive healthy university students (female n=40, male n=44; age range=17-35 years of age) were randomly allocated to one of five TENS treatment regimes referred to as:

- burst TENS
- modulation TENS
- random TENS
- continuous TENS
- double-sized electrode continuous TENS (doub.size.elec.).

The respective pulse patterns in each of the groups are shown in Fig.3.1. All stimulators were preset to deliver a pulse frequency of 80Hz, except random TENS in which the frequency ranged between 14-188Hz. TENS was delivered via two 2 cm² disposable electrodes (double sized electrode group used 4 cm²) placed 1 cm apart on the ventral surface of the arm overlying the median nerve, 3 cm above the first wrist crease. Experimental procedures have been described previously (see Pain Induction). During treatment cycles, TENS was maintained at a 'strong but comfortable' level. The results previously reported (Exp. 3.1) for sham and control TENS (in which the stimulator was not switched on) were used to demonstrate generalised treatment effects, and statistical comparisons between active TENS treatments (burst, modulation, random, continuous and double sized electrodes) were made.

Mean±SD TENS intensity levels were:

burst TENS	5.1±1.7 mA above SDT
modulation TENS	18.7±9.7 mA above SDT
random TENS	6.7±5.6 mA above SDT
continuous TENS	5.9±4.0 mA above SDT
doub. size. elect. TENS	4.8±3.0 mA.above SDT

The intensity of modulation TENS was found to be significantly higher than other treatment groups ($P < 0.001$, unpaired t-test). No significant differences (one-way ANOVA) were found across the remaining active treatment groups.

Results of Experiment 3.2

The mean \pm SD results for ice pain threshold and ice pain tolerance are shown in Table 3.3.

Ice Pain Threshold: Marked heteroscedascity was observed and the data was logarithmically transformed prior to statistical analysis. Changes in ice pain threshold during treatment cycles, and total change across the 50 minute treatment session, were calculated as described in Exp. 3.1 (paired t-test showed no significant differences between the two pre-treatment cycles, and one-way ANOVA showed no differences across the treatment groups).

A significant increase in ice pain threshold occurred within five minutes of 'switch on' when the mean of all active TENS treatment groups combined, were compared to sham (Mean \pm SD 'during' cycle 1 (+5min): sham (Exp. 3.1)= 1.7 ± 6.8 s ($n=11$), all active TENS (Exp. 3.2)= 6.2 ± 6.5 s ($n=60$), $P < 0.05$, unpaired t-test). All active TENS groups showed a significant elevation in total change in ice pain threshold over the 50 minute treatment session when compared to sham TENS (Fig.3.7).

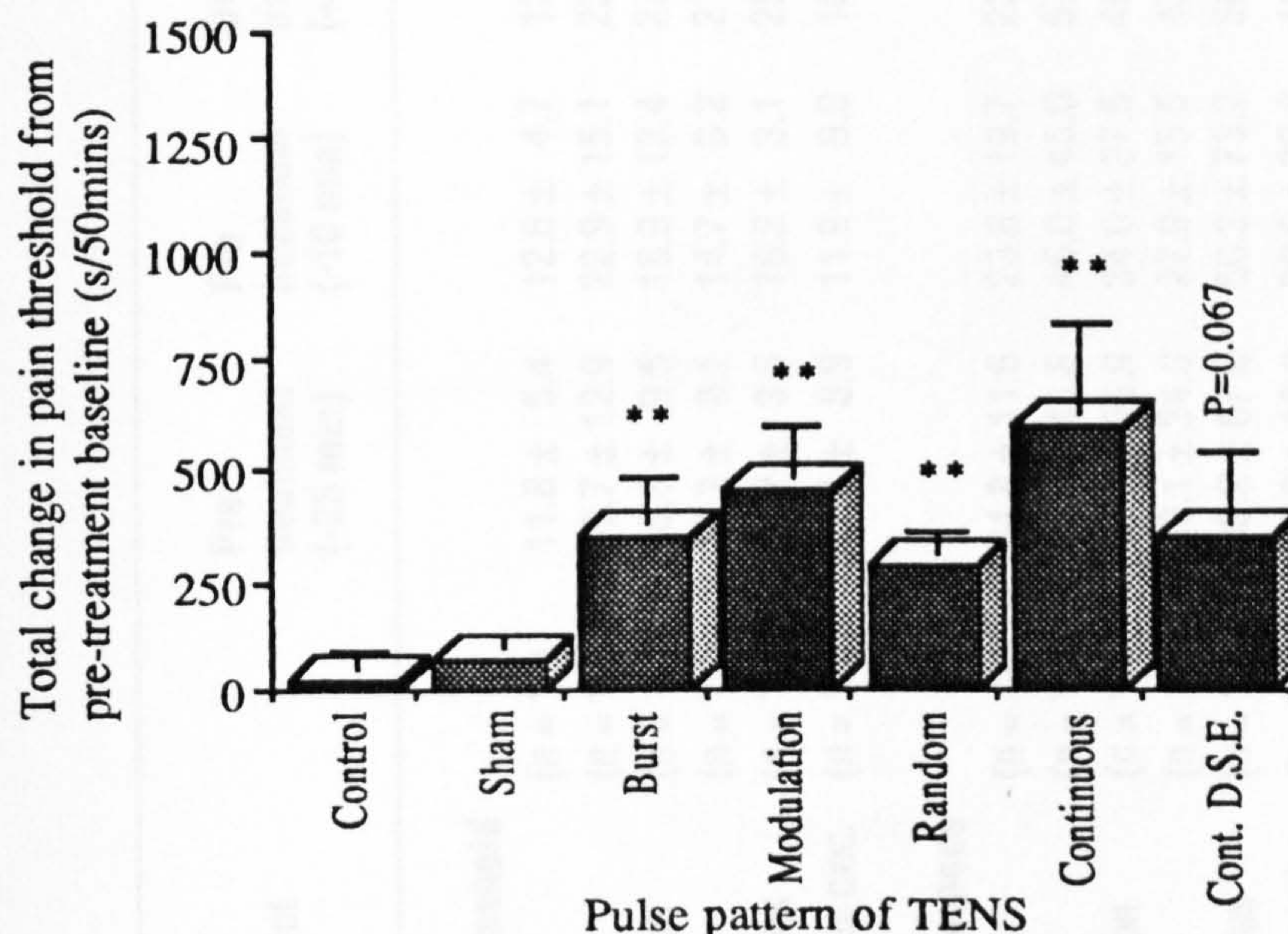


Fig.3.7 Mean \pm SE total change in ice pain threshold during a 50 minute treatment session for different TENS pulse patterns in healthy subjects (Exp.3.2). (**= $P < 0.01$, unpaired t-test, TENS group v sham; $n=12$ for each group except sham where $n=11$).

Treatment		Pre treatment (-25 min)	Pre treatment (-10 min)	During treatment (+5 min)	During treatment (+20 min)	During treatment (+35 min)	During treatment (+50 min)
Pain threshold							
Control	(n = 12)	11.8 ± 5.4	12.6 ± 4.7	12.2 ± 4.0	13.3 ± 5.5	12.0 ± 3.7	13.4 ± 4.1
Burst	(n = 12)	19.7 ± 12.9	22.9 ± 15.1	23.7 ± 14.2	25.6 ± 13.2	33.4 ± 24.6	32.8 ± 26.5
Modulation	(n = 12)	15.3 ± 9.5	18.9 ± 13.4	27.3 ± 19.8	26.7 ± 17.6	25.6 ± 20.1	26.7 ± 20.6
Random	(n = 12)	16.3 ± 9.1	14.7 ± 9.2	21.2 ± 10.7	20.8 ± 9.6	22.3 ± 13.8	21.3 ± 12.4
Continuous	(n = 12)	18.2 ± 3.5	18.2 ± 3.1	25.7 ± 14.7	31.5 ± 25.9	31.8 ± 22.6	35.6 ± 25.6
†Doub. size elec.	(n = 12)	12.1 ± 8.9	11.9 ± 9.9	16.9 ± 11.2	19.6 ± 13.7	21.0 ± 18.0	20.5 ± 16.7
Pain tolerance							
Control	(n = 12)	24.8 ± 11.6	23.8 ± 19.7	22.5 ± 20.3	21.3 ± 22.1	23.6 ± 25.6	24.3 ± 27.9
Burst	(n = 12)	51.1 ± 45.8	46.0 ± 45.0	57.2 ± 71.4	57.2 ± 68.5	47.2 ± 63.3	56.6 ± 83.0
Modulation	(n = 10)	40.7 ± 56.9	34.0 ± 37.5	49.6 ± 65.8	37.8 ± 45.4	31.5 ± 27.6	29.9 ± 23.5
Random	(n = 11)	39.1 ± 34.0	27.9 ± 15.5	43.3 ± 33.0	45.5 ± 46.6	44.6 ± 45.6	51.3 ± 55.7
Continuous	(n = 12)	49.2 ± 67.6	60.2 ± 73.2	56.6 ± 78.4	64.0 ± 78.0	83.7 ± 96.5	95.4 ± 111.7
Doub. size elec.	(n = 12)	19.0 ± 13.0	20.6 ± 20.8	18.2 ± 11.8	17.9 ± 12.9	19.2 ± 18.3	23.2 ± 23.4

Table 3.3 Mean±SD (s) ice pain threshold and ice pain tolerance by TENS treatment (continuous mode) and by time (6 successive observations at 15 minute intervals) for different pulse patterns in healthy subjects (Exp.3.2).

Continuous TENS produced the greatest magnitude of response but the response was reduced when the size of electrode was doubled. Random TENS produced the smallest increase in ice pain threshold but also the least inter-individual variation in response. One-way ANOVA on the total change in pain threshold between the active TENS group showed no significant differences between active TENS groups ($F_{4:55}=0.79$). No significant differences in total change in ice pain threshold were found between the continuous TENS group used in the present study and those found in Exp. 3.1 (Mean \pm SD total change (s/50min): Exp. 3.1=+712 \pm 582, Exp. 3.2=+601 \pm 696, $P=0.48$, unpaired t-test).

Ice Pain Tolerance: Three subjects were excluded from the data as they tolerated cold immersion of the hand up to the 5 minute limit. Changes in ice pain tolerance were calculated in an analogous manner to ice pain threshold data. Differences were observed between the combined mean of active TENS groups and sham TENS (Mean \pm SD total change (s/50min): combined active TENS=+407 \pm 1372, sham=-43 \pm 378, $P<0.05$, unpaired t-test). One-way ANOVA showed no significant differences in the change in pain tolerance between active TENS groups ($F_{4:52}=1.13$, see Fig 3.8).

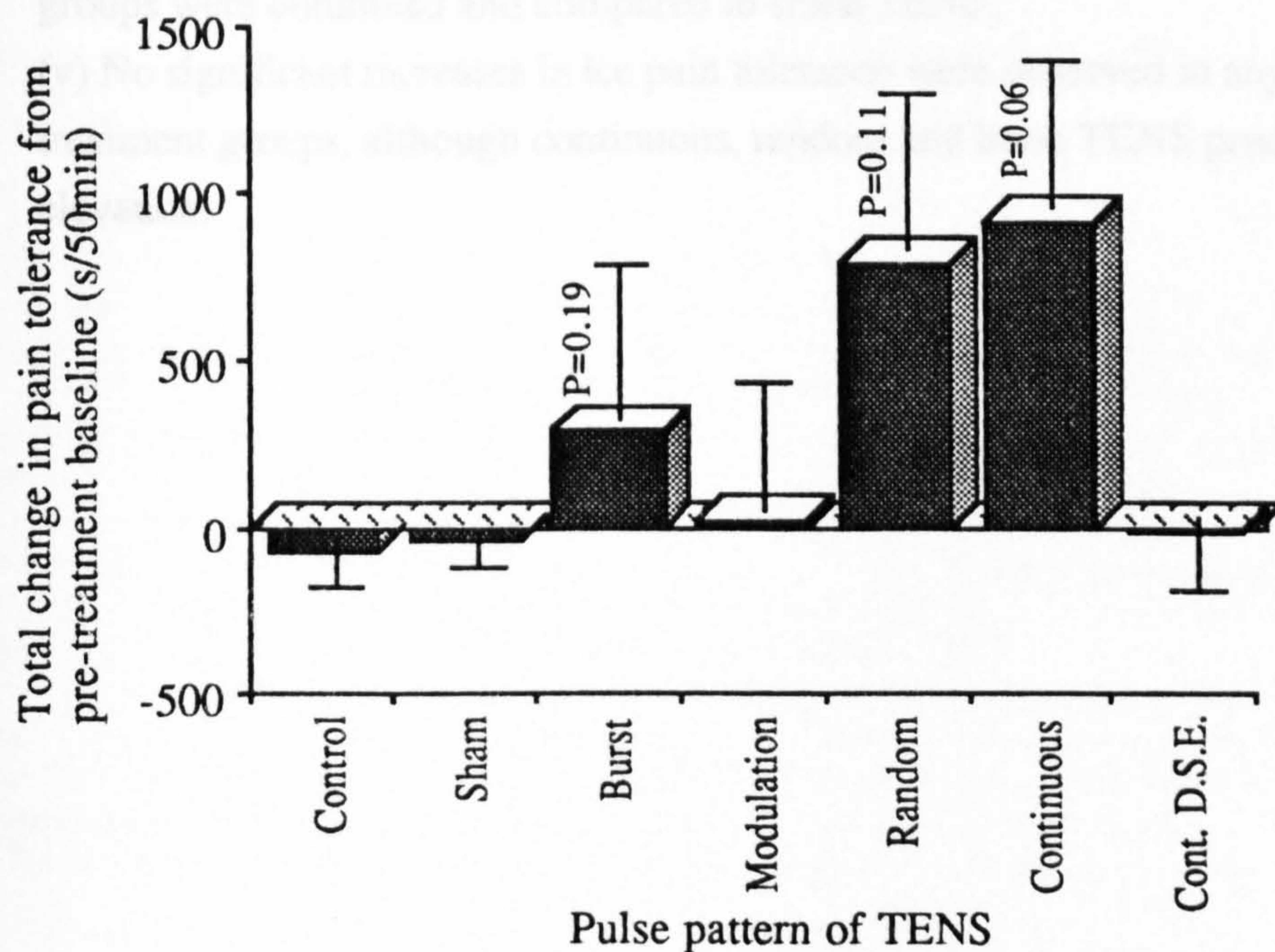


Fig.3.8 Mean \pm SE total change in ice pain tolerance during a 50 minute treatment session for different TENS pulse patterns in healthy subjects (Exp.3.2). (P value = unpaired t-test, TENS group v sham; n=12 for each group except sham where n=11).

Continuous TENS produced the largest increase in ice pain tolerance but increasing the size of the electrodes reduced the magnitude of this response (Fig.3.8). As in Exp. 3.1, large inter-individual response were observed across the treatment groups.

Personality: Mean \pm SD Eysenck Personality Questionnaire results fell within the norms for students (Table 3.2) but no relationships were observed with baseline ice pain threshold, baseline ice pain tolerance and the magnitude of response (total change) to TENS over the 4 treatment cycles.

Main findings of Experiment 3.2

- (i) Active TENS groups produced a significant elevation in ice pain threshold when compared to sham TENS.
- (ii) No significant differences in the magnitude of increase in ice pain threshold were observed across the active TENS groups, although continuous TENS produced the largest magnitude of response.
- (iii) The increase in ice pain threshold achieved during continuous TENS was reduced (non-significantly) when the size of the electrodes were doubled.
- (iv) A significant increase in ice pain tolerance was observed when all active TENS groups were combined and compared to sham TENS.
- (v) No significant increases in ice pain tolerance were observed in any of the active treatment groups, although continuous, random and burst TENS produced an elevation.

Experiment 3.3

Analgesic effects of different modes of TENS on cold-pressor pain in healthy subjects.

The aim of Experiment 3.3 was to compare the effects of 4 stimulation modes of TENS:

- (a) continuous mode TENS, applied to produce electrical paraesthesia within the painful area at:
 - (i) low ('conventional' TENS) intensity,
 - (ii) high ('intense' TENS) intensity
- (b) burst mode TENS, applied to a muscle mass distant to the site of pain but myotomally related to the painful area at:
 - (iii) low ('burst' TENS) intensity,
 - (iv) high (AL-TENS) intensity.

Subjects and procedures

Sixty TENS-naïve healthy university students (female n=30, male n=30; age range=19-35 years of age) were randomly allocated to one of five TENS treatment groups referred to as; conventional TENS, intense TENS, burst TENS, AL-TENS, sham TENS. Stimulating characteristics and site of electrode application are described in Table 3.4.

STIMULATING MODE	ELECTRODE PLACEMENT	PULSE PATTERN	PULSE FREQUENCY	PULSE INTENSITY (Amplitude)	MUSCLE ACTIVITY
Sham	Wrist & arm	None	None	None	None
Conventional	Wrist/Median nerve	Continuous	80Hz	Strong but comfortable	None
Intense	Wrist/Median nerve	Continuous	80Hz	Intense	Tetanic/fasciculatory
Burst	Arm/Brachioradialis	Burst (2.3Hz)	80Hz	Strong but comfortable	None
Acupuncture-Like	Arm/Brachioradialis	Burst (2.3Hz)	80Hz	Intense	Twitching/phasic

Table 3.4 Modes of TENS. The different electrical characteristics of TENS used in Exp. 3.3. Electrodes were applied to the ipsilateral arm with respect to the 'painful' hand.

Appropriate adjustments in pulse amplitude (intensity) were made by the subject during the course of the experiment to maintain the appropriate intensity level. Mean \pm SD TENS intensity levels were:

conventional TENS	2.4 \pm 1.4mA above SDT
intense TENS	8.9 \pm 8.0mA above SDT
burst TENS	2.7 \pm 0.9mA above SDT
AL-TENS	14.2 \pm 8.4mA above SDT

One-way ANOVA found significant differences between these groups ($F_{3,43}=11.25$, $P<0.01$).

Pain Induction: Slight modifications were made to the procedure. Pain threshold and pain intensity rating measurements were taken during 8 experimental cycles each lasting 10 minutes (Fig.3.9). Pain threshold was recorded as previously described (Exp. 3.1 and 3.2). After the report of 'pain' the subjects hand remained immersed in cold water for a further 20 seconds, and on removal of the hand subjects placed a cross on a visual analogue scale (VAS; where 0=no pain and 10=the worst pain imaginable) to rate the intensity of the pain immediately prior to removal from the cold water. No subjects requested to withdraw the hand before the 20 second period elapsed. Two pre-treatment cycles were followed by 3 during-treatment cycles (TENS on) and three post-TENS (TENS off) cycles. Thus the effects of post-TENS analgesia could be examined.

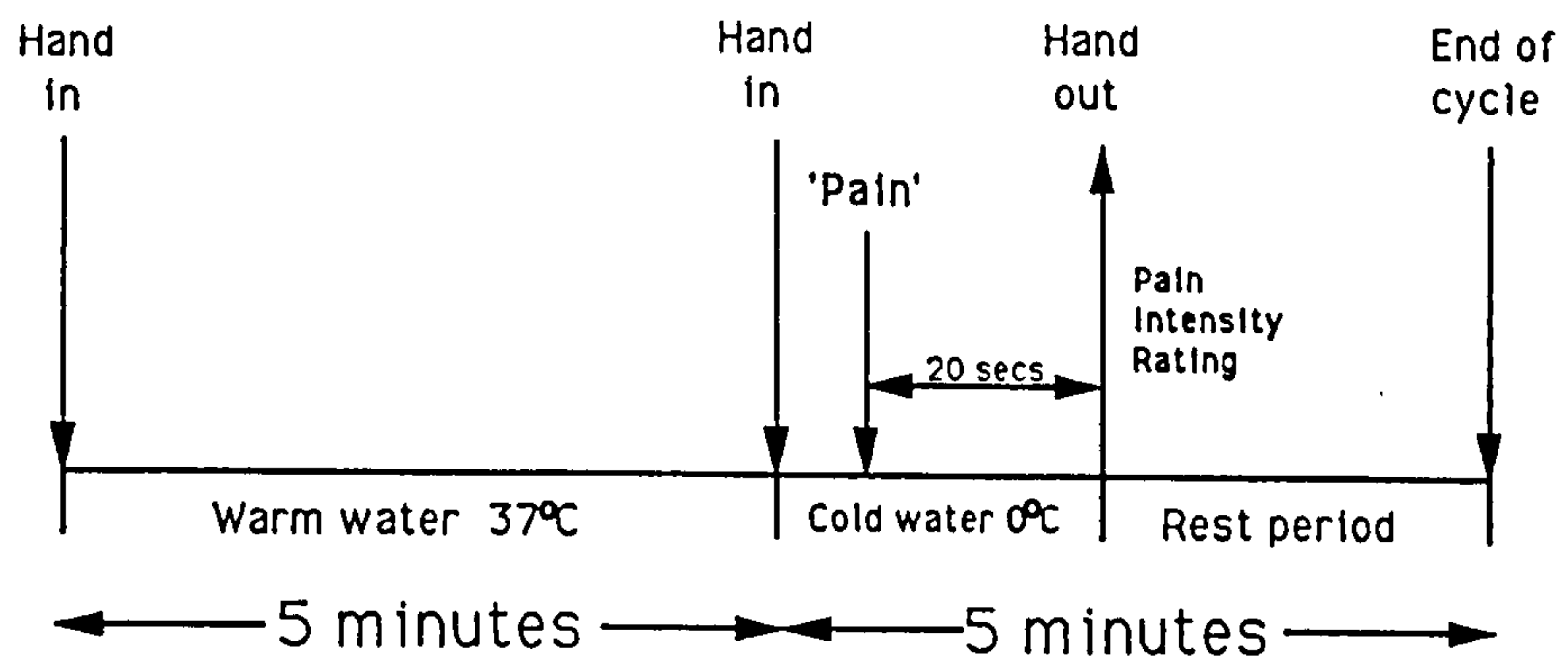


Fig.3.9 Cold-pressor pain (one cycle - modified for Exp.3.3).

Results of Experiment 3.3

The mean \pm SD results for ice pain threshold and pain intensity ratings are shown in Table 3.5.

Mean±SD	PRE-TREATMENT			DURING TREATMENT			POST-TREATMENT		
	-10 mins	-01 mins	+10 mins	+20 mins	+30 mins	40 mins	50 mins	60 mins	
<u>Pain Threshold (s)</u>									
Sham	15.1±11.8	14.4±12.9	16.2±15.0	15.0±12.3	16.1±14.1	14.5±13.0	14.6±13.3	14.4±13.6	
Conventional	15.5± 8.5	17.7± 9.0	23.1±17.3	24.7±15.4	23.3±13.7	17.2± 8.6	18.9± 9.0	17.2± 7.5	
Intense	15.2± 9.5	15.1± 9.3	19.3± 8.6	25.1±17.2	27.4±15.7	18.7±10.5	18.9±10.0	19.8±12.5	
Burst	14.3± 9.8	14.6± 9.8	17.1±13.2	20.2±17.9	18.9±12.8	17.0±11.6	16.5±11.5	19.0±13.6	
Acupuncture-Like	13.9±11.4	14.5±11.9	18.8±13.9	21.7±20.3	23.7±21.5	20.8±17.0	20.5±17.0	19.1±14.0	
<u>Pain Rating (VAS units)</u>									
Sham	4.7± 1.9	4.7± 1.7	5.0± 1.7	5.2± 2.3	5.2± 2.2	5.5± 2.0	5.4± 2.1	5.2± 2.1	
Conventional	4.6± 2.0	4.7± 2.0	5.0± 2.1	5.2± 2.0	4.9± 2.0	5.7± 2.1	5.5± 1.8	5.7± 1.6	
Intense	4.6± 2.0	4.9± 1.9	4.4± 1.7	4.5± 2.3	4.3± 2.1	4.8± 2.0	5.3± 2.1	5.7± 2.3	
Burst	5.2± 1.8	5.2± 2.0	4.9± 1.9	4.9± 2.4	4.9± 2.4	5.3± 2.6	5.4± 2.2	5.6± 2.3	
Acupuncture-Like	6.1± 1.3	6.4± 1.7	6.3± 1.7	6.2± 1.9	6.2± 2.2	6.4± 2.1	6.5± 2.4	6.6± 2.2	

Table 3.5 Mean±SD (s) ice pain threshold and ice pain tolerance by TENS treatment and by time (6 successive observations at 15 minute intervals) for different modes of TENS in healthy subjects (Exp.3.3).

Ice Pain Threshold: Mean pre-treatment threshold was calculated for each individual (no significant differences were found between the two pre-treatment observations; paired t-test). One-way ANOVA found no significant differences in pre-treatment mean across the treatment groups, and changes in pain threshold from pre-TENS baseline were calculated by subtracting pre-treatment mean (for each individual) from successive during-treatment observations. Total increase in ice pain threshold compared to pre-treatment mean was calculated as the area under the curve for changes in pain threshold; (i) during-TENS (30 minutes) and (ii) post-TENS (30 minutes). Comparisons were made on the total change in pain threshold between during- and post-TENS cycles.

The mean change in pain threshold (from pre-TENS baseline) for the three during- and three post-TENS cycles is shown in Fig.3.10.

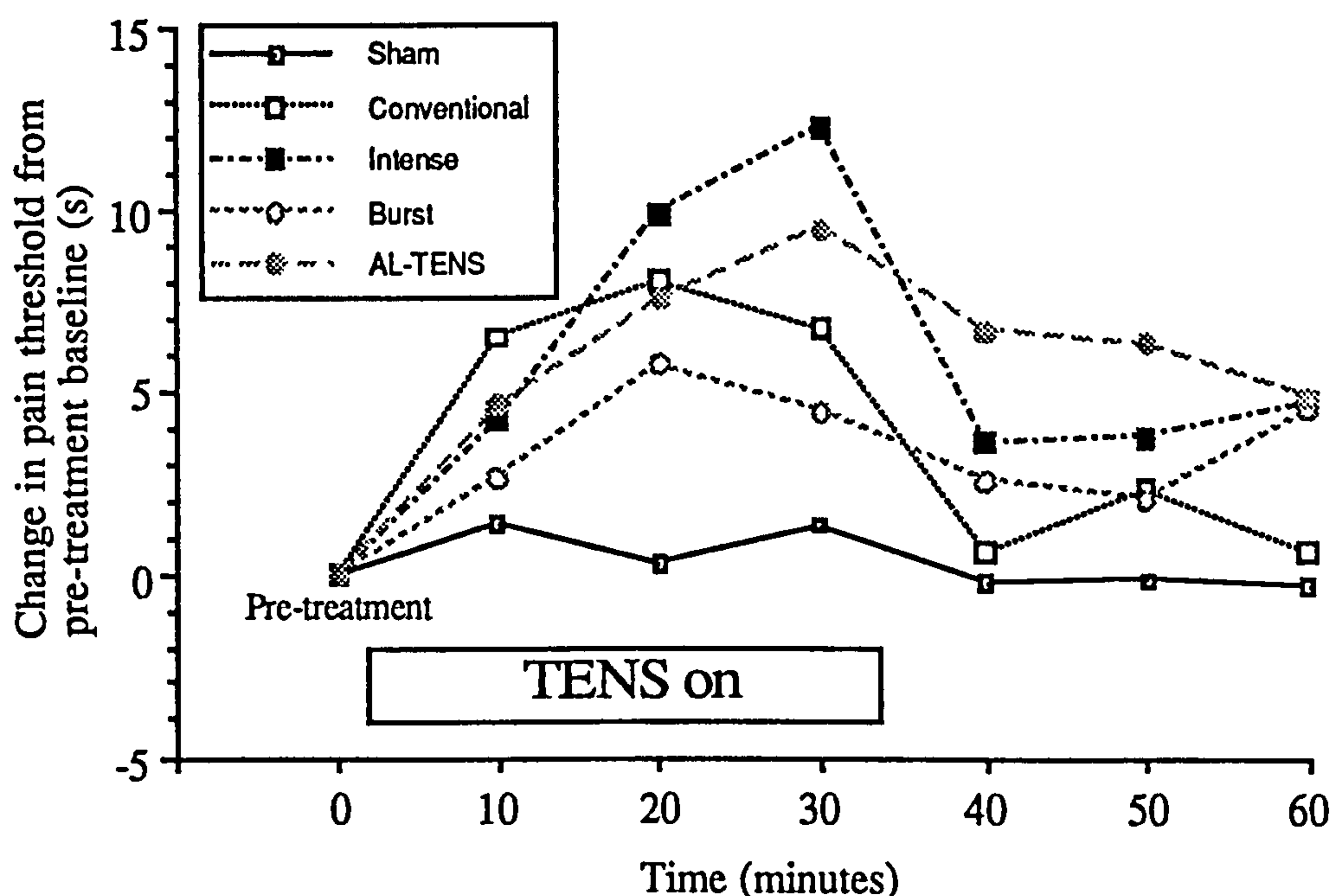


Fig.3.10 Mean change in ice pain threshold during different modes of TENS in healthy subjects (Exp.3.3, n=12).

Pain threshold changed little over the course of the experiment in the sham TENS group. Conventional, intense and AL-TENS groups showed a rapid (within 10 minutes) increase in pain threshold when compared to sham TENS. A significant increase in ice pain threshold occurred in the conventional, intense and AL-TENS

groups when compared to sham (Fig.3.11). The rise in ice pain threshold observed in the burst TENS group failed to reach significance ($P=0.14$). No significant differences in the increase in ice pain threshold was observed between the active TENS groups (one-way ANOVA on total change between conventional, intense, burst and AL-TENS). Nevertheless, intense TENS showed the largest, and burst TENS the smallest, increase in ice pain threshold.

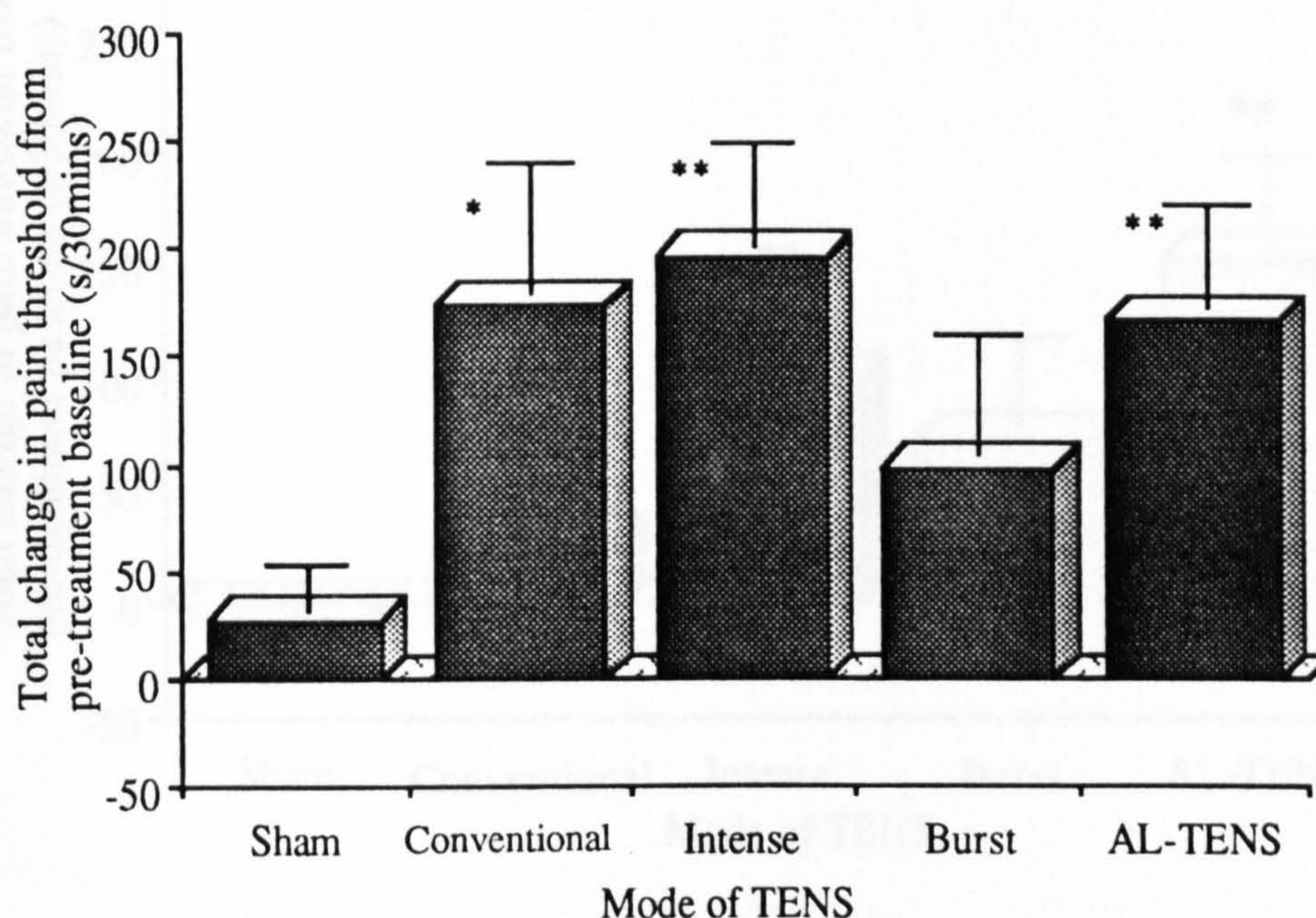


Fig.3.11 Mean \pm SE total change in ice pain threshold during TENS (30 minute treatment session) for different modes of TENS in healthy subjects (Exp.3.3). (*= $P<0.05$, **= $P<0.01$, unpaired t-test, TENS group v sham; $n=12$).

The elevation in pain threshold produced by conventional TENS reached a plateau within thirty minutes whereas the elevation produced by intense and AL-TENS was still rising (Fig.3.10). A rapid and significant decrease in pain threshold occurred with TENS switch off (within 10 minutes) in both the conventional and intense TENS groups. By contrast, the increase in pain threshold in the AL-TENS group was sustained for over thirty minutes after TENS switch off. One-way ANOVA ($F_{3:44}=2.53$, $P\ 0.05>0.1$) just failed to show any significant differences in the post-TENS change in pain threshold between the active TENS groups. However, intense and AL-TENS produced a significant elevation in ice pain threshold post-TENS when compared to sham (Fig.3.12).

Furthermore, AL-TENS (and to a lesser extent intense TENS) produced a significant elevation in ice pain threshold when compared to conventional TENS (Mean±SD total change post-TENS (s/30mins): AL-TENS v conventional TENS, $P<0.05$, intense TENS v conventional TENS, $P=0.06$, unpaired t-test).

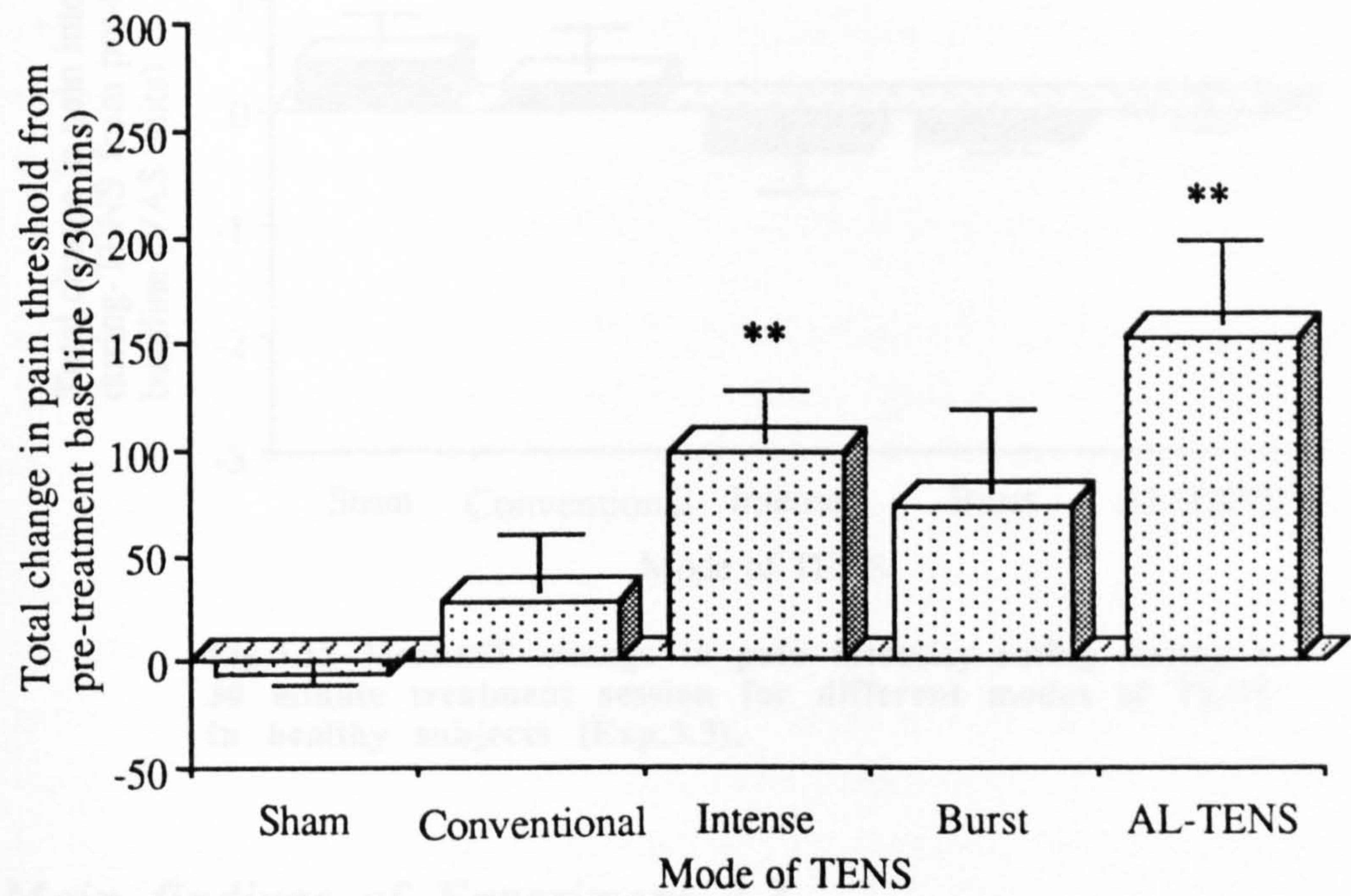


Fig.3.12 Mean±SE total change in ice pain threshold post-TENS (30 minute treatment session) for different modes of TENS in healthy subjects (Exp.3.3). (**= $P<0.01$ unpaired t-test, TENS group v sham; $n=12$). AL-TENS and intense TENS were found to produce a significant increase in ice pain threshold post-TENS when compared to sham. Furthermore, a significant decline in ice pain threshold occurred between, during and post-treatment cycles for continuous and intense groups ($P<0.05$, paired t-test).

Pain intensity rating: Similar statistical analysis were performed on pain intensity rating scores. No significant differences were found between pre-treatment cycles 1 and 2. Pre-treatment means were calculated and one-way ANOVA showed no significant differences between the TENS groups. Total change in pain intensity rating during TENS cycles was calculated and the results shown in Fig.3.13. No significant differences between sham TENS and any of the active TENS treatment groups were observed.

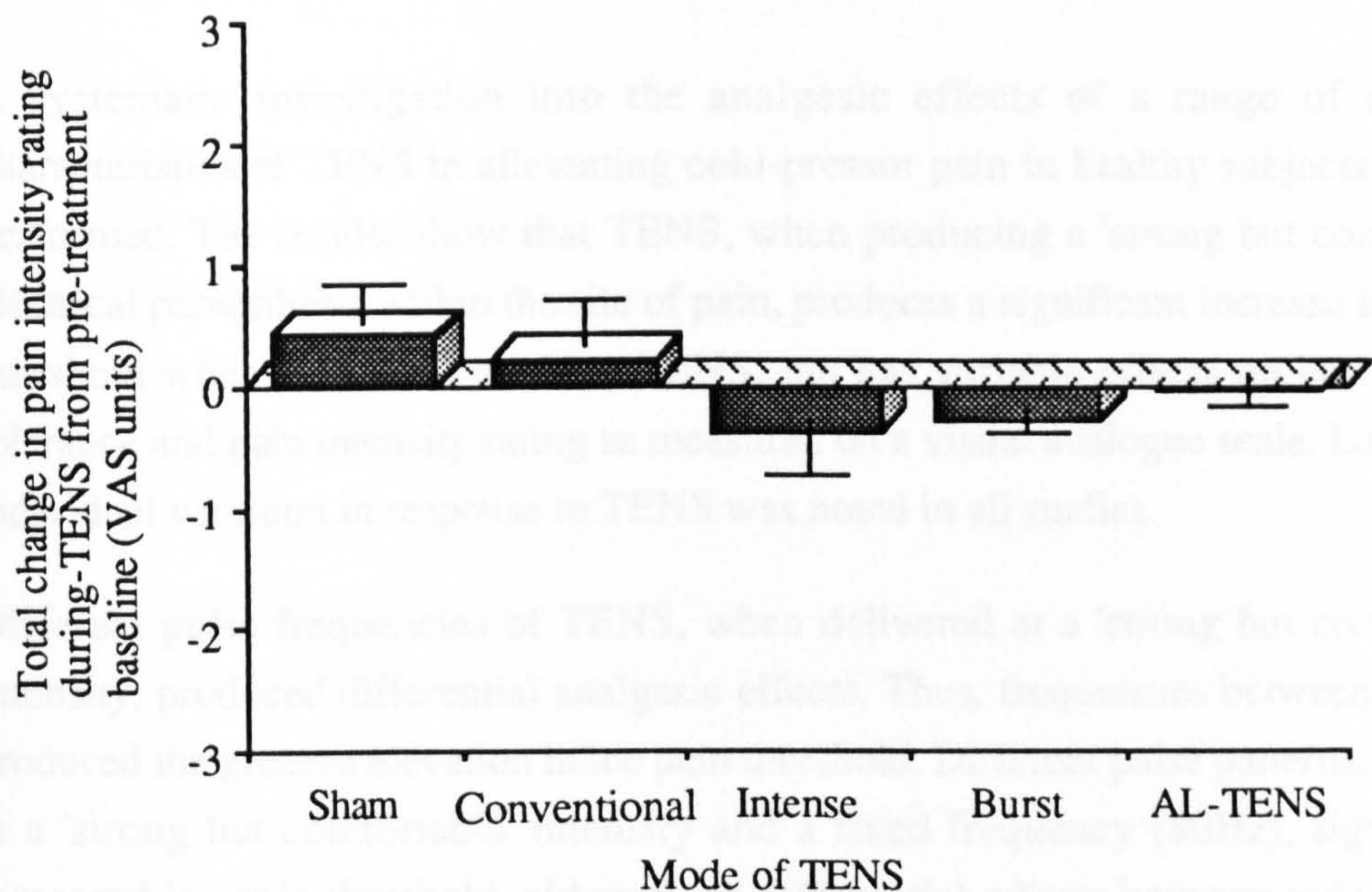


Fig.3.13 Mean±SE change in pain intensity rating during a 30 minute treatment session for different modes of TENS in healthy subjects (Exp.3.3).

Main findings of Experiment 3.3

- (i) Burst TENS, when applied over a muscle mass myotomally related to the site of pain, produced an increase in ice pain threshold only when the intensity of stimulation was sufficient to produce phasic muscle contraction (i.e. AL-TENS).
- (ii) Continuous TENS, when applied to produce electrical paraesthesia within the painful area, produced an increase in ice pain threshold at both low and high intensity stimulation.
- (iii) A significant post-TENS increase in ice pain threshold was achieved by AL-TENS, and to a lesser extent by intense TENS.
- (iv) TENS produced no significant effects on pain intensity ratings as measured on a VAS.

DISCUSSION

A systematic investigation into the analgesic effects of a range of electrical characteristics of TENS in alleviating cold-pressor pain in healthy subjects has been performed. The results show that TENS, when producing a 'strong but comfortable' electrical paraesthesia within the site of pain, produces a significant increase in ice pain threshold when compared to sham TENS, but has variable effects on both ice pain tolerance and pain intensity rating as measured on a visual analogue scale. Large inter-individual variation in response to TENS was noted in all studies.

Different pulse frequencies of TENS, when delivered at a 'strong but comfortable' intensity, produced differential analgesic effects. Thus, frequencies between 20-80Hz produced the greatest elevation in ice pain threshold. Different pulse patterns, delivered at a 'strong but comfortable' intensity and a fixed frequency (80Hz), significantly increased ice pain threshold, although no differential effects between pulse patterns was found. However when these pulse patterns were utilised at different current intensities and different sites, differential analgesic effects were observed. Thus, burst mode TENS applied to a muscle mass myotomally related to the site of pain, only increased ice pain threshold if the intensity of stimulation was sufficient to produce strong forceful contractions i.e. AL-TENS. Moreover, a significant post-TENS analgesia was achieved by AL-TENS and intense TENS, but not conventional, or burst TENS groups. These findings are discussed in detail below.

Pulse Frequency

Experiment 3.1 has shown that different pulse frequencies produce differential analgesic effects. Thus, TENS frequencies of 20-80Hz produced the greatest analgesia, while frequencies below and above this level (10Hz and 160Hz) although still significantly elevating pain threshold, produced effects of lesser magnitude. As no significant differences in stimulus intensity were observed across the treatment groups, the frequency of pulse delivery was the governing factor under these conditions.

By contrast to the findings of the present study, an earlier study of Ashton et al. [1984], carried out in this laboratory, found TENS at a frequency of 8Hz appeared to raise ice pain threshold (although there was a very large variation in response), but TENS at 100Hz was ineffective. The discrepancy in results between the present investigation and the Ashton et al. study may be due to differences in experimental

method. In the present study, smaller electrodes were applied closer to the wrist to achieve a strong electrical paraesthesia within the hand rather than the arm as in the Ashton et al. study. Different stimulators with slightly different specifications were used in the two studies. The use of iced water, as opposed to crushed ice, may have reduced temperature variability from pockets of air.

Small (non-significant) differences in pre-treatment observations across treatment groups (Table 3.1), were noted in Experiment 3.1 and the Ashton study. This may have been due to the short TENS familiarisation session prior to the start of the experiment, since active TENS groups had higher pre-treatment pain threshold and tolerance values than control or sham TENS groups. It is not possible to say whether this variation was due to chance, psychological effect or a real treatment response. Nevertheless such effects were reduced in Experiments 3.2 and 3.3 in which this TENS familiarisation session was omitted.

A stimulus frequency of 80Hz produced a large and reproducible analgesic effect shown by the small individual variation (Fig.3.4a and b). This finding agrees with the observation of Sjölund [1985] who found that over a range of peripheral nerve stimulating frequencies (10-160Hz), 80Hz produced the maximal suppression of the C-fibre evoked flexion response in the rat. Chung et al. [1984b] found that the higher the frequency of electrical peripheral conditioning stimuli (within a range of 0.5-20Hz), the more powerful the inhibition of primate spinothalamic tract cells. Stimulation intensities strong enough to activate C-fibres were used. Therefore the results from both animal and human studies suggest that higher frequencies of TENS produce a more effective analgesia. However, the results of animal studies can only be applied with extreme caution to the treatment of clinical pain, but it is notable that frequencies of 40-100Hz are generally reported to be most beneficial in the clinical environment [Woolf 1989]. Unfortunately such frequencies are often difficult to attain with commercially available stimulators as they lie on the steep part of a logarithmically calibrated frequency control dial as shown in Chapter 2.

As mentioned earlier, TENS may produce analgesia by several interactive mechanisms although in its conventional form, high frequency (10Hz and above) low intensity ('strong but comfortable') TENS is thought to act at a spinal level by closing 'pain gates' in the dorsal horn. The exact mechanism by which changing pulse frequency alters the effects of TENS is unknown. Nevertheless, the primary aim of conventional

TENS is to selectively activate large diameter sensory nerve fibres. Factors which influence the firing of peripheral nerve fibres include pulse width, pulse amplitude and pulse frequency [Woolf 1989]. Thus, the greater the pulse width or the higher the pulse frequency, the lower amplitude (current intensity) required to excite the nerve (Fig.3.14).

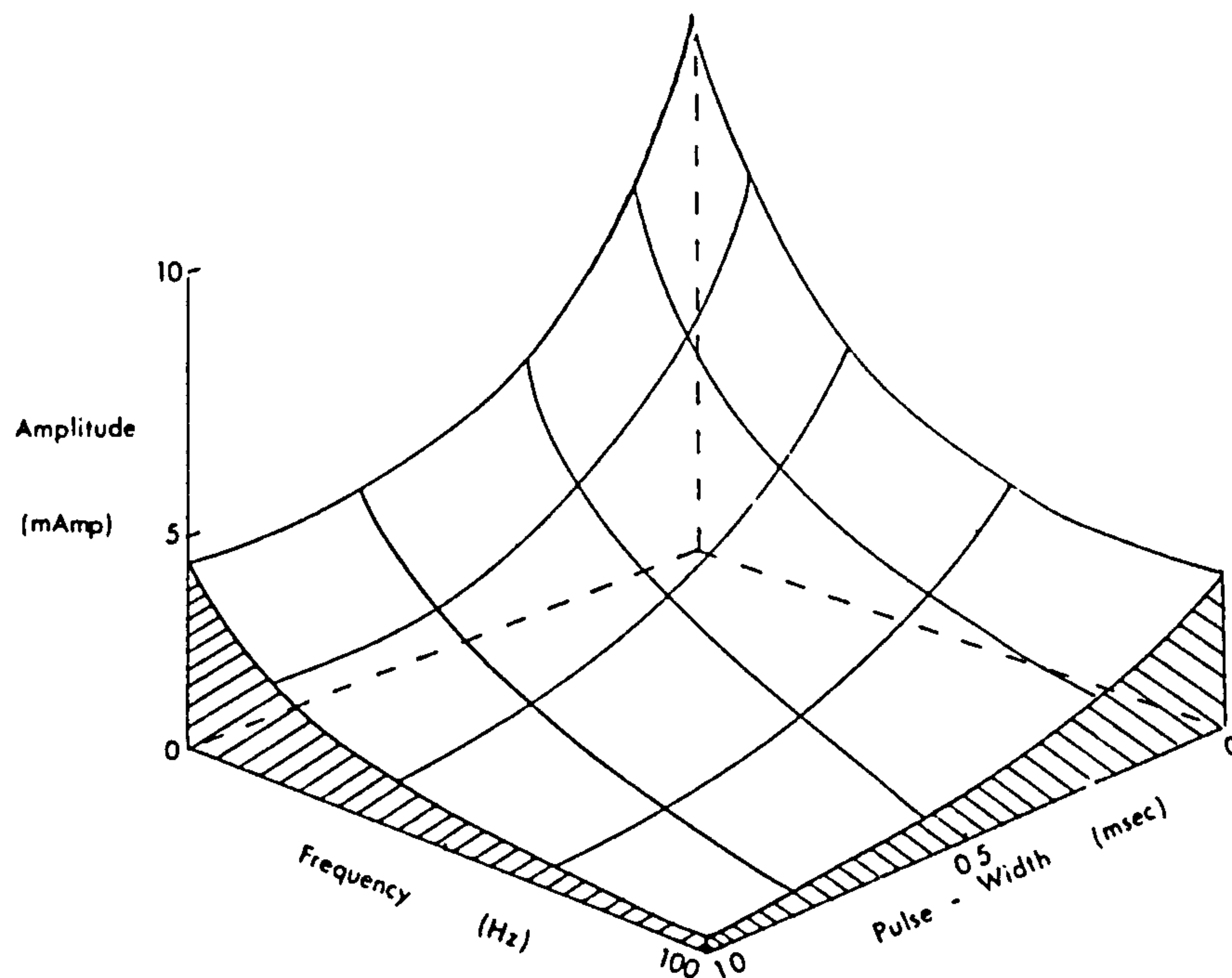


Fig.3.14 A three-dimensional surface indicating the theoretical relationship between pulse-width and frequency in determining the amplitude of a pulse necessary to activate a nerve. From Woolf [1989].

At low pulse frequencies insufficient peripheral nerves may be activated to produce an analgesic effect. Recently Macefield and Burke [1991] recorded a reduction in the peak-to-peak amplitudes of early latency waveform components of somatosensory evoked potentials (SEPs) following prolonged activation of cutaneous afferents by vibration. The group attributed such changes to a depression in central excitability possibly reflected by changes in synaptic transmission at the cuneate nucleus and thalamo-cortical levels. Thus the reduction in TENS analgesic effects observed at very high rates of stimulation in the present study (160Hz) may be due in part to synaptic fatigue, possibly at second and higher order neurone sites in the central nervous system.

Pulse Pattern

Of the different pulse patterns of TENS used in Experiment 3.2, all significantly increased ice pain threshold in healthy subjects when applied to produce a 'strong but comfortable' paraesthesia within the site of pain. The increase in ice pain threshold was of a similar magnitude to that observed in Experiment 3.1, and large inter-individual variation in response to TENS was noted. Although no significant differences in the magnitude of increase in ice pain threshold between different pulse patterns was observed, random TENS produced the smallest increase and continuous TENS the largest increase in ice pain threshold.

Eriksson et al. [1979] suggested that a requirement of AL-TENS, produced by high intensity burst mode stimulation, is the activation of deep muscle afferents. However it is unlikely that the subjects using burst mode TENS in Experiment 3.2 achieved AL-TENS, as no observable muscle twitching occurred at the wrist in any subjects, and the intensity of stimulation required to achieve a 'strong but comfortable' level in the burst TENS group was no greater than that in other groups. Recently Field et al. [1990] reported no significant differences between burst and continuous mode TENS in the treatment of chronic back pain. Although the intensity of stimulation used by the patients was not reported, it was found that patients applied both modes of TENS at a 'strong non-painful' level. This low intensity burst TENS is thought to be similar to conventional TENS and is sometimes preferred by patients for reasons of comfort [Mannheimner & Lampe 1988a].

Subjects using modulation TENS required a higher intensity of stimulation, as measured by the Frye Analyser, to reach a 'strong but comfortable' level, although no muscle twitching was observed in any subjects. Variation in stimulator design may have accounted for this difference since the pulse wave form delivered by modulation TENS was found to differ slightly from that of the other types of TENS. Ekström and Sjölund [1988], examined the effects of modulating pulse frequency and pulse duration (width) on the C-fibre reflex in anaesthetised rats and found that neither improved analgesic effect. The present study has shown that modulation of pulse amplitude (current intensity) when presented at a 'strong but comfortable' intensity was no more efficacious than other patterns of stimulation.

With regard to random stimulation, Cheng and Pomeranz [1987] reported a successful trial using a new stimulator called a Codetron which randomly switches stimuli among

six electrode channels, activating each site for 10 seconds. They found that 90% of patients obtained benefit with such a device. Although the mechanism by which tolerance occurs is far from understood, it is believed that the nervous system undergoes some adaptive change to regular, repetitive stimulation (habituation), thus reducing analgesia produced by TENS [Pomeranz & Niznick 1987]. Random TENS, because of the irregular pulse presentation, may prevent such habituation of the nervous system and so prolong the analgesic effect. Although the clinical efficacy of this pattern of stimulation has yet to be evaluated, preliminary observations by the author suggest that the majority of patients with the availability of random mode stimulation on the Xenos stimulator dislike the sensation of 'randomness' of pulse delivery when compared to continuous or burst pulse patterns.

The size of the stimulating electrodes appears to be a further variable in determining TENS analgesia. The elevation of pain threshold following 80Hz continuous TENS was *reduced* by doubling the size of electrodes. This finding is somewhat surprising as a larger electrode size might be expected to increase the activation of large fibres. Nevertheless, smaller electrodes would deliver a higher current density to the point of attachment on the skin surface which may produce greater analgesia [Librach 1988]. It has been suggested that with the use of large electrodes the stimulator may fail to deliver sufficient current to activate peripheral nerves because of the fall off in current density with length [Brennen 1976], yet the electrodes used in the present study (2 cm² and 4 cm²) were smaller than many commercially available electrodes thus reducing such an effect. Furthermore the stimulating current passed to the large electrodes was not significantly less than that used with the small electrodes. Additional experiments with a range of different electrode sizes are needed.

Ice pain tolerance was increased by burst, random, continuous and to a small extent modulation TENS compared with controls, although the change did not reach statistical significance. As with ice pain threshold, larger electrodes reduced the size of response.

Modes of Stimulation

In Experiment 3.3 TENS increased experimental pain threshold when applied to:

- (i) produce an electrical paraesthesia within the site of pain,
- (ii) a muscle mass myotomally related to the site of pain only if the intensity of stimulation was sufficient to produce strong forceful contractions, i.e. AL-TENS.

Thus conventional TENS, intense TENS and AL-TENS significantly increased ice pain threshold in the hand. Burst TENS applied at a low intensity to the ipsilateral brachioradialis muscle (with respect to the 'painful' hand) also increased ice pain threshold, but this increase failed to reach statistical significance. The increase in pain threshold associated with conventional and intense TENS fell significantly in the post-TENS cycles (when compared to during TENS cycles). However, both intense TENS and AL-TENS produced a significant post-TENS analgesia. Although TENS significantly increased ice pain threshold, it had a variable effect on the intensity of pain (as rated on a visual analogue scale) achieved within 20 seconds after the onset of pain threshold.

The sustained post-TENS analgesia achieved using AL-TENS (>30 minutes), compared to the short post-TENS analgesia achieved with conventional (continuous) TENS (<10 minutes), is consistent with clinical reports [Sjölund et al. 1990]. Nevertheless, clinical reports on the use of AL-TENS are few in comparison to conventional TENS. Andersson et al. [1976] found that the production of phasic muscle contraction over large muscle nerve bundles segmentally related to the painful site, by delivering low frequency single pulses, produced pain relief in only 1 of the 8 patients. However, the production of fasciculatory muscle contraction within the site of pain by high frequency pulses produced pain relief in seven of the 12 patients. Delivering pulses in low frequency trains of pulses has been shown to markedly increase the intensity of stimulation accepted, and also the degree of analgesia experienced, by patients [Eriksson & Sjölund 1976]. Thus, Eriksson and Sjölund [1976] found that in a group of 50 patients, 30 did not respond to conventional TENS but 10 of these responded to AL-TENS. Further studies by the same group [Eriksson et al. 1979; Eriksson et al. 1984], found that approximately 30 % of 123 patients with a variety of chronic pain conditions needed to use AL-TENS to obtain relief of pain, and 13 out of 34 patients with facial pain who did not respond to conventional TENS required AL-TENS to produce relief.

Duranti et al. [1988] found a marked and lasting increase in muscular (vastus medialis) pain threshold to electrical stimulation in healthy subjects, following administration of AL-TENS to both ipsilateral and contralateral vastus medialis. Recently, a number of newer non-portable stimulating devices have appeared which utilise the principle of AL-TENS, including the Codetron [Cheng & Pomeranz 1987] (which also randomises pulse presentation) and Likon [1990] although these have yet to be validated.

Intense (continuous) TENS has been described by Mannheimer and Lampe [1988a] as high intensity (current) and high frequency (100-150Hz) stimulation administered for about 5-15 minutes at the highest tolerable level. Such intense TENS produces tetanic, fasciculatory muscle contractions. In Experiment 3.3 the stimulating parameters of intense TENS were similar to those suggested by Mannheimer and Lampe (i.e. 80Hz, 200 μ s, highest tolerable level), and produced a marked increase in ice pain threshold during stimulation, which fell rapidly on TENS switch off, although not back down to baseline levels. Although the effects of intense TENS have been previously reported [Melzack 1975b; Jeans 1979], stimulating characteristics were different to those applied in the present study. Intense TENS may have a value clinically during minor surgical operations [Strassburg et al. 1977].

Differences in the analgesic effects of stimulation modes may be attributed in part to differing mechanisms of action. Conventional TENS, acting via segmental inhibition of nociceptive input by the excitation of large diameter afferent fibres, would accord with a rapid onset and offset of analgesia associated with a neuronal mechanism. By contrast, AL-TENS acting via a supraspinal descending pain inhibitory pathway and the liberation of neuromodulators such as endorphins, would show a slower onset and offset [Sjölund & Eriksson 1985]. This is supported by the naloxone reversibility of AL-TENS but not conventional TENS [Sjölund & Eriksson 1979] suggesting a role for opioid peptides in analgesia associated with AL-TENS. However, Chung et al. [1984a] reported that spinothalamic cells of anaesthetised monkeys were inhibited during high intensity (activating C-fibres), low frequency (3Hz trains of 30Hz pulses), peripheral nerve stimulation. This inhibition outlasted stimulation by 20-30 minutes, and occurred in intact, decerebrate and spinalised monkeys. This suggests that antinociception associated with high intensity low frequency stimulation depends to some degree upon spinal cord neuronal circuitry. Sjölund [1988] found that low frequency (0.1-5Hz trains of pulses) peripheral stimulation of dissected muscle rather than skin nerves was more effective in suppressing the C-fibre evoked flexion in lightly anaesthetised rats. Furthermore, pulse train repetition rates of around 1Hz, and activation of Group I-III rather than Group I-II muscle afferent fibres, produced the greatest reduction of C-fibre response. Thus, analgesia associated with AL-TENS may be produced by a number of interactive peripheral, spinal and supraspinal mechanisms.

It has been suggested that brief intense TENS produces peripheral blockade of nociceptive transmission [Mannheimer & Lampe 1988b]. Thus high intensity TENS

would activate both small and large diameter fibres and produce antidromic block of nociceptive impulses transmitted in A-delta and C-fibres [Campbell & Taub 1973; Ignelzi & Nyquist 1979]. Moreover the rapid decline in analgesia on 'TENS switch-off' with brief intense TENS, as observed in Exp. 3.3, substantiates the findings of previous reports using similar TENS characteristics [Janko & Trontelji 1980; Pertovaara & Hamalainen 1982].

The effect of TENS on sensory and affective components of pain

An interesting finding of the three experiments was the reproducible increase in ice pain threshold produced by TENS, in comparison to the variable effects of TENS on pain tolerance and pain intensity rating measured on a visual analogue scale. This suggests that TENS exerts its primary effects on the sensory components (i.e. pain threshold) rather than affective components (i.e. intensity/tolerance) of pain. Clinical observations are consistent with such findings as patients often report increased mobility during TENS which may be associated with an elevation in pain threshold. Thus TENS may prove successful in conditions where a lowering pain threshold is the common cause of pain as in arthritis.

Summary

The results of this systematic investigation into analgesic effects of different electrical characteristics of TENS has found that:

- (i) TENS, when applied to produce a 'strong but comfortable' electrical paraesthesia within the painful area, increased in ice pain threshold but had variable effects on ice pain tolerance and pain intensity rating.
- (ii) Differential TENS effects occur across a range of pulse frequencies, and pulse frequencies between 20-80Hz produced the largest elevation of ice pain threshold.
- (iii) Although no significant differential effects were observed with a variety of pulse patterns, continuous mode TENS produced the largest elevation of ice pain threshold.
- (iv) Burst mode TENS, when applied over a muscle mass myotomally related to the site of pain, produced an increase in ice pain threshold only when the intensity of stimulation was sufficient to produce phasic muscle contraction (i.e. AL-TENS).
- (v) AL-TENS (and intense TENS) produced a prolonged post-TENS analgesia.

These results may be helpful to clinicians in selecting pulse frequencies, pulse patterns and stimulating modes for TENS treatment in patients with pain. Thus, continuous, 80Hz stimulation, producing a 'strong but comfortable' paraesthesia within the painful site, should be the primary TENS treatment choice in the clinic. In certain circumstances, where such stimulation is ineffective, aggravates the pain or cannot be applied within the painful site, other stimulating characteristics (i.e. AL-TENS) should be tried before dismissing a patient as a 'TENS failure'.

Large inter-individual variation in response to TENS was observed in both pain patients (Chapter 2) and healthy volunteers experiencing experimental pain (Chapter 3). However, the cause and site of pain (Study 2.1, 2.2 and 2.3), and/or psychological variables (Study 2.2, Exp. 3.1, 3.2) were not shown to be related to the degree of TENS response. Experiments investigating electrophysiological changes (evoked potentials (EPs)) during TENS suggest that TENS affects the processing of sensory information. Thus, changes in electrophysiological activity may be related to patient response to TENS. To examine this possibility, an investigation into the effects of TENS on spontaneous EEG and cortical evoked potentials was performed, as described in the next chapter.

CHAPTER 4

THE EFFECT OF TENS ON THE SPONTANEOUS ELECTROENCEPHALOGRAM (EEG) AND SOMATOSENSORY EVOKED POTENTIALS

INTRODUCTION

The recording of the electrical activity of the brain via electrodes applied to the surface of the scalp is termed electroencephalography (EEG). EEG has proved a useful research tool in the investigation of gross brain function and is of increasing importance in psychopathology and psychopharmacology for clinical assessment. It has been suggested that ongoing electrical activity of the brain, or spontaneous EEG, reflects states of arousal and relaxation, and more recently that pain may cause changes in spontaneous EEG [Chen et al. 1989]. To date, TENS effects on spontaneous EEG remain unknown. Studies utilising somatosensory evoked potentials (i.e. the response to a somatosensory stimuli, SEP) suggest that TENS affects the processing of sensory information at several levels in the nervous system (i.e. peripheral, spinal, subcortical and cortical). Moreover, the peak-to-peak amplitudes of the waveform components of baseline SEPs may be related to individual response to TENS. Since brain activity may reflect response to TENS a study of the effects of TENS on spontaneous EEG and SEPs was undertaken.

EEG variables

A variety of EEG measures are now used routinely to assess cerebral activity of which spontaneous EEG and cortical evoked potentials are most commonly used.

Spontaneous EEG: "The electric potential field on the scalp has been likened to the surface of the sea on which floats a number of buoys - the electrodes - the varying vertical displacements of which represent fluctuations of electrical potential." [Cooper et al. 1980b]. In its spontaneous or ongoing state EEG is rhythmic (Fig.4.1) and this rhythmicity enables quantification.

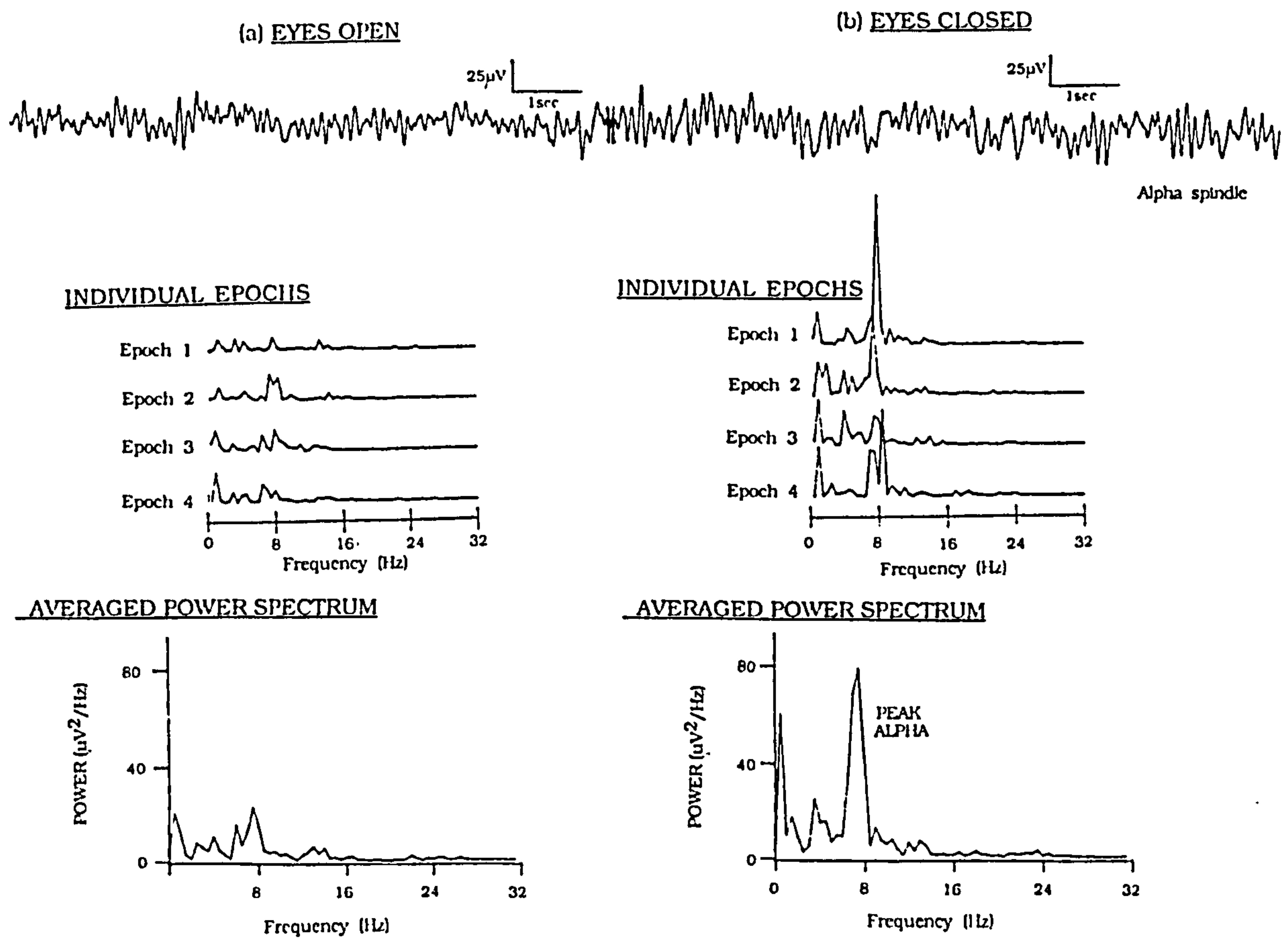


Fig.4.1 Spontaneous EEG recorded from O1 (left occipital referenced to linked mastoids) with (a) eyes open and (b) eyes closed in a healthy subject. Top trace shows Spontaneous EEG in 'raw' form. Note the difficulty in detecting and measuring changes in EEG activity despite the occurrence of alpha spindles with eyes closed. Thus, spontaneous EEG is split into epochs and transformed from the time domain into the frequency domain by the calculation of the power spectrum for each epoch using Fast Fourier Transform (middle trace). The average of these individual epochs is calculated and averaged power spectrum is measured across traditional frequency bands (lower trace). Note the increase of alpha activity with eyes closed.

Methods of EEG analysis are now aided by computers and based on the calculation of EEG power ($\mu\text{V}^2/\text{Hz}$) within traditionally fixed frequency bands (power spectrum). For review see Kunkel [1984]. Although the division between frequency bands is arbitrary, each band seems to reflect different types of brain activity (Table 4.1) and characteristic changes in the amplitude and frequency of spontaneous EEG are associated with different states of arousal (Table 4.1).

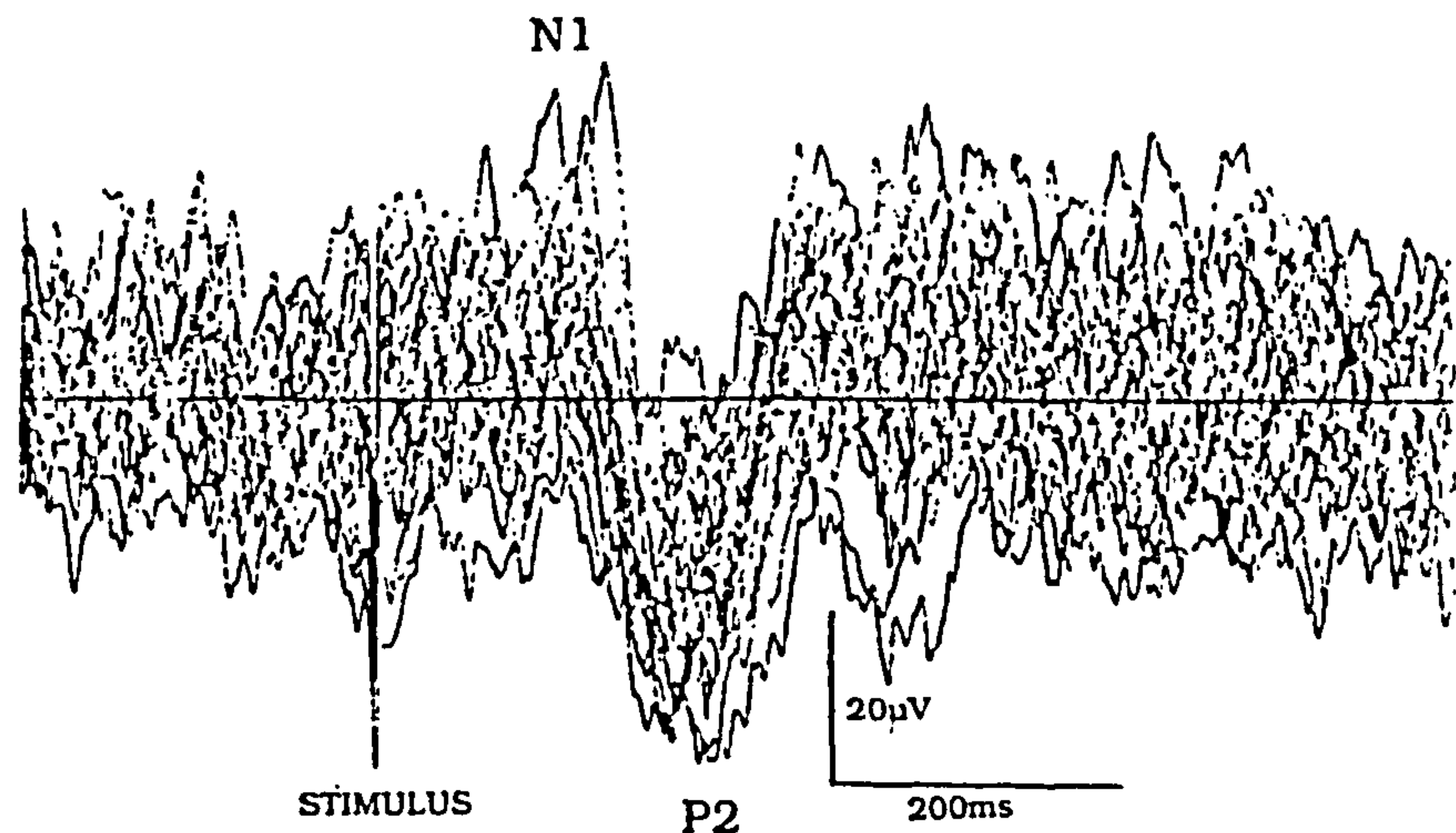
Wave band	Frequency (Hz)	Approximate amplitude (μV)	Characteristic Associated activity
Delta	0- 3.5	100	deep sleep
Theta	4- 7.5	100	some pathological states
Alpha	8-13.5	50	awake relaxation, eyes closed
Beta	14-40.0	20	increased arousal, mental activity
Slow beta	14-25.5		
Fast beta	26-40.0		

Table 4.1 Electroencephalographic wavebands. From Ashton [1987].

Slow, high voltage synchronous waves, characterise the relaxed state and are prominent in normal subjects when eyes are closed (Fig.4.1b). Fast, low voltage unsynchronised waves characterise high arousal states and are prominent in normal subjects when eyes are open (Fig.4.1a). It has been suggested that spontaneous EEG is the average of the multifarious activity of many small zones of the cortical surface beneath the electrode, and reflects local currents flowing in dendrites of the superficial cortex [Cooper et al. 1980a].

Cortical Evoked Potentials (EP): EPs reflect the cortical response to external stimuli (auditory (AEP), somatosensory (SEP), visual (VEP)). In practice, stimuli are presented several times so that the cortical response is enhanced in contrast to the background activity and signal averaging is used to produce an averaged evoked potential. Thus, despite variation in the shape and size of an evoked response elicited by single stimuli, a consistent waveform is created from the averaged response of a number of stimulus presentations (Fig.4.2a).

(a) 35 INDIVIDUAL TRIALS



(b) AVERAGED EVOKED RESPONSE

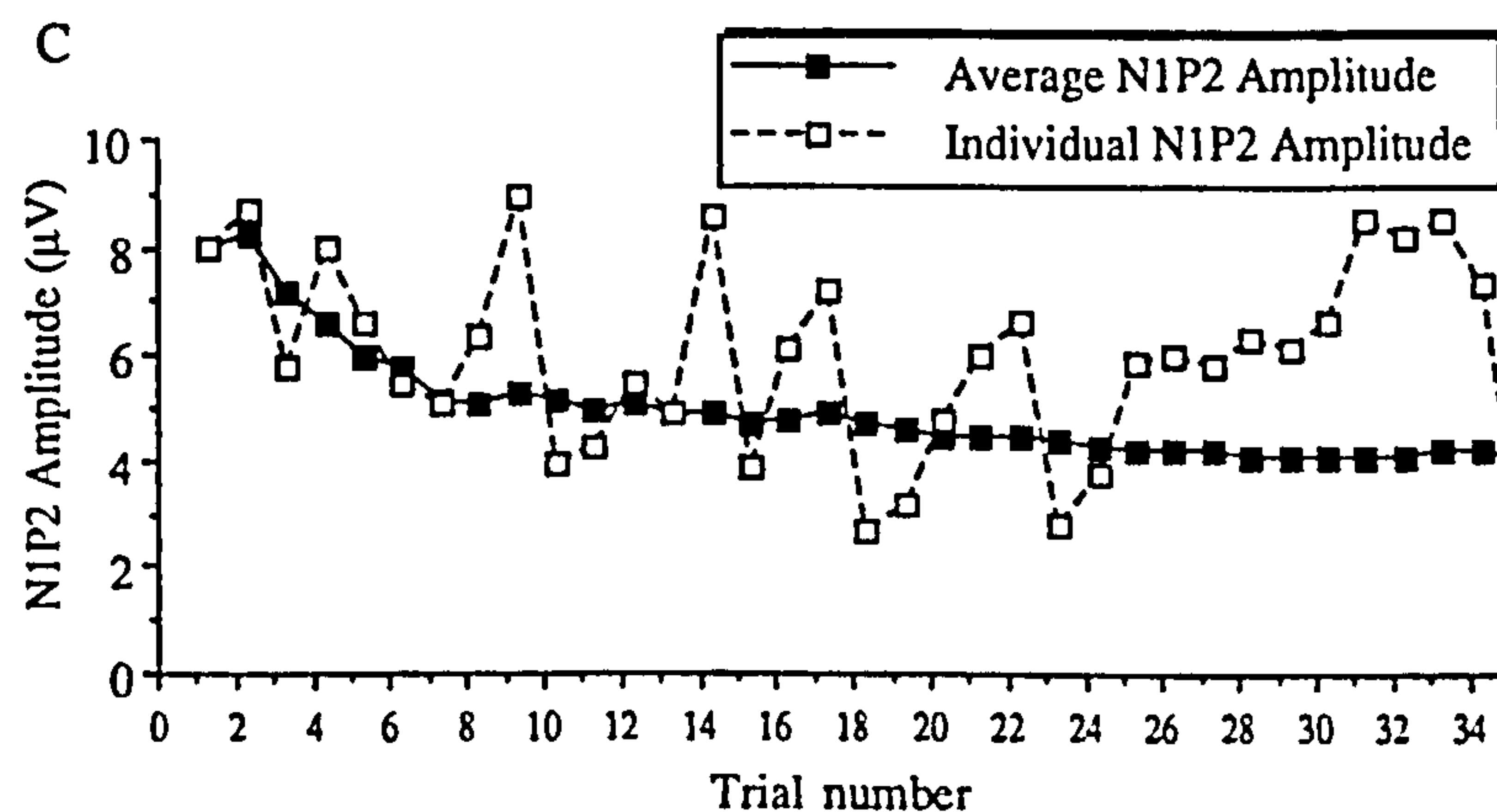
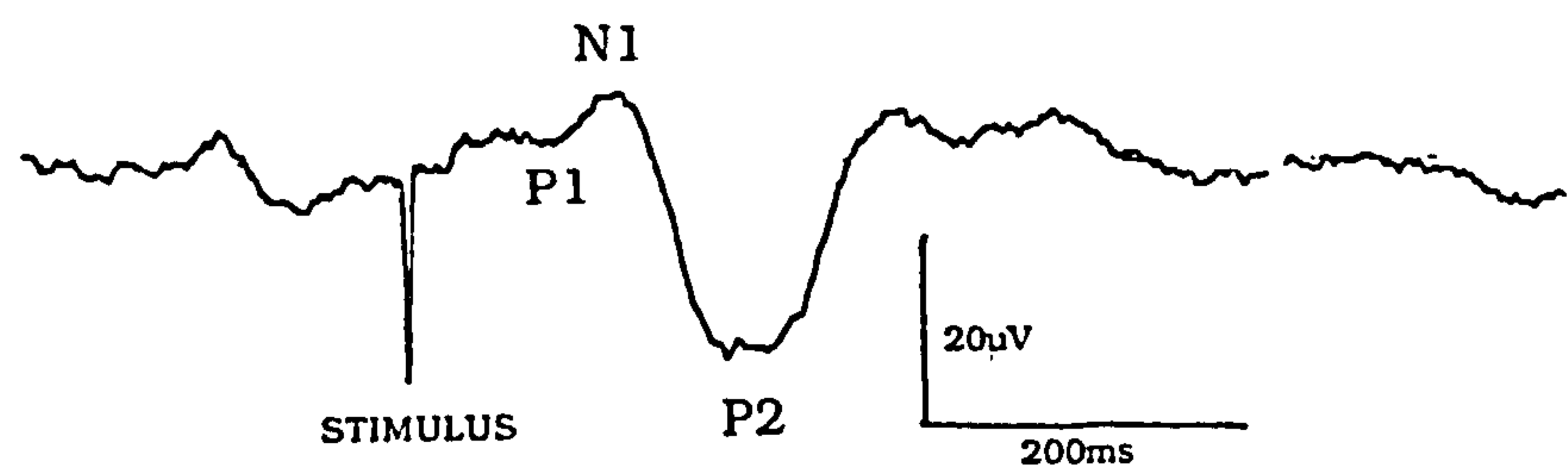


Fig.4.2 Average Somatosensory Evoked Potential (SEP). Recorded at Cz (vertex) to the delivery of 35 monophasic square wave electrical pulses at a 'strong but comfortable' intensity to the index finger of the left hand. (a) The recording of individual trials, (b) averaged response of the individual trials, (c) graph to show the relationship between peak-to-peak N1P2 amplitude of individual trials and growing averaged response. Note the large variability of individual SEPs. Pre-stimulus spontaneous EEG averages to zero and post-stimulus time locked SEPs enhance to create a characteristic waveform.

Measurement of latencies and peak-to-peak amplitude of the waveform components following the stimulus allows quantification of the EP. Hence, EPs are categorised into [Desmedt & Cheron 1982]:

- (i) Far-field EPs - which occur <20 ms post-stimulus and reflect peripheral and spinal transmission of the afferent nerve volley.
- (ii) Early near field EPs - which occur 20-80 ms post-stimulus and reflect initial thalamo-cortical processing.
- (iii) Late near field EPs - which occur 80-500 ms post-stimulus and reflect generalised cortical processing.

For reasons of brevity EP waveform components occurring within 80 ms post-stimulus are referred to as early latency EPs and those occurring later than 80 ms as late latency EPs. Following an evoking stimulus the early latency waves are labelled according to polarity and latency of occurrence (i.e. P14=positive wave occurring 14ms post-stimulus), whereas late latency waves are labelled according to polarity and order of occurrence (P1=1st positive wave, N1=1st negative wave). In general peak-to-peak amplitudes of SEPs increase and latencies decrease in states of heightened arousal and increasing stimulus intensity. Opposite changes occur during relaxation, distraction and decreasing stimulus intensity.

EEG changes related to pain

Spontaneous EEG: Recent studies have examined changes in spontaneous EEG during pain and analgesic intervention. In studies utilising the cold-pressor pain technique in healthy subjects, Chen et al. [1989] found that the induction of pain increased both delta and beta activity; Gotliesbsen and Arendt-Nielsen [1990] reported increases in delta and decreases in alpha power, while Backonja et al. [1990] recorded increases in alpha activity. Differences in these reports may be attributed in part to the variety of electrode positions used and the 'fluid' nature of electrical brain activity.

Evidence suggests that centrally acting analgesics increase delta and theta activity and reduce alpha activity in spontaneous EEG, although it is not clear whether these changes are specifically due to analgesic effects [for review see Martin & Kay 1977]. Aspirin has also been reported to reduce alpha activity [Fink & Irwin 1982], although contrasting reports exist [Sulc et al. 1973].

Somatosensory Evoked Potentials: It has been claimed that certain waveform components of the somatosensory evoked potential (SEP) recorded from the human scalp can serve as correlates of laboratory pain and analgesia [for review see Chapman et al. 1979; Chapman & Jacobson 1984; Bromm, 1985]. Peak-to-peak amplitudes of late waveform components of the SEP (N1P2 - 150-400 ms post-stimulus) have been shown to increase with increasing stimulus intensity and the subjective report of pain intensity. Electrical [Joseph et al. 1991], thermal [Carmon et al. 1978] and laser CO₂ [Bromm et al. 1983] stimuli are commonly used to elicit such 'pain potentials', although much work has centred on tooth pulp stimulation [Chatrian et al. 1975; Harkins & Chapman 1978; Chen et al. 1979]. However, objections have been raised to the interpretation of the results of experiments using tooth pulp stimulation, as they do not control for SEP changes at stimulation intensities below the painful range [Cruccu et al. 1983]. Recent investigations, using non-painful and painful SEPs, have shown no significant changes in SEP amplitudes at the point of pain perception [Miltner et al. 1989]. Hence, the relationship between EPs and the subjective report of pain may be relative rather than absolute, and late components of the SEP (150-400 ms post-stimulus) may represent a perceptual processing of stimulus intensity irrespective of pain perception. Bromm et al. [1983] have also suggested that ultra-late components of SEPs, with peak latencies around 1260ms, correlate with C-fibre activity in man. However, it is likely that such potentials would also be affected (and even swamped) by emotional and cognitive influences involved in the processing of pain perception. Further investigation is therefore necessary to confirm the existence of these ultra-late potentials.

Analgesics reduce both the subjective report of a painful evoking stimuli, and the amplitudes of late SEP components [Rohdewald et al. 1982]. Opiates produce a reduction in the late components of pain induced SEPs [Buchsbaum 1984], although it is not possible to determine whether these changes were due to analgesic, psychotropic, attentional or expectational processes. Moreover, aspirin has been shown to reduce SEP components during painful [Chen & Chapman 1980] and possibly non-painful stimuli [Ashton et al. 1984b], suggesting that changes in the amplitudes of these components may not be specific to the pain system.

EEG changes related to TENS

Spontaneous EEG: No effects of TENS on spontaneous EEG have been previously reported, although acupuncture has been found to decrease delta and theta activity, and increase alpha and beta activity during relief of tension headache [Manna et al. 1984]. The same group found that ischaemic experimental pain increased theta activity in healthy subjects, and that acupuncture increased alpha activity and decreased pain rating [Varrassi et al. 1986]. Whether these changes in spontaneous EEG were primarily due to the reduction of pain remains to be determined. Nevertheless, it seems unlikely that the EEG changes observed during acupuncture were produced by opioid release as opiates have been shown to increase delta and theta power, and to decrease alpha power [Martyn & Kay 1977; Bromm 1989]. Furthermore, Rosenblatt et al. [1982] and Saito et al. [1983] suggest that changes in spontaneous EEG observed during acupuncture, may be due to changes in arousal, rather than to changes in pain.

Somatosensory Evoked Potentials: TENS, when applied at a site dermatomally related to the evoking stimuli, has been shown to reduce the peak-to-peak amplitudes of both early and late waveform components of the SEP in healthy subjects [Chapman et al. 1983; Salar et al. 1980; Francini et al. 1982; Golding et al. 1986; Nardone & Schieppati 1989]. This reduction in SEP amplitude during TENS has been attributed to changes in the processing of sensory information at all levels in the nervous system (i.e. peripheral, spinal, subcortical or cortical). It has also been suggested that naloxone can reverse this reduction in late latency SEP amplitude [Salar et al. 1980]. Furthermore, Golding et al. [1986] suggested that the baseline peak-to-peak amplitude of an individual's SEP may be related to response to TENS. Healthy subjects with small SEPs showed smaller elevations in experimental pain threshold than subjects with large baseline SEPs. Hence Golding et al. suggested that patients with small SEPs were less likely to respond to TENS.

Aims of Chapter 4

Although TENS has been found to reduce the amplitudes of both early and late latency SEPs in healthy subjects, no studies have examined the effects of TENS on spontaneous EEG.

The aim of Chapter 4 was to investigate the effects of TENS on:

- (i) Late waveform components of the SEP.
- (ii) Power spectrum of spontaneous EEG.

It was hoped that the results would provide information on the mechanisms of TENS action. Furthermore, the utility of baseline SEP and spontaneous EEG in predicting response to TENS was examined. Thus, three experiments were designed to:

- (i) Examine the effects of TENS on late latency components of the SEP (Exp.4.1).
- (ii) Examine the effects of TENS on spontaneous EEG in healthy subjects (Exp.4.2).
- (iii) Examine the effects of TENS on pain intensity rating and spontaneous EEG in pain patients (Exp. 4.3).

THE EXPERIMENTS

EEG Recording Techniques-General Methods

General EEG recording techniques are described below. Figure 4.3 gives an overview of the EEG recording system and the functions of individual components in the system are described in Appendix C.

Electrode placement

The number and placement of scalp electrodes used during recording varies depending upon the experimenter's requirements and the equipment available. The initial description of standard electrode positions (called the 10-20 system for electrode placement) was given by Jasper [1958] and used by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (Fig.4.4).

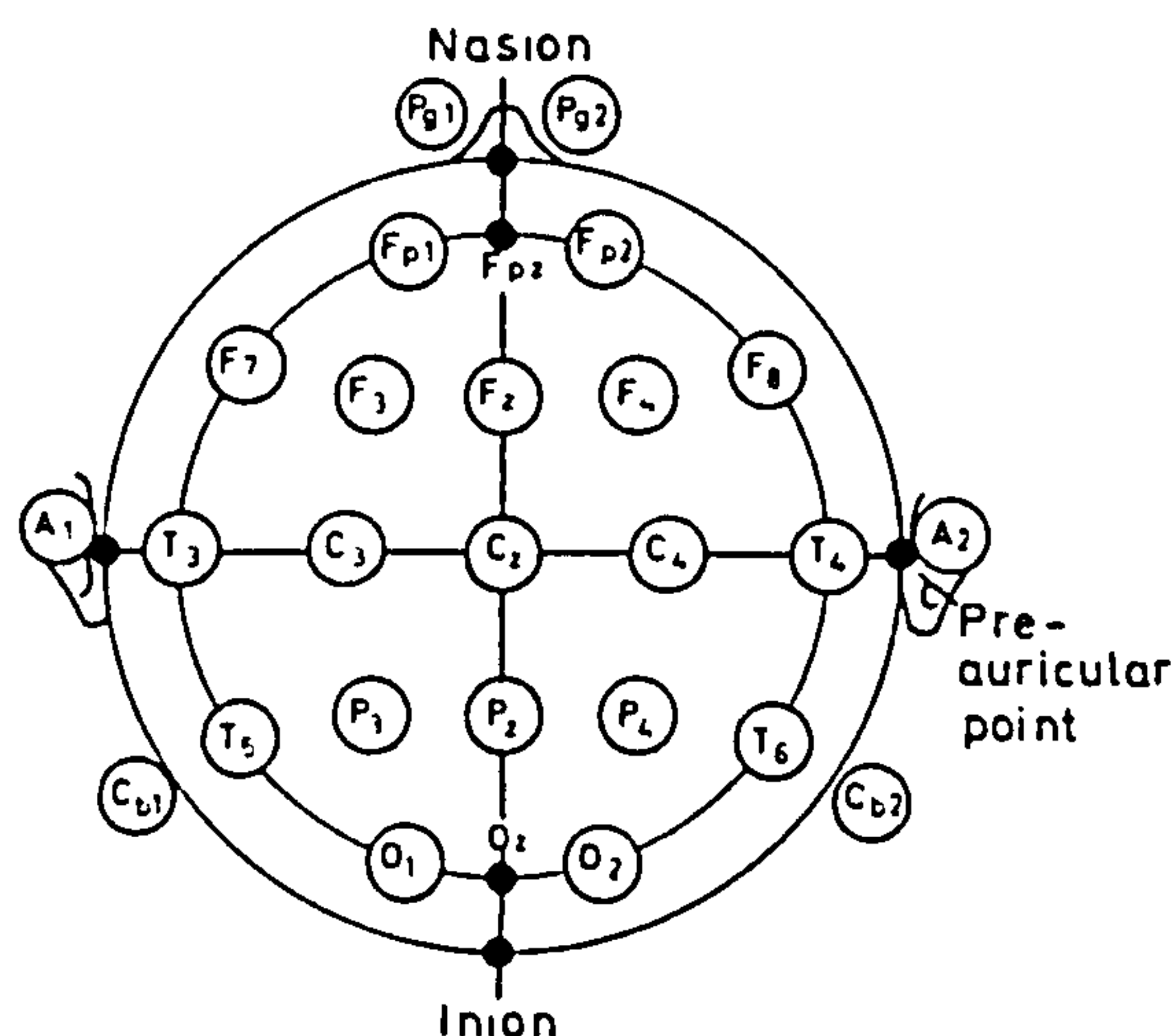


Fig.4.4 The 10-20 system of electrode positions as originally described by Jasper 1958. For full description see Cooper et al. [1984].

A reference electrode is chosen as a point to which brain potentials are compared and in the experiments that follow electrodes attached to the mastoid process of both sides of the head were linked (termed linked mastoids - LM) and used as reference, (although other reference points (ears) can also be used). Such a derivation is termed common reference and is placed so as to minimise the possibility of picking up potentials from the brain.

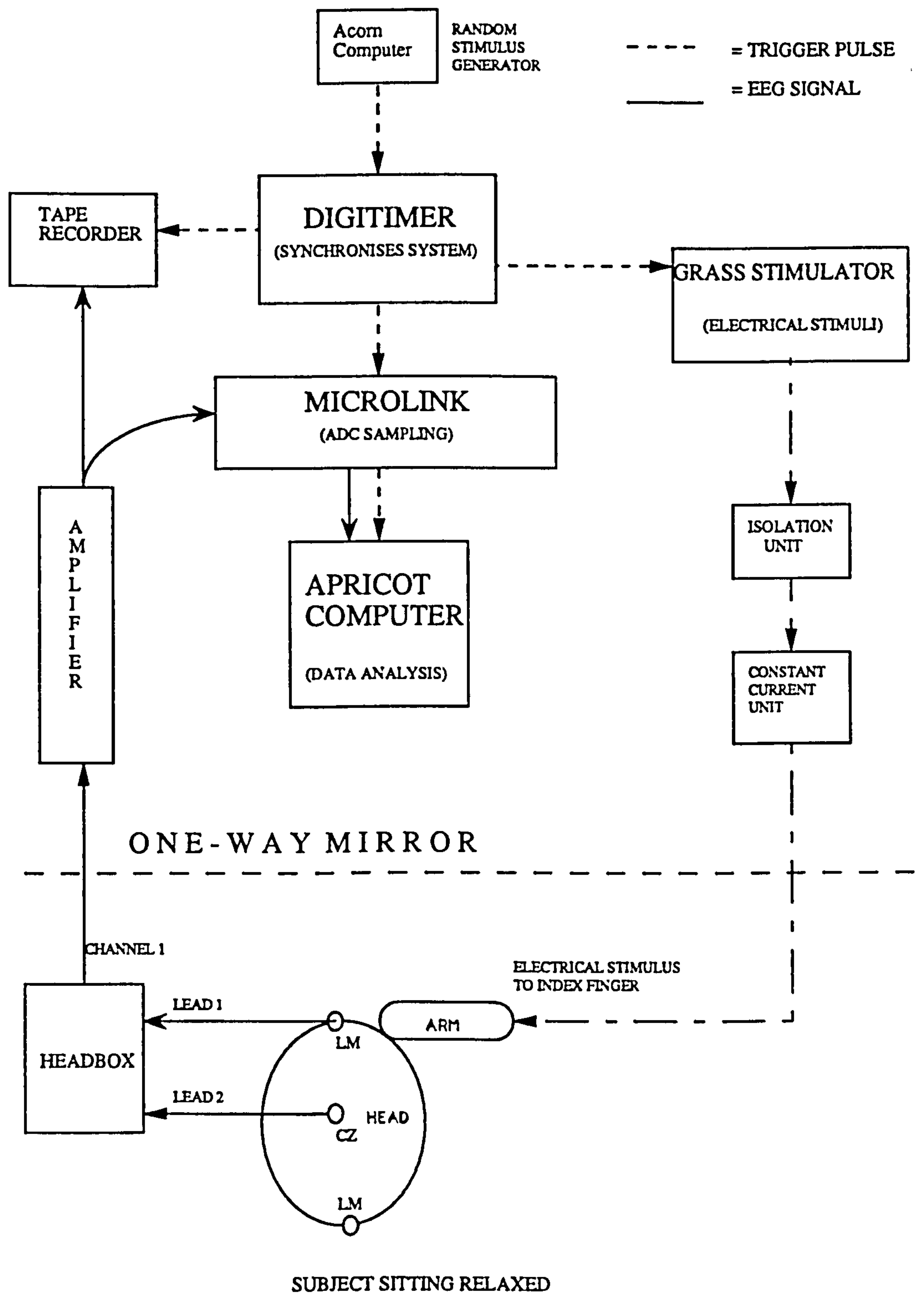


Fig.4.3 Overview of recording system (see text and Appendix C for full description of the function of the components of the recording system).

In the experiments that follow EPs were recorded at Cz (vertex - somatosensory cortex), and spontaneous EEG at C3 (left somatosensory cortex - for high frequency activity) and O1 (left occipital - for low frequency activity). These commonly used sites were chosen to optimise the recording of the respective EEG variables. A nasion electrode (Nz), placed between the eyes, was used to monitor electro-oculographic (EOG) activity.

Recording procedure

Subjects or patients sat in a temperature controlled (21°C) room and the experimenter in an adjoining laboratory; communication was by means of a two-way intercom and observation by a one-way window (Fig.4.5).



Fig.4.5 EEG recording. Subject sitting during an experiment with experimenter in adjoining laboratory. Under normal recording conditions the subject would be unable to see the experimenter due to differential lighting.

Silver-silver chloride cup electrodes filled with a conductive gel (hypertonic saline jelly - Dracard), were attached to the surface of the scalp by adhesive. The resistance (or more correctly the impedance) between electrodes and scalp was small (below 2Kohms) and matched with respect to a reference electrode on the forehead (used as a zero potential reference), thus reducing electrical artefact (see Appendix C).

Scarification of the surface of the skin underlying the electrode, using a syringe with a blunted needle, was performed to reduce impedance, which was measured by an impedance meter.

Electrode leads were connected to the amplifier via a headbox (which selects recording channels, i.e. the comparison of primary (Cz, C3 or O1) and reference (LM) electrodes). High and low pass filters were set to improve signal to noise ratio (see Appendix C), and signals amplified to a range of 100 μ V. The Microlink 3 converted the EEG signal from analogue (voltage) to digital (numerical) prior to storage in the Apricot Xen computer (Analogue-to-Digital Conversion (ADC) sampling rate=128 samples/sec/channel with 8 bit resolution). Biodata CEAN 400 computer software (Computerised Electroencephalographic ANalysis) was used to collect and analyse spontaneous EEG and SEP data. EEG signals were simultaneously monitored on-line using a cathode ray oscilloscope and recorded onto FM tape (Racal) for subsequent off-line analysis.

Spontaneous EEG and SEP recordings generally lasted 1.5 minutes during which subjects were asked to sit as still as possible with either:

- (i) eyes closed to optimise the recording of low frequency activity,
- (ii) eyes open to fixate on a dot (to reduce eye movements) and optimise the recording of high frequency activity.

Artefact

After recording, but prior to EEG analysis, an experienced EEG technician (Mr V.R. Marsh - VRM) examined raw EEG off-line (tape replay) for signs of artefact due to:

- (i) the patient, i.e. eye movements (Electro-oculographic - EOG) or muscle potentials (Electromyographic - EMG),
- (ii) electrical interference external to patient, i.e. TENS and recording equipment.

A full description of the problems of EEG artefacts is given in Appendix C.

As EOG is a main source of artefact, a nasion electrode was placed between the eyes used to monitor EOG. Correction of primary recording channels (i.e. Cz-LM; C3-LM; O1-LM) for EOG artefact was performed by an experienced EEG technician (VRM) at the end of the experiment using methods described by Verleger et al. [1982], and Thom and Andersen [1984] as follows:

(i) In spontaneous EEG recording, EOG contaminated epochs were rejected. No EOG artefact was noted when recording spontaneous EEG with eyes closed (Exp. 4.2 and 4.3b).

(ii) In SEP recording (Exp. 4.1) primary recording channels were compensated for EOG artefact by subtracting a proportion of EOG recorded at the nasion electrode.

EMG artefact was monitored on-line via a cathode ray oscilloscope and was reduced by relaxing or changing the posture of the patient prior to recording. TENS artefact, due to the electrical pulses of TENS, was readily identifiable both on-line and in the graphical display of the power spectrum (Fig.4.6). The results of 2 patients were omitted from statistical analysis in Experiment 4.3 due to TENS artefact.

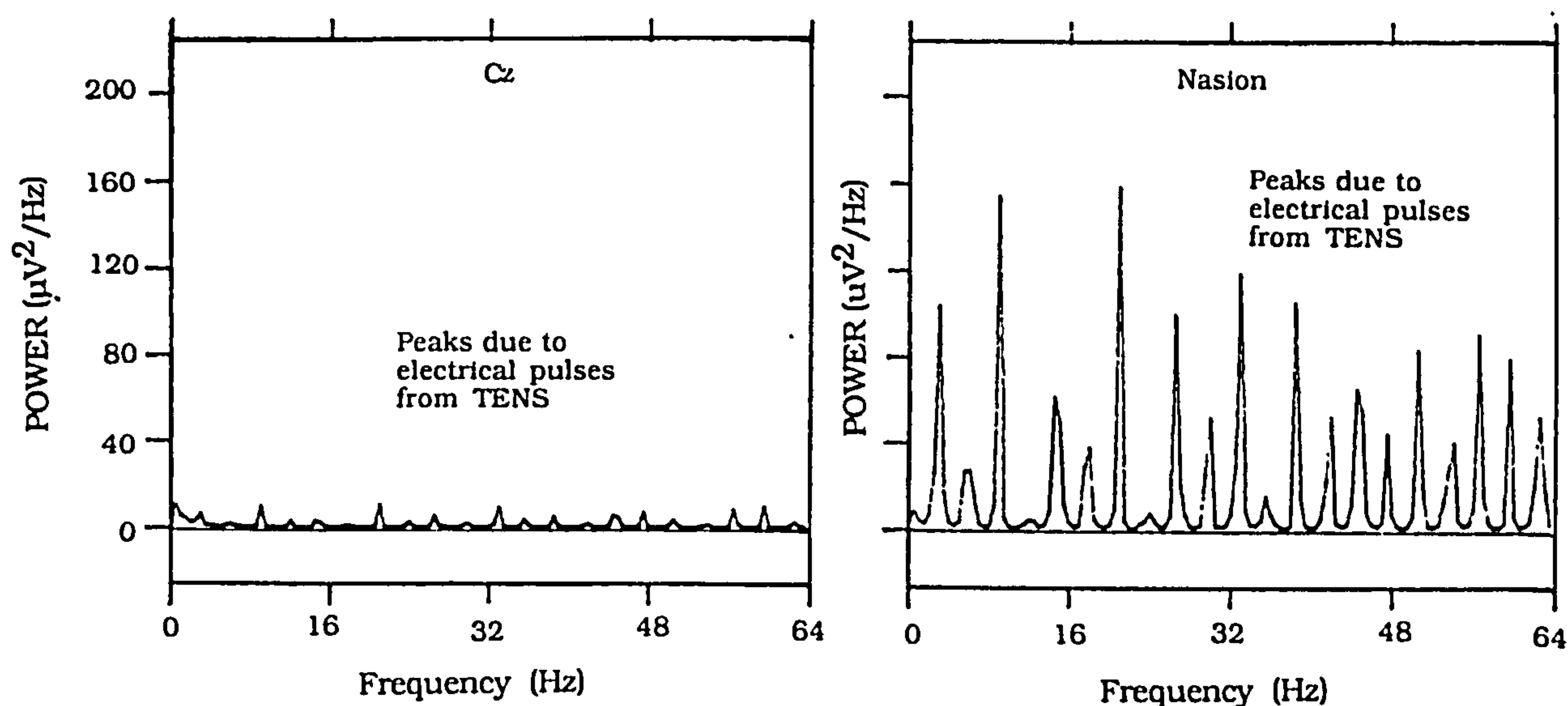


Fig.4.6 TENS artefact contamination of spontaneous EEG. Identification of TENS artefact is made simple because of the large peaks occurring in power spectrum recorded at both Cz and Nz electrodes. Of note is the large power recorded at Nz.

EEG analysis

Spontaneous EEG: The Biodata CEAN 400 computer software (and other EEG computer programs) subdivides a length of spontaneous EEG into a number of shorter segments of equal duration called 'epochs'. Thus, an epoch is a basic period of time during which the EEG is sampled, and may be anything from a few seconds to

minutes. Epochs are separated by a small time interval to allow the computer to store the large volume of incoming data, and although sampling is not continuous the fact that epochs are equally spaced throughout the recording makes it unlikely that any alteration in the steady state spontaneous EEG activity will go undetected.

Once collected, the spontaneous EEG needs to be analysed. A powerful and widely used method of EEG analysis is based on the calculation of the Fast Fourier Transform (FFT) from which a graph of power ($\mu V^2/Hz$) against frequency (Hz), termed power spectrum, is created. Power spectrum is extremely useful in identifying the components of complex waveforms, thus making comparisons of EEG portions (i.e. pre- and post -drug) possible. The FFT is a mathematical procedure (algorithm) used to re-organise the EEG from its conventional form in the time domain into the size and distribution of the frequencies that make it up (i.e. the frequency domain). Creating power spectrum involves substantial computations which are not possible to perform in real-time by the CEAN 400 system. Thus, when all the data had been collected it was saved on the winchester disk of the Apricot computer and analysed off-line using FFT [for review see Kunkel 1984].

The power spectrum for each epoch and for every channel is calculated and then averaged, to give an averaged power spectrum. The power in each of the conventionally defined EEG frequency bands can be calculated and the power at any particular frequency found using interactive cursors (see Fig.4.1).

Cortical Evoked Potentials: An averaged evoked potential is created by the repeated presentation of a stimulus in order to enhance the cortical response in contrast to spontaneous EEG activity. Thus, EEG data is collected during several recording 'sweeps' (or cycles). The Apricot computer (via CEAN 400 software) coordinates a sequence of time locked events (triggered by the digitimer), to present the stimulus (via the stimulating unit), collect EEG data (via the Microlink) and create the average evoked response on-line. Random or irregular inter-stimulus intervals are used to reduce habituation. The latencies and peak-to-peak amplitudes of respective component waves of the averaged evoked potential are measured as indices of response (see Fig.4.2, for review see Bromm [1984]).

Experiment 4.1

The effect of TENS on late components of the somatosensory evoked potential.

The aim of Experiment 4.1 was to investigate the effects of TENS on the latency and peak-to-peak amplitude of the N1 and P2 components of the SEP, elicited by 'strong but non-painful' electrical stimuli administered to the index finger.

Subjects and procedure

Twenty healthy university students (female $n=12$, male $n=8$; age range=20-23 years of age) participated in the present study. All were naive to the experimental procedure, and each was randomly allocated into either (i) active TENS, or (ii) sham TENS groups.

SEP recordings were made in the morning. Electrode positions were Cz (vertex) and Nz (nasion) referenced to LM (linked mastoids); amplifier settings; high pass filter=1s, low pass filter=1kHz, range 100 μ V; compensation of primary electrodes (Cz-LM) for EOG artefact was performed off-line (by VRM) using a method of subtraction [Verleger et al. 1982; Thom & Andersen 1984].

SEPs were recorded during 7, 10 minute experimental cycles (i.e. 2 x pre-TENS; 3 x during TENS; 2 x post-TENS) with subjects sitting in a relaxed awake state while fixating a dot. SEPs were elicited by 35 square wave electrical stimuli (pulse width 200 μ s), randomly delivered (in time 1.2-5 s) to the index finger of the left hand via two carbon rubber electrodes ($2 \times 1 \text{ cm}^2$) at a 'strong but non-painful' intensity. The intensity of the evoking stimulus was determined prior to the start of the experiment by increasing stimulus intensity (pulse frequency=3Hz) until rated as 7 on a verbal rating scale where 0=imperceptible and 10=painful. Subsequent stimulus intensity ratings were measured on a visual analogue scale (VAS) immediately after each SEP recording.

A Microtens 7577 was used to produce TENS, via $2 \times 4 \text{ cm}^2$ carbon rubber electrodes placed 1cm apart on the ventral surface of the left arm overlying the median nerve, 3cm above the first wrist crease. TENS was switched on prior to the start of cycle 3 and switched off at the end of cycle 5.

The electrical characteristics of TENS were monitored using the Frye Analyser and set by the experimenter as follows:

- (i) pulse intensity - 'strong but comfortable' with no observable muscle activity,
- (ii) pulse pattern - continuous,
- (iii) pulse frequency - 80Hz,
- (iv) pulse width - 200 μ s.

Sham TENS was administered as described in Chapter 3 by a modified stimulator (no current output) and a coloured suggestion, re-inforced with a digital display on the Frye Analyser.

Results of Experiment 4.1

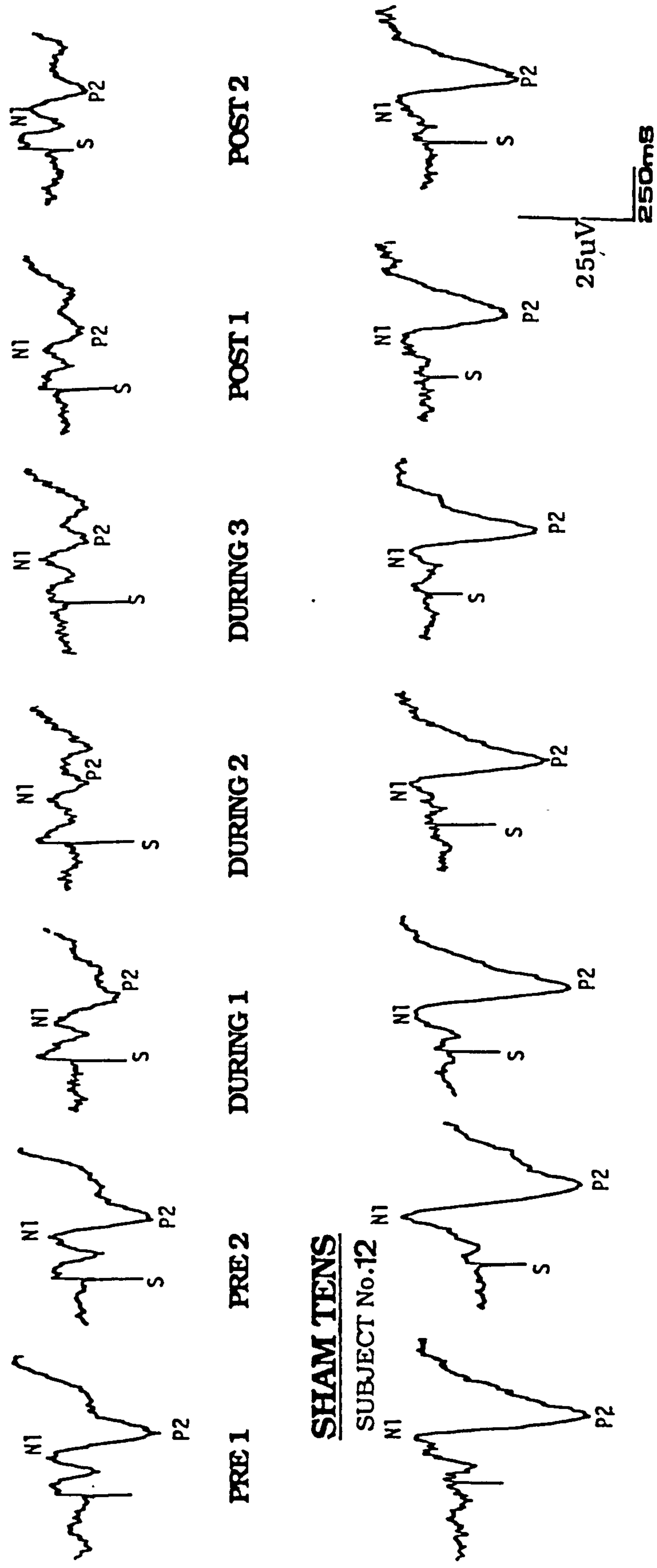
Marked inter-subject variability in the intensity of the evoking stimulus to achieve a 'strong but non-painful' level was observed (range=0.5-21mA above sensory detection threshold - SDT). The SEP was characterised by a series of positive and negative waves P1, N1 and P2 as shown in Fig.4.7 (Mean \pm SD latency: P1=not measured, N1=144.4 \pm 29.8ms, P2=210.3 \pm 36.3ms, n=20). Mean \pm SD N1P2 amplitude and stimulus intensity ratings are shown in Table 4.2.

Mean \pm SD	TIME (mins)						
	Pre 1 -10	Pre 2 -01	Drg 1 +10	Drg 2 +20	Drg 3 +30	Post 1 +40	Post 2 +50
N1P2 (μ V)							
TENS	23.5 \pm 8.4	22.3 \pm 7.4	17.2 \pm 6.6	16.3 \pm 5.5	16.5 \pm 7.3	15.0 \pm 6.7	15.4 \pm 5.9
Sham	17.8 \pm 10.1	17.9 \pm 9.2	15.7 \pm 10.1	15.2 \pm 9.7	15.1 \pm 8.9	13.3 \pm 6.1	15.4 \pm 7.0
STIMULUS INTENSITY							
TENS	6.2 \pm 1.9	6.2 \pm 1.8	4.9 \pm 3.0	4.6 \pm 2.9	4.6 \pm 2.8	4.5 \pm 2.3	4.8 \pm 2.3
Sham	6.7 \pm 1.5	6.4 \pm 1.8	6.3 \pm 1.6	6.1 \pm 1.6	6.0 \pm 1.6	6.0 \pm 1.6	6.1 \pm 1.8

Table 4.2 Mean \pm SD results of Exp.4.1. Mean N1P2 peak-to-peak amplitudes and evoking stimulus intensity rating for TENS and sham groups. Pre=pre-treatment, Drg=during-treatment, Post=post-treatment N1P2=Peak-to-peak amplitude of N1P2 (μ V), Stimulus intensity=Intensity of evoking stimulus measured on a visual analogue scale (VAS) where 0=imperceptible and 10=painful

ACTIVE TENS

SUBJECT No.4



SHAM TENS

SUBJECT No.12

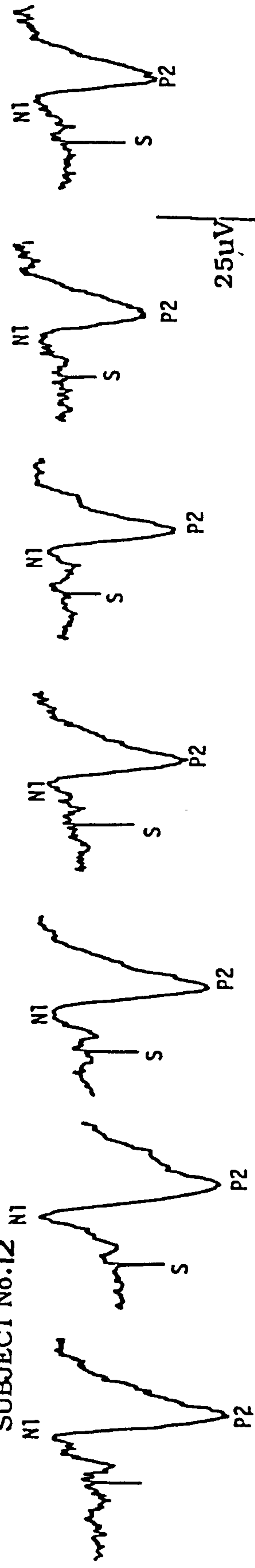


Fig.4.7 Effect of active TENS and sham TENS on the somatosensory evoked potential (Exp. 4.1). A marked reduction in N1P2 amplitude was observed during active but not sham TENS.

A pre-treatment mean of cycle 1 and 2 was calculated as pre-treatment baseline (no significant differences in pre-treatment cycles 1 and 2 for (i) N1P2 amplitudes, $P=0.7$; (ii) intensity rating of the evoking stimulus, $P=0.4$, paired t-test). No significant differences in baseline N1P2 amplitudes or intensity rating of the evoking stimulus were observed between sham and TENS groups (unpaired t-test); thus the change in N1P2 and intensity rating during treatment was calculated for each cycle and individual by subtracting the pre-treatment mean from subsequent during and post-treatment cycles (Fig.4.8).

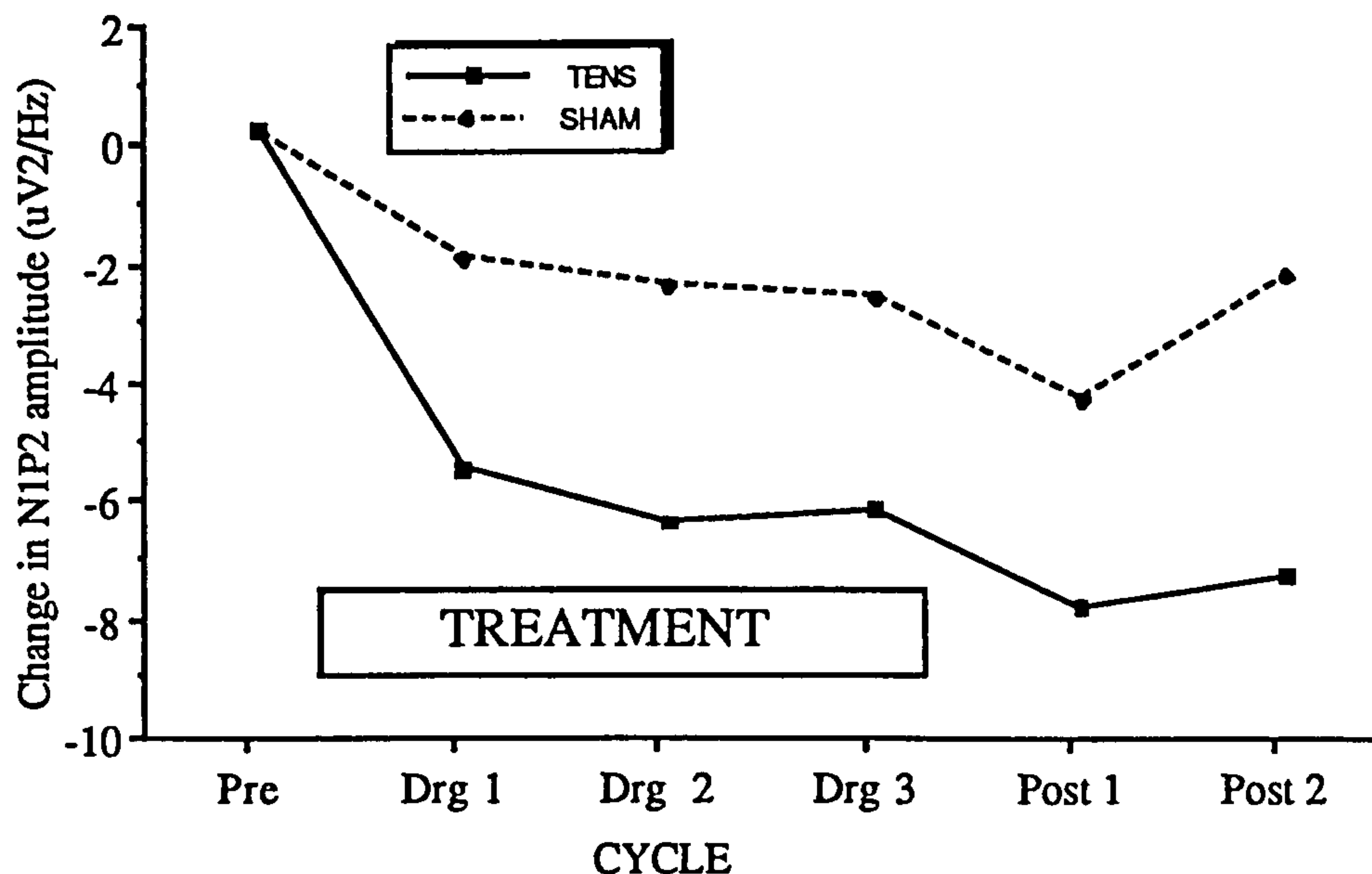


Fig.4.8 Mean change in peak-to-peak N1P2 amplitude from pre-treatment baseline in active and sham TENS groups (Exp. 4.1). Unpaired t-test TENS v sham mean change across during-Drg- ($n=3$ cycles, $P=0.04$) and post ($n=2$ cycles, $P=0.02$) treatment cycles.

Mean change in N1P2 amplitude and VAS across the (i) 3 during treatment and (ii) 2 post-treatment cycles, for each individual, were used as summary measures of response (Table 4.3).

TENS produced a significant reduction in N1P2 amplitude when compared to sham both:

- (i) during treatment cycles (Mean change in N1P2 amplitude: TENS= $-6.2\mu\text{V}$, sham= $-2.4\mu\text{V}$, $P=0.04$, unpaired t-test),
- (ii) post-treatment cycles (TENS= $-7.7\mu\text{V}$, sham= $-3.5\mu\text{V}$, $P=0.02$, unpaired t-test).

SUB	TMT	mA EP	N1P2 PEAK-TO-PEAK AMPLITUDE (µV)			STIMULUS INTENSITY RATING (0=IMPERCEPTABLE ---> 10=PAINFUL)		
			Mean PRE (n=2)	Mean DURING (n=3)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=3)	Mean POST (n=2)
1	TENS	5.5	29.6	25.9	22.2	7.1	5.3	4.6
2	TENS	9.4	14.0	9.7	9.0	5.0	0.5	1.7
3	TENS	6.5	17.2	12.3	12.0	7.6	6.0	6.0
4	TENS	11.2	24.4	12.3	12.6	1.6	0.5	1.0
5	TENS	0.5	17.0	14.4	9.4	5.7	5.6	4.4
6	TENS	10.6	26.8	20.1	8.4	7.7	7.2	7.1
7	TENS	9.0	16.8	12.9	6.4	7.3	7.2	6.6
8	TENS	6.2	32.8	24.4	20.4	6.9	8.4	8.0
9	TENS	21.0	18.6	18.5	17.8	5.4	4.7	4.0
10	TENS	9.5	31.8	16.1	23.4	7.3	1.7	3.4
MEAN			22.9	16.7	15.2	6.2	4.7	4.7
11	SHAM	9.5	13.2	16.0	12.8	7.8	5.4	3.6
12	SHAM	12.0	40.2	38.0	29.0	3.8	2.9	3.3
13	SHAM	18.7	13.0	6.3	7.7	5.8	5.8	6.1
14	SHAM	1.1	15.3	13.2	15.5	5.9	6.5	6.5
15	SHAM	7.0	15.2	13.3	10.4	8.8	8.4	8.8
16	SHAM	3.7	16.8	13.9	13.5	7.0	6.3	6.3
17	SHAM	10.8	9.8	5.8	7.3	6.5	5.6	5.4
18	SHAM	2.7	9.6	8.8	11.2	5.0	5.0	5.3
19	SHAM	17.6	26.6	20.8	20.5	6.9	7.1	7.2
20	SHAM	8.9	18.6	17.2	15.5	7.9	8.2	7.9
MEAN			17.8	15.3	14.3	6.6	6.1	6.0

Table 4.3 Individual change in SEP amplitude and rating of stimulus intensity during TENS and sham in pain-free healthy subjects (Exp. 4.1). SUB = Subject no.: TMT = treatment Group: TENS = Transcutaneous Electrical Nerve Stimulation: SHAM= Sham TENS Mean PRE = Mean of two pre-treatment measures: Mean DURING = mean of three during treatment measures: Mean POST = mean of two post-treatment measures. Mean was calculated for each group. Statistical analysis was performed by calculating changes during treatment (by subtracting PRE from DURING for each individual) and performing two sample unpaired t-test between groups.

TENS also reduced the intensity rating of the evoking stimulus, although this failed to reach significance. (Mean change (VAS units): (i) during treatment cycles, TENS=-1.5, sham=-0.4, $P=0.19$; (ii) post-treatment cycles, TENS=-1.5, sham=-0.5, $P=0.15$, unpaired t-test, see Table 4.3). No relationships (Pearson correlation coefficients) were observed between baseline N1P2 and either: (i) change in the intensity rating of the evoking stimuli during TENS, or (ii) change in N1P2 amplitude during TENS.

Mean N1 and P2 latencies were calculated for each individual for pre-, during and post-treatment cycles, and subjected to the same statistical analysis as above. No significant changes in latencies were found between TENS and sham groups (Mean change in latency during treatment: N1, TENS=2.1ms, sham=0.9ms, $P=0.7$; P2, TENS=3.0ms, sham=3.9ms, $P=0.84$, unpaired t-test)

Main findings of Experiment 4.1

- (i) Marked inter-subject variability in the current intensity necessary to produce a 'strong but comfortable' evoking stimuli was observed.
- (ii) TENS produced a significant reduction in N1P2 peak-to-peak amplitude when compared to sham. However sham also reduced N1P2 amplitude but to a lesser magnitude.
- (iii) The reduction in N1P2 amplitude was not dependent upon pain perception as the evoking stimulus was non-painful. Thus, TENS effects may not be specific to the pain system.
- (iv) No significant changes N1 or P2 latency were observed during TENS.

Experiment 4.2

The effect of TENS on resting awake EEG in healthy subjects. A preliminary report.

The TENS-induced reduction in peak-to-peak amplitudes of late waveform components of the SEP (Exp. 4.1) suggests that TENS affects the processing of sensory information. By implication TENS may also produce changes in spontaneous EEG. Although the effects of TENS on spontaneous EEG are unknown, it has been suggested that pain and analgesics may induce changes in spontaneous EEG [Bromm et al. 1989]. Hence, acupuncture has been shown to increase alpha activity during the reduction of tension headache [Manna et al. 1984]. The aim of Experiment 4.2 was to examine the effects of TENS on spontaneous EEG in healthy pain-free subjects. Conditions were optimised for the recording of alpha activity by recording EEG at O1 (left occipital electrode position), with eyes closed and filters set to reduce the recording of high frequency activity.

Subjects and procedure

Sixteen healthy paid students (female n=6, male n=10; age range=21-33, mean=25.6 years of age) participated in the study. All were naive to the experimental procedure but had attended the laboratory for a brief familiarisation session prior to the recording session. Subjects were randomly allocated into either (i) active TENS (TENS), or (ii) sham TENS (sham) groups.

Spontaneous EEG recordings were made in the morning; electrode positions were O1 (left occipital) and Nz (nasion) referenced to LM (linked mastoids); amplifier settings; high pass filter=0.2s, low pass filter=30Hz, range=100 μ V. Each EEG recording was re-examined (by VRM) for EOG and/or TENS artefact contamination. No such contamination was observed in any subject.

Spontaneous EEG was recorded in 6, 5 minute cycles (i.e. 2 x pre-TENS; 2 x during TENS; 2 x post-TENS) with subjects sitting in a relaxed awake state with eyes closed to optimise alpha activity. Subjects were requested to make their 'mind as blank as possible'. EEG recording lasted 1.5 minutes, separated by a 3.5 minute rest period. Active TENS (TENS) or sham TENS (sham) was administered immediately after the recording of pre-treatment cycle 2, and switched off immediately upon cessation of the recording of during TENS cycle 2 (duration of treatment=21.5 mins). During TENS

recordings were taken at +15 min and + 20 min after 'switch on'. Each recording acquired 25, 2 second epochs and averaged spectra were computed off-line using FFT (Biodata software) for spectral analysis. Power spectrum ($\mu V^2/Hz$) was analysed in the following (traditional) frequency bands:

- delta,0.0 to 3.5Hz,
- theta,4.0 to 7.5Hz,
- alpha,8.0 to 13.5Hz,
- slow beta,14.0 to 25.5Hz,

with a resolution of 0.5Hz. Peak alpha frequency was also measured.

A Microtens 7757 was used to produce 'strong but comfortable' TENS. Stimulating characteristics were monitored using the Frye Analyser and fixed by the experimenter as follows:

- pulse pattern=continuous,
- pulse frequency=80Hz,
- pulse width=200 μs ,
- electrode impedance <1Kohms .

TENS was delivered via two 8cm² carbon rubber electrodes placed 10 cm apart, straddling the spinal cord at L1/L2. Subjects in the active TENS group were asked to increase the intensity (pulse amplitude) of TENS to a 'strong but comfortable' level and to make subsequent adjustments to maintain this intensity during the course of the experiment. Sham TENS was administered as described in Chapter 3 and no subjects questioned the procedure.

Results of Experiment 4.2

Mean \pm SD power for each cycle and frequency band is shown in Table 4.4.

	MEAN \pm SD POWER SPECTRUM ($\mu V^2/Hz$)					
	Pre-1 -10mins	Pre-2 -05mins	During-1 +15mins	During-2 +20mins	Post-1 +25mins	Post-2 +30mins
DELTA						
TENS	21.2 \pm 10.2	19.6 \pm 8.9	21.2 \pm 11.3	20.4 \pm 11.9	20.5 \pm 10.0	17.1 \pm 7.8
Sham	19.5 \pm 6.6	19.0 \pm 7.1	18.5 \pm 6.4	19.0 \pm 10.0	20.1 \pm 6.7	20.0 \pm 6.8
THETA						
TENS	15.0 \pm 12.0	14.9 \pm 10.2	15.6 \pm 11.8	14.1 \pm 7.8	15.0 \pm 8.6	14.1 \pm 7.2
Sham	14.8 \pm 9.1	16.3 \pm 10.4	13.8 \pm 8.4	14.3 \pm 8.8	15.1 \pm 9.4	17.1 \pm 8.2
ALPHA						
TENS	91.1 \pm 37.5	84.0 \pm 45.0	99.2 \pm 52.5	85.5 \pm 58.5	84.2 \pm 59.5	78.8 \pm 49.5
Sham	101.8 \pm 59.7	105.3 \pm 74.2	106.3 \pm 65.4	91.1 \pm 39.1	102.9 \pm 58.1	104.6 \pm 72.8
BETA						
TENS	15.4 \pm 8.4	14.1 \pm 6.6	21.2 \pm 12.3	16.7 \pm 6.7	15.4 \pm 9.3	25.9 \pm 20.0
Sham	19.3 \pm 15.8	20.2 \pm 17.3	18.0 \pm 14.3	17.8 \pm 10.5	20.4 \pm 17.5	19.5 \pm 13.1

Table 4.4 Mean \pm SD power spectrum during active (n=8) and sham TENS (n=8) in pain-free healthy subjects. N.B. Beta = slow beta.

No significant differences were observed in the 2 pre, during or post-treatment cycles for any frequency band (paired t-test). Thus mean pre, during and post treatment power was calculated for each individual (Table 4.5). Fig.4.9 shows a graphical display of the power spectrum for a subject receiving active TENS and a subject receiving sham TENS.

The following range of pre-treatment baseline power for respective frequency bands were recorded:

Delta	9.5 to 39.5 $\mu\text{V}^2/\text{Hz}$
Theta	3.0 to 35.0 $\mu\text{V}^2/\text{Hz}$
Alpha	11.5 to 310.2 $\mu\text{V}^2/\text{Hz}$
Slow beta	3.4 to 57.8 $\mu\text{V}^2/\text{Hz}$

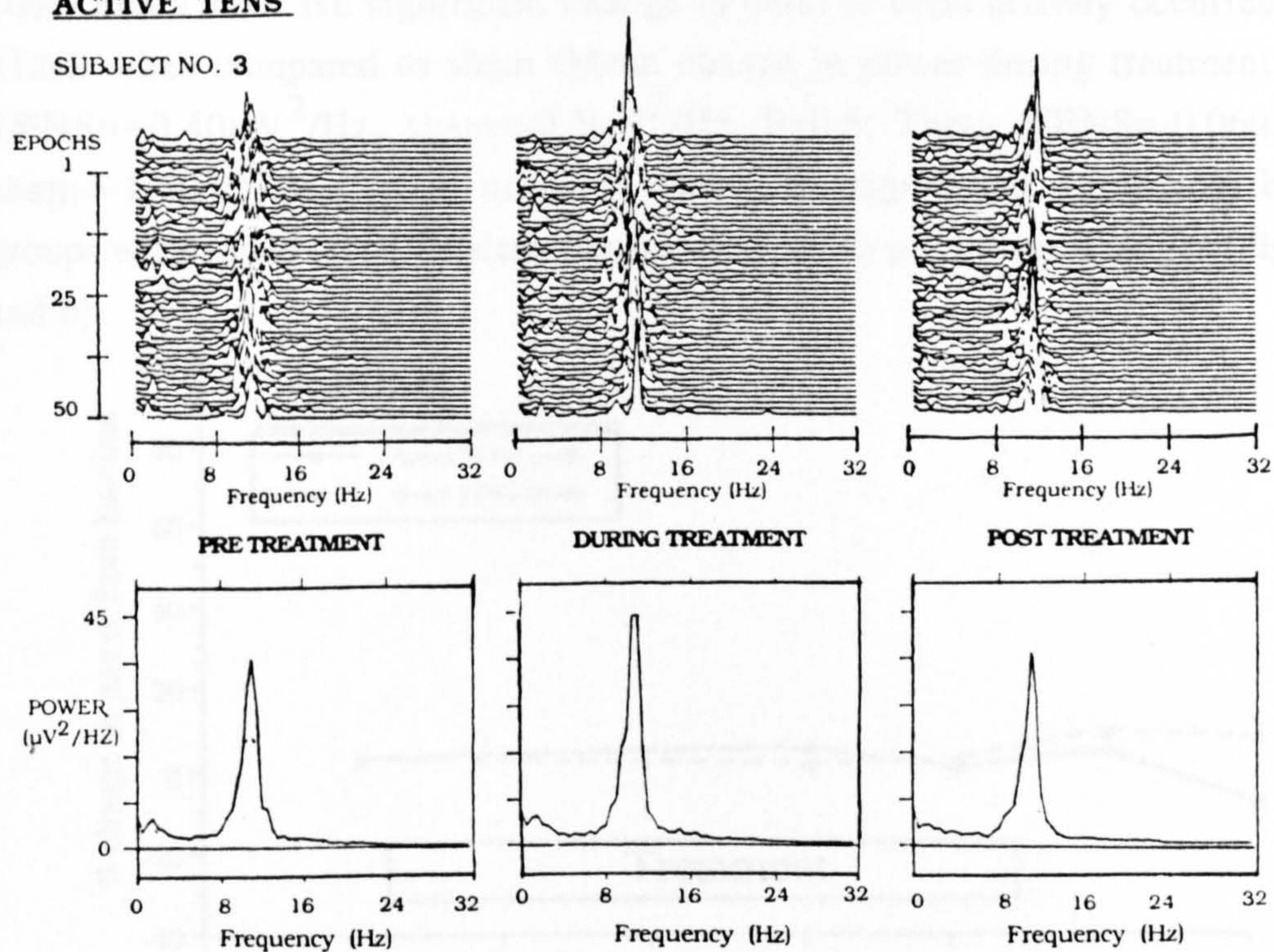
Although wide inter-subject variability in pre-treatment power were observed (especially in alpha power), no significant differences in pre-treatment power was found between sham and TENS groups for any frequency band (unpaired t-test TENS v sham). Therefore changes in power during treatment were calculated for each individual and used as a summary measure of treatment effect. Because of the wide inter-individual variability in pre-treatment baseline power spectrum, percentage change during treatment (from pre-treatment baseline) was also calculated for each individual. This percentage change in power spectrum would account for subjects with low baseline power showing small absolute changes in power spectrum during treatment.

SPECTRAL POWER ($\mu V^2/Hz$)											
SUB	TMT	DELTA		THETA		ALPHA		BETA			
		Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	
1	TENS	22.0	16.5	17.5	23.5	22.0	20.5	188.5	168.0	157.5	23.5
2	TENS	13.5	15.0	13.5	19.0	14.0	17.5	42.5	53.5	57.5	4.5
3	TENS	25.0	27.0	22.5	17.5	17.0	16.0	158.5	183.0	140.5	24.0
4	TENS	39.5	43.5	25.0	35.0	33.5	24.0	212.0	195.5	159.5	15.5
5	TENS	18.5	15.0	14.5	5.5	7.0	7.0	38.5	57.5	49.0	13.5
6	TENS	9.5	9.0	8.0	3.0	3.0	3.5	11.5	15.0	18.5	5.5
7	TENS	22.5	29.0	35.0	9.5	13.0	21.5	15.0	19.5	28.5	19.0
8	TENS	13.0	11.5	14.5	6.5	9.5	6.5	34.0	47.0	41.0	12.5
MEAN		20.4	20.8	18.8	14.9	14.9	14.6	87.6	92.4	81.5	14.7
9	SHAM	11.4	13.2	11.6	5.6	5.6	5.9	23.2	22.9	25.7	9.4
10	SHAM	22.6	22.3	26.9	21.3	26.8	27.9	310.2	357.6	335.6	19.3
11	SHAM	11.1	10.9	14.1	10.8	9.8	10.9	39.9	28.6	30.7	57.8
12	SHAM	30.2	30.0	29.3	28.5	20.1	22.7	168.4	130.4	158.8	25.2
13	SHAM	17.1	16.6	17.5	7.4	10.0	10.2	27.4	31.4	35.2	5.4
14	SHAM	14.8	14.8	15.8	29.8	24.1	23.6	94.1	102.0	97.2	10.6
15	SHAM	21.7	21.0	19.2	13.1	9.2	8.8	147.0	92.0	109.2	17.2
16	SHAM	24.9	21.3	26.2	7.9	6.4	6.3	18.2	24.4	37.6	13.4
MEAN		19.2	18.8	20.1	15.6	14.0	14.6	103.6	98.7	103.8	19.8
		$p=0.58$		$p=0.44$		$p=0.45$		$p<0.05$			
										20.0	

Table 4.5 Individual change in power spectrum during TENS and sham in pain-free healthy subjects (Exp.4.2) SUB = Subject no.: TMT = treatment Group: TENS = Transcutaneous Electrical Nerve Stimulation: SHAM= Sham TENS Mean PRE = Mean of two pre-treatment measures: Mean DURING = mean of three during treatment measures: Mean POST = mean of two post-treatment measures. Mean was calculated for each group.Statistical analysis.was performed by calculating changes during treatment (by subtracting PRE from DURING for each individual) and performing two sample unpaired t-test between groups.

ACTIVE TENS

SUBJECT NO. 3

**SHAM TENS**

SUBJECT NO. 12

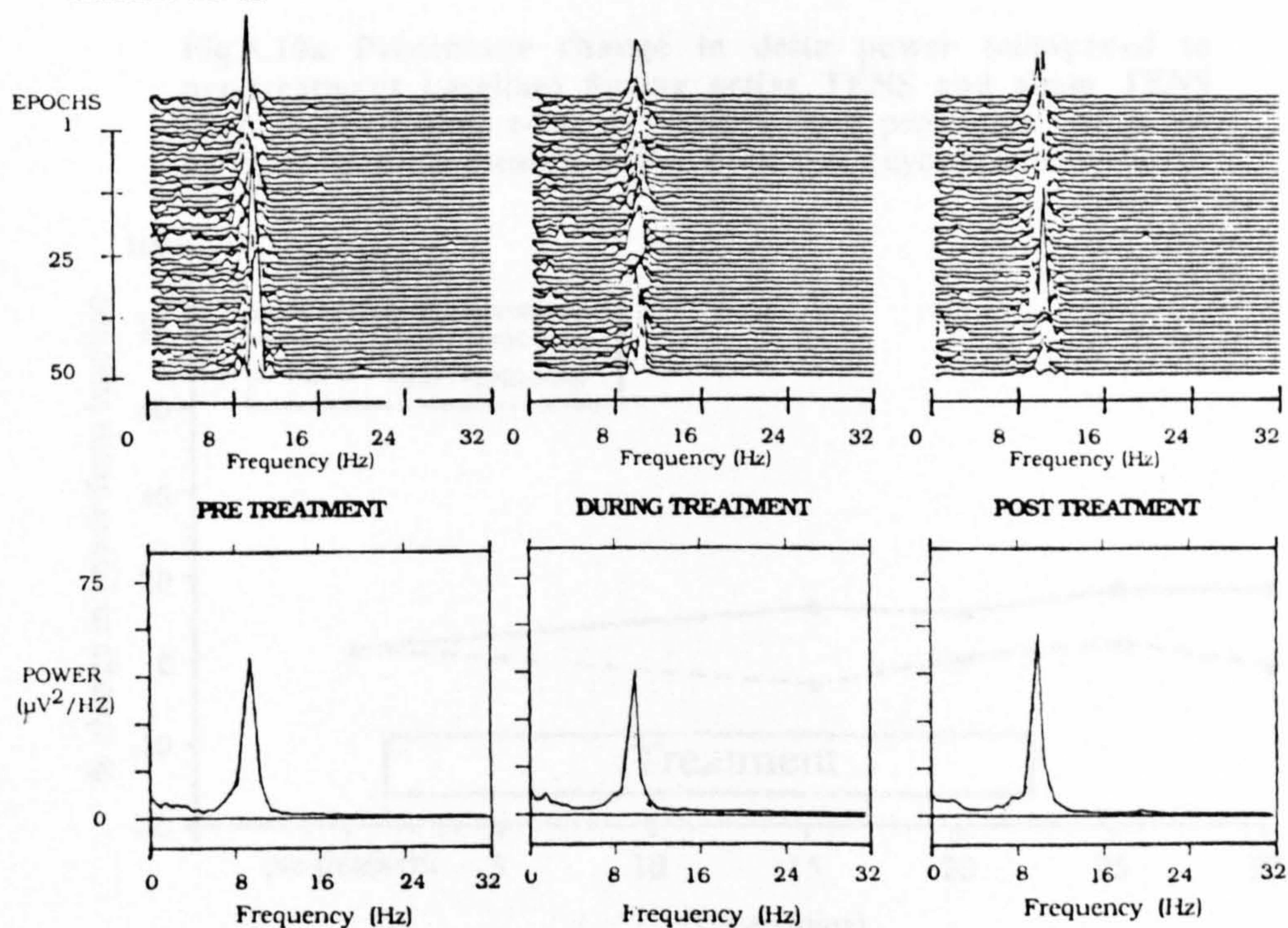


Fig.4.9 Graphical display of power spectrum in (a) one subject receiving active TENS and (b) one subject receiving sham TENS. Individual epochs (50 pre- during and post-) and averaged spectra are shown.

Delta and Theta: No significant change in delta or theta activity occurred during TENS when compared to sham (Mean change in power during treatment: Delta; TENS=+0.40 $\mu\text{V}^2/\text{Hz}$, sham=-0.5 $\mu\text{V}^2/\text{Hz}$, $P=0.6$; Theta; TENS=-0.06 $\mu\text{V}^2/\text{Hz}$, sham=-1.5 $\mu\text{V}^2/\text{Hz}$, $P=0.4$, unpaired t-test). No significant differences between groups were found when the data was transformed to percentage changes (Fig. 4.10a and b).

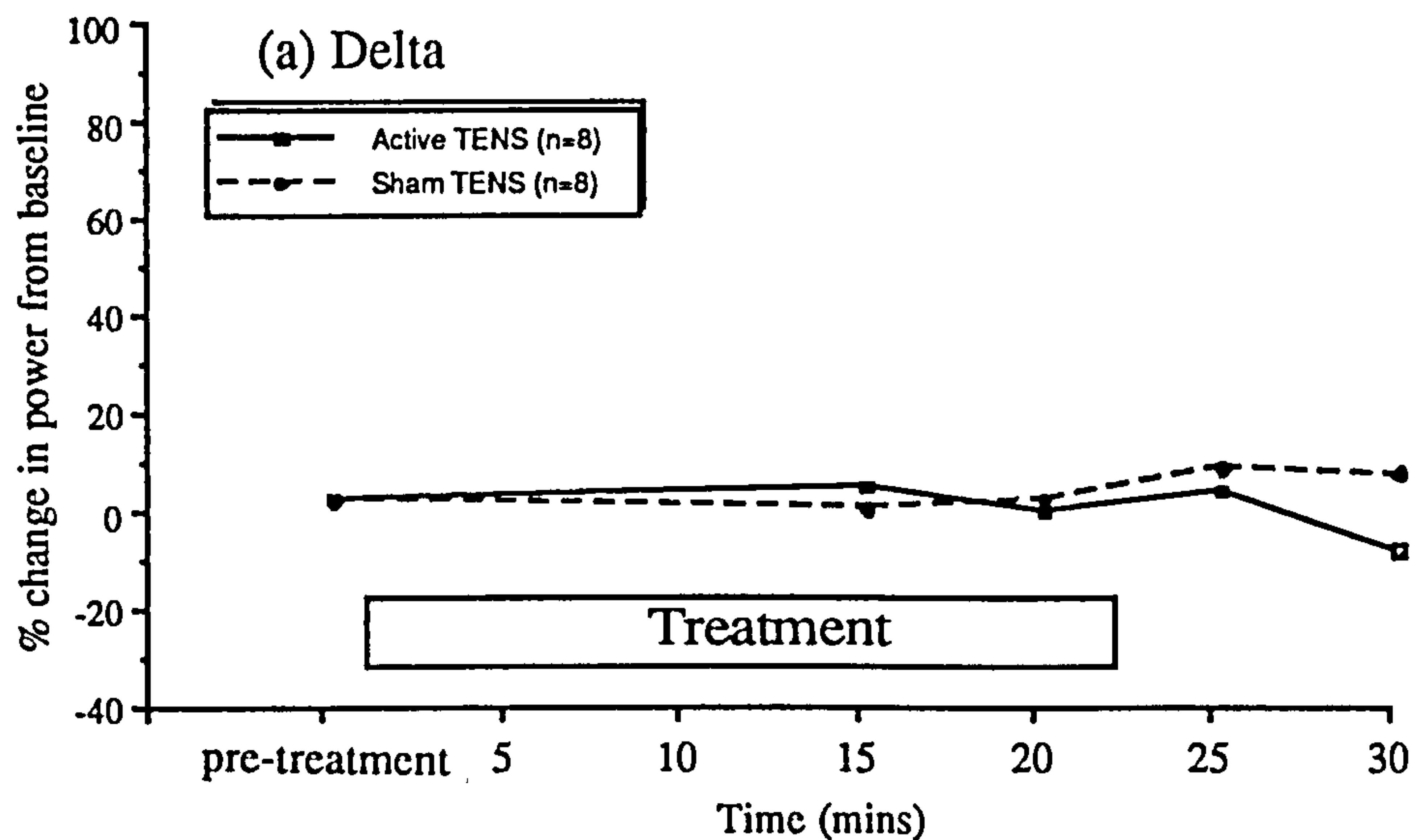


Fig.4.10a Percentage change in delta power (compared to pre-treatment baseline) during active TENS and sham TENS (Exp. 4.2). Unpaired t-test on TENS v sham percentage change for during and post-treatment cycles $P=0.6$ (mean of 2 cycles per individual).

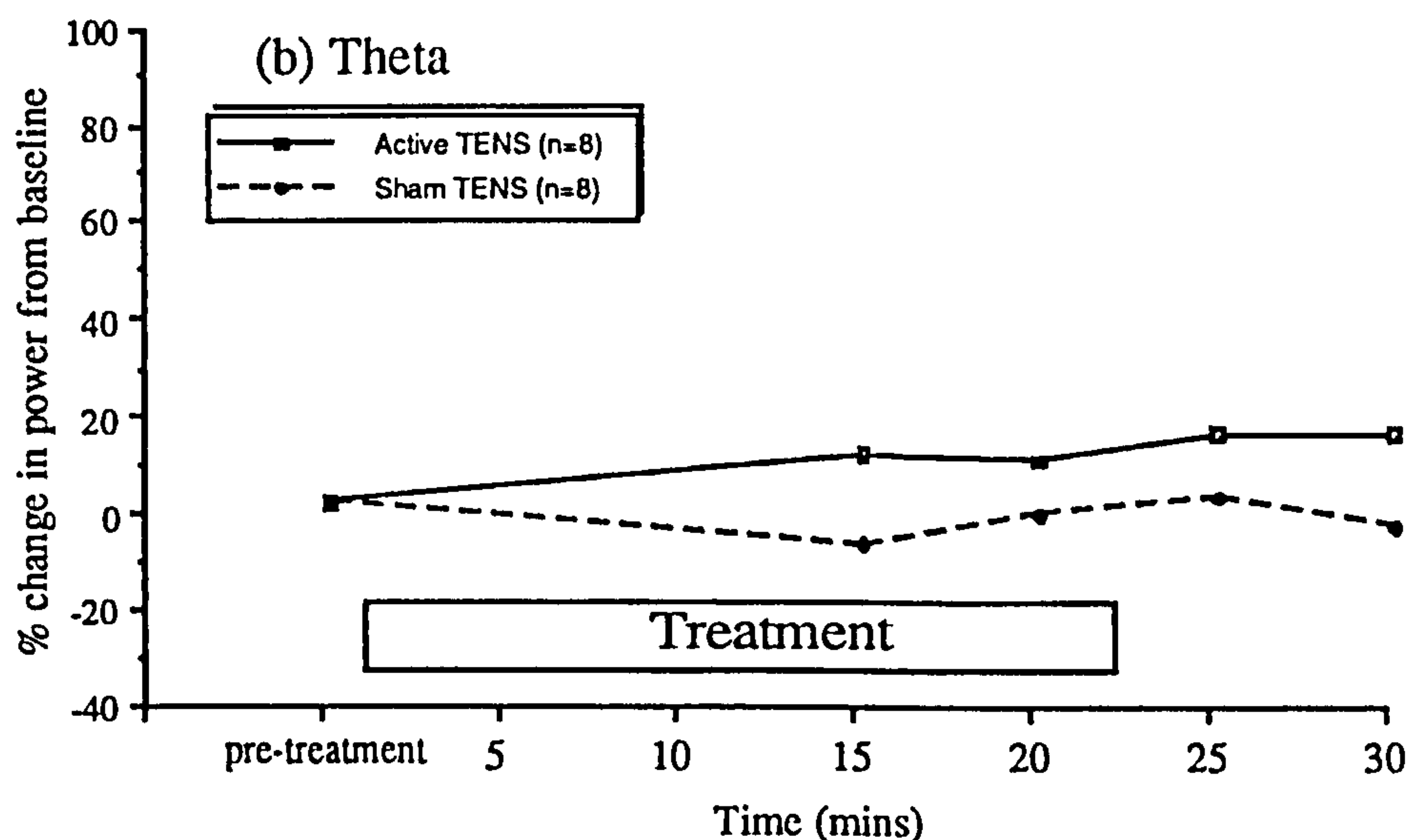


Fig.4.10b Percentage change in theta power (compared to pre-treatment baseline) during active TENS and sham TENS (Exp. 4.2). Unpaired t-test on TENS v sham percentage change for during and post-treatment cycles, $P=0.4$ (mean of 2 cycles per individual).

Alpha: Although a rise in alpha activity was observed during active TENS (Table 4.4) this failed to reach significance (Mean change; TENS=+4.8 $\mu\text{V}^2/\text{Hz}$, sham=-4.9 $\mu\text{V}^2/\text{Hz}$, $P=0.45$). The 21.3% rise in alpha activity during active TENS, when compared to the 2.1% reduction during sham, just failed to reach statistical significance ($P=0.064$, unpaired t-test, Fig.4.10c).

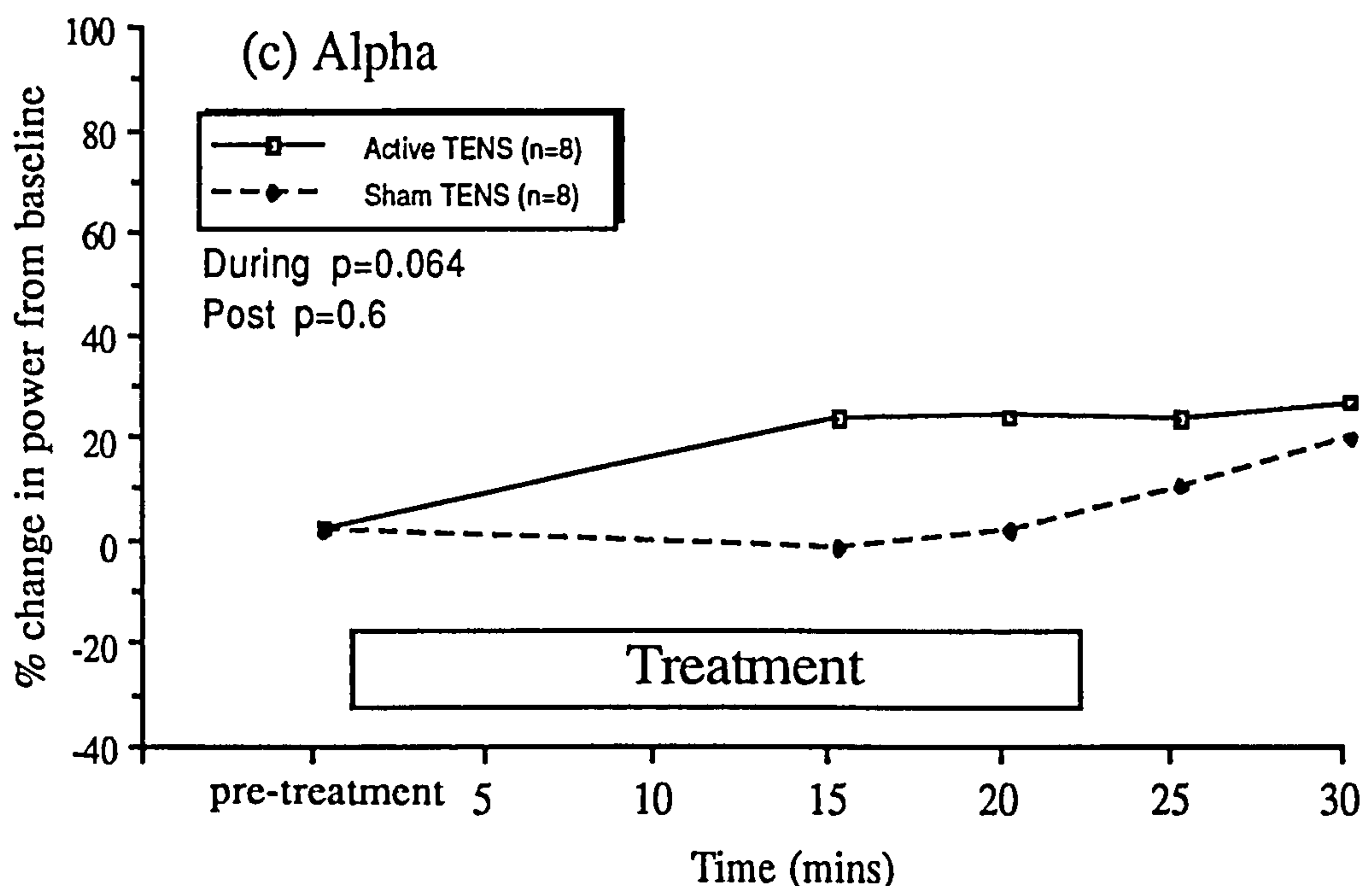


Fig.4.10c Percentage change in alpha power (compared to pre-treatment baseline) during active TENS and sham TENS (Exp. 4.2). Unpaired t-test on TENS v sham percentage change for during and post-treatment cycles (mean of 2 cycles per individual).

Examination of individual results found that alpha activity increased (by more than $1\mu\text{V}^2/\text{Hz}$) in 6 out of 8 subjects during TENS, compared to 4 out of 8 during sham (Table 4.5).

Peak Alpha Frequency: Pre-treatment peak alpha frequency ranged from 9-11.5Hz and no significant changes in peak alpha activity were observed during or post-treatment (with respect to pre-treatment baseline).

Slow Beta: A significant increase in beta power was observed during TENS (Mean change; TENS=+4.2 $\mu\text{V}^2/\text{Hz}$, sham=-1.9 $\mu\text{V}^2/\text{Hz}$, $P<0.05$, unpaired t-test). A rise in beta activity (of more than $1\mu\text{V}^2/\text{Hz}$) was observed in 6 out of 8 subjects during TENS, compared to 2 out of 8 during sham. A 40.1% increase in beta power was

observed during TENS and was attributed to large increases by subjects 2 and 8 (Table 4.5, Fig.4.10d).

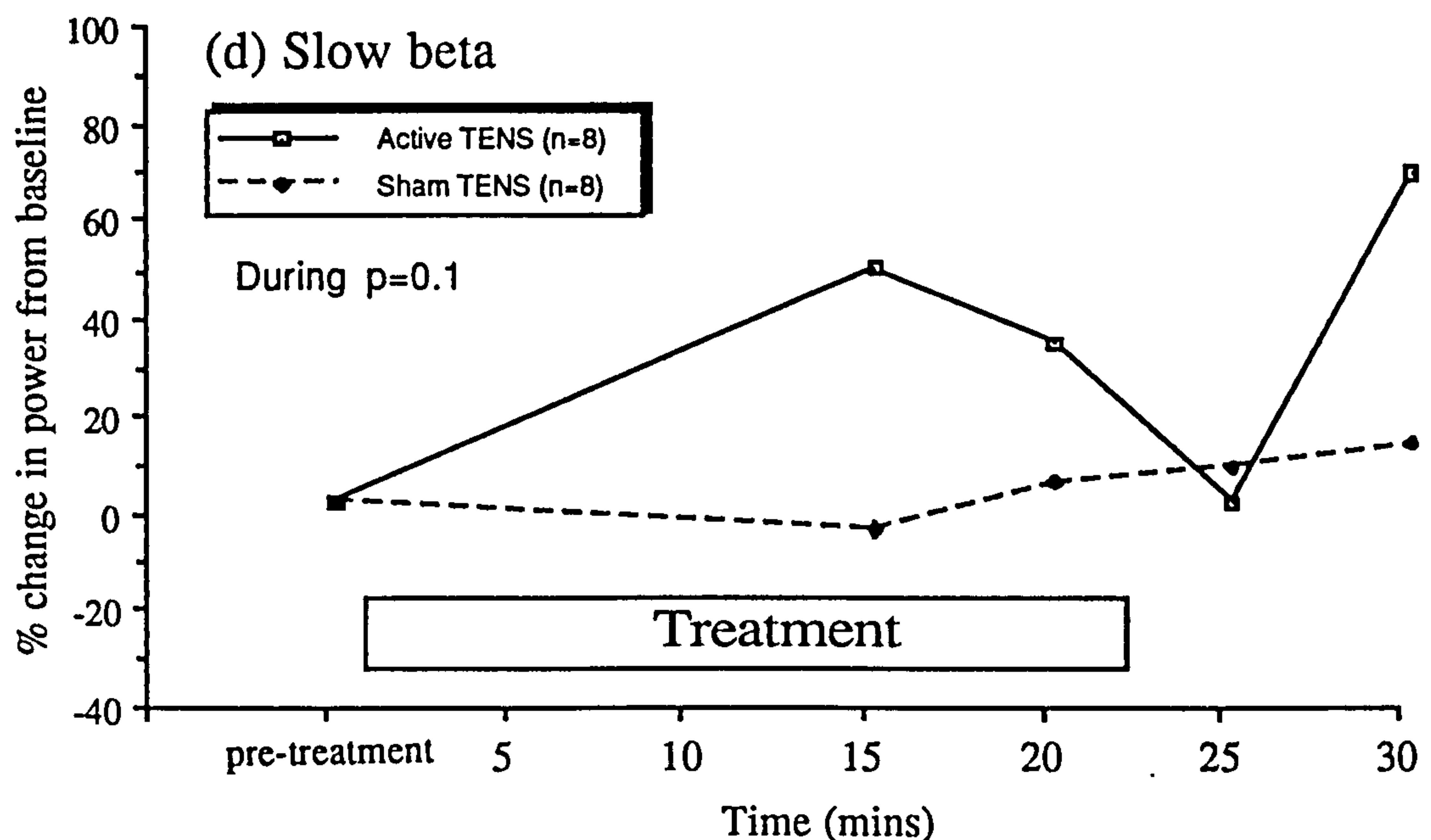


Fig.4.10d Percentage change in power spectrum (compared to pre-treatment baseline) during active TENS and sham TENS (Exp. 4.2). Unpaired t-test on TENS v sham percentage change for during and post-treatment cycles, $P=0.1$ (mean of 2 cycles per individual).

Main findings of Experiment 4.2

- (i) Wide inter-individual variation in baseline power was observed across all frequency bands, although inter-cycle variation within subjects was small.
- (ii) A significant increase in absolute beta activity was observed during TENS (Table 4.5).
- (iii) Although no significant changes in absolute alpha power were observed during TENS, a hint of an increase in alpha activity was found when data was transformed to percentage change from baseline.

Experiment 4.3

The effect of TENS on spontaneous EEG and pain intensity in chronic pain patients during TENS.

The results of Experiment 4.2 suggest that beta and possibly alpha activity increase during TENS in pain-free healthy volunteers. No significant changes in EEG power were observed in other frequency bands. The aim of Experiment 4.3 was to extend the findings of Experiment 4.2 by investigating the effects of TENS on spontaneous EEG of patients who use TENS to control a chronic pain condition. Furthermore, relationships between baseline SEP and spontaneous EEG with chronic pain intensity and response to TENS were examined.

Patients and procedure

The experiment was split into two parts:

- Exp. 4.3a. High frequency activity - to optimise the recording of beta activity (at C3 with eyes open),
- Exp. 4.3b. Low frequency activity - to optimise the recording of alpha activity (at O1 with eyes closed).

Thirty one patients using TENS to successfully control their chronic pain condition, were randomly selected from NPRC files to participate in either Exp. 4.3a (n=15, female n=11, male n=4; age range=37-66, mean=52.1 years of age), or Exp. 4.3b (n=16, male n=7 female n=9; age range=42-77, mean=61.1 years of age). Patients receiving anxiolytics, psychotropics, neuroleptics or centrally acting analgesics were excluded from the study. Patients were requested not to take any analgesics 24 hours prior to the experiment. Patients were classified according to the International Association for the Study of Pain (IASP) classification of chronic pain conditions [for full explanation of terms see IASP 1986] and an author's diagnostic classification [Johnson et al. 1991a] as follows:

Experiment 4.3	a	b		a	b		a	b
Anatomical Region	(n)	(n)	Aetiology	(n)	(n)	Diagnostic Clusters	(n)	(n)
Head or face	1	0	Trauma	5	6	Deafferentation	3	1
Cervical	0	1	Infective	0	1	Entrapments	5	4
Upper limb	3	3	Inflammatory	1	1	Neuralgia	1	3
Thoracic	1	2	Toxic	2	1	Spondylosis	3	3
Lower back	6	3	Degen./mechan.	6	2	Myofascial	1	2
Lower limb	3	6	Dysfunctional	1	3	Sympathetic	2	3
Two sites or more	1	1	Other/unknown	0	2			

Spontaneous EEG recordings were made in the morning; electrode positions were either; C3(Exp. 4.3a) or O1 (Exp. 4.3b), referenced to LM (linked mastoids). Amplifier settings; high pass filter=0.2s, low pass filter=100Hz, (Exp. 4.3a); 30Hz (Exp. 4.3b), range=100 μ V. All recordings were examined off-line (by VRM) for signs of EOG and/or TENS artefact.

EEG was recorded in 6 (2 x pre-TENS; 2 x during TENS; 2 x post-TENS), 5 minute cycles each lasting 1.5 minutes and separated by a 3.5 minute rest period. Patients sat in a relaxed awake state either; fixating a dot with eyes open (Exp. 4.3a), or with eyes closed (Exp. 4.3b). Patients were requested to make their minds 'as blank as possible' during EEG recording. Twenty five, 2 second epochs were acquired and averaged spectra computed off-line using fast fourier transform. EEG power (μ V²/Hz) was analysed in the same frequency bands as Exp. 4.2, although fast beta activity (26.0-40.0Hz) was also measured in Exp. 4.3a.

TENS was administered immediately after pre-treatment cycle 2, and remained 'switched on' for 21.5 minutes. During TENS recordings were taken at +15 min and +20 min after 'switch on'. Patients were asked to rate the intensity of their pain on a visual analogue scale (where 0=no pain and 10=worst pain imaginable) at the end of each cycle.

Patients were in possession of either a Microtens 7757 or a Tiger Burst stimulator, and prior to the start of the experiment patients applied TENS electrodes to the site normally used to control the pain condition. The stimulator remained switched off until the during TENS cycles. All patients administered TENS to achieve a 'strong but comfortable' electrical paraesthesia within the painful site, and subsequent adjustments to maintain this intensity of stimulation were made during the course of the experiment. Patients used the following electrical characteristics of TENS as recorded by the Frye Analyser:

Experiment		4.3a	4.3b
Continuous mode TENS		n=12	n=11
Burst mode TENS		n=3	n=5
Pulse width		200 μ s	200 μ s
Pulse frequency (Hz)	median	29	29
	range	10-128	16-176
Pulse intensity (mA above SDT)	median	11	20
	range	2-23	4-44

Results of Experiment 4.3a and b

Exp. 4.3a and Exp. 4.3b were analysed in an identical manner. Thus, mean±SD was calculated for each cycle and frequency band. No significant differences were observed in the two pre-, during or post-treatment cycles for any frequency band (paired t-test), therefore mean pre-, during and post-treatment power was calculated for each individual. TENS effects were examined by subtracting pre- from during TENS power for each individual. Percentage change in power from pre-treatment baseline was also calculated as in Exp. 4.2. Paired t-tests were performed to examine differences between pre- and during TENS recordings.

Pre-treatment baseline power spectrum

The range of pre-treatment baseline power recorded for respective frequency bands are shown below:

	Exp. 4.3a	Exp. 4.3b
Delta	17.4 to 64.2µV ² /Hz	9.4 to 146.8µV ² /Hz
Theta	5.1 to 43.0µV ² /Hz	6.5 to 49.9µV ² /Hz.
Alpha	3.8 to 58.8µV ² /Hz	7.0 to 197.9µV ² /Hz.
Slow beta	7.1 to 43.6µV ² /Hz	9.0 to 54.6µV ² /Hz.
Fast beta	2.5 to 55.9µV ² /Hz.	not measured

Wide inter-patient variability in baseline power was observed in both Exp. 4.3a and Exp. 4.3b. Of note was the large increase in inter-patient variability in alpha power in Exp. 4.3b when recording conditions were optimised to record low frequency activity. The large and spurious delta activity observed in patient 10 in Exp. 4.3b remains unexplained, although examination of raw EEG discounted artefact contamination due to EOG which can manifest in this frequency range.

Baseline power spectrum was not correlated to either:

- (i) baseline pain intensity rating,
- (ii) change of pain intensity during TENS,
- (iii) change in spontaneous EEG during TENS,

for any of the frequency bands measured (Pearson correlation coefficient) in either Exp. 4.3a or Exp. 4.3b.

Exp. 4.3a High frequency activity

Two patients (no. 7 and 11) were omitted from statistical analysis due to the occurrence of TENS artefact (see Fig.4.6). Mean pain intensity rating decreased during TENS with concurrent increases in mean theta, alpha, and slow beta activity, and a decrease in delta activity (Table 4.6).

	MEAN±SD POWER SPECTRUM ($\mu V^2/Hz$)					
	Pre- -10mins	Pre-2 -05mins	During-1 +15mins	During-2 +20mins	Post-1 +25mins	Post-2 +30mins
DELTA	33.6±13.2	31.1±11.7	29.6±13.9	27.4± 9.0	31.9±12.8	32.1±12.4
THETA	12.5±10.6	12.0± 9.0	13.2± 9.6	13.7±10.6	13.6±12.1	13.7±12.7
ALPHA	17.8±16.5	16.1±12.6	20.4±16.7	20.0±15.7	19.4±17.9	18.7±16.6
SLOW BETA	17.8±12.0	16.3± 8.7	19.2± 9.5	16.7± 8.4	16.0± 8.7	16.6± 8.6
FAST BETA	14.0±17.5	10.6±10.3	12.7±11.3	7.0± 3.6	9.1± 6.7	8.2± 6.4
PAIN RATING	4.5± 2.3	4.5± 2.3	2.8± 1.8	2.4± 1.9	3.8± 2.7	4.4± 2.7

Table 4.6 Mean±SD power spectrum of chronic pain patients during treatment with TENS (n=13). Part 1 High frequency activity (Exp. 4.3a).

Pain Intensity Rating: Baseline pain intensity rating ranged from 1.4-9.7 units on the visual analogue scale (VAS units). A significant reduction in pain intensity rating was observed during TENS (pre v during:=-2.0 VAS units, $P<0.01$, paired t-test) which began to return to pre-treatment baseline in post-TENS cycles (pre v post:=-0.4 VAS units, $P=0.08$, paired t-test).

Delta and Theta: No significant changes in either delta or theta power was observed during TENS (Delta=-1.2 $\mu V^2/Hz$, $P=0.5$; Theta=+0.9 $\mu V^2/Hz$, $P=0.3$, paired t-test). Similarly no significant differences were found when the data was transformed to percentage changes (Fig.4.11).

Alpha: There was a hint of an increase in alpha activity during TENS (+2.1 $\mu V^2/Hz$, $P=0.09$, paired t-test, see Table 4.7). When data was transformed to percentage changes this rise in alpha activity of 13.3% reached statistical significance ($P=0.01$ paired t-test, see Fig.4.11). Examination of individual results showed that an increase in alpha activity during TENS (of 1 $\mu V^2/Hz$ or more) was observed in 8 out of 13 patients (Table 4.7).

SUB	TMT	DELTA POWER ($\mu\text{V}^2/\text{Hz}$)			THETA POWER ($\mu\text{V}^2/\text{Hz}$)			ALPHA POWER ($\mu\text{V}^2/\text{Hz}$)		
		Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)
1	TENS	46.5	61.7	66.4	10.0	12.9	11.9	11.7	14.4	12.0
2	TENS	26.0	24.6	26.7	5.1	6.2	4.6	3.8	4.8	3.7
3	TENS	37.9	36.4	40.8	12.1	13.7	14.5	33.2	44.0	52.5
4	TENS	19.3	19.3	22.3	10.3	17.5	16.3	27.0	36.3	34.9
5	TENS	24.9	23.9	25.6	43.0	42.2	53.8	58.8	58.2	60.4
6	TENS	28.5	22.2	25.5	7.0	7.1	6.6	5.3	5.9	5.4
7	TENS	64.2	*	43.1	13.0	*	9.8	4.7	*	3.9
8	TENS	24.9	24.9	21.7	6.4	7.4	8.1	17.5	20.0	19.0
9	TENS	31.5	29.0	29.2	8.9	10.1	9.6	17.6	17.7	18.2
10	TENS	30.0	22.4	39.4	6.3	6.2	7.2	9.2	10.4	10.7
11	TENS	35.3	*	31.5	7.7	*	6.4	13.4	*	11.0
12	TENS	33.6	29.7	29.6	8.7	8.1	8.5	7.1	9.5	6.8
13	TENS	42.4	29.8	30.4	22.3	17.6	19.9	21.1	16.6	14.4
14	TENS	17.4	16.0	17.7	5.7	5.3	5.5	9.4	8.8	10.8
15	TENS	22.8	30.0	29.9	17.5	20.4	22.2	14.4	16.2	22.4
MEAN		32.4	28.5 <i>p=0.5</i>	32.0	12.3	13.5 <i>p=0.3</i>	13.7	16.9	20.2 <i>p=0.09</i>	19.1
SUB	TMT	SLOW BETA POWER ($\mu\text{V}^2/\text{Hz}$)			FAST BETA POWER ($\mu\text{V}^2/\text{Hz}$)			PAIN INTENSITY RATING (no pain 0—>10 worst imaginable)		
		Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)
1	TENS	11.5	12.3	11.8	4.8	5.6	6.2	7.6	6.8	7.5
2	TENS	7.3	8.3	7.6	2.5	3.1	3.0	3.2	2.9	3.3
3	TENS	23.3	30.6	27.4	8.6	15.0	10.0	2.1	1.0	0.7
4	TENS	18.3	25.9	23.3	7.9	11.7	12.6	1.7	0.9	1.0
5	TENS	11.4	13.8	11.5	5.0	6.2	3.9	3.7	3.1	4.0
6	TENS	7.1	6.3	6.2	4.3	3.2	3.1	5.3	1.4	4.0
7	TENS	8.8	*	7.5	9.5	*	7.9	1.4	0.5	0.5
8	TENS	17.4	19.8	17.8	6.3	4.4	3.4	5.4	0.9	6.1
9	TENS	7.8	6.0	5.8	7.6	4.7	4.7	4.7	4.3	5.4
10	TENS	22.5	25.9	25.5	7.9	5.6	10.6	5.6	4.7	6.3
11	TENS	20.1	*	15.6	26.0	*	16.4	4.4	3.4	3.3
12	TENS	8.5	14.2	10.4	7.4	15.6	9.5	4.3	3.5	4.5
13	TENS	43.6	25.9	19.0	55.9	23.1	6.3	9.7	2.4	9.5
14	TENS	30.1	27.6	33.1	7.4	7.3	7.7	6.5	1.5	4.2
15	TENS	17.5	16.7	21.5	23.0	22.0	24.4	1.9	1.4	0.7
MEAN		17.0	18.0 <i>p=0.8</i>	16.3	12.3	9.8 <i>p=0.6</i>	8.6	4.5	2.6 <i>p<0.01</i>	4.1

Table 4.7 Individual change in power spectrum during TENS in pain patients. Part 1 High frequency activity (Exp.4.3a) SUB = Subject no.: TMT = treatment Group: TENS = Transcutaneous Electrical Nerve Stimulation: SHAM= Sham TENS Mean PRE = Mean of two pre-treatment measures: Mean DURING = mean of three during treatment measures: Mean POST = mean of two post-treatment measures. Mean was calculated for each group. Statistical analysis was performed by calculating changes during treatment (by subtracting PRE from DURING for each individual) and performing a paired t-test between groups.

Beta: No significant changes in either slow or fast beta power was observed during TENS (Mean change in power pre v during: Slow beta=+0.5 $\mu\text{V}^2/\text{Hz}$, P=0.8; Fast beta=-1.6 $\mu\text{V}^2/\text{Hz}$, P=0.6, paired t-test).

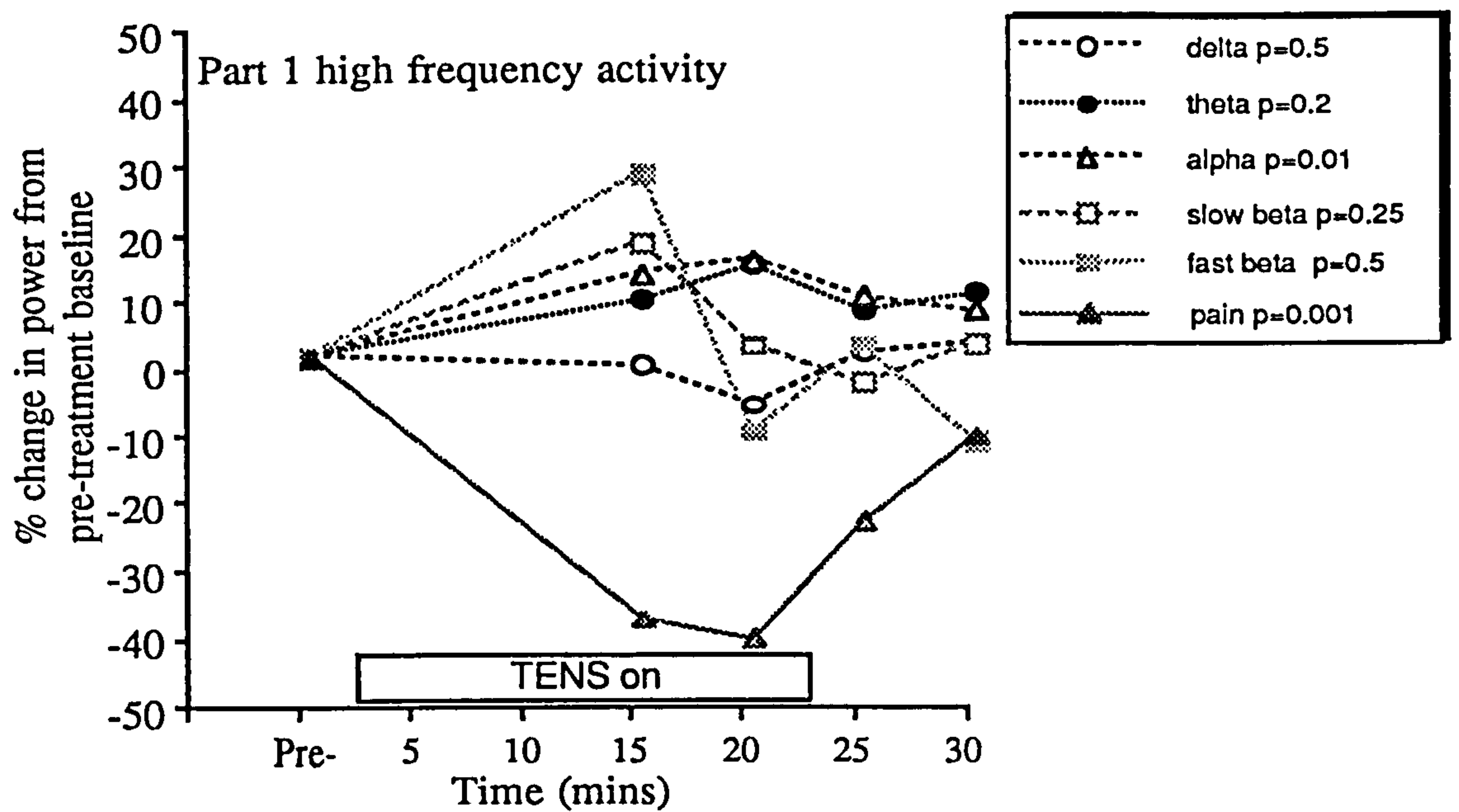


Fig.4.11 Percentage change in power spectrum and pain intensity rating (compared to pre-treatment baseline) during TENS treatment of chronic pain conditions (Exp. 4.3a). Paired t-test on pre- v during (mean of 2 cycles/individual) TENS treatment (n=13).

Exp. 4.3b Low frequency activity.

No patients were omitted from analysis as no observable TENS artefact were noted in either raw EEG or power spectrum. As observed in Exp. 4.3a the decrease in mean pain intensity rating during TENS was accompanied by increases in theta, alpha and slow beta power and a decrease in delta activity (Table 4.8).

	MEAN±SD POWER SPECTRUM ($\mu V^2/Hz$)					
	CYCLE (TIME MINS)					
	Pre- -10	Pre-2 -05	During-1 +15	During-2 +20	Post-1 +25	Post-2 +30
DELTA	28.8±27.6	27.8±30.2	24.0 ±19.4	23.7±15.7	22.5±17.1	24.3±20.0
THETA	17.4±14.0	17.1±13.5	18.4±15.3	19.4±14.4	18.2±14.7	16.0±10.8
ALPHA	78.4±57.1	74.9±51.4	87.1±57.8	87.5±59.9	81.5±60.1	83.1±59.1
BETA	28.1±16.4	25.5±12.8	30.5±18.0	32.5±23.7	27.6±14.6	30.1±19.7
ALPHA FREQ.	9.5±0.8	9.7±0.9	9.5±0.7	9.5±0.7	9.5±0.8	9.4±0.7
PAIN RATING	4.5±1.9	4.5±1.8	2.9±1.9	2.8±1.9	2.9±2.2	3.0±2.3

Table 4.8 Mean±SD power spectrum of chronic pain patients during treatment with TENS (n=16). Part 2 Low frequency activity (Exp. 4.3b)

SUB	TMT	DELTA POWER ($\mu V^2/Hz$)			THETA POWER ($\mu V^2/Hz$)			SLOW BETA POWER ($\mu V^2/Hz$)		
		Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)
1	TENS	17.9	22.0	20.2	22.2	25.1	24.6	32.1	31.2	36.5
2	TENS	13.6	15.4	14.8	9.3	9.1	9.6	*	*	*
3	TENS	16.1	16.0	15.9	12.2	14.0	13.9	11.6	9.5	13.9
4	TENS	13.1	12.9	13.2	13.6	16.0	13.3	41.6	75.8	64.3
5	TENS	13.7	14.6	15.3	14.4	20.7	16.4	38.0	39.3	38.7
6	TENS	9.4	10.6	10.1	7.1	8.1	9.0	25.4	24.4	25.6
7	TENS	30.1	22.3	18.5	8.5	8.1	7.7	9.0	8.6	6.5
8	TENS	10.0	8.8	9.8	6.5	5.1	4.9	26.4	22.0	22.2
9	TENS	33.0	33.7	30.7	49.9	56.7	39.5	54.6	53.1	54.0
10	TENS	146.8	78.4	83.5	19.0	19.3	15.4	46.4	63.4	45.8
11	TENS	14.9	14.0	15.0	7.9	7.9	7.1	12.6	13.6	11.7
12	TENS	26.8	30.3	28.6	7.0	8.2	8.2	13.5	14.4	17.9
13	TENS	30.9	30.5	35.1	29.5	30.8	36.2	22.7	23.0	24.5
14	TENS	16.3	17.5	14.2	6.3	9.5	7.5	29.5	34.6	25.6
15	TENS	48.3	42.6	36.4	45.9	46.5	42.0	30.1	46.7	31.6
16	TENS	11.5	12.1	13.1	16.1	17.4	18.4	10.3	12.4	13.7
MEAN		28.3	23.9 <i>p=0.3</i>	23.4	17.2	18.9 <i>p<0.01</i>	17.1	26.9	31.5 <i>p=0.1</i>	28.9

SUB	TMT	ALPHA POWER ($\mu V^2/Hz$)			ALPHA FREQUENCY (Hz)			PAIN INTENSITY RATING (No pain 0 → 10 worst imaginable)		
		Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)	Mean PRE (n=2)	Mean DURING (n=2)	Mean POST (n=2)
1	TENS	53.9	78.4	71.9	8.0	8.5	8.0	2.8	1.5	1.7
2	TENS	84.0	84.6	81.8	11.0	10.7	10.5	4.5	2.2	2.3
3	TENS	31.6	29.2	36.2	9.0	8.5	8.2	3.7	2.2	1.1
4	TENS	71.7	92.3	58.7	10.0	10.0	10.0	6.1	5.5	5.0
5	TENS	133.2	142.9	139.3	10.5	10.0	10.5	3.2	2.0	2.5
6	TENS	31.7	41.2	58.1	9.2	9.2	9.5	3.7	3.0	2.4
7	TENS	61.9	71.8	43.9	11.0	10.2	10.2	5.5	2.0	3.2
8	TENS	24.0	25.3	33.5	10.5	10.0	9.7	5.7	0.3	0.3
9	TENS	197.9	186.1	182.3	9.0	9.2	9.2	8.4	7.0	9.1
10	TENS	88.6	123.5	68.9	9.7	9.7	10.0	1.6	0.6	0.9
11	TENS	32.8	35.2	36.3	9.7	10.0	9.7	5.3	3.9	2.6
12	TENS	7.0	8.0	8.3	*	*	*	5.9	5.0	5.0
13	TENS	100.1	105.7	121.2	9.0	8.7	8.5	4.5	2.0	1.8
14	TENS	37.9	49.4	53.2	9.2	9.2	9.5	5.7	5.1	5.3
15	TENS	165.4	208.9	196.9	9.0	9.0	9.0	3.3	2.4	3.1
16	TENS	104.2	113.8	126.1	9.0	9.0	9.0	1.0	0.7	0.8
MEAN		76.6	87.3 <i>p=0.01</i>	82.3	9.6	9.5 <i>p=0.2</i>	9.4	4.4	2.8 <i>p=0.01</i>	3.0

Table 4.9 Individual change in power spectrum during TENS in pain patients. Part 2 Low frequency activity (Exp.4.3b) SUB = Subject no.: TMT = treatment Group: TENS = Transcutaneous Electrical Nerve Stimulation: SHAM= Sham TENS Mean PRE = Mean of two pre-treatment measures: Mean DURING = mean of three during treatment measures: Mean POST = mean of two post-treatment measures. Mean was calculated for each group. Statistical analysis was performed by calculating changes during treatment (by subtracting PRE from DURING for each individual) and performing a paired t-test between groups.

Pain Intensity Rating: Baseline pain intensity rating ranged from 1.0-8.4 VAS units and a significant decrease in pain rating was observed during (-1.6 VAS units, $P<0.01$), and post-TENS treatment cycles (-1.5 VAS units, $P>0.01$, paired t-test). All patients showed a decrease in pain intensity rating during TENS (Table 4.9).

Delta and Theta: No significant change in delta power was observed during TENS (mean change= $-4.4 \mu V^2/Hz$, $P=0.3$, paired t-test). A small but significant rise in theta power ($+1.7 \mu V^2/Hz$, $P>0.05$) was observed during TENS and 9 out of 16 patients showed an increase (of over $1 \mu V^2/Hz$) in theta power (Table 4.9). This finding was confirmed when the data was transformed to percentage change ($+10.6\%$, $P>0.05$) (Fig. 4.12).

Alpha: A significant increase in alpha power ($+10.6 \mu V^2/Hz$, $P>0.01$, see Table 4.9) was observed during TENS. This was confirmed when data was transformed to percentage changes (Mean percentage change= 15.8% , $P>0.01$, paired t-test, see Fig.4.12). Examination of individual results showed that 13 out of 16 patients showed an increase in alpha power (of over $1 \mu V^2/Hz$) during TENS.

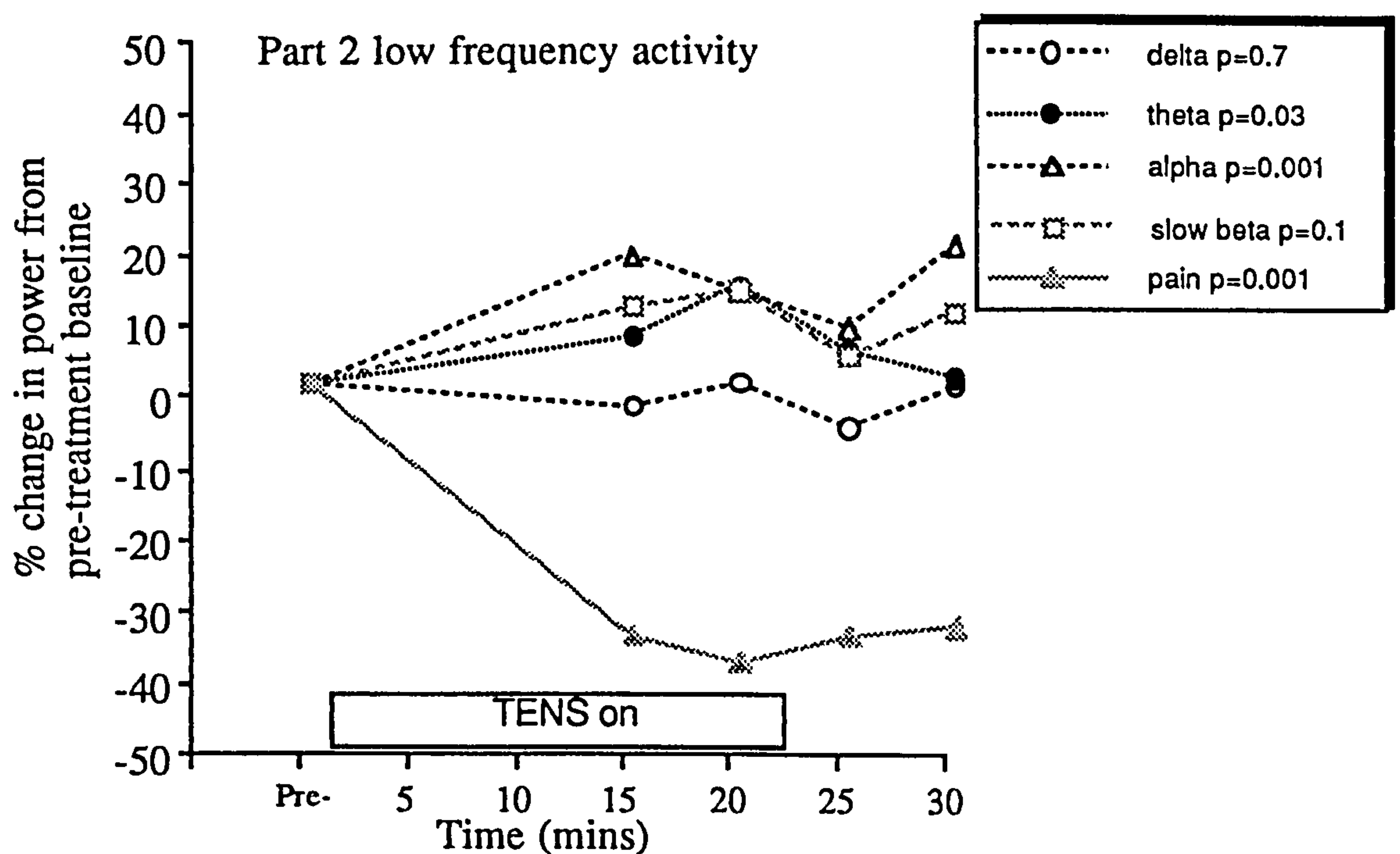


Fig.4.12 Mean percentage change in power spectrum and pain intensity rating (compared to pre-treatment baseline) during TENS treatment in chronic pain patients (Exp. 4.3b). (a) Delta, theta and slow beta activity. (b) alpha power and frequency (n=16) P =paired t-test pre v during.

Peak Alpha Frequency: Baseline peak alpha activity ranged from 8.0-11.0Hz and no significant changes occurred during TENS (Mean change=-0.1Hz, P=0.2).

Beta: A hint of an increase in slow beta power ($+4.6\mu\text{V}^2/\text{Hz}$, P=0.1) was observed during TENS and 6 out of 15 patients showed an increase in slow beta activity of $1\mu\text{V}^2/\text{Hz}$ or more.

Main findings of Experiment 4.3

- (i) Wide inter-patient variability in baseline power was observed in all frequency bands. Variability between baseline cycles 1 and 2 was small and non significant.
- (ii) No relationships were found between baseline power and either baseline pain intensity rating, or the change in pain intensity during TENS.
- (iii) A significant reduction in pain intensity rating was observed during TENS when compared to pre-treatment baseline.
- (iv) General increases in theta, alpha and slow beta and decreases in delta activity were observed in both parts of the experiment during TENS, although these changes were small (less than $10\mu\text{V}^2/\text{Hz}$).
- (v) Under conditions to optimise the recording of fast wave activity (Exp. 4.3a) no significant changes in any of the power spectrum indices were observed during TENS, although there was a hint (P=0.09) of an increase in alpha activity.
- (vi) Under conditions to optimise the recording of low frequency activity (Exp. 4.3b) a significant increase in alpha activity during TENS was observed (P=0.01).
- (vii) No relationships were found between the magnitude of this increase in alpha activity with the magnitude of reduction in pain intensity rating. A small but significant (P=0.05) increase in theta activity was also observed.

DISCUSSION

Three experiments were performed to examine the effects of TENS on SEPs and spontaneous EEG. TENS was found to reduce the peak-to-peak amplitude of the N1P2 (140ms-260ms) SEP complex in healthy subjects, confirming previous reports. No significant changes in latency of these components were observed. TENS produced changes in spontaneous EEG in both healthy pain-free subjects and chronic pain patients. Thus, a significant increase in beta activity (and possibly alpha activity) was observed during TENS (compared to sham) in healthy subjects. TENS also produced significant increase in alpha activity in chronic pain patients, although no change in beta activity was noted. A small but significant increase in theta activity during TENS was also observed in pain patients, when conditions were optimised to record low frequency activity (Exp. 4.3b). No relationships between baseline power spectrum and either baseline pain intensity ratings, or the change in pain intensity during TENS were found to occur in the pain patients. These findings will now be discussed in detail.

The effect of TENS on late components of the SEP

The finding that TENS reduced the N1P2 peak-to-peak amplitude of the SEP confirms previous reports [Francini et al. 1982; Ashton et al. 1984b; Golding et al. 1986; Nardone & Schieppati 1989]. No significant changes in N1 or P2 latencies or intensity rating of the evoking stimulus occurred during TENS.

Desmedt [1989] suggests that evoked potentials represent compound profiles built up of a sequence of distinct components of neuronal activity. The early waveform components of an EP reflect transmission of the afferent nerve volley, and initial thalamo-cortical processing and anticipatory mechanisms which prime the cortex for stimulus identification and evaluation. Later components (>80 ms) are involved with the perceptual processing that leads to stimulus identification. Distraction of attention can markedly reduce the size of these late SEP components and may therefore influence the effect of TENS on the SEP. Miltner et al. [1989] has shown that distraction can reduce the amplitude of late components of somatosensory evoked potentials elicited by both painful and non-painful stimuli and such attentional

manipulations can provide a powerful method to decrease the perception of pain. Sham TENS also reduced the N1P2 amplitude of the SEP, although to a lesser magnitude than active TENS, which suggests that the effects of placebo have played only a minor role.

Golding et al. [1986] reported a reduction of the amplitude of both early and late components of SEPs during TENS, and as early potentials are less susceptible to changes in attention they suggested that TENS disrupted the flow of sensory information (i.e. the evoking stimuli) at a number of levels in the sensory nervous system.

Recent evidence from Nardone and Shieppati [1989] suggests that TENS 'gates' somatosensory volleys both in the periphery, through a 'busy-line' effect on large diameter afferent fibres, and centrally at the level of cuneate nucleus. The group recorded far field and early near field SEPs at: (i) Erb's point, (ii) the spinous process of the sixth cervical vertebra (C6), and (iii) the scalp at C4 and C3. SEPs were elicited by electrical stimulation of the median nerve at the wrist or index finger in 15 healthy subjects and TENS was applied 1 cm proximal to the electrodes used to elicit the SEP. TENS reduced the amplitudes of incoming afferent volleys recorded at Erb's point which suggested a peripheral blockade of transmission of the SEP volley. This was attributed to a 'busy line' effect in large diameter fibres, in which impulses evoked by the SEP stimulus may: (i) be in the absolute refractory period of those produced by TENS, or (ii) collide (antidromic collision) with those induced by TENS. To measure the central contribution of TENS, unconditioned reference SEPs were evoked by stimulating with a current strength yielding an Erb's point potential of an amplitude equal to that obtained during TENS. In this case the amplitudes of the early near field components of the SEP (N14 and N18) were greater than those recorded during TENS which Nardone and Schieppati attributed to the effects of TENS in the central nervous system (CNS), possibly at the level of the cuneate nucleus.

In contrast, Golding et al. [1986] found reductions in amplitudes of both early and late SEP components but reported no change in wave amplitudes recorded at the median nerve, which suggested that TENS produced no peripheral blockade. However, no data in support of this statement was presented. Furthermore, no changes in the amplitudes of early components of the SEP were found by Francini et al. [1982]. However, difficulty in recording and identification of these small amplitude early

potentials from both Erb's point and the surface of the scalp may account for such discrepancies. As a reduction in N1P2 amplitude can be elicited from non-painful as well as painful stimuli, it appears that TENS effects at the cortical level are not exclusive to the pain system.

Although the utility of the evoked response as a measure of treatment effects on the response to sensory stimuli has been demonstrated, marked inter-subject variability in both baseline SEP amplitudes and response to TENS were observed. Golding et al. [1986] suggested that baseline SEP amplitudes may be predictive of an individual's response to TENS and that individuals with large peak-to-peak N1P2 amplitudes produce greater response to TENS. No such relationships were observed in the present study. However, in this and the Golding et al. study, the intensity of the evoking stimulus was fixed subjectively (at a 'strong non-painful' level), and therefore subjects received different absolute current intensities. As peak-to-peak amplitudes of the SEP are dependent on the intensity of evoking stimuli, this makes comparisons of inter-subject baseline amplitudes difficult. The value of baseline SEP amplitudes as a predictive measure of response is examined in more detail in Chapter 6.

The effect of TENS on spontaneous EEG

Large inter-subject variability in both baseline spontaneous EEG measures and changes in spontaneous EEG during TENS, were found in both pain-free patients and chronic pain patients. However, some generalised TENS effects were found. These are summarised below:

	Exp. 4.2	Exp. 4.3a	Exp. 4.3b
(<->=no change)	Pain-free subjects	Pain patients	Pain patients
Delta	<-->	<-->	<-->
Theta	<-->	<-->	Increase
Alpha	?Increase?	?Increase?	Increase
Alpha frequency	<-->	not measured	<-->
Slow beta	Increase	<-->	?Increase?
Fast beta	<-->	not measured	<-->
Pain intensity	not measured	decrease	decrease

Thus, a significant increase in alpha activity and a reduction of pain intensity rating occurred during TENS in chronic pain patients. This increase in alpha activity also occurred, although to a lesser extent, in pain-free subjects. Slow beta activity was found to increase during TENS in pain-free subjects and possibly in pain patients

under conditions optimising low frequency activity. A small but significant increase in theta activity was also found to occur during TENS in pain patients.

Nevertheless, changes in power spectrum indices were small (less than $10\mu\text{V}^2/\text{Hz}$) across all frequency bands in both Experiments 4.2 and 4.3 and such small changes in power spectrum, accompanied with large inter-subject variability in baseline spectral indices, can hinder statistical comparisons. Hence, subjects with low baseline EEG activity may show smaller absolute changes in spontaneous EEG. Therefore percentage changes in power were calculated in an attempt to account for this inter-individual variability in baseline activity. This problem was highlighted in Experiment 4.2 where subject 12 showed an decrease in alpha activity of $-22\mu\text{V}^2/\text{Hz}$ (-22% of baseline power) whereas subject 6 showed an increase of $+3.5\mu\text{V}^2/\text{Hz}$ (+30.5% of baseline power).

Furthermore, changes in spontaneous EEG appear to be more readily detected when conditions are optimised to increase low frequency activity by recording from occipital region with eyes closed.

(a) Pain-free subjects

The effect of TENS on overall power spectrum was small when compared to sham TENS, although a significant increase in beta (and possibly alpha) activity was observed. The increase in beta activity from $14.7\mu\text{V}^2/\text{Hz}$ to $19.0\mu\text{V}^2/\text{Hz}$ (Table 4.5) was attributed to increases in beta activity in 6 out of 8 subjects in the TENS group compared with 2 out of 8 in the sham. However, a spurious increase in beta activity which occurred in post-TENS cycle 2 (Fig.4.10), where mean beta activity rose by approximately 80% in the TENS group was attributed to a large increase in beta activity shown by subject 7 (Table 4.5). It has been suggested that rises in beta activity reflect heightened states of arousal, and that the increase in beta during TENS in pain-free subjects may in part be due to a change in arousal associated with the 'unfamiliar' paraesthesia experienced during TENS. An alternative explanation may be an increase in asynchronous high frequency potentials produced by electromyographical (EMG) activity, although EMG was not prominent on examination of the raw EEG. Contamination with high frequency TENS artefact also seems unlikely as these artefacts can be easily identified on power spectrum graphs (Fig.4.6).

The general increase in alpha activity which was observed during TENS in healthy pain-free subjects was highlighted when data was transformed to percentage change in

alpha activity from pre-treatment baseline ($P=0.064$). Although the majority (6/8) of subjects showed some degree of increase in alpha activity during TENS, half (4/8) of the subjects receiving sham TENS also showed increases in alpha activity. Thus the increase in alpha activity observed during active TENS under these conditions may be due in part to placebo effects.

In summary, increases in beta activity and possibly alpha activity occurred during TENS but not placebo in pain-free subjects. These changes may have been due to:

- (i) TENS interfering with general somatosensory processing,
- (ii) TENS activating analgesic mechanisms (i.e. release of opioids),
- (iii) TENS affecting attention/distraction,
- (iv) an overlying TENS placebo response,

but this remains to be determined. Additional controlled experiments utilising larger sample size examining the effects of both acupuncture and TENS will be required to confirm these findings.

(b) Chronic pain patients

Experiment 4.3 was designed to optimise the recording of (a) beta activity and (b) alpha activity in separate populations of patients using TENS successfully to control a chronic pain condition. TENS significantly reduced chronic pain intensity in all patients coupled with a concurrent rise in alpha activity. This finding is consistent with that of Manna et al. [1984] who found an increase in alpha activity during the relief of tension headache in patients receiving acupuncture. In contrast to the present findings, Manna's group also showed significant reductions in delta and theta activity. However, theta activity was found to increase during TENS treatment under conditions to optimise the recording of alpha activity (Exp. 4.3b). No significant changes in delta or beta (fast and slow) power were observed in Exp. 4.3a and Exp. 4.3b, although an increase in slow beta activity occurred ($P=0.1$) when recording conditions were optimal for low frequency activity (i.e. a similar finding to that for healthy pain-free subjects, Exp. 4.2).

TENS produced a significant reduction in pain intensity within 15 minutes in all patients, although this reduction was short lived and pain intensity ratings began to return to pre-treatment levels within 5 minutes of TENS switch-off.

Although the increase in alpha, theta (and beta in Exp. 4.3b) activity, and decrease in delta activity, followed the same time course as changes in pain intensity rating (Table

4.8), no relationships were observed between the degree of increase in alpha and theta activity and the degree of pain reduction during TENS in Exp. 4.3b. Moreover, the results of Experiment 4.2 imply that alpha activity may increase during TENS application in pain-free subjects. Therefore, the effects of TENS on spontaneous EEG may be due to a combination of effects unrelated and related to pain. TENS effects unrelated to pain may include:

- (i) changes in the quality and quantity of sensory information reaching the cortex produced by the electrical paraesthesia,
- (ii) attentional/distractional changes.

TENS effects related to the pain may include:

- (i) the reduction of the intensity and quality of the pain by sensory modulation (spinal 'gating') or the release of neuromodulators (i.e. opioids),
- (ii) TENS placebo effects [Levine et al. 1978].

However, as experiments examining the effects of TENS on EEG in pain patients were uncontrolled, further studies are necessary to substantiate these suggestions.

Baseline spontaneous EEG and clinical pain

No relationships were observed between baseline pain intensity rating and baseline power spectrum. Thus, no simple objective measure of clinical pain in its chronic state was found by measuring spontaneous EEG under the present conditions.

Only recently has the effect of pain on spontaneous EEG activity been investigated. Three groups have examined the effects of experimental pain (cold-pressor) on power spectrum in healthy subjects. During immersion of a limb in cold water, Chen et al. [1990] found a rise in delta and beta activity; Gotliesben and Adrent-Nielsen [1990] found an increase in delta and a decrease in alpha; Backonja et al. [1990] found an increase in alpha. The variability of results obtained during essentially similar experiments may be due in part to:

- (i) different changes in power occurring in different regions of the brain,
- (ii) inter-individual variation in response to the pain stimulus,
- (iii) electrophysiological changes due to cold-pressor (circulatory) rather than 'pain' effects.

With the advent of topographical brain mapping [Maurer 1989] measurement and analysis of regional changes in spontaneous EEG activity will be made easier.

However, experiments measuring EEG changes during an acute intervention of an experimental pain stimulus rather than a chronic condition, may represent changes in stress and vigilance [Chen et al. 1990] rather than pain per se. Thus, it seems unlikely that an objective measure of pain in its chronic state will manifest in the spontaneous EEG due to the complex, 'fluid' nature of the brain's electrical activity, coupled with the lack of knowledge on the physiological significance of spontaneous EEG.

Summary

In summary, the results of experiments presented in this chapter have shown that:

- (i) TENS reduced the peak-to-peak amplitudes of late components of the SEP elicited by a non-painful stimulus in healthy subjects.
- (ii) TENS increased beta activity (and possibly alpha) of spontaneous EEG in pain-free subjects.
- (iii) In chronic pain patients, alpha (and possibly theta) activity increased during pain reduction by TENS.
- (iv) Wide inter-individual variability in baseline SEP amplitudes and spontaneous EEG were observed, although no relationships between the degree of response to TENS and these baseline measures were found.

As the reduction in SEP amplitude did not depend upon a painful evoking stimulus, it is suggested that TENS effects are not specific to the pain system. This suggestion is supported by the finding that changes in spontaneous EEG activity occur during TENS in pain-free subjects. No relationships were observed between baseline EEG variables and patient response to TENS, although the patients investigated were long-term TENS responders. Differences in baseline measures may be more apparent between groups of non-responders and responders and the utility of baseline SEPs and spontaneous EEG as a predictor of response to TENS merits further investigation (see Chapter 6).

Because of the rather non-specific changes in SEPs and spontaneous EEG during TENS (occurring with and without the presence of pain), it was decided to investigate the effects of TENS on neuropharmacological variables. Thus, Chapter 5 examines the effects of TENS on concentrations of opioid peptides and 5-hydroxytryptamine which may provide a more specific measure of TENS analgesic effects.

CHAPTER 5

THE PHARMACOLOGY OF TENS ANALGESIA

INTRODUCTION

The pharmacology of the analgesic effects of TENS (and acupuncture) is poorly understood [for review see Thompson 1989; MacDonald 1989]. Research on antinociceptive mechanisms in the dorsal horn of the spinal cord and descending pain inhibitory pathways arising from supraspinal structures (Fig.1.5) has suggested that many neurotransmitters and neuromodulators may be involved. These include serotonin (5-Hydroxytryptamine; 5-HT) [Yaksh 1979], noradrenaline [Xie et al. 1983], dopamine [Fitzgerald 1986], gamma-amino butyric acid (GABA) [Duggan & Foong 1985], glutamate [Jensen & Yaksh 1984], opioid peptides [Sjölund & Eriksson 1979; Mayer et al. 1977], and vasoactive intestinal peptide (VIP) [Kaada et al.1984]. At present it appears that three substances (beta-endorphin, methionine-enkephalin (met-enkephalin) and 5-HT) play a fundamental role in antinociceptive mechanisms and may therefore be important in the mechanism of TENS analgesia.

Opioid peptides (beta-endorphin and met-enkephalin)

There is considerable evidence that endogenous opioids are involved in acupuncture analgesia and by implication in acupuncture-like TENS (AL-TENS). Indirect evidence is provided by studies using the opioid antagonist naloxone [for review see He 1987]. These show that acupuncture analgesia is reversed by naloxone both in patients with pain and in normal volunteers subjected to experimental pain [Mayer et al.1977]. Direct measurement of opioid peptides has been hampered by difficulties in assay, but Clement-Jones et al. [1980b] demonstrated the release of beta-endorphin but not met-enkephalin into the cerebrospinal fluid (CSF) during acupuncture and electroacupuncture. A limited number of studies examining biochemical changes in the peripheral circulation have given conflicting results. Malizia et al. [1979] found an increase in plasma concentration of beta-endorphin during electroacupuncture in healthy subjects, while Kiser et al. [1983] reported increased plasma concentrations of

met-enkephalin but not beta-endorphin during acupuncture analgesia in 20 chronic pain patients.

Less information is available concerning the involvement of endogenous opioids in TENS analgesia. Pain reduction during conventional (high frequency low intensity) TENS does not appear to be naloxone-reversible [Woolf et al.1978; Abram et al.1981; Freeman et al.1983; Hansson et al.1986]. However, Sjölund and Eriksson [1979] showed that AL-TENS does produce a naloxone-reversible analgesia. The release of beta-endorphin into the CSF during high intensity TENS has been reported in patients and normal subjects [Sjölund et al. 1977; Salar et al. 1981]. Conflicting reports exist on changes in plasma beta-endorphin in healthy subjects. O'Brien et al. [1984] found no significant changes in plasma beta-endorphin concentrations before, during or after AL-TENS in 42 healthy volunteers subjected to experimental pain subjects. In contrast, Facchinetti et al. [1984] found an increase in both plasma concentrations of beta-endorphin and beta-lipotrophin during high frequency TENS in 12 healthy volunteers.

5-HT

A role for 5-HT as a transmitter in the descending pain inhibitory pathways which are activated during acupuncture analgesia has been established [for review see Han & Terenius 1982]. Reports on 5-HT involvement in TENS analgesia is sparse although Woolf et al. [1980] found that analgesia obtained by segmental peripheral stimulation in the rat was significantly reduced by pre-treatment with the 5-HT depleting agent parachlorophenylalanine (PCPA).

Aims of Chapter 5

In view of the sparse and conflicting information outlined above, the aim of the present chapter was to measure changes in peripheral and CSF concentrations of beta-endorphin, met-enkephalin and 5-HT during TENS and acupuncture. Unfortunately ethical and financial restraints made it impossible to measure CSF concentrations within the time course of this work, although ethical approval and financial support has finally been obtained and an investigation started. Thus, a pilot experiment was conducted in collaboration with the Department of Biochemistry at Newcastle General Hospital to investigate changes in peripherally circulating opioid peptides and 5-HT in patients who obtained relief of chronic pain with TENS and acupuncture treatment.

EXPERIMENT 5.1

The effect of TENS and acupuncture on concentrations of beta-endorphin, met-enkephalin and 5-HT in the peripheral circulation.

Patients and subjects

Thirteen chronic pain patients and 7 pain-free subjects (of similar age) participated in the present study (female $n=13$, male $n=7$; age range=25-75, mean=52.3 years of age). The chronic pain patients were randomly selected from Newcastle Pain Relief Clinic files to create the following groups:

- (i) TENS - seven patients whose pain was controlled successfully with TENS.
- (ii) Acupuncture - six patients whose pain was controlled successfully with manual acupuncture.

Patients were requested not to use analgesics (including TENS and acupuncture) 12 hours prior to the experiment. A third group, pain-free subjects, acted as a time control and consisted of seven pain-free members of the public with similar ages to the pain patients. These subjects were administered 'sham' TENS. The thirteen patients had a variety of chronic pain conditions (classified according to the International Association for the Study of Pain classification of chronic pain conditions [IASP 1986] and the author's classification [Johnson et al. 1991a]) including:

Experiment 5.1					
Anatomical Region	(n)	Aetiology	(n)	Diagnostic Clusters	(n)
Cervical	3	Trauma	4	Deafferentation	2
Upper limb	3	Infective	2	Entrapment	2
Thoracic	1	Inflammatory	1	Neuralgia	3
Lower back	5	Degen./mechan.	4	Spondylosis	3
Two sites or more	1	Dysfunctional	1	Myofascial	1
		Other/unknown	1	Other/Unknown	2

Procedure

Subjects lay on a comfortable bed in a temperature controlled (21°C) room. A 12 ml sample of venous blood was taken from the antecubital vein, via an indwelling butterfly, every 15 minutes. Six experimental cycles (2 x pre-treatment; 2 x during treatment; 2 x post-treatment) were made. Both the TENS and sham TENS groups received 30 minutes stimulation (i.e. TENS was switched on immediately at the end of cycle 2 and switched off after cycle 4). Acupuncture needles were inserted immediately

at the end of cycle 2 and removed after cycle four. Patients completed a visual analogue pain rating scale (0 = no pain to 10 = worst pain imaginable) at the end of each cycle to assess the intensity of their pain at that particular time.

Treatment

TENS: Patients were in possession of either a Microtens 7757 or Tiger Burst stimulator and Tenzcare electrodes (3M-no.6225). Patients were asked to administer TENS to the usual anatomical site to control their pain. All patients applied their electrodes to achieve a 'strong but comfortable' electrical paraesthesia within the painful area. None used AL-TENS. The electrical characteristics of TENS, as monitored with the Frye Analyser, were:

pulse pattern	continuous n=5	burst n=2,
pulse width	200 μ s	
pulse frequency	median=43Hz	range=22-204Hz
pulse amplitude	median=14mA above SDT	range=5-37mA above SDT
electrode impedance	<2kohm.	

Pain-free subjects: These were used to compare pre-treatment baseline measures with pain patients and as time controls. Thus, sham TENS was administered with a coloured suggestion that "*TENS is stimulating at a subthreshold level which you may not feel yet we still expect it to change the levels of substances we are measuring in the blood.*", as previously described in Chapter 3. Electrodes were applied to the lower back straddling the spinal cord at L1/L2. No subjects questioned this procedure.

Acupuncture: Patients were regularly attending Professor J.W.Thompson (JWT), a trained acupuncturist, for treatment of chronic pain and were all known to respond. Acupuncture was administered by JWT to points normally used to control the pains of these patients. One to 7 needles (depending upon the patient) were inserted for a period of 30 minutes, and intermittently twirled.

Collection and preparation of samples

Twelve ml of venous blood was collected from the antecubital vein, 2 ml of which was stored in an Eppendorf tube at -10°C for 5-HT analysis. The remainder of the blood was split into two 5ml plastic EDTA tubes each containing 50 μ l of 2.3 M citric acid, mixed and centrifuged at 14,000 rpm for 30s. Plasma was decanted into plastic tubes containing 150 μ l glycine HCL buffer (1.6% glycine in 1M-HCL)/ml plasma, and flash frozen in liquid nitrogen and stored at -80°C [Clement-Jones et al. 1980b].

All opioid peptide assays were performed by Miss A. Weddell (AW) in the Department of Biochemistry at Newcastle General Hospital. Mrs S. Wright-Honari performed

5-HT assays in the Department of Psychiatry at the University of Newcastle upon Tyne. The following procedures were employed.

Beta-endorphin: Beta-endorphin was assayed by a two-site, solid phase immunoradiometric method supplied by Nichols Institute, San Juan Capistrano, USA [for reference see Allegro], employing antibodies recognising two separate epitopes on the beta-endorphin molecule - one immobilised on to a plastic bead and the other radio-labelled with ^{125}I thus forming a 'sandwich' complex with the peptide [Wardlaw & Frantz 1979].

200 μl of plasma were incubated with 100 μl of labelled antibody in the presence of the antibody coated bead for 24 hours at room temperature. Samples and control plasma were assayed simultaneously using a standard curve. After aspiration and twice washing with 2.5ml of phosphate buffered saline to remove any unbound labelled antibody, the tubes were counted for two minutes in a NE 1600 gamma counter and values read from the computer generated IRMA-SPLINE curve fitting. The assay has a sensitivity of 2.9 pmol/l and a normal range of 3 to 11 pmol/l. It shows a cross-reactivity of 16% with beta-lipotrophin.

Met-enkephalin: Met-enkephalin was assayed by radioimmunoassay (RIA) using reagents supplied by Incstar Corp., Stillwater, USA [for reference see Immuno Nuclear Corporation], after an initial extraction technique. Plasma samples were acidified with 1M HCL (100 μl) and allowed to thaw at 4°C before addition to a C18 Sep-pac cartridge activated with methanol and washed with water. Samples were applied under reduced vacuum ensuring contact with the ODS silica for a minimum of 3 minutes. After washing with acetic acid (4%) the sample was eluted with methanol (1.6ml) dried at 37°C to 500 μl and freeze dried then reconstituted in RIA buffer (500 μl of 25% human serum albumin in 0.05M phosphate pH 7.4) prior to RIA.

Frozen aliquots of the top aqueous standard (2175 pmol/l) were serially diluted with buffer for the standard curve. Standards and samples (200 μl) were incubated with antisera (100 μl of 1/900) and tracer (100 μl) for 24 hours at 4°C before separation of bound from free tracer by precipitation with rabbit gamma globulin (100 μl) and saturated ammonium sulphate solution (500 μl). After decanting, the tubes were counted for two minutes in a NE 1600 gamma counter; the amount of antibody bound label being inversely proportional to met-enkephalin in the tube. Sample concentrations were read from the computer generated non-linear standard curve fitting. The assay had a sensitivity of 35 pmol/l and a within batch precision of 11.7% at 475 pmol/l and

10.1% at 982 pmol/l (n=15); recoveries above 94% were obtained [Clement-Jones et al.1980a].

5-HT: A 1ml sample of blood which was kept in the freezer was defrosted and 5-HT assay was performed according to Marshall et al. [1987]. 450 µl of distilled water was added to 150µl of defrosted blood and 100µl of zinc sulphate (10% w/v) was added to this aliquot, mixed thoroughly and centrifuged at 12000g for 7 minutes. Sodium hydroxide was added (20µl: 20% w/v) to an aliquot (400µl) of the supernatant, mixed well and centrifuged at 12000g for 7 minutes. Supernatant was removed to autosampler tubes for subsequent assay by HPLC, using electrochemical detector.

Stock solutions of 5-HT (100mg/l) were prepared in water and kept in aliquots of 0.1ml at -20°C. Standard solutions (final concentration of 100µg 5-HT/l) were prepared from the stock solutions in buffer taken through the procedure and assayed every fifth sample. All the samples and standards were measured in duplicate. Blanks were not included in every assay as no peaks apart from the solvent front appeared on the resulting chromatogram. The assay had a sensitivity of 4µg/l.

Results of Experiment 5.1

Prior to statistical analysis data was transformed to allow for the sensitivity of the assay, thus:

- (i) beta-endorphin levels below the sensitivity of the assay (<2.9pmol/l) were transformed to 2.9pmol/l,
- (ii) met-enkephalin levels below the sensitivity of the assay (<35.0pmol/l) were transformed to 35.0pmol/l.

No measurements of 5-HT fell below the sensitivity of the assay. A logarithmic transformation was performed to take into account the skewed distribution and marked heteroscedascity (i.e. increase in SD with increasing mean) of the data as shown in Table 5.1.

	CYCLE					
	Pre 1 -15mins	Pre 2 -01mins	During 1 +15mins	During 2 +30mins	Post 1 45mins	Post 2 60mins
Beta-endorphin (pmolL ⁻¹)						
Pain Free	6.2±3.3	6.3±2.8	5.3±2.6	4.6±2.1	5.7±2.7	4.4±1.8
Acupuncture	5.0±1.6	5.5±2.7	5.9±3.6	4.8±1.8	4.1±1.4	5.5±2.3
TENS	5.8±1.9	4.9±1.0	5.5±1.4	5.7±2.4	5.5±2.3	5.1±1.6
Met-enkephalin (pmolL ⁻¹)						
Pain Free	48.1±17.7	48.6±22.4	47.7±22.0	52.8±39.7	51.4±29.8	54.6±27.2
Acupuncture	43.7±14.6	44.2±14.0	48.8±18.0	40.0± 7.6	42.5±13.8	41.7±10.9
TENS	61.5±25.2	49.9±19.4	86.3±40.9	84.7±48.8	72.5±43.2	90.4±58.8
5-HT (ugL ⁻¹)						
Pain Free	67.7±32.1	70.7±38.7	74.6±43.2	75.7±39.7	75.3±40.6	67.7±28.4
Acupuncture (n=5)	91.8±48.8	99.4±56.8	98.8±51.7	113.0±54.8	105.4±51.9	103.0±57.2
TENS	81.6±51.0	79.3±40.6	80.7±45.9	76.3±54.6	90.1±47.6	95.0±46.5
Pain Intensity (VAS units)						
Pain Free	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Acupuncture	5.5±1.0	5.7±0.9	4.2±2.0	3.4±2.2	3.3±2.2	3.5±2.5
TENS	3.5±2.6	3.2±2.8	1.5±1.4	0.7±0.9	1.1±1.4	1.2±1.7

Table 5.1 Mean±SD concentrations of peripherally circulating substances during TENS (n=7) and acupuncture (n=6) in chronic pain patients (Exp.5.1).

No significant differences were observed between the pre-treatment recordings of cycle 1 and 2 for beta-endorphin, met-enkephalin and 5-HT (Paired t-test irrespective of treatment groups). These pre-treatment values were also found to be highly correlated (Pearson correlation coefficients, $r > +0.8$). Thus, pre-treatment baseline mean was calculated for each individual for each analyte measured; no significant differences in these pre-treatment means were found between treatment groups (one-way ANOVA) However, patients in the acupuncture group had higher baseline pain intensity ratings than those in the TENS group although this just failed to reach significance ($P=0.1$ unpaired t-test, see Table 5.2). General treatment effects were examined by calculating the mean of the 2 'during treatment' cycles and the 2 'post-treatment' cycles for each individual as shown in Table 5.2. Thus, the pre-treatment mean was subtracted from the during and post treatment values for each individual to obtain the change from pre-treatment baseline and one-way ANOVA and unpaired student t-tests were used to examine differences between groups.

SUB	TMT	Beta-endorphin (pmol/l)		Met-enkephalin (pmol/l)		5-HT (ug/l)		Pain Intensity Rating (0= No pain ---> 10 = Worst pain)		
		PRE	DRG	POST	PRE	DRG	POST	PRE	DRG	POST
1	PFC	8.5	8.8	8.6	68.5	114.0	113.5	0.0	0.0	0.0
2	PFC	9.5	6.0	5.6	82.0	54.5	54.0	0.0	0.0	0.0
3	PFC	10.1	6.9	7.1	38.6	42.0	56.3	0.0	0.0	0.0
4	PFC	<2.9	3.8	4.5	44.2	<35.0	<35.0	0.0	0.0	0.0
5	PFC	3.7	3.4	3.7	<35.0	36.3	42.1	0.0	0.0	0.0
6	PFC	5.7	<2.9	<2.9	35.2	<35.0	<35.0	0.0	0.0	0.0
7	PFC	3.5	<2.9	<2.9	<35.0	<35.0	48.5	0.0	0.0	0.0
MEAN		6.3	5.0	5.1	48.4	50.3	53.0	0.0	0.0	0.0
PFC										
8	ACUP	5.5	5.2	7.2	70.0	50.0	65.0	6.0	3.0	4.0
9	ACUP	<2.9	3.0	<2.9	<35.0	<35.0	<35.0	6.1	4.3	3.8
10	ACUP	3.1	3.2	<2.9	41.0	53.0	39.0	6.9	7.0	6.7
11	ACUP	5.0	4.1	6.4	36.0	40.2	40.5	5.5	5.0	4.0
12	ACUP	6.8	9.8	3.8	59.9	58.2	<35.0	5.0	0.5	0.0
13	ACUP	8.3	6.8	4.2	35.1	<35.0	<35.0	4.2	2.9	1.6
MEAN		5.3	5.4	4.6	46.2	45.2	41.6	5.6	3.8	3.3
ACUP										
14	TENS	4.0	4.3	5.0	67.5	104.5	<35.0	4.9	2.8	2.8
15	TENS	3.9	3.3	3.5	<35.0	161.0	167.5	0.9	1.9	1.5
16	TENS	5.2	6.2	4.3	<35.0	45.0	<35.0	8.0	1.5	3.5
17	TENS	6.2	5.4	4.8	70.0	92.0	84.0	1.0	0.0	0.0
18	TENS	5.8	6.9	6.1	<35.0	59.5	116.0	1.5	0.0	0.0
19	TENS	4.5	4.3	4.0	72.0	77.0	70.5	5.0	1.1	0.0
20	TENS	7.7	8.9	9.1	57.0	60.5	68.0	2.0	0.5	0.0
MEAN		5.3	5.6	5.3	53.0	85.6	82.3	3.3	1.1	1.1
TENS			n.s.			p=0.1	n.s.		[p<0.01]	

Table 5.2 Individual changes in peripheral concentrations of opioid peptides and 5-HT (Exp. 5.1). SUB = subject number, TMT = treatment group, PFC = Pain-free control, Acup = Acupuncture patients, TENS = TENS patients. The mean of the two pre, during (DRG) and post-treatment cycles were calculated for each individual, <2.9, or <35.0 = below the sensitivity of the assay. Change in concentrations pre v during treatment were calculated and P values calculated using one-way ANOVA across the three groups. A significant reduction in pain intensity rating was found between pre v during treatment for acupuncture [p<0.01, paired t-test] and TENS [p<0.01, paired t-test].

Pain Rating: Fig.5.1 shows a significant reduction in pain intensity rating during both TENS and acupuncture, when compared to pre-treatment baseline, which was sustained in post-treatment cycles (mean \pm SD TENS; pre=3.3 \pm 2.7, during=1.1 \pm 1.0, $P<0.05$: Acupuncture: pre= 5.6 \pm 0.9, during= 3.8 \pm 2.0, $P<0.05$, paired t-test). No significant differences were observed between TENS and acupuncture groups (unpaired t-test).

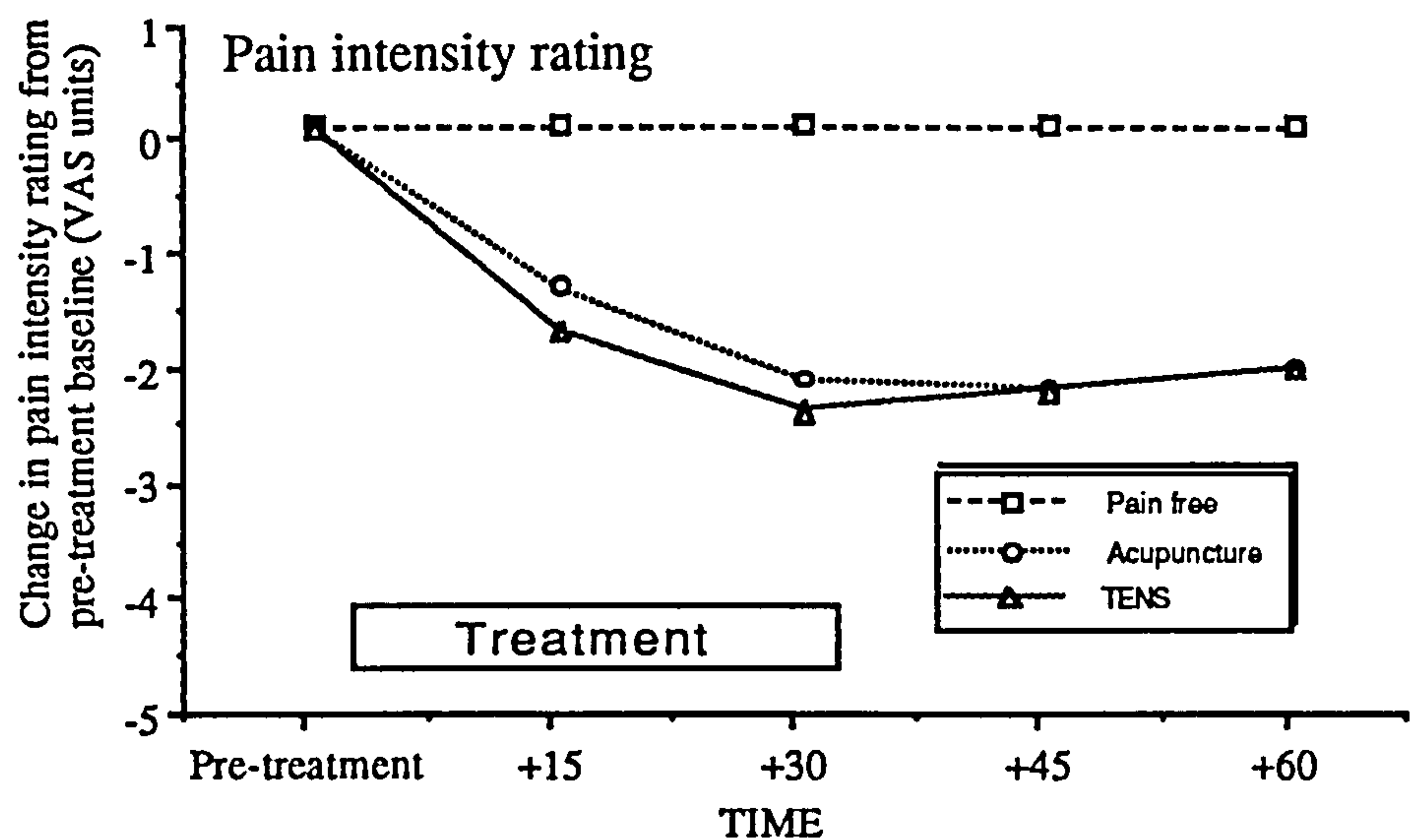


Fig.5.1 Mean change in pain intensity rating (measured on a VAS) during TENS (n=7) and acupuncture (n=6) in chronic pain patients (Exp. 5.1). Pain-free subjects (n=7) received sham TENS. Time = minutes.

Beta-endorphin: Pre-treatment levels irrespective of treatment group (Mean=5.6 pmol/l, range <2.9-11.3pmol/l) were similar to those reported by the RIA kit manufacturers (Mean=8.4 pmol/l n=83 healthy subjects, [see reference Allegro]). A wide range of baseline plasma concentrations of beta-endorphin have been reported in healthy subjects (mean \pm SD):

- (i) 16.7 \pm 4.0 pmol/l [Malizia et al. 1979],
- (ii) 6.1 \pm 2.1pmol/l [Wardlaw & Frantz 1979],
- (iii) 9.7 pmol/l [O'Brien et al. 1984].

The mean pre-treatment baseline level of beta-endorphin recorded from pain-free subjects in the present study was 6.14 \pm 3.21pmol/l and not significantly different from pain patients (unpaired t-test). No significant changes in beta-endorphin were observed between the treatment groups (one-way ANOVA see Fig.5.2).

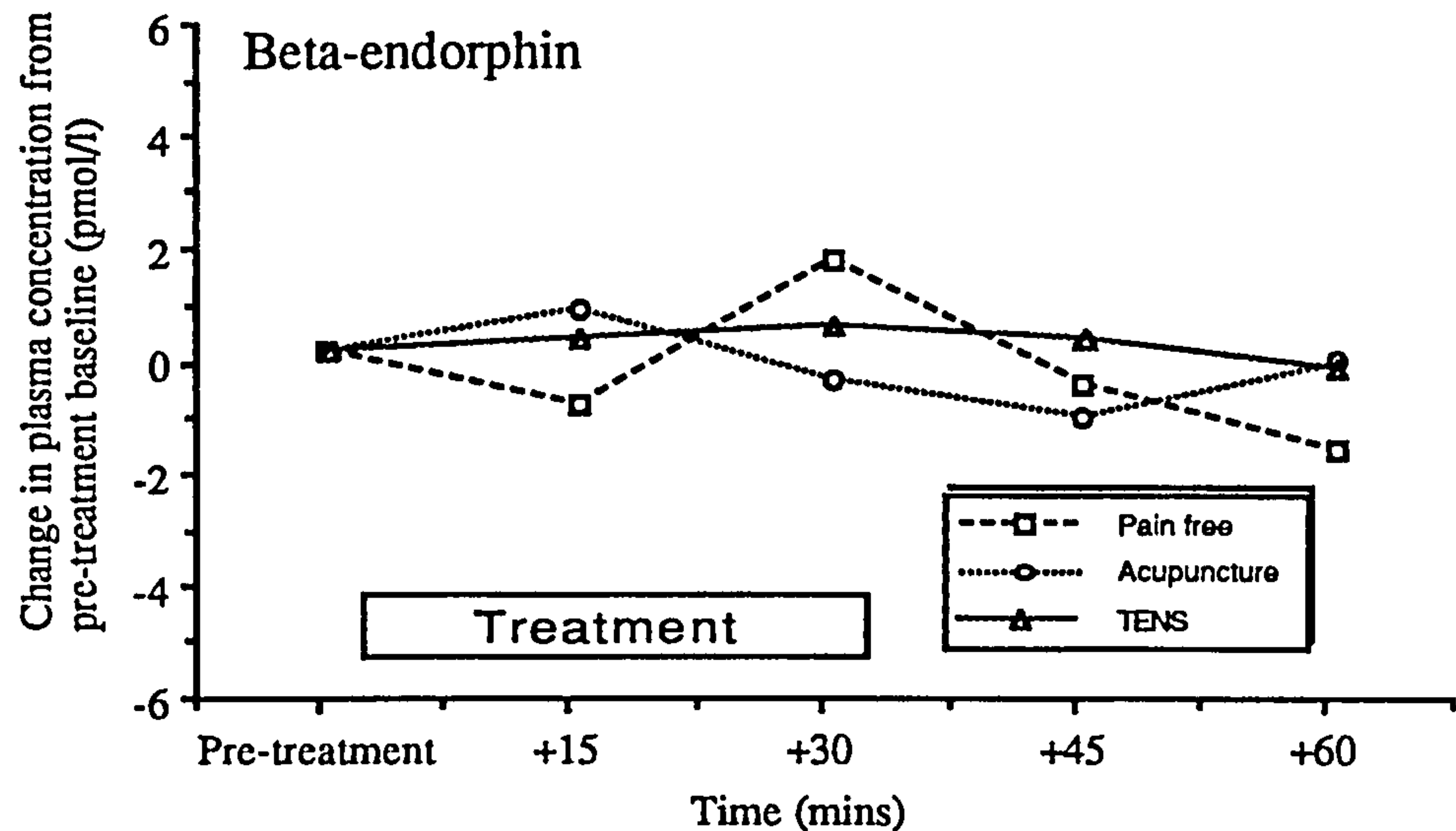


Fig.5.2 Mean change in concentration of peripherally circulating beta-endorphin during TENS (n=7) and acupuncture (n=6) in chronic pain patients (Exp. 5.1). Pain-free subjects (n=7) received sham TENS.

Met-Enkephalin: Pre-treatment met-enkephalin levels irrespective of treatment group (mean=49.2 pmol/l, range=<35.0-100.0pmol/l) were consistent with Clement-Jones et al. [1980b] (14-140 pg/ml (7-70pmol/l), but broader than RIA kit manufacturers (range=14-61 pmol/l n=9 healthy subjects). Of interest is the manufacturer's report of met-enkephalin levels of 14 pmol/l despite the sensitivity of the assay being 35pmol/l! [see reference Immuno Nuclear Corporation]. No significant differences in plasma met-enkephalin were observed between pain-free subjects and pain patients. Met-enkephalin was found to increase in all patients during TENS and one subject dominated these results with an increase from <35.0-161pmol/l (Table 5.2). The increase in met-enkephalin during TENS just failed to reach statistical significance when compared to either pain-free or acupuncture groups (mean±SD change in met-enkephalin during treatment: TENS=+32.6±42.9 pmol/l, Pain-free=+1.9±22.0pmol/l, $P<0.1$; Acupuncture=-0.9±10.6pmol/l, $P<0.09$, unpaired t-test, see Fig.5.3).

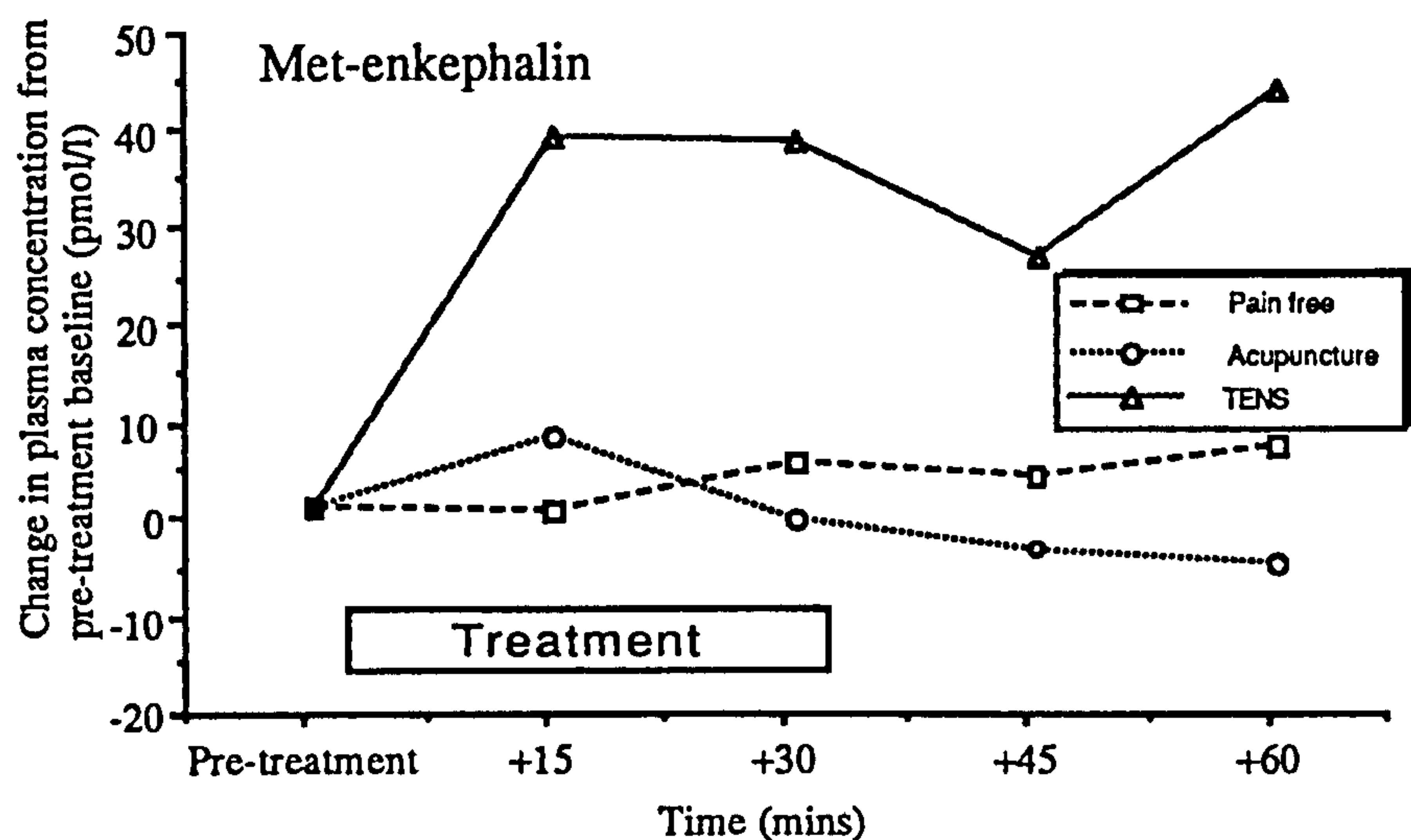


Fig.5.3 Mean change in concentration of peripherally circulating met-enkephalin during TENS (n=7) and acupuncture (n=6) in chronic pain patients (Exp. 5.1). Pain-free subjects (n=7) received sham TENS.

5-HT: Pre-treatment levels (mean=80.3 μ g/l range 40-194 μ g/l) were similar to those reported by Marshall et al. [1987] (90-140 μ g/l). No significant changes in 5-HT occurred during or post-treatment in any groups although all groups showed an increase in 5-HT post-treatment when compared to pre-treatment baseline (Fig.5.4). However, examination of individual results showed that a post-TENS increase in 5-HT of over 10 μ g/l occurred in 5 out of 6 patients (see Table 5.2).

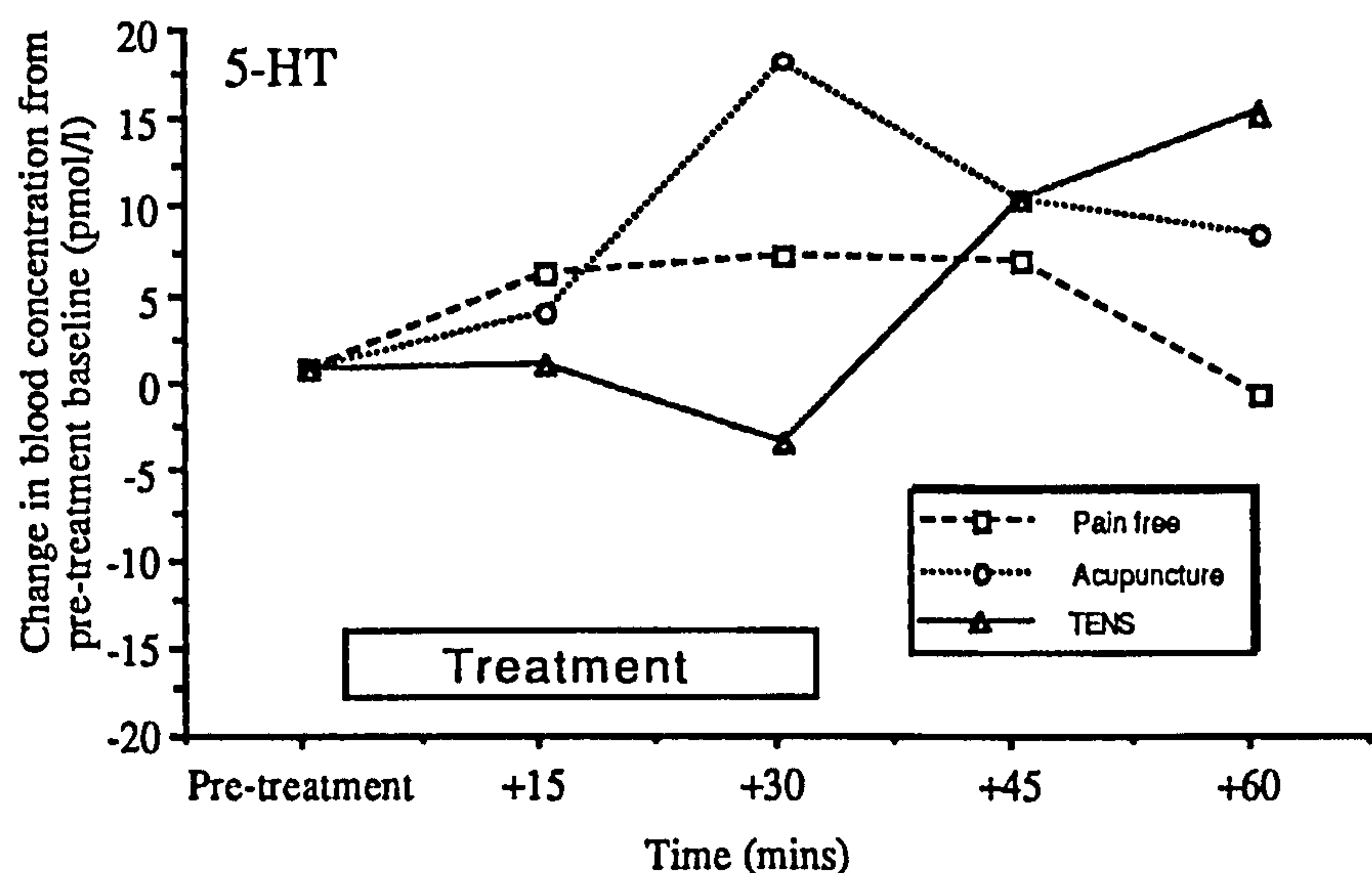


Fig.5.4 Mean change in concentration of peripherally circulating 5-HT during TENS (n=7) and acupuncture (n=5) in chronic pain patients (Exp. 5.1). Pain-free subjects (n=7) received sham TENS.

Main Findings Experiment 5.1

- (i) An increase in peripheral met-enkephalin concentration occurred during TENS although this increase just failed to reach statistical significance when compared to pain-free subjects who received sham TENS ($P=0.1$).
- (ii) No significant differences in peripheral concentrations of opioid peptides or 5-HT were found between pain-free healthy subjects and chronic pain patients.
- (iii) No significant changes in peripheral concentrations of opioid peptides or 5-HT were found after treatment with TENS or acupuncture.
- (iv) During a 30 minute treatment session, TENS and acupuncture significantly reduced the intensity of chronic pain in patients.

DISCUSSION

The main finding of the present study was an increase in plasma met-enkephalin which occurred in all pain patients during TENS treatment. However, this rise in met-enkephalin just failed to reach statistical significance when compared to pain-free patients receiving sham TENS. Acupuncture produced no such increase. Both TENS and acupuncture had little effect on plasma beta-endorphin or 5-HT. Both TENS and acupuncture significantly reduced pain intensity ratings within 15 minutes of administration. The possible mechanisms of these changes in relation to analgesic effects are discussed below.

Met-enkephalin

The increase in met-enkephalin during TENS in chronic pain patients is interesting in that no such report has been noted previously. However this finding needs to be confirmed in a larger study sample. Met-enkephalin has been implicated in central 'pain modulating' mechanisms due to the high concentration of enkephalins localised within the substantia gelatinosa of the dorsal horn of the spinal cord [Bennett et al. 1982]. Thus, enkephalinergic interneurons may play an important part in TENS analgesia. However, it seems unlikely that the peripheral change in met-enkephalin as measured in this and other experiments [Clement-Jones et al. 1979; Clement-Jones & Besser 1983] was due to central release because met-enkephalin cannot cross the blood brain barrier as a consequence of poor lipophilic properties. Met-enkephalin is also rapidly degraded by a number of circulating, non-specific, amino- and metallo-peptidases resulting in a half life of 2 to 3 minutes [Hambrook et al. 1976]. As time from venepuncture to flash freezing may take up to 5 minutes it is possible that variations in time to flash freezing may seriously alter met-enkephalin concentrations. However sample handling was standardised by one individual and it therefore seems unlikely that differing degrees of degradation can account for all of the observed increases in met-enkephalin concentration during TENS.

Enkephalins are widely distributed in the peripheral nervous system including high concentrations in the adrenal medullary chromaffin cells [Clement-Jones et al. 1980c], other sources being the gut, sympathetic ganglia and peripheral autonomic neurones [Smith et al. 1981]. It has been suggested that, during stress, enkephalins are released along with adrenaline and reach the nervous system through the circulation. Stress is

an important and potent activator of the analgesic system and a variety of non-painful stressors (restraint, hypoglycaemia) can induce a naloxone-reversible analgesic state [Fields 1987b]. Thus, the increase in peripherally circulating met-enkephalin noted in this experiment during TENS may be due to a stress-like release mechanism.

Met-enkephalin has been implicated in acupuncture analgesia and Kiser et al. [1983] reported increases in plasma met-enkephalin but not beta-endorphin during acupuncture treatment of twenty chronic pain patients. By contrast, Clement-Jones et al. [1980b] reported no significant changes in CSF met-enkephalin in 10 pain patients successfully treated with low frequency acupuncture. Our findings show no change in plasma met-enkephalin levels during symptomatic relief of chronic pain using acupuncture, although it is possible that changes may occur outside the time course of this experiment.

Beta-Endorphin

Studies suggest that chronic pain patients have lower CSF concentrations of beta-endorphin-like material than pain-free patients [Sjölund et al. 1977; Akil et al. 1978; Almay et al. 1978]. Reports on levels of plasma beta-endorphin in chronic pain patients are less readily available. The present study showed no significant differences in plasma levels of beta-endorphin between pain-free subjects and chronic pain patients. However it has been reported that CSF concentrations of beta-endorphin are substantially higher than those found in plasma (i.e. 27-144 pmol/l n=10, Clement-Jones et al. [1980c], for review see Clement-Jones & Besser [1983]).

It seems unlikely that beta-endorphin would cross the blood brain barrier due to its large size. Terenius [1979] suggested that endorphins produced within the peripheral circulation would be less likely to be involved with pain reducing mechanisms than endorphins produced within the CSF. Our findings lend support to such a theory as no peripheral changes in beta-endorphin were detected during symptomatic relief of chronic pain by acupuncture and TENS. Thus, the present study does not support the findings of Malizia et al. [1979] who reported increased plasma beta-endorphin during acupuncture. However it is possible that a delayed increase of plasma beta-endorphin may have occurred outside the time course of the experiment. Our findings are consistent with those of O'Brien et al. [1984] and contrast with those of Facchinetti et al. [1984] in that no changes in plasma beta-endorphin after TENS were observed. The

lack of change in CSF levels coupled with the evidence showing the ineffectiveness of naloxone to reverse analgesia produced by low intensity high frequency TENS suggests that beta-endorphin does not play a role in conventional TENS [Sjölund & Eriksson 1979].

5-HT

No change in platelet 5-HT occurred in any group during or post-treatment in the present study. No significant differences in pre-treatment 5-HT were observed between chronic pain patients and pain-free subjects. Thus, the present findings do not support those of Mao et al. [1980] who reported higher baseline peripheral concentrations of 5-HT in healthy subjects as opposed to chronic pain patients.

Although serotonin does not pass the blood brain barrier its precursor tryptophan does and thus peripheral 5-HT may reflect central 5-HT [Messing & Lytle 1977]. Nevertheless, the relationship between central and peripheral 5-HT remains to be determined [Mao et al. 1980]. Cheng and Pomeranz [1981] using mice, suggested that high-frequency noxious stimulation (electroacupuncture) did not activate the release of endorphins but may result in 5-HT release. Woolf et al. [1980] found that analgesia produced by segmental peripheral stimulation in the rat was significantly reduced by pre-treatment with PCPA or by spinalisation. It has been established that serotonergic neurones form part of descending pain inhibitory pathways in the CNS (see Fig.1.3). However 5-HT is considered as a pain-producing substance in the periphery (excitation of tissue chemoreceptors) when liberated as a result of injury.

Summary

The main finding of this preliminary study was the first known report of an increase in plasma met-enkephalin but not beta-endorphin during TENS analgesia in chronic pain patients. Whether this increase is confined to patients who obtain relief of pain during TENS, or whether it also occurs during TENS in pain-free subjects remains to be determined. Hence it is uncertain if such an increase in met-enkephalin plays a role in the relief of pain accompanying TENS. Acupuncture produced no changes in any of the biochemical variables measured although a significant reduction in pain intensity

was obtained. No differences in any pre-treatment biochemical measures were observed between pain-free subjects and pain patients but because of small sample numbers these findings need to be substantiated.

The previous chapters have examined the clinical use of TENS by chronic pain patients, the optimal characteristics of TENS to reduce experimental pain and the effects of TENS on the electrical activity of the brain and peripheral concentrations of opioid peptides and 5-HT. Thus clinical, electrophysiological and neuropharmacological factors have been shown to be influenced by TENS. The relationship between these factors and patient response to TENS is examined in Chapter 6.

CHAPTER 6

FACTORS RELATED TO PATIENT RESPONSE TO TENS

INTRODUCTION

"After 7 years familiarity with transcutaneous stimulation, the present authors are still unable to predict whether or not a particular patient will obtain long lasting pain relief." Bates and Nathan [1980].

At present it is still not possible to predict whether a patient will respond to TENS. Consequently TENS is administered on an empirical basis. However, the results presented in Chapter 2 suggest that 41.4% of patients given a trial of TENS fail to respond. Therefore it is important to investigate factors which may be related to patient response to TENS in order to elucidate the underlying mechanisms of treatment failure and thus to improve clinical efficacy. These factors are discussed below.

Factors related to pain

As indicated in Chapters 1 and 2, some pain conditions (e.g. visceral and psychogenic) are *less likely* to respond favourably to TENS than others (see Table 1.2a and b). Johansson et al. [1980] searched for predictors of TENS response in 72 patients and found that patients with neurogenic or extremity pain showed favourable responses. However, only short-term TENS effects were observed and patients were classified as responders and non-responders on the basis of a 30 minute treatment session. By contrast, Reynolds et al. [1983] found no association between the site and cause of pain in 200 patients and treatment outcome, but reported that patients with pain of more than one year duration showed less favourable responses to TENS. It is most frustrating to both physician and patient when TENS fails to control a pain condition which normally responds. This suggests that factors unrelated to pain may influence patient response. Despite a large number of trials which have examined TENS efficacy

in the treatment of a variety of pain conditions, few studies have examined factors unrelated to pain which may influence patient response.

Factors unrelated to pain

A number of pre-existing sociological, psychological, electrophysiological and neuropharmacological factors may determine patient response to TENS.

Sociological

Reynolds et al. [1983] examined the value of questionnaires which recorded pre-existing physical and social factors in determining the response of 200 chronic pain patients to TENS. Patients who used tranquillisers, had undergone multiple surgical operations, or were unemployed because of the pain condition, were found to respond poorly to TENS, although none of these factors reached statistical significance. Success with TENS was found in retired patients. Age, sex, and the use of analgesics were not found to reflect patient response to TENS, a finding consistent with that of Johansson et al. [1980].

Psychological

Nielzén et al. [1982] examined the effects of psychiatric and physical disorders on the success of TENS in 66 chronic pain patients and found that mentally ill patients, patients with pathological personality traits, and patients without any physical cause for pain were failures to TENS treatment. Johansson et al. [1981] found that patients with high 'Lie' scores on the Eysenck Personality Inventory (EPI, the forerunner to the EPQ) showed favourable responses. The 'Lie' score measures the consistency of answering within the questionnaire although it may also reflect social compliance. Therefore the EPQ may be of value in predicting patient response to TENS.

Evoked Potentials

The results presented in Chapter 4 have shown that TENS reduces the peak-to-peak amplitudes of late latency waveform components of the SEPs. No relationships were observed between baseline SEP amplitudes and response to TENS although only pain-free subjects were examined (Exp.4.1). The predictive value of SEPs in determining TENS response was discussed by Golding et al. [1986] who suggested that subjects with large baseline SEP amplitudes (both early and late latency components) produce a greater reduction of both SEP amplitudes and experimental pain during TENS. However subjects received different current intensities of evoking stimuli to elicit the

SEP, which had been fixed perceptually to produce a 'strong non-painful' electrical pulse. As baseline SEP amplitudes are related to the current intensity of the evoking stimuli, inter-individual differences in SEP amplitudes may have been due in part to inter-individual differences in the current intensity of the evoking stimuli. Furthermore healthy pain-free subjects rather than patients with a chronic pain condition were examined. The utility of SEP amplitudes in predicting patient response to TENS merits further investigation. It has been suggested that individuals producing 'augmenting' responses to visual evoked potentials may show more favourable responses to TENS [Johansson et al.1981].

Augmenters/Reducers

The concept that certain individuals can be described as 'augmenters' or 'reducers' according to the way in which they respond to different intensities of sensory stimuli was originally proposed by Petrie [1967] to account for individuality in pain and suffering. It was suggested that augmenters tend to enlarge their perception of sensory stimuli at increasing stimulus intensities while reducers tend to diminish their perception at increasing stimulus intensities. The idea of augmenters and reducers has received some support from evoked potential studies, and it has been shown that augmenters increase peak-to-peak amplitudes of SEP waveform components with increasing intensities [Buchsbaum & Silverman 1968; Buchsbaum 1976]. It has been suggested that augmenters have a low tolerance to pain and respond favourably to analgesic treatment [Buchsbaum 1984]. Johansson et al.[1981], investigated augmenting/reducing responses in a group of 30 chronic pain patients and found that augmenters to visual evoked potentials (i.e. increase in peak-to-peak amplitude of visual evoked potential waveform components with increasing stimulus intensity) showed a favourable response to TENS. Reducers responded poorly to TENS.

Spontaneous EEG

No previous studies have investigated the relationship between baseline spontaneous EEG and response to TENS. However the results presented in Chapter 4 suggest that TENS produces variable effects on spontaneous EEG in both pain-free subjects and pain patients. Although no relationships were found between baseline spontaneous EEG and patient response to TENS (Exp.4.3), the patient population was biased toward responders. A comparison between responders and non-responders is therefore necessary.

Experimental pain threshold

The results presented in Chapter 3 found wide inter-subject variability in response to TENS in healthy subjects experiencing experimental pain. Although response to TENS was not related to an individual's baseline pain threshold, comparisons were made difficult as subjects were assigned to different treatment groups and consequently received differing electrical characteristics of TENS. Golding et al. [1986] found that subjects with low baseline thresholds to experimental pain produced larger responses to TENS consistent with the augmenting/reducing concept. Thus, responders would correspond to patients with low baseline pain threshold and large baseline SEP amplitudes. Unfortunately, Golding et al. did not correct pain threshold measurements for inter-individual variations in sensory detection threshold so that high uncorrected pain threshold measurements may have been due in part to high sensory detection thresholds.

Neuropharmacological

The results of Exp.5.1 suggest that plasma concentrations of met-enkephalin may increase during TENS whereas no significant changes in peripheral concentrations of beta-endorphin or 5-HT were observed during TENS. Johansson et al. [1981] investigated the relationship between baseline CSF endorphin concentrations and response to TENS in 22 patients and found that TENS responders had lower levels of fraction I level endorphins. This was consistent with the group's previous work [von Knorring et al.1979] which suggested that augmenters had lower levels of endorphins in CSF. Although measurement of levels of CSF opioids was not possible in the present investigation, plasma levels of opioid peptides may reflect patient response to TENS.

Aims of Chapter 6

Previous studies in this thesis have examined the effects of TENS on a number of clinical, psychological, electrophysiological and neuropharmacological factors in both pain-free subjects and chronic pain patients. Hence TENS was found to:

- (i) reduce chronic pain in patients and experimental pain in healthy subjects (Study 2.2 and Exp. 3.1, 3.2, 3.3),
- (ii) reduce peak-to-peak amplitudes of late latency components of the SEP in healthy subjects (Exp. 4.1),
- (iii) increase a combination of alpha, beta and theta activity of spontaneous EEG in chronic pain patients (Exp. 4.3) and pain-free subjects (Exp.4.2),
- (iv) increase plasma concentrations of met-enkephalin in pain patients (Exp. 5.1).

Factors related to patient response to TENS are largely unknown. Therefore, a prospective study was undertaken to investigate the relationship between a variety of baseline measures and the response to TENS in patients undergoing a trial of TENS for the treatment of a chronic pain condition. The study was double-blind in that both patient and experimenter did not know whether the patient would respond to treatment. Thus the aim of the study reported in Chapter 6 was to investigate the relationships between pre-existing:

- (i) psycho-social factors,
 - (ii) experimental pain threshold and tolerance measurements,
 - (ii) evoked potential amplitudes and spontaneous EEG recordings,
 - (iii) plasma concentrations of opioid peptides,
- and patient response to TENS.

EXPERIMENT 6.1

Factors related to patient response to TENS

Patients and Procedure

Twenty nine patients (female n=16, male n=13; age range=30-75, mean=52.2 years of age) with a variety of chronic pain conditions participated in the study. All new patients given a trial of TENS were asked to attend the research unit prior to the follow-up appointment at the clinic (between 1-2 months). Patients on psychotropic drugs or with mobility problems were excluded from the study.

TENS Questionnaire: Patients completed a modified TENS multiple choice questionnaire designed to record pre-existing sociological variables and the use of TENS in the month prior to attending the research unit (see Appendix A). Recordings included: patient details, occupation, length of current pain condition, whether employment was lost due to the pain, stimulator model and settings used, the number of hours of stimulator use, the degree of pain relief obtained, time to onset and offset of analgesia and any adverse reactions. In addition visual analogue scales were used to assess the patient's:

- (i) opinion on the adequacy of instruction on stimulator use by the clinic,
- (ii) initial confidence in treatment success,
- (iii) opinion on the logic of TENS as a treatment for chronic pain.

Electrical characteristics of TENS: The electrical characteristics of TENS during treatment were recorded on a Frye Analyser as previously described in Chapter 2. Patients were asked to apply TENS as they usually would to control their pain.

Personality, anxiety and depression: All patients completed an Eysenck Personality Questionnaire (EPQ) [Eysenck & Eysenck 1975] and a Hospital Anxiety and Depression (HAD) scale [Zigmond & Snaith 1983].

EEG recording: General recording techniques have been described in Chapter 4. The following recordings were made:

- (i) auditory evoked potentials (AEP),
- (ii) somatosensory evoked potentials (SEP) to two intensities of electrical stimuli (i.e. 2.5 and 5.0 mA above SDT),

(iii) spontaneous EEG with eyes open and closed.

Recordings were made in the morning; electrode positions were Cz (vertex) and Nz (nasion) referenced to LM (linked mastoids).

(i) Auditory Evoked Potential (AEP): Recorded as a measure of general cortical response to sensory stimuli. AEPs were recorded to 30 tones (1000Hz, 60dB, 200ms) delivered through earphones at randomly varied intervals 1-3s. Patients were asked to count mentally the number of tones so as to standardise attention across the group. Amplifier settings: high pass filter=0.2s, low pass filter=30Hz, range=100 μ V [for full description of AEP recording see Ashton et al. 1988].

(ii) Somatosensory Evoked Potential (SEP): SEPs were recorded as a measure of patient response to electrical stimuli at two current intensities:

(a) 2.5mA above SDT,

(b) 5.0mA above SDT.

The evoking stimulus was delivered as a monophasic, square wave electrical pulse (pulse width=200 μ s). Thirty stimuli were delivered randomly in time (inter-stimulus interval between 1-3 s) via two electrodes straddling the proximal interphalangeal joint. Amplifier settings: high pass filter=1s, low pass filter=1KHz, range =100 μ V.

Latencies and peak-to-peak amplitudes of P1N1, N1P2 and the Root Mean Square value between 50-550 ms were calculated for each individual. Root Mean Square (RMS) value was taken as a general measure of response to stimuli. RMS value was calculated as the square root of the mean of the squared deviation of the waveform from baseline, for all data points lying between the time window 50-550 ms [Golding et al. [1986].

(iii) Spontaneous EEG: Spontaneous EEG was recorded with eyes open and eyes closed. Each recording acquired 25, 2 second epochs and averaged power spectra were computed off-line using fast fourier transform. Power spectrum (μ V²/Hz) was analysed in the traditional frequency bands as described in Exp. 4.2. Amplifier settings were set to optimise the recording of slow wave activity as follows: high pass filter=0.2s, low pass filter=30Hz, range=100 μ V.

Sensory detection threshold, pain threshold and pain tolerance: Sensory detection threshold, (SDT), pain threshold and pain tolerance were determined using square wave electrical stimuli delivered to the index finger of the left hand, via two

0.5cm² carbon rubber electrodes (the same as used to elicit SEPs) straddling the proximal interphalangeal joint. Stimuli were presented at a frequency of 10Hz and a 5ms pulse width, as such parameters have been found reliable in inducing an aching pain sensation (unpublished observations). SDT was recorded as the current at which '*you can feel the first electrical pulses*', pain threshold as '*the point at which the pulses first become painful*', and pain tolerance as '*the point at which the pulses become unbearable - and the pulses will be terminated immediately*'. When stimulus strength reached the level of pain tolerance it was switched off immediately.

Plasma concentrations of opioid peptides: A 10ml venous blood sample was collected from the antecubital vein prior to the start of the experiment. Baseline plasma concentration of beta-endorphin was measured using a immunoradiometric method supplied by Nichols Institute and met-enkephalin by radioimmunoassay using reagents supplied by Incstar Corp. as previously described in Chapter 5.

Four month follow-up: Postal questionnaires were sent to all patients 4 months from the date of attendance at the research unit (see Appendix A). Questionnaires recorded whether patients continued to use the stimulator. Patient notes were also examined at the 4 month interval to ascertain whether stimulators had been returned. Of 10 patients asked, 8 returned to the unit for follow-up assessment and EEG recording (female n=6, male n=2; age range=35-72, mean=50.5 years of age) .

Results of Experiment 6.1

Classification of responders and non-responders: The degree of pain relief achieved during TENS was assessed by two identical visual analogue scales (where 0=no pain and 10=worst pain imaginable) and a multiple choice question (see Appendix A). As no significant differences were found between the two VAS scores ($P=0.8$, paired t-test) the mean VAS score was calculated for each individual. This mean VAS measure was found to be highly correlated with the the degree of pain relief measured by the MCQ ($r=+0.90$, $P<0.01$, Spearman rank correlation coefficient). Thus, the mean VAS for each individual was used as a measure of response to TENS.

Seven out of 29 patients (24%) obtained no relief of pain with TENS; the remaining 22 patients reported pain relief between 2-10 units on the VAS (Fig.6.1). Therefore, the 7 patients who achieved no relief of pain during TENS were classified as non-

responders. Unpaired t-tests (for continuous data) and Mann-Whitney 2-sample rank tests (for categorical data) were performed to examine differences in factors between the responders and non-responders; Pearson correlation coefficients were used to examine relationships between these factors and degree of pain relief reported with TENS.

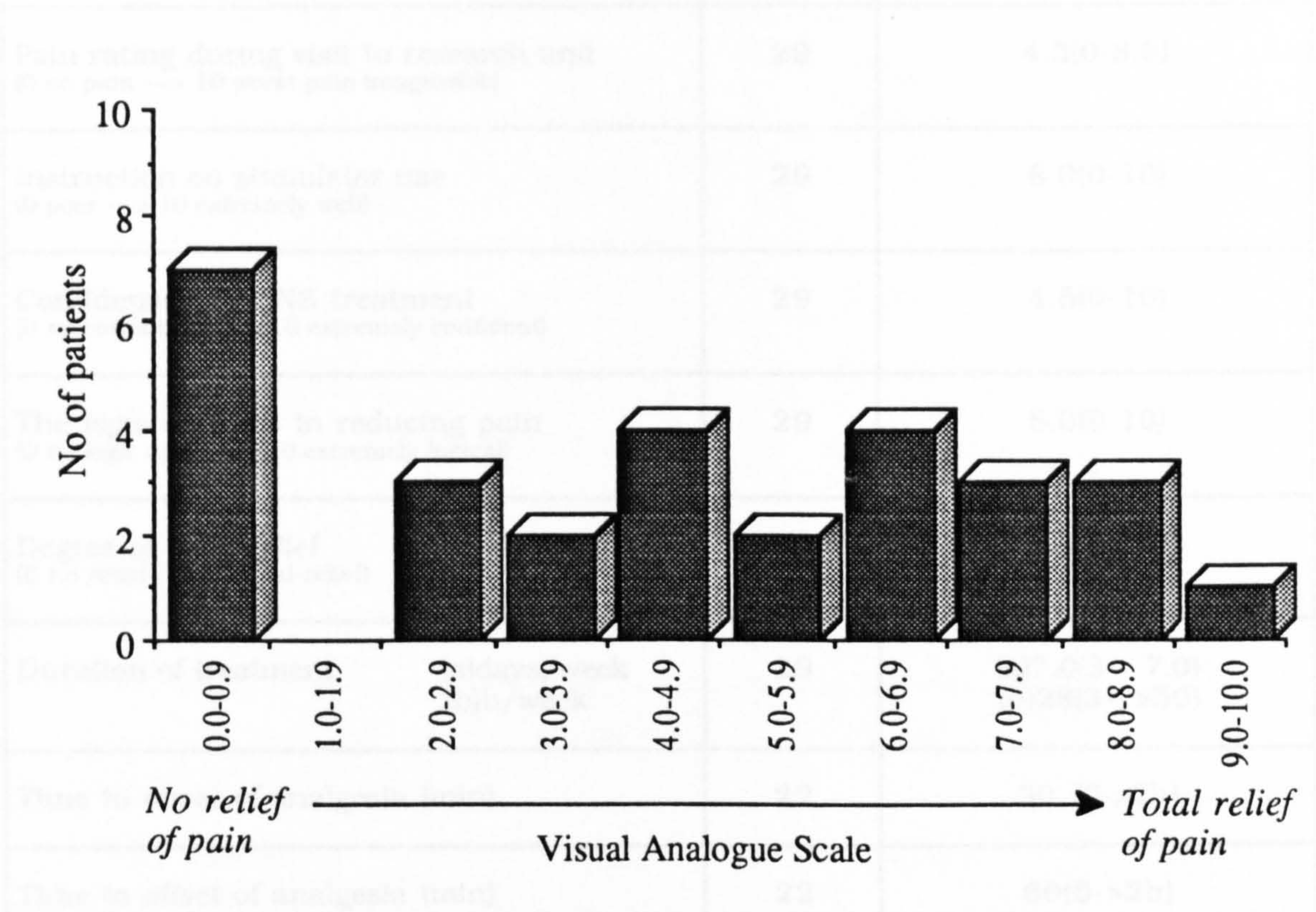


Fig.6.1 Histogram of pain relief obtained during TENS in 29 chronic pain patients (Exp.6.1). Patients with VAS scores of <1 (n=7) were classified as non-responders

TENS Questionnaire: The results of the TENS questionnaire are summarised in Table 6.1. Table 6.2 compares the results from the questionnaire, EPQ, HAD and pain threshold measures between responders and non-responders. The intensity of the patient's pain during the visit to the research unit (i.e. present pain rating) is shown in (Fig.6.2).

QUESTION	n	Median (range)
Age of study population (years) (a)female (b)male (c)all	(a)16 (b)13 (c)29	(a) 45(35-72) (b) 57(30-75) (c) 47(30-75)
Pain rating during visit to research unit (0 no pain ---> 10 worst pain imaginable)	29	4.3(0-8.6)
Instruction on stimulator use (0 poor ---> 10 extremely well)	29	8.0(0-10)
Confidence in TENS treatment (0 no confidence ---> 10 extremely confident)	29	4.5(0-10)
The logic of TENS in reducing pain (0 no logic at all ---> 10 extremely logical)	29	5.0(0-10)
Degree of pain relief (0 no relief---->10 total relief)	29	4.8(0-10)
Duration of treatment (a)days/week (b)h/week	29	(a)7.0(3- 7.0) (b)28(3- >50)
Time to onset of analgesia (min)	22	30 (0->2h)
Time to offset of analgesia (min)	22	60(0->2h)
	n	No of patients (%)
Pulse pattern preference (a)continuous (b) burst (c) both	29	(a)20(69%) (b) 4(14%) (c) 5(17%)
Change of TENS efficacy with use (a) increase (b) unchanged (c) decrease	27	(a) 5(18%) (b)18(67%) (c) 4(15%)
Use TENS in combination with other drugs	29	23(79%)
Incidence of skin reactions (ie irritation or rash)	29	3(10%)

Table 6.1 Summary of answers to TENS questionnaire (Exp. 6.1).

VARIABLE	RESPONDERS (n=22)	NON- RESPONDERS (n=7)	P value (Unpaired t-test)
Age (years)	50.4±11.9	57.8±15.3	0.3
Sex	Male n=9 Female n=13	Male n=4 Female n=3	n.s.
Duration of pain condition (years)	4.4±5.0	6.9±3.2	0.3
Unemployed due to pain	8 out of 22	1 out of 7	n.s.
Eysenck Personality Questionnaire	P 2.1±1.0 E 10.7±6.3 N 10.8±5.8 L 12.7±4.1	P 2.1±1.7 E 10.8±5.2 N 11.7±5.5 L 9.0±5.6	0.9 1.0 0.8 0.2
Hospital Anxiety & Depression scale	A 7.8±4.5 D 5.6±3.0	A 5.6±3.9 D 4.8±4.8	0.3 0.7
Confidence in TENS	5.0	3.3	0.6
Sensory Detection Threshold (mA)	2.1±0.7	2.8±1.3	0.2
Pain Threshold (mA above SDT)	2.7±2.2	1.3±0.7	0.1
Pain Tolerance (mA above pain threshold)	3.0±2.9	3.1±3.1	0.7
Beta-endorphin (pmol/l)	7.4±4.9	11.9±17.4	0.56
Met-enkephalin (pmol/l)	39.6±7.8	41.9±15.7	0.86

Table 6.2 Comparison between responders and non-responders for factors measured in Exp. 6.1. Mean±SD, n.s.=non significant.

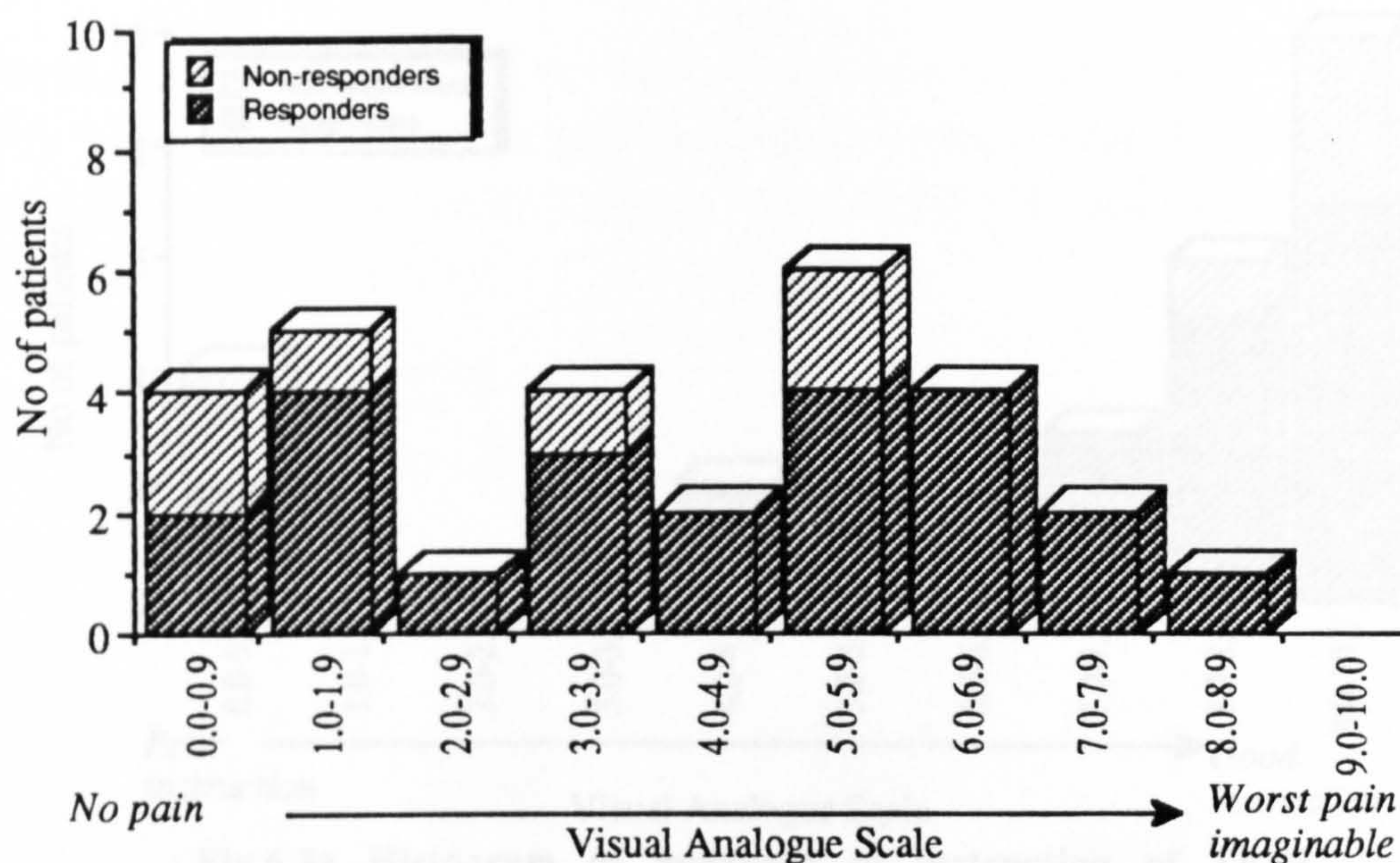


Fig.6.2 Histogram of pain intensity rating in 29 chronic pain patients during the visit to the laboratory (Exp.6.1).

Although no patients were in the 'worst pain imaginable' category, 13 out of 29 (45%) had over 50% pain, and 4 out of 29 (14%) were in no pain. No significant differences were found in present pain intensity rating between responders and non-responders.

The majority of patients (23 out of 29(79%)) were using TENS 7 days a week. Six out of 7 non-responders used the stimulator on a daily basis in the hope of development of TENS effects during the trial period. Eighteen (62%) patients reported using TENS for over 28 h/week, of which 13 (45%) patients reported using TENS on a daily basis for over 6 h/day. In the 22 responders the median time to onset of analgesia was 30 minutes and offset of analgesia 1 hour. The majority of patients used a continuous pulse pattern of TENS (20 out of 29(69%)); 5 out of 29 (17%) preferred burst; 4 out of 29 (14%) used both continuous and burst equally. None of the patients in possession of a Xenos stimulator (which has random mode stimulation) used random pulse delivery as the primary stimulating mode. Two out of 9 (22%) patients reported using random mode on an occasional basis. No significant differences were found between responders and non-responders for any of the variables mentioned above (Mann-Whitney U-tests).

The majority of patients thought that TENS techniques were instructed extremely well at the clinic (20 out of 29 (69%) scoring >7 VAS units), although 6 out of 29 (21%) reported poor instruction (0 VAS, Fig.6.3a).

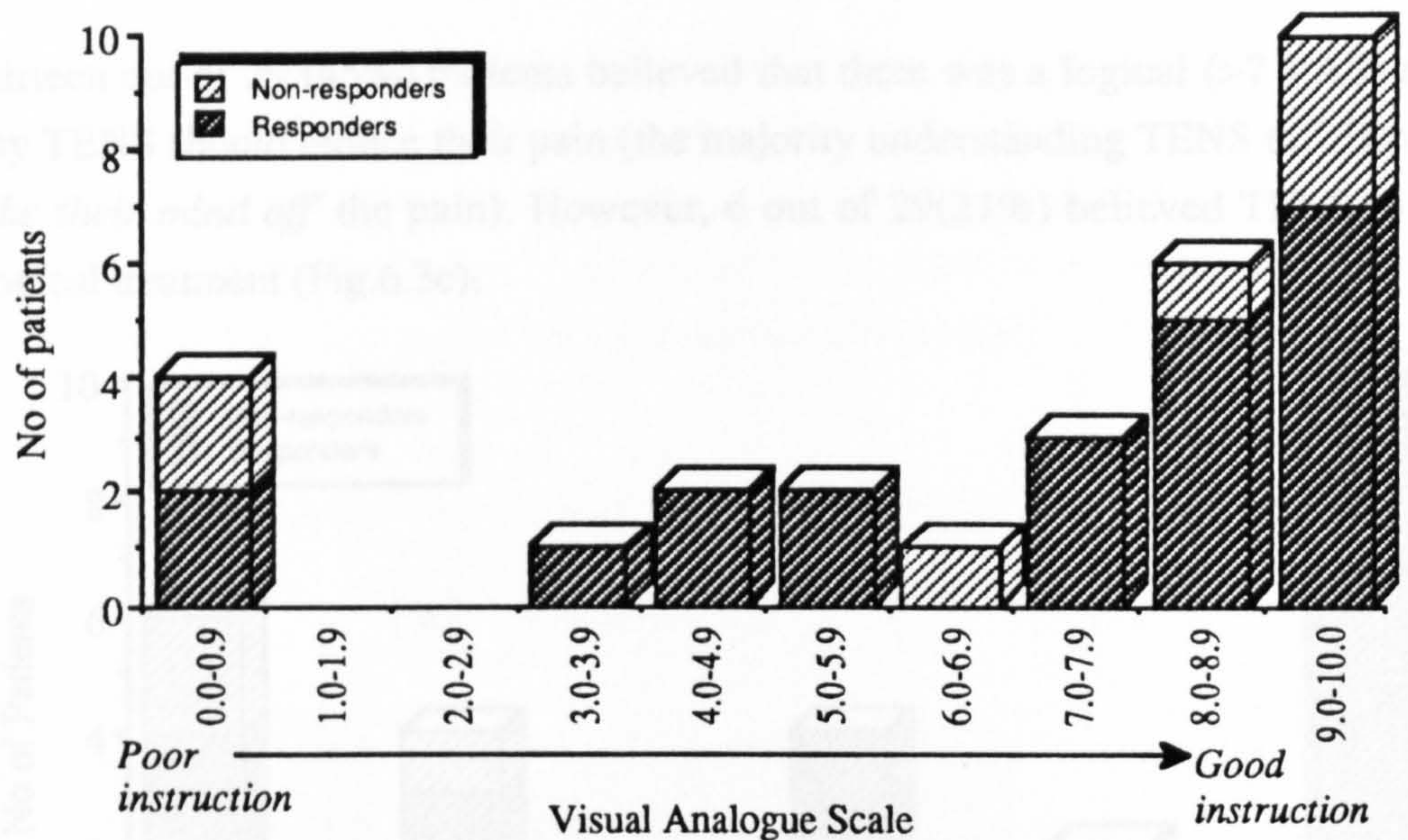


Fig.6.3a Histogram of adequacy of instruction of TENS techniques at the clinic as rated by 29 chronic pain patients (Exp.6.1).

Few patients (7 out of 29 (24%) scoring >7 VAS units) were confident of the success of TENS and 6 out of 29 (21%) reported zero on the VAS (Fig.6.3b).

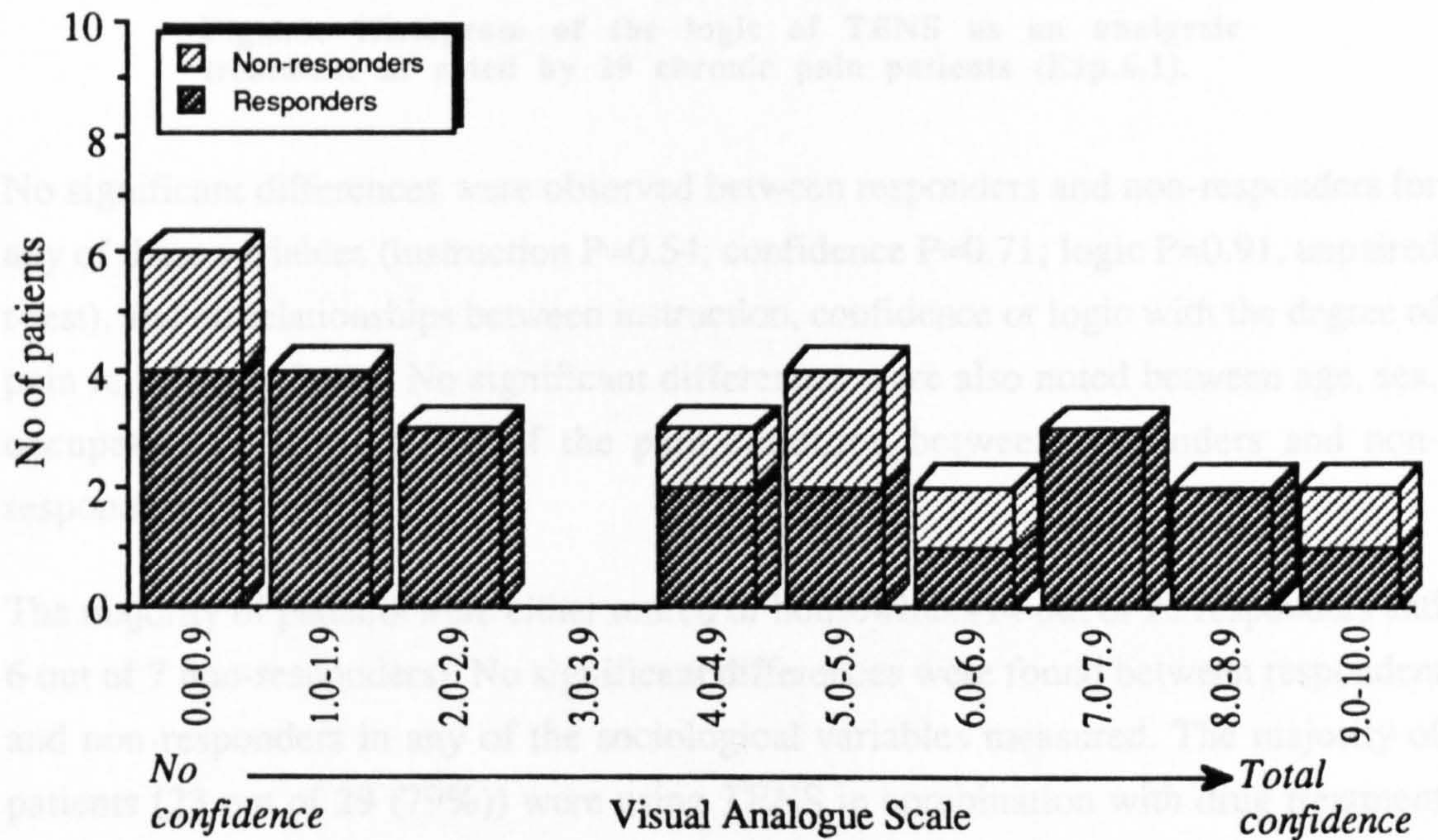


Fig.6.3b Histogram of initial confidence of TENS success as rated by 29 chronic pain patients (Exp.6.1).

Thirteen out of 29 (45%) patients believed that there was a logical (>7 VAS) reason why TENS should reduce their pain (the majority understanding TENS to '*distract*' or '*take their mind off*' the pain). However, 6 out of 29(21%) believed TENS to be an illogical treatment (Fig.6.3c).

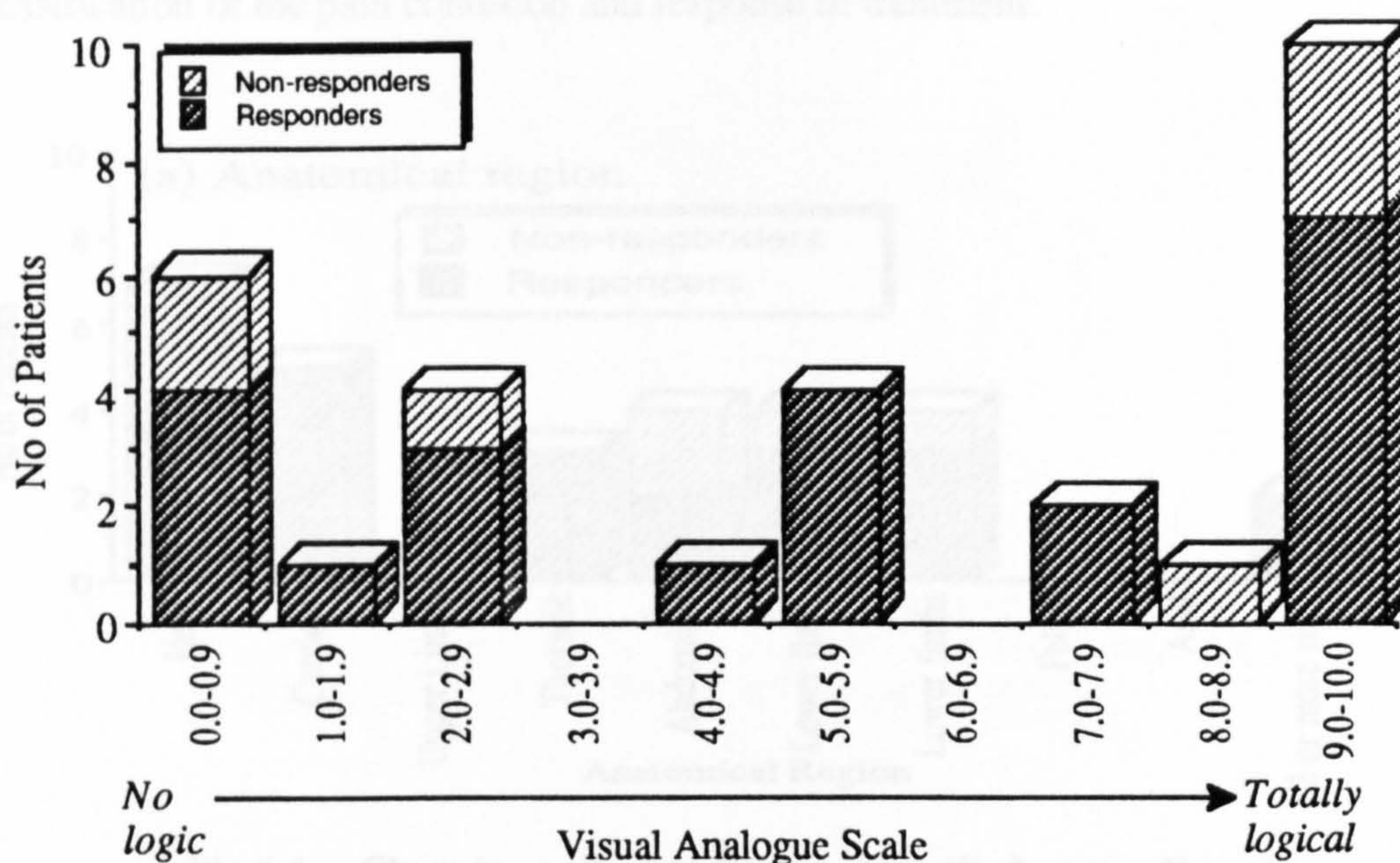


Fig.6.3c Histogram of the logic of TENS as an analgesic treatment as rated by 29 chronic pain patients (Exp.6.1).

No significant differences were observed between responders and non-responders for any of these variables (instruction $P=0.54$; confidence $P=0.71$; logic $P=0.91$, unpaired t-test), and no relationships between instruction, confidence or logic with the degree of pain relief were found. No significant differences were also noted between age, sex, occupation or the duration of the pain condition between responders and non-responders (Table 6.2).

The majority of patients were either retired or housewives (14 out of 22 responders and 6 out of 7 non-responders). No significant differences were found between responders and non-responders in any of the sociological variables measured. The majority of patients (23 out of 29 (79%)) were using TENS in combination with drug treatment and 14 out of 29 (48%) patients were using TENS in combination with primary analgesics [Thompson 1984]. The incidence of skin reaction was low (3 out of 29(10%)) and the majority of patients (18 out of 29(60%)) found that the efficacy of TENS had remained stable over the trial period.

Pain classification: A variety of pain conditions were represented in the study (Fig.6.4 a-c) and of the 7 non-responders, 3 had pains associated with the head and face, 2 with the abdomen, 1 lower back and 1 lower limb; 3 had pains of unknown aetiology. Careful examination of the population revealed no relationships between the classification of the pain condition and response of treatment.

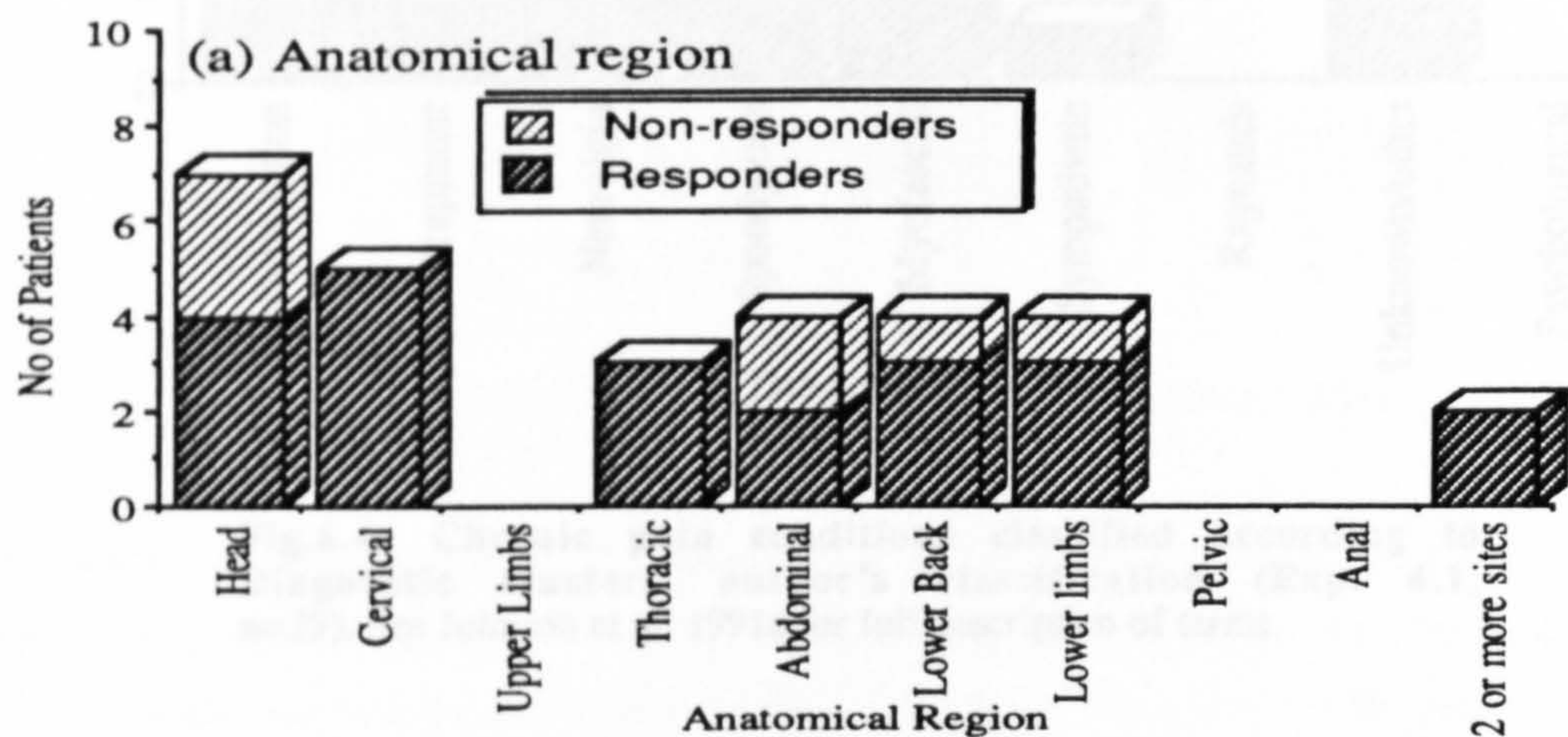


Fig.6.4a Chronic pain conditions classified according to Anatomical region, IASP Axis I (Exp. 6.1, n=29). See IASP [1986] for full description of terms.

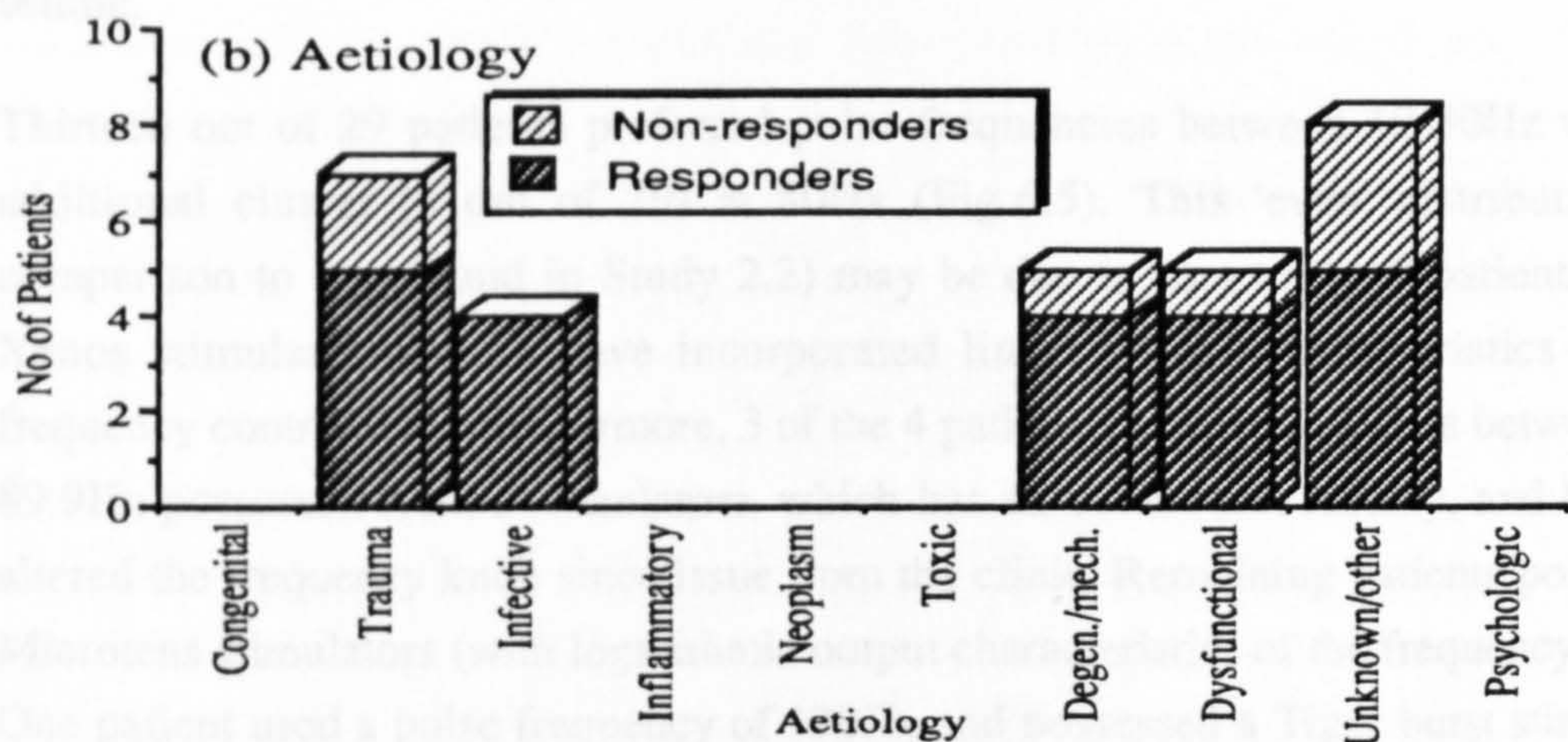


Fig.6.4b Chronic pain conditions classified according to Aetiology, IASP Axis V (Exp.6.1, n=29). See IASP [1986] for full description of terms. Degen/mech = degenerative/mechanical.

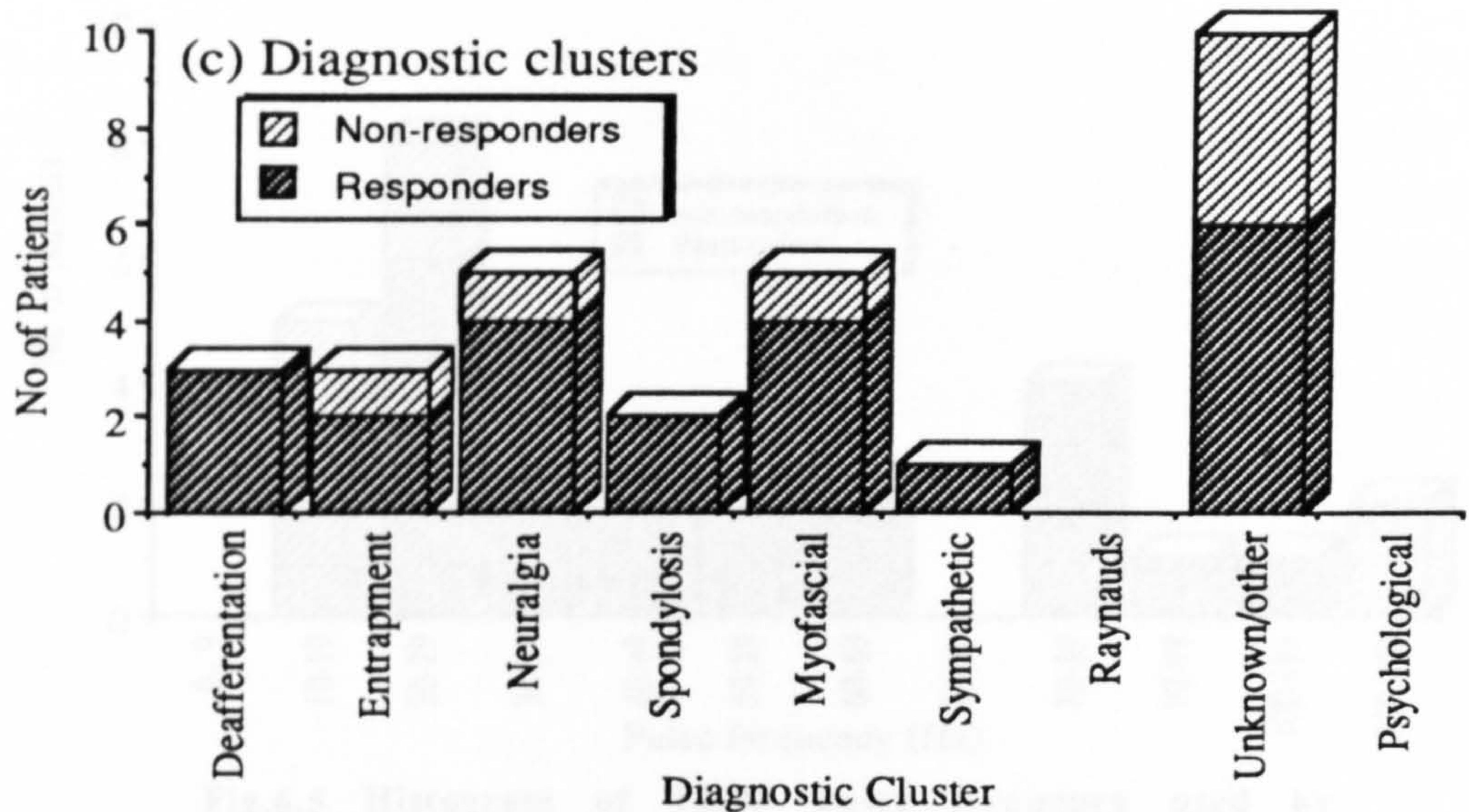


Fig.6.4c Chronic pain conditions classified according to Diagnostic clusters, author's classification (Exp. 6.1, n=29). See Johnson et al. 1991a for full description of terms.

Electrical characteristics of TENS: The majority of patients (23 out of 29(79%)) used therapy settings below 10mA above SDT. No significant differences in either SDT or therapy levels were found between responders and non-responders and no relationships were observed between the degree of pain relief and SDT or therapy setting.

Thirteen out of 29 patients preferred pulse frequencies between 10-30Hz with an additional cluster (4 out of 29) at 80Hz (Fig.6.5). This 'even' distribution (in comparison to that found in Study 2.2) may be due in part to the 9 patients using Xenos stimulators which have incorporated linear output characteristics on the frequency control dial. Furthermore, 3 of the 4 patients using frequencies between 80-89.9Hz possessed Xenos stimulators, which has an 80Hz reset facility, and had not altered the frequency knob since issue from the clinic. Remaining patients possessed Microtens stimulators (with logarithmic output characteristics of the frequency dials). One patient used a pulse frequency of 120Hz and possessed a Tiger burst stimulator with a maximum frequency output of 120Hz. No significant differences in pulse frequency used by the 7 responders and 22 non-responders were observed.

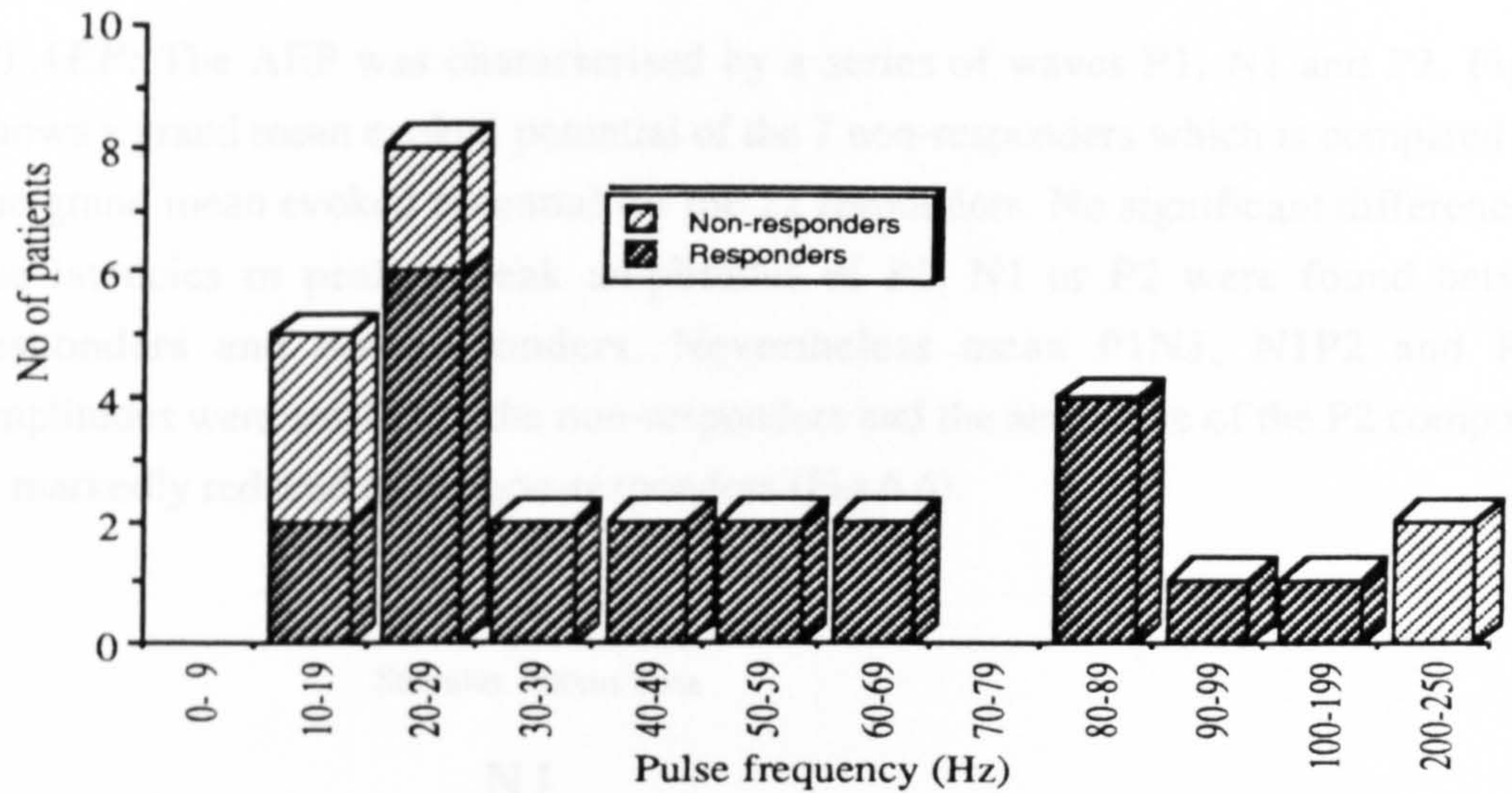


Fig.6.5 Histogram of TENS pulse frequency used by patients in Exp. 6.1 (n=29).

Personality, anxiety and depression: EPQ scores were within the range for normals [Eysenck & Eysenck 1975], and the mean HAD scores across the group were below that expected for clinical anxiety (>10) and depression (>10). Nonetheless 4 patients had anxiety ratings above 10 (all responders) and 2 had depression scores above 10 (both responders). No significant differences in either EPQ or HAD measures were found between responders and non-responders (Table 6.2).

EEG variables

a) Baseline Evoked Potentials: Peak-to-peak amplitudes and latencies of the late waveform components of the auditory and somatosensory evoked potentials are summarised in Table 6.3.

MEAN±SD	Intensity of evoking stimuli (VAS unit)	Latency (ms)			Peak-to-peak amplitude (µV)		
		P1	N1	P2	P1N1	P1N2	RMS
AEP							
Non-responders	*	57.0±14.0	114.0±34.8	208.3±27.3	12.4±5.3	16.0±7.5	4.6±1.1
Responders	*	57.0±8.5	105.4±14.2	201.8±21.7	14.3±5.1	20.0±7.0	5.4±1.6
P value		1.0	0.5	0.6	0.4	0.2	0.2
2.5mA SEP							
Non-responders	2.2	98.2±18.6	129.0±26.7	180.0±41.0	4.0±1.4	5.3±2.9	4.5±1.6
Responders	3.4	99.4±20.3	139.2±25.5	176.0±103.0	9.4±4.9	12.6±6.5	4.9±2.3
P value	0.1	0.9	0.4	0.9	0.01	0.01	0.6
5mA SEP							
Non-responders	5.2	90.2±38.5	117.3±40.3	199.5±32.2	4.1±3.6	7.1±8.2	4.2±2.1
Responders	5.7	95.1±16.6	139.1±22.4	203.0±45.0	10.5±5.8	14.5±3.5	5.7±2.1
P value	0.5	0.7	0.3	0.9	0.01	0.01	0.15
5mA-2.5mA SEP							
Non-responders	2.7	-1.8±33.6	-3.8±24.7	15.7±26.9	0.2±3.3	0.4±3.0	-0.4±1.1
Responders	2.4	-6.0±19.1	-1.2±20.2	-19.2±24.0	1.3±5.8	1.9±6.3	0.8±1.6
P value	0.6	0.3	0.8	0.2	0.6	0.4	0.07

Table 6.3 Mean±SD latencies and peak-to-peak amplitudes of late components of SEPs and AEPs in TENS responders and non-responders (n=29 chronic pain patients, Exp. 6.1). P value = unpaired t-test non-responders v responders.

(i) **AEP:** The AEP was characterised by a series of waves P1, N1 and P2. Fig.6.6 shows a grand mean evoked potential of the 7 non-responders which is compared with the grand mean evoked potential for the 22 responders. No significant differences in the latencies or peak-to-peak amplitudes of P1, N1 or P2 were found between responders and non-responders. Nevertheless mean P1N1, N1P2 and RMS amplitudes were smaller in the non-responders and the amplitude of the P2 component is markedly reduced in the non-responders (Fig.6.6).

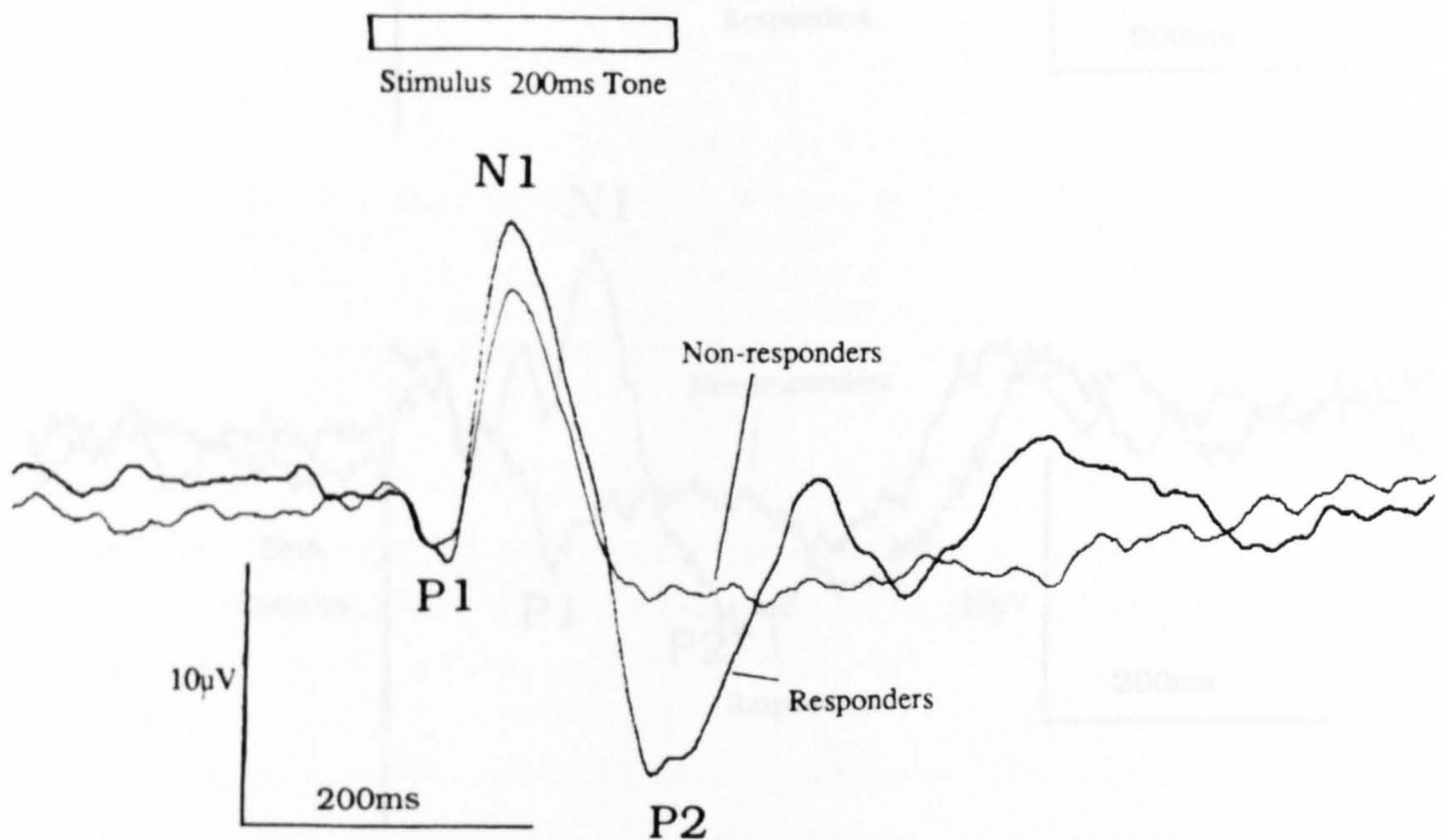


Fig.6.6 Grand average AEP for chronic pain patients classified as TENS responders (n=22) and non-responders (n=7), Exp. 6.1. Recordings taken at Cz referenced to linked mastoids.

(ii) **SEP:** SEPs were recorded to evoking stimuli of 2.5mA above SDT and 5.0mA above SDT. In some subjects SEP components were poorly defined and measurement of waveform components (especially P1) was often difficult. No significant differences in the latency of either P1, N1 or P2 was found between responders and non-responders (Table 6.3).

Responders had significantly larger P1N1 and N1P2 amplitudes at both intensity levels of SEP (Table 6.3). The SEP was poorly defined in non-responders with the apparent absence of the N1 waveform (Fig.6.7a and Fig.6.7b).

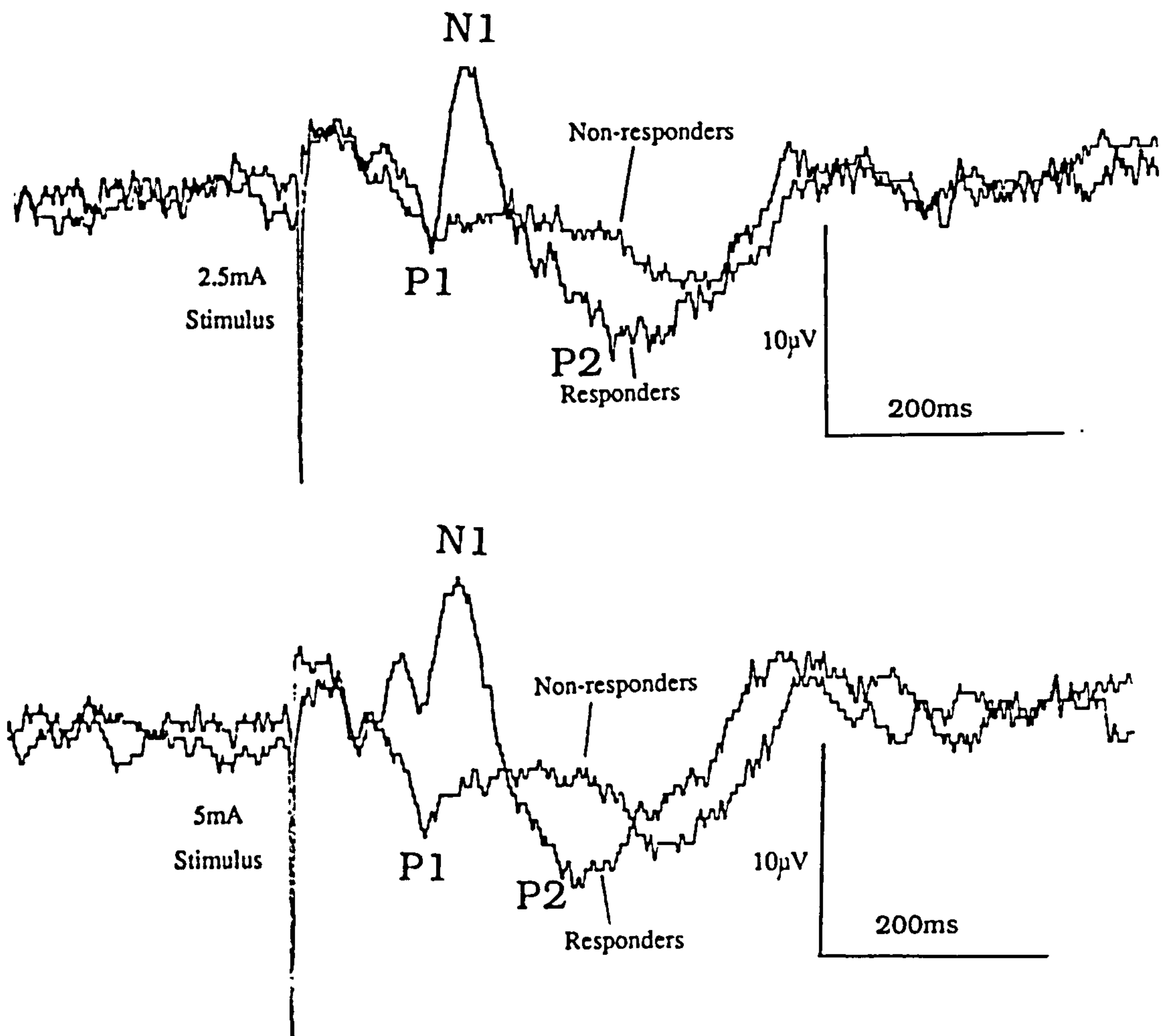


Fig.6.7 Grand average SEP elicited at (a) 2.5mA above SDT and (b) 5.0mA above SDT for chronic pain patients classified as TENS responders (n=22) and non-responders (n=7), Exp. 6.1. Recordings taken at Cz referenced to linked mastoids.

Although non-responders had lower RMS (between 50-550 ms post-stimulus) to SEPs elicited at the higher intensity, this failed to reach significance ($P=0.15$). In general, the greater the degree of pain relief achieved with TENS the larger the baseline amplitudes of the SEP (Fig.6.8). However, these correlations just failed to reach significance (N1P1; 2.5mA $r=+0.36$, 5.0mA $r=+0.36$; N1P2; 2.5mA $r=+0.34$, $P=0.1<0.05$, Pearson correlation coefficient; N1P2 5mA $r=+0.2$, n.s.).

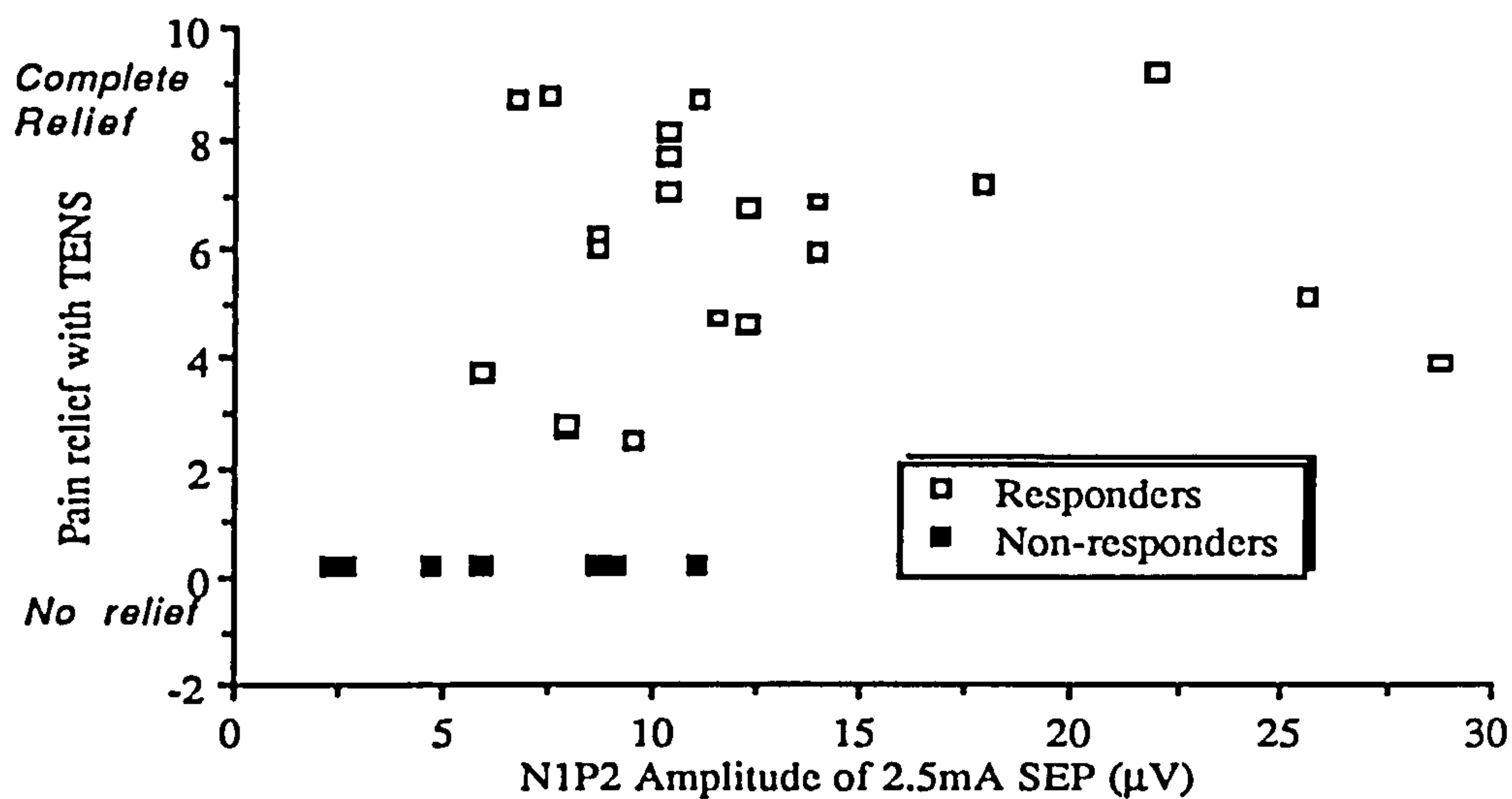


Fig.6.8 Relationship between degree of pain relief obtained with TENS and the peak-to-peak amplitude of the SEP elicited from a 2.5mA above SDT stimulus (Exp. 6.1, n=29). Size of SEP=µV, degree of pain relief measured on a VAS where 0=no relief, 10=total relief. Pearson correlation coefficient $r=+0.34$, $df=29$, $P=0.1<0.05$).

No significant differences in either latency or peak-to-peak amplitudes of P1, N1 and P2 were found between the two intensity levels of SEP although responders showed a larger incremental increase in RMS between 2.5mA and 5.0mA evoking stimuli than responders ($P=0.07$, see Table 6.3).

b) *Baseline spontaneous EEG*: Table 6.4 summarises the results.

MEAN±SD	POWER SPECTRUM (µV ² /Hz)		
	Eyes open	Eyes closed	Eyes closed-Eyes open
Delta			
Non-responders	167.0±149.0	61.2±28.2	-107.0±125.0
Responders	89.8± 73.1	114.5±71.1	24.0± 85.7
P value	0.2	0.01	0.04
Theta			
Non-responders	34.7±33.0	19.6± 8.2	-15.1±36.2
Responders	22.6±15.0	50.3±58.6	27.7±58.0
P value	0.4	0.05	0.03
Alpha			
Non-responders	44.4±27.8	53.9±51.9	9.5±42.2
Responders	32.1±26.2	102.2±81.5	70.1±68.4
P value	0.3	0.08	0.01
Beta			
Non-responders	17.4± 8.3	18.6±10.8	1.1±15.3
Responders	21.4±11.6	30.2±13.2	8.8± 8.5
P value	0.3	0.04	0.2
Alpha frequency (Hz)			
Non-responders	8.7±0.8	7.8±3.5	-0.8±3.5
Responders	8.4±2.7	8.7±2.1	0.3±2.3
P value	0.7	0.6	0.5

Table 6.4 Mean±SD power spectrum for chronic pain patients classified as TENS responders (n=22) or TENS non-responders (n=7), Exp. 6.1. Recordings taken at Cz referenced to linked mastoids. Unpaired t-tests were performed to examine differences between groups.

No significant differences in power were found between responders and non-responders for any frequency band when recording with eyes open. However, non-responders showed significantly less power across all frequency bands when recording with eyes closed (Table 6.4).

Pain threshold and pain tolerance: No significant differences in SDT or pain tolerance were found between responders and non-responders. Non-responders were found to have lower thresholds to experimental pain although this just failed to reach statistical significance ($P=0.1$, see Table 6.2). No significant relationships in pain threshold and the degree of pain relief achieved with TENS measured on the VAS were found ($r=+2.4$, Pearson correlation coefficient).

Plasma concentrations of opioid peptides: Plasma concentrations of opioid peptides were analysed as described in Chapter 5. Thus, beta-endorphin and met-enkephalin values recorded below the sensitivity of the assay were transformed to 2.9 pmol/l and 35pmol/l respectively (see Chapter 5). Baseline plasma concentrations of beta endorphin ranged from <2.9 pmol/l to 47 pmol/l (mean=8.1, median=5.6). No significant differences in baseline plasma concentrations of beta endorphin were observed between responders and non-responders (Table 6.2). Baseline plasma met-enkephalin concentrations ranged from <35 pmol/l to 79.8pmol/l, and 16 out of 25 patients had baseline met-enkephalin concentrations below the sensitivity of the assay. No significant differences in baseline met-enkephalin concentration between responders and non-responders were observed.

Follow-up: Twenty two (76%) patients replied to a postal questionnaire sent at the four month follow-up. Of the 7 non-responders classified in this study by the visual analogue scale score, 6 had returned stimulators. The seventh patient reported that the stimulator was now effectively reducing the pain. Four patients initially reporting a favourable TENS response at the 1 month follow-up were no longer achieving benefit at the 4 months follow-up and had returned stimulators to the clinic. One of these patients reported a rebound exacerbation of pain post-TENS despite relief during stimulation. Whether the declining TENS efficacy observed was due to the development of tolerance or an initial placebo response to TENS is not known. However, a further 3 patients still using TENS at the 4 month follow-up also reported declining effect.

Examination of Newcastle Pain Relief Clinic records revealed that 10(34%) patients had returned stimulators to the clinic within four months of issue. All of these patients reported that TENS was ineffective in reducing their pain, as recorded on the postal questionnaire. Hence further statistical analysis was performed as follows:

All patients who had returned stimulators after 4 months ($n=10$) were classified as non-responders and similar statistics as described above were performed on the data collected at the 1 month period. The following additional information was found:

- (i) No significant differences were found in pain threshold between responders and non-responders.
- (ii) Non-responders had a significantly lower peak-to-peak amplitudes of the N1P1 ($P<0.05$) and possibly N1P2 ($P=0.13$) components of the AEP.
- (iii) Non-responders had significantly smaller peak-to-peak N1P1 amplitudes ($P<0.05$) and possibly (RMS values, $P=0.13$) of the SEP elicited at 5.0mA above SDT.
- (iv) No significant differences were found for N1P2 amplitudes of the SEP elicited at either 2.5 mA above SDT or 5.0mA above SDT.
- (v) Non-responders had lower power in the delta ($P<0.05$) and possibly alpha ($P=0.15$) and beta ($P=0.11$) frequency bands with eyes closed.

Eight patients (out of ten asked) attended the research unit for EEG recording at the four month follow-up. The 2 patients refusing to attend were non-responders; thus only 1 non-responder returned for follow-up. No significant changes in any of the variables measured occurred between the two visits (paired t-tests). Hence it appeared that the clinical, sociological, psychological, electrophysiological and neuropharmacological variables measured during the study remained stable over the four month follow-up period.

Main findings of Experiment 6.1

- (i) Seven out of 29 patients given a trial of TENS to control a chronic pain condition failed to obtain satisfactory analgesia with TENS by the 1 month follow-up.
- (ii) Sociological and psychological variables (TENS questionnaire, EPQ and HAD scale) were not related to patient response.
- (iii) Poor patient response to TENS was associated with:
 - (a) small baseline peak-to-peak amplitudes of the late components of SEPs,
 - (b) low spontaneous EEG activity across most frequency bands when recorded at Cz with eyes closed.

(iv) Patients with low pain threshold to electrical stimuli also showed poor response to TENS although this failed to reach significance. Sensory detection threshold and pain tolerance were not related to patient response to TENS.

(v) At the 4 month follow-up a further 4 patients reported treatment failure and another 3 patients reported declining efficacy of TENS. Whether these effects were due to the development of tolerance or declining placebo effects remains to be determined.

DISCUSSION

In this prospective study of 29 patients undergoing a trial of TENS to control chronic pain, the relationship between a number of pre-existing factors and patient response was examined. The results have shown for the first time that patients responding poorly to TENS have small peak-to-peak amplitudes of late waveform components of SEPs, and low spontaneous EEG activity when recorded with eyes closed. Pre-existing sociological, psychological, and neuropharmacological factors did not appear to reflect response to TENS treatment. These findings suggest that patients who show poor cortical response to sensory stimuli (reflected by small amplitude EPs) are less likely to respond to TENS. These findings will be discussed below.

TENS Efficacy

At the one month follow-up, 7 out of 29 (24%) patients failed to respond to treatment. One of these patients reported an increase in TENS efficacy between the 1st and 4th month follow-up and therefore continued to use a stimulator. The reasons for this delayed analgesic effect are not known, although experimentation with stimulator settings may have established more beneficial electrical characteristics for TENS. At the 4 month follow-up a total of 10 (34%) patients had reported non-response to TENS and all of these patients had returned stimulators to the clinic. The decline in efficacy between the 1 and 4 month follow-up may be due to either:

- (i) the decline of an initial placebo response at 1 month,
- (ii) the development of tolerance to TENS analgesia.

A further 3 patients still using stimulators had detected a decrease in TENS efficacy and were concerned about it.

Despite the biased nature of the patient population, due to the exclusion of patients with mobility problems, those taking psychotropic drugs and an unknown number of patients who refused to participate in the study, the findings were similar to those reported in Study 2.1 where it was found that approximately 25% of stimulators were returned within the first 6 month (see Fig.2.2).

TENS Questionnaire

The answers to the TENS questionnaire (Table 6.1) were similar to those observed in the population of responders examined in Study 2.2 (see Table 2.1). The incidence of skin reactions was lower in the present study probably due in part to improvements in

the teaching of electrode techniques by nurses in the clinic, and the availability of self-adhesive electrodes which would reduce the incidence of allergic reactions to Micropore adhesive tape. The majority of patients were using TENS on a daily basis (for 4 h/day (median)). This included non-responders who used TENS on a daily basis in the hope that an analgesic effect might develop with time. This occurred in one patient.

Electrical characteristics of TENS

All patients applied TENS to produce a 'strong but comfortable' electrical paraesthesia within the painful site. No significant differences were noted between the electrical characteristics of TENS used by non-responders and responders. Furthermore the electrical characteristics of TENS were not related to either the site or cause of pain or to the degree of response, a finding consistent with Study 2.2. An even distribution of pulse frequencies was used by the patients in the present study (compared with that reported in Study 2.2, see Fig.2.11) due to the incorporation of linear pulse frequency output characteristics in Xenos stimulators which were issued to 9 patients. The cluster of patients who used pulse frequencies between 80-90Hz were using the 80Hz default setting of the Xenos stimulator.

Factors related to patient response to TENS

Factors related to pain

No significant relationships between the site and character of pain with patient response to TENS were observed in the present study. However evidence suggests that pain of neurogenic origin and/or located at the extremities responds favourably to TENS [Johansson et al.1980]. No such analysis was performed in the present study. At the four month follow-up, 4 patients with pains in the vertex region of the head had reported poor response to TENS. Loeser et al. [1975] also reported that patients with head pains responded poorly to TENS (see Table 2.1). This may be attributed in part to the inability to achieve electrical paraesthesia within the scalp because of the difficulty of electrode placement within the hair. Sponge electrodes (rather than carbon rubber electrodes which require gel and tape) can be applied directly to the scalp, and may improve TENS treatment of head pains.

Factors unrelated to pain

Sociological

No significant differences between responders and non-responders were observed in any of the sociological factors measured. Thus, initial confidence in TENS success was not related to treatment outcome, and some patients who believed TENS would not help their pain were overjoyed at its success. Of the patients who reported poor instruction, all (4) had mastered basic TENS techniques by a combination of trial and error and reading the manufacturers instruction pamphlet. Although the duration of the pain problem was greatest in non-responders, a finding consistent with that of Reynolds et al. [1983], this failed to reach statistical significance. Furthermore occupation, loss of employment because of the the pain, age, sex and the use of analgesics were not related to treatment outcome.

Psychological

In contrast to the findings of Johansson et al. [1980] who found that patients with high L scores on the EPI showed favourable responses to TENS, no significant differences were observed between non-responders and responders in any of the personality traits measured by the EPQ (Table 6.2). High L scores are often associated with social compliance, indicative of suggestible patients who may report treatment success to 'please' the experimenter. This may account for the findings of Johansson et al. because patients were classified as responders and non-responders according to a short (30 minute) TENS treatment session and were therefore more susceptible to placebo effects. Nielzén et al. [1982] found that patients with pathological personality traits responded poorly to TENS. The present study revealed no significant differences between responders and non-responders with respect to HAD scale scores, which measures anxiety and depression.

EEG variables

The results of the present study suggest that patients who produce small cortical responses to sensory stimuli respond poorly to TENS. Thus, non-responders are characterised by small peak-to-peak amplitudes of late latency components (P1N1 and N1P2) of the SEP and low baseline spontaneous EEG power when recorded with eyes closed.

Evoked potentials

Golding et al. [1986] found a positive correlation between baseline SEP amplitudes and response to TENS in alleviating experimental pain in healthy subjects. However, as SEP amplitudes are dependent upon the intensity of the evoking stimuli, the inter-individual variability in baseline SEP amplitude recorded in the Golding et al. study may have been due in part to inter-individual variability in the current intensity of the evoking stimulus (which was fixed perceptually across the subject population at a 'strong but comfortable' level). This problem was addressed in the present study by delivering a standard current intensity of evoking stimuli to all patients.

Although no significant differences in the latency or peak-to-peak amplitudes of AEPs occurred Fig. 6.6 shows that the grand mean AEP of non-responders was characterised by the absence of the P2 late component. Moreover AEPs and SEPs were positively correlated (N1P2 amplitude: AEP v 2.5 mA SEP, $r=+0.42$, $df=28$, $P<0.05$), implying that this non-responsiveness to external stimuli occurs across sensory modalities within the same individual. Although it has been suggested that AEPs and SEPs are reduced in depressed patients compared with normals [Shagass et al. 1985], no relationships were found between HAD scores and AEP or SEP amplitudes in the present study. This would suggest that depression or anxiety were not factors contributing to the small SEP amplitudes under the present conditions.

In general, patients rated the intensity of the evoking stimuli as 'weak' on the visual analogue scale. Consequently the resultant SEPs were small. Utilisation of higher intensities of evoking stimuli may have evoked more clearly defined SEPs. A possible source of error when using peak-to-peak measures is the correct identification of waveform peaks by the experimenter. This problem was minimised in the present study by confirmation of correct peak identification by an experienced EEG technician (VRM). Root mean squared (RMS) value was used as an overall measure of SEP response and does not require peak identification and may reduce experimenter error. However no significant differences in RMS (between 50-550 ms) were found between responders and non-responders. This was attributed to the large time window used in RMS calculation which would encompass a conglomerate of waveform components each reflecting separate events; these are more reliably measured using peak-to-peak amplitudes (as performed in the present study), or RMS calculation within narrow time windows.

Spontaneous EEG

This is the first report to relate baseline spontaneous EEG activity to patient response with TENS. Patients showing favourable responses to TENS had significantly greater power within all frequency bands while recording with eyes closed, thus maximising synchronised slow wave EEG activity. No such differences in spontaneous EEG were noted with eyes open. However because of the lack of understanding of the physiological significance of spontaneous EEG activity, an explanation for such findings is difficult. Nonetheless, changes in states of arousal are reflected in changes in spontaneous EEG activity and therefore baseline arousal may influence TENS effects. Furthermore it has been suggested that baseline spontaneous EEG correlates with personality and certain pathological states [Golding et al.1985]. With the advent of more powerful EEG analytical techniques and topographical brain mapping the utility of spontaneous EEG as a predictor of response to TENS (and other treatments) merits further investigation.

Augmenters and reducers

The concept of augmenters and reducers was originally described by Petrie [1967] to account for individuality in pain and response to the external environment. It was suggested that augmenters may have a low tolerance to pain and reducers a high tolerance to pain. This concept received support from SEP studies where it was suggested that augmenters increased the size of the evoked response to increasing intensity of stimulation while reducers decreased the size of evoked response with increasing stimulus intensity. Further claims that augmenters respond better to pharmacological pain-relieving agents such as morphine [Buchsbaum et al.1981a; 1981b] and show greater responses to naloxone [Buchsbaum et al.1983] have yet to be validated.

Johansson et al. [1981] reported that the failure of response to TENS in 24 chronic pain patients was related to a tendency of these patients to 'reduce' visual evoked potentials. This finding was supported in part by the results of the present study, in which patients responding favourably to TENS produced larger incremental increases in RMS, and SEP amplitudes (although non-significant) elicited at both low and high intensity evoking stimuli (Table 6.3). Unfortunately only two stimulus intensities were used and the differences in peak-to-peak amplitude and RMS between these two stimuli were small. Such findings merit further study.

Sensory detection threshold, pain threshold and pain tolerance

It has been previously suggested that augmenters (and by implication TENS responders) have low pain thresholds [Buchsbaum 1984]. Further evidence was provided by Golding et al. [1986], who found that healthy subjects with low thresholds to experimental pain showed favourable responses to TENS. By contrast, the results of the present study suggest that patients who respond favourably to TENS may have high thresholds to pain, although this finding failed to reach statistical significance. However the failure of the Golding et al. study to correct pain threshold values for individual differences in sensory detection threshold may account for this discrepancy. Thus, the present study found non-responders to have higher sensory detection thresholds (non-significant) which would increase uncorrected pain threshold values of non-responders with respect to the TENS responders group.

Neuropharmacological

Von Knorring et al. [1978] have suggested that baseline SEPs and augmenting/reducing responses may be related to baseline endogenous opioid peptide levels. In a population of chronic pain patients they found that augmenters had low pain thresholds and low CSF levels of endogenous opioid peptides [Almay et al. 1978]. No differences in baseline levels of peripherally circulating beta-endorphin and met-enkephalin were observed between responders and non-responders in the present study.

Follow-up

Four out of 29 patients who initially responded to TENS reported TENS treatment failure at the four month follow-up. This may be due either to the development of tolerance and/or a decline in an initial placebo response. When the data was re-analysed with the inclusion of these 4 patients in the 'non-responding' group, the distinction in electrophysiological measures (i.e. spontaneous EEG and SEP) between responders and non-responders became less significant. This may suggest that a continuum of differing degrees of response rather than distinct patient populations of responders/non-responders exists. Unfortunately it was not possible to compare changes in electrophysiological measures between the one and four month follow-up. Such information may provide the key to understanding the development of tolerance to TENS analgesia which has been attributed to central nervous system adaptation (or habituation) to peripheral conditioning stimuli [Pomeranz & Niznick 1987].

Implications for the mechanism of TENS failure.

As EPs reflect the cortical response to external stimuli, and TENS is an external stimulus, it may be inferred that patients with little CNS response to external stimuli are less likely to respond to TENS. This has been shown by:

- (i) the small baseline EP amplitudes observed in non-responders in this and the Golding et al. [1986] study,
- (ii) the small incremental rise in EP with increasing stimulus intensity in non-responders in this and the Johansson et al. [1981] study.

It has been suggested that EPs reflect excitatory and inhibitory (post-synaptic) potentials related to the processing of an incoming (stimulus-induced) afferent volley. Thus, it may be inferred that individuals showing large SEP responses may produce greater 'waves of excitation and inhibition' within the CNS with a concurrent release of larger amounts of transmitters. These transmitters may in turn be involved in the modulation of nociceptive transmission. Furthermore as non-responders show 'reducing responses' to external stimuli they may be unable to compensate for poor cortical responses to TENS as each incremental rise in the intensity of TENS results in only a small incremental rise in cortical response.

Summary

In this prospective investigation to find factors related to patient response to TENS, 7 out of 29 patients given a trial of TENS to control a chronic pain condition failed to respond at the 1 month follow-up. Patients showing poor response to TENS were characterised by:

- (i) small baseline peak-to-peak amplitudes of the late components of SEPs
- (ii) low spontaneous EEG activity across most frequency bands when recorded at Cz with eyes closed.
- (iii) low pain threshold to electrical stimuli presented to the index finger, although this failed to reach statistical significance.

Sociological and psychological variables (TENS questionnaire, EPQ and HAD scale) were not related to patient response. A further 4 patients reported treatment failure and another 3 patients reported declining efficacy of TENS at the 4 month follow-up. Whether these effects were due to the development of tolerance or declining placebo effects remains to be determined.

Despite the possible utility of EEG measurements in predicting patient response to TENS, it seems unlikely that such measurements could be employed in the clinic due to lack of availability of equipment, trained staff and time to perform the EEG recording and analysis. Therefore the quickest and simplest method of assessing response to TENS remains to be by a 1-2 month home trial.

CHAPTER 7

DISCUSSION

OVERVIEW

Clinical, electrophysiological, neuropharmacological, psychological and sociological factors that influence the analgesic effects and clinical efficacy of TENS have been examined in this thesis. The results suggest that TENS provides successful long-term pain control in 58.6% of patients given a trial (Study 2.1) and that any type of pain may respond (Study 2.2). However previous literature suggests that TENS is most efficacious for pains of neurogenic (neuropathic) origin.

Despite the relative success of administering TENS on an empirical basis in which the patient determines by trial and error appropriate stimulator settings, 41.4% of patients fail to respond and half of these using TENS on a long-term basis achieve less than 50% relief of pain. Thus, a systematic investigation to examine the analgesic effects of different electrical characteristics of TENS was performed on healthy subjects in an attempt to determine optimal stimulator settings. It was found that continuous mode stimulation at 80Hz producing a 'strong but comfortable' electrical paraesthesia should be the primary TENS treatment choice in the clinic. Nevertheless, differential analgesic effects were noted using a range of pulse frequencies, with 20-80Hz proving most beneficial (Exp. 3.1); no differential effects were observed between a range of pulse patterns (Exp. 3.2). However, burst mode TENS applied at an intensity sufficient to produce phasic muscle twitches at a site distant yet myotomally related to the site of pain (acupuncture-like TENS) produced a powerful analgesia both during and after stimulation (Exp. 3.3). The clinical implications of this form of TENS was discussed.

Electrophysiological factors were found to be influenced by TENS. Thus, TENS reduced peak-to-peak amplitudes of the late waveform components (N1P2) of somatosensory evoked potentials (Exp. 4.1) and increased alpha, beta and theta activity of spontaneous EEG in healthy subjects (Exp. 4.2) and/or pain patients (Exp. 4.3). Furthermore, as TENS produced changes in SEPs elicited by non-painful stimuli, and also changes in spontaneous EEG in pain-free subjects, it was suggested that the effects of TENS may be due in part to changes in sensory processing at several

levels in the nervous system which may not specific for the perception of pain. The surprising finding that TENS increased peripherally circulating met-enkephalin was attributed to a stress-like response although this finding remains to be confirmed using a larger population sample (Exp. 5.1).

Patient response to TENS was related to baseline SEP amplitudes and spontaneous EEG. Thus, patients with small peak-to-peak amplitudes of the SEP, and low power spectrum of spontaneous EEG showed poor response to TENS (Exp. 6.1). Deficiencies in stimulator design (Study 2.2) and the under-use of a variety of stimulation modes (Exp. 3.3) may be further factors contributing to poor patient response. Patient response to TENS was not related to biochemical, psycho-social, personality or pain related factors (Exp. 6.1). These points are discussed in detail below.

CLINICAL USE OF TENS

This thesis has provided much information of benefit to therapists, patients and manufacturers concerned with TENS treatment techniques. From the large number of previous studies performed to examine the effectiveness of TENS (for summary see Table 1.2) it has been shown that superficial somatic, deep somatic and neurological pains are more likely to respond than visceral or psychogenic pain.

Indications and Efficacy: Essentially TENS can be used to treat any localised acute or chronic pain. Post-operative pain was the first form of acute pain successfully treated with TENS [Hymes et al. 1974] and TENS has been used post-operatively for abdominal and thoracic surgery [Cooperman et al. 1977], total hip replacements [Pike 1978] and lumbar spine operations [Solomon et al. 1980]. It has been shown that TENS can reduce labour pain and that optimal analgesia is achieved using two sets of electrodes, the first set placed T10/L1 (for the first stage of labour) and the second set placed at S2-S4 (for the second stage of labour) [Augustinsson et al. 1977]. Other forms of acute pain successfully treated with TENS include traumatic pain (i.e. fractured ribs), acute arthritis, acute myalgia and myofascial pain syndrome.

The results presented in Chapter 2 have shown that a wide range of chronic pain conditions may be successfully treated with TENS (Study 2.1 and 2.2), although TENS has been shown previously to be particularly suited to the treatment of pain of neurogenic origin (Table 1.2a). Chronic pains not responsive to TENS include those

poorly localised and/or psychogenic and visceral in origin. However Study 2.2 has found that no particular condition should be excluded from a trial of TENS on the grounds of a *pain that usually fails to respond*. Other indications for TENS treatment include ischaemic chronic pain states. Kaada [1983] found that TENS not only diminished pain in patients with ischaemic leg ulcers but also decreased the size and even healed such ulcers. Angina pectoris can also be relieved by TENS administered over the chest at the site of the referred pain [Mannheimer et al. 1982].

Placebo response: It is difficult to control clinical trials of TENS (and other physical treatments) in a double-blind cross-over design, due to the sensory differences associated during placebo (sham) TENS compared with active TENS. Recently the efficacy of TENS has been questioned by Deyo et al. [1990a] who found that TENS produced no statistically significant effect in reducing low back pain in 145 patients when compared to sham. The group concluded that their results were due to successful blinding and that many reports in the literature on the success of TENS could be attributed to placebo response. However a number of factors may have contributed to the negative findings of Deyo et al.. The use of strong suggestion during sham TENS may have markedly increased placebo response, as 42% of patients reported improvement in low back pain during sham TENS. This is higher than that normally expected for placebo response (i.e. 30%). Hence, the experimenters may have administered a stronger suggestion to patients receiving sham TENS to convince the patient that the stimulator was functioning correctly. Recruitment of the patients by newspaper advertisements was likely to attract an atypical sample of back pain sufferers who may have shown poor responses to a variety of previous treatments. Thus the sample may have been biased toward non-responders [Lancet 1991].

Although it is recognised that TENS, in common with all other forms of pain therapy, has a significant placebo component, recent double-blind, randomised controlled trials have confirmed the earlier uncontrolled studies that TENS is effective in controlling pain. The bulk of controlled trials have been performed on patients with acute (post-operative) pain due to the convenience of comparing the short-term effects of active TENS against sham TENS under experimental conditions in a hospital ward [for review see Woolf 1989]. Although fewer controlled studies are available for chronic pain, Thorsteinsson et al. [1977] found that active TENS was three times more effective in reducing pain from chronic neuropathies than placebo TENS. Taylor et al. [1981] also found that active TENS was significantly greater in reducing osteoarthritic pain than placebo over a one year period.

The results presented in Chapter 3 suggest that the primary effects of TENS cannot be attributed to placebo response as significant differences in analgesia were found between healthy subjects receiving active TENS and sham TENS. Sham TENS was successfully administered to TENS-naïve subjects using a combination of verbal and visual suggestion. On questioning subjects at the end of the experiment the majority were surprised to learn that a 'dummy stimulator' had been used.

Advantages of TENS: Over half of patients given a trial of TENS continue to use the therapy on a long-term basis and in general, patients showing an initial favourable response continue to use the therapy for many years. Such findings emphasise the importance of this treatment in the management of chronic pain, especially as patients may have undergone a number of unsuccessful treatments prior to referral to the Pain Relief Clinic (by physicians). A major advantage of TENS therapy is that it does not interfere with ongoing drug treatment or delay diagnostic investigation. Thus, TENS could be administered more frequently by GPs and other 'front-line' therapists in the symptomatic control of a wide range of pain conditions. Furthermore TENS is relatively cost-effective. After the initial capital outlay for the purchase of the stimulator (approximately £65-£85) the running costs (tape, gel, batteries) are low. When the stimulator is no longer required by the patient it can be re-issued to another patient without any further capital outlay, in contrast to drug therapy. However educating the patient about TENS techniques can be both time and labour consuming in comparison to writing a prescription. This may deter the use of TENS as a primary treatment.

The only adverse effects reported by patients in this investigation was due to either drying out of electrode gel, which produced a prickly 'mosquito bite' sensation, or an allergic reaction to the electrode adhesive tape. Replenishment of gel and the use of self adhesive electrodes can overcome these minor problems. Contraindications include patients using heart pacemakers of the "on-demand" type as TENS pulses may interfere or 'drive' the pacemaker. Manufacturers also recommend that electrodes should not be placed on the anterior aspect of the neck to avoid stimulation of the vagal nerves on the carotid sinus which may produce hypotension, and stimulation of the laryngeal nerves which may produce laryngeal spasm [Sjölund et al. 1990]. No drug-TENS interactions were found in Study 2.2 although a reduction in analgesic intake was reported by many patients.

Long-term TENS users: Long-term users of TENS adopt similar operational procedures to treat chronic pain. Thus, all patients examined in Study 2.2 applied

TENS in its 'conventional' form, to produce a 'strong but comfortable' electrical paraesthesia within the painful area as instructed by staff at the clinic. The majority of these patients reported a rapid onset and offset of analgesia, with pain relief only occurring during stimulation. Therefore to control their pain, patients used stimulators over the entire day. Nevertheless about one fifth of patients achieved lengthy post-TENS analgesia (>2h) using this technique. The results from Chapter 3 suggest that a greater number of patients could achieve lengthy post-TENS analgesia by the implementation of acupuncture-like TENS.

ELECTRICAL CHARACTERISTICS OF TENS

The finding that half of the patients using TENS on a long-term basis obtained less than 50% relief of pain (Study 2.2) suggests that patients may not be utilising the most efficacious electrical characteristics of TENS. Chapter 3 systematically examined the analgesic effects of different electrical characteristics of TENS in alleviating cold-pressor pain in healthy subjects.

Pulse frequency: Differential TENS effects occur across a range of pulse frequencies, with 20-80Hz producing the most beneficial analgesic effects. As 80Hz produced a large and reproducible analgesia (Exp. 3.1) and Sjölund [1985] found that 80Hz produced the greatest reduction in C-fibre reflex in rats, 80Hz may be a good reference pulse frequency to use when trying a new patient on TENS in the clinic. NEEN Pain Management Systems have incorporated this frequency as a default setting on their new Xenos stimulators. Nevertheless the large variation in pulse frequencies and pulse preferences used by patients coupled with the consistency of frequency and pattern choice on subsequent treatment sessions suggest that patients 'tune in' to their particular stimulating preference. However, stimulator design may seriously hinder the patients choice as frequencies above 40Hz are difficult to obtain in many commercially available stimulators. This may seriously reduce TENS efficacy. Furthermore, the use of specific pulse frequencies by patients was not found to be related to the cause and site of pain.

Pulse pattern: No significant differences in the analgesic effects of different pulse patterns (when applied at a 'strong but comfortable' intensity) were found in healthy subjects (Exp. 3.2). Continuous mode TENS produced the greatest (non-significant) elevation of ice pain threshold. However, patients showed preferences for pulse

patterns and the majority preferred continuous mode TENS although 23% of patients reported that they could only achieve relief of pain when using burst mode TENS. With this low intensity TENS, different pulse patterns may be utilised for reasons of comfort unrelated to analgesic mechanisms. The use of continuous mode TENS as a primary TENS treatment choice was discussed in Chapter 3.

Stimulating mode: In certain circumstances where conventional stimulation is ineffective, aggravates the pain, or where it is not possible to apply electrodes over the painful site, other stimulating characteristics should be used. Acupuncture-like TENS produced a powerful analgesic effect in healthy subjects (Exp. 3.3) and should be utilised more readily in clinics. Sjölund and Eriksson have demonstrated the value of AL-TENS as an additional TENS technique [for review see Sjölund & Eriksson 1985]. Thus, approximately one third of patients who do not respond to conventional TENS show favourable response to AL-TENS. Furthermore AL-TENS produced a marked post-TENS analgesia in healthy subjects experiencing experimental pain, in comparison to conventional TENS, as shown in Exp. 3.3. This finding implies that AL-TENS may benefit patients who can only administer TENS for short periods of time.

MECHANISM OF TENS ACTION

Although the elucidation of the mechanism of action of TENS was not a primary aim of this thesis, a number of important findings have relevance.

During stimulation: The finding in Chapter 3 that TENS produced a marked increase in cold-pressor pain threshold, but had variable effects on pain tolerance and pain intensity ratings suggest that the primary effects of TENS are on the sensory rather than affective components of pain. Furthermore, as TENS reduced the peak-to-peak amplitudes of late waveform components of the SEP elicited by non-painful stimuli (Exp. 4.1), it is likely that TENS produces effects on the general processing of sensory information irrespective of the presence of pain. The consistent use of specific pulse frequencies and pulse patterns by patients on subsequent treatment sessions, and the lack of relationships between the cause and site of pain and stimulator settings, implies that patients used such settings for reasons of comfort unrelated to specific pain mechanisms (Study 2.2 and 2.3). This is further evidence of non-specific TENS effects.

It was impossible to determine whether the reduction in SEP amplitude was due to changes in transmission of afferent information at either peripheral, spinal or supraspinal sites (Exp. 4.1). However recent work by Nardone and Schieppati [1989] suggests that TENS may inhibit peripheral transmission of the somatosensory volley in large diameter fibres and centrally at the level of the cuneate nucleus. Thus, in its conventional form, TENS may block (by antidromic collision) transmission of any ongoing activity in large diameter peripheral fibres which may occur during injury. Furthermore increasing the intensity of TENS may recruit A-delta fibres and antidromically block ongoing activity in A-delta fibres [Chung et al. 1984a; 1984b].

However, evidence suggests that TENS inhibits the onward transmission of nociceptive information by a gating mechanism in the spinal cord as originally proposed by Melzack and Wall [1965]. The rapid onset and offset of the analgesia associated with conventional TENS, shown both by pain patients (Study 2.2) and healthy subjects (Exp. 3.3), is consistent with such a neuronal gating mechanism. Further evidence for generalised TENS effects was provided by Exp. 4.2 and 4.3 where changes in power spectrum during TENS were observed in pain free subjects and pain patients. The increase in alpha activity observed during TENS in these experiments suggest that TENS may affect states of arousal because an increase in alpha activity is often associated with a corresponding increase in relaxation. Nevertheless knowledge concerning the physiological significance of spontaneous EEG is sadly lacking and a fuller explanation of these changes is not possible.

No effects of TENS on peripheral concentrations of beta-endorphin or 5-HT were found in patients during symptomatic relief of pain during TENS. Of surprise was the rise (non-significant) in met-enkephalin. It was suggested that this may be due to peripheral release of met-enkephalin following a stress-like response to TENS. However only six patients were examined and therefore further studies utilising larger sample numbers are needed to confirm this finding.

Post-TENS analgesia: The short post-TENS analgesia (up to 1 hour) occurring after the prolonged activation of cutaneous afferents associated with conventional TENS has been attributed to a post-stimulatory depression (approximately 1 hour) in central excitability [Macefield & Burke 1991]. By contrast, the lengthy (over 2 hour) post-TENS analgesia achieved by one fifth of patients (Study 2.2) and during AL-TENS (Exp. 3.3) may be due to the activation of descending pain inhibitory pathways

and the release of opioid peptides. In this respect, AL-TENS but not conventional TENS has been shown to be naloxone reversible [Sjölund & Eriksson 1979].

FACTORS RELATED TO PATIENT RESPONSE TO TENS

The results presented in Chapter 6 suggest that patient response to TENS is related to a number of factors which are discussed below.

Factors related to pain: Previous studies have shown that certain pain conditions are more likely to respond to TENS, (i.e. neurogenic) than others (i.e. psychogenic). However, the results of Chapter 2 show that any type of pain may respond which suggests that factors other than the cause and site of pain may be related to patient response to TENS. No relationships were found between social factors related to the pain condition (i.e. the duration of the pain condition), or the electrical characteristics of TENS adopted during treatment, and response to TENS.

Psychological: In contrast to the findings of Johansson et al [1980], but consistent with the findings of Andersson et al. [1976], the results presented in this thesis suggest that traits in personality as measured using the EPQ were not related to TENS response in either healthy subjects or pain patients. Furthermore no relationships were found to exist between clinical depression and/or anxiety and patient response to TENS.

EEG variables: One of the most important findings within this thesis is the relationship between patient response to TENS and baseline EEG measures. Hence, patients with small peak-to-peak amplitudes of late components of baseline SEPs and low baseline power spectrum show poor response to TENS. As EPs reflect the cortical response to external stimuli and TENS is an external stimulus, it may be inferred that individuals with little CNS response to external stimuli are less likely to respond to TENS.

Neuropharmacological: The finding that peripherally circulating met-enkephalin increases during TENS was surprising and confirmation of these findings in a larger patient sample is necessary. However, patient response to TENS was not related to baseline levels of peripheral opioid peptides. Opioid peptides produced within the periphery are less likely to be involved in pain mechanisms than opioids produced in the CNS. Therefore, further experiments are underway to examine changes in CSF

concentrations of opioid peptides and GABA during TENS. Unfortunately preliminary results are not yet available.

In summary it appears that an important factor which may influence response to TENS is an individual's intrinsic central response pattern to external stimuli. Thus, individuals differ in their overall "setting" of nervous system response which may account for inter-individual differences in response to TENS. Patients with high spontaneous EEG activity and large cortical responses to sensory stimuli show favourable responses to TENS. The CNS of these patients appears therefore to amplify to a greater extent the incoming afferent barrage (TENS or SEP induced) to produce a large SEP response. It has been suggested that cortical responses are related to waves of excitatory and inhibitory synaptic potentials [see Cooper et al. 1980a], thus, it may be hypothesized that responders to TENS release larger quantities of neurotransmitters (some of which may be involved in antinociception) during stimulation. This inter-individual variation in response to external stimuli may have implications for inter-individual variability in response not only to TENS but to other analgesic treatments (i.e. acupuncture). Obviously such a hypothesis needs validation through experimental investigation and the author feels that this field of research merits further investigation.

IMPROVEMENTS IN TENS PROCEDURE

The results presented in this thesis suggest that improvements in the administration of TENS techniques would increase clinical efficacy. Patients, therapists and manufacturers could all play a role.

Patients: The assessment of a patient's response to TENS can sometimes be difficult. Thus it is important for patients to understand that TENS is a treatment which may symptomatically relieve, rather than cure, the pain problem. Furthermore the analgesic effects produced by the electrical paraesthesia of TENS may be qualitatively different from those experienced by traditional pharmacological (drug) treatments and patients must be made aware of this difference. Patients must learn the correct TENS application procedures and be prepared to play an active role in maintaining TENS analgesic effects. Thus unlike drug treatment the patient must spend time to find the most appropriate stimulation site; and attention should be given to appropriate settings and successful treatment regimes for use in future treatment sessions.

Therapist: The most important role of the therapist is to administer TENS correctly and to provide the patient with appropriate instructions at the initial trial session in the clinic. At this trial session it is important to evaluate patient requirements so that:

- (i) elderly patients are not given stimulators which may be too complicated to use,
- (ii) patients with pains located in regions of the body which are difficult to apply electrodes (i.e. back) are supplied with self adhesive electrodes,
- (ii) patients who need to treat two or more sites of pain are supplied with dual channel stimulators.

Patients may readily dismiss TENS as a failure if they feel it is inconvenient to use.

A two month home trial is necessary to evaluate fully the treatment response. Ideally a one month follow-up appointment during this trial could provide the patient with additional information on alternative stimulating techniques and advice on improving TENS efficacy if the stimulation modes used by the patient are not producing pain relief. If this initial follow-up assessment is left too long the patient may have already lost faith in the technique and further suggestions by the therapist to improve TENS efficacy may prove useless. Regular TENS treatment assessments should then be made to monitor progress and to instruct fully the range of stimulating techniques available. It is the authors experience (personal observations during Exp. 6.1) that at the one month follow-up some patients fail to understand some of the facilities available on the stimulators (for example changing pulse frequency). Misconceptions of stimulator use do occur and can be remedied at an early follow-up appointment.

Manufacturers: Possibly the greatest improvements in TENS treatment techniques can be made by manufacturers. Manuals accompanying stimulators should provide a comprehensive patient orientated guide on TENS application. Appropriate information should also be provided for the therapist on different stimulation techniques, and the theory behind the incorporation of the multitude of gadgets now appearing on stimulators. This is exemplified by burst mode facility incorporated on stimulators for the production of AL-TENS, although many company sales representatives and therapists are unaware of this fact.

Inadequacies in stimulator design as reported in this thesis have been noted by TENS manufacturers. Recently, a new stimulator 'The Xenos', has been designed by NEEN Pain Management Systems, and it provides a variety of impressive features including a linear frequency and intensity output characteristics (see Table 1.5) and an 80Hz frequency reset button. Unfortunately the Xenos stimulator remains deficient by the

absence of a visual display for frequency or intensity settings attained during stimulation. The stimulator also provides an array of facilities which may appear daunting to some patients who may prefer a simple design of stimulator. It has been suggested that the analgesic efficacy of TENS may also be improved by concurrent use of certain drugs including tryptophan, tricyclic antidepressants and D-phenylalanine [Thompson 1989]. Although a number of patients under study in Chapter 2 were using TENS in combination with tricyclic antidepressants it was not possible to determine any drug-TENS interactions. Clinical trials on the use of these drug-TENS combinations may prove useful.

FUTURE DIRECTIONS

The findings presented within this thesis support the conclusions of a recent editorial in the Lancet [1991] in that "*..it may be irrelevant to subject TENS to further trials.*". Thus the long-term efficacy of the technique as a means to control pain has been established in an overwhelming number of clinical trials and a wide range of pain conditions have been shown to respond to TENS treatment. However, the results of Study 2.1 suggest that 41.4% of patients given a trial of TENS fail to respond and of those responding about half fail to achieve over 50% pain relief. Future studies should aim to elucidate the mechanism of TENS failure. The findings of Exp. 6.1 that electrophysiological measures reflect patient response to TENS suggest that a patient's intrinsic state of cortical activation to external stimuli, may be an important determinant of response. Further studies utilising EPs may improve our understanding of the mechanism of TENS effects and inter-patient variability in response. Furthermore, studies are underway (by the author) to examine the release of opioid peptides and GABA into the CSF during TENS in pain-free patients awaiting hip surgery. The findings may be used to improve TENS efficacy by suggesting possible drug/TENS combinations.

Recently a range of non-portable stimulators (i.e. Codetron & Likon), utilising a wider range of electrical characteristics (i.e. frequencies up to 5000Hz, multi-electrodes and patterns) have been developed. It has been claimed by the manufacturers that these stimulators achieve greater analgesic efficacy and also cure a range of ailments. These stimulators remain to be validated in the clinic.

Despite the extensive use of electrotherapy both past and present, many in the medical profession still remain sceptical on the use of electrical stimulators in mainstream medicine. In this respect the plea from the Reverend John Wesley which he used to end his *Desideratum* is as appropriate now as it was in 1759:

"Before I conclude, I would beg one Thing (If it not be too great a Favour) from the Gentlemen of the Faculty, and indeed from all who desire Health and Freedom from Pain, either for themselves or their Neighbours. It is That none of them would condemn they know not what: That they hear the Cause, before they pass Sentence: that they would not pre-emptorily pronounce against Electricity, while they know little or nothing about it. Rather let every candid Man take a little Pains, to understand the Question before he determines it. Let him for two or three weeks (at least) try it himself in the above-named Disorders. And then his own Senses will show him, whether it is a mere Play-thing, or the noblest Medicine yet know in the World."

Quoted from Hymes [1988].

CONCLUSION

The following important findings were presented within this thesis:

- (i) Of patients given a trial of TENS, it was estimated that 58.6% continue to use stimulators on a long-term basis (Study 2.1).
- (ii) Any type of pain may respond to TENS treatment (Study 2.2). However, certain pain conditions are more likely to respond than others.
- (iii) There were no relationships between the electrical characteristics of TENS used by patients during TENS treatment and the cause and site of pain (Study 2.2). However, patients utilise specific pulse frequencies and patterns and use these settings on subsequent treatment sessions. It was suggested that patients utilised specific pulse frequencies and pulse patterns for reasons of comfort (Study 2.3).
- (iv) Pulse frequencies between 20-80Hz were found to produce the greatest analgesic effects on experimental pain in healthy subjects (Exp. 3.1). No differential effects were found between different pulse patterns (Exp. 3.2).
- (v) AL-TENS provided powerful analgesia during and post-TENS on experimental pain in healthy subjects (Exp. 3.3). AL-TENS can be applied at sites distant from but myotomally related to, the site of pain.

- (vi) TENS reduced the amplitude of SEP components in pain-free subjects (Exp. 4.1), and increased alpha (and beta and theta) activity in spontaneous EEG in both pain free subjects (Exp. 4.2) and chronic pain patients (Exp. 4.3).
- (vii) A non-significant increase in peripheral concentration of met-enkephalin was found during TENS in pain patients (Exp. 5.1).
- (vii) Patients with small SEP amplitudes and low spontaneous EEG activity show poor responses to TENS.

In conclusion TENS has been shown to be an important therapy for the treatment of chronic pain. However certain patients fail to respond or respond poorly to treatment and this may be due to a combination of pain-related and pain-unrelated factors. Thus, patients with poorly localised, psychogenic or visceral pains are less likely to respond to TENS than those with localised pain of neurogenic origin. However, any pain condition may respond. Of factors unrelated to the pain, the patient's intrinsic central response pattern to external stimuli appears to be related to the response to TENS. Furthermore, it appears that TENS effects are mediated, to some extent, via the processing of sensory information not specific for the pain system, as changes in electrophysiological recordings occur in pain-free healthy subjects.

Clinically, the analgesic efficacy of TENS could be improved by optimising the electrical characteristics of TENS utilised by patients and by improving stimulator design. Moreover, as TENS does not interfere with the diagnosis or treatment of pain conditions, and allows the patient to safely control safely his or her own treatment regime, TENS could and should be administered more readily as a primary analgesic therapy.

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APPENDICES

APPENDIX A

TENS QUESTIONNAIRES

The following TENS Questionnaires were used to assess stimulator use and were administered by:

- (i) postal communication,
- (ii) the author during a visit by the patient to the research unit.

The TENS questionnaire was used in Study 2.2, 2.3, and Exp. 4.3, 5.1. A modified version of this questionnaire was used in Experiment 6.1.

(1) TENS QUESTIONNAIRE

Introduction

We are asking all patients who have previously used a Transcutaneous Electrical Nerve Stimulator (TENS) to complete this questionnaire to help us improve existing machines. If you no longer use TENS we would still like you to attempt the questions as best you can. Please read the instructions carefully.

(A) PERSONAL DETAILS (Please complete)

NAME_____

ADDRESS_____

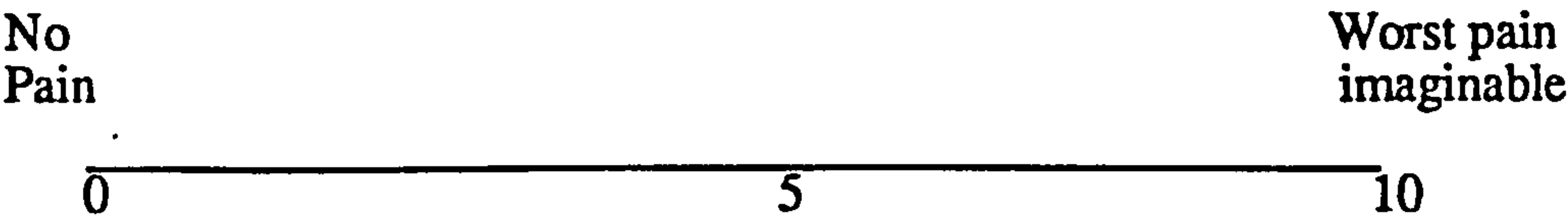
DATE OF BIRTH _____AGE _____

DATE & TIME _____

(B) PAIN RATING SCALE (not to scale)

INSTRUCTIONS

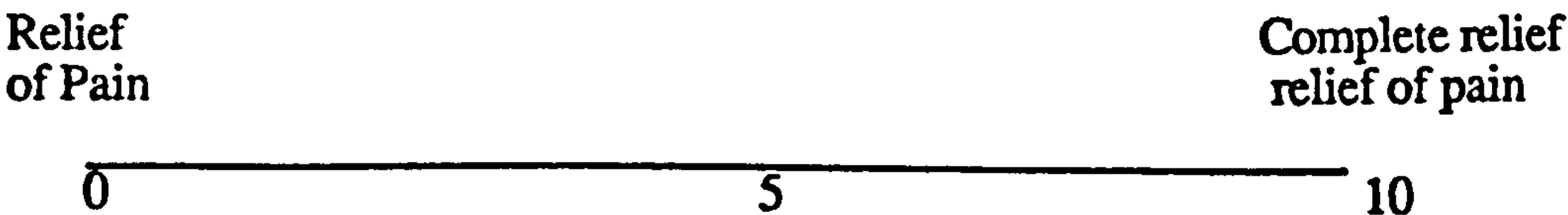
1. Mark with a small cross (x) the point on the 10cm line which represents your pain at the moment.



(C) PAIN RELIEF WITH TENS (not to scale)


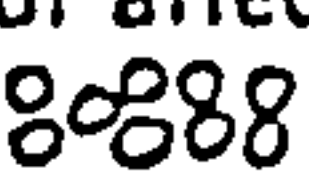

INSTRUCTIONS

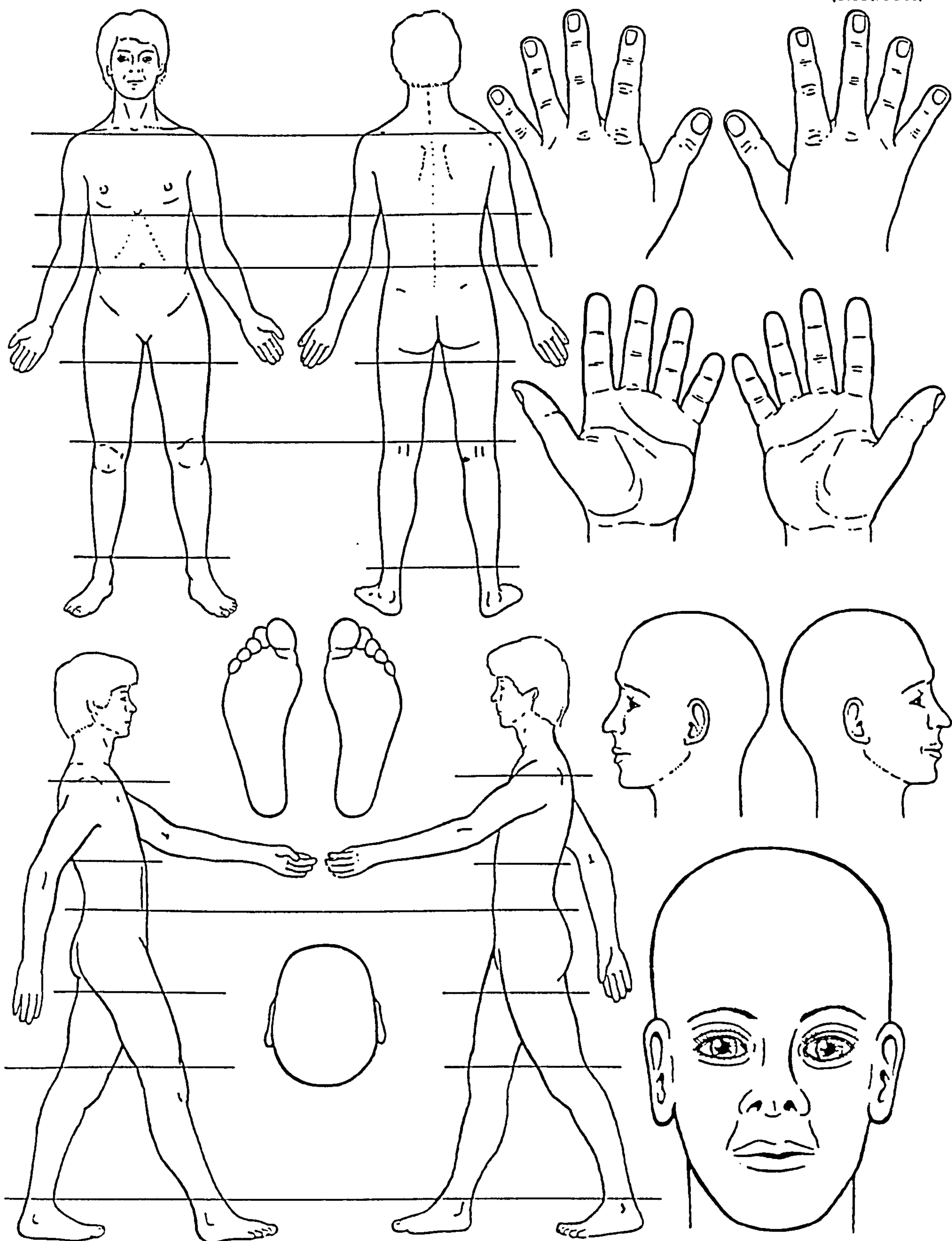
2. Mark with a small cross (x) the point on the 10cm line which represents the relief you have obtained with TENS.



(D) PAIN DIAGRAM

INSTRUCTIONS

1. Please put a line around your affected area and mark: where you have pain ; where you have numbness ; and where you have pins and needles . For example, see over.
2. If you use a transcutaneous electrical stimulator please indicate with crosses where you place the pads (electrodes)



(E) MULTIPLE CHOICE QUESTIONS

INSTRUCTIONS

Please draw a circle around the number for the answer which is most appropriate. There are no right or wrong answers. Please circle only one answer unless instructed otherwise. Get a friend to help if necessary.

1. Are you still in possession of a stimulator loaned to you by the clinic ?
 1. Yes
 2. No. I returned it in _____ (year only).
 3. I use a stimulator not given to me by the clinic
2. If you no longer use a stimulator why did you stop ?
 1. It did not relieve the pain.
 2. It aggravated the pain.
 3. The stimulator was unpleasant.
 4. The electrodes irritated the skin.
 5. Other, please explain _____
3. What is the model of your stimulator ?
 1. Cannot remember.
 2. RDG Tiger Pulse.
 3. RDG Tiger Burst.
 4. Spembly.
 5. Microtens.
 6. Other, please specify _____
4. Have you,
 1. Used the stimulator at least once within the past 24 hours.
 2. Used the stimulator at least once within the past week.
 3. Used the stimulator at least once within the past month.
 4. Used the stimulator at least once within the past year.
 5. Not used the stimulator for at least a year.
5. When you were first issued with a stimulator did it relieve your pain,
 1. Better than it does now.
 2. About the same as it does now.
 3. Worse than it does now.
6. Do you set the switch on the stimulator to,
 1. Always continuous never burst
 2. Occasionally continuous & occasionally burst.
 3. Always burst never continuous.
7. Does the stimulator reduce your pain,
 1. Not at all
 2. Less than 10%
 3. Between 10-30%
 4. Between 30-60%
 5. Between 60-100%

8. When you switch the stimulator on, how long does it take before you start to get some pain relief ?

1. Immediately.
2. Less than 1/2 hour.
3. 1/2 - 1 hour.
4. 1 - 2 hours.
5. More than 2 hours.

9. How long does it take before the original level of pain returns once the stimulator has been switched off ?

1. Immediately.
2. Less than 1/2 hour.
3. 1/2 - 1 hour.
4. 1 - 2 hours.
5. More than 2 hours.

10. How often do you use the stimulator?

1. Once a month
2. Once a fortnight
3. Once a week
4. 2 - 4 times a week
5. 5 - 7 times a week
6. Everyday

11. For how long do you normally leave the stimulator switched on at any one time ?

1. Less than 1/2 hour.
2. Between 1/2 hr - 1 hr.
3. Between 1 - 2 hours.
4. Between 2 - 4 hours.
5. Between 5 - 8 hours.
6. More than 8 hours.

12. On an average day do you normally use the stimulator at least once between the following times, (circle either yes or no).

- | | |
|------------------------------------|----------|
| 1. Between 6.00 a.m. and 9.00 a.m. | yes / no |
| 2. Between 9.00 a.m. and mid-day | yes / no |
| 3. Between mid-day and 3.00 p.m. | yes / no |
| 4. Between 3.00 p.m. and 6.00 p.m. | yes / no |
| 5. Between 6.00 p.m. and 9.00 p.m. | yes / no |
| 6. Between 9.00 p.m. and midnight | yes / no |
| 7. Between midnight and 6.00 a.m. | yes / no |

13. How many times do you use the stimulator on a typical day ?

1. Once.
2. Twice.
3. Between 3 - 6 times.
4. More than 6 times.

14. What is the total number of hours that you use the stimulator on a typical day ?

1. Less than 1.
2. Between 1-3.
3. Between 3-5.
4. Between 5-7.
5. More than 7.

15. While using the stimulator are you normally
 1. Sitting or lying down
 2. Standing or walking around
 3. Sometimes sitting, sometimes standing
16. Do you ever go outside when wearing the stimulator ?
 1. Often.
 2. Sometimes.
 3. Never.
17. Do you place the electrodes on the same spot,
 1. Always.
 2. Sometimes.
 3. Never.
18. Have you ever had any skin complaints (i.e. rash or allergy) due to your electrodes, tape or gel?
 1. Yes
 2. No
 3. Don't know
19. Do you change the rate/frequency (R) button everything you use the stimulator?
 1. Yes
 2. No
20. Which do you prefer?
 1. Fast pulses
 2. Slow pulses

SPECIAL QUESTION FOR TIGER PULSE USERS

Only answer this question if you possess a Tiger Pulse Stimulator.

- 21 Which switch setting on the front of the stimulator do you prefer to use
 1. Up.
 2. Down.
 3. Both, up or down depending on the pain.
 4. Both up and down has the same effect.

Please list the names of any pain killers that you take.

**Thank you for completing this questionnaire. The results will
hopefully benefit future TENS users.**

(2) MODIFIED TENS QUESTIONNAIRE

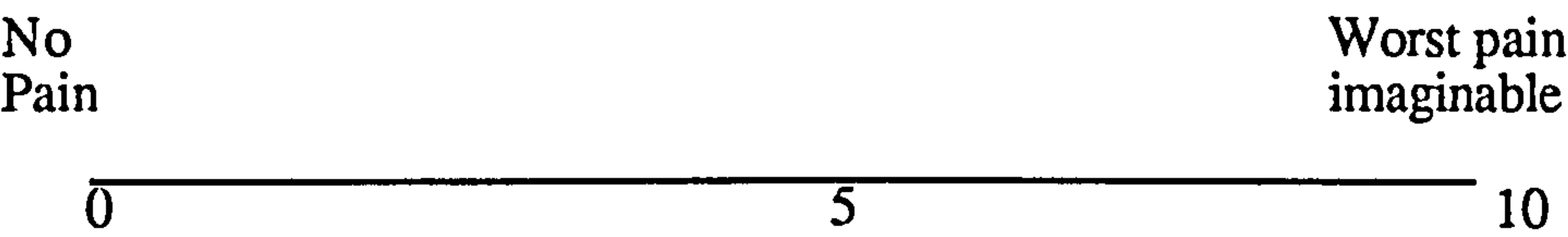
The following questions were *additions* to TENS Questionnaire 1 and used in Experiment 6.1

- 1. What is your occupation ?
- 2.. How long have you had the pain for which you were prescribed a stimulator ?
- 3.. Did you loose the ability to work because of your pain ?
- 4. Do you think the stimulator is too complicated to use ?

VISUAL ANALOGUE SCALES
(not to scale)

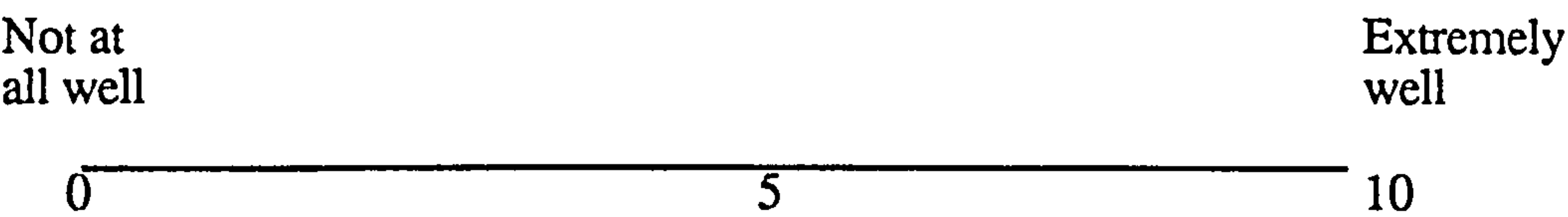
PRESENT PAIN RATING SCALE

- 1. Mark with a small cross (x) the point on the 10cm line which represents your pain at the moment.



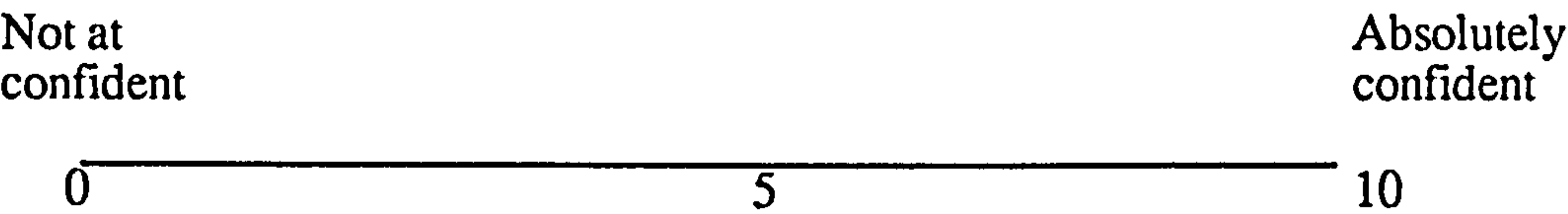
INSTRUCTION ON TENS TECHNIQUES

- 2.. When you were first issued with a stimulator how well were you instructed upon its use ?



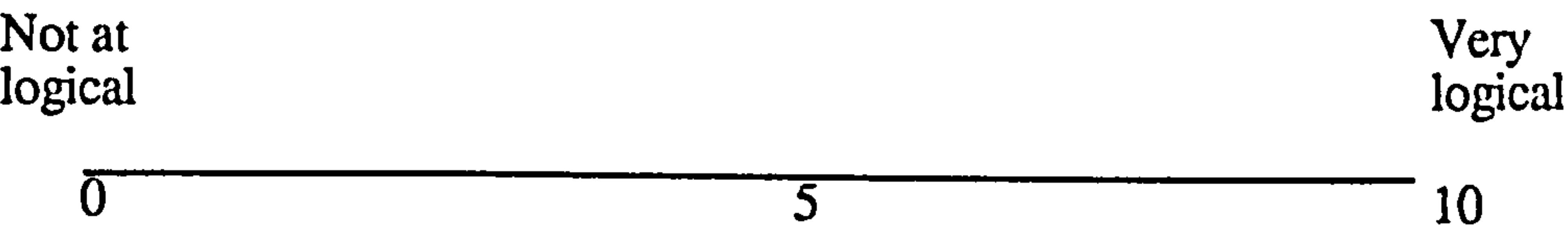
CONFIDENCE IN TENS TREATMENT

- 2. When you were first issued with a stimulator how confident were you that it would be successful in reducing your pain ?



THE LOGIC OF TENS AS A TREATMENT FOR CHRONIC PAIN

- 3. How logical does this type of treatment seem to you (i.e. do you understand how the stimulator relieves your pain) ?



(3) TENS follow-up Questionnaire

NAME _____

OCCUPATION _____

Does the stimulator help your pain ?

Do you still use the stimulator ?

If not why ?

Have you returned the stimulator to the clinic ?

**Please remember to complete the EPQ and HAD questionnaires. and
return them in the pre-paid envelope.**

I would like to take this opportunity to thank you for *all* of your help during the study.

APPENDIX B

Statistical Procedures

The majority of statistical procedures used in this thesis were performed using Minitab Data Analysis Software. Minitab is a general statistical package and was used on an Apricot Xen computing system and University mainframe [Ryan et al. 1985].

Statistical advice was sort from the Department of Medical Statistics at Newcastle University who explored data sets with powerful statistical procedures (i.e. split-plot ANOVAs) using "Genstat" data analysis software. No additional relationships were found for any of the data sets. For this reason the statistical procedures mentioned within the thesis have been restricted to the description of Minitab Data Analysis only.

Descriptive Analysis: Initial data analysis determined whether the variables measured were continuous or categorical. Continuous (or quantitative) variables can be defined as those measured on a continuous scale, i.e. age, visual analogue scale scores, pain thresholds. Categorical (discrete or qualitative) variables can be defined as those measured on discontinuous scales i.e. sex, multiple choice answers. Data sets were described by histograms, means, standard deviations and standard errors (for continuous variables), and medians (for categorical variables).

Summary measures: Experiments examining treatment effects were analysed as follows. Prior to statistical analysis the data was plotted on a histogram. Continuous variables were examined (visually) for normality and data sets with skewed distributions were logarithmically transformed prior to statistical analysis. A suitable summary measure of response was identified and calculated for each individual i.e. total change in ice pain threshold during treatment (Chapter 3) or mean change in EEG power during v pre TENS (Exp. 4.2). These summary measures were then analysed by simple statistical techniques (i.e. t-tests) as though they were raw data. For a full description of the use of summary measures in serially collected data the reader is referred to Matthews et al. [1990].

Parametric Analysis: Parametric statistical procedures were performed on all continuous data sets. Paired student t-tests (2-tailed) were used to compare measurements on the same individual, i.e. pre-treatment cycles 1 and 2, or pre-treatment mean against during treatment mean. Unpaired student t-tests (2-tailed) were used to compare two means when the data was not paired, i.e. differences between treatment groups for subjects allocated AL-TENS against subjects allocated conventional TENS (Exp. 3.3). One-way ANOVA was used to compare differences between three or more groups, i.e. differences in visual analogue scale scores between different categories of chronic pain classified according to anatomical region (Study 2.2).

Non-parametric Analysis: Non-parametric procedures were used to compare categorical variables in a similar manner to that described for parametric analysis. Thus, Wilcoxon signed rank test (equivalent parametric test = paired t-test), Mann-Whitney U-tests (unpaired t-test) and Kruskal-Wallis (one-way ANOVA) were used to examine differences in medians.

Correlation: The association between two independent variables was measured using the Pearson product moment correlation coefficient for parametric analysis and the Spearman rank correlation coefficient for non parametric analysis. As correlation coefficients test for linear associations, raw data was plotted and exploratory

transformations to linearity were performed (i.e. logarithmic, reciprocals square root) prior to analysis.

Heteroscedascity: An important assumption when applying parametric statistical procedures is that the variance within groups should be constant (i.e. Homoscedascity). Heteroscedascity (from the Greek hetros, other or differently, and skedannumi, to scatter or disperse) occurred in the results of Chapter 3 when the variance within groups was not constant, i.e. variance increased with increasing mean group response. Thus, data was logarithmically transformed prior to statistical analysis to make distribution of the data set more symmetrical (normal).

APPENDIX C

(i) Components of the EEG recording system.PA 400

Amplifier: A 4 channel amplifier provides a maximum output for signal amplitudes from 10 μ V (peak-to-peak) to 50 mV (peak-to-peak) and allows a number of frequency bands to be selected using high and low pass filters within an overall range of 0-10KHz.

The Microlink Interface: Serves 3 main functions:

- (i) Control of the high speed sampling of EEG signals and their conversion from analogue (voltage) to digital (numerical) form.
- (ii) Allows the computer to control other equipment (i.e. stimulator units used during EP recording) thus synchronising the start of the sampling of EEG with stimulus onset.
- (iii) Allows the computer to sense events from other equipment (i.e. digitimer) thus initiating programmed operations remotely.

The Apricot Computer: This is the heart of the system and controls every aspect of operation from the initial stages of data collection through its display and initial processing to the printing and storage of final results.

The Software: Biodata CEAN 400 software running under MS-DOS (MicroSoft-Disk Operating System) provides a variety of special programs for the collection and analysis of EEG and evoked potential data i.e.

- (i) Collection and analysis of the background EEG
- (ii) EEG evoked potential averaging

Digitimer (D4030): Provides (a) series of accurately timed periods which may be easily changed and reset during an experiment and (b) an overall recycling function to enable repetition of the experiment. Events initiated during EEG recording include the triggering of (i) the Microlink to start sampling EEG and (ii) the Grass Stimulator to send electrical stimuli or an audiometer to send an auditory tone. The digitimer is also interfaced with an Acorn computer with a program providing random stimulus presentation during EP recording.

Grass Dual Pulse Digital Stimulator (S8800): The Grass Stimulator is a general purpose, rectangular pulse, dual output electrical stimulator and provides stable electrical stimuli. Outputs are referenced to ground and are square wave positive voltages. Several accessory units are required.

- (i) **Grass Constant Current Unit (CCU1):** To convert the constant voltage output of the Grass stimulator to a constant current operation and thus maintain the current intensity of evoking stimuli. This is important as large changes in resistance may occur at the skin electrode-interface.
- (ii) **Grass Stimulus Isolation Unit (SIU 5):** Isolation of the stimulus signal from ground reference reduces the ground current between stimulating and recording systems (the primary source of stimulus artefact) and provides greater safety for direct human and animal stimulation.

Acorn computer: Provides a menu driven pseudo random stimulus presentation program to trigger the Grass stimulator via the digitimer.

Racal Store 4DS FM Tape Recorder: Provides the recording of 4 data channels (3 EEG channels and 1 synchronising pulse from digitimer) and 1 voice channel on 6.25mm (1/4in) magnetic tape for off-line analysis of EEG.

(ii) Artefacts

By definition an artefact is any any recorded electrical potential which does not originate in the brain and can be produced by:

- (i) EEG equipment,
- (ii) electrical interference external to patient and recording system, (i.e. fluorescent lighting)
- (iii) electrodes and leads, (i.e. poor electrode application),
- (iv) the patient (i.e. muscle potentials or eye movements).

Artefacts due to the stimulus (i.e. an electrical pulse) are produced by the spread of stimulus current to the recording electrodes and may obliterate the display of the desired response. Stimulus artefacts can be alleviated by:

- (i) isolating the stimulus pulse from ground, using an isolation unit, and thereby reducing the circulating ground currents between stimulator subject and recording instrument,
- (ii) space stimulating and recording electrodes far apart,
- (iii) use a small stimulator pulse width i.e. (200 μ s).

Nevertheless stimulus artefacts precede the evoked response in time and can be used to distinguish the time of the stimulus.

Artefacts due to muscle potentials manifest as high frequency potentials and can be reduced by relaxing or changing the posture of the patient. Eye movement artefacts are produced by the potential difference of 100mV existing between cornea and retina and are monitored using nasion electrodes placed around the eye. Monitoring eye movements at the nasion enables off-line analysis of electro-oculographical (EOG) activity and the subsequent rejection of contaminated epochs (in spontaneous EEG recording) or compensation of primary electrodes by subtracting a proportion of EOG recorded at the nasion electrode (in EP recording) [Verleger et al 1982, Thom and Andersen 1984].

APPENDIX D

Addresses of suppliers

Microtens 7757 and Xenos TENS units.

NEEN Pain Management Systems, Old Pharmacy Yard, Church Street, East Dereham, Norfolk, NR19 1DJ, U.K.

RDG Tiger burst and Tiger Pulse TENS units. Frye Analyser.

RDG-Electromedical, 429 Brighton Road, Croydon, Surrey, CR2 6UD.

Spembly 9000 TENS units.

Spembly Medical Limited, Newbury Road Andover, Hampshire, SP10 4DR, England.

Met-enkephalin

INC star Ltd., Atlantic Antibodies, Bulldog house, Winnersh, Berks, RG11 5AB.

Human Beta-endorphin

Biogenesis Ltd., 12 Yeomans Park, Yeomans Way, Bournemouth, BH8 OBJ.

CEAN 400 (Computerised Electroencephalographic ANalysis system)

Biodata Ltd., 10 Stock Street, Manchester, M8 8QG, U.K.