In the name of God the beneficent and the merciful

UNIVERSITY
of
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The effect of topical anaesthesia on hand tremor in man.

A Thesis Submitted for the Degree of Doctor of Philosophy in the Faculty of Biomedical and Life Sciences

Division of Neuroscience and Biomedical systems

By

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Abstract

Tremor is the most common movement disorder met in clinical practice. Tremor is defined as an involuntary, rhythmic oscillation of a body region. Not all tremors are pathological. Tremor often causes occupational disability. It can affect the head and lower limbs but it mainly affects the upper limbs. Tremor is an interesting physiological phenomenon, which is present in all living organisms. It can also seen as a symptom of underlying dysfunction of the nervous system.

At first sight tremor looks simple but in fact it is a most complex physiological phenomenon. There are a number of different types of tremor, which are often confused with one another. This presents a practical problem for differential diagnosis and clinical management. Currently, tremor can be classified into rest and action tremors. Action tremors can be subdivided into postural, kinetic, intention and task specific types. Accurate diagnosis of tremor is important to both patient and clinician because the assessment of prognosis and the selection of treatment depend on the type of tremor. Electromyography and accelerometry are reliable and convenient techniques that are widely employed in the study of tremor. They have been used to measure tremor frequency, amplitude and other characteristics. The amplitude of most tremors is very variable. In contrast, the frequency of tremor is quite stable.

The underlying causes of tremor have been investigated by many authors but the mechanisms causing tremors remain unclear. However, the precise mechanisms of

tremor generation are not so important in this project. The principal question raised in this project was: does topical anaesthesia have a significant action on tremor amplitude?

Pozos and Iaizzo (1992) investigated the effect topical anaesthesia on essential tremor of the hand. In an earlier study Pozos and Mills (1985) investigated the effect of topical anaesthesia on clonus, resting physiological tremor and physiological action tremor of the ankle joint. Both of these studies reported significant decrease in tremor amplitude after the application of topical anaesthesia. In contrast, the data presented in this thesis clearly show that there was no significant effect by either the placebo or topical anaesthesia on the magnitude of postural tremors, during movement or in a small number of case studies.

The effects of topical anaesthesia or a placebo spray on hand tremor were investigated in a total of 37 volunteers. Postural tremor was studied in 19 subjects. Movement tremor was studied in 12 subjects. Six cases pathological tremor were also investigated. The volunteers were blinded to the nature of the spray, which had been applied to their skin of the upper limb. Hand tremors were recorded by using a two-axis accelerometer (ADXL210E Analog Devices) that was attached to the middle finger of right hand. Electromyogram recordings were made from flexor and extensor muscle groups of forearm at the same time. The tremor acceleration and electromyography were recorded, digitised and stored on PC.

Subsequently, the power spectrum of the tremor was calculated. The tremor energy in four bands, 2-6 Hz, 6-12 Hz, and 12-20 Hz and the total band 2-20 Hz were studied. The electromyogram was filtered and its root mean square value was

calculated. A Bland Altman analysis was employed to investigate the mean difference of the signals after application of a topical anaesthetic or placebo spray. The confidence interval of the mean difference was calculated. If the confidence interval did not contain zero, the difference was statistically significant.

In all these band frequencies studied no significant difference was found between the tremor after application of xylocaine and placebo sprays. The results of these studies are that skin anaesthesia did not change tremor amplitude. It is concluded that topical anaesthesia is not likely to be useful as a tool for the clinical management of tremor.

Table of Contents

Chapter 1 General Introduction and Literature Review

Chapter 2 General Methods and Materials

Chapter 3 Effect of xylocaine on postural tremor in the hand

Chapter 4 Effect of xylocaine on tremor in the hand during movement

Chapter 5 Topical anaesthesia and pathological tremors: some case studies

Chapter 6 Effects of topical anaesthesia and placebo on skin sensations

List of Tables

List of Figures

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There is no doubt in my mind that this thesis on the effect of topical anaesthesia on hand tremor in humans will prove an important route for further clinical research. For this reason I would like to thank most sincerely my supervisor, Dr. R.H. Baxendale, for all his advice, support and patience during my research project.

Author's Dedication

To my family

Chapter 1

General Introduction and Literature Review

1.1 Introduction

Tremor is known to be the most common of all movement disorders (Britton, 1995) and it has been given different interpretations by clinicians since ancient times. Galen described tremor in the second century. He described tremor as: "Voluntary movements caused by weakness of the force that supports and moves the body" (Zesiewicz and Hauser, 2001). Pratensis (1549) described a postural tremor as 'voluntary' movement resulting from opposing muscle actions.

Tremors are defined in the current clinical literature as involuntary, rhythmic and oscillatory movements of body parts. Tremor may affect the head, face, jaw, voice, tongue, trunk or extremities. It may affect the quality of life by causing physical disability, such as impairment of the ability to work or daily living activities or recreational activities (Velickovic and Gracies, 2002). There are a number of different types of tremors, which are often confused with one another. Differentiation of tremors on clinical grounds is also difficult, for example, essential tremor is often misdiagnosed as Parkinson tremor (Rajput, 1995)

In 1904 Holmes reported that the tremor frequency is different in different types of diseases. Tremor frequency is often used to aid in the diagnosis of neurological disease. Indeed the selection of treatment type is often dependent on the tremor type.

Tremor research has developed rapidly in the past few years because clinicians and neuroscientists have become more interested in the oscillatory phenomena occurring under normal and abnormal conditions. The tremor frequency, amplitude, burst duration and patterns are commonly evaluated using electromyography (EMG) (Milanov, 2001). The tremor amplitude is often variable and depends on several physiological and emotional factors. Tremor frequency is usually a relatively constant feature, although fluctuations can occur (Cleeves and Findley, 1987; Deuschl, Krack, Lauk and Timmer, 1996; Freund, Honberg and Hefter, 1987; Gresty and Buckwell, 1990). The frequency ranges of different types of tremors overlap on range 3-12 Hz (Deuschl, Zimmermann, Gender and Lucking 1995; Findley and Cleeves, 1989).

1.2. Neurophysiology of tremor

Quantitative studies of tremor have been promoted by the development of neurophysiological techniques and accelerometers capable of recording tremor movement. This has allowed features such as tremor frequency, amplitude and other physiological characteristics to be investigated. It remains a matter of debate if accelerometric or electromyographic analysis is superior for the evaluation of tremor (Milanov, 2001). However, electromyography allows detection of the pattern of muscle activation, which may be useful (Milanov, 2001).

The pattern of muscle activation has been studied extensively with surface and needle EMG. Since EMG measures motor neuron activity indirectly, it provides information about the central nervous system commands, which generate the oscillatory movements. The temporal relationship of antagonistic muscle activity as

well as the modulation of motor units firing can also be obtained from EMG recordings (Lou and Jankovic, 1991).

Tremor of limb segments is known to be the result of complex interactions between the mechanical properties of the limb and the synchronisation of motor units firing. This involves peripheral reflex mechanism and central oscillators. (Lou and Jankovic, 1991). This is shown diagrammatically in figure 1.1. The mechanical properties of a limb determine the frequency and amplitude of tremor. The muscle, bones and other soft tissue of a limb comprise a mechanical system that is analogous to a mass attached to a set of springs. Such a system has a natural frequency at which it oscillates when a force is applied (Lou and Jankovic, 1991).

Central neural oscillators may also generate tremor (Lou and Jankovic, 1991). Two major pathological tremors, Parkinsonian tremor and cerebellar kinetic tremor, are associated with identifiable lesions in the central nervous system involving either the nigrostriatal system or the dentate nucleus. Three interconnecting neuronal loops in the central nervous system have been identified as potential generators of oscillations or tremors (Lee and Stein, 1981). One loop, involving basal ganglia, thalamus and cortex generates tremor in Parkinson's disease possibly due to some modulating effect which the nigrostriatal dopaminergic system normally exerts on striatal neurones. Another loop that seems to be capable of generating tremor involves the cerebellum, red nucleus and inferior olive. Cerebellar tremor, rubral tremor and palatal myoclonus are associated with lesions in this system. Oscillation in the third loop involving the spinal cord and muscle receptors results in physiological tremor and enhanced physiological tremor.

In summary, the literature suggests that both central oscillators and peripheral mechanisms play an important role in the genesis of most tremors.

1.3. Classification of tremor

Tremors may be classified by three features (1) its appearance in limb segments during a maintained posture or during movement, (2) its aetiology, such as Parkinsonian or dystonic tremor, (3) by mechanical characteristics such as tremor frequency (Findley and Koller, 1994).

1.3.1. Classification of tremor by appearance

Resting tremor is described as an involuntary, rhythmic oscillation of a body part that is supported against gravity. It may be evident in the upper extremities such as when the patient's hands are resting in the lab or hanging freely during walking. The frequency of rest tremor usually ranges from 3 to 6 Hz. Parkinson's disease is the most common pathological cause of resting tremor (Zesiewicz and Hauser, 2001).

Action tremor occurs during voluntary contraction of skeletal muscles. It may be divided into postural, isometric and kinetic tremors (Velickovic and Gracies, 2002). Postural tremor occurs when the affected body part maintains a position against gravity such as holding arms outstretched in front of the body. Physiological tremor is the most common form. It is usually not visible to the eye, but it becomes obvious when using a laser pointer on a distant screen. Kinetic tremor occurs during voluntary movement. An example is cerebellar tremor, which becomes evident when a patient performs a finger-to-nose test or during daily living activities e.g. drinking or eating. Kinetic tremor may be further classified as simple or intention tremor.

Simple kinetic tremor occurs during movement of extremities, such as flexion-extension movement of the wrist. Intention tremor is associated with visually guided movements toward a target, for example, when performing the finger to nose test. Isometric tremor occurs while holding up heavy weights. Task-specific tremor is associated with specific task or movement, such as writing or speaking. (Zesiewicz and Hauser, 2001).

1.3.2. Classification of tremor by Aetiology

Physiological tremor is a small amplitude, rapid and irregular oscillation at 8-12 Hz of the hand (Velickovic and Gracies, 2002). It may occur at rest. It is unlikely to be caused by activity in the central nervous system since, by definition at rest there is no neuromuscular activity. It has been attributed to the ballistocardiogram (Yap and Boshes 1967; Marsden, Meadows, Lange and Watson 1969). There are small mechanical perturbations originating in the arterial pulse, which produce oscillations at about 10 Hz by peripheral passive mechanical resonance.

Enhanced physiological tremor is another type of tremor that is seen in both healthy people and patients. It is a postural tremor of the hands with a frequency range of 8-12 Hz when the limbs are outstretched. It has been described as a mechanical resonance because the tremor frequency changes with loading (Lakie, Walsh and Wright, 1986). It has been proposed that it originates in resonance in the peripheral stretch reflex loop. (Halliday and Redfearn, 1956; Hagbarth and Young, 1979; Sakamoto and Nishida, 1992).

Conditions known to cause enhanced physiological tremor include the following: thyrotoxicology, hypoglycemia, β-adrenergic drugs, dopaminergic drugs and adrenaline. Adrenaline increases the sensitivity of the muscle spindles and thus enhances rhythmic afferent activity. This leads to greater synchronisation of the afferent volley and enhanced reflex activity, an ultimately synchronised motor unit firing (Deuschl, Raethjen, Lindemann and Krack, 2001).

Essential tremor is the most common movement disorder in familial cases. It usually occurs before a person reaches 30 years (Smaga, 2003). It may be inherited, but the exact genetic defect has not been identified (Hallett, 1991). The tremor amplitude increases as the hand approaches a target. The frequency of essential tremor lies in the range 4-12 Hz. The aetiology, pathology, pathophysiology and neuro-pharmacology of essential tremor are generally poorly understood.

Essential tremor is an action tremor, either postural or kinetic in character. It mainly affects the hands. It is usually bilateral with a frequency of 4 Hz to 12 Hz and largely symmetrical. (Louis, 2001) The upper limbs are affected in about 95% of patients. The head is affected in about 34% of patients. Essential tremor is less common in the lower limbs, with 20% of patients affected. It can also affect the voice in about 12% of patients, as well as the face and trunk (5% of patients) (Elble, 2000a). In a 10-year follow up study (Elble,2000b) the frequency of the essential tremor was seen to decrease and the amplitude increased.

The prevalence of essential tremor ranges from 0.4% to 6.7% in persons over 40 years old so it is the most common type of tremor (Brin and Koller, 1998; Bharucha, Bharucha and Bharucha, 1988; Haerer, Anderson and Schoenberg, 1982). Many

studies have shown that essential tremor is up to 20 times more common than Parkinsonian tremor (Louis, Ford and Frucht, 2001; Bain, Findley and Thompson 1994). However, some experts suspect that the essential tremor might be over-diagnosed by clinicians (Schrag, Munchau and Bhatia, 2000).

Parkinson's disease is associated with a slow degeneration of a small area in the midbrain called the substantia nigra. The age of onset is typically 60–70 years, but not uncommonly before 60 years, and both sexes are equally affected. The tremor commonly involves the head, jaw, neck, facial muscles, tongue and upper extremities but not the lip, which suggests the tremor of Parkinson disease in those cases. Parkinson's disease is associated with a slow degeneration of a small area in the midbrain called the substantia nigra. Specifically, excitatory and inhibitory dopaminergic neurones are affected. (Lenz, Normand, Kwan, Andrews, Rowland and Jones, 1995). The frequency lies in the range 4-6 Hz for the hand. It can also affect the head, trunk, jaw and lips. (Anouti and Koller, 1995; Sandroni and Young, 1994).

Parkinsonian tremor typically occurs at rest and becomes less prominent during voluntary movement. It usually occurs first in the distal part of one upper limb and over time, moves proximally. Ultimately, the tremor spreads to affect the other upper extremity, again in a distal to proximal pattern. Seventy per cent of patients with Parkinson's disease have tremor. Other Parkinsonian patients have early postural instability and akinesia. (Bhidayasiri, 2005).

Action and postural tremors occur in patients with Parkinson's disease. They can occur alone or in combination. Parkinsonian tremor is most commonly a combination of postural and kinetic tremors. Pure resting tremors or pure postural

/kinetic tremors are rare. The variability of the clinical expression of tremors in Parkinson's disease makes diagnosis difficult. It is based on a general diagnosis of Parkinson's disease rather than on specific features of tremors. Only the rest tremor component is by itself, a positive diagnostic criterion for Parkinson's disease (Bhidayasiri, 2005).

Kinetic tremor is the most common type of cerebellar tremor. It presents as a unilateral or bilateral tremor with a peak frequency below 5 Hz. The tremor amplitude increases during goal-directed movements. Cerebellar tremor is due to diseases or lesions of the cerebellum and cerebellar outflow tracts. Classically, the lesion lies within one cerebellar hemisphere or is caused by a stroke, tumour or neural degeneration of the cerebellum nuclei. These lead to an action tremor on the same side of the body as the lesion. Midline cerebellar diseases may cause tremor of the arms, the head or the trunk (Anouti and Koller, 1995).

Cerebellar postural tremor can also follow cerebellar damage. It has a frequency range of 2.5 to 4 Hz. The milder form of tremor has a more rapid frequency at 10 Hz and it appears in more distal limb segments (Hallett, 1991).

Other tremors

Orthostatic tremor is defined as postural tremor of the legs associated with the initiation of standing, walking or sitting. The frequencies range from 13 to 18 Hz. (McManis and Sharbrough, 1993; Gates, 1993).

Multiple sclerosis is the most common cause of the cerebellar postural tremor (Zesiewicz and Hauser, 2001). Tremor can also be associated with peripheral neuropathies where it is clinically similar to essential tremor but the aetiology is different. It can be caused by demyelination or by diabetic peripheral neuropathies (Anouti and Koller, 1995).

1.3.3. Classification of tremor by physiological factors

Physiological tremor is probably the best-known form of tremor. It consists of three main components: a mechanical component, a reflex component and a central component.

Mechanical component

This is responsible for the main frequency components of tremor in most normal subjects (Deuschl et al, 2001). The mechanical component consists of a damped oscillation which is driven by several factors: a resonance at 8 Hz (Timmer, Lauk, Pfleger and Deuschl 1998), a cardioballistic effect which is a small impulse due to the arrival of the pulse wave followed by a damped oscillation (Marsden, 1984). The resonance frequency can be identified by spectral analysis of position or accelerometer signals or from EMG signals. The mechanical tremor components can be characterised by loading the extremities with weights to change the resonance frequency (Deuschl et al, 2001).

Reflex component

Muscle spindles are very sensitive to small oscillations in muscle length (Matthews, 1981). The mechanical oscillations of physiological tremor are associated with rhythmic modulation of spindle activity, but reflex-induced modulation of the electromyogram occurs only when tremor is enhanced by fatigue or by drugs (Lakieet al., 1986; Stiles, 1976, 1980; Young and Hagbarth, 1980). The principal rhythmic component of physiological tremor is referred to as mechanical reflex tremor, not mechanical tremor (Stiles, 1983). Marsden and Meadows (1968) studied adrenaline-induced tremors. They reported that adrenaline increases the sensitivity of the muscle spindles and thus enhances rhythmic afferent activity. This leads to greater synchronisation of the afferent volley and enhances reflex activity.

Any movement in one direction e.g. a flexion will stretch the extensor muscles and cause an afferent volley eliciting reflexes in the extensors. While the extensor is activated, the flexor will be stretched causing an afferent volley from the flexors. When the reflex gains and the conduction time for the afferent and efferent conduction are appropriate, an oscillation will result (Stein, Lee and Nichols, 1978; Stein and Lee 1981).

Reflex and mechanical contributions to tremor can be identified during loading and unloading of the limb (Deuschlet al. 2001). In the unloaded condition significant peaks are found in the frequency spectrum of the EMG and accelerometer signals. In the loaded condition the peaks that are shifted to the lower frequencies are due to mechanical factors whilst those mediated by reflexes are unaltered.

Central component

This component has been attributed to different mechanisms (Elble and Koller, 1990). Neither somatosensory nor visual feedback seems to play a significant role (Stephens and Taylor, 1974). The central component may be caused by motor neurones firing at 8-12 Hz. This does not produce a fused contraction (Allum, Dietz, and Freund, 1978; Freund, 1983). The unfused contractions are subsequently synchronised by reflex mechanisms. However, Elble and Randall (1976) demonstrated that single motor units fire at much higher frequencies, up to 22 Hz. Spectral analyses of both EMG and tremor showed coherence at the 8 to 12 Hz in both signals. This was explained by either Renshaw cell inhibition in the spinal cord or central oscillators located in the inferior olive or thalamus (Elble and Koller, 1990). This idea has been expanded in several studies that investigate subjects with congenital mirror movements. Here the 8-12 Hz components are coherent in both arms (Koster, Lauk, Timmer, Wenter, Guschlbauer, Glocker, Danek, Deuschl and Lucking, 1998). In normal subjects these components do not cohere (Lauk, Koster, Timmer, Guschlbauer, Deuschl and Lucking, 1999; Raethjen,Pawlas, Lindemann,Wenzelburger and Deuschl, 2000). Patients with mirror movements have bilateral projections of the cortico-spinal tract, making it likely that this tremor component is transmitted through the tract. This implies that the oscillator is located either within or central to the motor cortex.

It has been reported that movements of the digits and forearm are regulated through an 8-12 Hz pattern of bursts in motor neurones (Vallbo and Wessberg, 1993) which is independent of the stretch reflex (Wessberg and Vallbo, 1996). This rhythm is transmitted to both agonists and antagonists (Wessberg and Kakuda, 1999). This reflects a common central input.

Rajcthjen, Pawlas, Lindemann, Wenzelburger and Deuschl (2000) reported that 8-12 Hz central components contributed to the clinical expression of physiological tremor. They estimated that central components made a significant contribution to tremor amplitude in only 30% of normal subjects. They believe this contribution to be much higher in persons with enhanced physiological tremor. They found reflex-driven tremor was found in only 2% of normal subjects.

All these studies suggest that the central component of physiological tremor is due to synchronisation at the cortical level by mechanisms inherent in the organisation of the motor system.

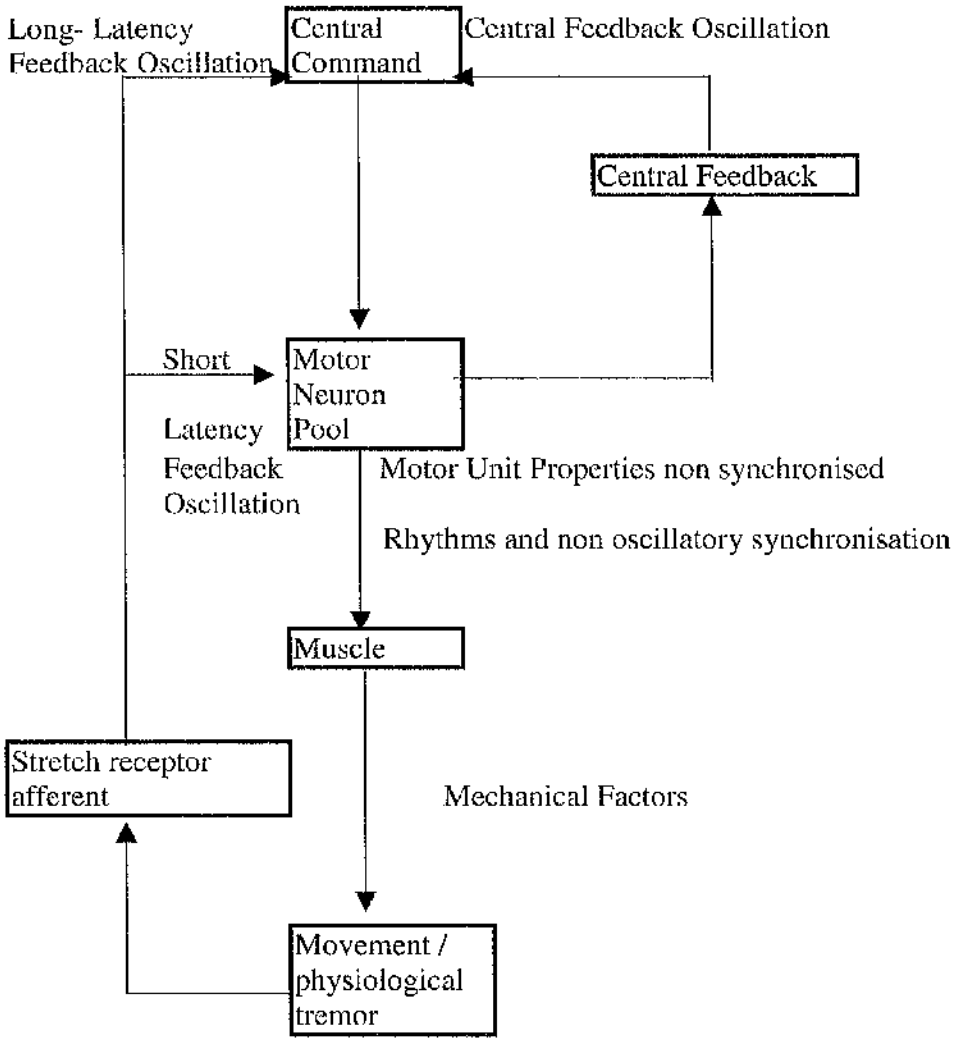
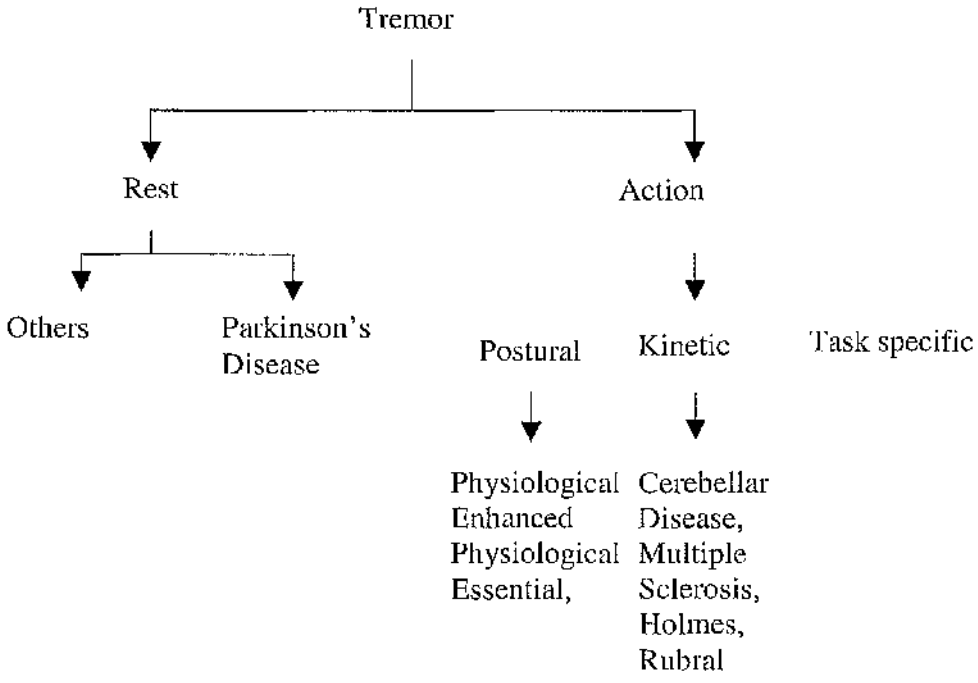


Figure 1.1 A diagram showing motor pathways where 10 Hz physiological tremor may arise.

From McAuley and Marsden, (2000).



Tremor Type	Site	Amplitude	Frequency Range
Parkinson disease	Hand, Head, Trunk	Medium	3-6 Hz
Postural	Hand, Head, Voice	Low-Medium	4– 12 Hz
Kinetic	Arm, Hand	High	Variable
Task Specific	Distal muscles of arm	Variable	4 – 10 Hz

Figure 1.2. The diagram shows the classification of tremor. The table shows the characteristics of tremor.

1.4. Clinical Management of Tremor

There are three main ways in which tremor is managed clinically. Most commonly, they are left untreated because they do not interfere too significantly with the patient's daily living activities. In addition, there are drugs which can be used to manage the tremor. In a small number of severe cases, a neuro-surgical solution will be sought. Each of these will be described in turn. The next section (1.4.1) will describe aspects of the treatments of essential tremor. Section 1.3.2 described how this is the largest patient group i.e. there may be 20 times more cases of essential tremor than Parkinsonian tremor. There are alternative treatments for the smaller patient groups but they are not reviewed here.

1.4.1. Non-pharmaceutical and non-surgical treatments

The risks and cost of neurosurgery and the difficulties of unwanted side effects in drug therapy have lead many people to try more natural treatments. Essential tremor is one of the most common movement disorders. The report prevalence of essential tremor varies greatly with estimates from 0.8 to 2200 per 10000 populations. The majority of studies estimate the prevalence between 40 and 400 per 10000 of populations (Louis, Ottman, Ford and Hauser, 1998). Tremor can develop at any age, but typically it begins in middle age. Essential tremor increases in prevalence with increasing age. It is estimated that between 1 and 5 of every 100 persons aged over 60 years is affected. (Louis et al. 1998).

It is well known that adding weights to a tremulous limb can reduce the amplitude of the tremor thought it does not eliminate the tremor as originally thought (Lynos,

Pahwa, Comella, Fisa, Elble, Fahn, Jankovic, Juncos, Koller, Ondo, Sethi, Stern, Tanner, Tintner and Watts, 2003). Such loading may be helpful while performing directed tasks such as eating or drinking. This technique is helpful in identifying psychogenic tremor, as weight tends to decrease organic tremor but increase psychogenic tremor (Lyons et al, 2003). The use of relaxation techniques such as meditation, yoga, hypnosis and biofeedback approaches can reduce tremor in some patients for short periods (Lyons et al, 2003). These techniques are particularly useful during time of increased stress.

1.4.2. Pharmacological management

Drug treatment for some types of tremor is well established. A range of drugs used is given in Table 1.1. It is clear from the length of this drug list that there is no single popular drug treatment, which is more effective than another. The difficulties with effective drug treatment may reflect problems of drug entry to the brain through blood brain barrier. In addition, since the origins of tremor are complex, many sites in the brain will be involved.

Some drug therapies may be satisfactory in some patients and ineffective in others. In addition, the mode of action of each drug is unclear. The drugs may also have side effects either centrally, i.e. somnolence is associated with Gabapentin or peripherally i.e. the β-blocker actions of propranolol.

However, at present there are no easy cures or treatments of tremor. Neither are there any drugs that can slow the progression of tremor (Lyons et al, 2003).

A variety of drugs have been used to treat tremor in Parkinson's disease. The principle drugs used include: levodopa, dopamine agonists, anticholinergics and budipine. Clozapine, propranolol and clonazepam have also been used as second line treatments (Wasielewski, Burns and Koller, 1998).

Anticholinergics, such as trihexylphenidyl, are effective in tremor management but rarely used now because of their side effects like drowsiness. Anticholinergics are not generally recommended for use in patients with cognitive problems or in elderly patients (Katzenschlager, Sampaio and Costa, 2003).

Levodopa can produce remarkable reductions in tremor in patients with Parkinson's disease. In contrast, dopaminergic treatment is less successful in improving akinesia and rigidity in Parkinsonian patients (Koller and Hubble, 1990). However, there are few double blind, randomised trials specifically designed to assess the efficacy of drug treatment in the management of tremor in early Parkinson's disease (Koller, 1986; Wasielewski, Burns and Koller, 1998; Hughes, Lees, and Stern, 1990).

The dopamine agonists pramipexole and ropinirole are probably the most effective anti-tremor drugs (Navan, Findley and Jeffs, 2003; Pogarell, Gasser and van Hilten, 2002; Schrag, Keens and Warner, 2002). Two other dopamine agonists, pergolide and bromocriptine also produce good results (Korczyn, Brunt and Larsen, 1999; van Laar, Lledo and Quail, 1999). Dopamine agonists are also useful in patients with advanced Parkinson's disease even when treatment with levodopa and anticholinergics has failed (Pogarell, Gasser and van Hilten, 2002).

Clinical trials in which there has been transplantation of embryonic dopamine neurones into the brains of patients with Parkinson's disease have taken place over

the last 15 years (Freed, Breeze and Rosenberg, 1990; Lindvall, Brundin and Widner 1990; Freed, Breeze, Rosenberg, Schneck, Krick, Qi, Lone, Zhang, Snyder,Wells, Ramig, Thompson, Mazziotta, Huang, Grafton, Brooks, Sawle, Schroter and Ansari 1992).Since that time, a number of open clinical trials have described clinical improvements after transplantation. The validity of these observations is uncertain because of the small numbers of subjects, variable inclusion criteria and a lack of controls.

The strongest clinical conclusions come from double blind trials with a large group of patient volunteers. One such study followed patient progress for five years after transplantation (Freed, Bjugstad, Breeze,Greene, Eidelberg and Fahn 2002). They found no improvement of tremor in the transplantation group.

A second double-blind trial was published by Olanow, Goetz, Kordower, Stoessl, Sossi, Brin, Shannon, Nauert, Perl, Godbold and Freeman in 2003. This study was designed to test the effect of tissue dose. The result of sham operations were compared to transplants of tissue from two embryos or six to eight embryos per patient. The results were followed over a period of 2 years. PET scanning showed greater outgrowth of neurites from the larger dose transplants at 12 months. The growth from the smaller grafts caught up with the larger dose grafts after 24 months. There was no change in patients who received sham operations. However, this study failed to see any improvement in unified Parkinson's disease rating scale (UPDRS) motor "off" scores in the transplanted group compared to controls.

There limitations to wide scale testing and application of neuro-transplantation. One is the limited availability of human embryonic neurons. Laboratory production of

large quantities of neurons from stem cells could solve this problem. However, there are still major ethics issues to be resolved.

Tremor type	Medication	Possible side effects
Essential Tremor	Alcohol	Abuse, adverse general health Effects
	Propranolol (Inderal)	Congestive heart failure, bronchospasm, sympathetic response to hypoglycaemia blocked, bradycardia, nausea, vomiting, depression, impotence, fatigue, insomnia
	Clorazepate (Tranxene)	Sedation, addiction, increase limited by fatigue, paradoxical agitation
	Clonazepam (Klonopin)	As for Clorazepate
	Botulinum toxin	Severe muscle weakness
	Gabapentin (Neurontin)	Somnolence, fatigue
	Primidone (Mysoline)	High incidence of initial side effects; flu-like symptoms with ataxia (25%); rare bone-marrow suppression
Rest tremor Parkinson disease	Trihexyphenidyl (Artane)	Dry mouth, blurred vision, dizziness, nausea/vomiting
	Carbidopa levodopa (Sinemet)	Involuntary dyskinetic movements, rare CNS effects
	Amantadine (Symmetrel)	Multiple CNS effects
Cerebellar tremor	Buspirone (Buspar)	Poor response.
Orthostatic tremor	Clonazepam (Klonopin)	CNS depression, drowsiness, ataxia

Table 1.1. Drugs used in the treatment of tremor.

1.4.3. Surgical treatment of tremor.

Surgical therapy for tremor is only considered if drug therapy fails to produce adequate relief. There are multiple reports regarding the efficacy of thalamotomy for essential tremor. (Lynos, Pahwa, Comella, Eisa, Elble, Fahn, Jankovic, Juncos, Koller, Ondo, Sethi, Stern, Tanner, Tintner and Watts, 2003). These reports have consistently shown that over 90% of patients have experienced improvements in tremor contralateral to the side of the thalamotomy. Long-term follow-up studies have indicated that the benefits of thalamotomy can continue for up to 20 years (Lyons et al, 2003). One study of the use of stereotactic thalamotomy in the treatment of tremor (Goldman, Ahlskog and Kelly, 1992) evaluated eight patients with essential tremor following ventral intermediate thalamotomy (seven unilateral, one bilateral). It reported that contralateral tremor resolved or was markedly improved in all patients at a mean follow-up date of 17.3 months after surgery. Two patients reported mild dysarthria, and one patient suffered mild cognitive impairment. Janckovic, Cardoso, Grossman and Hamilton, (1995) evaluated six essential tremor patients at a mean interval of 53.4 months after VIM thalamotomy. They found that five of the patients had total resolution or moderate to marked improvement in contralateral tremors.

An earlier study by Mohadjer, Goerke and Milios (1990) reported that at a mean follow up of 8.6 years after thalamotomy, 89% of the 65 patients with essential tremor showed improvement. 86% percent of the 42 patients with Parkinsonian tremor improved. Postoperative complications included weakness, dysarthria and confusion. In addition, bleeding in the thalamus or in the subdural or epidural area

was recorded during surgery. This is very serious and can lead to death, paralysis, aphasia or cognitive deficits.

Variation in morbidity and mortality statistics can be related to different techniques of the procedure. Bilateral thalamotomy is not recommended due to increased morbidity and mortality rates. One of the main concerns is the risk of speech difficulty associated with bilateral thalamotomy. Tasker (1993) reported a life time mortality experience with thalamotomy of <0.5%.

Stereotactic surgery can alleviate contralateral limb tremor in patients with Parkinson's disease, essential tremor, dystonic tremor syndromes, writing tremor, Holmes' tremor, post-traumatic tremor and tremulous multiple sclerosis (Goldman and Kelly, 1995). The preferred intra-cerebral target in the surgical treatment of Parkinsonian tremor is the sub-thalamic nucleus rather than the nucleus ventralis intermedius of the thalamus (Obeso, Olanow, Rodriguez-Oroz, Krack, Kumar and Lang, 2001). The thalamus has been the target of choice for stereotactic surgery for relief of essential, dystonic and Holmes' tremor. Lesions placed in the nucleus ventralis oralis posterior or zona incerta may be as effective as those in the nucleus ventralis intermedius. In cases of multiple sclerosis, the zona incerta may be the preferred target (Alusi, Worthington, Glickman and Bain, 2001). Presently deep brain stimulation is considered to be safer than stereotactic surgery (Schuurman et al., 2000).

Deep Brain Stimulation

Deep-brain stimulation through an electrode implanted in the thalamus can be used as an alternative to thalamotomy for the treatment of drug-resistant tremor. In 1987, Benabid and his colleagues successfully treated a number of Parkinsonian patients, whose tremor was not improved by drug treatment, with chronic stimulation of the ventro-intermediate nucleus of thalamus (Benabid, Pollak and Louveau, 1987). This followed the pioneering work of several neurosurgeons who had applied electrical stimulation to different thalamic nuclei to treat tremor or other dyskinesias (Bechtereva, Kambarova and Smirnov, 1975; Brice and McLellan, 1980; Mazars, Merienne and Cioloca,1980; Andy, 1983; Siegfried, 1986).

Subsequently, Benabid and his colleagues reported on a larger group of patients who had received thalamic stimulation. This included 26 patients with Parkinson's disease and 6 patients with essential tremor. They found tremor suppression in 88% of these patients (Benabid, Pollak, and Gervason, 1991).

In 1992 a European multi-centre study started. Its aim was to evaluate the efficacy of chronic unilateral or bilateral thalamic stimulation in the treatment tremor. The study followed 110 patients attending 13 centres over 12 months. It found improvement in the tremor in 85% of Parkinsonian patients and in 89% of the patients with essential tremor. The effects of stimulation on other Parkinson symptoms such as rigidity and its effect on the activities of daily living were also evaluated. It was found that the drug treatments were unchanged over the period, probably because some Parkinson symptoms were not controlled by thalamic stimulation (Limousine, Speelman, Gielen and Janssens, 1999). Earlier studies also found that only one third of

Parkinsonian patients have their drug dosage decreased whilst being treated with thalamic stimulation. The drug dosages in patients with essential tremor show similar trends (Benabid, Pollak and Gervason,1991; Benabid, Pollak and Seigneuret, 1993).

The effects of stimulation and thalamotomy in improving the functional abilities of patients with drug-resistant tremor due have been compared (Schuurman, Bosch, Bossuyt, Bousel, van Someren, Merkus and Speelman, 2000). In this study, 68 patients were randomly assigned to undergo thalamotomy or thalamic stimulation. The patient group included: 45 with Parkinson's disease, 13 with essential tremor and 10 with multiple sclerosis. Thalamic stimulation and thalamotomy were found to be equally effective for the suppression of drug-resistant tremor, but thalamic stimulation had fewer adverse effects and results in a greater improvement in function.

However, Ondo, Jankovic and Schwartz (1998) stated that the surgical approach to the target in the brain is dangerous and this form of surgery is limited to a small number of very serious cases.

Topical anaesthetic actions and penetration into skin.

Previous studies have been made into the action of topical anaesthetics on tremor. (Pozos and Iazos, 1992; Pozos, Mills and Iazos 1994; Mills and Pozos, 1995). This section will cover the literature on the actions of topical anaesthetics on sensory nerves in human skin.

In the resting state, the neurone has a membrane potential of about -70 mV. The resting potential is largely determined by the concentration gradients of 2 major ions, K^+ and Na^+ and their relative membrane permeabilities. Local anaesthetics inhibit depolarisation of the nerve membrane by interfering with both Na^+ and K^+ currents (Gmyrek and Dahdah, 2006). Two theories have been proposed to explain this. The membrane expansion theory postulates that the local anaesthetic is absorbed into the axon membrane where it causes expansion of the membrane leading to narrowing of the sodium channels. This hypothesis has largely given way to the specific receptor theory. This theory proposes that the local anaesthetic diffuses across the cell membrane and binds to a specific receptor site at the opening of the voltage-gated sodium channel. This leads to alterations in the structure or function of the channel and inhibits sodium ion movement. This blocks depolarisation and action potential transmission. Blockade of leak K^- currents by local anaesthetics may also contribute to conduction block by reducing the ability of the channels to set the membrane potential (Gmyrek and Dahdah, 2006).

Nerve fibres are categorized into three groups A, B and C on the basis of their axon diameter (Erlanger and Gasser, 1937). The A fibres are the largest diameter and myelinated. B fibres are of moderate diameter and myelinated. Type C fibres are the smallest and unmyelinated. Local anaesthetics affect each group differently (McKenzie, Burke, Skuse and Lethlean, 1975). The smaller diameter fibres are more sensitive and as result C fibres are blocked more easily than A fibres. The anaesthetic must act on several millimetres of the axon to block the transmission of the nerve.

This gross classification of afferent axons by fibre size can be extended to incorporate information on types of sensory endings and adaptation characteristics. Details of this are given in table 1.2. In brief, the Aβ axons in cutaneous nerves include those from Meissner's corpuscles and hair follicles (classified as FA I), Pacinian corpuscles (classified as FA II), Merkel's disks (classified as SA I) and Ruffini endings (classified as SA II). The pain sense is associated with Aδ and C axons arising from free nerve endings.

The stratum corneum, the outermost layer of skin, is the principle barrier to penetration of any drug through the skin (Koh, Harrison, Flock, Marchitto and Martin, 2003). Topical anaesthesia is effective in the most superficial 2-3 mm of skin (Koh et al., 2003) . Removal of the stratum corneum by tape stripping increases the penetration of topical anaesthetics about eightfold (Kao, Patterson and Hall, 1985). Another method of increasing the penetration across the stratum corneum of topically applied local anaesthetics is by iontophoresis. (Sarpotdar and Zatz, 1986; Greenbaum and Bernstein, 1994; Monteirro-Riviere, 1990).

The main reason for the application of topical anaesthetics is to reduce cutaneous pain sensation in a clinical setting. Most studies test pain sensation after application. Jeffrey, Dale, Stephen, Kevin and Timothy (2003) investigated pain after topical anaesthesia produced by 4 and 10% lidocaine in 50 adult volunteers. The sensation was tested by application of laser light five and ten minutes after application of topical anaesthetic. The pain felt after each pinprick using the 0 - 10 scale were tested. 86% of the participants described the sensation of the laser ablation as non painful i.e., "puff of air", "no sensation". The others described the sensation as a "pinch", "poke" or "sting". No difference in pain scores after application of 4% and 10% lidocaine or after 5 minutes or 10 minutes of application.

1.5. Local anaesthesia of skin as a treatment for tremor

It is clear that whilst tremor is a major clinical problem, there is no satisfactory treatment available. One novel approach has been to try to change the reflex components of tremor by reducing the cutaneous sensory inputs with topical anaesthesia.

Techniques based upon the modification of information transmission in the brain have been used successfully for the rehabilitation of movement disorders and spasticity (Kelly, Baker and Wolf, 1979). Topical anaesthesia has been used to reduce cutaneous inputs (Sabbahi, De Luca and Power, 1981; Sabbahi and De Luca, 1982; Wolf and Minkwitz, 1989; Agostinucci and Power, 1992; Arsenault, Belanger, Durand, De Serres, Fortin and Kemp, 1993; Agostinucci, 1994). These studies have reported varying results, ranging from no effect on motor neurone excitability in

normal subjects (Arsenault et al., 1993) to increased range of joint movement during gait in patients recovering from stroke (Sabbahi et al., 1981). Pozos and Iaizzo (1992) investigated the use of topical anaesthesia of the forearm in the treatment of patients with essential tremor. The patients were concurrently treated with propranolol. They reported a significant reduction in the amplitude of tremor, 20-30 minutes following application. They found no change in the frequency of the tremor. This probably indicates that the tremor frequency is mostly determined by mechanical characteristics and that the amplitude is mostly determined by reflex characteristics.

Topical anaesthesia of skin decreases the excitability of motor neurones supplying muscles in the lower limb (Sabbahi and De Luca, 1981). These experiments use an H reflex testing method. The authors had no information about the mechanism which reduced the H reflex excitability. They speculated that the change was brought about by modulation of gamma motor neurone activity.

Many factors are known to affect the H-reflex recovery. These include: inhibition of the motor neurone pool by group II afferents (Magladery and Porter, 1951), recurrent inhibition by Renshaw cells (Haase, 1975), Ib afferent inhibition (Hufschmidt, 1966), feedback from the muscle spindles and joint receptors leading to inhibition (Taborikova and Sax, 1969), supraspinal inhibition (Taborkova, 1973) and depletion of the transmitter substances (Taborihova and Sax, 1969).

Sabbahi and Deluca (1981) added modulation of cutaneous afferent nerves to this list. They tested the amplitude of soleus H reflexes before and after application of 20% benzocaine to produce topical anaesthesia of various areas of skin on the leg.

The skin covering gastrocnemius-soleus, quadriceps, anterior tibial muscles and hamstring were investigated. In other experiments, areas of skin corresponding to the L2, L3, L4, L5, S1 and S2 dermatomes of the lower limb were anaesthetised. They found similar results in both experiments. The amplitude of H-reflexes increased following application of the anaesthetic whilst the amplitude of the Achilles tendon reflex remained unchanged. The authors reported that input from cutaneous afferents might have an important inhibitory effect on the gamma motor neurones supplying soleus. Earlier, Sabbahi and Sedgwick (1976) tested monosynaptic reflexes during natural mechanical and thermal stimulation to the skin. Cutaneous stimulation produced inhibition of the H reflexes.

The effect of topical anaesthesia on motor performance has been investigated in patients with a range of clinical problems such as stroke, head injury and familial spino-cerebellar degeneration (Sabbahi, 1987). Clinical studies report an increase in the active and passive range of movement of joints, improved speed of movement as well as reductions of muscle stiffness (Sabbahi, Roy, De Luca and Van Volkinburg; 1983; Sabbahi and De Luca, 1981). The authors reported that the degree of improvement varied between head-injured and stroke patients. The improvement occurred within 15-30 minutes after xylocaine application. Mills and Pozos (1985) reported a significant reduction in the amplitude of the physiological clonus, physiological action tremor at the ankle in normal volunteers after application of topical anaesthesia to the skin of the leg, ankle and proximal half of the foot. In addition, pathological clonus in spinal cord injured volunteers was also reduced. Furthermore, Wolf and Minkwitz (1989) studied the Achilles tendon reflex, H-reflexes and the range of motion of the ankle in stroke patients before and after application of a benzocaine anaesthetic spray to the skin of the lower limb. They

reported no significant difference between the application of a placebo spray and benzocaine spray. In both cases the excitability level of motor neurones increased and there was improvement in the subject's ability to perform a motor task. The authors attributed these effects of skin stimulation to the topical application of the spray rather than to any drug action.

Similar studies have been performed in the upper limb. Sabbahi, Mason and Gleeson (1985) studied the H-reflex of the flexor carpi radialis muscle in normal volunteers. The reflexes were elicited by electrical stimulation of the median nerve. They applied topical anaesthetics to the skin of the anterior forearm, anterior arm, posterior forearm and posterior arm and this resulted in increased amplitude of H-reflexes. The authors reported that all skin areas of the upper limb, except for the posterior forearm, provided inhibitory inputs to the flexor gamma motor neurone pool of the flexor carpi radialis. It appears that posterior forearm skin provided a strong excitatory input to the flexor gamma motor neurone pool of the flexor carpi radialis.

Several experiments demonstrate the existence of ongoing inhibitory and excitatory effects from skin afferents on the alpha and gamma motor neurone pools via segmental and supra-segmental pathways. The reduction in the activity or discharge from cutaneous afferents, caused by topical anaesthesia, changes the excitability of the motor neurone pools (Sabbahi and De Luca 1981, 1982).

1.6. Innervation of forearm hairy skin

Each peripheral cutaneous nerve contains afferent and efferent nerve fibres innervating a particular skin area. The skin region supplied by afferent fibres in one

dorsal root is called a dermatome. The dermatomes of adjacent dorsal roots overlap extensively. The extent of overlap varies with modality of sensation. For instance, it is less for pinprick pain than for light touch (Greger and Windhorst, 1996).

At least six different kinds of endings occur in the skin as shown in Fig.1.3. (Moffat and Mottram, 1987). There are two major types of receptor response to sustained stimulation: slow adapting (SA) and fast adapting (FA) see table 1.2. Each of these types subdivides into two subgroups: SA I, SA II and FA I, FA II. These four cutaneous afferent types innervate the human hand.

The properties of mechanoreceptors in human hairy skin of the back of hand were studied by Jarvilehto, Hamalainen and Soininen (1981). They identified a total of 264 mechano-receptive units. 66% were classified as slowly adapting (SA) and 34% as fast adapting (FA) units. Most SA I and FA units were able to signal the stimulus amplitude on the basis the of number of impulses. Only FA units could signal the stimulus velocity.

There are some differences between the characteristics of receptors in hairy and glabrous skin. Receptors in human hairy skin do not seem to differ from the corresponding receptors in other animals (Jarvilehto et al., 1981).

The first account of hairy skin receptor responses to joint movements was published by Edin and Abbs, 1991. They found that more than 90% of the 121 receptors located on the back of the hand responded to finger movements. The receptors in the human hairy skin provide information on nearby joint positions and therefore may play a specific role in proprioception, kinaesthesia and motor control, (Benoni and Edin, 1992). However, the receptors in hairy skin play a more important role than

those in glabrous skin in providing information on joint position and movements. Hairy skin lacks the tight connections to subcutaneous tissues that are present in glabrous skin and can therefore be both moved and stretched with little resistance by movements at nearby joints. Every joint of the human body is covered by hairy skin and thus skin may be able to signal information on movements (Hulliger, Nordh, Thelin and Vallbo, 1979).

1.7. Skin receptors

There have been several investigations of the sensations or perceptions associated with activation of each type of afferent. (Johnson, 2001). The SA I afferent system provides a high quality neural image of the spatial structure of objects and surfaces. It is the basis of form and texture perception. The FA system provides a neural image of motion signals from the whole hand. The Pacinian corpuscle system provides a neural image of vibrations transmitted to the hand from objects contacting the hand. Lastly, the SA II system provides a neural image of the skin stretched over the whole hand (Johnson, 2001). Some slowly adapting SA receptors show graded responses to finger movements even when they were located 6 to 7 cm from the joint (Edin and Abbs, 1991).

The receptors in human hairy skin do not differ in their characteristics from the receptors in human glabrous skin or from receptors in the hairy skin of animals (Jarvilehto, Hamalainen and Laurinen, 1976). Both glabrous and hairy skin contains receptors that respond to maintained indentation. These are the Merkel and Pimkus-Iggo corpuscles, which lie immediately below the epidermis, and the Ruffini corpuscles, which lie deeper (Greger and Windhorst, 1996).

Rate of adaptation	
Fast	Slow
FA I-Meissner or Hair Follicle Surface receptors Small field Localised epidermis Edge sensitive- feels like localised flutter- used for recognising texture	SA I Merkel Surface receptors Small field Localised epidermis Edge sensitive-used for noting fine surface edges
FA II---Pacinian Deep receptors Largest field Localised dermis Activated by diffuse vibration e.g. tapping with a pencil	SA II Ruffini Deep receptors Large field Localised dermis Sensitive to lateral skin stretch used for joint position in finger

Table 1.2 Summary of the types of cutaneous mechanoreceptor and some of their distinguishing properties.

The left panel shows the characteristics of fast adapting receptor types (FA I, II). The right panel shows the characteristics of slow adapting receptor types (SA I, II).

1.8. Skin structure:

The skin is the largest organ in the body accounting for 16% of body weight. (Greger and Windhorst, 1996). It has several important functions including sensation. The skin structure consists of three layers: epidermis, dermis and subcutaneous fat.

1.8.1. Epidermis

The epidermis layer contains no blood vessels and depends on the underlying dermis for nutrient delivery via diffusion through the dermo-epidermal junction. Most layers

of epidermis are only 0.1 to 1.5 millimetres thick. The epidermis is made up of five layers: the basal cell layer, the squamous cell layer, the stratum granulosum, the stratum lucidum and the stratum corneum.

1.8.2. Dermis

The dermis lies under the epidermis and supports it. The dermis is 1.5 to 4 millimetres thick. The main components of the dermis are collagen and elastin. It contains most of the skin structure including sweat and oil glands, hair follicles, nerve endings, blood and lymph vessels.

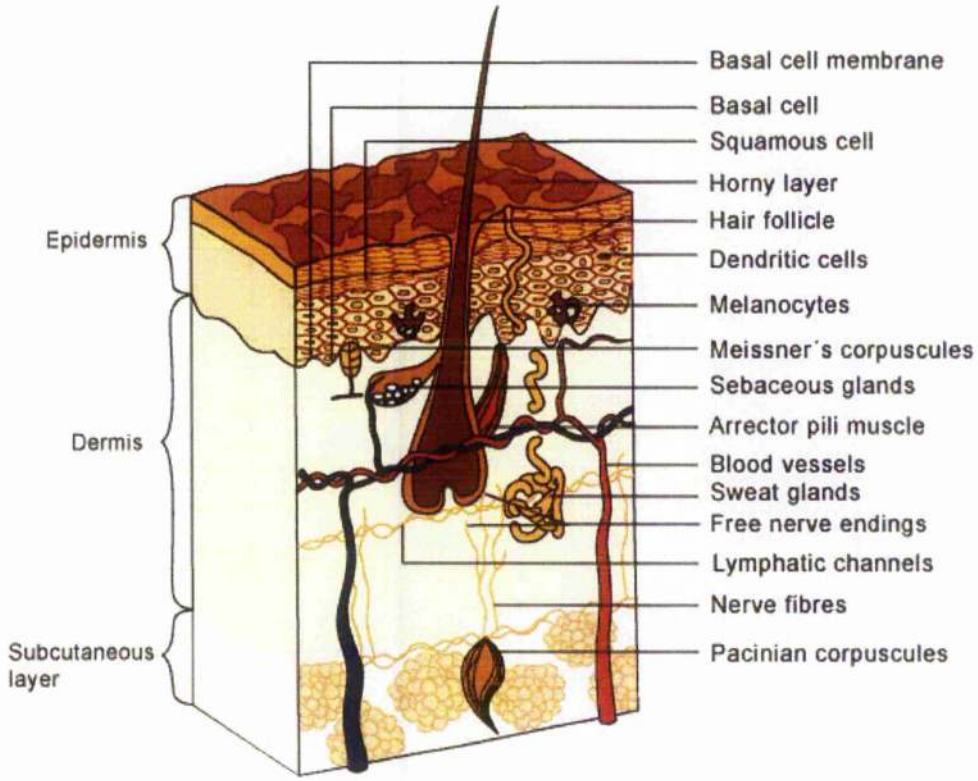


Figure 1.3. The structure of skin with details of receptor localisation.

From Dermatology Information Service Department of Clinical Social Medicine, University of Heidelberg.

(downloaded from http://skincancer.dermis.net/content/e01geninfo/e7/index_eng.html)

1.9. Anatomy of the arm

1.9.1 Muscles of forearm limb

The muscles of the forearm are mostly slender and they have long and narrow tendons. The flexor muscles of the anterior forearm are supplied by median or ulnar nerve while the more posterior extensors are supplied by the radial nerve. This is illustrated in figure 1.4. The muscles of anterior surface of the forearm are best described in three layers. The superficial layer comprises pronator teres, flexor carpi radialis, palmaris longus and flexor carpi ulnaris. Flexor digitorum superficialis comprises the intermediate layer and the deep layer comprises flexor pollicis longus, flexor digitorm profundus and pronator quadratus.

1.9.2. Dermatomes of the upper limb

Dermatomes bear a close topological relationship to spinal segments as illustrated in figure 1.5. For example, the median nerve is a mixed nerve that originates from the C6 to T1 spinal nerve roots and the lateral and medial cords of the brachial plexus. It supplies mainly the anterior compartment of the forearm and the thenar muscle group. It carries cutaneous sensation from the lateral two thirds of the anterior aspect of the palm and the lateral 3 fingers, including the dorsal surface of the terminal phalanges. The C7 nerve root supplies cutaneous sensation of the middle finger. The cutaneous sensation of the index and the thumb is in C6 or C7 nerve roots. The median nerves gives rise to a pure motor branch called the anterior interosseous nerve that supplies the anterior forearm muscles.

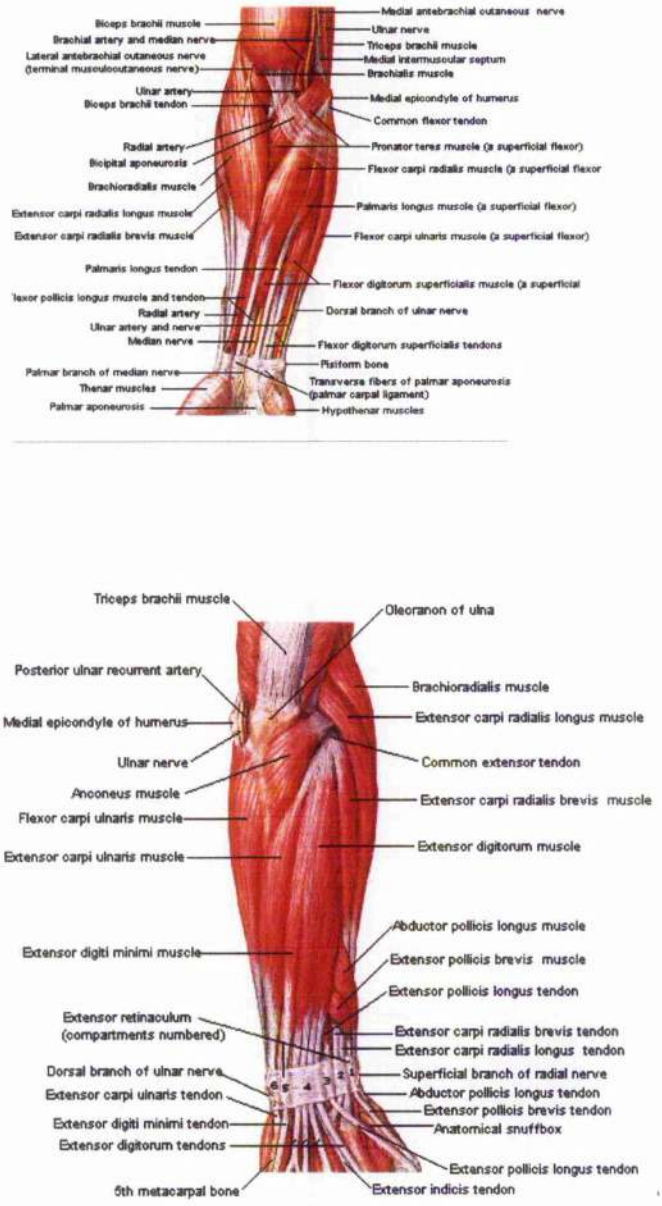


Figure 1.4. Illustration of the positions of the forearm muscles.

The upper panel shows an anterior view and the lower panel shows a posterior view. Interactive Atlas of Human Anatomy by Frank H. Netter. Published by Ciba Medical Education.

The ulnar nerve originates from the C8 and T1 spinal roots. It innervates the flexor carpi ulnaris muscles, the hypothenar muscle groups, palmar and dorsal interossei muscles, and the deep head of the flexor policis brevis, as well as the adductor pollicis muscle. It supplies the cutaneous sensation of the medial side of the hand over the hypothenar muscle group.

The radial nerve is derived from the C5, C6, C7, C8 and T1 spinal nerve roots and the posterior cord of the brachial plexus. The motor branches of the radial nerve motor innervate the triceps brachii, anconeus, brachioradialis, extensor carpi radialis longus, and brevis, as well as the posterior compartment of the forearm. The sensory branch of the radial nerve arises from the C6, C7 roots and supplies the lateral aspect of the back of the hand (Nalty and Sabbahi, 2001).

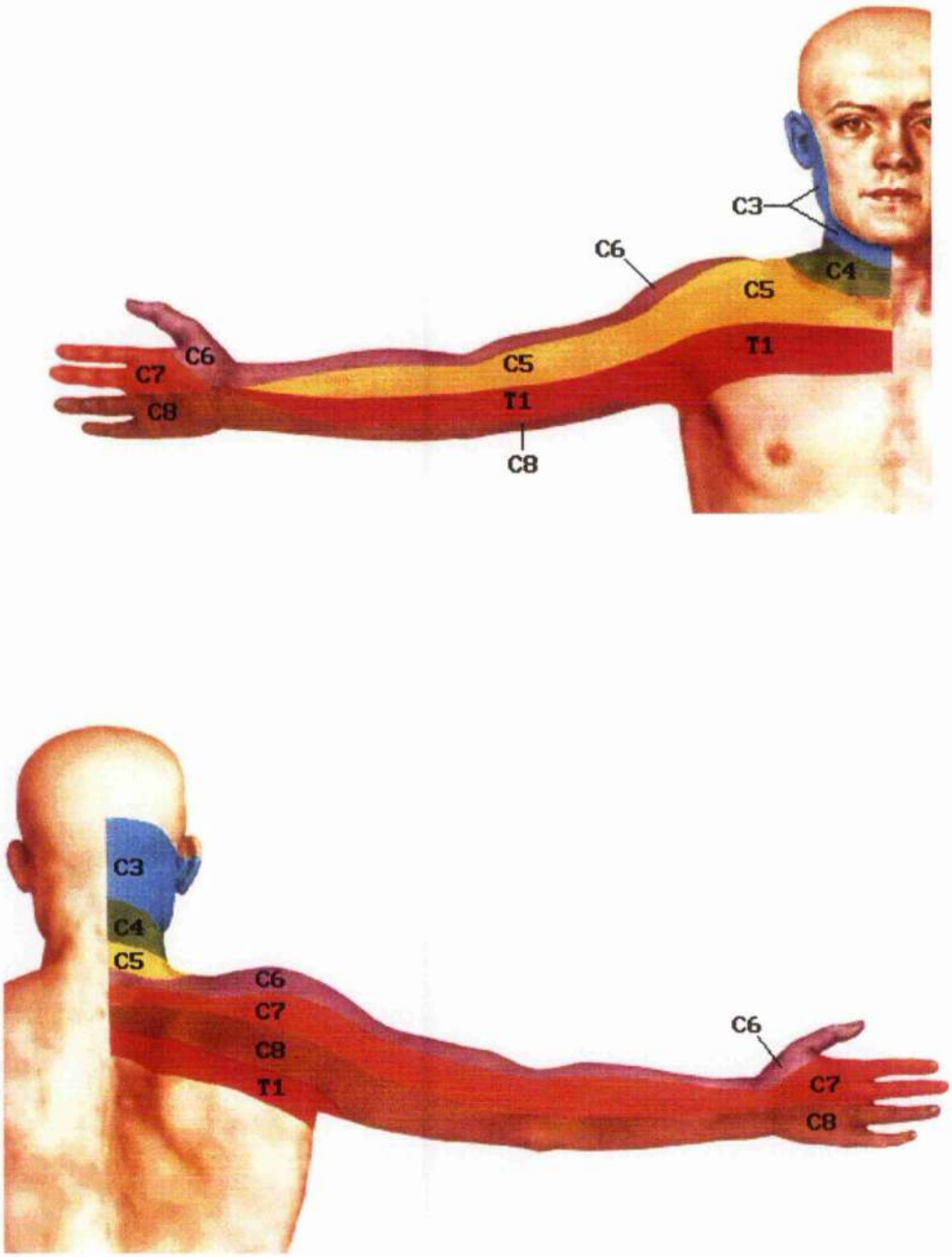


Figure 1.5. The upper limb surface and their relation to spinal cord segments.

This figure shows the upper limb surface and its relation to spinal cord segments, as indicated by numbered letter, C, cervical; T, thoracic. (Interactive Atlas of Human Anatomy by Frank H. Netter. Published by Ciba Medical Education

1.10. Aims of investigation

The present study will address four main questions about the effect of topical anaesthesia on hand tremor:

1. Is there any difference in physiological tremor at rest in normal subjects after the application of a placebo and a xylocaine spray?

2. Is there a difference in muscle activity of the forearm at rest after application of a placebo and xylocaine spray?

3. Does any difference in physiological tremor during movement in normal subject after application of placebo and xylocaine spray?

4. Is there a difference in pathological tremor at rest after application of a placebo spray and xylocaine?

Chapter 2

General Methods and Materials

This chapter provides details of the materials and methods that were used in several experiments. Materials and methods specific to particular experiments will be described in the appropriate chapter.

2.1. Volunteers

Thirty-six adult volunteers, both male and female, participated in these experiments. They had no history of neurological disease or muscular disorders. Their mean age was 28 years. All subjects gave their informed consent in accordance with the protocol approved by the Glasgow University Research Ethics Committee. They were free to withdraw from the experiment at any stage. None of the subjects withdrew from the experiments. Neither did they report any kind of discomfort during the tests. Each volunteer made two visits to the laboratory. Each visit lasted approximately one hour. During the first visit, the nature of the experiment was explained, consent was obtained and the volunteer was familiarised with the experiment. The last part of this visit consisted of the first recording session. This was done with either a local anaesthetic or a placebo spray applied to their skin. On the second visit the other spray was used. The sequence of placebo local anaesthetic was randomised by asking the volunteer to select a sealed envelope containing the sequence of sprays.

2.2. Experimental set up

The general experimental set up is shown in figure 2.1. Each volunteer was seated comfortably in a chair. Their forearm was extended and supported by a frame. Their fingers, hand and wrist joint were free to move. Surface electromyograms were recorded from Flexor Carpi Radialis and Extensor Carpi Radialis muscles. A biaxial accelerometer was attached to the distal end of middle finger to record flexion-extension and lateral - medial deviation of the hand.

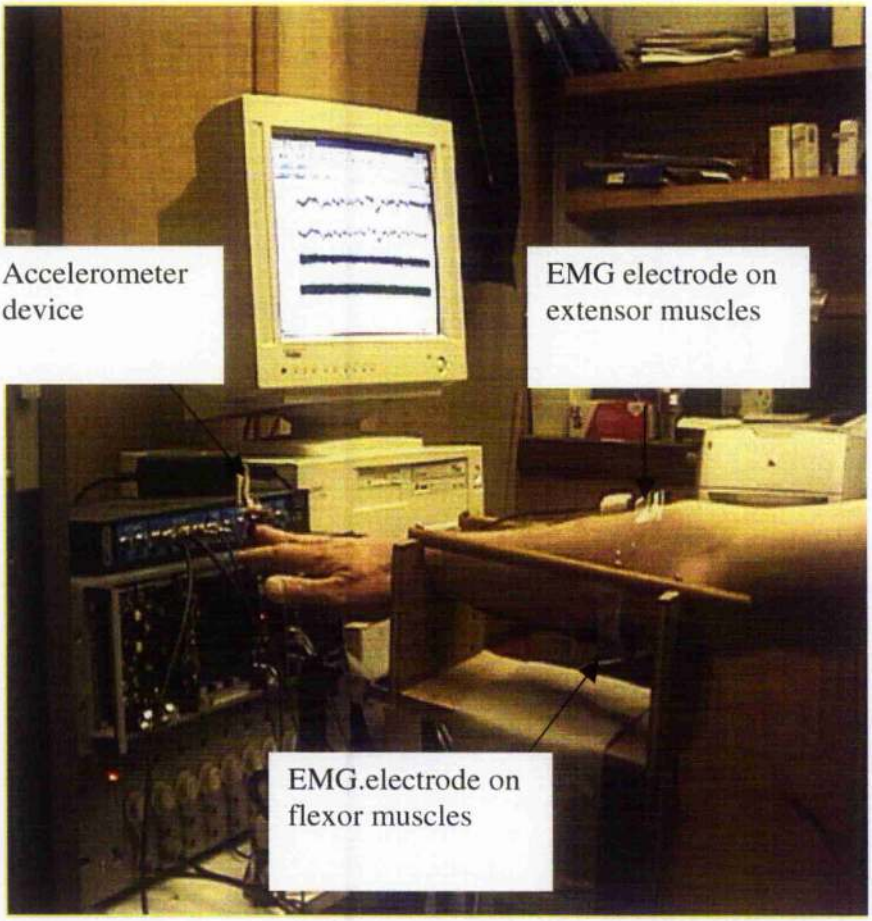


Figure 2.1. The general experimental set up for the first series of experiments.

The instrument shown include:
1. two EMG electrodes and amplifiers, which were placed 2-3cm below the elbow joint.
2. a biaxial accelerometer attached at the end of middle finger,
3. the Neurolog isolator unit, EMG amplifier, a CED 1401 interface unit and PC.
Notice the subject's arm is supported leaving the hand and wrist joints free to move.

2.3.1. Electromyography Recording

Two electromyography-recording systems were used. The first system, described in section 2.4.1, was used in the experiments described in chapter 4. The second system described in section 2.4.2 was used in the experiments reported in chapter 5.

2.4.1. EMG Recording System 1

Two identical EMG recording channels were used. Each used small, skin mounted EMG pre-amplifiers with integrated electrodes. These are shown in figure 2.2. The amplifier weighed 13.4 grams. The electrode discs were 7 mm in diameter and they were separated by 20 mm. This device eliminated connecting wires and so movement artefacts were kept to minimum. The EMG signal was pre-amplified by x100. The amplifier bandwidth was –3 dB at 10 Hz to 5 kHz. The EMG signals were then passed to a Neurolog NL 820 isolator amplifier whose gain was x10. The signal was subsequently conditioned with a Neurolog NL 106 AC/DC with a gain of 1. Any DC offset was removed before the EMG was digitised.

2.4.2 EMG Recording System 2

In the experiments described in chapter 5 and the case studies, a commercial Neurolog system was used to record two channels of EMG. An earth strap 2 cm broad was fastened round the upper arm with Velcro. Two silver/silver chloride discs 9 mm in diameter were taped over the muscle belly. The electrodes were separated by 20 mm. The electrodes were connected to an NL 822 amplifier. Its gain was set at x1000 and it had a high pass filter set at 3 Hz. The EMG signal was passed to a NL

820 isolator unit with a gain of x1. The EMG signals were then digitised by the CED 1401.

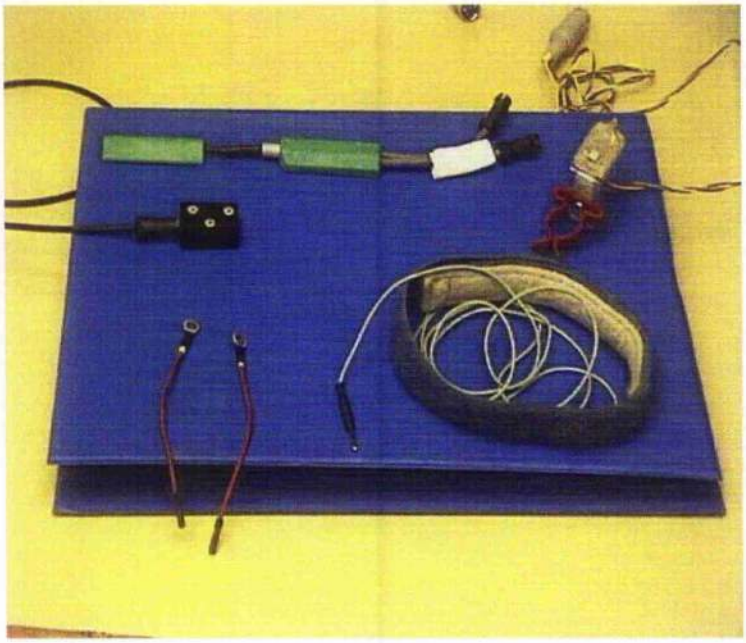


Figure 2.2. Several small items of experimental equipment.

An electrogoniometer is shown top left. An Analog Devices ADXL 210E biaxial accelerometer is shown top right. The Velcro earth strap is shown in the lower right position. In the middle left position is an integrated EMG electrode/amplifier and on the bottom left is a pair of silver/silver chlorides electrodes.

2.5. Accelerometers

An ADXL210E accelerometer (Analog Devices, Leeds, United Kingdom) was used. This is a very small two-axis accelerometer with mounted on an integrated circuit with its associated amplifiers. The total dimension of the chip was 5 mm x 5 mm x 2 mm. Its operating range was ± 10g. It is robust and it can survive a transient shock of 1000g. It is designed to measure both dynamic accelerations e.g. vibration as well as static acceleration e.g. gravity. The manufactures specification sheet reports an interaction between the two axes of at most 2%. The accelerometer was supplied with a DC excitation voltage of 4.5 volts. The output from each channel was connected to the Neurolog system NL 106 AC/DC amplifier with gain x10 to remove offset DC before being digitised by the CED 1401. The output of both accelerometer channels after amplification was 80 millivolts equal to 1 metre/second/second.

2.6. Digitisation

All signals were digitised by CED 1401 Micro II interface (CED Ltd; Cambridge, England). The EMG and acceleration signals were digitised at 1024 Hz and stored in a PC. Spike 2 software, version 3.15, was used to process the signals.

2.7. Recording Protocol

During a typical experiment recording session, the subject was asked to hold a fixed position or make small movements for a period whilst the EMG and accelerometer outputs were recorded simultaneously. These recording episodes lasted 20-60 seconds. In general several short episodes were recorded close together of 4 periods

of 20 seconds. There was then an interval of up to 15 minutes before a subsequent recording episode. Figures 2.3a/b show typical recordings.

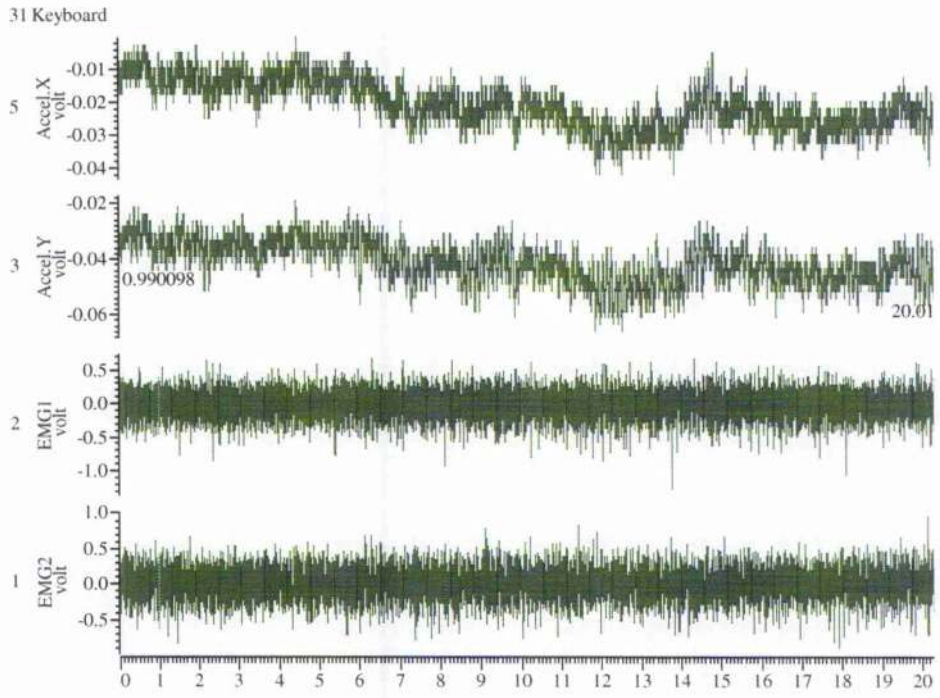


Figure 2.3.a. Specimen recording hand tremor at rest in normal subject for a period of 20 seconds.

These data were recorded in a neurologically normal volunteer. The top two traces show the output signals of the accelerometer. Accel X: shows acceleration in the x- plane. This is the lateral/medial plane. Accel Y: shows acceleration in the y-plane. This is the anterior/ posterior plane.

The lower two traces show the surface electromyograms. EMG1: electromyogram is recorded from Extensor Carpi Radialis muscles forearm extensor muscles group. EMG2: electromyogram is recorded from Flexor carpi Radialis muscles. Forearm flexor group.

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

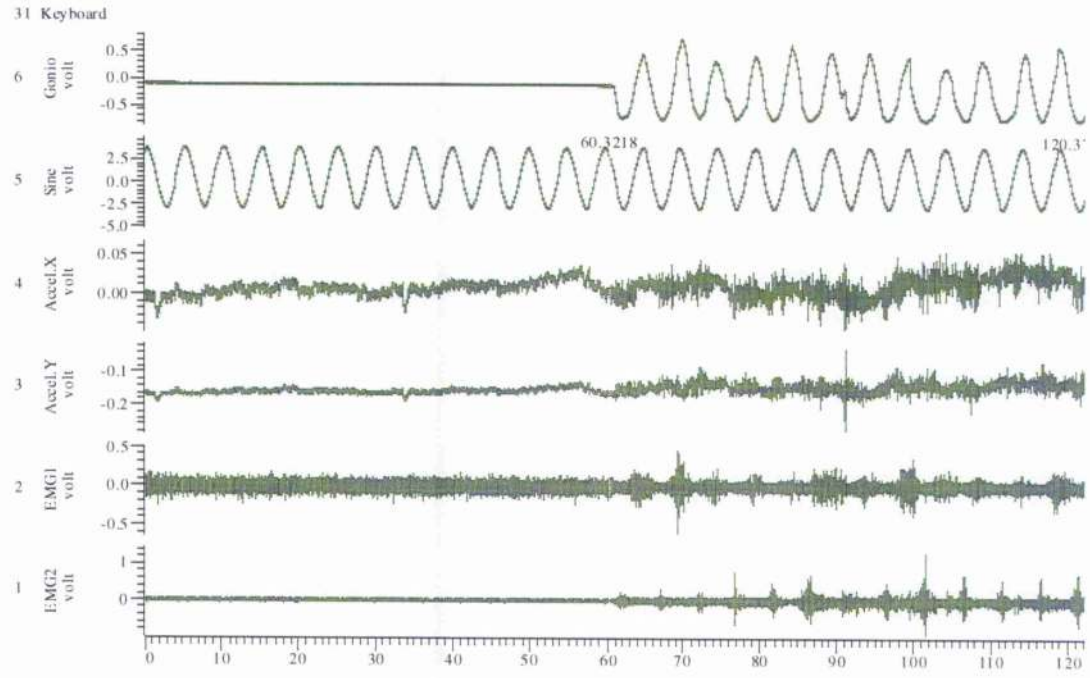


Figure 2.3.b. Recordings of hand tremor from a normal subject over a period of 2 minutes.

The volunteer maintains a stationary position of the hand, supporting it against gravity for the first 60 seconds and then the volunteer tracks a sine wave. The top two traces wave show:

Gonio : channel 6 illustrates the movement of flexion-extension by goniometer. The initial 60 seconds shows the wrist in a neutral position at 180 degrees. It is then followed by flexion of 40 degrees and then to 30 degrees of extension.

Sine: sine wave in channel 5 is a guide to control movement of the volunteer.

The peak-peak magnitude of the movement is from neutral position of the hand to full flexion of the wrist and extension to the neutral position.

Channels 1-4 are as described in figure 2.3a. The lower traces show the surface electromyogram. EMG1 is recorded from forearm extensor and EMG2 is recorded from forearm flexor group muscles.

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

2.8. Analysis

Interesting sections of each data were identified using vertical cursors. Spike 2 was then used to calculate a power spectrum from this section of the trace.

2.8.1. Accelerometer power spectrum analysis

Power spectra based on 1024 points were calculated. A typical example is shown in figure 2.4. The energy concentration in three defined frequency ranges were measured. These were 2-6 Hz, 6-12 Hz and 12-20 Hz. The area of the spectra to be measured were specified with 4 cursors. The area of the spectrum between each cursor were measured. The data was transferred to text file and subsequently saved as Excel files.

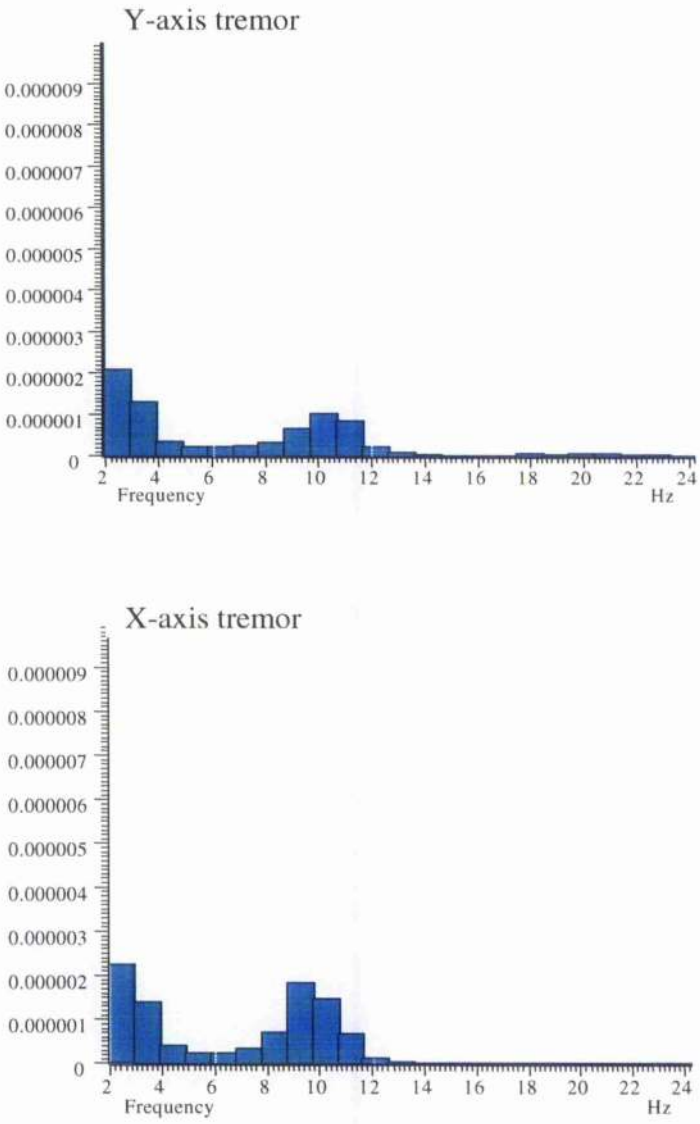


Figure 2.4. Typical spectra for postural tremor in a normal volunteer.

The top panel shows the spectrum of y-axis tremor in the flexion/extension plane and the lower panel shows x-axis tremor in the medial/lateral plane. They were recorded at the same time.

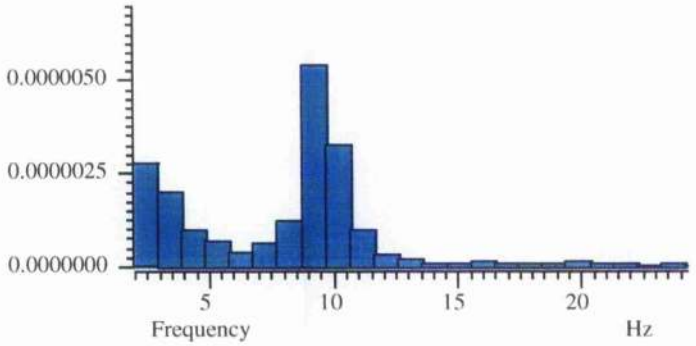
The tremor energy is expressed as volts^2.

Windowing of data

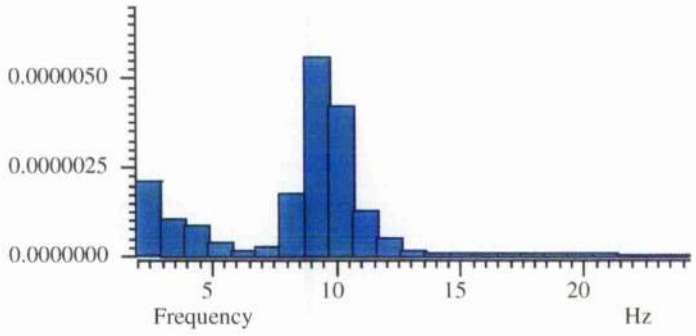
The experiments were performed over a period of two years. The data in chapter 3 were recorded and processed using spike 2, version 3.15. The data in chapters 4 and 5 were recorded and processed in spike 2 version 5.03. The later version allows windowing of the data. This improves the resolution of the spectra and the author wished to investigate how windowing might affect the data in chapter 3.

A brief comparison of data was made without any widowing and with Hanning or Hamming windowing. The results of the same data processed without and with windowing are shown in figure 2.5. These show that the effects of windowing are relatively minor in this case and that the simpler data processing in chapter 3 did not degrade the spectra significantly.

No window



Hanning



Hamming

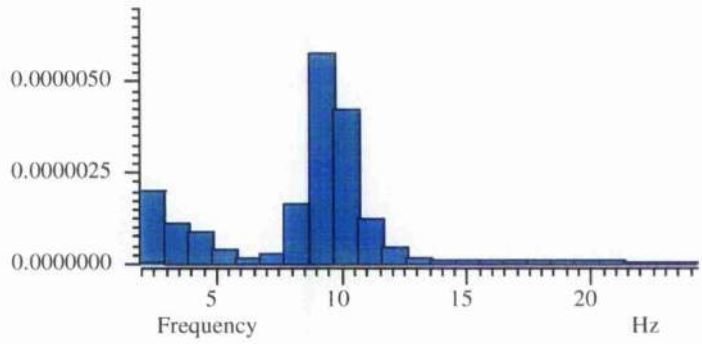


Figure 2.5. Windowing of data.

This shows a frequency spectrum of y axis (flexion/extension) tremor at rest in one normal subject calculated without windowing the data in on the top panel, with a Hanning window in the middle panel and with a Hamming window in the bottom panel.
The tremor energy is expressed as volts^2.
It shows no significant difference in the spectra.

2.8.2. EMG Analysis

The EMG signals recorded in these experiments were typically low amplitude. They were subjected to a bandstop digital filter centred at 50 Hz with a filter width transition gap of 7.4 Hz. Whilst this was successful in removing the contribution of the mains frequency artefact to the EMG signal it also removed part of the EMG spectrum. The filtering had a significant effect on the EMG signal. If the filter was not used the low level EMG would be distorted by the 50 Hz component contributed by the mains supply. It was considered best to filter the signals and then compare all the signals after they had been processed in the same way.

The root mean square value of the EMG signal after filtering was calculated using Spike 2. These data were transferred to text files and ultimately saved as Excel files.

2.9. Statistical analysis

The advice of the Robertson Centre for Biostatistics at Glasgow University was sought and followed.

Various features of the electromyogram and accelerometer signals were measured. For each volunteer several the features were measured: for example, the RMS EMG or area within a frequency range of the tremor spectrum and the mean of the four episodes was calculated. After two visits to the laboratory each volunteer then had a mean value for that feature in the two experimental conditions. The difference in the two means was calculated for all volunteers and this allowed a confidence interval of the mean difference to be calculated. The result was deemed to be significant if the 95% confidence interval did not include zero.

2.10. Application of sprays to the skin

2.10.1. Xylocaine

A spray of 10% Xylocaine, manufactured by Astra Zeneca UK Ltd., was used. This Xylocaine spray contains ethanol, methanol natural, polyethylene glycol 400, essence of banana, saccharin and purified water. It was applied to the skin of the upper limb (all of the arm and forearm except for extensor forearm and the hand). After spraying a little massage made sure the whole area was covered.

2.10.2. Placebo

A placebo spray was made up to match the colour, viscosity and packaging of the Xylocaine spray. It was applied to the same skin areas, as the Xylocaine with the same technique.

The volunteers were unaware as to whether a Xylocaine or a placebo spray had been applied to their skin.

2.11. Electrogoniometer Recording

In the experiments described in chapter 4 the volunteers were asked to make sinusoidal movements of their wrist. A sinusoid was displayed to the volunteer on an oscilloscope screen and they tracked this with their movement. This is illustrated in figure 2.3b. A Feedback PFG605 Function Generator (Electroplan, Royston, UK) was used to generate low frequency sinusoidal signals at 0.1 – 0.5 Hz. These were

displayed on an oscilloscope to allow the volunteer to control the speed of movement at the wrist. The output of the function generator was also digitised and stored.

The wrist movement was detected by a twin axis goniometer (SG65 Biometrics Ltd., Gwent, UK), which was taped to the dorsum of the hand. The distal end block to the dorsal surface over the third metacarpal was measured with the centre axis of hand. The proximal end block was placed distally on the dorsal forearm near the wrist. Only one axis was used to track the movement. The goniometer measured a range of angular movement of $\pm$ 60 degrees. It weighed 15 grams and did not interfere with the free movement of the wrist. The goniometer signal was amplified and its output was digitised at 100 Hz by the CED 1401.

Chapter 3

Effect of xylocaine on postural tremor in the hand

3.1 Introduction

Topical anaesthesia of areas of skin covering the upper and lower limbs has been used successfully to enhance the rehabilitation of patients affected with stroke, head injury and familial spino-cerebellar degeneration (Sabbahi, 1987). The active and passive range of movement of the upper and lower limb joints showed a substantial increase after anaesthesia (Sabbahi, Roy, De Luca and Van Volkinburg, 1984). The speed and range of movement of upper limbs during reaching, raising the arm above the head, abduction, flexion movements of the arm and handling tasks all improved after topical anaesthesia. In the lower limbs, the range of movement at the ankle and knee also improved after topical anaesthesia (Sabbahi, De Luca and Powers, 1981). Patients without soft tissue contractures showed a greater increase in the active range of movement after anaesthesia. In addition, there was improvement in the gait of hemiparetic patients and several patients went on to walk without canes (Sabbahi, De Luca and Johnson, 1982). The authors reported that the extent of functional improvement during the treatment programme varied. Furthermore, patients with normal cutaneous sensation to superficial touch showed more variable responses following topical anaesthesia. The action of the local anaesthetic is thought to be confined to the skin. Sabbahi and De Luca (1982) did not find any trace of local anaesthetic in the bloodstream during their experiments.

Topical application of local anaesthetic to most areas of skin of the lower limb has been shown to reduce significantly the amplitude of physiological action tremor at the ankle and pathological clonus (Pozos, Mills and Iaizzo, 1984; Mills and Pozos, 1985). The one exception to this is that topical anaesthesia of the skin over anterior tibialis had no effect on ankle tremor (Pozos et al., 1984).

Topical anaesthesia has also been studied as an adjunct to treatment with propanolol for the suppression of essential tremor on hand tremor (Pozos and Iaizzo 1992). The combined treatment significantly reduced the amplitudes of tremor accelerations and electromyograms.

The present study was designed to investigate the effect of topical anaesthesia by 10% xylocaine on physiological tremor of the hand in normal subjects.

3.2 Aims

The aims of the study were:

1. To investigate the frequency spectrum of hand accelerations before and after application of topical anaesthesia.

2. To investigate the surface electromyogram of flexor and extensor muscle groups in the forearm before and after application of topical anaesthesia.

3. To investigate if the tremor changes are associated with changes of muscle activation.

3.3 Methods and Materials

3.3.1 Volunteers

Nineteen adult volunteers, both male and female, participated in these experiments. They had no history of neurological disease or muscular disorders. Their mean age was 28 years. All subjects gave their informed consent in accordance with the protocol approved by the Glasgow University Research Ethics Committee. They were free to withdraw from the experiment at any stage. None of the subjects withdrew from the experiments. They did not report any kind of discomfort during the tests. Each volunteer made two visits to the laboratory. Each visit lasted approximately one hour. The nature of the experiment was explained during the first visit and informed consent was obtained. The volunteer then participated in the first recording session. This was done with either a local anaesthetic or a placebo spray applied to their skin. On the second visit the other spray was used. The sequence of placebo or local anaesthetic was randomised by asking each volunteer to select a sealed envelope containing the sequence of sprays.

3.3.2 Experimental set up

The general experimental set up was described earlier in section 2.2 and shown in figure 2.1.

3.3.3 Position of forearm

The subject's forearm was extended horizontally in the prone position and supported by a frame. The fingers, hand and wrist joint were free to move.

3.3.4 Position of EMGs recording electrodes

In this experiment two small skins mounted EMG amplifiers with integrated electrodes were used. These are shown in figure 2.2. One amplifier was placed on the posterior forearm over Extensor Carpi Radialis some 2-3 cm below the elbow joint space. A second EMG amplifier was placed over the Flexor Carpi Radialis. The position of recording amplifiers is shown in figure 2.1. of the General Methods chapter.

3.3.5 Recording Protocol

The subject extended their right hand horizontally in the prone position. The forearm was supported except for the hand. The wrist joint was free to move. The tremor was recorded in four episodes each lasting 20 seconds. Surface electromyograms and x-axis (lateral/medial deviation of hand) and y-axis (flexion/extension of hand) acceleration were recorded simultaneously. Typical recording episodes are shown in figure 3.1.

3.3.6 Power spectra at rest

Figure 3.2 shows power spectra for one volunteer. They were calculated from a 20-second recording taken 30 minutes after the application of xylocaine spray (right panel) or placebo spray (left panels). The upper pair of spectra shows the spectra of y-axis tremor and the lower pair shows x-axis tremor. All of the spectra show a peak at about 10 Hz but the magnitude of this is different in each case.

3.4 Results

The mean energy in each frequency range was calculated as described in figure 3.3. The difference in means was calculated for each person. The difference in mean for all nineteen volunteers was then used to calculate a confidence interval. The staff of the Robertson Centre for Biostatistics recommended this method of analysis. In summary, if the confidence interval contains zero, there are no significant differences between the effects of the placebo and the local anaesthetic.

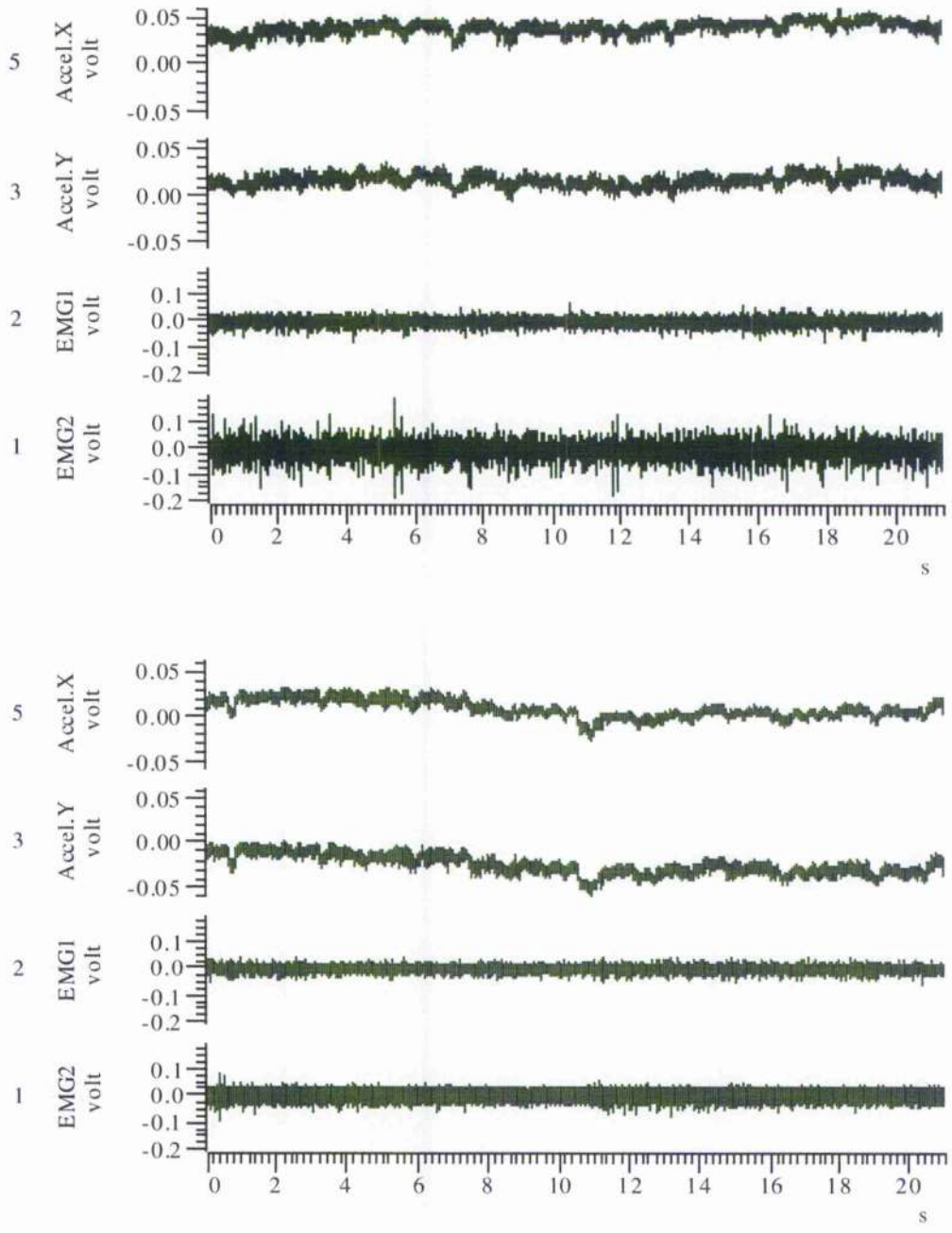


Figure 3.1. Recordings for 20 seconds of postural tremor of the hand tremor in normal subject.

The top panel was recording 30 minutes after application of xylocaine spray. The lower panel was 30 minutes after the application of the placebo spray. The panel shows recordings of surface EMG from Extensor Carpi Radialis (EMG1) and Flexor Carpi Radialis (EMG2) and tremor in a lateral /medial plane (Accel X) and anterior posterior plane (Accel Y).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

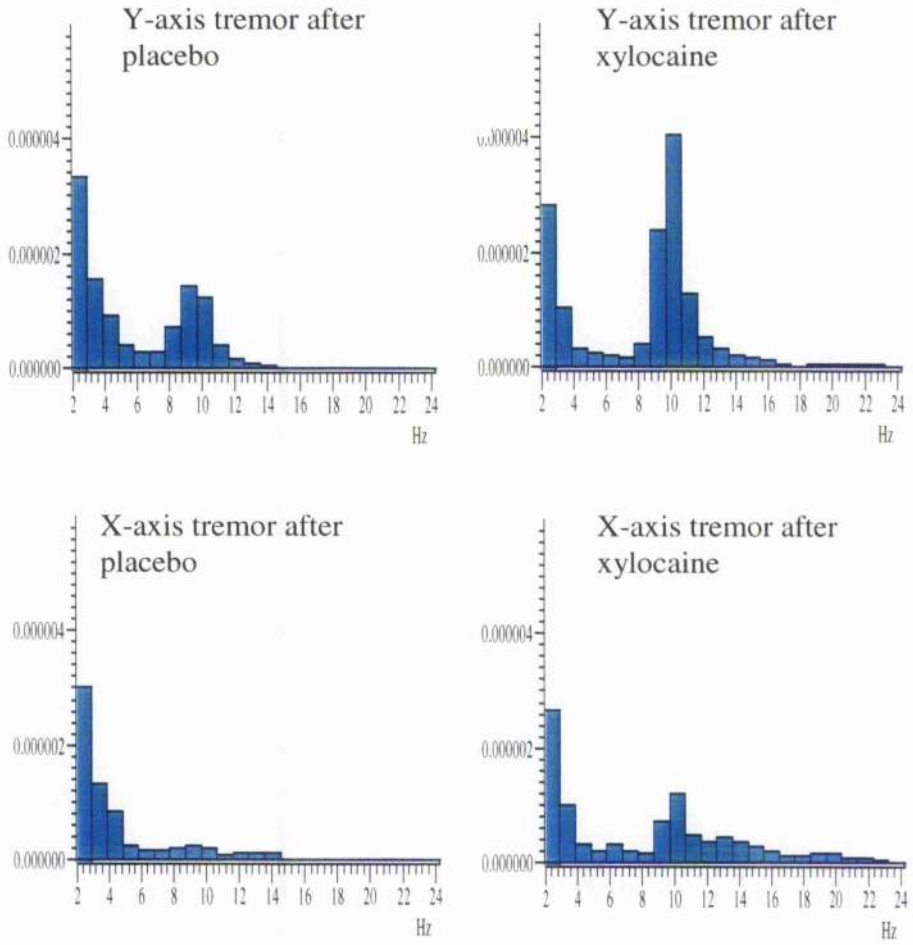


Figure 3.2. Power spectra for x and y-axis tremor in normal subject at rest.

The left panels show results obtained 30 minutes after the application of the placebo. The right panels shows results obtained 30 minutes after application of a 10% xylocaine spray.

Y-axis is flexion/extension tremor and X-axis medial/ lateral tremor. Power spectra based on 1024 points were calculated for 20 seconds data samples.

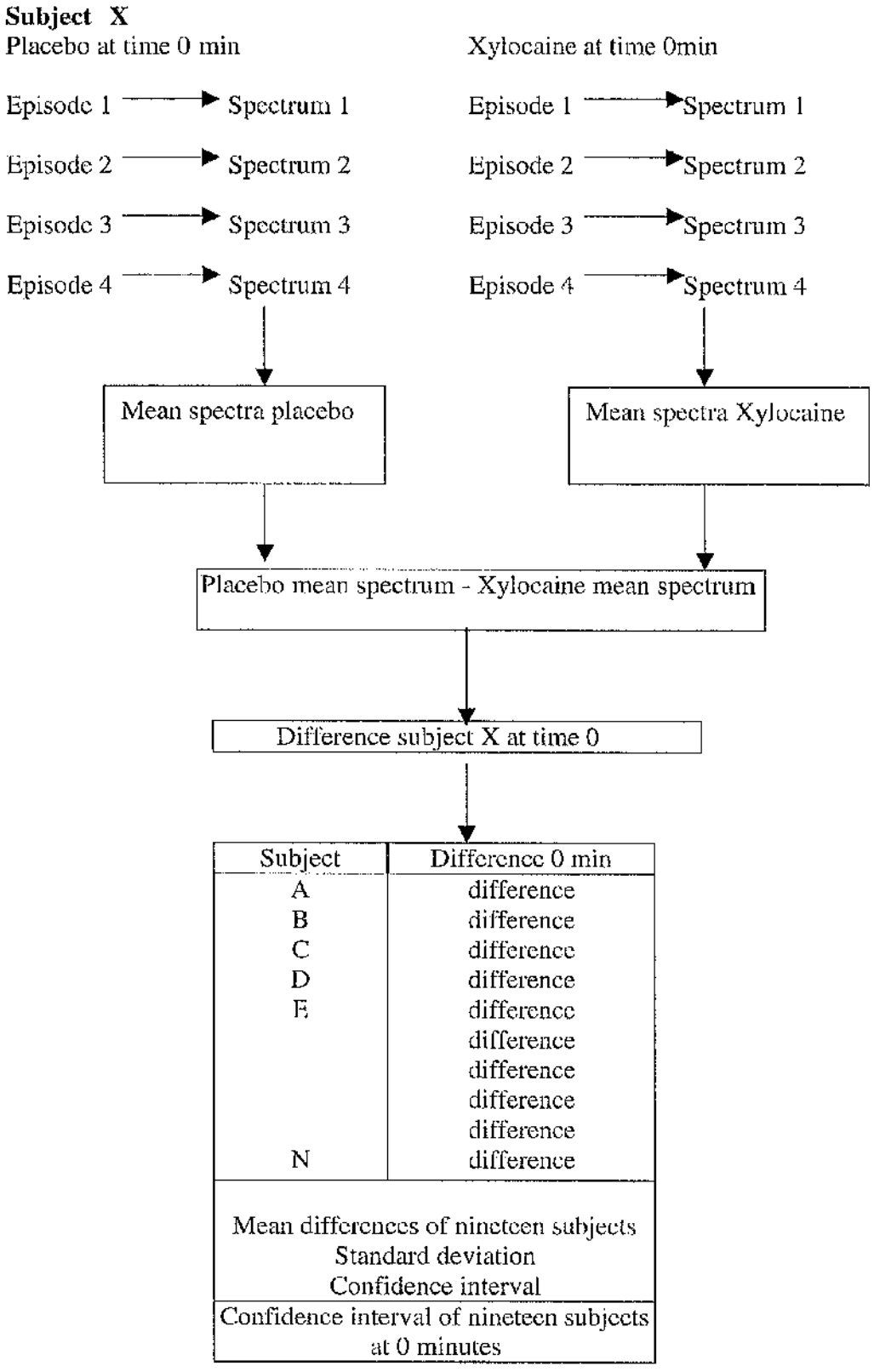


Figure 3.3. The calculation of confidence intervals.

3.4.1 Y-axis tremor after the application of xylocaine or placebo sprays

Table 3.1 contains a summary of the mean differences of y-axis tremor spectra (placebo - xylocaine) and confidence intervals. A separate set of data is shown for each of the three frequency bands studied, 2-6 Hz, 6-12 Hz, and 12-20 Hz. An analysis is also shown for the whole tremor band 2-20 Hz.

The top panel in table 3.1 shows the mean differences in y-axis tremor at the start of the two experiments. This is before the application of the placebo or xylocaine spray. No significant difference is observed. This is an encouraging finding since it means that resting tremor must have been similar in the volunteers on the two days of testing.

However, the subsequent measurements at 15, 30, 45 and 60 minute intervals after the application of the spray also show no significant differences. The mean differences are consistently negative in all frequency bands between 15 and 60 minutes, except for the 2-6 Hz band at 30 minutes. Given the way the mean difference is calculated, this must mean that the tremor contained more energy after the xylocaine spray than after the placebo spray. Even with this consistent small change the result did not achieve statistical significance.

Time	Frequency Band	Mean Difference	Confidence Interval		
0 min	2-6 Hz	0.35	-0.22	0.91	ns
	6-12 Hz	0.00	-2.02	2.01	ns
	12-20 Hz	0.07	-0.02	0.16	ns
	2-20 Hz	0.42	-2.25	3.08	ns
15 min	2-6 Hz	-0.14	-1.22	0.94	ns
	6-12 Hz	-1.06	-3.19	1.08	ns
	12-20 Hz	-0.11	-0.28	0.07	ns
	2-20 Hz	-1.30	-4.69	2.08	ns
30 min	2-6 Hz	0.59	-0.39	1.57	ns
	6-12 Hz	-0.66	-2.24	0.91	ns
	12-20 Hz	-0.08	-0.19	0.03	ns
	2-20 Hz	-0.15	-2.82	2.51	ns
45 min	2-6 Hz	-0.03	-1.03	0.97	ns
	6-12 Hz	-0.12	-1.18	0.95	ns
	12-20 Hz	-0.09	-0.22	0.05	ns
	2-20 Hz	-0.23	-2.43	1.97	ns
60 min	2-6 Hz	-0.47	-1.33	0.38	ns
	6-12 Hz	-0.97	-2.31	0.37	ns
	12-20 Hz	-0.32	-0.71	0.07	ns
	2-20 Hz	-1.76	-4.35	0.82	ns

Table 3.1. The mean differences between y-axis tremor spectra (placebo -xylocaine) for nineteen volunteers.

Data are presented for four-frequency ranges and at intervals up to 60 minutes after application of the spray. The confidence intervals are also shows for each case. All the intervals contain zero and so it can be concluded that no significant difference exists between the application of xylocaine and the placebo.

Each value in the table is multiplied by 10^6 for clarity.

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	7.39	4.20	5.13	4.28	5.51
2	22.81	22.19	15.15	14.09	17.21
3	4.76	7.12	7.51	6.29	7.56
4	6.57	4.79	4.34	3.63	4.83
5	10.09	14.59	8.60	7.37	6.47
6	4.54	4.35	4.81	5.19	4.77
7	7.51	4.64	4.68	6.62	4.80
8	4.67	3.90	3.56	3.97	5.40
9	18.11	18.57	15.75	12.40	10.94
10	7.92	4.35	6.07	5.43	5.44
11	6.21	6.04	4.66	4.34	5.22
12	5.10	4.52	5.29	5.83	6.46
13	3.88	4.43	4.46	4.32	4.41
14	6.86	6.80	5.83	4.35	4.72
15	14.80	14.48	17.33	12.12	7.51
16	10.98	18.23	17.66	13.21	12.84
17	12.43	9.45	6.68	10.92	9.84
18	7.76	14.04	10.42	8.36	25.80
19	12.02	15.57	7.15	8.32	4.25

Table 3.2. Effect of topical anaesthesia on y-axis postural tremor for 19 subjects.

Tremor energy in the frequency range 2-20 Hz at intervals up to 60 minutes after application of xylocaine spray. Each value in the table has been multiplied by 10^6 for clarity.

Subjects 2, 9, 15, and 17 show high tremor energy before the xylocaine application Their tremor is subsequently reduced. Subjects 3, 16 and 18 have low initial tremor energy which increases after xylocaine application. However, it can concluded that there are no significant changes in tremor after xylocaine application ($P = 0.678$, ANOVA).

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	6.56	4.52	5.29	5.24	4.07
2	11.23	10.89	12.88	14.19	12.12
3	6.12	6.04	4.28	3.79	3.45
4	3.97	4.54	11.88	4.67	4.57
5	17.22	24.44	12.69	11.30	6.51
6	9.37	4.99	4.21	3.31	4.88
7	6.58	9.83	7.46	6.67	4.62
8	5.52	4.50	5.74	3.88	4.14
9	18.28	12.52	9.58	9.33	10.94
10	7.00	9.96	7.79	7.68	8.03
11	6.13	8.00	4.53	2.47	5.64
12	4.69	3.40	7.11	6.91	5.91
13	6.44	4.41	5.48	5.02	5.21
14	4.26	3.47	5.33	3.89	3.51
15	13.92	11.35	8.10	6.31	4.38
16	10.51	6.61	9.06	8.39	6.99
17	8.02	8.09	7.77	8.84	7.00
18	12.16	9.36	9.38	15.49	8.78
19	22.48	11.68	12.64	9.05	7.78

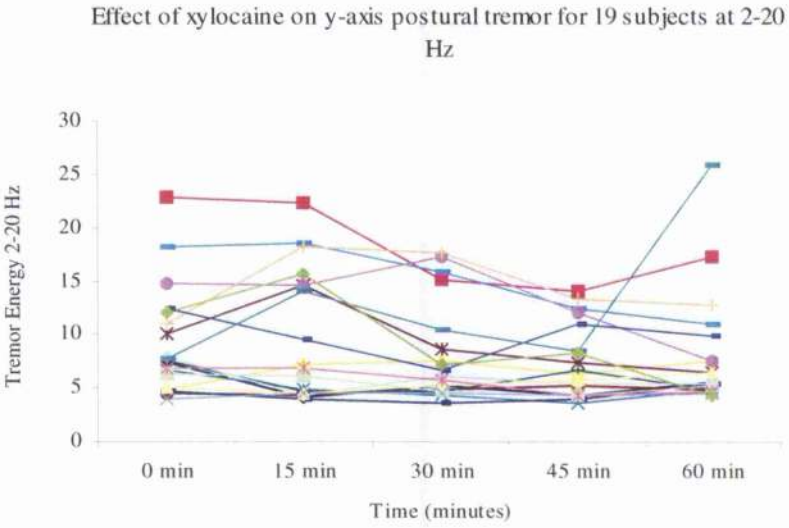
Table 3.3. Effect of placebo spray on y-axis postural tremor for 19 subjects.

Tremor energy in the frequency range 2-20 Hz at intervals up to 60 minutes after application of xylocaine spray. Each value in the table has been multiplied by 10^6 for clarity.

Subjects 19 shows a strong initial tremor which decreases after the placebo spray . Subjects 3 and 16 show low initial tremor which decreases further after placebo.

However, it can concluded that no significant changes in postural tremor occur after the application of the placebo spray (P = 0.134, ANOVA).

(A)



(B)

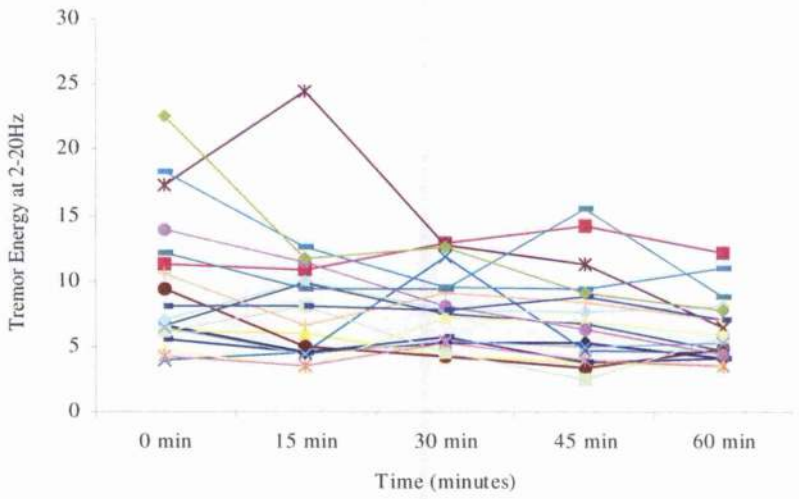


Figure 3.4a, b. Effects of xylocaine and placebo sprays on y-axis tremor energy in the frequency band 2-20 Hz.

The upper figure (A) shows effect of xylocaine on y-axis tremor in 19 volunteers. The lower figure (B) shows tremor after placebo spray in the same volunteers.

The volunteers with higher energy tremor shows reductions of tremor after the application of xylocaine or placebo sprays. The volunteers with lower energy tremor show less change after the xylocaine or placebo spray.

Table 3.4 shows the means and standard deviations of the resting Y-axis tremor energy in 19 neurologically normal volunteers. Data representing the tremor amplitude before and after the application of a placebo (P) or topical anaesthetic (TA) spray are presented. The table shows details of tremor in three frequency bands: 2-6 Hz, 6-12 Hz, 12-20 Hz and for the whole tremor band 2-20 Hz.

The Y-axis tremor energy was measured at five time points between 0 minute and 60 minutes after the application of the spray. Figure 3.5 shows graphs of these data. The top panel, figure 3.5A shows the mean Y-axis tremor for the 2-20 Hz band in each condition. The lower panel, figure 3.5B shows bar charts of the means and standard deviations.

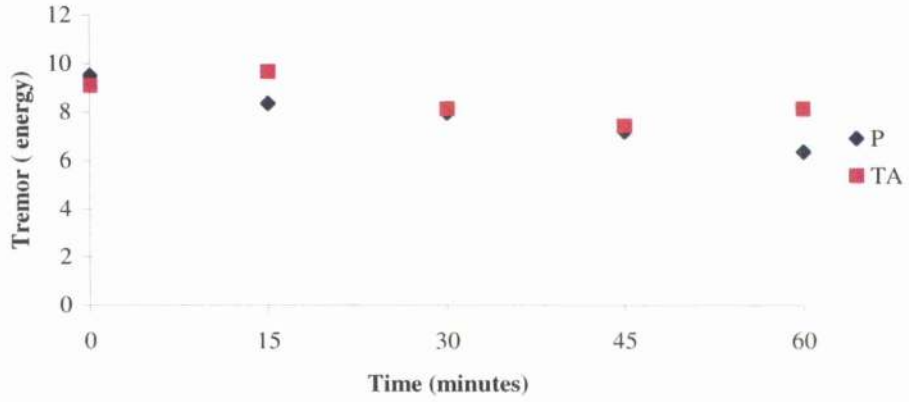
There was no statistically significant change in the tremor over the period of the experiment. The data were subjected to an ANOVA test using the General Linear Model in Minitab version 13. This gave values of $p = 0.679$ for the tremor after xylocaine application and $p = 0.134$ for the tremor after the placebo application.

Time	Frequency Band	Mean P	SD P	Mean TA	SD TA
0 min	2-6 Hz	4.26	1.29	3.91	1.11
	6-12 Hz	4.67	4.37	4.68	4.45
	12-20 Hz	0.57	0.38	0.50	0.32
	2-20 Hz	9.50	6.04	9.08	5.88
15 min	2-6 Hz	4.04	1.72	4.18	2.10
	6-12 Hz	3.92	4.39	4.98	5.31
	12-20 Hz	0.39	0.26	0.49	0.42
	2-20 Hz	8.35	6.37	9.65	7.83
30 min	2-6 Hz	4.47	2.11	3.88	1.26
	6-12 Hz	3.18	2.56	3.84	4.21
	12-20 Hz	0.30	0.10	0.39	0.30
	2-20 Hz	7.96	4.78	8.11	5.76
45 min	2-6 Hz	3.94	1.83	3.97	1.72
	6-12 Hz	2.94	2.41	3.05	2.85
	12-20 Hz	0.30	0.23	0.39	0.32
	2-20 Hz	7.18	4.47	7.41	4.90
60 min	2-6 Hz	3.66	1.49	4.13	1.49
	6-12 Hz	2.42	1.57	3.39	3.98
	12-20 Hz	0.26	0.16	0.58	0.89
	2-20 Hz	6.34	3.22	8.10	6.36

Table 3.4. The mean and standard deviations of y-axis tremor energy after placebo and topical anaesthesia for nineteen volunteers.

Data are presented for four-frequency ranges and at intervals up to 60 minutes after the application of the spray. The main and standard deviations are also shows for each case. The top panel shows the mean and standard deviation in Y-axis tremor at rest tremor at the start of the two experimental sessions. This is before the application of sprays. The values are shows that not statistically significant change over the 5 periods of measurement when tested with an ANOVA ($P = 0.134$) at 2-20 Hz. The changes after xylocaine were also not significant ($P = 0.679$). Each value in the table has been multiplied by 10^6 for clarity.

(A)



(B)

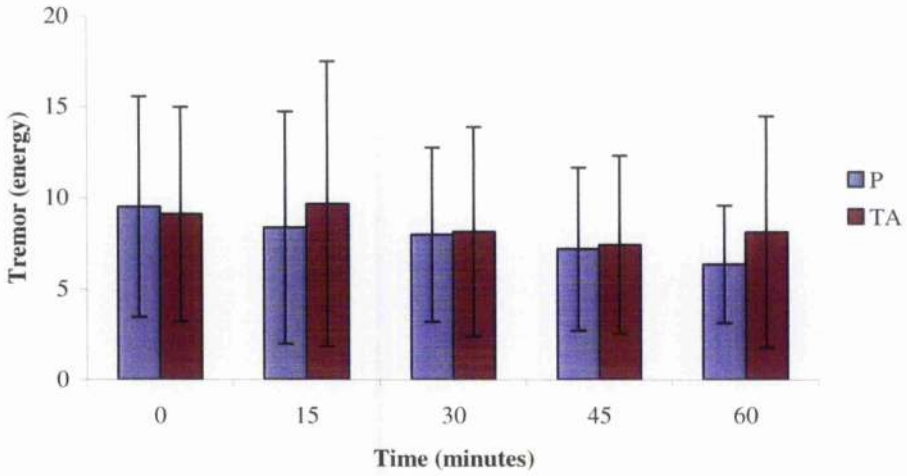


Figure 3.5. Mean and standard deviation of the y-axis postural tremor after application of either a placebo or a topical anaesthesia spray.

Data is shown for tremor energy in a frequency band of 2-20 Hz in nineteen subjects. The tremor energy is expressed as volts^2.

Panel A shows the mean values for the trials with xylocaine and placebo applications. Panel B shows a bar chart showing means and standard deviations.

There are no significant changes over the 60 minutes. See legend of table 3.4 for statistics.

3.4.2. X- axis tremor after the application of xylocaine or placebo sprays

The x-axis tremor was recorded from the same volunteers at the same time as the y-axis tremor. These acceleration signals were processed in the same way. The summary data are shown in table 3.5.

The result is very similar to that described previously for the y-axis tremor. The mean difference is not significant in any of the frequency bands at any of the times tested except for the 6-12 Hz band at 60 minutes. This is probably a chance observation. The mean differences are consistently negative, except for the lowest frequency band 2-6 Hz and 2-20 Hz at 30 minutes and at zero time in frequency band 2-6 Hz and 6-12 Hz. The only positive difference occurs at 30 minutes in the frequency band 2-6 Hz.

Time	Frequency Band	Mean Difference	Confidence interval		
0 min	2 - 6 Hz	0.12	-0.43	0.67	ns
	6 -12 Hz	0.01	-0.40	0.42	ns
	12 - 20 Hz	-0.22	-0.55	0.10	ns
	2 - 20 Hz	-0.09	-1.78	1.19	ns
15 min	2 - 6 Hz	-0.19	-1.04	0.66	ns
	6 -12 Hz	-0.40	-0.92	0.11	ns
	12 - 20 Hz	-0.19	-0.38	0.01	ns
	2 - 20 Hz	-0.78	-2.34	0.78	ns
30 min	2 - 6 Hz	0.33	-0.70	1.36	ns
	6 -12 Hz	-0.19	-0.71	0.33	ns
	12 - 20 Hz	-0.06	-0.35	0.23	ns
	2 - 20 Hz	0.08	-1.76	1.92	ns
45 min	2 - 6 Hz	-0.29	-1.25	0.66	ns
	6 -12 Hz	-0.14	-0.41	0.12	ns
	12 - 20 Hz	-0.04	-0.15	0.06	ns
	2 - 20 Hz	-0.48	-1.81	0.85	ns
60 min	2 - 6 Hz	-0.60	-1.39	0.20	ns
	6 -12 Hz	-0.39	-0.76	-0.01	s
	12 - 20 Hz	-0.09	-0.26	0.08	ns
	2 - 20 Hz	-1.07	-2.41	0.27	ns

Table 3.5 The mean differences between x-axis tremor spectra (placebo-xylocaine) for nineteen volunteers.

Data are presented for four-frequency ranges and at intervals up to 60 minutes after the application of the sprays. The confidence intervals are also shown for each case. All the intervals contain zero except for 60 minutes at 6-12 Hz.

It can be concluded that no significant difference exists between the application of xylocaine and the placebo. Each value in the table has been multiplied by 10^6 for clarity.

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	5.45	3.39	4.56	3.62	5.11
2	11.63	10.55	9.33	11.10	5.97
3	3.65	6.14	6.76	5.59	6.29
4	5.85	4.21	3.52	4.71	4.37
5	7.85	9.29	6.07	5.91	6.83
6	4.36	3.64	3.93	4.56	4.02
7	5.44	3.60	4.01	5.40	3.55
8	5.15	4.93	4.06	4.50	5.23
9	8.74	9.90	9.75	8.68	9.03
10	5.55	5.85	5.18	4.09	5.74
11	5.15	4.99	3.88	4.05	4.51
12	9.75	10.15	9.63	9.10	13.47
13	4.62	4.45	4.45	4.66	3.88
14	4.41	5.92	5.64	3.95	4.46
15	10.38	12.82	10.11	6.67	6.89
16	5.04	4.55	6.44	3.82	4.80
17	7.94	7.08	5.02	8.02	6.75
18	5.78	4.04	4.66	3.40	3.97
19	6.70	6.80	7.13	7.72	3.01

Table 3.6. The effects of topical anaesthesia on x-axis postural tremor for 19 subjects.

Data presented the frequency range 2-20 Hz and at interval of up to 60 minutes after application of xylocaine spray. Each value in the table has been multiplied by 10^6 for clarity.

There is no significant change in x axis postural tremor after the xylocaine spray ($P = 0.753$, ANOVA).

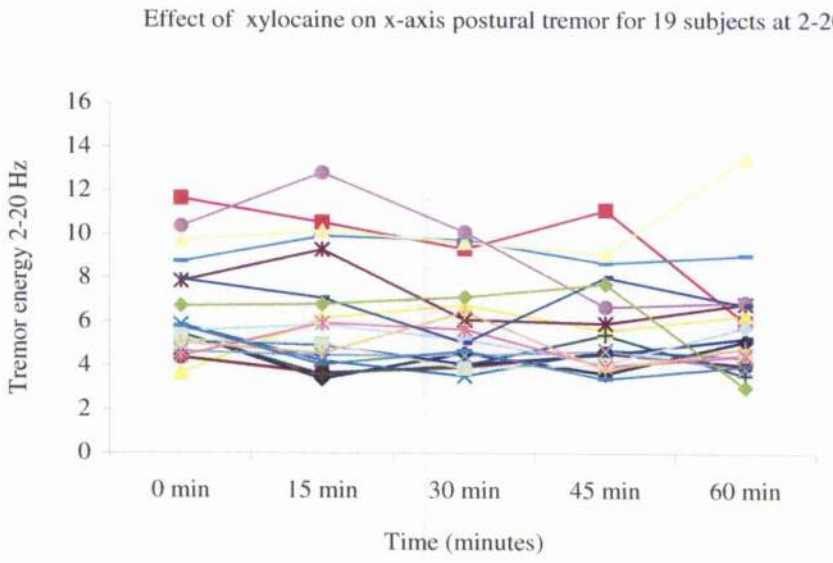
No. Subjects	0 min	15 min	30 min	45 min	60 min
1	5.38	3.81	4.20	4.34	3.27
2	8.17	7.00	9.48	9.13	8.32
3	4.39	3.33	4.93	3.49	3.25
4	3.00	3.89	10.97	4.10	3.57
5	8.31	9.28	4.15	5.79	4.84
6	5.30	4.05	3.57	2.80	3.84
7	5.21	6.64	5.43	3.91	3.83
8	6.81	5.18	6.73	3.84	4.40
9	9.35	9.85	6.81	7.24	7.67
10	6.15	9.17	10.49	7.35	6.80
11	4.65	6.59	3.92	2.10	4.55
12	10.94	10.04	7.80	10.14	8.48
13	6.01	4.23	5.11	4.56	4.86
14	3.96	3.34	4.48	3.44	3.46
15	7.57	7.47	7.95	6.45	3.83
16	6.37	4.68	6.29	5.63	4.17
17	6.49	4.63	4.75	4.05	3.39
18	4.46	4.50	4.10	8.26	4.41
19	11.84	6.99	8.23	6.77	4.88

Table 3.7. The effects of placebo spray on x-axis postural tremor for 19 subjects.

Data presented the frequency range 2-20 Hz and at interval up to 60 minutes after application of xylocaine spray. Each value in the table has been multiplied by $10^{\wedge 6}$ for clarity.

There are no significant changes in postural tremor after the application of the placebo ($P = 0.118$, ANOVA).

(A)



(B)

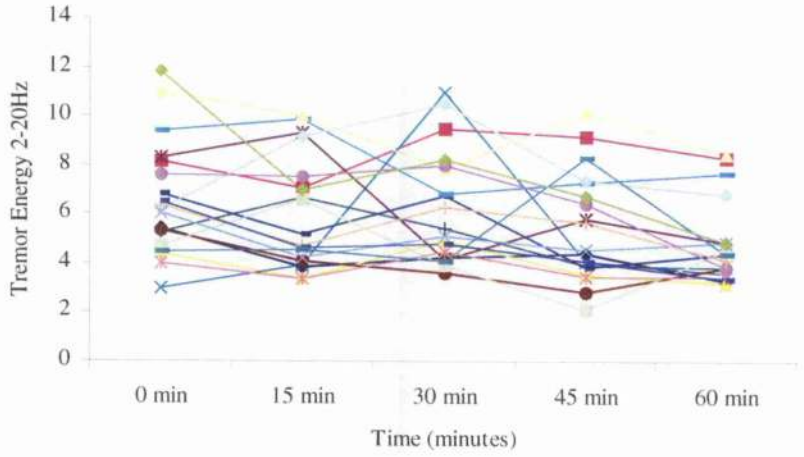


Figure 3.6a, b. Effects of xylocaine and placebo spray on x- axis tremor at frequency 2-20 Hz

The upper figure (A) shows effect of xylocaine on x-axis tremor. The lower figure (B) shows tremor after placebo spray.

Some subjects with higher tremor energies show reduction tremor after the application of xylocaine or placebo spray. Those with lower initial tremor shows no changes after the xylocaine or placebo.

Table 3.8 shows the mean and standard deviations of the X-axis postural tremor energy in the same volunteers. These data were recorded concurrently in the same sessions. The structure of the table is similar to 3.2.

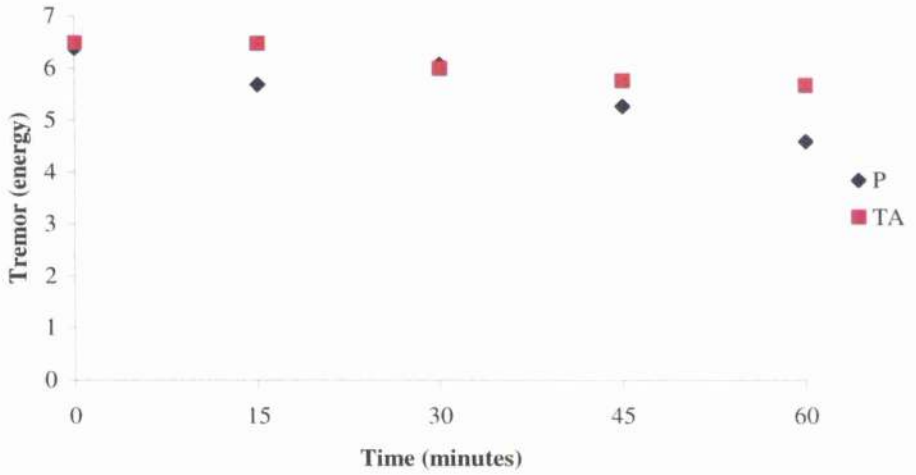
The data in the top panel in table 3.4 confirm that the X-axis tremor at rest is the same as at the start of the two experimental sessions. The lower panels show the tremor characteristics at 15 to 60 minute interval after the application of the sprays. There is no significant change in the tremor characteristics in 2-20 Hz band over this time after xylocaine ($P = 0.753$). The changes after placebo application were also not significant ($P = 0.118$). Figure 3.7 shows graphs of these data. The top panel, figure 3.7A, shows the mean X-axis tremor for the 2-20 Hz band in each condition. The lower panel, figure 3.7B, shows bar charts of the means and standard deviations. It is clear that there are no significant differences.

Time	Frequency Band	Mean P	SD P	Mean TA	SD TA
0 min	2-6 Hz	3.74	1.03	3.62	0.76
	6-12 Hz	1.85	1.34	1.84	1.35
	12-20 Hz	0.79	0.71	1.01	1.08
	2-20 Hz	6.38	3.08	6.48	3.19
15 min	2-6 Hz	3.34	1.22	3.52	1.29
	6-12 Hz	1.69	1.47	2.10	2.09
	12-20 Hz	0.65	0.56	0.84	0.73
	2-20 Hz	5.68	3.25	6.46	4.11
30 min	2-6 Hz	3.92	2.04	3.59	1.19
	6-12 Hz	1.49	1.08	1.68	1.38
	12-20 Hz	0.65	0.54	0.71	0.69
	2-20 Hz	6.06	3.66	5.98	3.26
45 min	2-6 Hz	3.36	1.58	3.65	1.62
	6-12 Hz	1.34	0.84	1.48	0.91
	12-20 Hz	0.57	0.46	0.61	0.48
	2-20 Hz	5.26	2.88	5.75	3.00
60 min	2-6 Hz	2.95	1.18	3.54	1.14
	6-12 Hz	1.16	0.67	1.54	1.43
	12-20 Hz	0.48	0.37	0.57	0.62
	2-20 Hz	4.59	2.23	5.66	3.19

Table 3.8. The mean and standard deviation for placebo and topical anaesthesia in X-axis tremor spectra for nineteen volunteers.

Data are presented for four-frequency ranges and at intervals up to 60 minutes after application of the spray. The data in the top panel confirm that the X-axis tremor at rest is the same as at the start of the two experimental sessions. The lower panels show the tremor characteristics at 15 to 60 minute interval after the application of the sprays. In 2-20 Hz band frequency there is no significant change in the tremor characteristics after placebo over the 5 period of measurement when tested with an ANOVA ($P = 0.118$). The changes after xylocaine were also not significant ($P = 0.753$). Each value in the table has been multiplied by 10^6 for clarity.

(A)



(B)

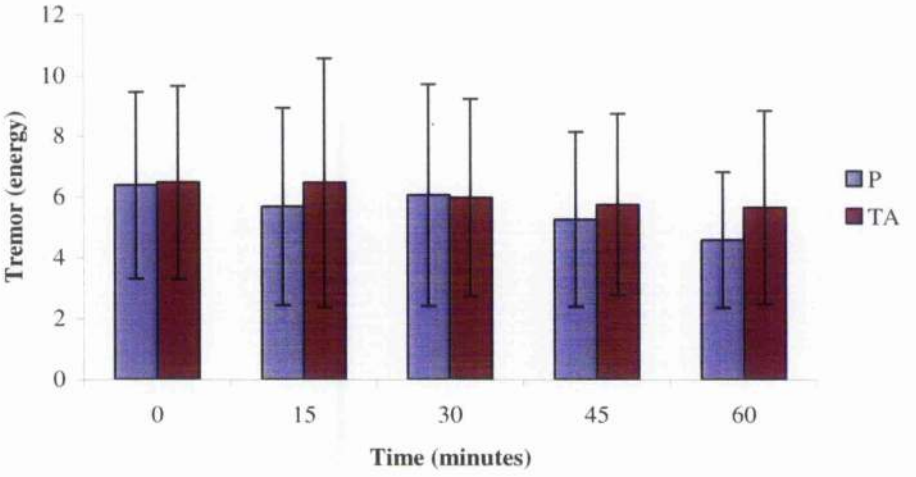


Figure 3.7 Mean and standard deviation of the x-axis resting tremor after application of either a placebo or a topical anaesthetic spray.

Data is shown for tremor energy in a frequency band of 2-20 Hz in nineteen subjects. The tremor energy is expressed as volts^2.
Panel A shows the mean values for the trials with xylocaine and placebo applications. Panel B shows a bar chart showing means and standard deviations.

It shows no difference before or after application of either xylocaine or placebo. See the legend of table 3.4 for statistics.

3.5.1. Effect of xylocaine and placebo sprays on the extensor electromyogram

Surface electromyograms were recorded from wrist flexor and extensor groups at the same time as the tremor recordings. The electromyograms were filtered to remove 50 Hz noise and then the root mean square value of the residual signal was calculated. The mean differences of RMS electromyogram in the two conditions, after the placebo and after the xylocaine sprays, were calculated. The analysis was identical to that used for the acceleration signals in tables 3.1 and 3.5.

The top panel in table 3.9 shows the mean differences in the RMS electromyogram of the extensor muscles of the forearm at the start of the two experiments. This is before the application of the placebo spray or the xylocaine spray. In this case, the mean difference is negative and the confidence interval does not contain zero. It can be concluded that the RMS value is significantly greater before the application of xylocaine than before the application of the placebo spray.

A significant difference also occurs 30 minutes into the experiment. The RMS value is greater after the application of the placebo spray. However, no significant differences exist at 15, 45 or 60 minutes after the application.

3.5.2. Effect of the xylocaine and placebo sprays on the flexor electromyogram

The flexor electromyogram was recorded from the same volunteers at the same time as extensor group electromyogram and the tremor. Table 3.10 shows the mean difference in RMS electromyogram for the flexor muscles. In this case no significant differences were recorded at any of the times after the application of the spray.

Time	Mean difference	Confidence	Interval	
0 min	-0.002	-0.004	-9.98E-05	s
15 min	-0.001	-0.003	0.001	ns
30 min	-0.002	-0.003	-0.001	s
45 min	-0.002	-0.004	0.0003	ns
60 min	-0.001	-0.003	0.001	ns

Table 3.9. The mean difference in RMS EMG of the wrist extensor muscles after placebo and xylocaine application.

The confidence intervals are also shown.

Time	Mean difference	Confidence Interval		
0 min	-0.003	-0.007	0.002	ns
15 min	-0.001	-0.003	0.002	ns
30 min	-0.001	-0.003	0.0002	ns
45 min	0.001	-0.001	0.002	ns
60 min	0.002	-0.0002	0.004	ns

Table 3.10. The mean difference in RMS EMG of the wrist flexor muscles after placebo and xylocaine application.

The confidence intervals are also shown.

3.6. Discussion

These experiments investigated postural physiological tremor of the hands of nineteen normal subjects after the application of a local anaesthetic spray or a placebo spray to the skin. The main finding is that there is no significant difference in hand tremor during the hour after the application of placebo and the xylocaine. Examination of the data in table 3.1 shows that no significant differences exist between y - axis tremor spectra after xylocaine and placebo applications in any frequency band at any time. Data in table 3.5 show that in 19 of the 20 tests the x-axis tremor is not significantly different after xylocaine or placebo application. The sole significant result in table 3.5 occurs at 60 minutes after the application in the frequency band 6-12 Hz. This is most probably a chance difference.

In both the y-axis and x-axis tremor the mean differences are more frequently negative than positive. In the 40 tests there are 8 positive differences and 31 negative differences. A positive difference indicates that the tremor is smaller after xylocaine than after the placebo. The negative differences suggest that tremor amplitude increases after the application of topical anaesthesia.

Overall the results here are in conflict with those in Pozos' studies (1985 and 1992). He reported reduction tremor after topical anaesthesia and this study found no change. Pozos and Iaizzo, (1992) investigated the effect of topical anaesthesia with 4% xylocaine including propranolol on six cases of essential tremor of the hand. They reported significant suppression of hand tremor and muscle activity. An earlier study by Pozos and Iaizzo, (1985) showed that topical anaesthesia reduced physiological action tremor at the ankle joint.

The difference in the result could lie in the selection criteria for the volunteers. Pozos investigated the effect of xylocaine on pathological tremor rather than on normal physiological tremor. Additionally the disparity between the results of this study and Pozos study, may lie in the different areas of skin anaesthetised. The Pozos experiments applied 4% xylocaine to the skin over the forearm flexor and extensor muscles. In the experiments reported here 10% xylocaine was applied to the whole arm except the posterior forearm. It can safely be assumed that 10% xylocaine is at least as effective as 4% xylocaine in producing topical anaesthesia. The experiments reported here anaesthetised a larger total area of forearm skin. Pozos did anaesthetise the posterior forearm skin

In addition, the RMS electromyograms of forearm extensors and flexors are shows in tables 3.9. and 3.10. Table 3.10 shows that here are no significant differences in the RMS electromyogram of the forearm flexor muscles. However, the RMS electromyograms of the extensor muscles do show significant differences. It can be seen from table 3.5 that all 5 mean differences are negative and that these reach significance twice; at the start of the experiment and at 30 minutes after application of the spray that could be relationship between EMG and tremor the extensor stiffness and mechanical causes of tremor. The negative difference indicates that the EMG is greater after the application of xylocaine than after the application of placebo.

Sabbahi, Mason and Gleeson (1985) studied the effect of topical anaesthesia of upper limb skin in normal subjects. They reported an increase in the H-reflex amplitude of the flexor muscles after topical anaesthesia. The results in this chapter do not show any difference in flexor electromyogram. However, the extensor electromyogram

does show some significant differences. These occur at the start of the experiment before any spray was applied and at after 30 minutes. These again are probably chance events and they do not relate to any significant changes in the tremors.

However, in the experiments reported here the posterior skin was not anaesthetised. The decision to avoid this area was based on the work of Sabbahi et al., 1985. They reported that anaesthesia of this area increased H reflexes in the forearm flexor muscles.

Chapter 4

Effect of xylocaine on tremor in the hand during movement

4.1. Introduction

The previous chapter described an investigation of the effect of xylocaine on physiological tremor at rest. Results were presented which showed no significant difference between the application of xylocaine and a placebo spray. This chapter will extend the study to investigate the effect of topical anaesthesia on tremor in normal volunteers during movement. The oscillations associated with voluntary movements can be 2-5 times greater than a physiological recording from the same limb (Pozos, Iaizzo and Petry, 1982 ; Iaizzo and Pozos, 1992). This phenomenon is easy to see in figure 2.3.b. The author wished to investigate the effect of topical skin anaesthesia in this larger amplitude movement related tremor.

It has been suggested that all tremors of man may have a common mechanism (Eke-Okoro, 1994). Voluntary movements may be associated with rhythmic neural activity in human motor cortex (Halliday, Conway, Farmer and Rosenberg, 1998). The B rhythm is one component of the cortical rhythms. It has a frequency range of 15-30 Hz. It is known that phasic voluntary movement is preceded by cortical desynchronization mostly in the B-frequency band between 10 and 13 Hz (Feige, Kristeva, Rossi, Pizzella and Rossini, 1996; Feige, 1999; Pfurtscheller, 1992;

Salmelin and Hari, 1994). The tremor associated with voluntary contractions is in the frequency range (4-12 Hz) and of large amplitude (Iaizzo and Pozos, 1992). Often more than one frequency component can be observed in power spectra. All these frequencies are associated with voluntary movements.

4.2 Aims

The experiments described in this chapter were performed to investigate the effect of topical anaesthesia and placebo application on tremor during movement. The aims of this study were to investigate frequency spectrum of hand acceleration during wrist movement before and after application of topical anaesthesia.

4.3 Methods and Materials

4.3.1 Volunteers

Twelve adult volunteers, with no history of neurological disease or muscular disorder, participated in these experiments. Two men and ten women were tested. Their mean age was 28 years. All subjects gave their informed consent in accordance with the protocol approved by the Glasgow University Research Ethics Committee. They were free to withdraw from the test at any stage. Subjects were tested at two sessions. Each session lasted about one hour.

4.3.2 Experimental set up

The general experimental set-up is shown in figure 4.1. A two-axis accelerometer was attached to the distal ends of the middle finger of the right hand. (See General

Methods section 2.5). The x and y axis tremor was digitised and stored on the PC as described in General Methods section 2.6. The spectra were calculated in the same manner as in the previous chapter.

4.3.3. Electrogoniometer Recordings

An electrogoniometer (SG65, Biometrics Ltd; Gwent, UK) was attached to the dorsum of the hand and to the lower part of the forearm to span the wrist. The volunteer was asked to make sinusoidal movements of their wrist. A sinusoid was displayed to the volunteer on an oscilloscope screen and they tracked this with their movement. A Feedback PFG605 Function Generator (Electroplan, Royston, UK) was used to generate low frequency sinusoidal signals at 0.1 - 0.5 Hz. These were displayed on an oscilloscope to allow the volunteer to control the speed of movement at the wrist. The output of the function generator was also digitised and stored. The goniometer signal was amplified and the CED 1401 digitised its output at 100 Hz.

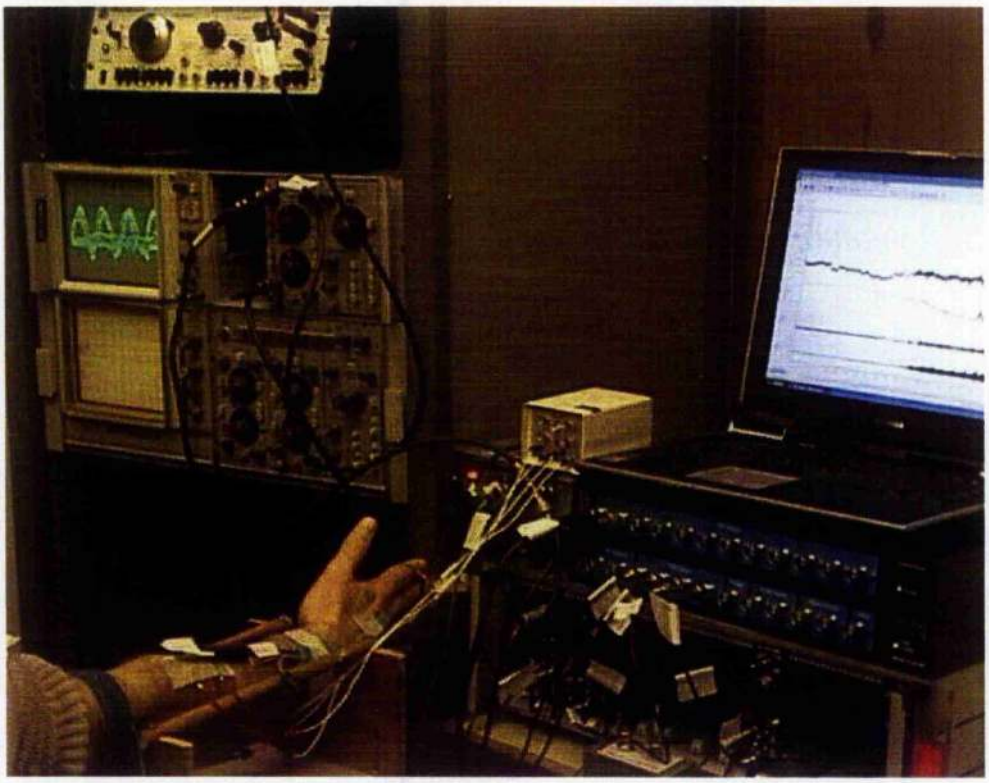


Figure 4.1. The general experimental set up.

The instruments included: a laptop computer and CED 1401 interface unit, a Neurolog system isolator unit and a NL 822 amplifier. Two EMG electrodes were placed 2 cm below the elbow joint with an earth strap around the arm. An electrogoniometer can be seen on the dorsum of the hand. A biaxial accelerometer was attached at the end of the middle finger.

4.4 Results

4.4.1 Tremor in normal subjects during hand movement

Figure 4.2 shows two recordings from a normal subject. Each recording lasts two minutes and they were made during two separate recording sessions. The top panel was recorded 30 minutes after the application of the placebo spray to the skin of the forearm covering the flexor and extensor muscles. The data shown in the lower panel were recorded 30 minutes after the application of the xylocaine spray. In each case the volunteer maintains a steady position for one minute then begins to make sinusoidal flexion/extension movements of their wrist. The onset of movements produces a visibly obvious increase in the tremor amplitude.

The increase in tremor in x-axis (lateral/medial deviation of the hand) and y-axis tremor (flexion/extension) when movement starts is clearly visible. In addition, the change in the electromyogram from forearm flexor group muscles shows a clear burst pattern. The changes in extensor EMG are less clear but there is a modulated increase.

Figure 4.3 shows power spectra at rest and during movement for one normal subject. Tremor power spectra are calculated for 60 seconds at rest and then 60 seconds during movement. The top panels show y-axis tremor and the lower panels show x-axis. In each pair the left panel shows movement and the right panel shows resting tremor. The most obvious difference between the tremor at rest and the tremor during

movement is that the magnitude of the tremor is much bigger during movement in both y and x-axes.

4.4.2 Effect of Xylocaine or the placebo spray on tremor spectra during movement

Figure 4.4 shows specimen data from one volunteer. The spectra were calculated for one minute of movement, made 30 minutes after the application of the placebo spray (left panels) or a topical anaesthetic spray (right panels). There are no obvious differences between the Y-axis spectra. The main peak lies at about 8 Hz and the amplitudes are similar. The speed of movement of the wrist on both days was similar. The volunteers tracked a sine wave at 0.1 or 0.5 Hz. Details of the method are given in section 2.11. The x-axis tremor is smaller than the y-axis tremor and there are again no obvious changes.

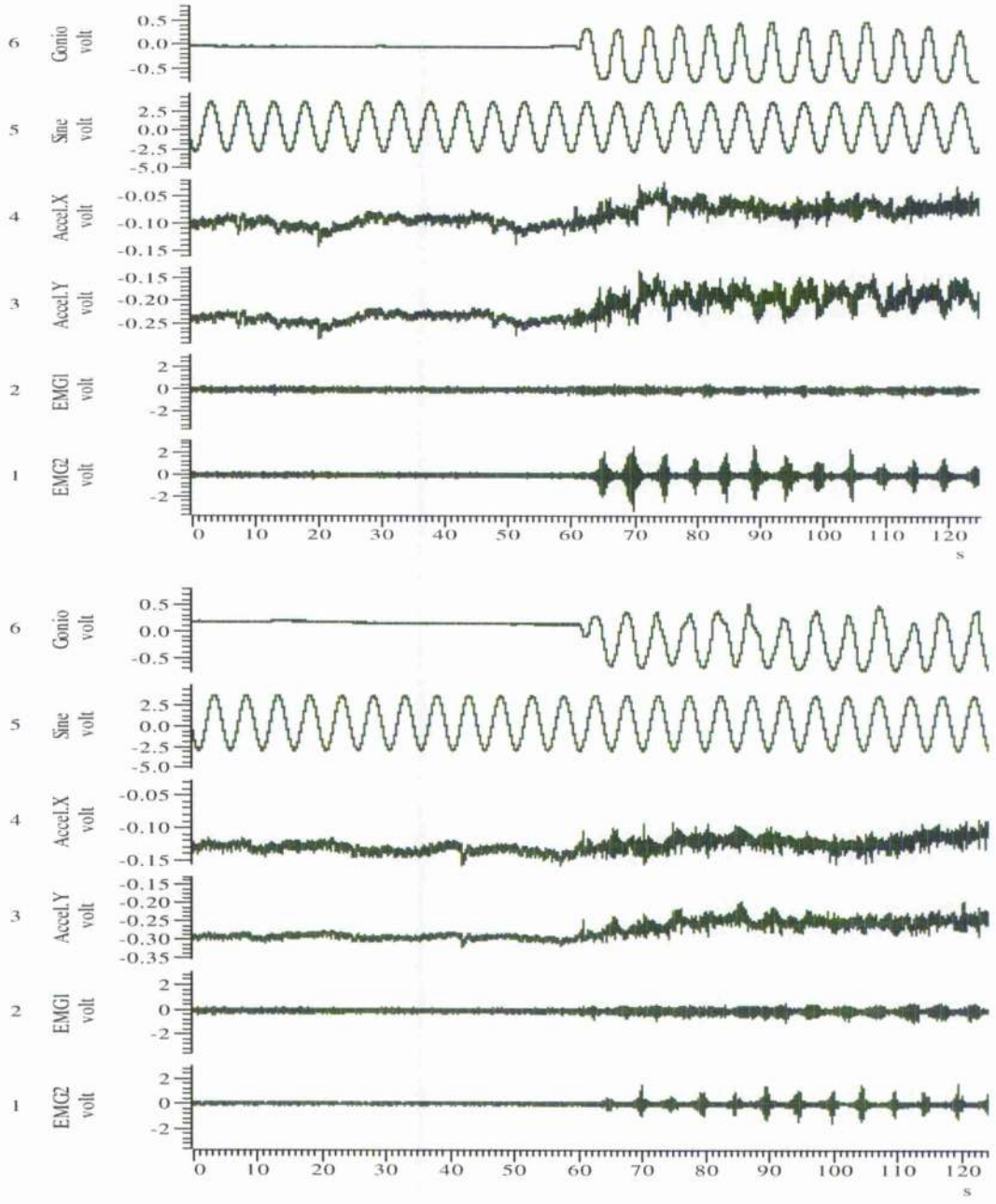


Figure 4.2. A recording of tremor during movement by a normal subject.

The upper panel was recorded 30 minutes after application of the placebo spray. The lower trace was recorded 30 minutes after application of the xylocaine spray. The first minute of the recording shows the volunteer at rest. This is followed by a period of tracking movements.
The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

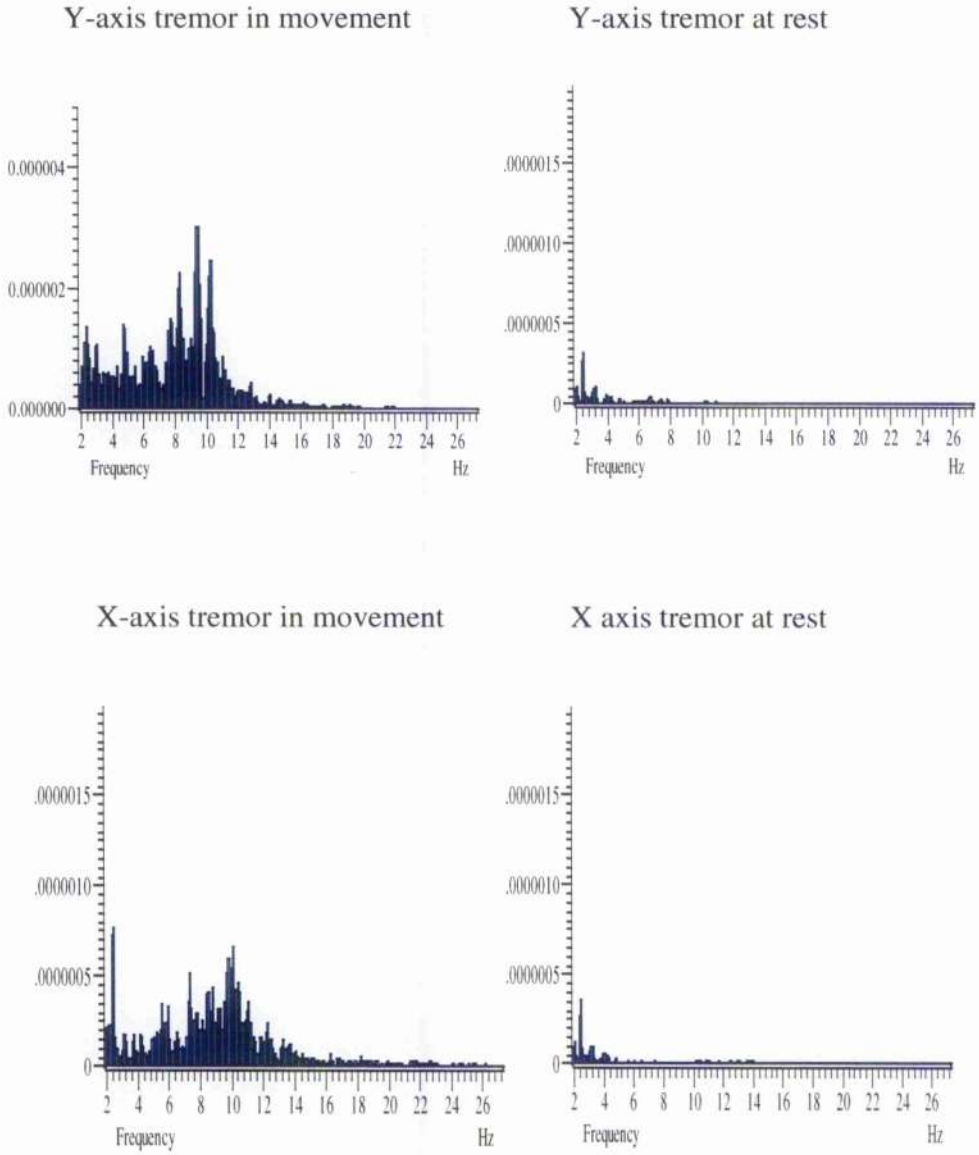


Figure 4.3 Power spectra for x and y-axis tremor in a normal subject.

Spectra are calculated for 60 seconds. Y-tremor (flexion extension) during movement and at rest is shown in the top pair. The lower pair shows x-axis tremor (medial lateral plane) during movement and at rest. The tremor energy is expressed in volts^2.

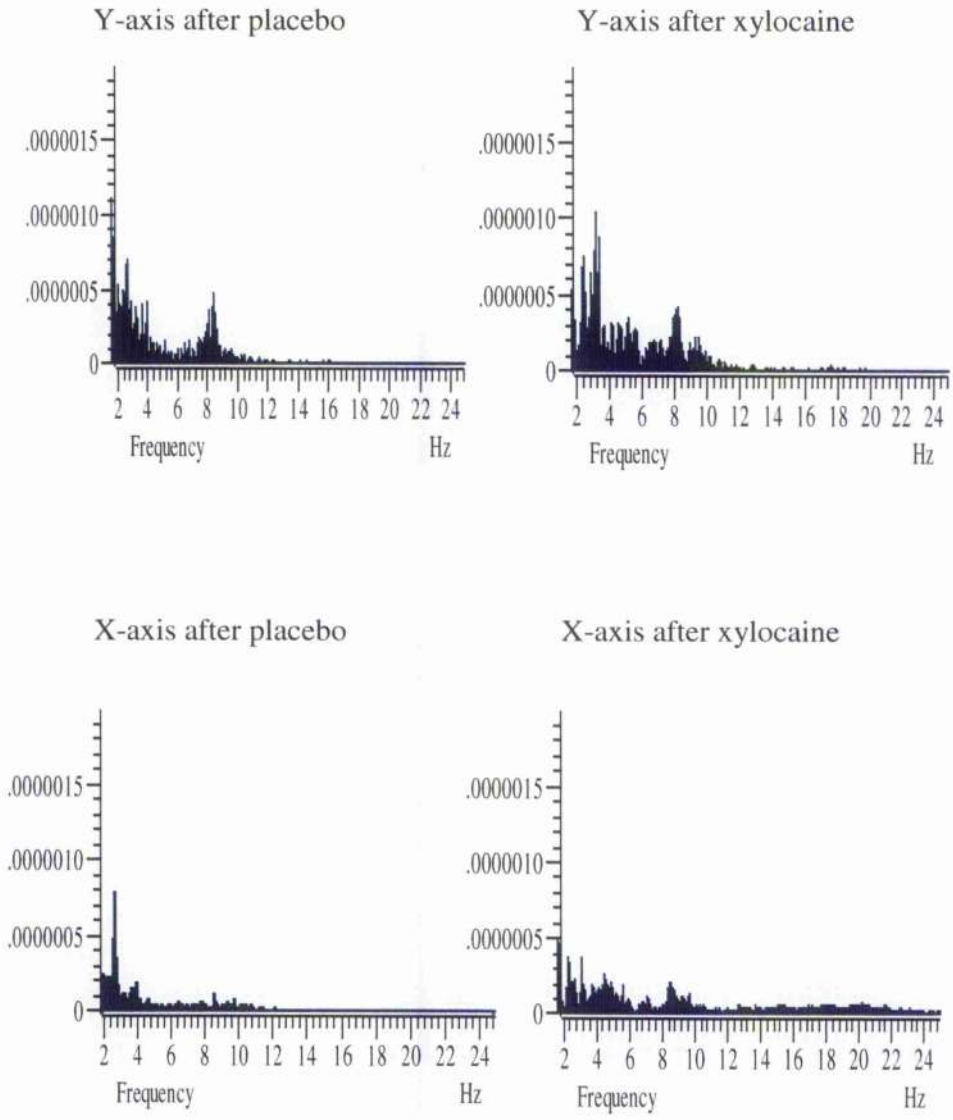


Figure 4.4. The tremor spectra during movements 30 minutes after the application of a xylocaine and placebo spray.

The upper panels show Y-axis tremor (flexion extension) and the lower panels show X-axis tremor (medial lateral). The xylocaine spray (right panels) the placebo spray (left panels) recordings were made at the same time and power spectra were calculated for recording of 60 seconds duration.

The tremor energy is expressed in volts^2.

4.4.3 Effects of xylocaine on y-axis tremor during movement

Table 4.1 contains a summary of the mean difference in tremor energy after the application of xylocaine and the placebo spray for twelve normal subjects. The confidence intervals are also shown. A separate set of data is shown for each of the three-frequency bands studied, 2-6 Hz, 6-12 Hz, and 12-20 Hz. The analysis is also shown for 2-20 Hz.

The top panel in table 4.1 shows the mean differences in Y-axis tremor at the start of the two experiments. This is before the application of the placebo spray or xylocaine spray. It shows that the mean difference in y-axis (flexion/extension) tremor is consistently positive i.e. tremor after the placebo spray is greater than tremor after the xylocaine spray. However, this difference is not statistically significant since the confidence intervals contain zero. This was encouraging since it means that volunteers began both experiments with similar tremor.

In addition, the results presented elsewhere in table 4.1 show no significant differences between application of xylocaine and placebo over one hour. The mean differences in all frequency bands are positive at 0 minutes, 15 minutes and negative at 30, 45 and 60 minute intervals. These negative values indicate an increase in energy after the xylocaine spray than after the placebo spray. None of the results showed statistical significance.

Time	Frequency Band	Mean Difference	Confidence Interval		
0 min	2-6 Hz	0.42	-0.42	0.42	ns
	6-12 Hz	0.96	-1.51	3.43	ns
	12-20 Hz	0.10	-0.28	0.48	ns
	2-20 Hz	1.48	-2.21	4.34	ns
15 min	2-6 Hz	0.05	-0.81	0.91	ns
	6-12 Hz	4.72	-3.77	13.20	ns
	12-20 Hz	2.63	-2.27	7.53	ns
	2-20 Hz	7.40	-6.84	21.64	ns
30 min	2-6 Hz	-4.44	-21.72	12.84	ns
	6-12 Hz	-3.19	-11.82	5.45	ns
	12-20 Hz	-1.83	-7.32	3.67	ns
	2-20 Hz	-9.46	-40.87	21.95	ns
45 min	2-6 Hz	-0.27	-2.39	1.86	ns
	6-12 Hz	0.39	-2.08	2.86	ns
	12-20 Hz	-0.25	-1.27	0.77	ns
	2-20 Hz	-0.13	-5.74	5.49	ns
60 min	2-6 Hz	-4.89	-14.57	4.80	ns
	6-12 Hz	-3.74	-11.64	4.16	ns
	12-20 Hz	-3.31	-10.07	3.45	ns
	2-20 Hz	-11.94	-36.28	12.41	ns

Table 4.1. The mean difference between y-axis tremor spectra (placebo - xylocaine) for twelve volunteers during hand movement.

Data are presented for four frequency ranges and at intervals of up to 60 minutes after the application of the spray. The confidence intervals are also shown. There is no significant difference between the application of the xylocaine and placebo for each case.

The values of the tremor spectrum area have been multiplied by 10^6 to make the values easier to read.

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	7.73	6.44	4.32	4.87	2.88
2	7.50	6.52	4.83	5.49	6.74
3	8.28	11.28	0.68	9.84	5.22
4	23.45	0.60	1.63	6.06	1.51
5	4.50	6.51	7.57	6.66	9.73
6	11.63	9.16	6.37	4.52	5.15
7	8.86	7.94	5.86	5.48	8.04
8	3.31	2.56	2.40	3.07	2.13
9	1.28	1.69	1.65	2.08	2.38
10	3.95	1.26	1.25	1.30	1.53
11	1.55	0.81	1.14	0.24	0.29
12	3.01	2.20	2.65	3.10	2.46

Table 4.2 Effects of xylocaine on y-axis tremor during movement

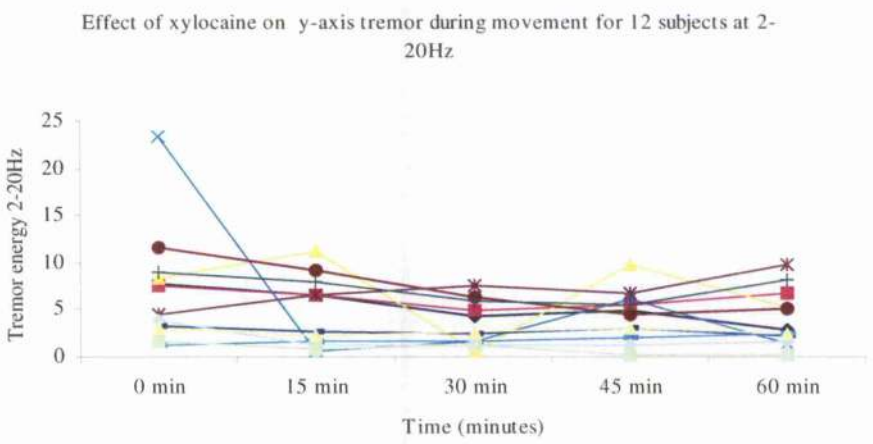
Data are presented for frequency range at 2-20 Hz and at intervals of up to 60 minutes after the application of placebo spray. The value of tremor spectrum area have been multiplied by 10^6. Subjects 4 and 6 shows high tremor at 0 minutes before the xylocaine spray and decrease tremor after xylocaine. Subjects 5 and 9 low tremor at 0 minutes and increase tremor after xylocaine. Subjects 10 and 11 low tremor but decrease after xylocaine. Subject 3, 7, 8 and 12 low tremor and the changes very small and unstable over one hour. However, there is no significant change in characteristic of tremor over 60 minutes P value 0.163. The data were subjected to ANOVA analysis using General Linear Model.

Subject No.	0 min	15 min	30 min	45 min	60 min
1	7.46	3.25	3.90	3.71	2.98
2	13.33	10.74	9.77	7.56	13.22
3	14.25	9.68	5.48	4.08	4.95
4	9.04	5.07	4.54	6.22	3.94
5	12.03	5.47	0.78	5.37	4.87
6	6.49	0.99	7.82	13.85	11.01
7	21.26	7.70	10.92	5.61	4.23
8	3.17	2.46	1.75	8.84	3.65
9	2.05	1.77	1.32	1.36	1.19
10	4.36	4.87	4.54	6.05	7.87
11	3.50	4.14	3.31	1.88	1.48
12	5.86	2.28	2.23	2.70	2.41

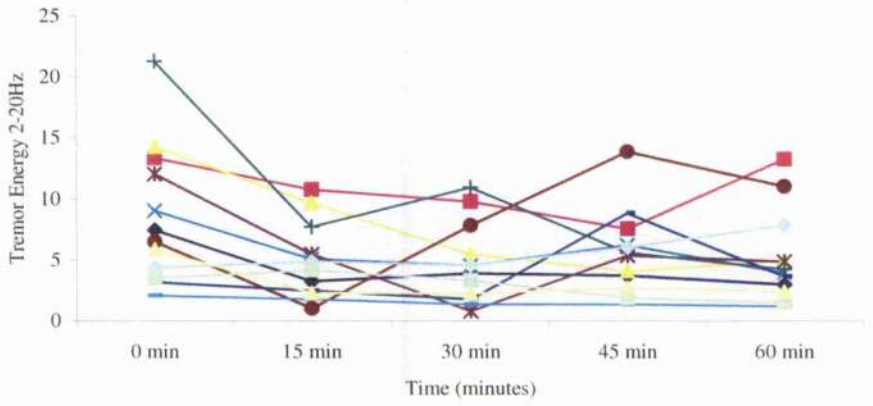
Table 4.3. Effects of placebo on y-axis tremor during movement

Data are presented for frequency range at 2-20 Hz and at intervals of up to 60 minutes after the application of placebo spray. The values of tremor spectrum area have been multiplied by 10^6. Subjects 2, 3, 5 and 7 shows high tremor at 0 minutes before the placebo spray and decrease tremor after placebo spray. Subjects' 1, 4,9,11, and 12 low tremors at 0 minutes and reduce tremor after placebo spray. Subjects 6 and 10 low tremor and increase after placebo spray. Subject 8 low tremor and the changes very small and unstable over one hour. However, there is no significant change in characteristic of tremor over 60 minutes P value 0.115. The data were subjected to ANOVA analysis using the General Linear Model.

(A)



(B)



Figures 4.5a, b Effects of xylocaine and placebo sprays on y-axis tremor during movement.

The upper figure (a) shows effect of xylocaine spray on y-axis tremor all subjects tremor below 15 and no changes on tremor except for subjects 4 high tremor at 0 minutes before xylocaine spray and big reduction on tremor after xylocaine spray.

The lower figure (B) shows effect of placebo spray on y-axis tremor. All subjects tremor below 15 and no changes on tremor except for subject 7 high above 20 and big reduction on tremor after placebo.

Table 4.2 shows the mean and standard deviations of the Y-axis tremor energy during movement in 12 neurologically normal volunteers. Data representing the tremor amplitude before and after the application of a placebo (P) or topical anaesthetic (TA) spray are presented. The table shows details of tremor in three frequency bands: 2-6 Hz, 6-12 Hz, 12-20 Hz and for the whole band 2-20 Hz.

The top panel in table 4.2 shows the mean and standard deviation in Y-axis tremor during movement at the start of the two experimental sessions. This is before the application of sprays. The values are very similar and the data in table 4.1 shows that the differences are not statistically significant after placebo or xylocaine over the 5 periods of measurement. Figure 4.5 shows graphs of these data. The top panel, figure 4.5A, shows the mean Y-axis tremor for the 2-20 Hz band in each condition. The lower panel, figure 4.5B, shows bar charts of the mean and standard deviations.

The data were subjected to ANOVA analysis and this showed that in neither case did the tremor energy change significantly over the period of the experiment ($p = 0.115$ for placebo data, $p = 0.165$ for xylocaine data).

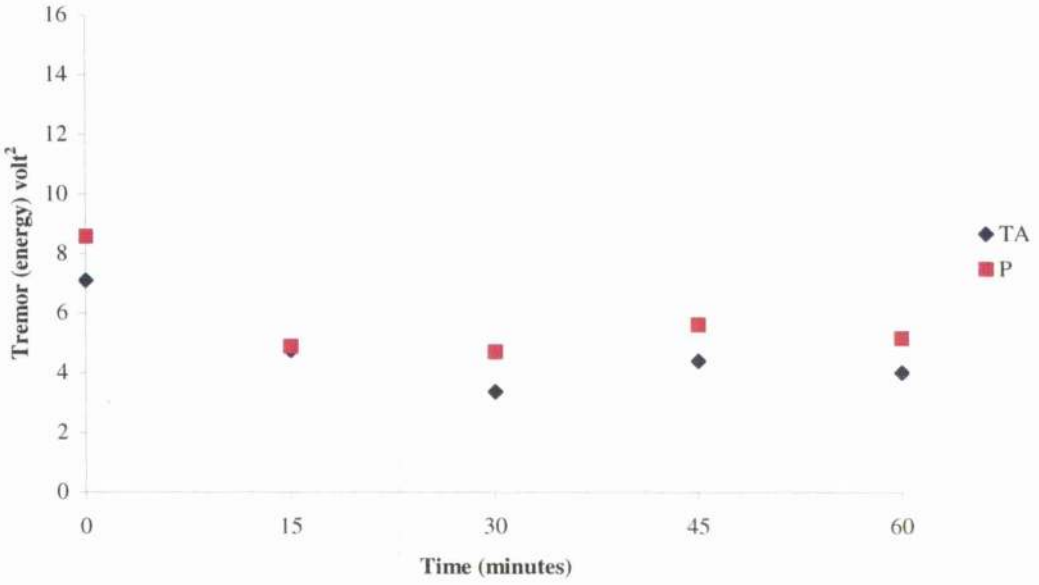
Time	Frequency Band	Mean Placebo	SD Placebo	Mean Xylocaine	SD Xylocaine
0 min	2-6 Hz	2.62	1.72	2.20	1.64
	6-12 Hz	5.11	3.59	4.15	3.90
	12-20 Hz	0.83	0.52	0.73	0.65
	2-20 Hz	8.57	5.69	7.09	6.07
15 min	2-6 Hz	1.78	0.99	1.73	1.21
	6-12 Hz	2.62	2.03	2.65	2.26
	12-20 Hz	0.47	0.30	0.37	0.26
	2-20 Hz	4.87	3.11	4.75	3.66
30 min	2-6 Hz	1.74	1.32	1.32	0.89
	6-12 Hz	2.45	2.15	1.70	1.36
	12-20 Hz	0.50	0.46	0.35	0.30
	2-20 Hz	4.70	3.29	3.36	2.33
45 min	2-6 Hz	2.50	1.49	1.70	1.83
	6-12 Hz	2.39	2.45	1.74	1.43
	12-20 Hz	0.71	0.57	0.96	1.68
	2-20 Hz	5.60	3.42	4.39	2.63
60 min	2-6 Hz	1.81	0.91	1.64	1.09
	6-12 Hz	2.81	2.85	1.94	2.08
	12-20 Hz	0.53	0.52	0.42	0.45
	2-20 Hz	5.15	3.73	4.00	2.94

Table 4.4. The mean and standard deviation for placebo and xylocaine spray in y-axis tremor spectra for twelve volunteers during hand movement.

Data are presented for four frequency ranges and at intervals of up to 60 minutes after the application of the spray. 2-20 Hz after placebo no significant changes over the 5 periods of measurements when tested with an ANOVA ($P = 0.115$). The changes after xylocaine were also not significant ($P = 0.163$).

The values of the tremor spectrum area have been multiplied by 10^6 to make the values easier to read.

(A)



(B)

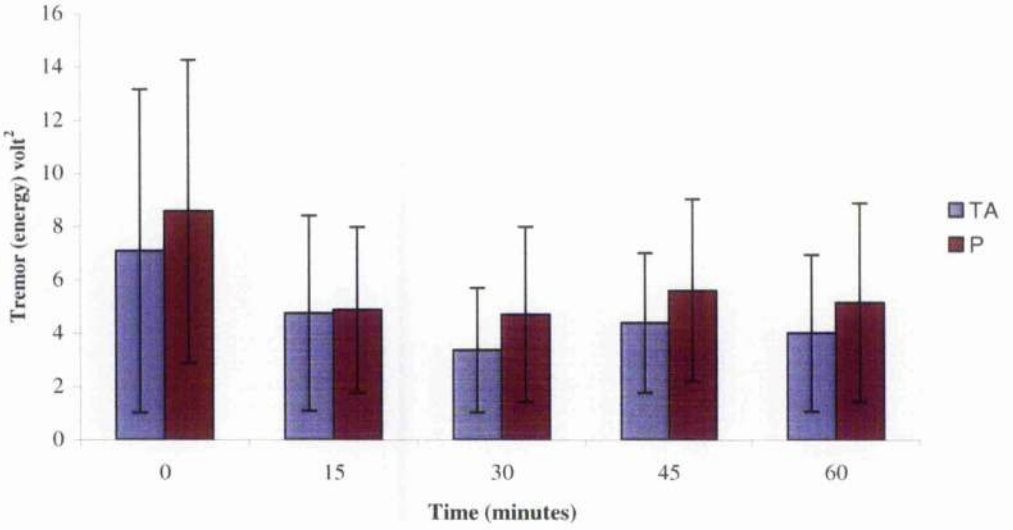


Figure 4.6. Mean and standard deviation of the y-axis tremor during movement after application of either a placebo or a topical anaesthesia spray.

Data is shown for twelve subjects in a frequency band of 2-20 Hz. No significant changes over 60 minutes see legend of table 4.2 for statistics.
Panel (A) shows the mean values and (B) shows the means and standard deviations.

4.4.4. Effects of xylocaine on x-axis tremor during movement

The x-axis tremor (medial / lateral deviation) was recorded from the same volunteers at the same time as the y-axis tremor. The mean difference between tremor after the placebo and after xylocaine (placebo- xylocaine) was calculated. The summary data are shown in table 4.5. The mean difference in tremor is shown in the frequency bands 2-6 Hz, 6-12 Hz, 12-20 Hz and 2-20 Hz. The confidence intervals are also shown.

The top panel of table 4.5 shows that there are no significant differences between the x-axis tremors at the start of the experiment. This agrees well with the data for y-axis tremor at the same time as shown in table 4.1.

Like the data presented in table 4.1, the mean differences in x axis tremor are not significant in any of the frequency bands at any of the times tested. Whilst the y-axis tremor differences were almost always negative, the x-axis tremor differences are all negative at 15 minutes after the application of the sprays and all positive after 30 min. At 45 and 60 minute intervals, the differences are a mixture of positive and negative values. In general, the positive values indicate reductions in tremor after topical anaesthesia but these are non-significant.

Time	Frequency Band	Mean difference	Confidence interval		
0 min	2-6 Hz	0.16	-0.14	0.47	ns
	6-12 Hz	-0.23	-1.34	0.88	ns
	12-20 Hz	0.02	-0.13	0.17	ns
	2-20 Hz	-0.05	-1.61	1.52	ns
15 min	2-6 Hz	-0.19	-0.49	0.11	ns
	6-12 Hz	-0.02	-0.62	0.41	ns
	12-20 Hz	-0.04	-0.13	0.05	ns
	2-20 Hz	-0.26	-1.25	0.30	ns
30 min	2-6 Hz	0.03	-0.32	0.38	ns
	6-12 Hz	0.09	-0.90	1.08	ns
	12-20 Hz	0.002	-0.14	0.14	ns
	2-20 Hz	0.12	-1.36	1.60	ns
45 min	2-6 Hz	0.02	-0.31	0.35	ns
	6-12 Hz	-0.11	-0.50	0.27	ns
	12-20 Hz	0.01	-0.10	0.13	ns
	2-20 Hz	-0.08	-0.91	0.75	ns
60 min	2-6 Hz	-0.02	-0.19	0.15	ns
	6-12 Hz	0.18	-0.44	0.80	ns
	12-20 Hz	0.03	-0.05	0.12	ns
	2-20 Hz	0.19	-0.68	1.07	ns

Table 4.5. The mean difference between x-axis tremor spectra (placebo - xylocaine) for twelve volunteers.

Data are presented for four frequency ranges and at intervals of up to 60 minutes after application of the spray. The confidence interval is also show for each case. All the intervals contain zero and so it can be concluded that no significant difference exists between the application of xylocaine and the placebo.

The values of the tremor spectrum area have been multiplied by 10^6 to make the values easier to read.

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	3.43	2.32	2.14	1.64	1.64
2	3.29	3.54	2.57	2.36	2.56
3	1.94	1.85	2.15	3.54	5.10
4	10.40	4.64	3.93	3.24	2.55
5	4.10	3.22	6.82	4.71	3.52
6	3.32	2.62	2.18	1.47	2.23
7	2.50	2.73	2.37	3.37	3.50
8	2.15	1.79	1.48	2.09	1.33
9	0.90	1.21	1.23	2.03	1.56
10	1.05	3.41	2.87	3.04	2.91
11	3.86	3.43	2.31	0.37	0.35
12	1.38	1.19	0.87	1.63	1.12

Table 4.6 Effect of xylocaine on x-axis tremor during movement

Data are presented for frequency range at 2-20 Hz and at intervals of up to 60 minutes after the application of xylocaine spray. The values of tremor spectrum area have been multiplied by 10^6. All subjects have low tremor energy at 0 minutes except for subject 4. In that case the tremor is reduced after TA. Subjects 1 and 11 show low initial tremor which reduces further after TA. Subject 10 shows tremor increases after TA. Overall, there is no significant change in the tremor energy over 60 minutes ($p = 0.743$). The data were subjected to ANOVA analysis using General Linear Model.

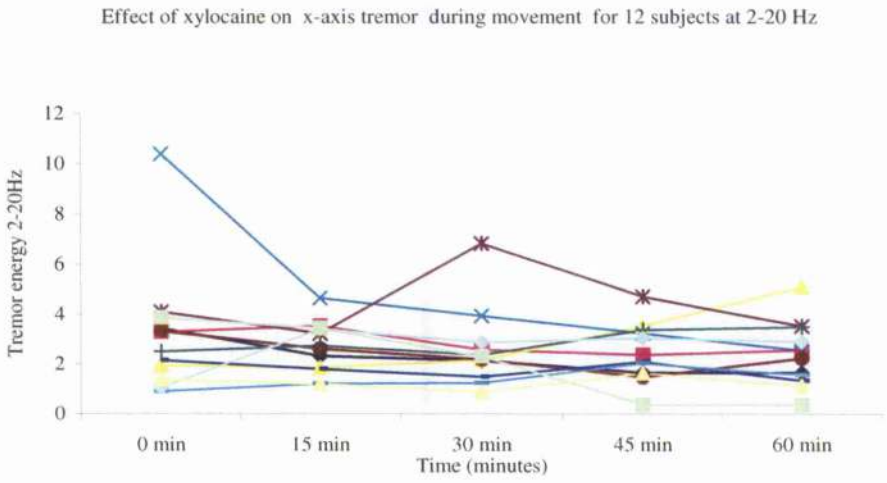
No. Subjects	0 min	15 min	30 min	45 min	60 min
1	2.18	1.84	2.47	1.96	1.59
2	3.48	2.61	2.84	5.04	4.09
3	6.12	4.09	9.72	4.17	4.59
4	4.55	2.98	1.49	2.67	2.12
5	5.99	3.43	5.22	2.77	6.33
6	3.11	2.77	1.85	2.43	2.30
7	5.47	2.17	3.32	3.04	1.88
8	1.66	1.35	0.80	1.68	2.55
9	1.21	1.13	0.64	0.59	0.79
10	1.27	1.82	2.08	1.84	2.39
11	1.24	1.27	1.16	1.19	0.92
12	1.48	0.80	0.81	1.12	1.17

Table 4.7. Effect of placebo on x-axis tremor during movement

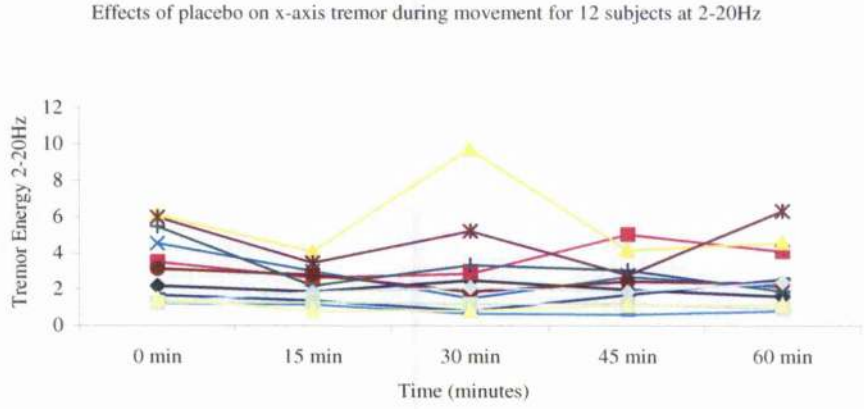
Data are presented for frequency range at 2-20 Hz and at intervals of up to 60 minutes after the application of placebo spray. The value of tremor spectrum area have been multiplied by 10^6. All subjects show low tremor at 0 minutes before placebo spray.

Subject 1, 9, 11 and 12 show reductions in tremor after placebo. Subjects 10 shows a small increase after placebo. However, there is no significant change in the tremor characteristics over the 60 minutes ($p=0.731$). The data were subjected to ANOVA analysis using the General Linear Model.

(A)



(B)



Figures 4.7a, b. Individual x-axis tremor during movement at intervals after the application of xylocaine and placebo sprays.

The upper figure (A) shows the effect of xylocaine spray on x-axis tremor. The lower figure (B) shows the effect of placebo spray on x-axis tremor. The magnitude of the x axis tremor was very low in all subjects.

Table 4.8 shows the mean and standard deviations of the X-axis tremor energy during movement in same volunteers. These data were recorded concurrently in the same sessions. The structure of the table is similar to 4.4.

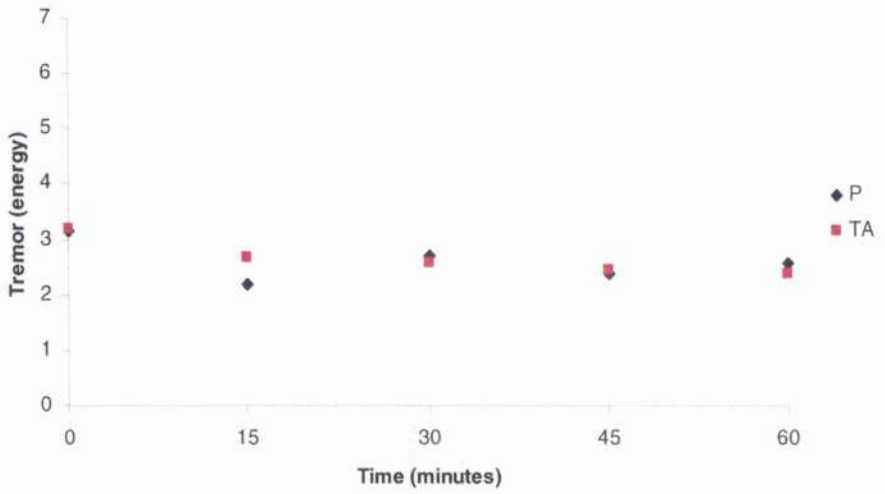
The data in the top panel in table 4.8 confirms that the X-axis tremor during movement is the same at the start of the two experimental sessions. The lower panels show the tremor characteristics at 15 to 60 minutes after the application of the sprays. Figure 4.7 shows graphs of these data. The top panel, figure 4.7A, shows the mean X-axis tremor for the 2-20 Hz band in each condition. The lower panel, figure 4.7B, shows bar charts of the mean and standard deviations. There is no significant change in the tremor characteristics over this time. ($P = 0.731$ for placebo data and $P = 0.743$ for xylocaine data).

Time	Frequency Band	Mean P	SD P	Mean TA	SD TA
0 min	2-6 Hz	0.94	0.49	0.77	0.39
	6-12 Hz	1.83	1.26	2.06	2.03
	12-20 Hz	0.37	0.28	0.35	0.26
	2-20 Hz	3.15	2.03	3.19	2.68
15 min	2-6 Hz	0.78	0.39	0.97	0.34
	6-12 Hz	1.18	0.65	1.42	0.77
	12-20 Hz	0.23	0.11	0.27	0.15
	2-20 Hz	2.19	1.15	2.66	1.25
30 min	2-6 Hz	0.85	0.61	0.82	0.30
	6-12 Hz	1.57	1.78	1.48	1.24
	12-20 Hz	0.28	0.27	0.28	0.15
	2-20 Hz	2.70	2.66	2.58	1.68
45 min	2-6 Hz	0.86	0.50	0.85	0.31
	6-12 Hz	1.26	0.81	1.37	0.92
	12-20 Hz	0.25	0.16	0.23	0.14
	2-20 Hz	2.37	1.47	2.46	1.36
60 min	2-6 Hz	0.79	0.39	0.81	0.36
	6-12 Hz	1.52	1.44	1.34	0.94
	12-20 Hz	0.25	0.16	0.21	0.13
	2-20 Hz	2.56	1.99	2.36	1.43

Table 4.8. The mean and standard deviation for placebo and topical anaesthesia spray in X-axis tremor spectra for twelve volunteers during hand movement.

Data are presented for four frequency ranges and at intervals of up to 60 minutes after the application of the spray. The values of the tremor spectrum area have been multiplied by 10^6 to make the values easier to read.

(A)



(B)

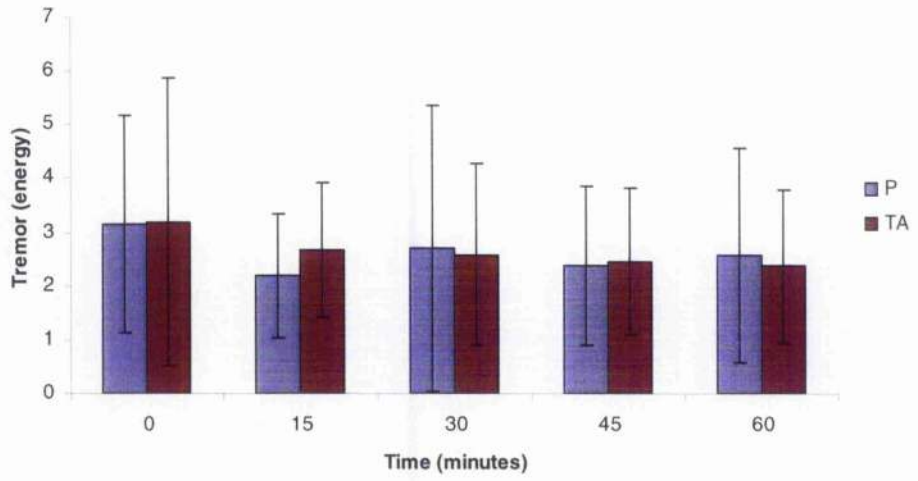


Figure 4.8. Mean and standard deviation for placebo and topical anaesthesia.

This shows the mean x-axis tremor in the frequency band 2-20 Hz, during movement for twelve subjects. (A) mean values (B) mean and standard deviations. No significant change was found over 60 minutes ($p = 0.731$ for placebo and $p = 0.743$ for topical anaesthesia, ANOVA).

4.5. Discussion

In the previous chapter the effect of topical anaesthesia on physiological tremor of the hand at rest was investigated. The results showed no significant differences between placebo and xylocaine in nineteen normal subjects. In this chapter the effect topical anaesthesia on tremor of hand during movement was investigated in twelve normal subjects. The data in tables 4.1 and 4.3 show that there is no significant difference between the application of the placebo and 10% xylocaine sprays.

The rationale of these experiments was that resting and movement tremors have different origins within the CNS. The tremor during voluntary movements in normal persons is much greater than resting physiologically in the same limb (Iaizzo and Pozos, 1992). This phenomenon was found during these experiments. It can be seen by comparing figures 3.2 and 4.3. The hope was that topical anaesthesia might have an effect, which was easier to identify during the larger amplitude movement tremor, particularly if this had a different mechanism of generation. This did not happen and it is clear that topical anaesthesia had no clear action on movement tremor.

This study found that tremor during movement was larger than tremor at rest. This confirms previous studies which showed that the neuromuscular system generating tremor is capable of dramatically increasing the tremor amplitude and decreasing the tremor frequency even in normal subjects (Pozos, Iaizzo and Petry, 1982). It could be that during movement, the receptor sensitivity to muscle length or tension changes may be triggering the amplitude-modulated EMG activity associated with tremor (Pozos et al., 1982).

Earlier similar studies by Mills and Pozos (1985) investigated the effect of topical anaesthesia on tremor during movement at the ankle. They reported a significant and sustained reduction in the tremor amplitude for 20-30 minutes after the application of 4% xylocaine. The previous chapter also discussed results by Pozos and Iazzio (1992), which showed that topical anaesthesia with 4% xylocaine suppressed essential tremor of the hand for 20 - 30 minutes. The paper by Pozos and Iazzio (1992) is the only study published to date about topical anaesthesia and tremor. There are other papers about digital nerve block and voluntary movements such as precision grip (Fisher, Galea, Brown and Lemon, 2002). In addition, the effect of topical anaesthesia of the foot, produced by the application of EMLA cream, on gait has been reported (McDonnell and Warden-Flood, 2000).

The data in this study are in conflict with those reported by Pozos, Mills and Iaizzo, (1984) and Mills and Pozos (1985). They found tremor suppression during movement of the ankle and this study found no difference between placebo and topical anaesthesia during movement at the wrist. The conflicting results could lie in the differences of methodology, for example the tremor generation mechanisms may be different in the upper and lower limbs. Alternatively, mechanical factors might be responsible, for example the muscle masses and dimension will be very different. Both experiments tested neurologically normal individuals over similar periods of time. Pozos and Mills tested seven volunteers comparing tremor before and after topical anaesthesia. They compared a control period with tremor of up to 30 minutes after topical anaesthesia. They reported a significant reduction in tremor after topical anaesthesia. Four of these volunteers returned later some months later for a second

test with a placebo spray. No significant differences were reported in this second test. They did not report how similar the magnitudes of the tremor were on the two tests.

This study tested 12 persons on two occasions and compared the effects of placebo and topical anaesthesia over 60 minute intervals. The volunteers were not informed as to the nature of the intervention. There was no difference in the tremor after application of placebo or topical anaesthetic sprays.

One possibility is that Pozos and Mills found their effect by chance due to short-term changes in the tremor amplitude. A second possibility is that tremor changes as a result of some sub-conscious change in the volunteers motor activity. Mills and Pozos do not state if their volunteers were blinded to the nature of the sprays. Both of these factors could be significant since their experiments tested only a small number of volunteers over very short periods.

Chapter 5

The effect of topical anaesthesia on pathological tremors: some case studies

5.1 Introduction

The previous chapters described investigations of the effect of topical anaesthesia on physiological tremors at rest and during movement. The volunteers who took part in these experiments had no history of neuropathology. The topical anaesthesia had no significant effect on resting tremor in normal persons or on the increased tremor during voluntary movement. A final question remained: does topical anaesthesia affect tremor in pathological cases?

The origins of pathological tremor were discussed in the General Introduction in Chapter 1. Pathological tremors have different causes, large amplitudes and different frequencies from resting physiological tremors.

There have been two earlier studies of the effect of local anaesthesia of skin on pathological tremors. Pozos and Iaizzo (1992) showed that anaesthesia of flexor and extensor forearm muscles of the hand caused a reduction in amplitude on essential tremor of the hand. There is an earlier study by Pozos et al., (1984) in which topical anaesthesia of the skin of the lower leg and the proximal one half of the foot were reported to reduce clonus at the ankle.

5.2. Aim

The aim of the experiments reported here was to investigate the effects of topical anaesthesia of skin on the pathological tremors seen in a series of case studies.

5.3. Methods and materials

Attempts to recruit patients with pathological tremor in Glasgow to the project were unsuccessful. The clinicians would not allow access to their patients since they felt that their patients were already fully committed to existing drug trials. The clinicians at the King Abdul-Aziz University Hospital, Jeddah, K.S.A. were able to provide suitable patients for this study. Patient access was allowed after the Neurology Clinical Committee had reviewed the research proposal and approved it.

A series of twelve adult patients were seen. Informed consent was obtained from each volunteer patient. They were not a carefully selected group. They reflected the range of cases available. All twelve volunteers participated in the experiment. Some of the twelve volunteers were poorly diagnosed. Some cases were complicated with other pathological problems e.g. stroke, cerebral palsy. Some volunteers already had prescribed medication, others did not.

Six cases are presented in detail in this thesis. Their clinical details have been given in table 1. Three cases were under medication and have a clear diagnosis. The one case of Parkinson's disease was complicated by diabetes and asthma. One volunteer was diagnosed with essential tremor and was treated with Primadone. One female volunteer, aged sixty years, was difficult to diagnose. Her condition was described as

'unknown type of tremor'. In addition, she was hypertensive and diabetic. She was prescribed Sinement. The remaining three cases who attended the hospital were not fully investigated or diagnosed and not under medication.

Experimental protocol

The design of experiments is described in detail in Chapter 2. The nature of the experiment was explained to each volunteer and informed consent was obtained. A two-axis accelerometer was attached to the middle finger of their right hand. The tremor accelerations were recorded for 60 seconds, digitised and stored on a laptop PC. The volunteers were blinded as to whether a xylocaine or placebo spray had been applied to the skin of their upper limb over the flexor and extensor muscle groups of the forearm. The sequence of placebo or local anaesthetic was randomised by asking the volunteer to select a sealed envelope containing the sequence of sprays to be applied.

The spectra were calculated for one minute in the manner described in Chapter 2. The EMG was recorded but has not been presented here because of the pressure of time available for the preparation of the thesis.

5.4 Comparative spectra of physiological and pathological tremor at rest

Figure 5.1 shows spectra of x and y-axis tremor recorded at the same time in a normal volunteer (top pair of spectra) and three specimen pathological tremors: one case of essential tremor, one case of an undiagnosed tremor and an example of Parkinsonian tremor. In each pair, the left spectrum is for x-axis tremor and the right

spectrum is for y-axis tremor. The top three pairs of spectra are shown with the same scales to allow easy comparison to be made. The bottom pair are shown with vertical scales 100X less sensitive to accommodate the very large tremor amplitude.

It is clear to see the pathological tremors all show much greater tremor energies than the normal physiological tremor in the y-axis. The differences are less clear in the x-axis tremor. The cases of essential tremor show larger tremor energy in both planes.

The volunteers with essential and undiagnosed tremor have their peak frequencies between 8-12 Hz in both axes. The volunteer with Parkinson's disease has a single peak at 4-6 Hz.

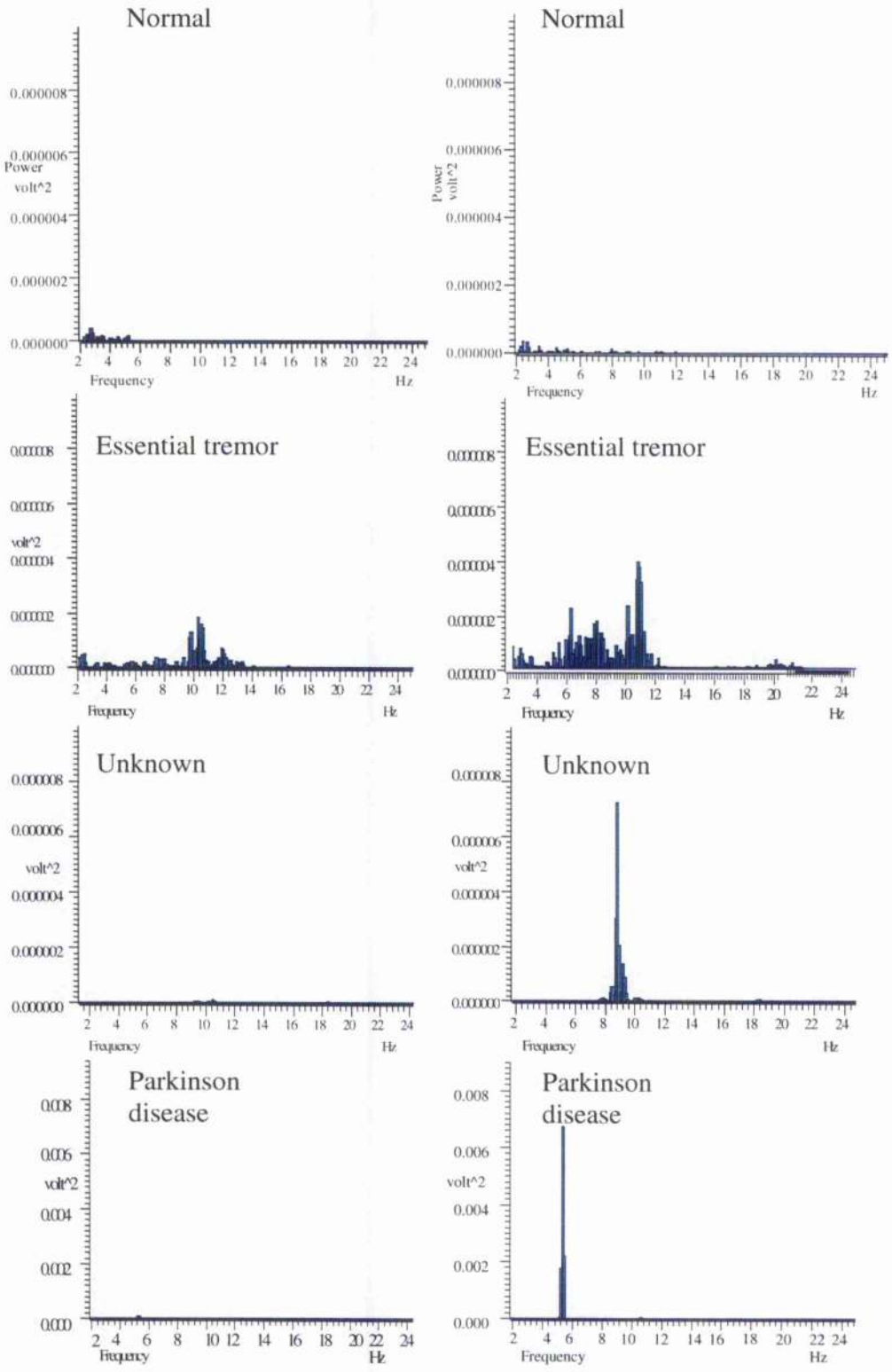


Figure 5.1. The power spectra for x and y-axis tremor in normal and pathological cases.

Each spectrum is calculated for 20 seconds of tremor at rest and before any application of sprays. X-axis tremor (medial lateral plane) is on the left of each pair and y-axis tremor (flexion extension plane) is on the right.
The ordinates show units of power in volts^2.

Table 5.1 shows the summary of experiments performed in the six case studies reported in this thesis. The second and third columns show the mean difference in tremor after xylocaine and placebo application. Thus a positive value shows that tremor after xylocaine was smaller than tremor after placebo application. A value close to zero suggests the effects of both applications were similar. A negative value shows that tremor after placebo was smaller than after the xylocaine. If xylocaine reduces the tremor there should be a majority of positive values in these columns.

The table 5.1 shows data for each patient at the start of the experiment with 0 minutes as a control and then at times after the application of the spray. The mean difference at the start of the experiment is close to zero in cases 2, 4, 5 and 6. Thus the tremor magnitude was similar at the start of both experiments. In cases 1 and 3 the mean differences are large suggesting that their tremor amplitude was different on the two days.

In case 1, all subsequent differences are negative in both the x and y- axis (xylocaine - placebo). Tremor after xylocaine application must be less than after the placebo. However, the size of this difference is variable. The tremor amplitude in this person must change significantly with time. This is clear in figure 1, which shows the raw recordings.

In case 3, all the differences are positive. Tremor after xylocaine application is smaller than after the placebo. The size of the effect is smaller than for case 1. The tremor amplitude must change less with time than it does for case 1. For cases 2, 4, 5 and 6, all the differences are small and close to zero. Their tremor is very stable and there is little difference between xylocaine and placebo applications.

Case Number	Age	Sex	Diagnosis	Medicine	Time	Tremor Y-difference	Tremor X-difference
1	63	M	Parkinson, Diabetic, Asthmatic.	Sinemet. Other medicines not recorded	0 min	-90.12	-12.06
					15 min	-35.07	-2.79
					30 min	-140.90	-1.26
					45 min	-5.74	-0.05
					60 min	-345.74	-9.44
2	23	F	Essential tremor	Primidone * Busperone**	0 min	0.62	0.18
					15 min	0.35	0.10
					30 min	0.38	0.11
					45 min	0.39	0.09
					60 min	0.53	0.14
3	60	F	Unknown tremor, Hyper-tensive, Diabetic.	Sinemet Other medicines not recorded	0 min	3.54	27.17
					15 min	4.52	9.08
					30 min	3.87	3.03
					45 min	3.65	-6.29
					60 min	2.64	-8.00
4	40	F	Unknown tremor	None	0 min	0.11	0.004
					15 min	-0.01	0.001
					30 min	-0.01	-0.009
					45 min	-0.01	-0.015
					60 min	0.01	-0.003
5	18	M	Unknown tremor	None	0 min	-0.07	-0.01
					15 min	0.002	0.02
					30 min	-0.01	0.001
					45 min	-0.001	0.003
					60 min	0.002	0.002
6	17	F	Unknown tremor	None	0 min	-0.02	-0.01
					15 min	-0.02	0.02
					30 min	-0.01	0.01
					45 min	-0.01	0.001
					60 min	-0.01	0.01

Table 5.1. Clinical details of the six patients whose tremor is described in this chapter.

The mean difference in X and Y-axis tremor between 2 – 20 Hz is shown. This is calculated as Xylocaine-Placebo. The values shown have been multiplied by 10^4.

*Primidone: first treatment, **Busperone: second treatment in case 2

5.5 Case studies

5.5.1 Case 1: Parkinson's disease

Figure 5.2 shows specimen recordings of x and y-axis tremor in this volunteer. The amplitude varies with time. It is clear the amplitude of y-axis tremor is much greater than that of the x-axis tremor. The upper panel shows tremor 30 minutes after the placebo application. The lower panel shows tremor 30 minutes after the xylocaine spray.

Figure 5.3 shows the power spectra calculated from these recordings. It can easily be seen that the peaks occur at the same frequency of approximately 6 Hz in both y-axis and x –axis spectra. In this case the amplitude of the peak in both the x and y-axis spectra are reduced after xylocaine application.

Inspection of the data in table 5.1 shows that this is a much stronger effect than would have been seen in the same person at 45 minutes after the start of the experiment. It is smaller than the effect at 60-minute intervals.

It is clear that the tremor amplitude changes substantially with time and that these changes are much larger than any that might be associated with the application of the sprays. In this case no significant effect due to the application of the topical anaesthetic can be detected.

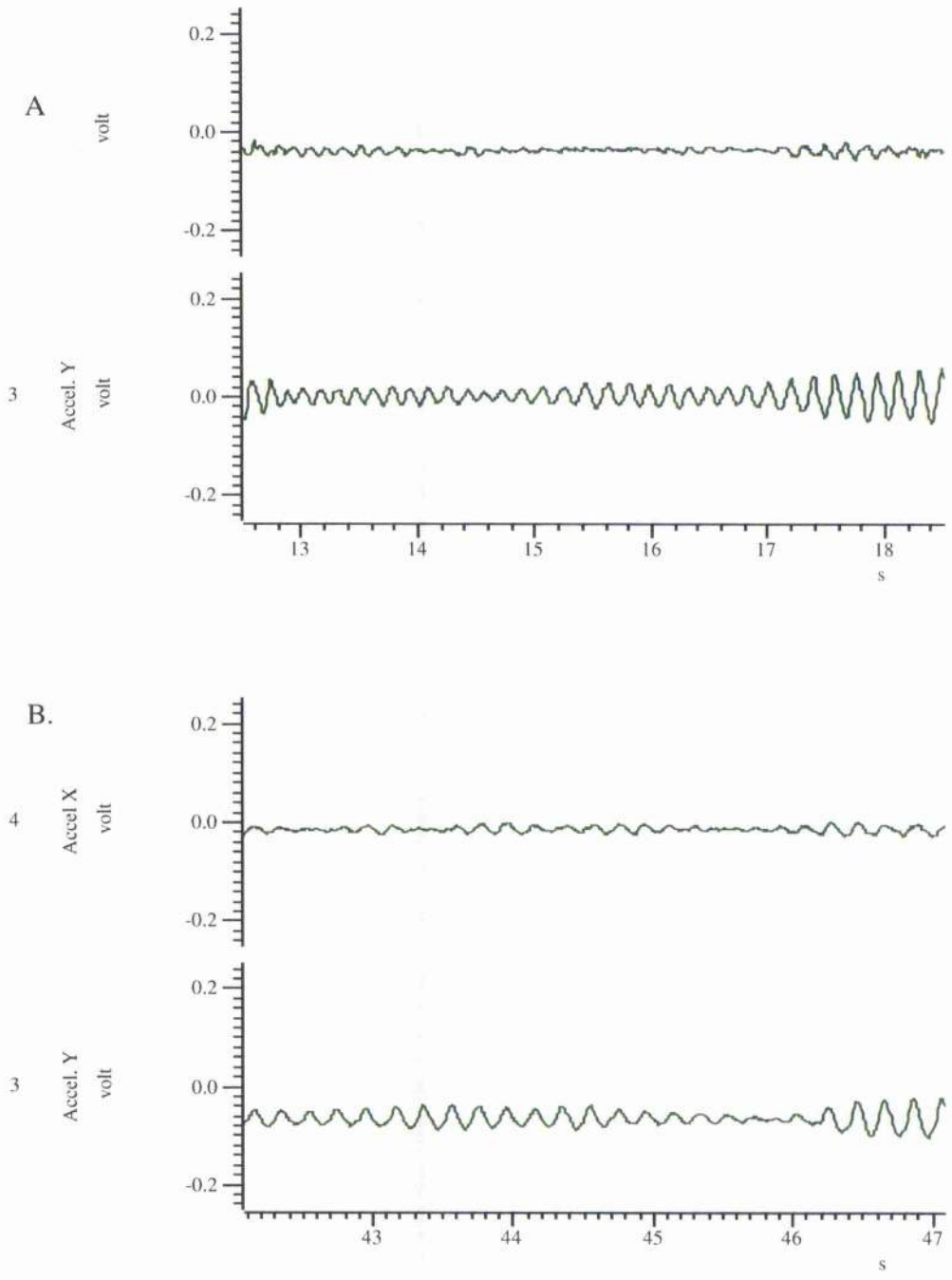


Figure 5.2. Recordings of the hand tremor in a volunteer with Parkinson's disease.

These were made 30 minutes after the application of a placebo (upper trace) and after the application of a spray containing 10% xylocaine (lower trace).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

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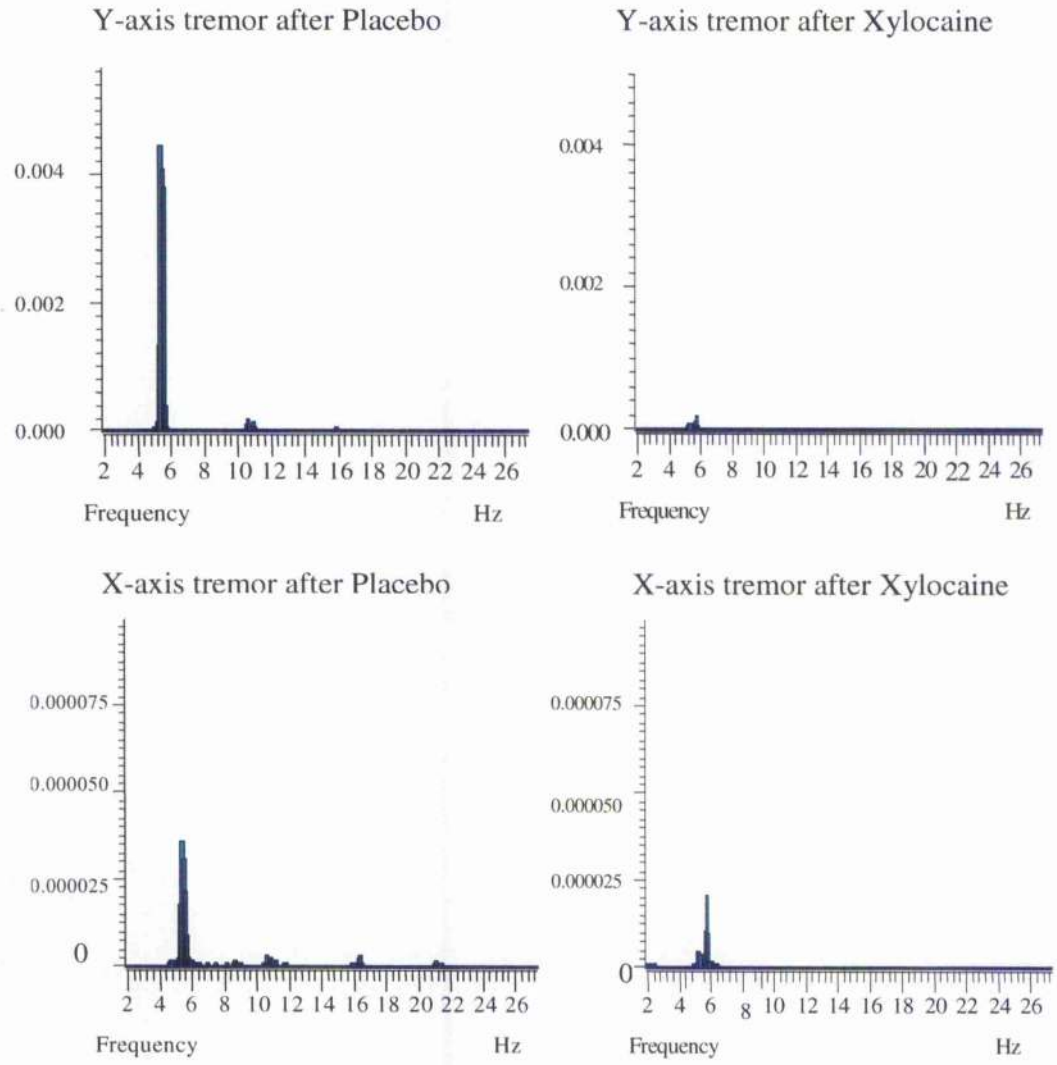


Figure 5.3. Power spectra for x and y-axis tremor in case 1 (Parkinson's disease).

See table 5.1 for details. Top pair of spectra is calculated for 60 seconds of y-axis tremor recorded 30 minutes after application of a placebo spray (top left) and a xylocaine spray (top right). Lower pair shows x-axis tremor at the same time. All axes are drawn to same scale to allow direct comparison of the spectra.

The ordinate shows tremor energy as volts^2.

5.5.2 Case 2: Essential Tremor

Figure 5.4 shows specimen recordings of x and y-axis tremor in this volunteer. It is clear the amplitude of tremor changes less with time when compared with the Parkinsonian tremor seen in case one. See figure 5.2. In figure 5.4 it can be seen that the amplitude of y-axis tremor is not much greater than that of the x-axis tremor.

The upper panel shows tremor 30 minutes after the placebo application. The lower panel shows tremor 30 minutes after the xylocaine spray. It can be seen visually that there is little effect.

Figure 5.5 shows the power spectra calculated from these recordings. The y and x-axis spectra show peaks at the same frequency of approximately 10 Hz. In this case the amplitude of the peak is similar after the xylocaine and placebo application. Inspection of the data in table 5.1 shows that there is very little difference between the tremor amplitude recorded after application of either the xylocaine or the placebo spray.

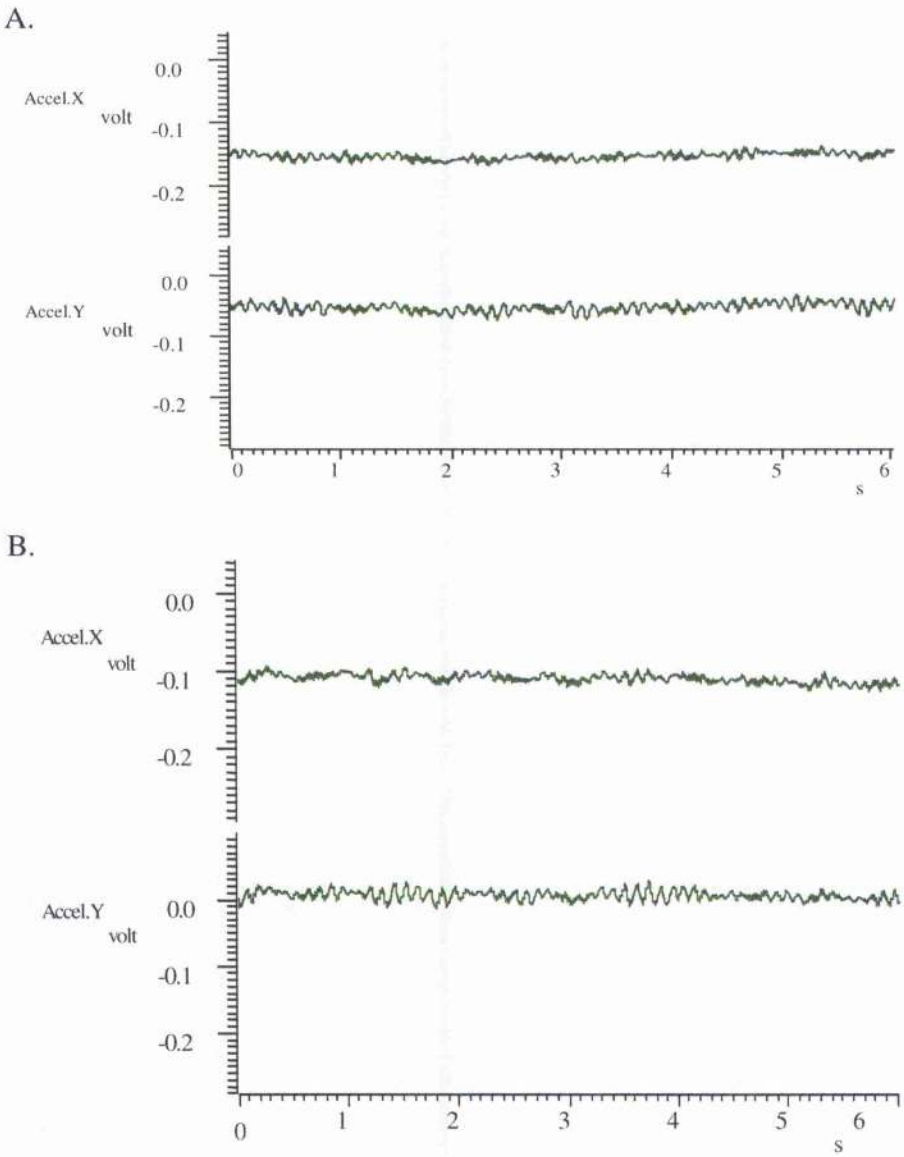


Figure 5.4. Recordings of hand tremor at rest for in this volunteer with essential tremor.

The recordings were made 30 minutes after the application of a placebo spray (A upper panel) or 30 minutes after a xylocaine spray (B lower panel).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

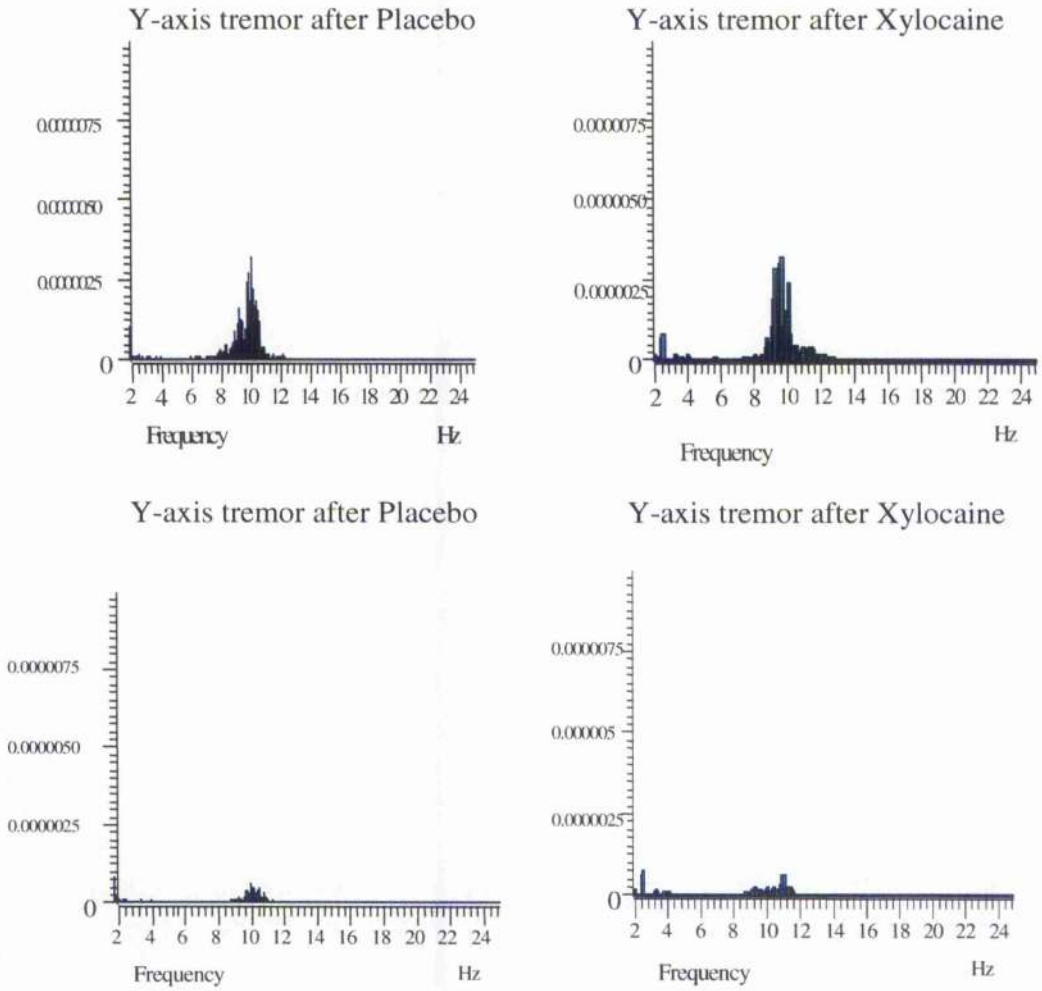


Figure 5.5. The spectra for x and y-axis tremors in case 2.

This person had essential tremor. See table 5.1 for details. The top pair of spectra is calculated for 60 seconds of y-axis tremor (flexion extension plane) at 30 minutes after application of a placebo spray (top left) and a xylocaine spray (top right). The lower pair of spectra show x-axis tremor (medial lateral plane).

5.5.3 Case 3: Tremor of unknown origin

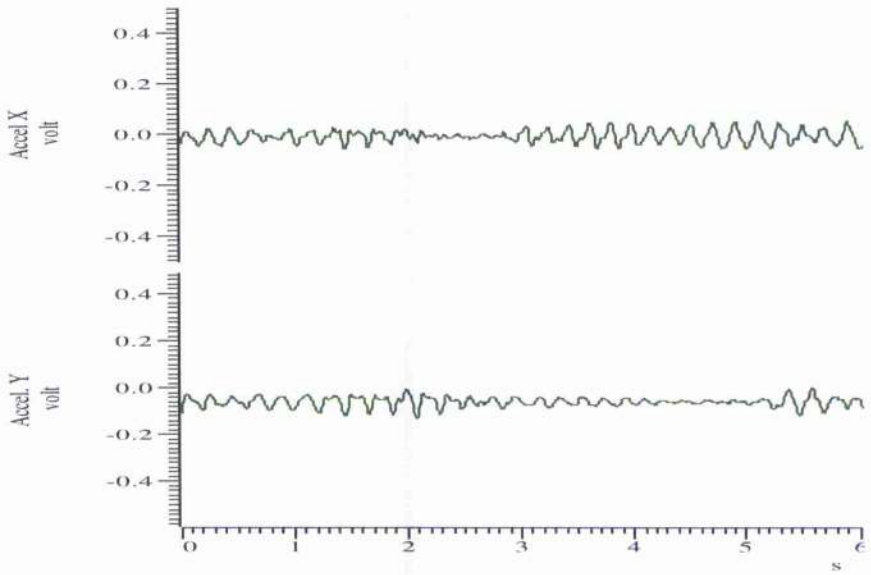
Figure 5.6 shows specimen recordings of y and x-axis tremor in this volunteer. The volunteer was under medication (Sinemet). The volunteer notes feeling that the drug had no effect on his condition. However, the medication was taken at night and the experiment was the following morning. The upper panel shows tremor 30 minutes after the application of the placebo. The lower panel shows tremor 30 minutes after the xylocaine spray.

The tremor amplitude varies with time and is similar to that seen in case 1 (Parkinson's disease). It is clear the amplitude of x-axis tremor is bigger than y-axis tremor in both examples. The amplitude of x-axis tremor after xylocaine application is bigger than after application of the placebo. The amplitude of the y-axis tremor is not much different from x-axis in table 5.1 at 30-minute intervals.

Figure 5.7 shows the power spectra calculated from these recordings. It can easily be seen that in both y-axis and x-axis spectra the peaks occur at the same frequency of approximately 5 Hz. The peaks are at similar frequencies as in case one (Parkinson's disease). In addition, both case 1 and 3 have been prescribed Sinement. Case 3 probably has Parkinson's disease.

The amplitude of the peak in the tremor spectrum increases after xylocaine application in the y and x-axis.

A.



B.

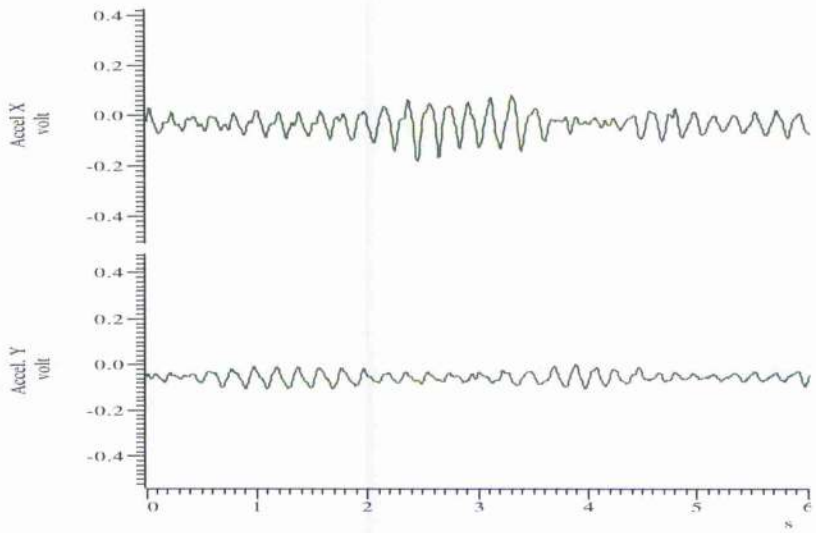


Figure 5.6. Recordings of hand tremor at rest for in this volunteer with an unknown tremor.

The recordings were made 30 minutes after the application of a placebo spray (A upper panel) or 30 minutes after a xylocaine spray (B lower panel).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

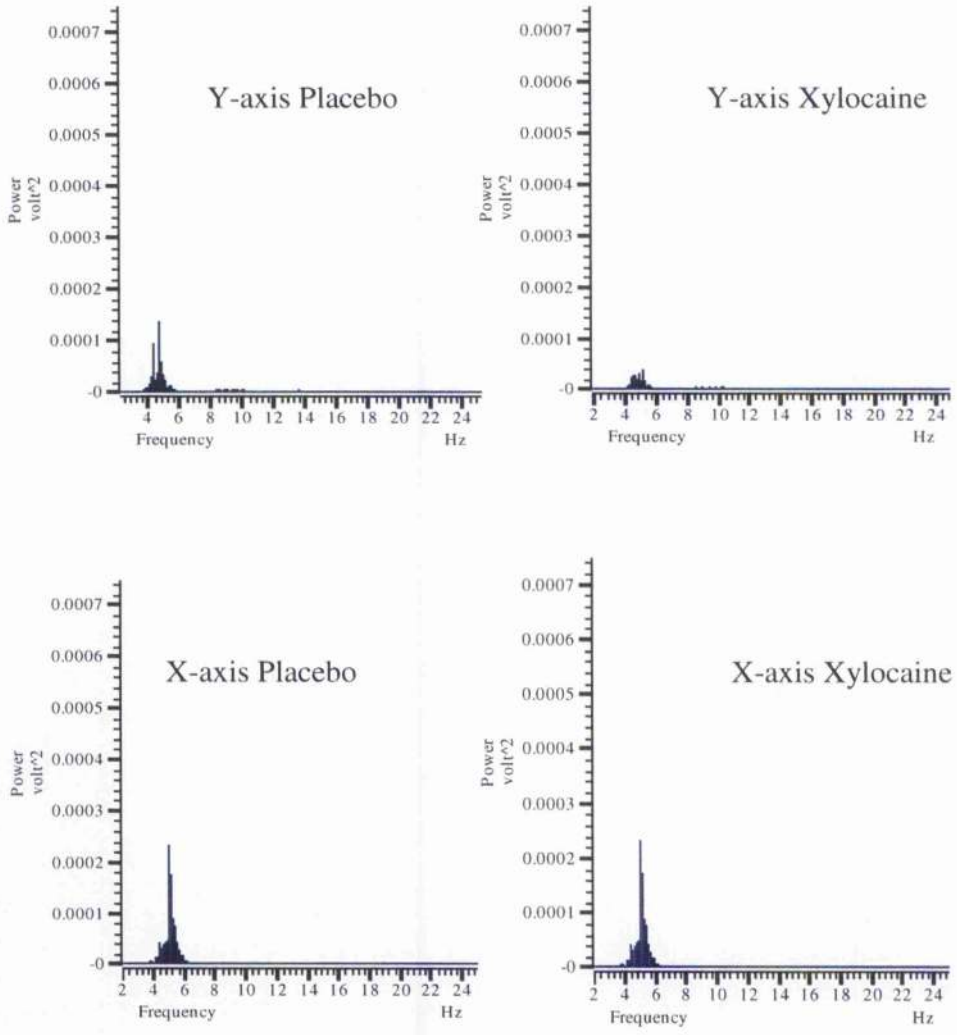


Figure 5.7. Power spectra for x and y tremor in case 3 (unknown tremor).

See table 5.1 for details. Top pair of spectra area calculated for 60 seconds of y-axis tremor at 30 minute intervals after the application of a placebo spray (top left) and a xylocaine spray (top right). The lower pair of spectra show x-axis tremor.

The ordinates show power in volts^2.

5.5.4 Case 4: Tremor of unknown origin

Figure 5.8 shows specimen recordings of the y and x–axis tremor in this volunteer. The upper panel shows tremor 30 minutes after the application of the placebo. The lower panel shows tremor 30 minutes after the xylocaine spray. It is clear the amplitude of y-axis tremor is much greater than that of the x-axis tremor.

Figure 5.9 shows the tremor spectra calculated from these recording. It can easily be seen that the peaks occur at the same frequency of approximately 8-10 Hz in both x and y spectra. In this case the amplitude of the peaks in the y-axis tremor are similar after xylocaine and placebo applications. The peak frequency of the x-axis tremor is also at 8-10 Hz and its amplitude is reduced after xylocaine. Inspection of the data in table 5.1 shows that this is a very small effect.

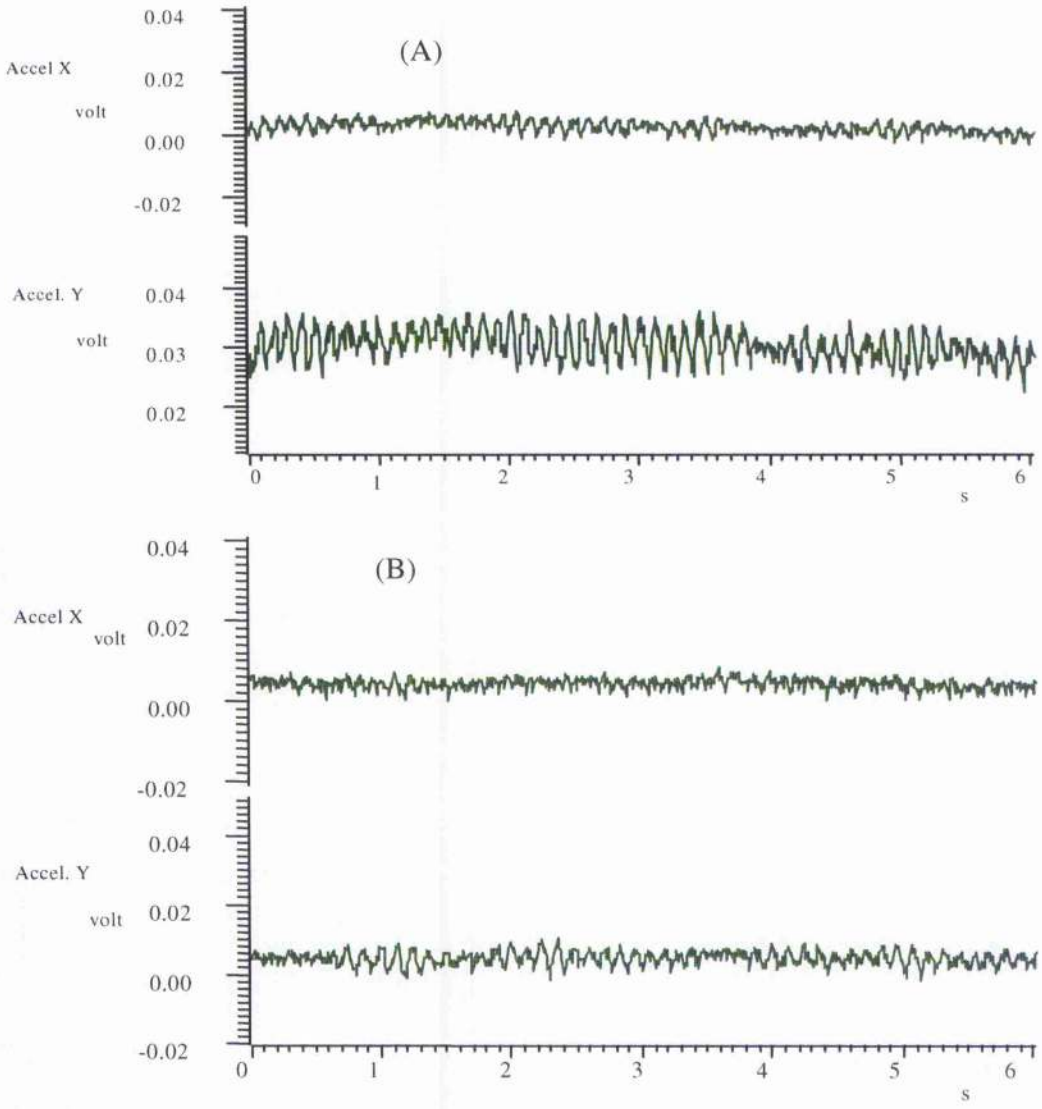


Figure 5.8 Recordings of hand tremor at rest for in a volunteer with an unknown tremor.

The recordings were made 30 minutes after application of a placebo spray (A upper panel) or 30 minutes after a xylocaine spray (B lower panel).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

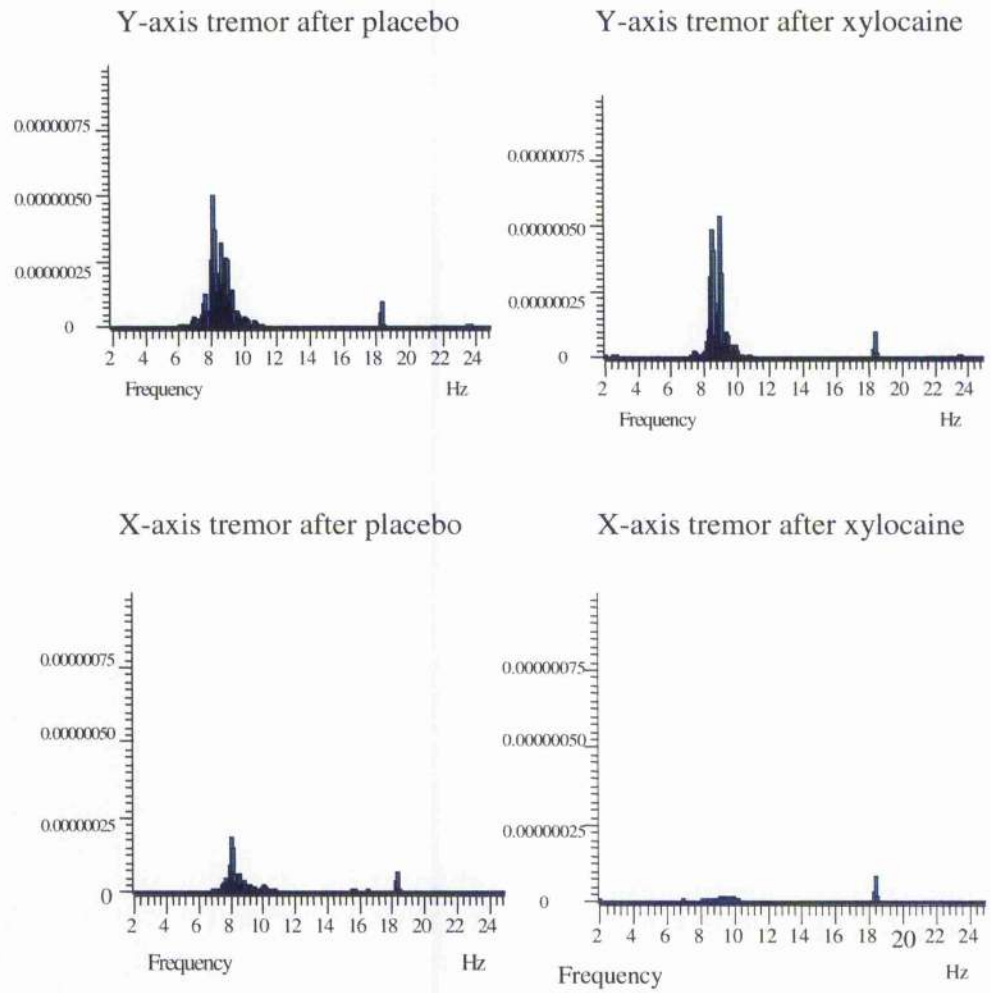


Figure 5.9. Spectra for x and y tremor in case 4 (unknown tremor).

See table 1 for clinical details. The top pair of spectra is calculated for 60 seconds of y-axis tremor 30 minutes after the application of a placebo spray (top left) and a xylocaine spray (top right). The lower pair of spectra show x-axis tremor.

The ordinates show power in volts^2.

5.5.5 Case 5: Tremor of unknown origin

This volunteer had no contractures or rigidity. The volunteer reported that his tremor started when he was 17 years old and in high school. The tremor was most obvious when he performed experimental tasks in the laboratory. In addition, his further diagnosis was complicated by his refusal to cooperate with clinical EMG studies.

Figure 5.10 shows specimen recordings of x and y-axis tremor in this volunteer. It shows almost no tremor at all during recording. The upper panel shows tremor 30 minutes after the application of a placebo spray. The lower panel shows tremor 30 minutes after the xylocaine spray. The amplitude of y and x-axis tremor is small and stable with time in both axes.

Figure 5.11 shows the tremor spectra calculated from these recordings. The y-axis tremor has a clear peak at 10 Hz, which is smaller after xylocaine application than it is after the placebo. The magnitude of the x-axis tremor is very small in both conditions.

The peak of the y-axis spectra after the placebo lies in the range 8-12 Hz. The tremor could be classified as physiological, essential, enhanced physiological or psychological tremor. There was a clear reduction in the amplitude of the y-axis tremor 30 minutes after the application of xylocaine. The data in table 5.1 shows that this effect was not consistent in other measurements. The position of the peak frequency was not changes. It is possible that this patient displayed psychogenic tremor, which was not elicited by the experimental conditions.

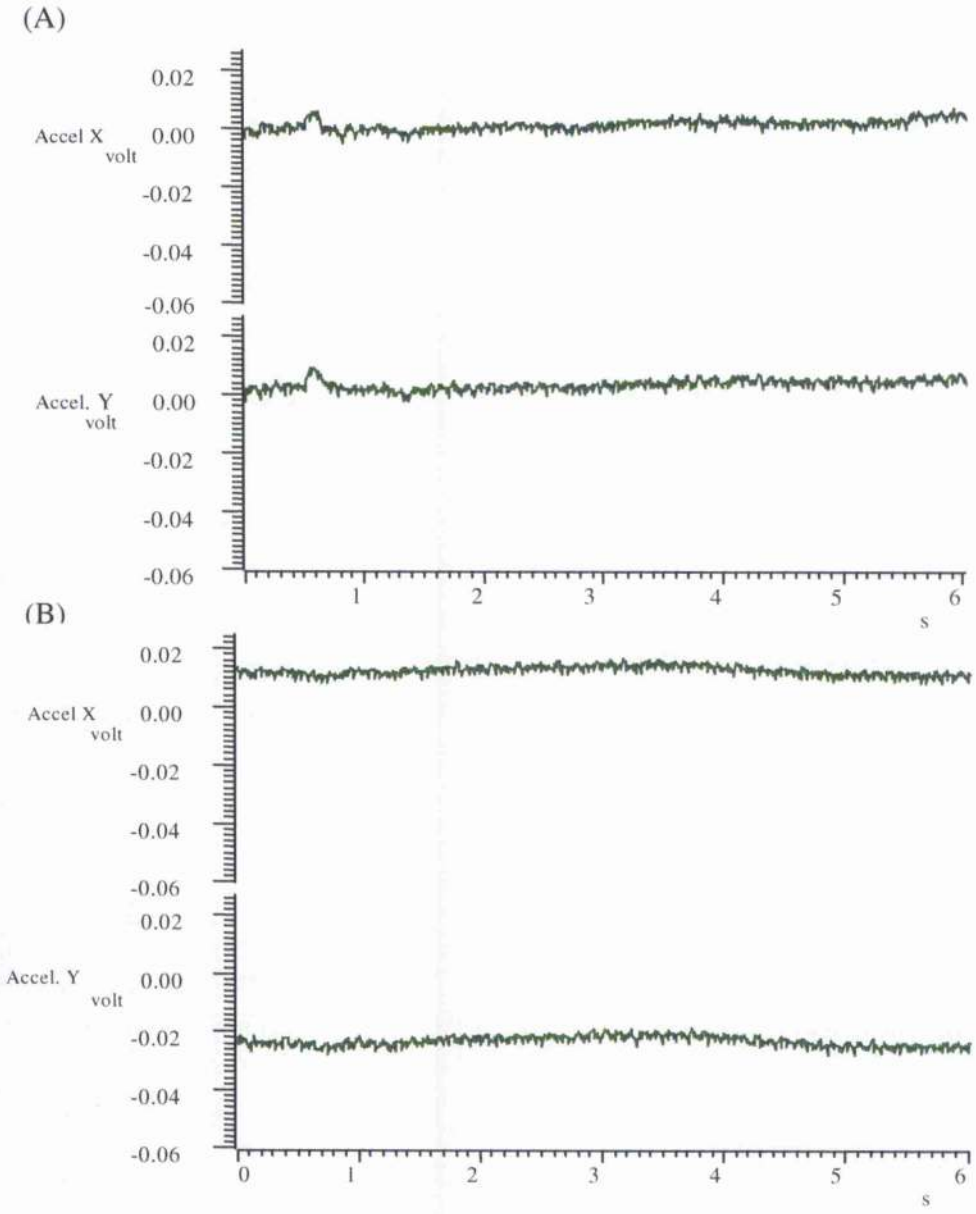


Figure 5.10 Recordings of hand tremor at rest in a volunteer with an unknown tremor.

The recordings were made 30 minutes after application of a placebo spray (A upper panel) or 30 minutes after a xylocaine spray (B lower panel).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

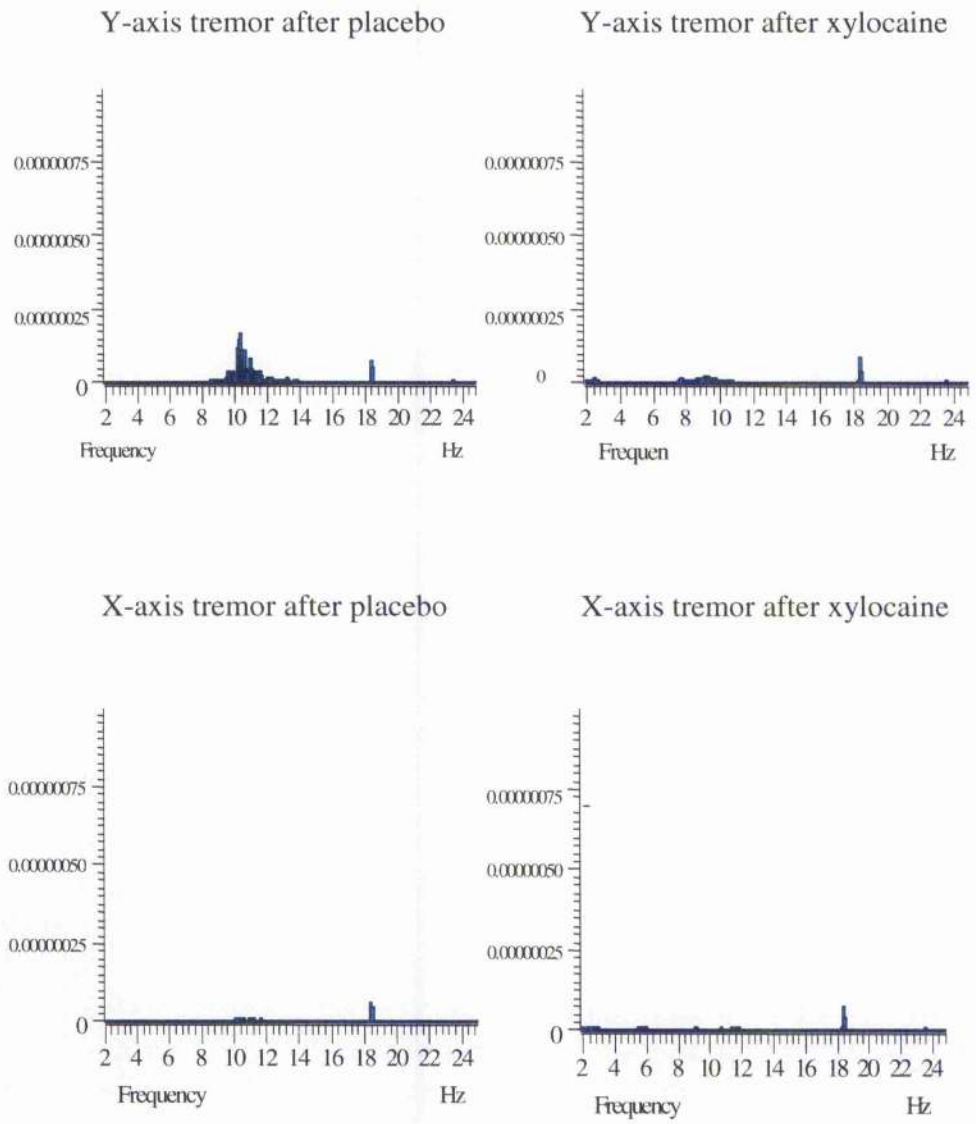


Figure 5.11. This shows spectra for x and y tremor in case 5 (unknown tremor).
See table 1 for clinical details. The top pair of spectra is calculated for 60 seconds of y-axis tremor 30 minutes after application of a placebo spray (top left) and a xylocaine spray (top right). The Lower pair of spectra show x-axis tremor.

The ordinates show power in volts^2.

5.5.6 Case 6: Unknown tremor

Figure 5.12 shows specimen recordings of x and y-axis tremor in this volunteer. The upper panel shows tremor 30 minutes after the application of a placebo. The lower panel shows tremor 30 minutes after the xylocaine spray. The amplitude of both the x and y-axis tremor is greater after the placebo than after the xylocaine.

Figure 5.13 shows the tremor spectra calculated from these recordings. It can easily be seen that y-axis tremor after xylocaine is bigger than y-axis after the placebo. The peaks in the x and y spectra occur at the same frequency, in the range 6-10 Hz. In this case the amplitude of the peak increases after xylocaine application. Inspection of the data in table 5.1 shows that this small effect would also have been present in the same person at 45 and 60 minute intervals after the application of the sprays.

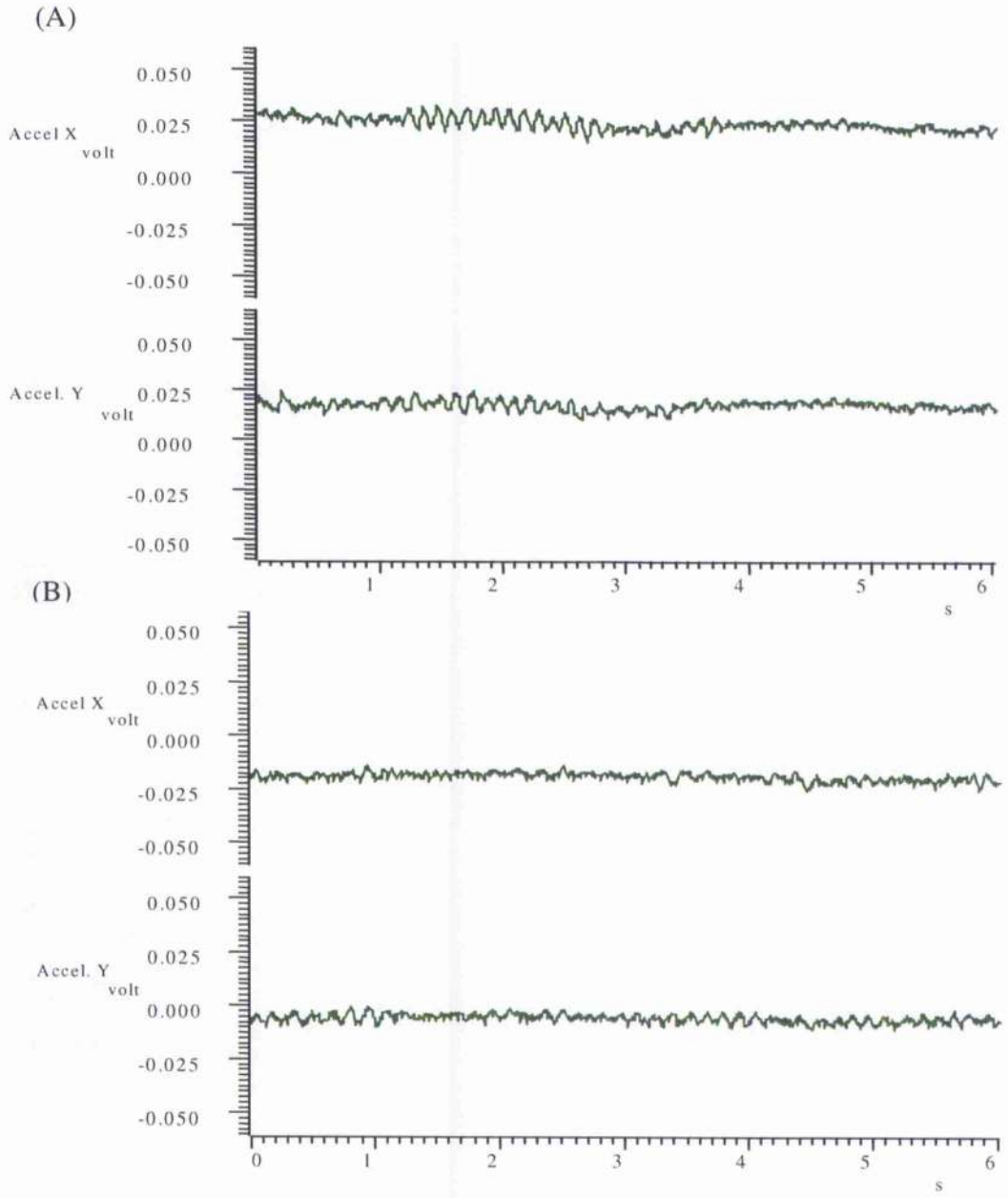


Figure 5.12. Data recording hand tremor of an unknown type at two visits.

The recordings were made 30 minutes after application of a placebo spray (A upper panel) or 30 minutes after a xylocaine spray (B lower panel).

The accelerometer calibration for both channels was 80 millivolts equal to an acceleration of 1 metre/second/second.

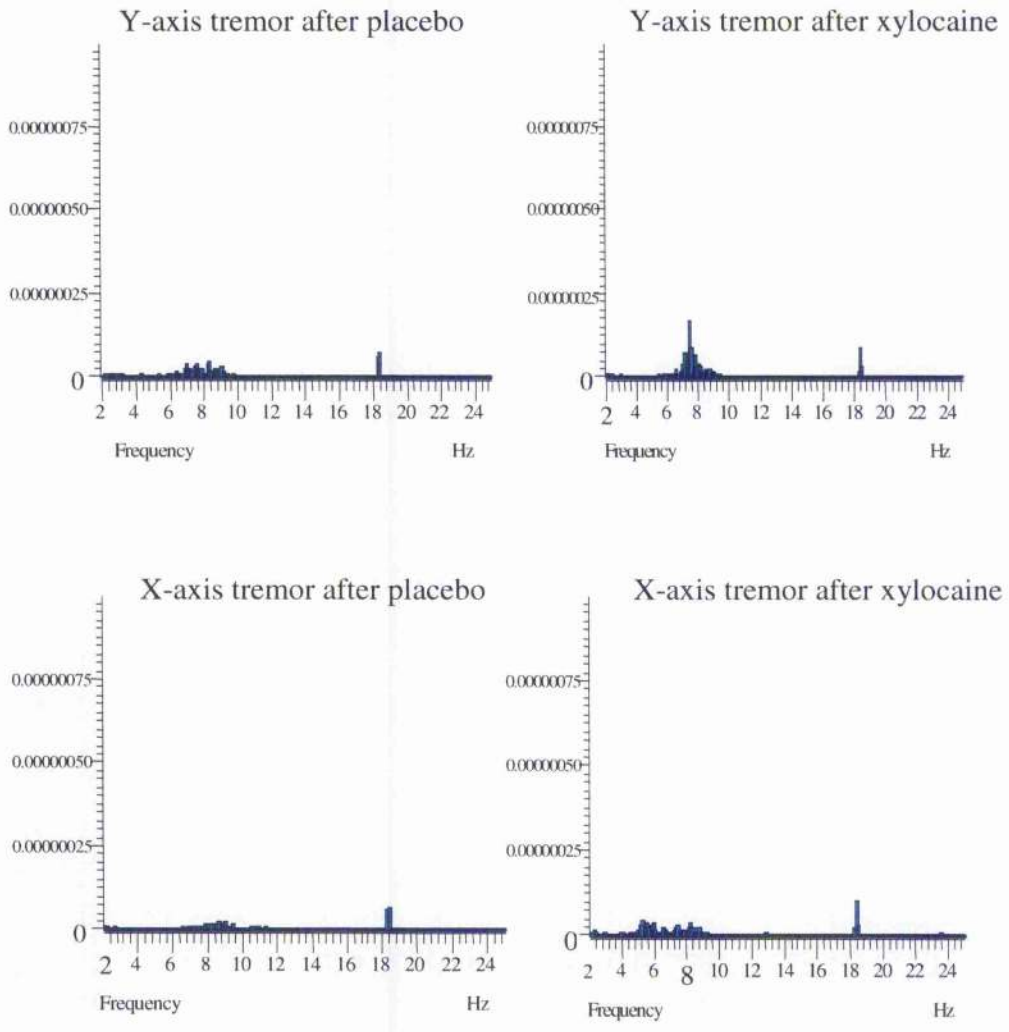


Figure 5.13. Spectra for x and y tremor in case 6 (unknown tremor).

See table 1 for clinical details. The top pair of spectra is calculated for 60 seconds of y-axis tremor 30 minutes after application of a placebo spray (top left) and a xylocaine spray (top right). The lower pair of spectra show x-axis tremor.

The ordinates show power in volts^2.

5.6. Discussion

Chapters 3 and 4 described investigations of the effect of topical anaesthesia on tremor in the hands of normal subjects at rest during voluntary movements of the wrist. Briefly, the results showed no significant difference between the tremors after topical anaesthesia or placebo. There was no evidence of tremor reduction after application of xylocaine. This chapter describes an investigation of the effect of topical anaesthesia on hand tremor in six cases of pathological tremor. Again, no evidence of reduction in pathological tremors was found.

Pathological tremors may occur as isolated movement disorders, such as essential tremor. Tremor may also be present as a manifestation of Parkinson's disease, cerebellar disease or other movement disorders. Although the amplitude of tremor often varies, the frequency is usually relatively constant for the affected individual. This may be seen, for example, in Case 1, (Parkinson's disease, figure 5.3) where the tremor frequency had a range 4-6 Hz. In case 2 (essential tremor, figure 5.5) the tremor frequencies had a range of 8-12 Hz.

Different pathological tremors appear likely to arise through a variety of different mechanisms (McAuley and Marsden, 2000). Tremors may be divided in to discrete categories according to their frequency and it is possible that tremors of similar frequency may have similar modes of generation (McAuley and Marsden, 2000).

The pathological cases presented here do not cover the whole range of pathologies. They reflect a sample of the cases seen in one clinical unit. They do contain example of more than one type of pathology. There are diagnosed examples of Parkinsonism

(case 1) and essential tremor (case 2). Case 5 is probably psychogenic tremor. Case 3 is possibly a second example of Parkinsonism. They are two or more examples of undiagnosed tremors. However, the data that presented in this study found no significant difference in the tremors after topical anaesthesia or after placebo application. Whatever the mechanism generating the tremor in these pathological cases, it did not change its behaviour after topical anaesthesia of the skin.

The results in this study are in conflict with those of Pozos and Iaizzo (1992). They reported a significant suppression of the amplitude of essential tremor of the hand after topical anaesthesia with 4% xylocaine in six cases. The results in this chapter are consistent with those in Chapters 3 and 4 i.e. that topical anaesthesia is indistinguishable from placebo effects. Pozos and Iaizzo also reported that in their experiments topical anaesthesia reduced resting tremors. The reasons for the differences between the results in that paper and the results reported here have already been discussed in chapter 3 and 4. In summary, the difference could be due to variations in methodology and the selection of criteria of the pathological cases.

Chapter 6

Effects of topical anaesthesia and placebo on skin sensations

6.1 Introduction

The previous chapters 3, 4 and 5 described investigations of the effects of topical anaesthesia and placebo sprays on postural tremor, tremor during movement and pathological tremor. The results show no statistically significant difference in tremor following the application of a topical anaesthesia or placebo spray.

These observations raise a final question: is there a difference in the skin sensation following application of these sprays? Surprisingly, none of the early studies of the effects of topical anaesthesia report any tests of skin sensation (Pozos and Iaizzo, (1992); Pozos et al., (1984); Pozos et al., (1982).

The aim of these studies to investigate if cutaneous sensation changes after application of the topical anaesthetic and placebo sprays.

6.2 Aims:

The three aims of the experiments reported in this chapter are:

1. To investigate heavy touch, pinprick and light touch sensations before and after the application of topical anaesthesia and placebo sprays.

2. To investigate the repeatability of tests light touch sensation.

3. To investigate change in the repeatability of the effects the topical anaesthesia on sensation.

6.3 Materials and methods

6.3.1 Subjects

Twenty adult volunteers both male and female were recruited from students and staff of Glasgow University. They were all neurologically normal. The experimental protocol was approved by the Research Ethics Committee. Informed consent was obtained from each volunteer. Each volunteer made two visits to the laboratory. Each visit lasted approximately one hour.

6.3.2 Testing protocol

The nature of the experiment was explained to the subjects. The sequence of application of placebo and local anaesthesia was randomised by asking the volunteer to select a sealed envelope containing the sequence of sprays.

Subjects were seated with their arm supported on a table. The skin area under investigation was shaved. A stamp was use to print an array of 64 spots on the skin of the anterior forearm on the medial aspect, 2 cm - 3 cm below the elbow joint. The array was 16 mm by 16 mm and the dot spacing are 1.5 mm.

6.3.4 Recording protocol

Subjects were instructed not to look at test area during the testing. Control tests were carried out before the application of either spray. Stimuli were applied to each of the 64 test points. All the results of the test were recorded on data collection sheet. This is illustrated in figure 6.1. The tests were repeated every 15 minutes for one hour.

6.3.5 Stimulation techniques

The spots marked on the skin were sequentially stimulated with a fine von Frey bristle to test light touch, a stiff bristle to test heavy touch and a pin to test pin prick sensation. The reported sensation at each spot was recorded on a results sheet. A typical set of responses is illustrated in figure 6.1.

6.3.6 Spray application

Details of the spray application were described in chapter 2, sections 2.10.

6.3.7 Data analysis

For each volunteer several features of skin sensation were recorded. For each class of stimulation, every positive response was recorded at the appropriate point on a grid. The total number of positive responses by each subject was calculated for each visit. ANOVA tests (Minitab version 14) were used to compare the number of positive responses for each type of stimuli over five time periods and two experimental sessions. A General Linear Model was used. The significance level was set at $P \leq 0.05$.

6.4 Results

6.4.1 Effects of xylocaine and placebo on cutaneous sensation

All 14 subjects were tested twice on different days to investigate the repeatability of sensations repeatability. Each mode of sensation was analysed separately.

Distribution of light touch points over 60 minutes after xylocaine application

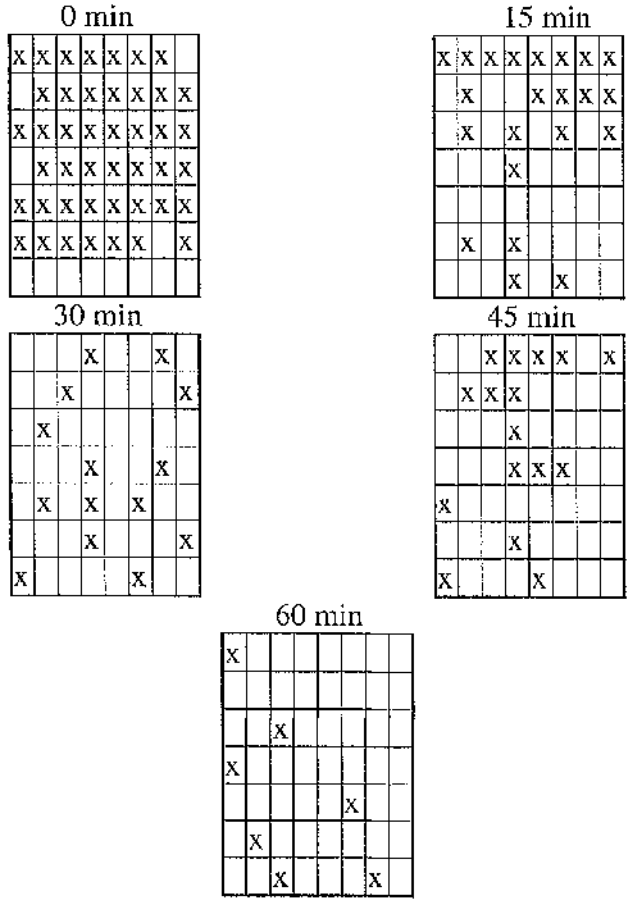


Figure 6.1 A specimen recording sheet for light touch sensation test.

These panels show a typical record of light touch sensation in one volunteer. X indicates a positive response to light touch stimulation. Blank cell indicate no response. Each panel shows the result of testing the same points at the specified time after the application of topical anaesthetic solution.

The volunteer's response gradually reduces with time.

6.4.2 Heavy touch sensation after xylocaine or placebo application.

Table 6.1a, b shows the number of grid points at which each volunteer reported heavy touch sensation. The upper section of the table shows the data recorded after application of xylocaine. The lower section shows the responses in the same volunteers after application of the placebo spray. In summary, these data show that all volunteers were sensitive at all points tested for the hour after application of either spray.

6.4.3 Pinprick touch sensation after xylocaine or placebo application

Table 6.2 a, b shows the results of pin prick tests of sensation in the same volunteers. The data are presented in a similar way to table 6.1. The results show that for 12 of the volunteers, pinprick sensation is present at all points tested after application of either spray.

Two volunteers show differences to this pattern. Subject 1 shows very small reductions in pinprick sensation 30 minutes after application of xylocaine but no change after application of the placebo. Subject 3 shows progressive reduction pinprick sensation at 30, 45 and 60 minutes after xylocaine application. This volunteer also reported much smaller reductions in sensation after the placebo spray.

(A)

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	64	64	64	64	64
2	64	64	64	64	64
3	64	64	64	64	64
4	64	64	64	64	64
5	64	64	64	64	64
6	64	64	64	64	64
7	64	64	64	64	64
8	64	64	64	64	64
9	64	64	64	64	64
10	64	64	64	64	64
11	64	64	64	64	64
12	64	64	64	64	64
13	64	64	64	64	64
14	64	64	64	64	64

(B)

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	64	64	64	64	64
2	64	64	64	64	64
3	64	64	64	64	64
4	64	64	64	64	64
5	64	64	64	64	64
6	64	64	64	64	64
7	64	64	64	64	64
8	64	64	64	64	64
9	64	64	64	64	64
10	64	64	64	64	64
11	64	64	64	64	64
12	64	64	64	64	64
13	64	64	64	64	64
14	64	64	64	64	64

Table 6.1 A, B Heavy touch sensation after application of xylocaine and placebo.

Part A shows the number of points at which each volunteer reported heavy touch sensation at intervals after the application of xylocaine. Part B shows the number of points at which each volunteer reported heavy touch sensation at intervals after the application a placebo spray.

(A)

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	64	64	57	64	64
2	64	64	64	64	64
3	64	64	55	44	19
4	64	64	64	64	64
5	64	64	64	64	64
6	64	64	64	64	64
7	64	64	64	64	64
8	64	64	64	64	64
9	64	64	64	64	64
10	64	64	64	64	64
11	64	64	64	64	64
12	64	64	64	64	64
13	64	64	64	64	64
14	64	64	64	64	64

(B)

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	64	64	64	64	64
2	64	64	64	64	64
3	64	64	64	60	62
4	64	64	64	64	64
5	64	64	64	64	64
6	64	64	64	64	64
7	64	64	64	64	64
8	64	64	64	64	64
9	64	64	64	64	64
10	64	64	64	64	64
11	64	64	64	64	64
12	64	64	64	64	64
13	64	64	64	64	64
14	64	64	64	64	64

Table 6.2 a, b. Pinprick sensation after application of xylocaine and placebo.

Part A shows the number of points at which each volunteer reported pinprick sensation at intervals after the application of xylocaine. Part B shows the number of points at which each volunteer reported pinprick sensation at intervals after the application of a placebo spray.

Subjects 1 and 3 in A show reductions in sensation after xylocaine application. Subject 3 also showed small decreases in sensation after placebo application.

6.4.4 Light touch sensation after xylocaine and placebo application.

Table 6.3 a, b shows the results of tests of light touch sensation in the same group of volunteers. The data are presented in a similar way to table 6.1.

The results of these tests are very different from those reported in tables 6.1 and 6.2. The mean number of light touch responses was 22 and 24 out of 64 tests before application of the sprays on the two days. The results also show big variation in number of positive responses between subjects. Some subjects reported few touches on both days, for example subjects 11 and 5. In contrast, some subjects report a large number of touches on both days, for example subjects 13 and 14.

Table 6.3 also shows the mean and the standard deviations of the number of positive responses at each time after application of the spray. The mean number of positive responses is lower in each test after application of xylocaine that it is at the corresponding time after application of the placebo. However, these differences are not statistically significant (ANOVA, $P = 0.149$)

The mean values do not fully represent the variation in individual response. These are illustrated graphically in figure 6.2. It can be seen that some individuals have a high initial response rate which persists after application of either spray. Others have a low initial response rate which is also little affected by the sprays. Subject 13 was very sensitive to light touch and this did not change. Subjects 5, 6 and 7 were insensitive to light touch and this did not change after xylocaine application.

Subject 11 had a low response rate in the initial test but after application of xylocaine there was a progressive reduction from the first test at 15 min and this continued for the full hour. In contrast, on the other trial, when this volunteer was exposed to the placebo spray, the same low initial response rate was also seen but this rose sharply during the experiment to reach positive responses to 54 of the 64 stimuli.

Subject 14 was very sensitive and the number of positive responses to light touch stimulation was reduced over the hour after application of the xylocaine but was unchanged after the application of the placebo.

These different patterns of responses are illustrated in figure 6.3. It shows examples of the four types of response observed. Figure 6.3 shows low light touch sensitivity not affected by either xylocaine or the placebo, high sensitivity not affected by xylocaine or placebo, low initial sensitivity which increased after xylocaine but not after the placebo and high initial sensitivity which fell after xylocaine but not after the placebo.

In summary there is no significant difference in the light touch sensation after the application of topical anaesthetic and placebo ($P = 0.781$, ANOVA).

(A)

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	15	11	16	10	19
2	12	9	8	7	10
3	14	14	10	10	8
4	19	17	18	18	16
5	9	8	6	5	4
6	9	6	12	8	8
7	11	10	8	10	10
8	35	17	9	11	7
9	25	11	7	6	24
10	21	11	16	19	29
11	10	7	2	2	5
12	23	16	19	3	7
13	49	35	45	33	55
14	52	22	14	16	7
Average	22	14	14	11	15
St. Dev.	14	8	10	8	14

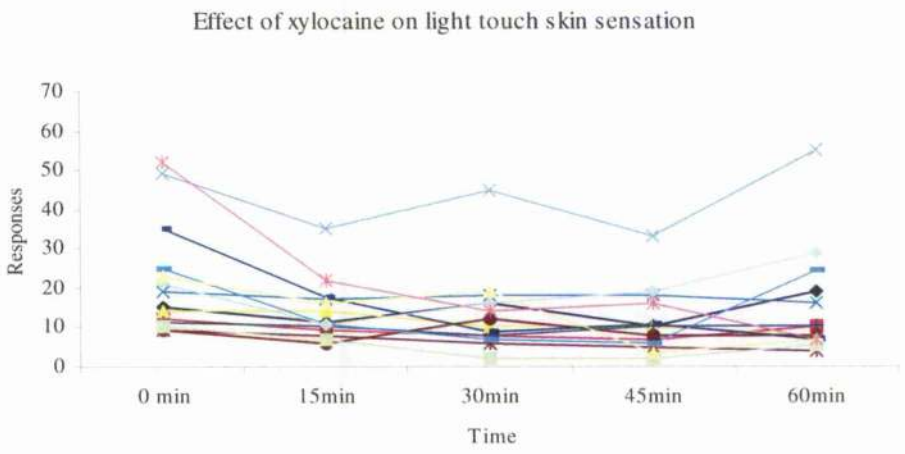
(B)

No. Subjects	0 min	15 min	30 min	45 min	60 min
1	16	10	8	5	7
2	16	32	13	8	15
3	16	15	8	2	16
4	19	8	4	1	8
5	8	4	0	6	2
6	10	4	1	0	0
7	18	13	13	13	20
8	38	17	28	4	4
9	26	64	49	46	56
10	19	14	26	18	33
11	6	33	36	35	54
12	36	17	38	37	24
13	49	29	29	41	44
14	53	57	60	64	64
Average	24	23	22	20	25
St. Dev	15	19	19	21	22

Table 6.3A, B Light touch sensation after xylocaine and placebo application.

Part A shows the number of points at which each volunteer reported light touch sensation at intervals after the application of xylocaine. Part B shows the number of points at which each volunteer reported light touch sensation at intervals after the application of a placebo spray.

(A)



(B)

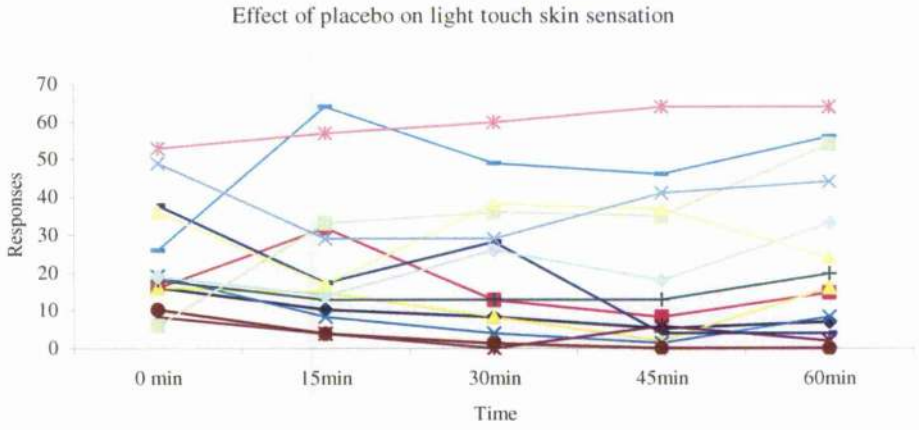


Figure 6.2 A, B Plot of the individual responses to light touch stimulation after application of placebo and xylocaine sprays.

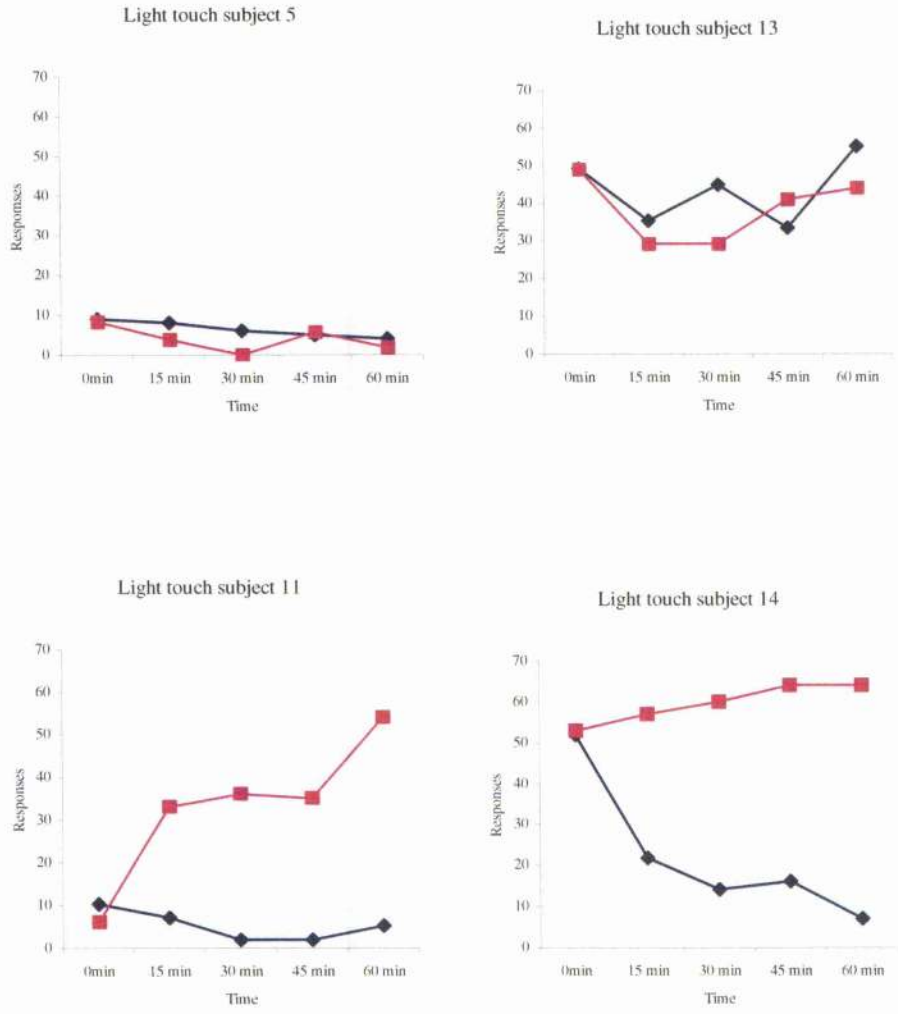


Figure 6.3. Effects of xylocaine and placebo sprays on light touch sensation.

The diamond symbols show data after placebo application. Dark squares show data after xylocaine application.

Subjects 5 and 13 show no change in light touch sensation after xylocaine or placebo spray.

Subject 14 shows reduction light touches after xylocaine. Subject 11 shows increase in light touch sensation after placebo application.

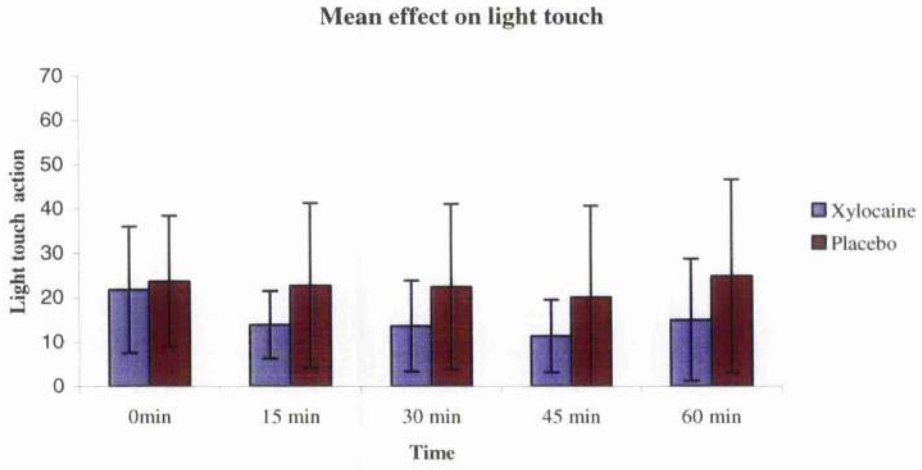


Figure 6.4 Mean and standard deviations of the response to light touch stimulation before and after application of placebo and xylocaine

The data shows clear no statistically significant changes after application of the placebo spray (P = 0.97, ANOVA).

The data shows a gradual reduction in light touch sensation over one hour after xylocaine application. This reduction was not statistically significant (P = 0.149 ANOVA).

There is no statistically significant difference between the mean number of positive responses to light touch stimulation after placebo or xylocaine over the 60 minutes (P= 0.781, ANOVA).

6.5 Repeatability data

The responses of a group of volunteers to repeated testing was investigated in two ways. Firstly, the responses to cutaneous stimulation was compared before the application of the sprays. These data are extracted from that already presented in tables 6.1 to 6.3. The responses to heavy touch and to pinprick stimulation are clear-cut. All 14 volunteers responded positively at all sites on all occasions. The data shown below in table 6.4 shows the responses of these volunteers to light touch stimulation at the beginning of both experiments i.e. before the blind application of placebo or xylocaine. It is clear that there are no differences in the response rates. This was confirmed by testing with an ANOVA test, (P= 0.470).

Subject	Day 1	Day 2
1	15	16
2	12	16
3	14	16
4	19	19
5	9	8
6	9	10
7	11	18
8	35	38
9	25	26
10	21	19
11	10	6
12	23	36
13	49	49
14	52	53

Table 6.4. A comparison of the number of positive responses to light touch stimulation at the start of the experiment on 2 days.

The table shows number of positive responses to light touch stimulation on two days. No spray was applied to the skin. There is no significant difference in the number of responses between the 2 days (P = 0.470, ANOVA).

A second set of six volunteer had their light touch sensation twice after application of xylocaine. Their data is summarised in table 6.5. Again there is a similarity in the results before the application of the spray. This continues at each of the testing times after the application of the xylocaine. There was no statistically significant differences between their responses on the two days (P = 0.308, ANOVA).

Subject	0 minutes		15 minutes		30 minutes		45 minutes		60 minutes	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
1	10	15	11	11	13	16	17	10	13	19
2	13	12	8	9	14	8	10	7	10	10
3	11	9	8	8	2	6	2	5	1	4
4	21	19	15	17	13	18	15	18	14	16
5	21	14	14	14	10	10	7	10	8	8
6	12	9	21	6	20	12	8	9	12	8

Table 6.5. A comparison of the number of positive responses to light touch stimulation after xylocaine application on 2 days.

The data shows similar on sensation on the 2 days. There are not statistically significant differences between the two days (P = 0.308, ANOVA).

6.6 Discussion

In the previous chapters 3, 4, and 5 the effect of xylocaine on tremor of the hand were investigated. The results showed no significant difference between the mean tremor amplitudes after application of placebo and xylocaine sprays. In this chapter the effects of topical anaesthesia and placebo sprays on light touch, heavy touch and pinprick sensation was investigated in 20 subjects.

There were no differences in pin prick of heavy touch sensation in almost all of the volunteers. One volunteer reported a reduction in pin prick sensation after xylocaine. Their light touch sense shows a similar reduction after xylocaine. However, their light touch is also reduced by the application of the placebo. This person's heavy touch sensation was unaffected over the same period.

The results in figure 6.4 show no significant changes in light touch sensation in the hour after application of xylocaine ($P = 0.149$) or placebo sprays ($P = 0.97$). Neither is there any difference between sensation after the two sprays ($P = 0.781$).

The reproducibility of each of the modes of sensation over two different days is clear. The data in table 6.4 shows no significant variation in 14 subjects over 2 days. The responses to light touch after stimulation after application of xylocaine is similarly consistent, though it was possible only to test six people in this part of the study.

These data show almost no variation in the number of positive responses to pin prick and heavy touch stimulation between people, between the same person on two days

and before and after placebo or xylocaine sprays. These senses are simply not affected by the application of xylocaine. However, the position is more complicated with the responses to light touch stimulation. The mean data shows no significant differences after application of xylocaine and placebo. In this aspect, it is like the heavy touch and pinprick sensation. However the response rates for light touch were much lower than for the other two senses. Some individuals have data which are consistent with a differential action of xylocaine and placebo. In figure 6.3 subject 14, it appears that light touch sensation is unaffected by the placebo spray but is sharply reduced by the xylocaine. However, in the same figure it is clear that subject 11 reports a sharp increase in light touch responses after the application of the placebo and that xylocaine appears to have no action. This raises the question of how accurately the volunteers reported their sensations or how many of the reported sensations were the product of illusions rather than the result of mechanical stimulation of the skin. It is beyond the scope of this discussion to address these questions.

In conclusion, these data show no statistically significant difference in light touch, heavy touch and pin prick sensation after the application of placebo and xylocaine sprays. The results are also consistent with some individuals, like subject 14, showing a differential response to placebo and xylocaine. This is the sole example of such behaviour and overall it is safe to conclude that the topical anaesthesia does not affect cutaneous receptors.

Chapter 7

General discussion

Tremor is a big problem for many patients since it affects many of daily living activity. It is also of interest to scientists and clinicians because its analysis may assist differential diagnosis and so help to a clarify the prognosis for the patient and identify potential treatments.

A number of scientific techniques have been used to investigate the origins and mechanisms of tremor. Most of the approaches assess the dependence of tremor on sensory input from the limb, rather than examining directly the central mechanisms which generate the tremor. One approach is to investigate the power spectra of tremor of the hand with and without loading of the hand by applying additional weights. The extra weight changes the mechanical components of tremor in a predictable way and leaves the neurological components unaffected (Deuschl et al, 2001). Other authors have investigated the relationship between tremor, motor unit activity and surface EMG with cross correlation and coherence measures (Halliday, Conway, Farmer and Rosenberg, 1999). This shows significant changes in the characteristics of the tremor with increased inertial loading. The most common experimental approach is to calculate some feature of the tremor spectrum. Some authors identify the amplitude of the peaks in the tremor spectrum (Gresty and Buckwell, 1990). The essential problem with this approach is that the spectrum may be complex with several smaller peaks, some of which may be ignored by the analysis. Others have analysed the whole tremor signal and calculated the root mean

square value (Pozos and Iaizzo, 1992). The difficulty here is that low frequency components, below 2 Hz, may reflect changes in limb position rather than changes in tremor. Higher frequency components, possibly above 20 Hz, may reflect other non-tremor features such as the firing of individual motor units (Findley and Koller, 1994). The data analysis in this thesis used a band frequency analysis and studied tremors in the following frequency ranges: 2-6 Hz, 6-12 Hz, 12-20 Hz and 2-20 Hz. These frequency ranges contain all the tremor frequencies described in the classification of tremors in chapter 1. These are listed in figure 1.2 of the General Introduction and Literature Review in Chapter 1.

Tremor amplitude is a variable and changes from minute to minute and day-to-day, even in the same person (Findley and Koller 1994). This makes the design of experiments to record and investigate tremor very difficult. The fluctuations in amplitude occur over a time scale of only a few seconds and establishing a baseline tremor is difficult. These observations are applicable for resting and action tremor in normal individuals. This can be seen in figures 3.1 and 4.2 of this thesis. It is an even bigger problem in cases of pathological tremor. Here the amplitude changes may be very large, as can be seen in figures 5.1 and 5.2, which show recordings of tremor in a case of Parkinson's disease (Case 1). There is often difficulty in finding a group of similar clinical cases and this depends on many factors, not least co-operation of the hospital and the physicians. There are also problems with patients who have other illnesses and who may have multiple medications, such as β blockers that may also affect their tremor. These features are very clearly seen in table 5.1.

Three main experimental aims were identified:

1. Does topical anaesthesia have an effect on physiological tremor at rest and during movements?

2. Does topical anaesthesia have an effect on the surface EMG of flexor and extensor groups in the forearm?

3. Does topical anaesthesia have an effect on pathological tremor?

7.1 Postural Tremor

Despite all the experimental difficulties listed before, it is clear that the first two aims have been achieved. Topical anaesthesia has the same action as a placebo application and the author concludes that it does not affect tremor at rest or during movement. This conclusion is based on the data in chapter 3 and 4. The same result is found for the six cases of pathological tremor presented in this thesis. The results shown here are clear but do not agree with some earlier studies published by Mills and Pozos, (1985) and Pozos and Iaizzo, (1992).

This thesis investigated the effect of topical anaesthesia on hand tremor in 37 volunteers: 19 normal subjects at rest, 12 normal subjects during movements and 6 pathological tremors at rest. The author hoped that topical anaesthesia, following the application of a 10% solution of xylocaine, would have a strong effect on cutaneous receptors and that this would lead to significant reductions in the amplitude of tremor. Previous studies by Mills and Pozos, (1985) and Pozos and Iaizzo, (1992) had shown that topical anaesthesia caused reductions in clonus, action tremor of the

ankle joint in the lower limb and essential tremor on the hand at rest. They used a 4% anaesthetic solution.

The experiments described in this thesis show no significant effects and difference between topical anaesthesia and placebo on hand tremor at rest and during voluntary movement in normal subjects. In addition, there was no significant effect on pathological tremor in a series of six case studies. It is possible that the topical anaesthesia applied to intact skin might not penetrate the skin in large enough quantities to have a desensitising effect. It is difficult to imagine that 4% xylocaine solutions produced topical anaesthesia but that a10% solution did not.

This study tested a much larger number of volunteers than Mills and Pozos. In this thesis 19 subjects were studied who had physiological tremor of the hand at rest compared to the Mills and Pozos studies in 1985 who investigated only 3 normal subjects in the physiological clonus on ankle joint of lower limb. The muscles in the forearm are innervated by the cervical nerve roots C5 to C8, while the calf muscles are innervated by L4, L5, and S1. Thus there must be substantial differences in the central nervous system pathways linking sensory neurones in these areas to the motor neurones. There are differences in mechanical features such as muscle length, mass and stiffness in the upper and lower limbs. In addition, the characteristics of motor units may vary subtly from subject to subject and the proportion of fast and slow motor units may also vary (McAuley and Marsden, 2000). It might be that the difference in results is due to the small sample sizes or to differences in the pathways controlling the upper and lower limbs.

7.2 Action Tremor

The author had hoped that the increased tremor amplitude during voluntary movements in normal volunteers might be affected by topical anaesthesia even though the smaller amplitude-resting tremor had not been changed. The increased amplitude of tremor during movement is probably caused by sub-tetanic firing and fluctuating recruitment of motor neurons that are near the threshold. The motor unit firing combines with cardioballistic factors to drive the limb at its natural frequency. The fluctuations in force and displacement may exceed the rhythmic components of physiological tremor dependent on the conditions under which tremor is measured. The effects of topical anaesthesia on hand tremor during movements have not been investigated previously.

This thesis investigated the effect of topical anaesthesia on hand tremor during movement in 12 normal subjects. Mills and Pozos, (1985) investigated physiological action tremor during movement of the ankle joint in 7 subjects. This study found no significant difference between tremor after topical anaesthesia or placebo application. Mills and Pozos, (1985) did find a significant difference. The difference in the results is probably due to the same factors described above.

7.3 Pathological Tremors

Pathological tremors have different origins from physiological tremors and often result from lesions within the central nervous system (McAuley and Marsden, 2000). Pathological tremors also tend to have much larger amplitudes. Fundamentally the same experiment of measuring resting tremor amplitudes after the application of

xylocaine or a placebo spray was repeated in a series of case studies of pathological tremors in the hope that topical anaesthesia might have a greater action than in the normal subjects. The result was consistent with those reported in Chapters 3 and 4. Topical anaesthesia had no significant effect on the pathological tremors.

In contrast, Pozos and Iaizzo in 1992 investigated the effect of topical anaesthesia on one type of pathological tremor, essential tremor of the hand. Their patients had taken Propanolol two hours before the application of the anaesthetic or the placebo. Propranalol is frequently used as a treatment for tremor and the differences attributed to the topical anaesthesia might be due to variations in the action of the Propranalol.

7.4 Conclusions

Tremor mechanisms have been investigated by many authors but the mechanisms causing tremors remain unclear. However, the precise mechanisms of tremor generation are not so important in this project. The principal question raised in this project was: does topical anaesthesia have a significant action on tremor amplitude? The long-term aim was to investigate the potential therapeutic use of topical anaesthesia in the management of pathological tremors.

The results clearly show that there is no significant action of placebo or topical anaesthesia on the magnitude of tremors at rest during movement or in a small number of case studies. There is no reason to suppose it offers a potential therapeutic treatment.

7.5 Future plans

Movement disorders cause function disabilities and they are consequences of most neurological disorders. Improved motor function in daily living activities is the most important goal of rehabilitation programs. The slow, progressive nature of these tremor producing neurological diseases presents an obvious need for long-term evaluation of tremor. There have been surprisingly few long-term studies of tremor and this is one clear topic that requires more study. In this context it may be worthwhile to investigate the effect of topical anaesthesia on tremor over longer periods and in large numbers of patients or volunteers.

The tremor patient must have a better quality of life.

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