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FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

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Modified Constraint-Induced Movement Therapy in Children with Congenital Hemiplegic Cerebral Palsy

by

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ABSTRACT

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MODIFIED CONSTRAINT-INDUCED MOVEMENT THERAPY IN CHILDREN WITH CONGENITAL HEMIPLEGIC CEREBRAL PALSY

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One new treatment strategy for children with hemiplegic cerebral palsy (CP) is constraint-induced movement therapy (CIMT). CIMT combines restraint of the less affected upper extremity and intensive exercise with the affected limb. CIMT has been shown to be effective in adults following stroke but it is not clear whether or not CIMT can readily be incorporated into clinical practice either with adults or children. An intervention that may be more practical involves the restraint element of CIMT without additional exercise (Forced use therapy-FUT). FUT has been only sparsely investigated, especially in children with CP. Different versions of CIMT protocols have been suggested as being 'child-friendly' but identifying a practical and effective protocol remains challenging. Part of a child-friendly protocol includes identification of the most appropriate type of constraint, as different splints have been used for different populations without justification of their selection. In this project, the aim was to identify the most appropriate splint from children's and parents' perspective as reflected by effectiveness and adherence to home-based FUT (feasibility study) and to investigate the functional effects of a modified version of CIMT (mCIMT) (effectiveness study) that was designed based on the findings of the feasibility study. A further aim of the study was to compare the effect of additional functional activities and feedback with constraint alone. Two questions emerged as being important during the course of the project; the first addressed poor recruitment to the effectiveness study and explored parents and therapist' views on the practicality and effectiveness of both the classic paediatric protocol and the one suggested by the present study. The second was to provide insight into the physiological effects of CIMT or other treatments that might explain variations in response. In this study a test using the lateralised readiness potential (LRP) component of the EEG that was appropriate for young children was developed and evaluated with a small sample of unimpaired children and children with CP.

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ABBREVIATIONS

AAUT: actual amount of use test

ADL: activities of daily living

AHA: assisting hand assessment

AOU: amount of use

APCP: association of paediatric physiotherapists

ARAT: action research arm test

AutoCITE: automated constraint induced therapy extender

CI: confidence interval

CIMT: constraint-induced movement therapy

CNS: central nervous system

CNV: contingent negative variation

COT: college of occupational therapists

CP: cerebral palsy

CPM: Raven's coloured progressive matrices

CVA: cerebrovascular accident

DST: dynamic systems theory

EEG: electroencephalogram

EMG: electromyography

ERP: event-related potential

EXCITE: extremity constraint induced therapy evaluation

FIM: functional independence measurement

FM: Fugl-Meyer assessment of motor recovery

fMRI: functional magnetic resonance imaging

FUT: forced use therapy

GMFCS: gross motor function classification system

ICMS: intracortical microstimulation

LRP: lateralised readiness potential

LTD: long-term depression

LTP: long-term potentiation

MAL: motor activity log

MB: mean baseline

mCIMT: modified constraint induced movement therapy

MEG: magnetoencephalography

MP: motor potential

NDT: neurodevelopmental treatment

PDMS: peabody developmental motor scales

PEDI: paediatric evaluation of disability inventory

PET: positron emission tomography

PMAL: paediatric motor activity log

QOM: quality of movement

QUEST: quality of upper extremity skills test

R&G: research & governance

RP: readiness potential or bereitschaftspotential

RT: reaction time

SMA: supplementary motor area

SPECT: single-photon emission computed tomography

TAUT: toddler arm use test

TMS: transcranial magnetic stimulation

UE: upper extremity

UMN: upper motor neuron

WMFT: Wolf motor function test

CHAPTER 1

INTRODUCTION

1.1 OVERVIEW

The most commonly used approach to the management of children with cerebral palsy (CP) is Neurodevelopmental Treatment (NDT), based on the Bobath approach. Although NDT has been used clinically for many years, there is a paucity of evidence for its effectiveness (Mark and Taub, 2004, Sterr and Saunders, 2006). Constraint-induced movement therapy (CIMT) and forced-use therapy (FUT) are new approaches informed by recent advances in the field of motor learning and for which there is growing research evidence for effectiveness. Despite this, many issues still need clarification and further research is required especially in children before conclusions can be made regarding the efficacy and practicality of these interventions. Arguably, the biggest problem that prevents this treatment from becoming widely used clinically is the issue of practicality. The great intensity and duration suggested by the original protocol of CIMT has been criticized as being impractical and consequently many children, parents and therapists decline to use it despite evidence for its effectiveness. This project, which falls into two main sections, was designed to gather preliminary data regarding two major issues for paediatric CIMT; firstly the appropriateness of different constraints and secondly the effectiveness of a home-based, 'child-friendly' regimen. The intervention tested in the second part of the study was designed based on findings of the first study and was significantly less intensive than the either adult CIMT protocol or other previously reported paediatric protocols. The survey investigating parents and therapists' views on CIMT was undertaken following the effectiveness study and addressed issues of recruitment and adherence, with the objective of informing the design of a practical and effective paediatric protocol. Interesting findings have been reported by a similar study conducted with adults (Page et al., 2002a). The physiological effects of CIMT have been examined in adults but not in children. The reason for this may be the lack of 'child-friendly' techniques. As part of this project, a preliminary study was undertaken to develop a simple child-friendly test to record the Lateralised Readiness Potential (LRP)

component of the Electroencephalogram (EEG) as a potential predictor of response to CIMT and indicator of physiological change in response to treatment.

The thesis presents a critical review of the literature concerning all the relevant areas of the project and comprises: a general overview of cerebral palsy with a special focus on hemiplegia and how hand function is affected; development of theories of motor control and motor learning, the variables affecting it and the underlying physiology, as well as the cortical changes occurring during learning and rehabilitation after a brain injury; a critical review of the literature on constraint-induced movement therapy (CIMT) and forced use therapy (FUT) in both adults with stroke and children with CP and of the outcome measures that were used in this study and rationale for selection. The methods and results of the feasibility study are presented along with a discussion on the main findings that informed the second part of the project, the effectiveness study. Detailed presentation of the methodology and results of the effectiveness study follows with a discussion of the findings, comparison with the results of other studies, presentation of the strengths and limitations of the project and suggestions for future research. The two complementary studies, the survey and the LRP study are then presented in detail before the conclusion that points out the main outcomes of this project.

CHAPTER 2

LITERATURE REVIEW

An overview of cerebral palsy, focusing on spastic hemiplegia and the upper limb is presented. The historical development of understanding motor control and motor learning is presented and recent advances have been critically reviewed, mainly in the context of plasticity and recovery. The literature published on CIMT and FUT is critically reviewed and discussed. A critical appraisal of potential outcome measures and rationale for the selection of those used in the study is presented.

2.1 CEREBRAL PALSY

This study was conducted with a group of children with congenital, spastic, hemiplegic cerebral palsy (CP). The reason for selecting this group was that the intervention that we tested is more appropriate for children with spastic hemiplegia than other types of CP. In addition, restricting the sample to congenital cerebral palsy only was considered to provide a more homogeneous group of participants. Thus, this chapter provides an overview of CP literature and discusses spastic hemiplegia, while especially dealing with upper limb difficulties.

2.1.1 Overview of cerebral palsy

Cerebral palsy (CP) refers to a non-progressive disorder of movement and posture arising in the developing brain. It may arise from a disorder of development or be acquired as the result of an insult to the central nervous system (CNS). The lesion may be in a single or multiple locations of the brain, cortical or subcortical (mostly in the territory of middle cerebral artery), while spastic hemiplegia has often been associated with periventricular lesions (Hoon et al., 1997, Niemann et al., 1994, Piovesana et al., 2001). Although the brain lesion is non-progressive, the resultant movement disorder may change depending on a variety of conditions such as the individual's development, the environment and exercise (Albright, 1996). Some cases might include a sensory component and other co-morbidities but this is not part of the classic definition of the condition (Scherzer and Tscharnuter, 1982). CP is not an etiologic diagnosis but a clinical descriptive term. Reservations have been expressed about the exclusive focus on motor deficit, given that CP may include impairments of

a wide range of functions. An updated definition has thus, been suggested (Bax et al., 2005):

'CP describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception and/ or behaviour and/ or by a seizure disorder'.

Indeed, common additional impairments in CP include cognitive impairments, behavioural problems, sensory impairments, such as astereognosia and impaired two-point discrimination and motor planning deficits (Mutsaarts et al., 2004, Odding et al., 2006). Impaired cognition may include both global and specific cognitive processes, such as attention or the capacity to incorporate and interpret information; this may further restrict learning, as suggested by therapists (Bartlett and Palisano, 2002), who reported that although the relationship between cognitive ability and acquisition of motor abilities is nonlinear, cognitive abilities below a certain cut-point clearly influence motor development. In the present study, the aim was to include children that could understand and follow simple instructions and thus, could comply with the study's protocol. The cognitive test (Raven's Coloured Progressive Matrices) used as a screening measure ensured that participants' cognitive level was not falling in the intellectually impaired category. Behavioural problems present in CP may include mood and anxiety disorders, rigidity, dullness, low frustration tolerance and aggressiveness (Bax et al., 2005). High levels of anxiety and frustration or anger and irritability were thought of as excluding factors for the present study, since the influence of these neuropsychological disorders has been suggested to be contradictory to the use of CIMT (Morris et al., 2006). Motor planning disorders are also very common in CP but these will be discussed later, as they are of particular interest in hemiplegia.

Aetiologies of CP are commonly divided into those of prenatal, perinatal and postnatal origin with the upper age limit for postnatal aetiologies varying between studies from the 28th postnatal day and up to the 5th year (Croen et al., 2001, Pharoah et al., 1989). However, information from magnetic resonance studies, as well as epidemiological studies strongly suggest that prenatal brain insults are the

predominant factors associated with CP, especially in term infants (Hoon et al., 1997). Prematurity is a major factor in CP and is noted in at least one-third of cases. Malformations of the CNS can also be a prenatal cause of CP. Regardless of gestational age or birth weight, the maternal prenatal condition may have a significant effect on the child's CNS development. General health status and untreated medical conditions may be relevant. The use of drugs, alcohol, tobacco, exposure to radiation or environmental pollutants during pregnancy are known to have some negative effects on fetal development but the possible relation to CP is not yet established (Cogher et al., 1992, Scherzer and Tscharnuter, 1982). There are also other aetiologies that are thought to be factors but this aspect will not be reviewed further as it is not directly relevant to the objectives of the present study.

Regarding the types of CP, spastic, dyskinetic (which includes choreoathetoid, and dystonic), ataxic and hypotonic types are widely recognized. The main focus in this study will be the spastic type of CP, as it affects the sample of children that have taken part in this study. The distribution of impairment in spastic CP is commonly described by the terms diplegic (upper limbs less affected than lower limbs), quadriplegic or tetraplegic (upper limbs affected as much as lower limbs), while hemiplegic CP implies involvement of two limbs on the left or the right side of the body and monoplegia can be any one limb (Cogher et al., 1992, Levitt, 1982, Stanton, 1992). It is estimated that the percentage of children with hemiplegia is about one third of all cases with CP (Brown et al., 1987). Hemiplegic CP is the most common type among children born at term and is second to diplegia among children born preterm (Wiklund and Uvebrant, 1991).

2.1.2 Spasticity and CP

Spasticity is a motor disorder associated with the upper motor neurone (UMN) syndrome that can lead to major disability, interfere with function and produce secondary complications, such as contractures. Spasticity is seen principally in anti-gravity muscles; flexors in the arm and extensors in the leg (Sheean, 1998, Wood et al., 2005). The most common definition for spasticity is the one by Lance (1980): *Spasticity is a motor disorder that is characterised by a velocity dependent increase in the tonic stretch reflex with exaggerated tendon reflexes, resulting from the hyper-*

excitability of the stretch reflex, as one component of the upper motor neurone syndrome.

However, this definition is widely viewed by clinicians as narrow and limiting since the term 'spasticity' is actually used to describe the variety of pathophysiological phenomena observed following an UMN lesion that are not related to the features described in the original definition. Thus, spasticity is not a pure motor disorder and does not exclusively result from hyperexcitability of the stretch reflex. A more recent definition suggested by Pandyan et al (2005) describes spasticity as *'disordered sensori-motor control, resulting from an UMN lesion, presenting as intermittent or sustained involuntary activation of muscles'.*

Traditionally, hypertonia has been exclusively attributed to muscle hyperactivity caused by spasticity. Nevertheless, hypertonia occurs even in the absence of electromyographic (EMG) activity, which indicates alterations in intrinsic muscle properties (Vaz et al., 2006). Following an UMN lesion, neurogenic changes can be rapidly accompanied by alterations in the mechanical properties of muscle and connective tissue, such as tendon compliance and physiological, morphological and histochemical changes in muscle fibres, resulting in increased stiffness. Decreased number of sarcomeres leads to shortening of the muscle length due to muscles not being extended through the normal range of movement for prolonged periods. These non-neural components influence the spastic muscle tone and can contribute to impaired movement, abnormal postures and deformity (Brown, 1994, Burridge et al., 2005, Sheean, 1998, Voerman et al., 2007).

Muscle fibres are highly adaptable to the amount and type of neural activity that they receive (Ponten et al., 2005). Maintaining or increasing contractile and connective tissue length is important and can be accomplished through exercise (Kilbride and McDonnell, 2000, Ostensjo et al., 2004). Recent studies (Kileff and Ashburn, 2005) have shown that in contrast to what was the clinicians' belief in the past, exercise does not have a detrimental effect on spasticity.

Although it is commonly assumed that there is a causal relationship between spasticity and function, there are cases in which spasticity may actually enhance function (Burridge et al., 2005, Kilbride and McDonnell, 2000). Spastic muscles are not paralysed. If spasticity is decreased or removed by treatment or drugs, the spastic muscles may be found to be strong or may be weak (Levitt, 1982).

Spasticity is the most common symptom in CP and is generally considered to be present in greater than fifty per cent of cases (Scherzer and Tscharnuter, 1982, Tardieu and Tardieu, 1987). Motor dysfunction appears as neural pathways become more functional. As the child develops, the spastic muscles fail to grow as rapidly as neighbouring structures, causing contractures and consequent impairment of function (Cosgrove, 1995, Scherzer and Tscharnuter, 1982).

The nature of impairment that characterises CP varies according to the time, location and degree of cerebral damage. Most of the children with CP have limb spasticity but hypotonus of the trunk. Children sitting with the trunk and head flopped forward usually are unable to correct themselves because they lack righting or equilibrium reactions (Eliasson et al., 1991).

Abnormal postures are another motor characteristic of children with spastic CP, which appear as unfixed deformities but become fixed contractures (Levitt, 1982). Abnormal postures are held by tight spastic muscle groups whose antagonists are weak and cannot correct the abnormal postures. Even if the antagonists are not very weak initially, they become weak eventually because of disuse. Muscle strength, which is an essential component of normal motor control has been shown to be deficient in CP and is directly related to functional performance (Damiano et al., 2001). The groups of muscles used in the movement patterns in children with CP are different from those used in unimpaired children of the same age. Atypical movement patterns occur as co-contraction of the agonist with the antagonist, instead of the normal relaxation of the antagonist. This blocks movement or makes it laboured. Absence of discrete movement is a characteristic feature of many children with spastic CP. These children lack the smooth, coordinated, effortless and subconscious action of muscle patterns seen in normal motor skills (Levitt, 1982).

2.1.3 Hemiplegia and Hand Function

Precision grip and manipulation of objects with independent finger movements are directly controlled by the motor cortex via corticospinal pathways but cerebral damage may prevent the development of skilled independent finger movements. These abilities usually develop during the end of the first year of the child's life, concomitant with maturation of the corticospinal tract. Thus, children with CP usually grasp with the entire hand, using a slow and clumsy power grasp (Eliasson et al., 1991, Myhr and von Wendt, 1991).

Disturbed sensory mechanisms also compromise fine manipulation (Charles and Gordon, 2005, Fedrizzi et al., 2003, Gordon et al., 2003). Brown et al (1987) compared the upper limb of children with hemiplegic CP with their non-affected limb and showed that there is significant distal weakness, loss of fine distal movements, reduced speed of movement, increase in muscle tone, increase in resonant frequency and decrease in functional ability. Impairments in fingertip force control and timing during object manipulation have also been described. A general slowness in speed of movement of the affected limb is usually present, beginning with a delay in the initiation of reaching and finishing with slowness in flexing the fingers to grasp the object. In addition, there is overextension of fingers and weak grasp. Abnormalities are also present in the control of fixating muscles of the wrist during the process of grasping. As an object is grasped, wrist extensors normally fix the wrist to act synergistically with the fingers, providing efficiency and power. In contrast, children with hemiplegia often flex the wrist towards the object, which disrupts the fixation of the wrist (Sugden and Utley, 1995, Utley and Sugden, 1998). Contribution of trunk movement towards movement completion has been shown to be larger for the impaired side in hemiplegic children (Steenbergen et al., 2000).

Recent research findings show that activity limitation in hemiplegic CP is not solely due to the disordered execution of movements but is also caused by disorders in the planning of movements (Steenbergen and Gordon, 2006). Children with hemiplegic CP exhibit a significant deficit in anticipatory control, which is used to scale the grip and load forces based on internal representations of an object's physical properties (Duff and Gordon, 2003, Eliasson et al., 1992). Eliasson et al (1991) found that

children with hemiplegia had considerable longer latencies between first and second finger contact, compared to unimpaired children or children with diplegia, indicating impaired anticipatory closure of the hand. Motor planning deficits have been especially connected with brain damage of the left hemisphere (Steenbergen and Gordon, 2006). Interestingly, planning deficits in hemiplegia are observed in the unaffected hand, as well; Dellatolas et al (2005) reported that only 15% of the participants were found to function in the normal range with the unaffected hand. Similar findings have been reported in adults after stroke (Nowak et al., 2007, Sunderland et al., 1999). Taken together, the findings suggest that the lack of anticipatory force scaling in the affected hand may be the result of impoverished sensorimotor mechanisms but a global planning deficit is also present in many cases.

2.1.3.1 Current approaches to physical management of upper limbs in CP

The greatest difficulty that children with hemiplegia face is performing tasks requiring bimanual manipulation. This is because as these children develop, they tend to acquire even greater skill with the less affected hand and increasingly neglect the impaired hand. Thus, they hardly ever use the affected limb in spontaneous manipulation during play or activities of daily living (ADL).

Children with hemiplegic CP usually receive ongoing physiotherapy and occupational therapy to prevent the development of limitation in range of motion and to improve their motor skills. Apart from the conventional physical and occupational therapy, these children frequently receive casting to improve the range of movement of their more affected upper limb, although the evidence for functional changes after casting is limited (Antilla et al., 2008). This is reasonable though since functional improvements can be expected to be observed after training- more efficiently in a real-life environment as transfer of skills from the clinic does not happen automatically (Ferguson and Rice, 2001, Ma et al., 1999, Sterr and Saunders, 2006)- and acquisition of specific motor skills.

The predominant current treatment method is the Neurodevelopmental Treatment (NDT). Its goal is to inhibit primitive 'abnormal' movement patterns and facilitate more 'normal' ones. These treatment outcomes are supposed to be achieved through physical handling of the child during movement, giving the child more 'normal'

sensorimotor experiences. Traditionally, the implicit assumption in NDT has been that improvement of 'normal' movements will lead to improvement in motor skills without necessarily working on those specific skills. Despite being used for many years as the primary treatment approach for CP, there is little scientific evidence to support the efficacy of NDT (Anttila et al., 2008, Fetters and Kluzik, 1996, Volman et al., 2002).

A more functional approach has been introduced in the field of paediatric rehabilitation that promotes the use of functional practice to elicit goal-directed movement. Not surprisingly, more current interpretations of NDT include the importance of functional skill practice in treatment. Applying a functional task context while treating children with CP has been suggested to elicit positive changes in the control of reaching movements (Volman et al., 2002). Given intensive practice, children with hemiplegia could probably acquire and retain internal representations of novel objects for anticipatory control, as shown by studies in which appropriate anticipatory fingertip force scaling in the affected hand occurred only after performing a large number of lifts with the same objects (Duff and Gordon, 2003, Steenbergen et al., 2007). The extensive, task-specific practice forms the basis for intervention strategies such as CIMT and FUT (Duff and Gordon, 2003, Fedrizzi et al., 2003). It should be noted though that CIMT / FUT is not suggested as a treatment that replaces conventional physiotherapy and occupational therapy. Instead, it can be used as a supplementary intervention, which could also take place at home, in a real-life environment for a set time period.

Review of the motor learning literature, which follows in the next chapter is aimed mainly to explore whether recent motor theories and advances in motor learning support the concept of extensive practice resulting in improved functional outcome in patients after cortical damage. .

2.2 MOTOR CONTROL AND LEARNING

The control of human voluntary movement is determined by the organisation of the (CNS). Motor learning is a continuous process and there may be similarities between normal development, skill acquisition and recovery following injury at the CNS. Learning is associated with practice leading to long and short-term changes in the capability for skilled movement. Practice is a fundamental part in the rehabilitation process of patients with impaired motor control.

This chapter explores motor control and learning, the development of the most important theories and the shift observed from one model to the other. The most important factors influencing motor learning will be presented, as well as the physiology and the cortical changes that occur during learning. This will be further explored in terms of the plasticity processes that can be observed in patients with impaired motor control and specifically, children. This area is considered to be the fundamental basis for therapeutic interventions, such as CIMT and FUT.

2.2.1 Motor control

2.2.1.1 Definition

"Motor control is the ability to regulate and direct the mechanisms essential to movement" (Shumway-Cook and Woollacott, 2001). Motor control is a multi-layered process and movement results from several streams of input. The individual generates movement to meet the demands of the task being performed within a specific environment. Thus, the field of motor control is directed at studying the nature of movement and how movement is controlled.

2.2.1.2 Theories

Theories reflect different views about how the brain controls movement. Theories of motor control are very important as they provide a framework upon which clinical interventions are based. A brief review will be presented here to describe how the most important theories have developed from earlier ones.

Reflex theory

The reflex theory was introduced by Sir Charles Sherrington in the early 1900s. He suggested that reflexes were the building blocks of complex behaviour. Sherrington's view of a reflexive basis for movement remained unchallenged for many years and influenced clinical practices. However, this theory does not explain how movement occurs in the absence of sensory stimulus or fast movements that occur too rapidly to allow for sensory feedback. The novelty problem is also an issue referring to the fact that a single stimulus can result in varying responses, while in addition, humans are able to perform new movements that have not been practiced before (Mulder, 1992, Shumway-Cook and Woollacott, 2001). It is however widely accepted that adequate control of movement requires both retrieval and suppression of learned actions and reflexes. Deficient inhibition might be of pathophysiological relevance in patients with impaired motor control, such as children with CP (Hummel et al., 2004, van Heijst et al., 1999). Sherrington's work was fundamental to better understanding of motor control and formed the basis for subsequent work.

Hierarchical Theory

This theory is based on Sherrington's work suggesting that motor control emerges from reflexes that are organized in a colon hierarchical way; higher levels exert control over lower levels. The development of human movement was thought to be based on the appearance and disappearance of a series of reflexes, while some brain pathologies were due to persistence of primitive reflexes. This theory gave rise to the neuromaturational theory of development, upon which NDT is based (Burke, 2007). As with Sherrington's work, a limitation of this theory is that it cannot explain the dominance of lower level reflexes in adults. However, a top down hierarchy can be observed in several aspects of the human behaviour and movement. For example, it has been shown that there is increased activity in the primary motor cortex when subjects initially try to perform a task but when they become skilled in this task, activity is decreased in the primary motor cortex and increased in sub-cortical areas (Floyer-Lea and Matthews, 2004).

2.2.2 MOTOR LEARNING

2.2.2.1 Definition

Motor learning is the process of acquiring the capability for producing skilled actions. This can be described as the finding of a solution that emerges from the interaction between the individual, the task and the environment. Motor learning is a set of processes associated with practice, leading to relatively permanent changes in the capability for movement (Schmidt and Lee, 1999).

Learning can be either short-term or long-term. Inherent to the notion of learning is the concept of memory. Short-term learning or short-term memory is thought to have limited capacity and a relatively short duration. Long-term learning occurs when a task is practiced and therefore, it is transferred from short-term to long-term storage (Schmidt and Lee, 1999). Long-term learning is associated with functional changes consistent with plasticity in the somatosensory and motor cortex (Floyer-Lea and Matthews, 2004).

2.2.2.2 Stages of motor learning

Learning a new skill includes relatively distinct phases. A 2-stage process has been proposed by various researchers. Recently an intermediate phase has been added (Doyon et al., 2003). According to the 3-stage models, motor skill learning can be divided into the early-cognitive phase, the intermediate-associative phase and the late-autonomous phase. During the first phase, the learner is concerned with understanding the nature of the task. Performance is usually inconsistent as different strategies are tried but the improvements are large, while considerable cognitive activity is required, as shown by the increased brain activity. This activity has been shown to decrease as the individual becomes more skilled in the task (Floyer-Lea and Matthews, 2004, Hummel et al., 2004, Wu et al., 2004). The associative stage of motor learning reflects a trial-and-error period. The learner makes more subtle adjustments refining a particular pattern. There is less variability in the performance but improvement occurs more slowly. The cerebellum seems to be important during this phase (Wu et al., 2004). After a period of practice, the learner enters the autonomous phase, in which attention is devoted to other aspects of the skill or a secondary task, since there is no more need for high degree of attention (Leonard, 1998, Schmidt and Lee, 1999,

Shumway-Cook and Woollacott, 2001). There is still controversy as to whether there is an area specifically devoted to executing automatic movements (Wu et al., 2004). It has been proposed that once the motor routine is established, the striatum in cooperation with other cortical and subcortical regions may mediate the long-term representation of the motor programme (Lafleur et al., 2002). Increased activation in the cerebellar dentate nucleus and basal ganglia seems to characterize later stages of motor learning (Doyon et al., 2002, Floyer-Lea and Matthews, 2004).

2.2.2.3 Theories of motor learning

Closed-loop theory

Closed-loop theory is one of the most influential, older perceptions about motor learning. The most important aspect is the concept of closed-loop systems, according to which sensory feedback is used for the ongoing production of skilled movement. Movements are regulated on the basis of two memory mechanisms, a perceptual trace and a memory trace. The memory trace is supposed to be the mechanism responsible for selecting and initiating the movement. The perceptual trace is built over a period of practice and becomes the internal reference of correctness. Each trial when learning a new skill provides feedback that tends to represent the correct movement. Eventually, a collection of traces (perceptual trace) develops that comes to represent the internal model. Closed-loop systems have their greatest strength in explaining movements that are slow but they cannot explain how humans make movements even in the absence of sensory feedback or perform novel tasks accurately. In addition, brain storage capacity would need to be limitless to be able to store a separate perceptual trace for every movement ever performed (Mulder, 1992, Schmidt and Lee, 1999).

Motor Programming Theory

The motor programme theory was developed to account for all the movements, even those that were executed without feedback. The motor programme has been defined as "a sequence of stored commands that is structured before the movement begins and allows the entire sequence to be carried out uninfluenced by peripheral feedback"; so learning is the acquisition of motor programmes (Mulder, 1992, Shumway-Cook and Woollacott, 2001). However, feedback is actually used in movement in several ways; before the movement, as initial information, during the movement for error detection

and after the movement to determine the success of the action. This theory cannot explain how motor learning can occur in the absence of motor training, as shown by studies on motor imagery, which resulted in improved task performance (Nyberg et al., 2006). As with the closed-loop theory there is the problem with the degrees of freedom linked to the storage problem (Mulder, 1992, Schmidt and Lee, 1999).

The Generalized Motor Programme or Schema Theory

To address the above issues, the concept of generalized motor programmes was introduced. These programmes require parameters in order to specify how the movement is to be expressed. The schema is formed after a movement has been performed several times by storing details in memory such as information about the muscular system and the environment, the response specifications, the sensory consequences and the response outcome. Thus, instead of accepting as many programmes as there are ways of performing a movement, there is one abstract programme governing a class of movements. This theory assumes that the generalized motor programmes already exist when a human is born but it does not explain how these are formed. A programme stored in the CNS that has all the details necessary to carry out a movement does not give a direct answer to the storage problem (Mulder, 1992, Mulder and Geurts, 1993, Schmidt and Lee, 1999).

The Dynamic Systems Theory

A more recent framework to explain motor development is the dynamic systems theory (DST). A number of fundamental principles characterize the approach. DST suggests that the motor behaviour is the end product of interacting, multiple subsystems. The most efficient motor behaviour results from the spontaneous self-organisation and the interaction of these subsystems to achieve a functional goal. These subsystems derive from three sources: the child, the task and the environment. One other principle of the DST is that the changes seen tend to be non-linear with step changes being the norm. Within the child, subsystems include not only motor factors but also factors such as biomechanics, temperament and cognition (Law et al., 2007, Sugden, 2007, Thelen, 1995). This provides an explanation of why all the patients with a specific pathology do not respond in the same way to a specific intervention. These are factors that one has to take into consideration when deciding whether a patient is an appropriate candidate for a treatment, such as in CIMT. DST differs

sharply from the traditional maturational accounts by proposing that even the universal milestones such as crawling, reaching and walking are learned through a process of modulating current dynamics to fit a new task through exploration and selection of a wider space of possible configurations. The assumption here is that infants are motivated by a task and that the task, not prespecified genetic instructions, is what constitutes the driving force for change. The concept that spontaneous self-organization results in the best movement solution challenges therapists to reconsider the traditional therapeutic rejection of "abnormal" movement patterns such as "W-sitting" that many children with CP spontaneously discover and use effectively (Law et al., 2007, Mastos et al., 2007). This approach provides a basis for treatment models that consider functional success the goal of treatment with less concern about the "normality" of the movement strategy and thus, provides a theoretical framework on which interventions like CIMT or FUT could be supported.

The Neuronal Group Selection Theory

The Neuronal Group Selection Theory (NGST) combines the 'nature' part of the Neuro-Maturationist Theories and the 'nurture' part of the Dynamic Systems Theory. Sporns and Edelman (1993) attempted to explain the individual variability seen in development with this theory. The NGST states that genetic information plays a substantial role in the primary determination of brain development. When the primary neuronal groups have been formed, development proceeds with selection on the basis of afferent information produced by experience. When selection has been accomplished, variability is reduced although it soon returns due to the constant exposure of the organism to a multitude of experiences. This afferent information results in new patterns to emerge while old patterns lose stability; particular tasks that have become associated with positive value may become more strong and stable. For instance, a dense area representing the interlimb coordination pattern of crawling may become less dense with age, as crawling is replaced by other forms of locomotion. This process is the 'secondary reportoire'. The secondary neuronal repertoires and their associated selection mechanisms form the basis of mature variable behaviour which can be adapted to environmental constraints (Hadders-Algra, 2000, Thelen, 1995). Children with CP not only have a limited motor repertoire but also from deficiencies (impairments in the processing of proprioceptive, tactile or visual information) in the process of selection. Practice, implying repetition of self-generated

sensory input and augmentation of movement-related afferent information is supported by this theory as a way to achieve a decrease of variation in motor output and thus, a better task-specific adaptation of motor behaviour (Hadders-Algra, 2001). Thus, this approach most closely supports the concept of CIMT and provides a theoretical framework that explains the functional effects that may be observed after application of this treatment in children with CP.

Despite the different approaches, all theories and especially the latest ones seem to agree that practice is an important variable that affects motor learning. Sensory information is essential for many tasks to be accomplished successfully. In children with CP motor deficits usually include impaired force production due to impaired selective muscle activity (Eliasson et al., 1992). Somatosensory processing may also be impaired though, thus affecting mechanisms of information processing; impaired precision grip in children with CP is associated with limitations in matching sensory properties of objects with efficient motor responses (Eliasson et al., 1991). Studies (Valvano, 2004) have shown that children with CP need more practice to develop the memory representation required for skilled movements. Extensive use of the affected hand and increased sensory flow is achieved through interventions like FUT and CIMT.

2.2.2.4 Variables affecting motor learning

Motor learning can be affected by different variables, intrinsic or environmental. Practice can be arranged in a number of ways; it has been found that introducing task variability (random practice) and allowing frequent and longer rest periods between repetitions (distributed practice) is more effective than blocked repetition of a single task (Albaret and Thon, 1998, Krakauer, 2006). Studies (Donovan and Radosevich, 1999, Moulton et al., 2006) have shown that the same amount of practice distributed over a longer training period results in significantly better skill acquisition. The contextual interference effect, which refers to the fact that random ordering of tasks during practice might decrement performance at an early stage of motor learning but enhances post-training retention and transfer appears to be a robust phenomenon (Immink and Wright, 2001). Random practice seems to result in comparatively deeper processing than blocked practice because of the effort required to regenerate the appropriate response patterns. Contextual interference promotes considering of each

movement as a problem to be solved rather than a sequence of muscle forces to be replayed (Krakauer, 2006, Simon and Bjork, 2002). These findings have also been confirmed with stroke patients (Hanlon, 1996) but still the majority of studies have used healthy subjects and therefore, the findings do not necessarily correlate with children with CP.

Sensory information is also playing an important role in the acquisition of motor skills. The brain makes use of the sensory information generated by movements, as indicated by the increased neural activity within the sensory areas of the brain during the first stages of motor learning (Nyberg et al., 2006). The association of movement and sensory flow is also shown by the fact that removal of a part of the sensory cortex that represents a digit results in adjacent areas receiving input from that digit (Jenkins and Merzenich, 1987). Feedback is sensory information that can be divided into intrinsic and extrinsic. Intrinsic feedback is inherent information that comes from the various sensory systems. It may occur during or after a motor response and include information such as visual concerning accuracy of movement or the position of the limbs during movement. The importance of sensory flow from the hand on the stability of the motor output maps has been established in humans. Anaesthetic block of the sensory fibers from the skin enveloping ulnar innervated muscles of the hand induces a significant and transient decrement of the excitable area. Sensory feedback is also important for recovery. Patients with poor recovery of motor function following stroke frequently show profound abnormal electromagnetic responsiveness of SI cortex (Rossini and Pauri, 2000, Whelan, 1996). FUT and CIMT result in increased proprioceptive afferent flow as a consequence of increased use of the affected hand. Intrinsic feedback is considered to be impaired in children with cerebral palsy due to disturbed sensory mechanisms (Fedrizzi et al., 2003, Gordon et al., 2003). Extrinsic feedback is information that supplements intrinsic feedback. It comes from an external source such as a therapist and might have to do with knowledge of performance or knowledge of results. Augmented feedback given after completion of a motor task has been shown to have a strong influence on motor learning, although providing too much feedback might degrade learning (Wulf et al., 1994, Wulf and Schmidt, 1994). Qualitative knowledge of results in the form of verbal encouragement may permit the therapist to provide motivation and support (Kilduski and Rice, 2003, Salmoni et al., 1984). In the effectiveness study a computer

game was used to provide feedback in the form of a score which represented the amount of use of the affected hand during the game; motivational cues were also given to encourage children to keep trying.

The predominant current treatment method for children with CP is still NDT. This treatment focuses more on practicing isolated movements than functional skills. However, recent findings suggest a more functional approach in the field of rehabilitation (Dromerick et al., 2006, Krigger, 2006). Applying a functional task context has been shown to result in larger improvements of reaching movements for children with hemiplegic CP compared to semi-functional or non-functional conditions (Volman et al., 2002). The presence of objects facilitates better motor performance than the absence of objects during training (Wu et al., 2000). Defining specific goals can also enhance motivation and the child's ability to learn, while participation of parents provides frequent opportunities of practicing throughout the day (Ahl et al., 2005). Bower and McLellan (1992) found that goals in the category 'achieve a motor skill' were achieved and maintained by children with CP if the skills could be incorporated into the child's everyday life. These findings support the idea of a home-based intervention used for children with CP on its own or supplementary to therapy in the clinic.

The protocol that was designed and tested in this study was informed by the literature on motor learning and the variables affecting it. The home-based intervention that children took part in was a form of random, goal-directed practice, distributed over a period of 2 months rather than 2 weeks, as suggested by the classic paediatric protocol. Most importantly the protocol included a great amount of practice, which is recognized to be one of the most important factors for effective motor learning (Duff and Gordon, 2003, Schmidt and Lee, 1999).

2.2.2.5 Physiology of motor learning

Traditionally, experiments exploring the physiology of motor learning have used neurophysiological recordings of cell activity while an animal was performing a task. In recent years, many human studies have also been presented. These studies use imaging techniques to identify the areas of the brain that are active in conscious humans while performing a motor task. There is no single area of the brain that

controls all aspects of learning. Group analysis of scans has revealed individual differences, which probably reflect the different rates and strategies that individuals use during skill performance (Doyon et al., 2003, Leonard, 1998). Different structures are involved in different tasks and in different phases of motor learning. Based on animal and human studies, several brain structures, including the striatum, cerebellum and motor regions of the frontoparietal cortices have been thought to be critical for the acquisition and/ or retention of motor skilled behaviours. The prefrontal cortex and anterior cingulate area 32 are engaged when subjects must decide on their own accord which movement to make and when attention is needed but not when the task has become automatic (Passingham, 1993). These areas, as well as the right parietal cortex are thought to be generally involved in processes such as working memory and decision-making (Cerasa et al., 2005, Takada et al., 2004). Frontoparietal areas have been suggested to play a role in generating mental movement representations and enhancing the processing of relevant information over non-relevant (Hanakawa et al., 2003, Hogan et al., 2006). The lateral and medial premotor areas are thought to mostly play a role in mediating the transition from idea to action (Matsumoto et al., 2007). Signals originating from the cerebral cortex are thought to be going through the basal ganglia and cerebellar loop circuits in order to be optimised in terms of reward value and sensorimotor accuracy, respectively (Hikosaka et al., 2002). Although the exact role of the cerebral cortex is not yet clear, one of its important roles is to provide common representations upon which the basal ganglia and the cerebellum can work together (Doya, 2000). The cerebellum is mostly active during the first phase of motor learning, while its role might be undetectable when the sequential movements are well learned. In contrast, the striatum and motor cortical areas have been suggested to be critical for the long- term storage of well-learned motor sequences (Doyon et al., 2003).

The structural and functional organisation of the nervous system is maintained dynamically throughout life, shaped by experience and central or peripheral injury (Nudo, 2003). Certain physiological mechanisms have been suggested as being involved with motor learning: activity-dependent synaptic plasticity, long-term potentiation, changes in the excitability of postsynaptic neurons and growth of new connections (Hallett, 2001, Leonard, 1998). Learning could be considered as a form of synaptic plasticity. Synapses are dynamic and their transmission could be

strengthened or weakened by a variety of conditions. Some synapses are more susceptible to change than others. Such changes in the synaptic neural transmission are suggested to be one of the primary ways of reorganisation of the nervous system during motor learning (Leonard, 1998). As presented in the next chapter, CIMT and FUT have been suggested to result in cortical reorganisation associated with the functional motor gains of patients.

The most widely studied model of synaptic mechanisms underlying learning comprises the phenomena of long-term potentiation (LTP) and long-term depression (LTD) (Charpier and Deniau, 1997, Nudo et al., 2001). LTP was first observed by Terje Lomo, who conducted a series of experiments on anaesthetized rabbits to explore the role of the hippocampus in short-term memory. Three years later in cooperation with Tim Bliss they found that on stimulating the perforant path and recording the synaptic responses in the granule cells, one or more brief episodes of tetanic (high-frequency) stimulation produced a potentiation of the monosynaptic response evoked by single shocks which could last for hours. The full report of this research was published in 1973, constituting the first description of LTP (Bennett, 2000).

Since its original discovery, LTP has been found to exist in the cerebellum, motor cortex and other CNS regions and has been regarded as the prototypic mechanism for a modified synaptic efficacy (Rossini and Pauri, 2000). The fact that LTP can most reliably be generated in brain regions involved in learning and memory has often been used as evidence for its functional relevance (Malenka and Nicoll, 1999). LTP induces enhanced neural transmission between the stimulated axon and the postsynaptic cell, while LTD has an opposite effect and induces depression of the excitatory postsynaptic potentials. This is a highly selective process depending on the degree of activity (Daoudal and Debanne, 2003, Rossini and Pauri, 2000). Animals in which LTP or LTD has been disrupted in the brain exhibit behavioural decrements in learning. These observations have lead to the belief that LTP and LTD play a critical role in learning and subsequent memory formation (Burrell and Sahley, 2004, Kavanau, 1997, Martin and Shapiro, 2000). The most prominent form, often referred to as associative LTP mainly represents the strengthening of a connection between two neurons that have been simultaneously active (Malenka and Nicoll, 1999). This

form of LTP follows the Hebbian learning rules. According to Hebb, the initial connection weights between neurons have a random value, usually small. During training and learning though, these values change. If one neuron is stimulating another neuron and at the same time the receiving neuron is also firing then the strength of the connection between the two neurons will be increased and vice versa (Daoudal and Debanne, 2003, Rossini and Pauri, 2000).

Although LTP and LTD are triggered rapidly they represent neural mechanisms that can cause long-term changes in the transmission characteristics of a synapse (Leonard, 1998, Malenka and Nicoll, 1999). This probably occurs through the synthesis of new proteins that takes place after the induction of LTP. Proteins are used to form new synapses and this is a process highly associated with long-term memory, although such forms of plastic changes occur usually during development and are generally not considered to be available to the adult brain (Hallett, 2001, Leonard, 1998).

Another mechanism that has been suggested to contribute to cortical plasticity is the occurrence of changes in the balance of excitation and inhibition. Some synapses that are normally present but physiologically silent, usually due to pre-synaptic inhibition, become strengthened when an adjacent area is either damaged or when demands on its circuitry are increased (Daoudal and Debanne, 2003). Thus, if inhibition is removed, the region of influence can be unmasked and this is the reason that this process is often called unmasking (Hallett, 2001, Leonard, 1998). Competition between neural representation with different activity levels is considered to be one of the fundamental principles of cortical plasticity. Interventions like CIMT which promote increased practice could be considered to highly adhere to these basic principles.

2.2.2.6 Cortical changes related to learning

Little is currently known about the changes in motor representation that occur in the brain over the entire course of motor learning. Shadmehr and Holcomb (1997) reported that within 6 hours after completion of practice, the brain engages new regions to perform the task. They further described a shift from prefrontal regions to the premotor, posterior parietal and cerebellar cortex structures. Adult cortical

plasticity has been demonstrated in several areas, including sensory and motor cortices. A generalised view of the functions of these areas would suggest that the primary motor cortex is of major importance in the execution of movement, the ventral and dorsal premotor areas in the sensory guidance of movement, the supplementary motor area in planning and coordination and the cingulate motor area in some of the emotional aspects of voluntary movement, including changes in autonomic function (Lemon and Griffiths, 2005).

Training, experience and environmental enrichment have been suggested to produce measurable changes in the brain. As Nudo et al (2001) discussed in their review, "if motor cortex map physiology in some way reflects the long-term storage of newly acquired motor programs, then alterations of neuronal morphology would also be expected". Indeed a substantial increase in brain weight has been shown to be caused by differential experience, which probably leads to increase in the processing capacity of the cortical regions concerned. These conclusions were initially drawn from early work with rats that were divided into 3 groups and placed in one of three environments: the enriched condition, the standard colony condition and the impoverished condition (Rosenzweig and Bennett, 1996). The findings of this study and others that followed revealed that motor learning resulted in thicker cerebral cortex, greater brain weight and neuron size and increased dendritic branching (Leonard, 1998, Nudo, 1999, Nudo, 2003, Nudo et al., 2001). Similar results were found with adults, as well (Turner and Greenough, 1985, Volkmar and Greenough, 1972). Other studies have found that depriving one eye of light in a young animal, starting at the age at which the eyes open, reduces the number of cortical cells responding to stimulation of that eye (Rosenzweig and Bennett, 1996). Pascual-Leone et al (1993) performed TMS in Braille readers and blind controls and showed that the cortical representation for the reading finger in proficient Braille readers is enlarged at the expense of the representation of other fingers. Increased cortical representation has also been shown for the digits of the left hand in string players compared to controls (Elbert et al., 1995). Similar results have been reported by others (Kleim et al., 2002, Pascual-Leone et al., 1994). Nudo et al (1996b) suggested that once a novel task is learned certain aspects of functional cortical topography remain altered for a long period of time. This may explain the long-lasting effects shown by imaging

studies after CIMT/ FUT (Kopp et al., 1999, Liepert et al., 2000, Schaechter et al., 2002). These studies will be reviewed in detail in the following chapter.
On the other hand, Meister et al (2005) found no differential activity in musicians, when comparing performance in simple and complex sequences. This may reflect the reorganisation that has occurred in this group allowing for a higher level of complexity without recruitment of additional neuronal resources. However, changes in the representational maps of the motor cortex might not occur with simple repetitive motor activity but only after learning of a new motor skill. Cortical reorganisation has been shown to occur only when the task practised is challenging, requiring participants to develop new skills (Kleim et al., 1998, Nudo et al., 1996a, Plautz et al., 2000, Rosenzweig and Bennett, 1996). Classen et al (1998) found that in humans repetitive, unskilled movements of the thumb could produce changes in the cortical representation but these changes degraded and returned to baseline within few minutes after completion of training. Instead, skill acquisition is a prerequisite factor in driving representational plasticity. Evidence for this has come from different studies; Plautz et al (2000) conducted a controlled study with seven squirrel monkeys, three of which were trained on a repetitive large-well retrieval task, requiring use of a limited set of distal forelimb movements in the absence of motor skill acquisition. The motor behaviour observed was highly successful, stereotyped and consistent, while there were no systematic effects on the representations of the forelimb in primary motor cortex. Although motor skill acquisition was clearly not present, a behavioural measure that changed during the training period and remained essentially stable thereafter was the movement speed. This finding may have implications regarding the measures used by researchers when trying to establish the effectiveness of a new therapeutic treatment. Changes in movement speed alone, in the absence of any other changes in behavioural measures may occur as a function of motivational state, also called dispositional learning and should therefore, not be considered as evidence for motor learning. Similarly increased forelimb strength alone has been shown to not be associated with cortical reorganisation (Remple et al., 2001). In contrast, Nudo et al (1996a) presented a study in which normal, intact primates were trained on a small-object retrieval task that required skilled use of the digits. Intracortical microstimulation (ICMS) was used to map the brain. The results showed that the movement representations of the monkeys that were trained, in contrast to controls, changed systematically, while specific tasks differentially altered movement

representations. These findings were confirmed by Kleim et al (1998) and Kleim et al (2002) and provide important information for clinicians and researchers who are seeking to develop new therapeutic interventions. Engaging the patient in a consistent repetition of a set of motor acts should not be considered to result in plasticity. Instead, new motor skills should be learned in a real-life environment; CIMT is operating in this context. A limitation with most of these studies is the lack of baseline measurements, which would increase confidence in the findings. The use of a control group adds to the studies' value but the small sample number does not allow for safe conclusions to be reached. The interindividual variability between subjects as to the effects of the experimental manipulation has been evident in brain imaging studies (Nudo et al., 1996b), which confirms the necessity for a large experimental and control group to be included in studies before being able to make definite conclusions.

New brain imaging techniques have contributed to our understanding of the relationship between cortical areas and learning. One group of techniques- functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) and single-photon emission computed tomography (SPECT) - measures regional blood flow and metabolic changes associated with function-related changes in neuronal firing level. Electroencephalography (EEG), magnetoencephalography (MEG) and Transcranial Magnetic Stimulation (TMS) analyse electromagnetic properties of the brain neurons. PET and especially fMRI have been widely used to provide a view of the distributed network subtending a given motor act, together with a relationship between function and anatomy. Unlike the electrical and magnetic measures, neuroimaging techniques allow task-related changes in brain activity to be localized with a high degree of precision (Sato et al., 2007). There are however limitations in both these techniques, including the inability to discriminate the activation directly linked to motor programming and execution from the sensory feedback from the moving parts (Rossini and Pauri, 2000). During the execution of a complex task, functional imaging is not capable of distinguishing the different contributions of different brain areas (Sack and Linden, 2003). The patterns of activation identified are dependent on the specific motor task in the scanner (Krakauer, 2007); the functional tasks performed by individuals while placed in the scanner are usually in a non-functional way (due to the position and environment while being tested). This raises

questions as to what degree this activity represents the one that would be performed in a more natural environment.

TMS lacks the precision found in microelectrode recordings, as individual corticospinal neurons project to several muscles and the result is a mosaic in which general patterns of hand, arm and shoulder projections can be distinguished but boundaries are imprecise (Butler and Wolf, 2007). TMS has also been criticised as to whether it actually detects the same cortical areas from one session to the other. Several approaches have been used to determine accurately the coil location on the skull and hence identification of the stimulation site in the brain in reference to a priori defined target areas. All these approaches assume inter-individual homogeneity and comparability of inter-area distances, as well as an inter-individual homogeneity in the relationship between skull location and cortical structure (Sack and Linden, 2003). TMS might not be adequate to measure physiological changes in patients. As some of these patients may achieve movement through the activation of relatively few corticospinal tract neurons, TMS may insufficiently activate these preserved neurons to elicit motor evoked potentials (Wittenberg et al., 2003). ICMS mapping might also not be perfectly reliable. Nudo et al (1996b) mentioned that the ICMS-derived maps of movement representations were somewhat variable from one mapping procedure to the next, even in the absence of specific manipulations. Similar observations have been reported by others (Plautz et al., 2000), suggesting caution in the interpretation of brain imaging findings.

In contrast to neuroimaging techniques, electrophysiological and magnetencephalographic methods allow non-invasive monitoring of brain processes in real time. Their supreme time resolution permits functional brain imaging at millisecond resolution (time resolution is on the minute order for neuroimaging techniques), while they are accessible and less alarming, especially for paediatric populations (Banaschewski and Brandeis, 2007, Coles and Rugg, 1995, Sato et al., 2007). EEG data were collected during this project as a first step to provide a child-friendly method for physiological assessment after CIMT or other interventions. This supplementary study will be described in detail in Chapter 7.

A fundamental part of the knowledge we have is based on studies conducted with non-human subjects. One arising question is how useful animal models are for understanding function in humans if there are species differences in the organisation of the motor system. Although the basic building blocks of the motor system are conserved across species, some characteristic features, such as skilled forelimb control for reach and grasp, have undergone separate evolution. Cortical and spinal damage is considered to be more devastating in humans than in animal models. Lemon and Griffiths (2005) confirm that primate models represent the best available model for understanding the vulnerability of the cortico-motoneuronal system to injury and the consequences on voluntary control of the hand. Although the study of animal models can help us to understand both normal and disease-affected human motor control, simple extrapolation will not help.

Many studies on motor control have invariably been done with healthy, unimpaired subjects to provide an insight into the cortical function and the changes occurring within the brain. Although this makes an important contribution to our knowledge, disease-affected motor function and recovery after injury have different characteristics, which also vary between individuals. An attempt to explore this area and the plasticity patterns in CP is presented below.

2.2.2.7 Plasticity and recovery of motor function

Injury to the CNS can affect neuronal function through direct damage to the neurons but also through indirect processes. Specific characteristics of the lesion, such as lesion size and location affect the extent of recovery (Friel and Nudo, 1998). Other important factors such as age, amount of training or use of pharmacological treatments (Butefisch et al., 2000, Ziemann et al., 2001) can also play a role in the extent of recovery after a CNS lesion. All brain areas do not show the same capacity for regeneration (Schmidt and Lee, 1999). However, despite the fact that the effects of injury to the CNS are difficult to reverse, recovery of function is usually seen in brain-injured animals and humans. As mentioned earlier, cortical maps are very dynamic and there are multiple pathways innervating any given part of the sensory or motor cortex, with only the dominant pathway showing functional activity. When one brain area becomes inactive, adjacent cortical areas can take over its former targets. This theory, known as vicariation of function, is particularly dependent on the amount of

use of the affected body parts. In other cases, transfer of function might occur to more remote areas of the hemisphere or sometimes it has been shown that the undamaged hemisphere may contribute to recovery by influence of the uncrossed component of the corticospinal tract (Nudo et al., 2001, Schmidt and Lee, 1999, Turton, 1998). The undamaged hemisphere seems to play a role early after stroke and achieves an important role if the damaged hemisphere does not recover well (Hallett, 2001). Fridman et al (2004) suggested that the dorsal premotor cortex of the affected hemisphere could reorganize to control movement usually assigned to primary motor cortex function but contribution of the premotor cortex of the intact hemisphere was more prominent in the severe cases. Liu and Rouiller (1999) also supported this view. The degree to which reorganization observed in spared tissue represents mechanisms related to restitution of the original function, behavioural compensation or both is still not entirely clear. Axonal sprouting, one of the mechanisms that have been suggested to explain reorganisation, is characterized by the growth of fibres from outside the immediate region of damage, which reoccupy denervated dendritic spines and may contribute to enduring functional changes in the later stages of recovery. The other mechanism involves unmasking of previous present but functionally inactive connections. This process could be due to several mechanisms and include increased excitatory neurotransmitter release, changes in membrane conductance that enhance the effects of weak or distant inputs or most possibly removal of inhibition to excitatory synapses (Chen et al., 2002, Kelly and Shah, 2002, Nudo, 1999, Nudo, 2003).

The details of the topographic reorganisation seem to depend heavily on the type of post-lesion training. In the absence of training, spared function in the affected body parts undergoes a further reduction in territorial extent. Liu and Rouiller (1999) performed a study to look at the mechanisms of recovery of manual dexterity after unilateral lesion of the sensorimotor cortex in adult primates. Adjacent areas of the remaining and still intact parts of the motor cortex were shown to develop a latent ability to control the functions of the previously altered areas. However, movements previously represented in the lesioned cortical territory did not reappear in zones adjacent to the lesion when there was no post-lesion motor training. When the monkeys received intensive training, not only was there no loss of the hand representation adjacent to the lesion but in some cases, there was even an expansion

in regions previously devoted to proximal movements (Nudo et al., 1996a, Nudo and Milliken, 1996). These data are consistent with findings from human studies (Nudo, 1999, Nudo, 2003, Nudo et al., 2001) and have led researchers (Floel et al., 2004, Friel and Nudo, 1998, Jones and Schallert, 1994, Kelly and Shah, 2002, Nudo et al., 1996b) to suggest that interventions like CIMT might be an appropriate option in the rehabilitation of patients with unilateral lesions.

2.2.2.8 Plasticity in children

Studies have shown that in children with congenital hemiplegia, the motoneuron pools of both hand muscles receive common synaptic input from axons provided by corticospinal tract fibres originating in the undamaged motor cortex (Chugani et al., 1996). Hallett (2001) discussed that the ipsilateral pathways may be more functional in children with prenatal or perinatal lesions. Maegaki et al (1999) reported that in children with congenital hemiplegia the cortical motor representation sites for the paretic hand were close to or at the same scalp sites as the intact hand, while Cao et al (1994) showed that the intact hemisphere was more strongly linked to the ipsilateral hand than was the case in the neurologically unimpaired group. In a study of 33 children with spastic hemiplegia and young adults by Carr et al (1993), EMG recordings from limb muscles during TMS indicated the presence of ipsilaterally projecting corticopinal fibers from the unaffected hemisphere but only in those cases where the lesion had occurred before or around the time when the corticospinal tract had reached caudal levels in the spinal. The study had several limitations, the most important being the heterogeneous sample in terms of participants' age and timing of insult, which are thought to be part of the variables that can influence the pattern and degree of brain plasticity. The results though indicated that the best function was seen in patients who presented a good recovery of the affected hemisphere. When there was no contralateral contribution, hand function was poor and intense mirror movements were present. This finding has been confirmed by more recent evidence (Gramsbergen, 2007, Nezu et al., 1999) that suggests that this ipsilateral projection involves the persistence of fibers which normally are present at early stages of development and which remain and sprout, because of the withdrawal of the contrallaterally projecting fibers from the damaged hemisphere.

Brain injury occurring at a younger age is often associated with more extensive reorganisation and better functional outcome. Brain lesions early in fetal development have been suggested to be less harmful than lesions acquired later, in both humans and animals (Chen et al., 2002, Maegaki et al., 1999). This suggestion has been initially based on animal studies showing that when produced in neonates, massive cortical lesions or complete corticospinal transections produce only subtle motor deficits in adulthood although the underlying mechanisms remained obscure (Vandermeeren et al., 2002). Caution must be taken though when comparing between animal and human models as the lesions which are imposed in animals are generally much larger than those which occur in the human. A reason for the suggested greater ability of the immature brain to reorganize has been the belief that synaptic connections present during early critical periods allow changes to occur at the level of axonal and dendritic branching, while in older people, changes are restricted to more localized formation (Johnston, 2003). However, the statement that the brain at early ages has an increased capacity to compensate for the effects of brain lesions has been recently questioned. There seem to be critical periods during development when the brain is particularly vulnerable to insult and others when outcome is more optimal. Children with prenatal lesions have been suggested to be at a greater risk of neurobehavioural deficits compared to middle childhood lesions that demonstrate the least severe impairments, possibly due to a period of peak synaptogenesis and dendritic arborisation during this developmental stage (Jacobs et al., 2007). When injury occurs to the developing brain, there is a transient disruption of fundamental neuroanatomical processes. This suggestion follows the lines of thought of the Neuronal Group Selection Theory and it can be surmised that a lesion of the brain at early age results in a loss or reduction of neuronal repertoires and impaired selection (Hadders-Algra, 2001). Muller et al (1991) suggested that the developmental profile of central conduction times to upper and lower limb muscles show an age-dependent acceleration with adult values not being reached before the age of about 10 years. A strong relation is now considered to exist between the stage of development of a particular brain area at the time of lesioning and the neural reorganization, while that stage differs with age for the different brain regions and probably even for specific fibre projections (Gramsbergen, 2007).

The latest theoretical models of motor control and learning suggest that intensity of practice and goal-directed treatment are critical factors that influence skill acquisition and motor development. Studies have stressed the need for rehabilitation to emphasise techniques that promote formation of appropriate internal models and not just repetition of movements that is not considered to result in plasticity. The home-based intervention that was examined in the present study was a form of random, functional, goal-directed practice, distributed over a period of 2 months. Whether this type of treatment could be considered practical was one of the research questions in the first study. A form of feedback was added as an additional type of sensory information because it was thought to enhance motor learning. Competition between neural representation with different activity levels is considered to be one of the fundamental principles of cortical plasticity that support the use of interventions like CIMT, which promote increased functional practice. Many authors have suggested (Johnston, 2003, Lebeer and Rijke, 2003) that in children with hemiplegia just as with adults, plasticity and reorganisation of the brain could be enhanced by increased functional use of the paretic limb. Rehabilitation aims to promote motor learning but it is now clear that transfer from the clinical setting to real-life environment is not easy to achieve (Ferguson and Rice, 2001, Ma et al., 1999, Sterr and Saunders, 2006). Therapeutic interventions that involve functional activities in the home environment, under everyday conditions may facilitate the transfer of motor skills from clinical to real-life situations. To explore to which degree FUT and CIMT operate in this window, a review of all the relevant studies in both adults and children was taken and is presented in the following chapter, along with the shortcomings that pose limitations to the interpretation of the findings.

2.3 CONSTRAINT-INDUCED MOVEMENT THERAPY AND FORCED USE THERAPY

Constraint-induced movement therapy (CIMT) is guided by a conceptual framework, an important part of which is the concept of "learned non-use". This concept grew out of research with nonhuman primates after somatosensory deafferentation of the dorsal root of the spinal nerve innervating one of the upper extremities. The theory states that affected upper limb use is negatively reinforced by its ineffectiveness to carry out activities of daily living (Miltner et al., 1999, Taub et al., 1999). Non-use of this limb is therefore learned through operant conditioning. After a period of spontaneous recovery, the animals continue not to use their affected limb as a result of this strongly learnt behaviour. The resulting ability of the limb is therefore 'masked'. By forcing the animals to utilize their hemiparetic limb, relearning reverses this behaviour (Glover et al., 2002, Taub et al., 1999).

Learned non-use was hypothesised to also occur in humans after neurological injury. This assumption was a big step as findings with primates cannot be directly translated to humans. The basic building blocks of the motor system are considered to be highly conserved across species and primate models have been confirmed to represent the best available model for the understanding of the vulnerability of the fast cortico-motoneuronal system to injury and the consequences of this for voluntary control of the hand. However, some characteristic features, such as skilled forelimb control for reach and grasp have undergone separate evolution, while cortical and spinal damage is generally more devastating in humans than in animal models (Lemon and Griffiths, 2005). Considering the pathological differences between the lesioned monkeys and the variety of hemispheric lesions in humans, the validity of extrapolation of the findings in deafferented monkeys to human patients could be questioned (Siegert et al., 2004, van der Lee, 2001). Another big step between Taub's experiments with the monkeys and the application of CIMT in adults after stroke was the assumption of similarities between two different models; the deafferented and the stroke model. This weak link between experiments and application in humans is even more obvious in the paediatric population and the use of CIMT in CP, however this will be discussed in more detail later in the chapter. Despite these questionable assumptions though, the

learned non-use concept is considered to be a behavioural phenomenon that is linked to the clinical picture of hemiplegia rather than the area of damage in the CNS that caused it. Sterr et al (2002) tested the learned non-use assumption in 21 people with upper-limb hemiparesis after brain injury and 21 age-matched healthy controls. They found that even though many movements could be performed successfully in the test, most patients used their less affected hand to perform these movements under spontaneous-use conditions. Participants underestimated the quality of movement (QOM) of their affected limb, as shown in the Motor Activity Log (MAL) test, where the subjective QOM ratings were much lower than when rated on the basis of the actual performance.

CIMT is an amalgamation of three basic elements: a) repetitive functional, task-oriented training of the affected extremity, b) restraining of the unimpaired extremity and c) a package of behavioural techniques designed to transfer gains made in the clinic to the real world (Pomeroy and Tallis, 2002, Taub et al., 2006b, van der Lee, 2001). Restriction of the upper extremity (UE) is accomplished by placing the limb in a restraining device for 90% of the waking hours, during a two-week period. At the same time, patients participate in activity sessions using the affected arm for 6 hours/day on 10 consecutive weekdays (Miltner et al., 1999, Page et al., 2002d). Training includes a behavioural technique termed "shaping", which involves selecting tasks appropriate for the motor deficits of the individual patient, progressively increasing the difficulty as the performance improves and providing immediate encouraging feedback when patients make even small gains (Miltner et al., 1999, Taub et al., 1999). The package of transfer techniques includes: a) a behavioural contract specifying when participants should wear the constraint and the tasks they should practice at home using the affected arm, b) tracked adherence to therapy requirements through a daily log and c) problem solving with participants to help them overcome barriers in their daily environment (Uswatte et al., 2006b).

The original CIMT has been extended to treat deficits in arm use in patients with traumatic brain injury (Page and Levine, 2003, Shaw et al., 2005), aphasia (Bogey et al., 2004, Kendall et al., 2006, Pulvermuller et al., 2001), unilateral spatial neglect (Freeman, 2001) and focal hand dystonia (Candia et al., 1999). An important additional adaptation of CIMT has been used to treat lower limb impairments

(Marklund and Klassbo, 2006, Vearrier et al., 2005). For the leg, restraint is not used but the patients are given intensive shaping to promote an improved pattern of walking. CIMT has also been used in combination with other therapies, such as botulinum toxin A (Levy et al., 2007, Page et al., 2003, Sun et al., 2006), functional electric stimulation (Gritsenko and Prochazka, 2004, Page and Levine, 2006), repetitive transcranial magnetic stimulation (Malcolm et al., 2007) and mental practice (Butler and Wolf, 2007, Page et al., 2007, Butler and Page, 2006) with promising results. For the purposes of the present study, the literature review will be restricted to studies reporting on the use and effectiveness of CIMT and modified versions (including forced use therapy-FUT-which involves only the restraining part of CIMT) in adults with stroke, to whom it is mainly applied and children with CP.

2.3.1 CIMT in adults with stroke

CIMT has been shown to be effective mainly in adults following a cerebrovascular accident (CVA) and the findings of many studies report that there is a long-term benefit (Blanton and Wolf, 1999, Dromerick et al., 2000, Kunkel et al., 1999, Miltner et al., 1999, Tarkka et al., 2005, Taub et al., 2006a, Taub et al., 1999), resulting in patients resuming a significant degree of independence in everyday life (Mennemeyer et al., 2006). Sabari et al (2001) reported a naturalistic case that supports the principles of CIMT. A woman sustained a cerebral infarct and then fell simultaneously, fracturing her right arm. Orthopedic intervention for her fracture mirrored the protocol of CIMT by immobilizing her right arm. Her significant recovery of left arm use over a 1-year-period was more extensive than what would be typically expected.

Substantial improvements have been shown in the performance time and quality of movement in chronic stroke patients. Such improvements are unlikely to be spontaneous as participants were several years poststroke and their condition had not improved for months to years (Kunkel et al., 1999, Miltner et al., 1999, Taub et al., 1993). Taub et al (2006a) conducted a trial to examine CIMT in chronic stroke patients against a placebo group that controlled for the duration and intensity of patient-therapist interaction and therapeutic activities. Outcome measures included the Motor Activity Log (MAL), the Wolf Motor Function Test (WMFT) and the Actual Amount of Use Test (AAUT). Improvements were larger for the CIMT group but the

persistence suggested by the authors over the 2 years follow-up is based only on the MAL scores. The AAUT is an in-laboratory measure of arm function that assesses the spontaneous use of the affected hand during activities of daily living (ADL). The WMFT and the MAL have been developed specifically for the evaluation of CIMT and have been used by many researchers. The WMFT consists of 17 items, 2 of which involve strength measures and 15 involve timed performance on various tasks (joint-segment movements and integrative functional movements), which are also rated on a 6-point functional ability scale. Reliability and validity have been supported (Morris et al., 2001, Wolf et al., 2001). The MAL is a semi-structured interview that requires participants (and sometimes caregivers) to rate how much (Amount of Use -AOU- scale) and how well (Quality of Movement -QOM- scale) they use their more affected limb during 30 ADL at home. Validity of MAL has been established but reliability remains questionable (Uswatte et al., 2005). Given that MAL is a subjective scoring by patients who are invested in the treatment it is an unblinded rating of arm use that should at least be used in combination with objective measures. This is demonstrated by studies (Bonifer and Anderson, 2003, Wittenberg et al., 2003), which reported positive changes according to the patient's MAL scores, although there was lack of significant functional improvements.

A randomized controlled trial (Dahl et al., 2008) showed significant improvements in favour of the CIMT group immediately post-treatment but the results were not maintained at the 6-month follow-up. This outcome is difficult to interpret as the authors don't specify the type of treatment the control group received, while the sample size was small, which may have lead to a type II error. Testing the long-term effects of CIMT was one of the main aims of the Extremity Constraint Induced Therapy Evaluation (EXCITE). The EXCITE (Winstein et al., 2003, Wolf et al., 2006) represents the first multisite, randomized, single-blind controlled trial to systematically examine a neurorehabilitation technique among patients with the ability to initiate extension movements at the wrist and fingers, who have experienced a first stroke within 3 to 9 months prior to enrollment. Participants in the intervention group received a standard 2-week CIMT. Adherence to the extralaboratory treatment components was monitored regularly via a physical sensor and timer placed in the mitt and by a home diary. Usual and customary care ranged from no treatment to the application of orthotics or various occupational and physical therapy approaches,

although only 48.9% of the control group received other treatments throughout the year. The main outcome measures were the WMFT and the MAL, while secondary measures were accelerometry, the AAUT and the Stroke Impact Scale, an index of the effect of intervention on participants' quality of life. Larger improvements were reported for the CIMT group on all measures with the exception of the 2 WMFT strength items, which however reached significance at the 12-month follow-up. Differences in gains between CIMT and control participants on the Functional Scale of the WMFT were not significant at 12-month follow-up. At 24-month post-treatment the improvements are reported to be retained or even improve further but the Functional Scale of the WMFT was not included in the measures (Wolf et al., 2008). Improvements in affected arm function were significant for both groups at the 12-month assessment point, suggesting that the sample had not reached a plateau of gains. The large difference in intensity of practice between experimental and control groups and the lack of standardised treatment for the latter makes it difficult to interpret the real value of CIMT, while the persistence of functional effectiveness in the long-term remains unclear.

Van der Lee et al (1999) used a form of CIMT that was modified in important aspects (training on a group basis using 'housekeeping activities, handicrafts and games in a relaxed atmosphere') and compared it with bimanual NDT. The treatment effect reported was not significantly different between the two groups, although the CIMT group performed better. This small treatment effect of CIMT could be attributed to the high functional status of participants that did not allow for further improvements or to the equal duration and intensity of treatment that the control group received. Other studies (Boake et al., 2007, Dromerick et al., 2000) that controlled for the intensity of treatment showed similar results. Both these studies were conducted with acute stroke patients and used an intervention less intensive than the original CIMT. Patients in the study of Dromerick et al (2000) were wearing a restraint for 6 hours per day and participated in treatment sessions for 2 hours daily, 5 days a week for 2 weeks. Boake et al (2007) tested an intervention that included mitt-wearing for 90% of the waking hours and training for 3 hours per day, 6 days a week for 2 weeks. Better performance was reported for the CIMT groups on all motor function measures but the advantage was statistically significant only on the pinch subtest scores of the Action Research Arm Test (ARAT) in Dromerick et al (2000), while in Boake et al (2007) significant

differences in Fugl-Meyer Assessment of Motor Recovery (FM) were found immediately post-treatment but not at the 3-month follow-up. Both studies had small sample numbers, while in the latter the rate of drop-outs was large. These results may point out the importance of including a control group that receives equivalent time of treatment. Unless CIMT is compared with other treatments in similar doses, its superiority over other motor therapies cannot be demonstrated (Dromerick, 2003).

The lack of homogeneity and sometimes appropriateness of the outcome measures makes it difficult to draw conclusions about the efficacy of CIMT (Bonaiuti et al., 2007). Objective measures need to be used and in contrast to many studies that have used only the WMFT and the MAL, a combination of measures may be necessary to reflect real-world improvements (Alberts et al., 2004). Some measures used by authors (i.e. Functional Independence Measurement-FIM) are not appropriate for evaluating unilateral rehabilitative interventions (Wolf, 2007), while speed of movement alone does not necessarily correlate with upper limb functionality (Bjorklund and Fecht, 2006, Dromerick et al., 2006). The large variability in intervention characteristics between studies is an illustration of the researchers' attempt to identify a more practical but also effective protocol. Modified types of CIMT will be explored in detail below. The Automated CI Therapy Extender (AutoCITE) may represent a practical option. It consists of a computer, 8 task devices arrayed in a cabinet on 4 work surfaces and an attached chair. A computer provides simple instructions that guide the patient through the entire treatment session. Completion of each instruction is verified by sensors built into the device before the next instruction is given. Patients have been treated entirely on a remote basis and the treatment effect was just as good as with the one-to one training (Lum et al., 2006, Taub et al., 2005).

The mechanisms through which CIMT produces motor improvements are not known, as yet. Imaging studies that explore the possibility of treatment-induced brain plasticity will be reviewed in detail. Kinematic analysis has recently started being applied as an evaluation measure after CIMT, providing insights into the spatiotemporal control of movement. An improved reaching movement involves a more pre-programmed control strategy; when the movement depends more on motor preprogramming, it will be more rapidly initiated, more efficient, direct and smoother.

Such an effect has been shown (Alberts et al., 2004, Caimmi et al., 2008, Wu et al., 2007b) after reduced forms of CIMT, including as less as 2 hours of training daily for 14 consecutive days.

2.3.2 Modified CIMT in adults

Despite the promising results reported by studies on the use of CIMT, this treatment method might not be easily implemented and compliance might be difficult for some patients. In a survey conducted by Page et al (2002a), most patients and therapists responded that they would not want to take part in CIMT because of the intensity of the practice schedule and the duration of the restraint schedule. More than 60% of the respondents believed that if the protocol lasted for more weeks with shorter practice sessions or fewer hours of splint wearing, they would definitely participate. Thus, a modified CIMT (mCIMT) was developed, combining structured, half-hour ADL practice sessions, 3 times/ week with restriction of the less affected upper limb 5 days/week for 5 hours, during a 10-week period (Page et al., 2002c, Page et al., 2001). Sterr et al (2002) supported the mCIMT concept by comparing the effects of 3-hour versus 6-hour daily training sessions with CIMT. They found that the 3-hour schedule significantly improved motor function in chronic hemiparesis, although less effectively than the 6-hour schedule. mCIMT provides a 250-hour restrictive device schedule so patients are actually getting more contact with the splint than they would with the original CIMT. The results of a case-report (Page et al., 2002c), a single-case study (Page et al., 2002b) and a randomised controlled trial (Page et al., 2004) suggested that mCIMT may be an effective method of improving function, although not so intensive as the original CIMT. A randomised controlled study, conducted with acute stroke patients (Page et al., 2005) reported greater improvements in the MAL, ARAT and FM against a control group that received equal intensity and duration of treatment. The small sample size though (5 patients in each group) did not allow for any statistical credibility. Using the same outcome measures, Page et al (2008) tested mCIMT against a time-matched exercise regimen, consisting of proprioceptive neuromuscular facilitation techniques and compensatory techniques and against no therapy in a total of 35 chronic stroke patients. The mCIMT group displayed significant improvements in ARAT and MAL compared to the control groups and considerable increases in FM scores, which were not statistically significant, though. The reason for this discrepancy might be the fact that ARAT exclusively measures

distal limb changes, where CIMT has the largest impact (Alberts et al., 2004, Koyama et al., 2007), whereas the FM measures changes on the entire arm. An intervention similar to AutoCITE was tested with 4 chronic stroke patients, who participated in online therapy sessions (Page and Levine, 2007a). Improvements on the MAL and WMFT were comparable with the ones reported by the AutoCITE studies. Investigation of mCIMT should be replicated by another research team, in a different setting. Confirming efficacy would increase the credibility of the findings.

Other modified versions of CIMT have also been suggested in addition to the classic mCIMT protocol described above. A review by Hakkennes and Keating (2005) concluded that CIMT might not be feasible and that modified forms appear to be effective although the limited data do not allow for definite conclusions. Promising results have been reported even with highly reduced intensity programmes with no constraint-wearing (Hakim et al., 2005) or informal constraint through therapists holding the less affected hand of the patient (Miller and Hale, 2005); most importantly such regimens seem to be preferred by patients. Stevenson and Thalman (2007b, Stevenson and Thalman, 2007a) suggested an intervention of 4 hours per day for 10 consecutive weekdays with restraint of the less affected hand for a goal of 90% of waking hours. Adherence was reported to have varied widely with some participants wearing the splint only during the training sessions. The positive effects implied by the authors are exaggerated if one considers that the only motor assessment, the Box and Block Test, the psychometric properties of which have not been established, did not show any significant differences while the Canadian Occupational Performance Measure, a subjective report was the only measure to reach significance at the 6-month follow-up. Distributing the amount of training over a longer period has been suggested to enhance motor learning (Donovan and Radosevich, 1999, Moulton et al., 2006). Dettmers et al (2005) tested an intervention that included intensive training for 3 hours a day for 20 days. Patients were also wearing a splint for an average of 9.3 hours a day. Repeated baseline measurements confirmed that the patients had reached a plateau. At post-treatment and at 6-month follow-up significant functional improvements were shown, while there was also a significant reduction in spasticity, especially for the shoulder. A randomised controlled trial (Wu et al., 2007a) showed significant effects on motor function after 2-hour therapy sessions, 5 times a week for 3 weeks, during which the control group received an equivalent time and intensity of

treatment, consisting of neurodevelopmental and compensatory techniques. Kinematic analysis (Lin et al., 2007, Wu et al., 2007b) showed that the modified form of CIMT produced a greater increase in the amount of preplanned control of reaching movement than did traditional rehabilitation. A normal reaching movement is composed of one accelerating and one decelerating phase. The authors demonstrated a higher percentage of movement time where peak velocity occurs (PPV), which indicates a longer acceleration phase, suggesting less online error correction and more feedforward control.

2.3.3 CIMT and modified versions in children

Over the last few years, research has aimed at testing CIMT in children with hemiplegic CP. Improvements have been shown in some cases, although the underlying mechanisms are unknown. Learned non-use cannot be directly translated for children, especially those with congenital CP, who have never experienced normal movement with their affected arm. DeLuca et al (2003) introduced the term 'developmental disregard' and suggested that a child with hemiplegic CP may not develop neural pathways involved in movement because of the lack of ability to experience age-appropriate sensorimotor stimuli that lead to the development of UE skills. 'Developmental disregard' has been viewed by some researchers (Taub et al., 2007) as a special case of learned non-use but the encouraging findings reported by studies on the use of CIMT with stroke patients cannot be directly translated to children with CP. Many studies on CIMT in children are case reports (DeLuca et al., 2003, Dickerson and Brown, 2007, Glover et al., 2002, Pierce et al., 2002, Yasukawa, 1990). Promising preliminary results have been reported by Echols et al (2001). Splint-wearing and functional activities were combined during a 2-week day camp for 7 hours a day and 5 days a week (Eliasson et al., 2003). The results for the 9 participants were inconclusive due to great inter-individual variability in the outcome. Similar observations were made by Charles et al (2001), who failed to show any improvement in hand function in three children with CP after 6 hours of daily treatment for 14 days. However, the Jebsen –Taylor Test of Hand Function that was used includes only timed items and might not be appropriate to capture qualitative changes.

In a single-case study, DeLuca et al (2003) described a protocol, which they termed as "Pediatric Constraint-Induced Therapy", that was given even more intensively than recommended for adults and involved the use of a full-arm, bivalved cast on the less affected UE for 24 hours a day for 3-weeks with 6 hours of daily exercise. The improvements reported were mainly based on outcome measures (Denver Developmental Screening Tool, PediatricMAL, Toddler Arm Use Test-TAUT) that are not appropriate for evaluative tools and their psychometric properties are unknown (Ketelaar et al., 1998). Taub et al (2004) tested the effects of Pediatric CIT but their conclusions were bold statements mostly because of the inadequacy of the measures they used, which were of questionable validity and reliability. At the follow-up only the PMAL was used, which was not administered to the control group. Similarly to adult studies, the superiority of CIMT cannot be concluded on when the control group receives a much less intensive treatment (2.2 hours per week compared to 42 hours/ week). In a randomised controlled study, DeLuca et al (2006) reported significant improvements in the Quality of Upper Extremity Skills Test (QUEST) within the experimental group that were maintained at 3 weeks post-treatment. Differences between Pediatric CIT and control groups did not reach significance. The authors encouraged researchers to investigate whether reduced treatment hours could prove effective and more child-friendly.

Gordon et al (2005) suggested a modified CIMT paediatric protocol as being more child-friendly than the original one used with adults. The main difference was that children were not required to wear a splint for 90% of the waking hours but only during the 6-hour daily practice for 10 days. Home practice was also required for at least 1 hour daily. Charles et al (2006) tested the effects of this intervention in a randomised controlled trial, where the control group did not receive any treatment. Significant improvements were shown for children in the intervention group in movement efficiency, performance and perceived usage. The effect sizes were robust and the changes were retained at the 6-month follow-up. Twelve months later improvements were still retained and a second dosage of the intervention was administered, resulting in further improvements (Charles and Gordon, 2007). This protocol has been criticised by Taub et al (2007) as resulting in limited effect sizes and questioned whether the reduction in effort for the children and therapists is worthwhile.

A considerably less intensive regimen was tested with 6 school-aged children that had sustained stroke. The intervention comprised daily restraint during one-to-one therapy for 2 hours each weekday for 4 weeks (Gordon et al., 2007). No improvements were shown at the end of the intervention. The reasons for this might be the 'light' regimen but most possibly it is the severe functional impairment of the affected hand of participants. Eliasson et al (2005) investigated the effects of a distributed version of CIMT. The experimental group wore a restraining glove for 2 hours daily for 2 months. The intervention was home-based and the parents were the ones responsible. Practiced tasks were carefully selected to be challenging and interesting for children. The Assisting Hand Assessment (AHA), an instrument that measures the effectiveness with which a child with hemiplegia makes use of their affected hand in bilateral tasks, showed that children who received CIMT improved their ability to use the hemiplegic limb, while the treatment effect remained at the follow-up, 4 months later. The actual time spent wearing the splint varied considerably, between 16 and 120 hours, with a mean of 59 hours. Interestingly, there was no correlation found between the time of restraint-wearing and the amount of improvement. The authors suggested that the overall approach had an effect on making the child more aware of their affected hand, even out of treatment hours. Another interesting finding is that the largest improvements were seen in older children. This comes in agreement with Naylor and Bower (2005), who tested a 4-week intervention that followed the principles of CIMT but did not include a contraint. Constraint was achieved by verbal encouragement to use the affected hand and by holding the child's less affected hand during activities. The programme was administered twice weekly for 1 hour by the child's regular therapist and as a home programme by parents the rest of the days. Significant improvements were reported until 1 month after the intervention on QUEST, which was the only measure used. QUEST is a measure that provides a mean functional score for the two limbs combined. A quantitative relationship between this test and unilateral involvement has not yet been established and thus, an additional measure for the affected limb specifically would be useful. Moreover, 3 out of the 9 participants were unable to successfully perform the test due to learning difficulties.

To summarise, optimal treatment amount and concentration are unknown (Mark and Taub, 2004). Original CIMT is not easily accepted, even by adults (Bonifer et al.,

2005). Few studies have considered the problem of patients' adherence to therapy requirements and the level of activity when the restraint is on; reports show that despite repeated encouragement, participants can only tolerate one to two thirds of the scheduled duration (Bonaiuti et al., 2007, Boylstein et al., 2005, Kaplon et al., 2007). When it comes to children with CP, it is even more difficult to draw conclusions since CP is a term that underlies a variety of different, complex pathologies. Many differences have been reported among paediatric participants as to the adherence to CIMT protocols and the engagement in functional practice. This however might be relevant to the differences between children's disability rather than the intervention, per se. Nevertheless, the adult protocol of CIMT is too demanding for children but reducing the intervention drastically may have repercussions for overall treatment efficacy. The different durations that have been tested illustrate the need for a more practical approach. FUT might be such an option.

2.3.4 Forced use therapy

2.3.4.1 Forced use therapy in adults

It is difficult to distinguish which element of the CIMT is the main reason for the improvements seen (Ploughman and Corbett, 2004). Intensive therapy alone has significantly better effects than lower intensity therapy (Sterr and Freivogel, 2003, Trahan and Malouin, 2002). However, DeBow et al (2003) who tested the effects of constraint and daily exercise in rats after intracerebral hemorrhage, suggested that improvements were observed only when the two elements of CIMT were combined, while neither therapy alone produced any substantial outcome.

FUT, which is the use of the constraint only (and not the intensive therapy, as well) is an interesting way to examine which element of CIMT is the one that produces the functional effects. Lum et al (2004) suggested that the key therapeutic factor of CIMT is the actual amount of use of the affected limb rather than the one-to one attention of therapists; this supports the concept of FUT. In a single-case FUT study (Ostendorf and Wolf, 1981), the patient took part in 3 one-week phases; baseline, experimental and after-intervention. Assessments were based on a 5-point, self-constructed scale. After FUT the time for completing the tasks was decreased but the quality of

movements showed little change across assessments. Limitations of the study design and the measurement tool make the results difficult to interpret. Wolf et al (1989) reported positive effects after a 2-week FUT in force and time-based measures but functional assessments were not included. Similarly, Pierce et al (2003) reported improvements after a 2 to 3-week restraining period but the only measure used was the timed components of the WMFT. Ploughman and Corbett (2004) tested an FUT approach, including mitt-wearing for 1 hour/ day, which was increased to 6 hours/day by the second week. The interesting finding is that none of the participants achieved 6 hours of daily constraint-wearing; the average time was 2.7 hours/ day, which has implications when designing an FUT intervention, especially for children, who are usually more frustrated by the use of a restraint and less compliant.

2.3.4.2 Forced use therapy in children

There is little published work on FUT in children. Therapists may not consider FUT a useful intervention because children, who have never experienced the ability to use their hemiplegic arm, may be less motivated to attempt activities without being given specific tasks to practice. As suggested by the literature (Nudo and Milliken, 1996, Nudo et al., 1996a, Plautz et al., 2000), functional practice is necessary for motor learning. Nevertheless, Yasukawa (1990) observed increased spontaneous use of the more affected limb in a 15-month old child with hemiplegic CP after 4 weeks of cast-wearing. Crocker et al (1997) reported two cases of children with hemiplegia that were treated using a forced use protocol. The minimum of 8 hours/ day that each child was required to wear the splint resulted in the withdrawal of the one child, who was averaging 4 hours/ day of wearing the restraint. The other child showed increased use of the affected limb after completion of therapy. Willis et al (2002) conducted a randomised controlled cross-over study, in which 12 children received a plaster cast on the less affected UE for 1 month. The Fine motor scale of the Peabody Developmental Motor Scales (PDMS) was used to assess functional changes. Improvements were shown but caution must be taken as the test was scored by 2 of the researchers who were not blinded to participant grouping. Variability between participants was large and so was the number of drop outs; 8 of the 25 children withdrew as they were unwilling to keep wearing the cast. Recently, FUT was compared with conventional therapy (Sung et al., 2005). A short-arm cast was applied, while occupational therapy was provided twice weekly in 30-min sessions for

6 weeks for both groups. The authors reported significant improvements in all measures but a review (Hoare et al., 2007) recommended caution in the interpretation of the findings of this study as the analytical processes were unclear and a further analysis found a significant treatment effect in only one of the measures (WeeFIM). The clinical significance of this treatment effect was questioned because of the mean difference between groups that was 1 point on a 56-point scale.

The evidence for the effectiveness of FUT is limited, especially in children. This lack of evidence can be attributed to the small sample number used in the few studies conducted and inadequate measures. Selecting the appropriate measure that quantifies changes on hand function and especially for children with unilateral impairments is not easy. However, instruments with unknown psychometric properties, based on subjective reports or others that have been developed for use with adults are not a proper option (Ketelaar et al., 1998). The variability in the type of constraint, the restraint duration, the length of intervention, the intensity of practice and the outcome measures weaken the ability to draw conclusions about efficacy and dosage. Especially with regard to the type of constraint, the literature shows a variety of constraints but in most cases, researchers have failed to justify their choice.

2.3.5 Brain imaging studies

The efficacy of CIMT and its modified versions in adults with CVA is supported by experiments, which show evidence of cortical reorganisation post-therapy. As discussed in the motor control chapter, the brain reorganises through different mechanisms but this is a highly selective process, dependent on the amount and type of exercise (Chen et al., 2002, Kelly and Shah, 2002, Nudo, 1999, Nudo, 2003). Despite the favourable findings reported for the physiological effects of CIMT, shortcomings are evident in most studies. An interesting study was conducted by Wittenberg et al (2003), who used TMS and PET to explore cortical changes in 16 patients that had sustained a single subcortical infarction 1 year or more prior to the study. Clinical measures (MAL, WMFT, Assessment of Motor and Process Skills-AMPS) were also employed. Sixteen patients were recruited and randomly allocated to either the CIMT group or the control group, which received therapy aimed at the less affected side for 3h/ day. After CIMT, the motor map size increased in the affected hemisphere, while there was a shift of the centre of gravity on the less

affected side. However, the change in map ratio affected-to-unaffected may be due to the map shrinkage on the less affected side as a result of prolonged restraint. Caution should also be taken as the increased activation of the ipsilateral motor cortex when moving the affected hand could not be shown when taking the patients as a group and thus, the issue of mirror movements may be the case. Another finding that suggests careful interpretation is the lack of significance in the clinical changes between groups. The only significant between-group difference was in MAL, which is a subjective report and cannot be considered reliable enough to base clinical conclusions. Despite the fact that subjects had sustained stroke more than a year before initiation of the study, multiple baseline measurements would provide evidence to support that any changes observed were due to treatment. A treatment-associated enlargement of the motor output map in the lesioned hemisphere has also been suggested by other studies (Liepert et al., 2000, Liepert et al., 2004, Liepert et al., 1998, Park et al., 2004), as well as decreased task-related cortical activation shown after CIMT, which may suggest an improved synaptic efficiency because the amount of cortical activation tends to decline as recovery takes place since less effort is required by the brain to achieve the same function. Especially interesting was the finding that while the patients maintained their improved limb use for at least 6 months, the expanded cortical motor representation reduced to normal size at 4-week and 6-month follow-up evaluations. However, limitations are present in most of the above studies (Kopp et al., 1999, Liepert et al., 1998, Liepert et al., 2001) due to the small sample numbers, lack of multiple baseline testing and absence of control groups. Schaechter et al (2002) employed fMRI and calculated a laterality index that reflected the distribution of activation in ipsi- and contralesional motor cortices. Prior to CIMT, activations in the contralesional hemisphere were stronger than in the control group. After CIMT, activations had further shifted towards the non-lesioned hemisphere. This study employed 2 pre-intervention and 3 post-intervention testing sessions but again the sample consisted of only 4 subjects, which may be the reason why changes did not reach statistical significance. In addition, the control group consisted of healthy, neurologically unimpaired adults; it might have been more adequate to compare with other stroke patients with similar characteristics.

Evidence of motor cortex reorganisation has also been shown after 'light' regimens of CIMT and FUT (Liepert, 2006, Liepert et al., 2001). Szaflarski et al (2006) followed a

markedly attenuated form of CIMT, including 30-min training sessions, 3 times a week for 10 weeks along with 5 hours of daily constraint-wearing. The researchers used fMRI and a very good battery of clinical measures to explore the combined physiological and functional effects of the intervention. A multiple baseline period was also applied. Johansen-Berg et al (2002) also tested a modified version of CIMT that limited treatment to twice daily 30-min exercise sessions and restraint to the affected limb for 90% of the waking hours for 2 weeks, conducted at home without therapist supervision. Both studies showed evidence of cortical reorganisation that correlated with the clinical measures although Szaflarski et al (2006) observed considerable inter-individual variation but the experimental group consisted of only 4 patients. It is reasonable to assume that the brain develops different strategies of recovery according to the lesion site or its capacity for dynamic neurological change in response to injury (Hamzei et al., 2006, Park et al., 2004). This is demonstrated by studies (Kim et al., 2004, Levy et al., 2001), which showed that in subjects with similar characteristics the pattern of reorganisation after CIMT was different, i.e. in some subjects, cerebral activation was almost exclusively confined to the affected hemisphere, whereas in others the location of activation was ipsilateral to the hand performing the task.

Findings from these studies must be interpreted with caution because of the limitations of the brain imaging techniques, small sample sizes, lack of baseline measurements, absence of control groups and lack of adequate clinical measures or correlation of those with the cortical changes observed. Inclusion of control groups are necessary to confirm that the changes do not occur by chance and that there is a relationship between observed increase in activation and improved performance (Krakauer, 2007). Indeed, the high correlation between cortical changes and functional improvements shown by some studies after different versions of CIMT and FUT (Dong et al., 2007, Ro et al., 2006) do suggest treatment-related brain reorganisation.

In children brain imaging studies that test the physiological effects of CIMT/ FUT are at an early stage. Sutcliffe et al (2007) reported the case of an 8-year old child with CP, who received modified CIMT consisting of 3 weeks of continuous casting and weekly 1-hour practice sessions. Consistent with adult stroke studies, fMRI showed

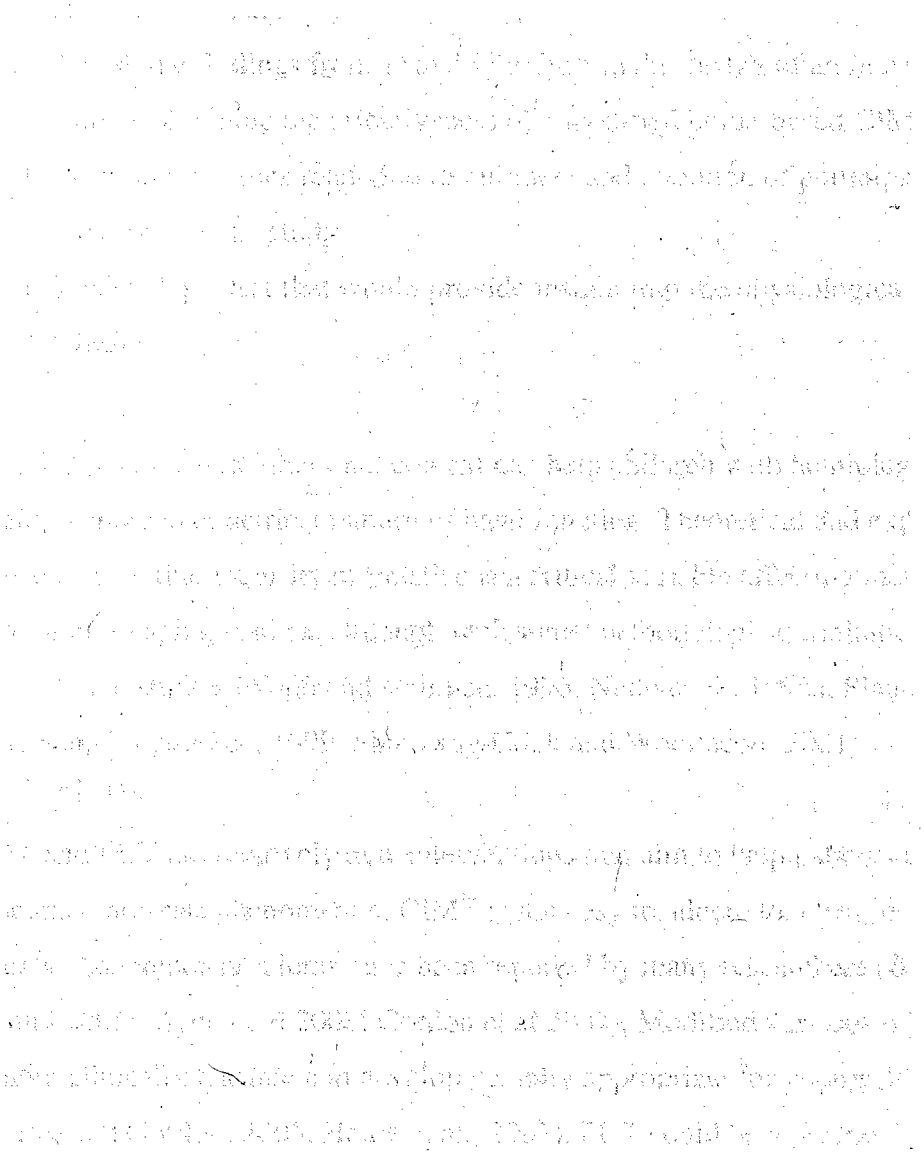
increased contralateral activity after therapy with a shift in laterality from the ispilateral to the contralateral hemisphere. In this case study, the authors did not use a baseline period but they managed to show an increase in all clinical measures although the psychometric properties of the primary one used (PMAL) have still not been established. Inconclusive results were presented by Juenger et al (2007) after an application of the adult version of CIMT in 10 adolescents with congenital hemiplegia. Physiological examination of the effects of CIMT/ FUT would be valuable in children as it would provide support for the clinical findings. A child-friendly measure that is also inexpensive would be the use of EEG and specifically, the recording of the lateralised readiness potential (LRP), a component that reflects cortical processes associated with preparatory mechanisms related to the execution of unimanual motor acts. Preliminary work towards development of this technique to be used as a physiological assessment with children formed part of this project and is presented in Chapter 7.

2.3.6 Potential hazards associated with CIMT

CIMT could be physically intrusive, especially for children. Wearing a constraint may impair balance and inhibit protective reactions, especially in patients with greater disability (Hart, 2005).

Animal studies (Bland et al., 2000, Humm et al., 1999, Kozlowski et al., 1996) have shown that restraining the less affected limb at a critically sensitive stage of development may compromise function. Early forced overuse in the rat model was suggested to result in long-lasting exacerbation of functional deficits. However, Bland et al (2001) conducted another study, the conclusions of which were contradictory to their previous work. They observed that 10 days of forced disuse of the affected forelimb beginning immediately after middle cerebral artery occlusion worsened the functional outcome but that forced overuse did not have such an effect. This discrepancy was hypothesised to be due to the difference in the location of the damage and is in agreement with Tillerson et al (2001), who also observed contrary results compared to previous studies. DeBow et al (2003) suggested that other reasons for the detrimental effects observed in some studies might be the immediate after the brain damage, intervention or the very demanding rehabilitation regimen. Findings in kittens (Martin et al., 2004) showed that prevention of limb use during weeks 3 and 8

produced permanent defects in the organisation of the cortico-spinal terminals and skilled paw use. However, the undamaged cortico-spinal system has been suggested to become less competitive through disuse thereby enhancing the relative competitive capacity of the damaged side (Salimi and Martin, 2004).



2.4 STUDY AIM AND OBJECTIVES

The aim of this research was to design a practical, yet effective protocol to be used with children with congenital, hemiplegic CP to improve their upper limb function in their everyday environment. To achieve this aim required fulfillment of the following objectives:

1) To identify the most appropriate constraint in terms of comfort, effectiveness and adherence from children and parents' perspective to be used in a home-based intervention
2) To determine the appropriate length of intervention and daily restriction of the less affected hand
3) To use the findings from 1) and 2) to inform the design of an intervention study to examine the effectiveness of a modified home-based CIMT protocol
4) To examine issues related to recruitment and retention of participants that arose during the study
5) To develop a test that would provide insight into the physiological effects of CIMT

Extended practice in a functional context can help children with hemiplegic CP develop a more symmetrical pattern of hand function. Theoretical and experimental evidence agree that intensity of practice is a critical variable affecting motor learning, while brain imaging studies, although with some methodological limitations, support observational studies (Nudo and Milliken, 1996, Nudo et al., 1996a, Plautz et al., 2000, Schmidt and Lee, 1999, Shumway-Cook and Woollacott, 2001).

CIMT and FUT are relatively new interventions that aim to help patients overcome the learned non-use phenomenon. CIMT is not easy to adhere to, even by adult patients. Adherence problems have been reported by many researchers (Brogardh & Sjolund 2006; Myint et al 2008; Gordon et al 2007). Modified versions of CIMT may be more clinically feasible and developmentally appropriate for young children (Charles and Gordon, 2005, Hoare et al., 2007). FUT could be a practical option as it does not require the continuous presence of a therapist however efficacy studies have been inconclusive.

The use of constraint at home offers a practical option that encourages relearning in an environment which provides better cues for retrieval after the therapy session has ended (Pickett et al., 2007, Sterr and Saunders, 2006). In a home-based intervention, where therapist supervision is not available adherence is more difficult to ascertain (Hakkennes and Keating, 2005, Richards et al., 2006). When it comes to children, this may be accomplished if parents take over the role of the therapist-supervisor, while children's motivation could be increased if activities have been tailored to meet each child's interests (Roberts et al., 2005).

Hoare (2004) stressed the need for future research to provide detailed information on participants' characteristics including severity of impairment, acceptance and adverse responses. Although practice seems to be the important treatment variable, it is also important to determine the role and significance of the restraint (Hart, 2005). The type of restraint is extremely important as it affects comfort, adherence and consequently treatment intensity (Gordon et al., 2005). Different restraining types might be suitable for different groups of children. Issues related to child's behaviour, age, degree of disability, psychological adjustment to the constraint, safety and parents' attitude might be the ones that should determine the type of constraint that is most appropriate. Researchers (DeBow et al., 2003, Glover et al., 2002) have encouraged further studies to examine the optimum restraint, length, quality and daily quantity of the rehabilitation regimen, based on adequate set of outcome measures. To address these issues, the present research project was designed.

CHAPTER 3

OUTCOME MEASURES

This chapter presents a review of the outcome measures that were used in this study and those that were considered but were eventually rejected along with the rationale for this choice. To satisfy the objectives of this study, a combination of measures was required. Some measures (actometer, videotapes, upper limb function tests) were included to examine different aspects of movement and how these were affected by the intervention, while others (questionnaire, daily log) to explore the parents' perspective.

3.1 Measures of activity

3.1.1 Tests of upper limb function

Different tests were reviewed and selection was based on the grounds of being appropriate for children with CP, for the specific age group that participated in the study and testing the functional outcome of the intervention as opposed to timed rating or impairment measurement.

3.1.1.1 The Melbourne Assessment of Unilateral Upper Limb Function

The primary aim of the effectiveness study was to test the effects of the intervention on the functional use of the hemiplegic limb. Most existing paediatric tests are designed to assess bilateral hand function and many do not focus specifically on quality of movement, which is the target area of CIMT.

The two tests that were considered appropriate to provide a qualitative assessment of the function of the hemiplegic limb in the present study were the Assisting Hand Assessment (AHA) and the Melbourne Assessment of Unilateral Upper Limb Function. AHA has been designed specifically for children with hemiplegic CP and assesses the effectiveness with which the child makes use of their affected hand in bilateral tasks. AHA is a very useful measure to test the hemiplegic upper limb function, especially since the aim of CIMT is to enhance the hemiplegic limb's input

in bilateral activities rather than promoting its use as a main hand. Unfortunately, AHA was only validated for children aged 18 months to 5 years at the time of initiation of the study, while a training course (which is compulsory before using the test) was not available in UK. The Melbourne Assessment of Unilateral Upper Limb Function was therefore chosen which has been designed for children with CP, validated for the ages of 5-15 years and provides a standardised means of scoring the affected limb's ability to perform unilateral functional tasks. Sensitivity to change, reliability and validity have been well documented (Bourke-Taylor, 2003, Krumlinde-Sundholm et al., 2007, Randall et al., 2001, Randall et al., 1999). A clinically relevant change is considered to be greater or equal to 12% in percentage score when there is a single rater (Randall et al 1999).

The Melbourne Assessment is based on sixteen items, involving reach, grasp, release and manipulation. Children's performance is recorded on a videotape for subsequent scoring. Item scores are finally summed to give a total raw score that is then converted to a percentage (normalised value).

3.1.1.2 The Quality of Upper Extremity Skills Test

Assessing the effects of intervention on the quality of movement of both upper limbs was considered to be part of the objectives of this study. Tests that were considered were the Jebsen-Taylor Hand Function Test, the fine-motor scales of the Peabody Developmental Motor Scales (PDMS) and the Quality of Upper Extremity Skills Test (QUEST). The first two tests do not assess quality of movement. In addition, the former is validated for typically developing children and the PDMS is validated for children with various disabilities, aged 2-5 years. Therefore, it is unclear whether these two tests are suitable for children with CP (Cusick et al., 2005, Haga et al., 2007). QUEST has been specifically developed and validated for children with CP, while reliability, validity and sensitivity to change has been shown in several studies (Fehlings et al., 2001, Graveline et al., 1999, Loewen et al., 1998, Haga et al., 2007, Law et al., 1991). The degree of score change that would be clinically relevant has not been established, yet.

The QUEST was designed so that scoring is related to severity of disability irrespective of age and is suggested to be suitable for children 18 months or older. It

includes items specifically related to hand function but also assesses movement of the adjacent joints. The test consists of four domains; dissociated movement, grasp, weight bearing and protective extension.

3.1.2 Actometer

Laboratory performance may inadequately represent real-world upper-extremity function. In this study the aim was to include an additional measure which would provide an indication of the actual amount of use of the affected hand. Different methods have been suggested for this measurement but many of them are either subjective reports or difficult for participants to use on their own. Some of these techniques have been used as a measure of gross movement, such as walking (i.e gyroscopes) but their relevance to quantifying upper limb function has not been established, yet (Luinge and Veltink, 2005, Tong and Granat, 1999, Uswatte et al., 2000). The activPAL was considered at the beginning of the study since it has been frequently used to monitor physical activity levels associated with everyday activities. The activPAL is a single-unit monitor based on a uni-axial accelerometer that can be applied easily by the user. The activPAL has mainly been used and validated in the adult population to measure static activities of sitting/ lying and standing and dynamic activities of moving and has never been used to measure upper limb function (Godfrey et al., 2007, Grant et al., 2006). Finding a way to capture and distinguish between both gross and fine, purposeful movement of the upper limbs in the child's everyday environment proved to be a difficult aim to satisfy using the existing monitors. Another indication of this difficulty is the fact that technicians have tried to develop devices but these cannot be considered to measure purposeful function; instead they usually measure muscle forces from the fingers during specific tasks (Pataky et al., 2007).

Taking into consideration the specific aims of the study and the above mentioned problems, the measures that were finally considered required careful interpretation of the findings keeping in mind their questionable validity. Accelerometers and actometers were thus considered to be the tools that were feasible to use, and that could most closely provide a representative record for the gross and fine, functional movement of the affected upper limb. Both tools are available as wireless sensors that allow for unobtrusive monitoring of movement (Hyde et al., 2008). The actometer is a

device that provides an indication of the activity of the limb to which it is attached. Actometers consist of adapted self winding watches which have been modified by removing various working parts (Figure 1). When the watch is tilted or moved, the pallet lever swings causing the wheel to advance the hands of the watch. The apparent passage of time is proprortional to the number of times the recorder is tilted or oscillated. The more movement made the greater the reading on the actometer. Data output from the device is in hours and minutes in a manner similar to an ordinary watch (Johnson, 1971). Actometers are considered to offer a practical and objective method to measure physical activity (Meijer et al., 1991), while studies (Eaton et al., 1996, Saris and Binkhorst, 1977) have provided support for their validity and reliability in detecting differences in the activity level among infants. The main criticism is that actometers are not equally sensitive to all movement and more rapidly decelerating movements might result in the recording of more activity units. The actometer's readings are not proportional to intensity of movement but provide a frequency or count measure of motor activity (Eaton et al., 1996, Johnson, 1971).

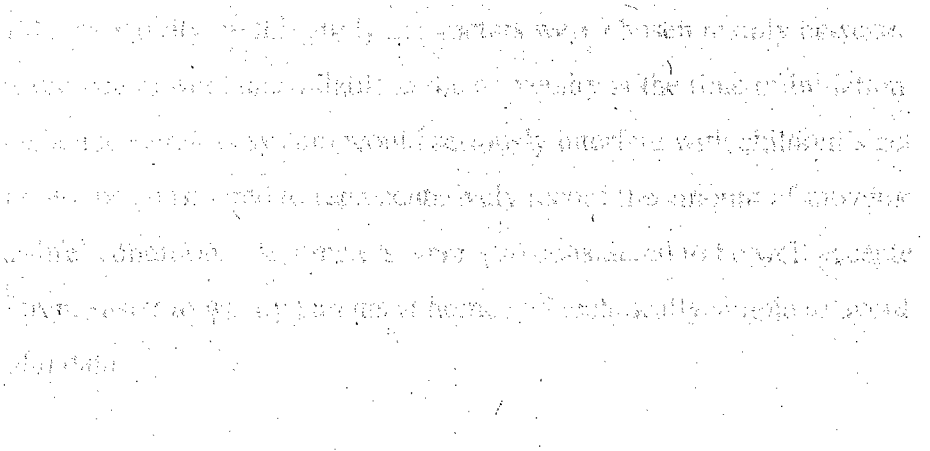


Figure 1. The actometer

Accelerometers are sensitive to acceleration of the limb to which they are attached and can give a rough index of the amount of movement. However, it has been shown that accelerometer readings on duration and speed of arm movement are reliable when averaged across subjects but not when individual recordings are examined (Uswatte et al., 2000). Studies (Estill et al., 2000, Uswatte et al., 2000, Vega-Gonzalez et al., 2005) have shown that trunk motion or sudden movements of the limb can frequently be the reason for recordings not being representative of the amount of limb movement. An additional problem with accelerometers is that data quality problems (i.e. errors in initializing accelerometers or downloading and storing recordings) are frequent, resulting in invalid or missing data (Estill et al., 2000, Uswatte et al., 2006a).

Although accelerometry probably provides a more accurate way to measure real-world arm activity, in this study actometers were chosen mainly because wireless accelerometers were unavailable at the university at the time of initiation of the study. Using a non-wireless system would seriously interfere with children's activities and could not be considered to representatively record the amount of movement under 'real-life' conditions. Actometers were also considered to be well accepted by young children, easier to use by parents at home and technically simple to avoid missing or invalid data.

The actometers used in this study have been validated in a previous study, which compared the activity levels of the dominant and non-dominant arm in healthy children when they were wearing a restraint on the dominant hand and without it

(Crossley, 2005). The results showed that the recordings of the actometer were similar for the same movements and that the two actometers were recording the same amount of activity for the same movement. The reliability of the actometer readings in response to the movements performed was also tested at the beginning of this study. Two healthy volunteers took part in this reliability testing. The actometer was attached to the first participant's wrist, readings were recorded and the first set of movements was performed. Recordings were taken again and then the actometer was applied to the other participant who was instructed to perform the same set of movements in as much as possible the same way. Six sets of movements were performed overall. The instructions given to subjects for each set were the following:

1) Hold the middle of the wand in the horizontal plane with your forearm pronated and turn the wand over until the palm faces the ceiling
2) Sit on this chair having the table in front at your waist level (adjusted chair) and rest your hands on your laps. Move your hand from laps to the dot drawn on the table and then return your hand to the initial position
3) Sit on this chair having the table in front at your waist level and put your hand on the cube placed on the dot of the table. Pick up and turn the cube over with one move till the bottom side is on top and then leave the cube back on the dot
4) Sit on this chair having the table in front at your waist level and put your hand on the cereal placed on the dot of the table. Pick up the cereal and put it in the glass
5) Sit on this chair having the table in front at your waist level and rest your hands on your laps. Pick up the cube from the floor and leave it on the table dot and then return your hand to the initial position
6) Sit on this chair having the table in front at your waist level and rest your hands on your laps. Place your hand on top of your opposite shoulder and then return your hand to the initial position

The non-parametric Spearman's Rho was calculated to reveal the correlation between the actometer readings for the two subjects; the results showed statistical significance ($r=.886$, $p=.01$) and thus, an acceptable level of reliability.

Actometer readings were also recorded while the two subjects performed activities, such as dish washing, drawing and cooking for 5 minutes each. In this trial subjects performed the activities on their own way without mirroring each other's moves. The

readings were highly variable in this case and observation confirmed Crossley's (2005) suggestions that large, gross motor movements produce a greater reading on the actometer than smaller, fine motor movements.

3.1.3 Videotape recordings

Videotaped evaluations have been used in many studies as they provide rich data that can be analysed both quantitatively and qualitatively. This type of assessment has been especially used with children in a variety of cases such as after botulinum toxin injections (Desiato and Risina, 2001, Hurvitz et al., 2003), in CIMT or FUT studies (Crocker et al., 1997, Eliasson et al., 2005, Ostendorf and Wolf, 1981, Taub et al., 2004) and in other cases that required evaluation of quality of movement (Fedrizzi et al., 2003, Sugden and Utley, 1995, Waters et al., 2004, Wright et al., 2001, Yokochi, 2001).

In the feasibility study, the aim was not to test the functional effects of a period of FUT but rather to record the immediate effect of the constraint on use of the hemiplegic hand. Thus, just as with the actometer, videotape recordings were selected as the most appropriate option since there was no adequate measure to provide the specific type of information that was required. .Data were analysed in a quantitative way to increase reliability of the results. Two raters were counting, using a stopwatch the length of time that each child was using their limbs in a specific way. The tool on which the raters scored the child's performance is presented in more detail in the Methods chapter.

3.2 Measures of parents' perspective

3.2.1 Questionnaire

Questionnaires are a useful tool for generating information about a group's views, attitudes and opinions especially if one can identify the possible scope of likely responses (Bell, 1993, Shepard, 1993). A questionnaire can be considered valid and reliable once its psychometric properties have been established. Such questionnaires are available and their reliability and validity are supported by published evidence. However in this study, the aim of the questionnaire was very specific, i.e. to provide information on the overall experience of the family and the child's attitude while

wearing each constraint and no standardised questionnaires existed that met these needs. Thus, a self-constructed questionnaire (Appendix 1) was used, comprising mainly closed questions. Detailed description of the content of the questionnaire and the development work is presented in the Methods chapter. The questionnaire was self-administered and completed by parents; this means that children's opinion on the different splints was not directly expressed. The researcher was present during completion to discuss any questions that parents might have felt they needed clarification on. This helped to avoid the high probability in self-administered questionnaires that some questions might be incorrectly completed or ignored and instructions might be misinterpreted (Bourque and Fielder, 1995, Hicks, 1999, Langley, 1987). The disadvantage of this approach is that the researcher's presence could have affected parents' responses, i.e. they might have responded in a way they would consider to be more desirable by the researcher. However, as the aim of the feasibility study was not hypothesis driven and respondents understood that the objective was to select the most appropriate splint, it is unlikely that they would have been biased in their responses.

3.2.2 Daily log

Daily logs have been used in several studies to document different aspects of participants' performance like sleep time (Merilahti et al., 2007), occurrence of disorder symptoms (Litz et al., 2007) and training intensity (Braun et al., 2007) outside the lab. CIMT studies have used daily logs to monitor the participants' adherence and to document the actual restriction time and the activities performed during the restraint hours (Blanton and Wolf, 1999, Crocker et al., 1997, Eliasson et al., 2005, Kunkel et al., 1999, Page and Levine, 2003, Pierce et al., 2002, Wolf et al., 1989). Due to lack of adequate measurements to evaluate performance at home, many researchers have relied on retrospective, self-report questionnaires (Taub and Uswatte, 2000). However, in this case there is a high possibility that some information might be inaccurate or left unmentioned if the person fills in the questionnaire after some time (Schmitt and Di Fabio, 2005).

Daily logs were used in both the feasibility and the effectiveness study (Appendix 2). The design of the daily logs was informed by discussions with therapists and supervisors.

In the feasibility study the log was used to gather information regarding the child's and family's experience of using the three constraints. It comprised open questions on basic issues that would determine whether a splint was appropriate, such as the amount of time of splint wearing, reasons for splint removal and complications that arose.

In the effectiveness study the log provided information on the amount of time of splint wearing and the activities children participated in. Actometer readings were also recorded on the daily log by parents once every week. During the second intervention phase, parents recorded daily the score achieved by the child on the computer game that was used additionally to everyday activities.

In conclusion, the daily log and questionnaire were chosen as the best way to gather information about children's adherence, performance and attitude, while being at home. At completion of the feasibility study, it became apparent that the questionnaire did not provide any additional information and thus, only daily logs were used for the effectiveness study. Videotape recordings offered a valuable measure to describe the way in which each splint affected children's hand use, while actometers provided a practical and objective quantification of spontaneous movement. The two primary measures used in the effectiveness study were chosen on the base of being age-appropriate, reliable, sensitive and repeatable (Charles and Gordon, 2005, Cusick et al., 2005) but also being able to provide a qualitative measurement of function for both hands and the affected hand specifically.

CHAPTER 4

THE FEASIBILITY STUDY

In this study three different constraints were tested in order to identify the most appropriate from children and parents' perspective. These three constraints are the most popular in CIMT paediatric studies. Another constraint that has been frequently used by researchers is the sling. A sling was not tested in this study as it would seriously affect children's ability to protect themselves in case of falling and this was considered to pose safety problems especially at home where the level of supervision of the children may not be as high as in the clinic. This is the reason that other researchers did not have the children wear the sling at home, despite using it in the clinical setting.

4.1 METHOD

4.1.1 Ethics approval

The study commenced after a favourable ethical opinion was obtained by the Isle of Wight, Portsmouth and South East Hampshire Local Research Ethics Committee and the community R&Ds of Southampton and Portsmouth (Appendix 3). The study was sponsored by the University of Southampton and received full R&G approval. Recruitment and consent was conducted under the guidelines set out in the MRC Clinical Trials Tool kit.

4.1.2 Objectives

1) To identify the most appropriate splint from children and parents' perspective as reflected by effectiveness and adherence to home based FUT.
2) To provide guidance for the development of a practical and effective protocol based on forced use principles. This protocol will be tested in terms of effectiveness in the subsequent study.

4.1.3 Participants

This study was conducted with a convenience sample (Bourque and Fielder, 1995, Fink, 1995). Convenience sampling does not allow for any generalization of the

results, as there is no statistical credibility with respect to error in the data (Fink, 1995, Fowler, 1993). The present study was not hypothesis driven and the aim was to examine a sample from the same population that would take part in the effectiveness study to describe the tendencies and behaviours observed rather than generating statistics about the population of children with spastic hemiplegic CP.

Selection criteria

CP is an umbrella term covering a variety of non-progressive but changing motor impairment syndromes secondary to lesions of the early developing brain (Rosenbaum, 2003). In fact, many different aetiologies occurring at different developmental stages might result in the same clinical type of CP. Due to these individual differences, a large degree of variation also exists in the pattern of hand and upper extremity development (Hanna et al., 2003). Taking into consideration this variation in motor performance among children with CP, the aim was to include a particular group of children that is feasible to study and more likely to benefit on the grounds of age, lack of co-morbidities and absence of contractures. The following criteria were therefore applied:

Inclusion criteria

1. Children who were between 5-11 years old
2. Congenital hemiplegic CP
3. Children performing above the 10^{th} percentile on the Raven's Coloured Progressive Matrices (Raven et al., 1998)
4. Normally using the affected upper extremity as a gross function in bilateral tasks. This was determined by observation and from discussion with the child's occupational therapist and pediatrician
5. Willingness of parents/ caregiver and child to cooperate
6. Informed consent by parents and assent by the child

Exclusion criteria

1. Fixed contractures limiting the movement of the affected upper extremity more than one quarter of the normal range

2. Physical, cognitive or behavioural problems that would seriously interfere with the child's ability to comply with the protocol

As this was a preliminary study, for which there were insufficient data on which to base a power calculation, we intended to recruit 15 children accepting that one or two may not complete the study. This sample, although small was considered to be enough to give indication of the effect size and the variability in response to the intervention. The lower age limit has been selected because there are some cognitive demands that needed to be satisfied so that the children could cooperate during the study. The upper age limit was set to ensure that the group was homogeneous in terms of age range. Children with significant cognitive or behavioural problems were excluded in an attempt to restrict the sample in children most likely to benefit from the particular intervention (Glover et al., 2002, Yasukawa, 1990). For the same reason children with fixed contractures or inability to use the impaired upper extremity as a gross functional assist were excluded. It is believed that in these children CIMT/ FUT could only cause great frustration (Yasukawa, 1990).

Recruitment process

At the beginning of this study, presentations were given to therapists and paediatricians to inform them about the project and the group of children that would be eligible for participation. The main collaborators in the recruitment process were two consultant paediatricians in each of the two research sites and the Child Health Information & Performance Manager in the main site. The latter was able to access a database where all the names and contact details of children with special needs were entered. Such a system was not available in the other research site. The collaborators in cooperation with their colleagues and paediatric therapists produced a list of children that could be eligible for the study, which included 14 children in the main site and 21 in the second.

A pack including the invitation letters (Appendix 4), parents' and children's information sheets (Appendix 5) and stamped addressed envelopes were forwarded to the families by the collaborators. After the initial contact was made, children had their assessment of eligibility for inclusion in the study followed by enrollment if they

satisfied all the inclusion and none of the exclusion criteria and following consent from parents (Appendix 6). During the first 3 months, there were only 4 positive responses and subsequent inclusions in the study, while 3 families had refused to take part. Reminder letters were sent out at that point, while ten more children were identified in cooperation with the paediatric therapists. Due to the limited response rate, an amendment was submitted at the ethics committee to extend the age range of the participants up to 16 years. This was considered necessary to obtain a larger sample although it would affect the homogeneity of the sample. Favourable ethical opinion was obtained on May 2005 (Appendix 3) and 15 letters were sent out. Interestingly, there were only two negative responses from this age group and no positive response. Eventually, nine children participated in the study, one of which withdrew before the final assessment. Two children withdrew from the study at an early point and thus, provided no data.

Screening process

Following consent, a screening process ensured that all potential participants satisfied the selection criteria. This process involved observation of the children during free play to ensure that they were able to use their affected hand as a gross function. The Raven's Coloured Progressive Matrices (CPM) was used to assess children's cognitive level. This is a non-verbal test designed for use with young children and old people for anthropological studies and for clinical work. It can be used satisfactorily with people with physical disabilities, like CP. The series of three subtests (labeled A, AB, B) constituting the CPM are arranged to assess the chief cognitive processes of which children under 11 years of age are usually capable. Each subtest contains a set of figures with increasing difficulty and with a part of the figure missing. The examinee's task is to recognize the structure of the (incomplete) figure and to select the missing piece out of six alternatives. Solution of the task requires visual analysis of the figure, through which relations between figure elements like identity, similarity, symmetry or spatial position need to be detected. Matrices have been thoroughly validated and scores are highly stable in a variety of cultures (Sandiford et al., 1997, Weichbold and Herka, 2003). The total score arises by adding one score for each correct answer. Afterwards the total score is considered in terms of the percentage frequency with which a similar score is found to occur amongst people of the same

age and country. In this way, examinees are then classified to 5 grades, with Grade I representing the "intellectually superior" and Grade V representing the "intellectually impaired" (Raven et al., 1998).

4.1.4 Setting

Participants were receiving treatment from community-based services in two PCTs in Southern England serving children in both mainstream and special needs schools. The screening process, splint construction, as well as the subsequent assessments were taking place at the clinic or the children's home, whichever was more convenient to families.

4.1.5 Design

This study in which three constraining devices were evaluated, was based on a crossover design. The reason for selecting this particular design was to enable each child to act as their own control, thus avoiding the difficulties of matching groups of children with each other. This study combines qualitative and quantitative research methods.

4.1.6 Development work

Before the study commenced there was an ad-hoc experimentation for different designs and materials for splints. This was done in cooperation with a physical therapist, who has many years experience in splint construction. A library of toys was obtained in order to enable children to perform tasks consistent with their age that would involve functional bilateral or unilateral use of hands.

Significant development work was done for the questionnaire that was used in this study. In deciding the content of the questions, a list was initially developed with parameters, which would determine the appropriateness of each splint. The questionnaire included items regarding the child's performance and behaviour while wearing the constraint, the degree of encouragement that the parents had to provide, the time that the whole process required from parents/ caregiver, any adherence or safety problems and complications that might have arisen during the intervention. Bearing in mind that it is always preferable to keep the questionnaire as short as possible with few open questions, some items were omitted as they did not provide

any additional information that could not be gathered by the other measures (Bourque and Fielder, 1995). "Double questions" or words that could be interpreted in different ways were avoided (Bell, 1993, Bourque and Fielder, 1995, Shepard, 1993), leading questions were excluded, as well as were presuming questions, which are often a source of error in questionnaires. The final form of the questionnaire consisted mainly of closed questions. In some of these, an explanation or clarification of the answer was required by the respondent. A closed-form questionnaire is easier and less time-consuming to fill out. Research methods literature (Bourque and Fielder, 1995, Shepard, 1993) suggests that a questionnaire should be primarily composed of closed-ended questions, while open questions should be sparingly used in self-administered questionnaires. When the responses are forced choice, the data tends to be more reliable. However, a problem with forced-choice answers is the issue of validity. In most cases, the researcher cannot be absolutely certain that the limited choices really captured the respondents' opinion. In the present study, the questionnaires were being filled out in the researcher's presence and such an incident was not recorded. The response choices in the questionnaire were of nominal and/ or ordinal level. The response categories were kept exhaustive but not too long, mutually exclusive but with easy to determine boundaries.

This questionnaire was constructed by the researcher and reviewed by supervisors and colleagues, who were asked to give feedback both on substance and structure. This process resulted in questions being reworded when they were indicated as being unclear. The pilot work also helped in differentiating some response choices under the closed-ended questions, as well as modifying the instructions that guided the respondents throughout the questionnaire. In particular the supervisors were asked for their opinion on whether any major topic had been omitted. After corrections were made, the questionnaire was distributed to a group of eleven people, who were native English speakers and had different educational levels. A diverse group of people was chosen to include an as much as possible the broadest representative sample of the population that would be required to fill out the questionnaires during the actual study. The respondents were asked to give feedback on the clarity of instructions, the logical ordering of the questions and the approximate length of time it took them to complete the questionnaire, while they were also asked to comment on the layout. The results indicated that the questionnaire required less than 10 minutes to be completed,

while there were no additional modifications suggested. Finally, the questionnaire was reviewed once again after the parents of the first two participants filled it in. There were no changes as a result of this stage.

4.1.7 Types of constraint

Three types of constraint were tested, all of which have been frequently used in paediatric CIMT or FUT studies. Type 1 was a mitt, made of fabric with a double-layer on the palmar side, forming a pocket into which a plastic splint was inserted to prevent finger flexion (Figure 2). Types 2 and 3 were made of thermoplastic. Type 2 extended from the fingertips to just below the elbow (Figure 3) and Type 3 extended from the fingertips up to the shoulder (Figure 4). Both were secured with velcro straps. The researcher constructed all of the restraining devices.

Figure 2. Mitten

Figure 3. Short splint

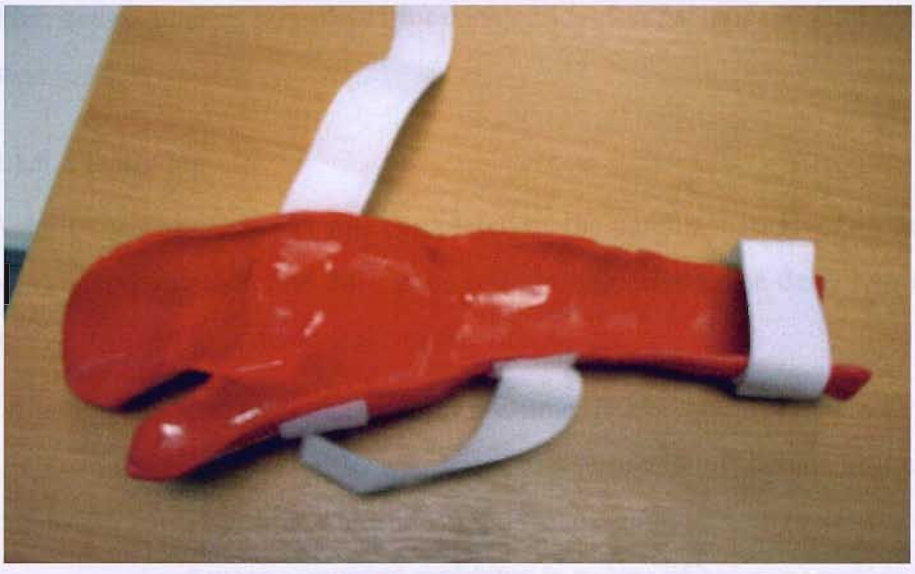
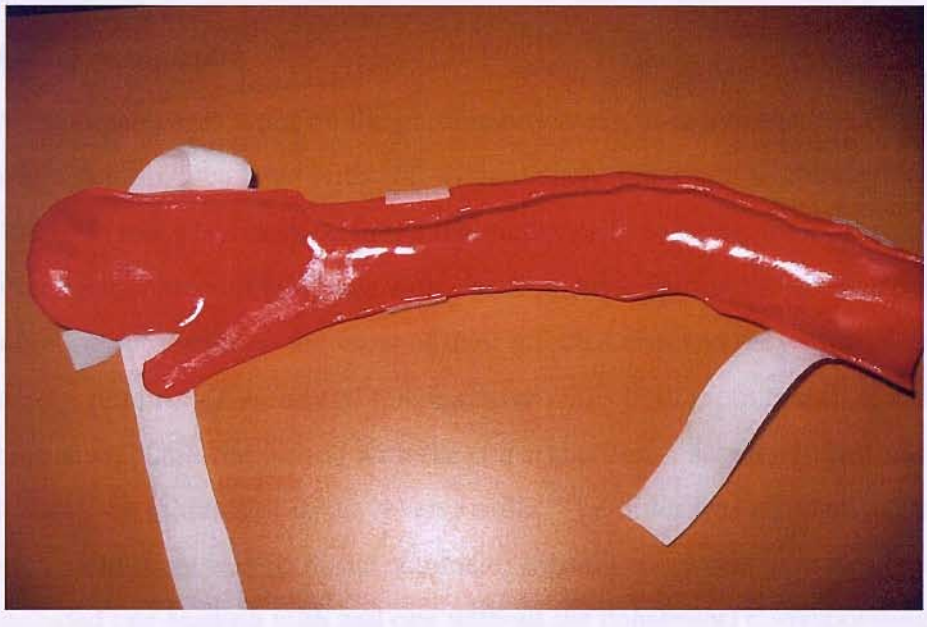


Figure 4. Long Splint



4.1.8 Outcome measures

4.1.8.1 Questionnaire

A questionnaire (Appendix 1) was used to confirm the responses recorded on the daily log, to provide information regarding the child's performance and attitude with each splint, as well as the parents' point of view as to the appropriateness of each splint.

Parents completed the questionnaire at the end of each restraining period resulting in three questionnaires completed for each child, after each of the three constraints had been used.

4.1.8.2 Daily log

A daily log (Appendix 2) was completed by the parents/ caregiver (depending on who was supervising the child during the restraining period). The daily logs consisted of open questions to provide information on:

a. The total daily amount of time the constraint was worn
b. The reason the constraint was removed on each occasion
c. The child's attitude and psychological adjustment to the constraint
d. Any encountered problems (e.g. loss of balance) and/ or any complications that were due to the constraint
e. Any additional concerns/ thoughts on behalf of the parent/ caregiver

4.1.8.3 Actometer

An actometer was worn on the participants' wrist to record the level of activity of the affected limb, measured with and without each constraint. Children were assessed during a 'free play' session in the laboratory prior to using any of the constraints and after each constraint had been worn for four days. During the assessments children wore the actometer on the wrist of their affected arm and they were offered a choice of toys requiring a variety of manipulative skills both gross and fine, and single and bi-manual. Children played with the constraint on for seven minutes and then without it for seven minutes or in the reverse order. The order was randomly selected. For each child there was an initial actometer reading and 3 sets of readings (each of which included one reading with and one without the constraint) corresponding to the 3 constraints.

4.1.8.4 Videotape recordings

The immediate effect of each constraint on the use of the hemiplegic hand was measured through video recordings made during a 14-minute free play session. This was taking place at the end of each restraining period either at the clinic or the children's home. Participants were videotaped while playing with the constraint on (7 minutes) and without it (7 minutes), simultaneously with recording of the actometer

readings. Parents were present during all the assessments, although they were not allowed to assist children with the toys. A Sony Digital Handycam, TRV 33E was used for the recordings. The camera was held by the researcher, who moved it around or zoomed in and out according to the movement being recorded. This was necessary to provide precise information and allow for proper analysis of the recordings and it was the reason why a tripod was not used.

Video recordings were analysed at a later date by the researcher and one more paediatric therapist using a standard report form (Appendix 7) which had been constructed by the two assessors and another occupational therapist. The report form allowed activities to be categorised into a) affected hand used as the only or main hand and b) affected hand not in use. Duration of each category of activity was recorded using a stopwatch. Assessors were able to play and replay the tape as often as needed. This form of report was chosen because there was a need for standardization of the information that would be collected.

4.1.9 Experimental procedure

The feasibility study took place between March 2005 and October 2005. Following screening and informed consent, the first splint was made for each child. A letter (Appendix 8) along with the parents' information sheet was sent to the children's GP and therapists to inform them of their participation in the study. During the first meeting, an actometer reading was taken to establish the level of activity of the child's affected hand. The intervention period comprised three parts, corresponding to the three restraining devices. Each device was tested for 4 days, in random order and assessments were taken after each constraint had been removed. Two days were allowed between each constraint period for assessments to be collected. The reason for choosing only 4 days for each splint to be tested was mainly to ensure compliance but it was also considered enough to provide the necessary information. Parents were instructed to apply the restraining device to the child only when they were being supervised for safety reasons but also to be able to observe their behaviour while wearing the constraint. Children were required to wear the constraint during productive hours, for a minimum of 1 hour/ day; no upper limit was specified. Parents were asked to apply the constraint to the child for as long as the child could cooperate

and feel comfortable with it. The amount of time that children would wear each splint as well as the degree of involvement in functional activities with each restraint was thought to be indicative of the appropriateness of each device. At the end of wearing of each splint, children were recorded on videotape to provide detailed information about how the constraint had affected the use of the upper limbs during this period. Actometer readings were taken with and without the splint, while the parent/ caregiver was requested to complete the questionnaire. The procedure of the study is shown graphically in the following flow chart (Figure 5).

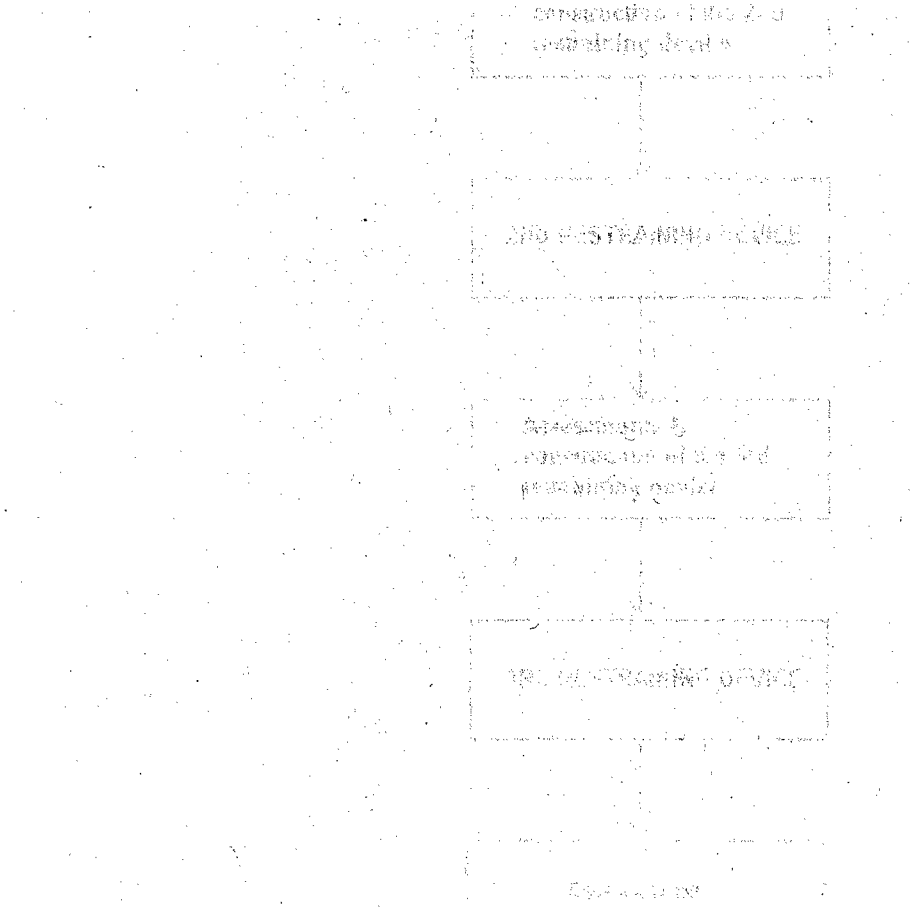
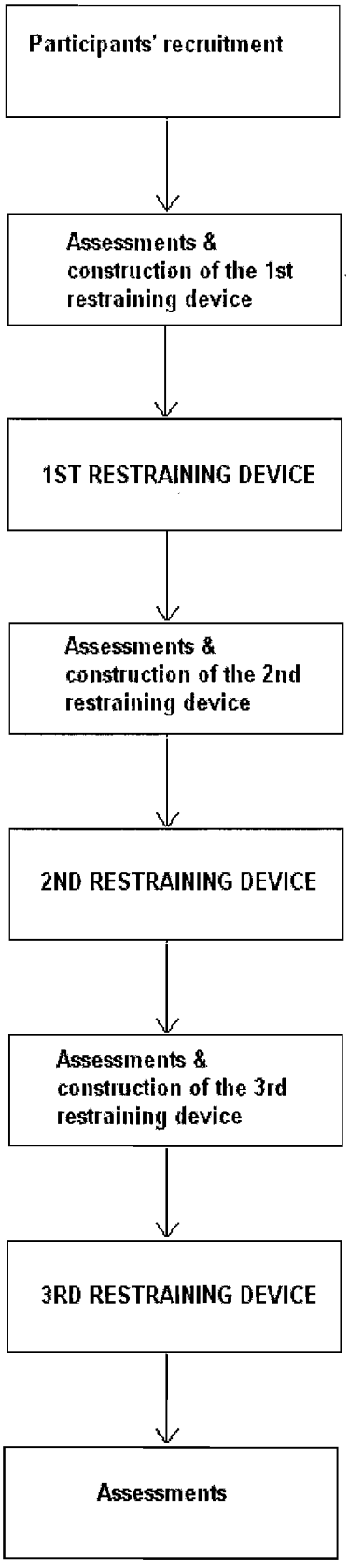


Figure 5. Flowchart of the procedure of the feasibility study



4.1.10 Data analysis plan

Content analysis was used to for the daily log data and the open questions from the questionnaire, while descriptive statistics were used for the rest of the questionnaire. Graphical displays of the actometer readings at the baseline and with each constraint are presented. One-way ANOVA was used (Fleiss, 1986, Hicks, 1999) to compute the reliability coefficient between the two assessors scoring the videotape recordings. All the syntaxes and results of the study are included in CD1.

Video analysis

The exact total time of the videos were calculated, with the splint on and off. The normalised values (percentage of the actual use compared to the total video time) were computed for each category of the report form on which therapists were recording the time that the child was using their affected and non affected hand, with and without each splint. The results are presented in tabular form and in pie charts.

4.2 RESULTS

This chapter presents a flowchart (Figure 6) that illustrates the progress of participants through the study. Their characteristics, in terms of age, sex and cognitive status are also presented. Parental responses to the questionnaire are summarized in tabular form. A review of the daily logs is presented along with graphical displays. This chapter further includes the output and graphical displays of the actometer, the inter-rater reliability for each of the categories in the video report form and the analysis of the videotape recording.

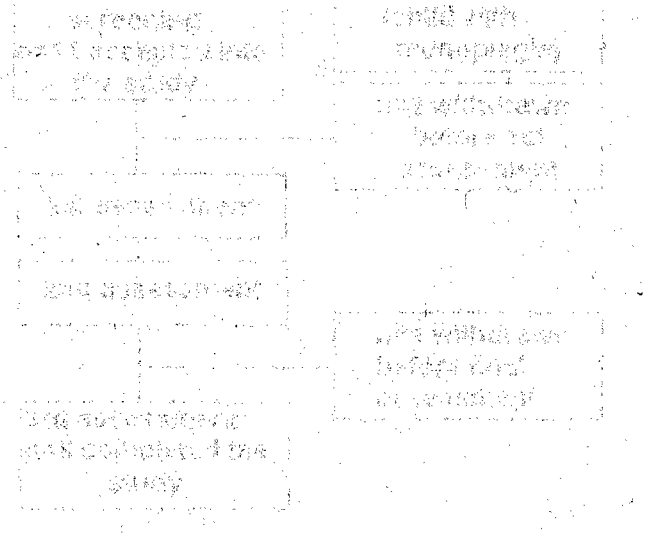
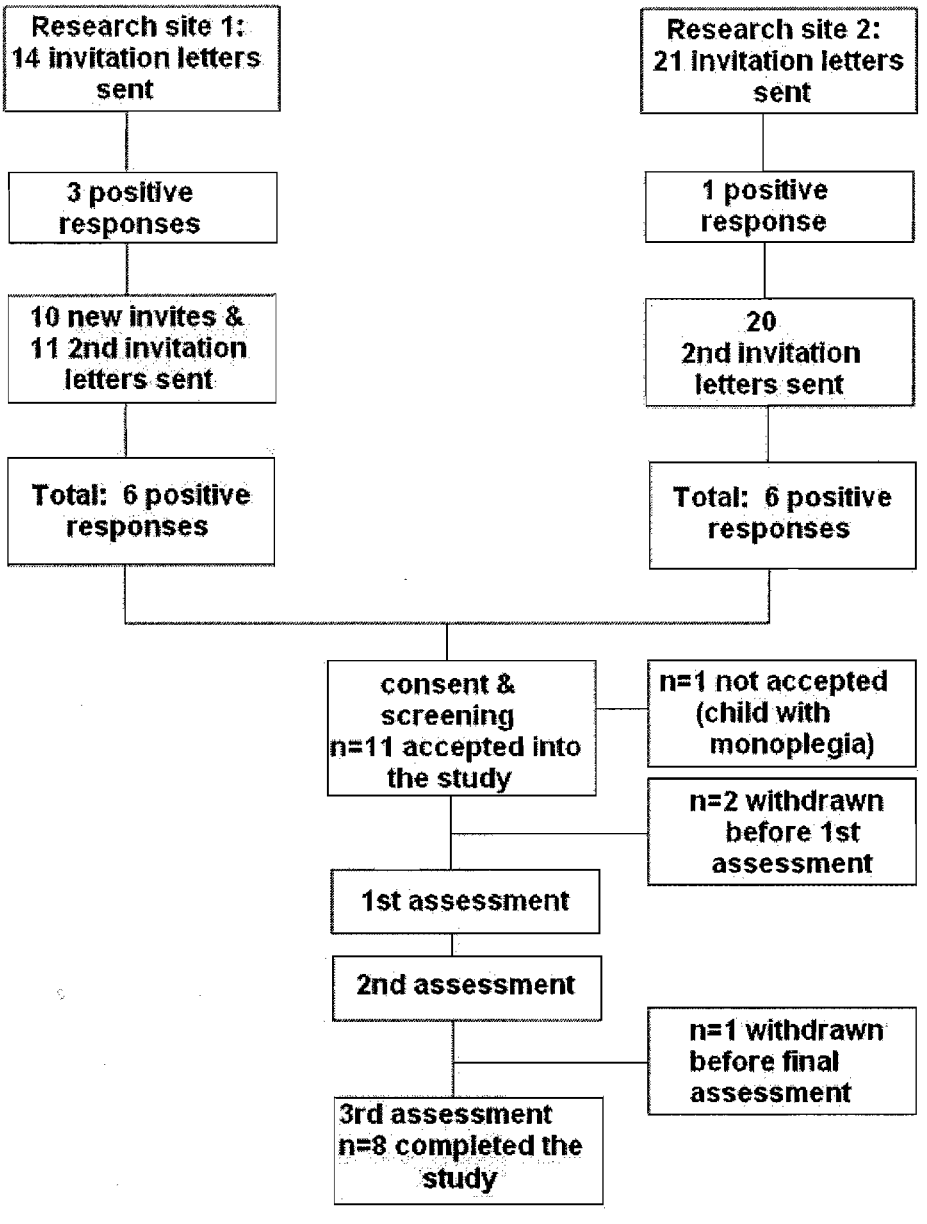


Figure 6. Flowchart illustrating the recruitment and progress of the participants in the feasibility study



4.2.1 Participants

The mean age of participants was 84.5 months or approximately 7 years (SD: 2 years). The cognitive level of each participant was determined in terms of percentiles and grades, according to the CPM. The individual characteristics of each child are summarized in Table 1.

Table 1. Feasibility study participants' characteristics

Child ID	Sex	Age (years/ months)	Grade according to CPM *
1	Male	(4/ 10)	III^{+}
2	Female	(5/ 5)	II^{+}
3	Male	(8/ 7)	II^{+}
4	Male	(10/ 1)	II^{+}
5	Male	(5/ 7)	II^{+}
6	Male	(8/ 1)	II
7	Female	(9/ 5)	IV
8	Male	(6/ 6)	I
9	Male	(4/ 11)	III^{-}

CPM: Coloured Progressive Matrices

CPM Grades: *I: "Intellectually superior"*
II: "Definitely above the average in intellectual capacity"
III: "Intellectually average"
IV: "Definitely below average in intellectual capacity"
V: "Intellectually impaired"

All the constraints were tested equally in order, i.e. equal times as the first, second and third splint. Thus, an order effect in the results would be highly unlikely.

4.2.2 Questionnaire

All three questionnaires were fully completed by 8 participants. One participant completed only the questionnaires for the mitten and the short splint because they did not return for the final assessment. Frequencies are illustrated (Tables 2-11) for the responses given to each question after using each constraint. In question 1, the responses were similar for all the constraints and varied between individuals (Table 2), while question 2 showed that most children needed 'some encouragement' from their parents in order to participate in functional tasks (Table 3). None of the children accepted the long splint 'very easily' and three participants accepted it 'reluctantly'. No children were 'unable to accept' any of the splints (Table 4).

Table 2. Frequency of responses to question 1: "Did your child engage in play activities or functional tasks while wearing the constraint?"

	Mitten	Short splint	Long splint
More than usual	1		1
Just as much as usual	3	5	4
Less than usual	5	4	2
Not at all			1

Table 3. Frequency of responses to question 2: "To what extent did you have to encourage them to do so?"

	Mitten	Short splint	Long splint
Great encouragement	1	4	3
Some encouragement	7	5	4
Little encouragement	1		
No encouragement			1

Table 4. Frequency of responses to question 3: "Did your child accept this type of constraint easily?"

	Mitten	Short splint	Long splint
Very easily	1	1	
Fairly easily	6	7	5
Reluctantly	2	1	3
Unable to accept it	0	0	0

Most children 'continued to be frustrated' by all the splints during the 4 days of the intervention, while one child 'became more frustrated as the days passed by' with the long splint (Table 5). Parents found the long splint to be more demanding compared to the other two, in terms of their time (Table 6). Question 6 aimed at gathering information as to whether splints were easily removable and if this created adherence problems. The responses are summarized in Table 7.

Table 5. Frequency of responses to question 4: "Did your child become used to wearing the splint?"

	Mitten	Short splint	Long splint
Yes, after the 1st day	3	3	1
Yes, after 2 days	2	2	3
No, they continued to be frustrated by the splint	4	4	3
No, they became more frustrated as the days passed by	0	0	1

Table 6. Frequency of responses to question 5: "How demanding was the constraint period in terms of your time?"

	Mitten	Short splint	Long splint
Very demanding		4	4
Quite demanding	5	2	3
Not very demanding	3	3	1
Not demanding at all	1		

Table 7. Frequency of responses to question 6: "Was the constraint easily removed by your child?"

	Mitten	Short splint	Long splint
Yes	8*	5*	5*
No	1	4	3

* **"If yes, did this create adherence problems?"**

No adherence problems (Mitten: n=2/ Short splint: n=1/ Long splint: n=1)

Yes, he/ she was taking it off often (Mitten: n=6/ Short splint: n=4/ Long splint: n=3)

Question 7 was related to any safety concerns the parents might have had. Their responses are displayed in Table 8. The only complication due to the constraints, as indicated from responses to question 8 was the slightly irritated skin when the splints became sweaty (Table 9).

Table 8. Frequency of responses to question 7: "Were there instances that you felt your child was at risk while wearing the constraint?"

	Mitten	Short splint	Long splint
Yes	3*	3*	6*
No	6	6	2

* **"If yes, why did you feel this way?"**

Due to affected balance (Mitten: n=3, Short splint: n=3, Long splint: n=6)

Table 9. Frequency of responses to question 8: "Were there any complications that you believe were due to the constraint?"

	Mitten	Short splint	Long splint
Yes	3*	4*	
No	6	5	8

* *Irritated skin and sweaty hand*

Most parents (n=7) would consent to their child's participation in a trial if they were to wear the short splint but not with the long splint (n=6) (Table 10). One additional question was added at the final phase of the study, when all the splints had been

tested. The responses to this question are summarized in Table 11 and reveal that most parents would consider the short splint to be the most appropriate, while no one would prefer the long splint.

Table 10. Frequency of responses to question 9: "Would you consent to your child's participation in a trial in which this type of constraint would be applied for a longer period?"

	Mitten	Short splint	Long splint
Yes	6	7	2
No	3*	2**	6***

"If not, would you please explain why?"

* -It was not close-fitting enough to restrain use of the able hand
-It was too hot to wear and too easy for him to take it off
-She would become too stressed when wearing the splint

** -It was too demanding on time/ supervision
-It would limit her with what she normally does and she would be very frustrated

*** -It made him not moving his constrained arm at all
-The splint was too frustrating. He/ She would not be persuaded to wear it for longer periods (n=4)
-The level of supervision required is not easy time wise

Table 11. Frequency of responses to question 10: "Which splint would you consider as the most appropriate if your child was to wear it for a longer period of time?"

	No of preferences	Reasons
Mitten	2	• Easier for the child to comply with • The child didn't try to take it off because it was not too restraining anyway • No problems with the straps being undone • Safer in terms of protective reactions
Short splint	6	• Restraining but comfortable enough • Safer (compared to the long splint) in case of loss of balance • Less hot and less easy to remove compared to the mitten • The child did not try to take it off
Long splint	0	

4.2.3 Daily log

Eight participants completed the daily log; one child withdrew before the final assessment, without returning the log. The constraints were either worn in one session every day (47.7% of the overall splint-wearing time), in two (48.8%) or very rarely in three sessions (6.6%). The mean splint-wearing time was 1 hour and 20 minutes but variability between participants and splints was observed (Figure 7). The mean time that the mitten was worn decreased on the fourth day. The maximum time that any splint was worn on one day was 5 hours; observed with the short splint. Minimum requirement of 1 hour wear of the long splint was only achieved on one of the four days by all participants, whereas this target was achieved on all but one day with the short splint and the mitten. Two children did not wear the long splint for all four days (one wore it for three days and the other one for two). Participants 1 and 5 wore some splints more than the other children.

The most frequent reason reported by parents for removing the splints (and especially the long splint) was frustration of the child. The mitten was most often removed because it became sweaty (although the study took place during winter time), while fulfilment of the minimum requirement of 1 hour use was also a very common reason.

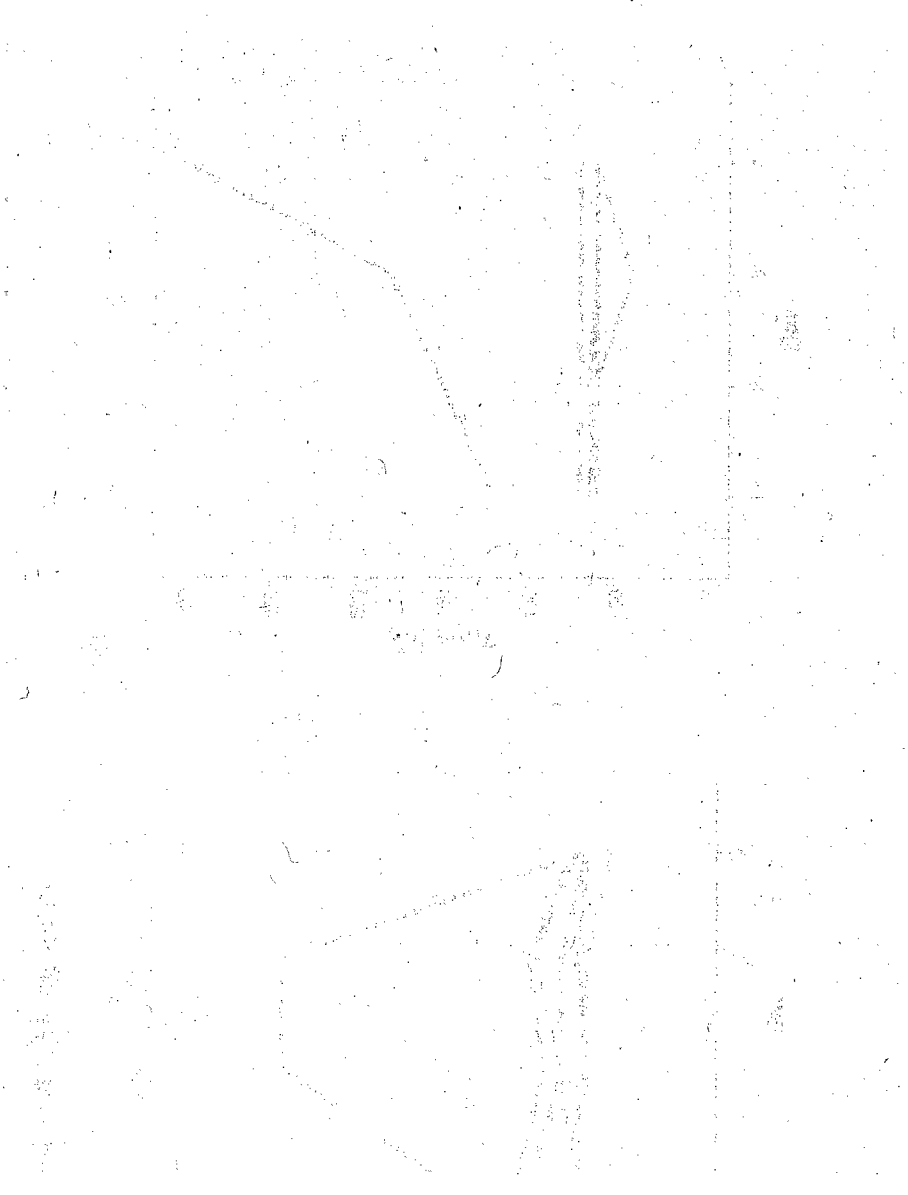
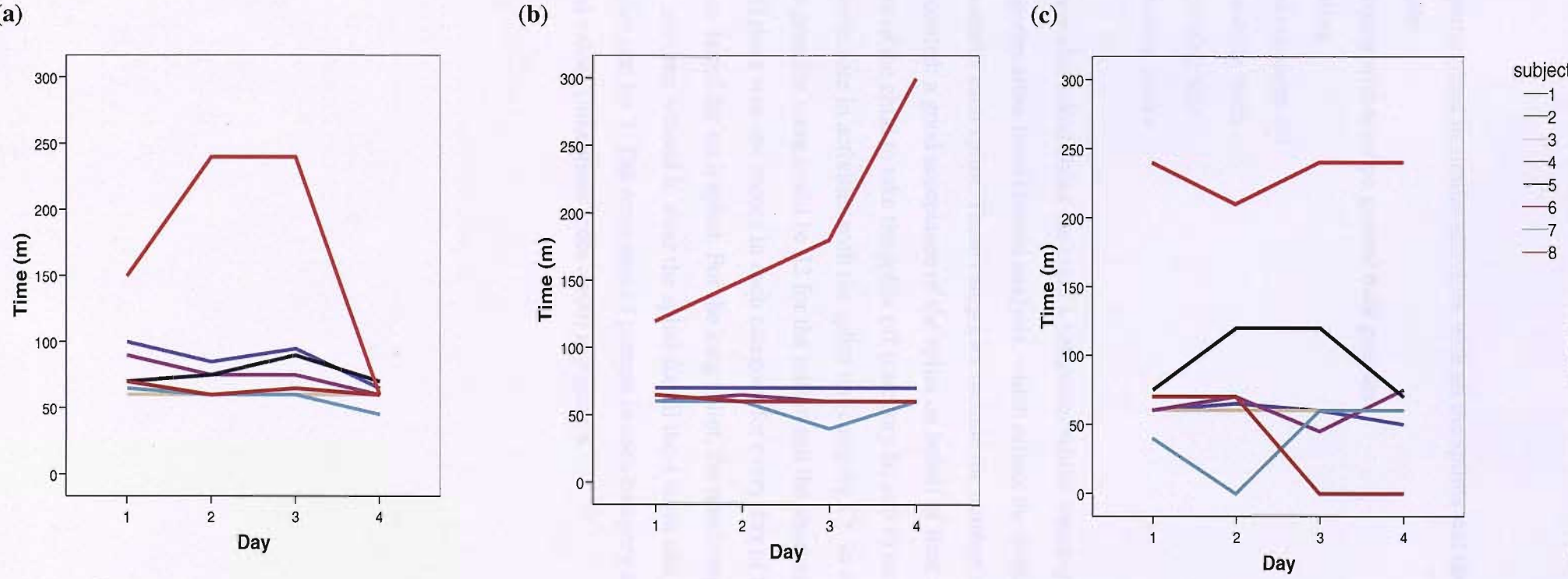


Figure 7. Time in minutes that each splint was reported to be worn by each participant during the 4 days of the intervention. (a) mitten, (b) short splint and (c) long splint

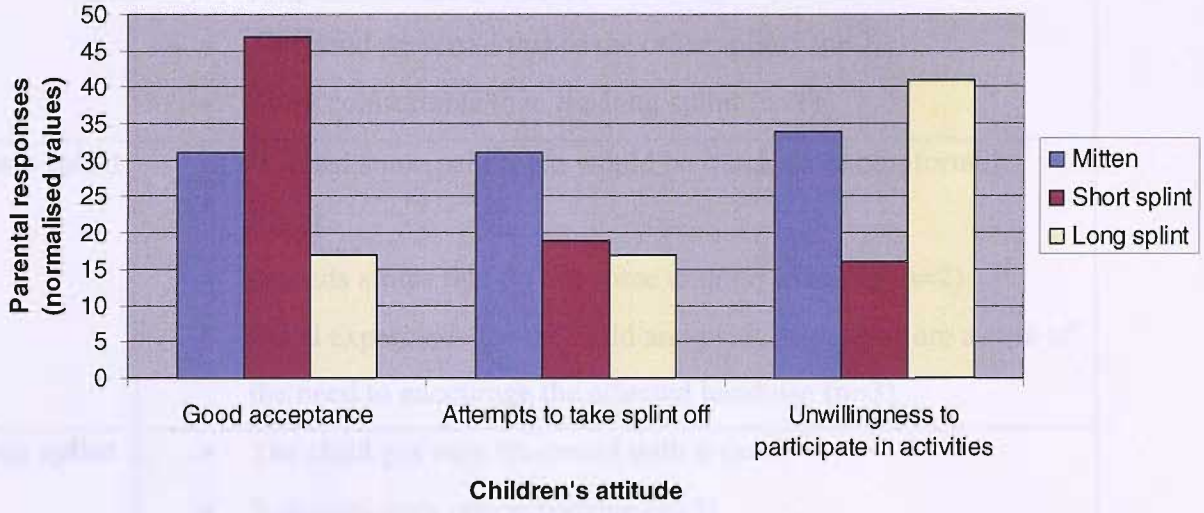


Children participated in similar activities with all the splints and the most common ones include:

- Playing with toys/ pc games/ ball/ puzzles
- Eating
- Taking shoes off
- Brushing teeth
- Combing hair
- Reading books

Parents were also asked about the child's behaviour whilst wearing the splint. Three main categories arose from content analysis, which reflect the overall attitude of children towards each splint. These categories include the number of times that the parents recorded: a good acceptance of the splint on behalf of their child (category A), b) attempts of the child to take the splint off (category B) and c) unwillingness of the child to participate in activities with the splint on (category C). In each category, the maximum possible score could be 32 for the mitten and the short splint, if for every child (n=8) there was one record in each category for every day of the 4 that the intervention lasted for each splint. For the long splint, the maximum score could be 29 because 2 children refused to wear the splint for all the 4 days; one wore it for 2 days and the other one for 3. The responses of parents in each category are presented as normalised values (maximum score =100) in Figure 8.

Figure 8. Children's attitude towards each splint, as reported by their parents on the daily log



Parents recorded safety problems and complications while their children were wearing the splints. Maximum scores were 32 for the mitten and the short splint and 29 for the long splint. The normalised values are presented in Table 12.

Table 12. Parental responses on safety problems and complications during the 4 days of intervention with each splint

	Mitten	Short splint	Long splint
No problems	72	81	34
Sweaty hand and arm	19	13	14
Impaired balance and diminished protective reactions	9	6	52

Parents' comments on the overall experience with each splint are presented in Table 13.

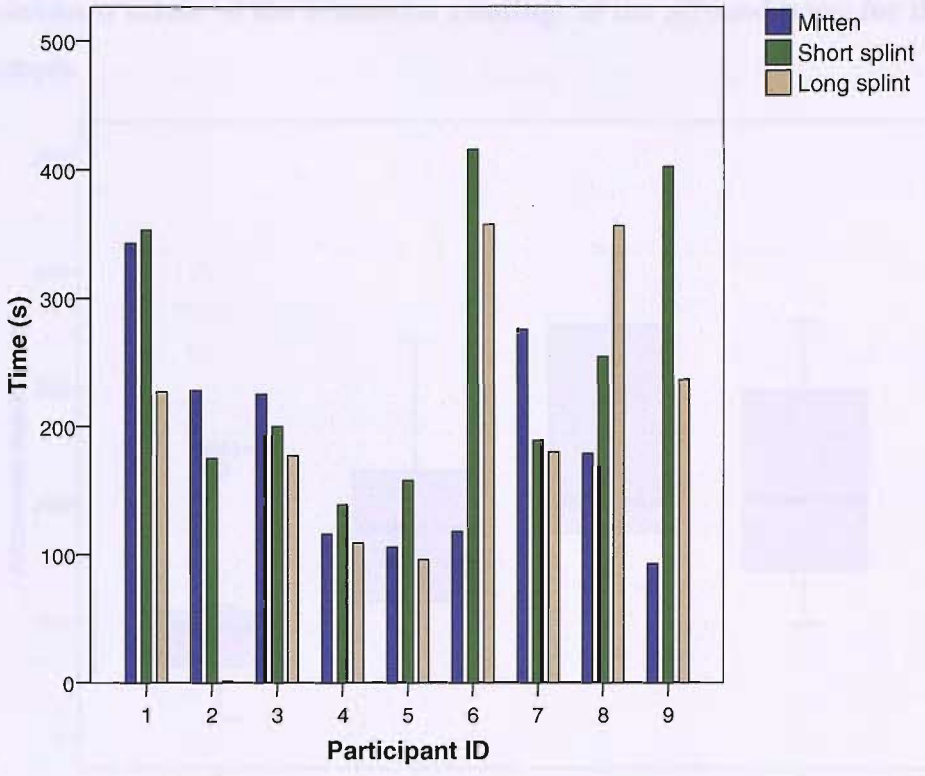
Table 13. Parents' comments for each splint

Mitten	• Not really restraining (n=3) • Easy for the child to take it off (n=3) • The child preferred this to the other splints (n=2) • More comfortable than the long splint (n=1)
Short splint	• If it had some padding it would be much more comfortable (n=1) • It needs straps that do not come undone so easily (n=2) • Good experience for the child and us; it made us more aware of the need to encourage the affected hand use (n=3)
Long splint	• The child got very frustrated with it (n=3) • It seemed very uncomfortable (n=3) • The straps come undone easily (n=3) • I was concerned about his balance (n=1) • It was difficult to persuade him to wear it (n=4)

4.2.4 Actometer

The actometer was worn on the affected forearm to record the level of activity with and without each constraint. The actometer readings (in seconds) correspond to the amount of arm activity and are presented graphically in Figure 9 for each participant for each of the 3 constraints.

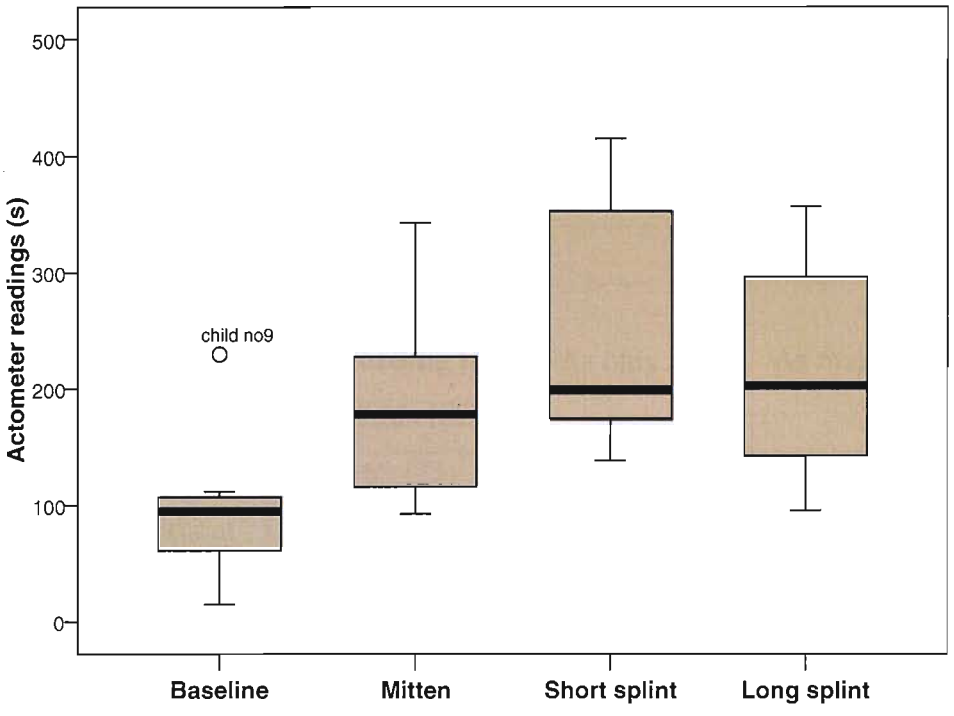
Figure 9. Actometer readings (s) with each splint



* #2: Data missing for long splint

Figure 10 illustrates the median, interquartile ranges and range of actometer values for each constraint. Median activity was higher with than without constraint in all cases, while both the range and quartile values of the actometer readings appear highest for the short splint.

Figure 10. Boxplot showing the median, interquartile range, maximum and minimum values of the actometer readings of the affected hand for the whole sample



4.2.5 Reliability coefficient

The videotape recordings were analysed by 2 paediatric therapists (including the researcher). The reliability coefficient (R) was calculated to ensure that the measure elicited reliable results. The R was calculated for each category of the videotape report forms to determine the reliability of each of these categories. The first child was excluded from the final analysis as his recordings were used as a pilot case to train the raters. Output for one-way ANOVA tests is included in CD1. Root mean square of between and within groups were entered in the following formula (Fleiss, 1986) to reveal the R: MS_{SUB} - MS_{ERR}/ MS_{SUB} + (n-1) MS_{ERR}. R for each category of the video report form was as follows:

-Affected hand used as only hand: R=0.87

-Affected hand used as main hand: R=0.45

-Affected hand not used at all: R=0.84

4.2.6 Videotape recordings

The long splint was the most effective device in promoting use of the affected hand as the only hand but the short splint also achieved this for 45% of the total time of the video recording (Table 14).

Table 14. Mean time (%) of use of affected hand during two consecutive videos of free play: one with and one without splint in place

		Mean actual duration of video recording in seconds (SD)	Mean time (%)-SD		
			As only hand	As main hand	Not used at all
Mitten	With	369 (73)	132 (36)-107	46 (12)-55	145 (39)-92
	Without	382 (28)	4 (1)-10	23 (6)-56	195 (51)-119
Short splint	With	373 (45)	167 (45)-136	38 (10)-61	119 (32)-80
	Without	393 (42)	6 (2)-14	25 (6)-41	202 (51)-122
Long splint	With	385 (28)	239 (62)-143	14 (4)-20	112 (29)-110
	Without	361 (40)	4 (1)-6	6 (2)-10	204 (56)-86

Using the analysis described in the Method chapter, pie charts were produced, which show the percentage of mean affected hand use with each of the 3 splints (Figure 11, 12, 13).

Figure 11. Mean affected hand use with the mitten

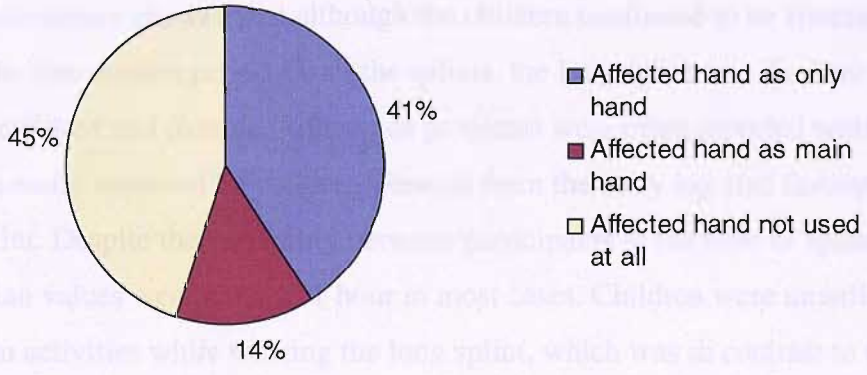


Figure 12. Mean affected hand use with the short splint

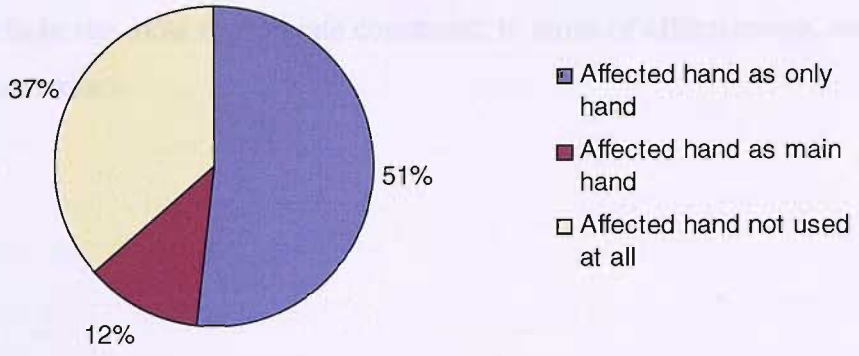
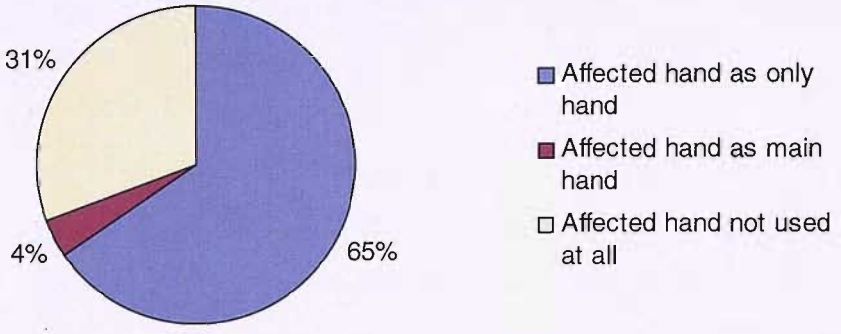


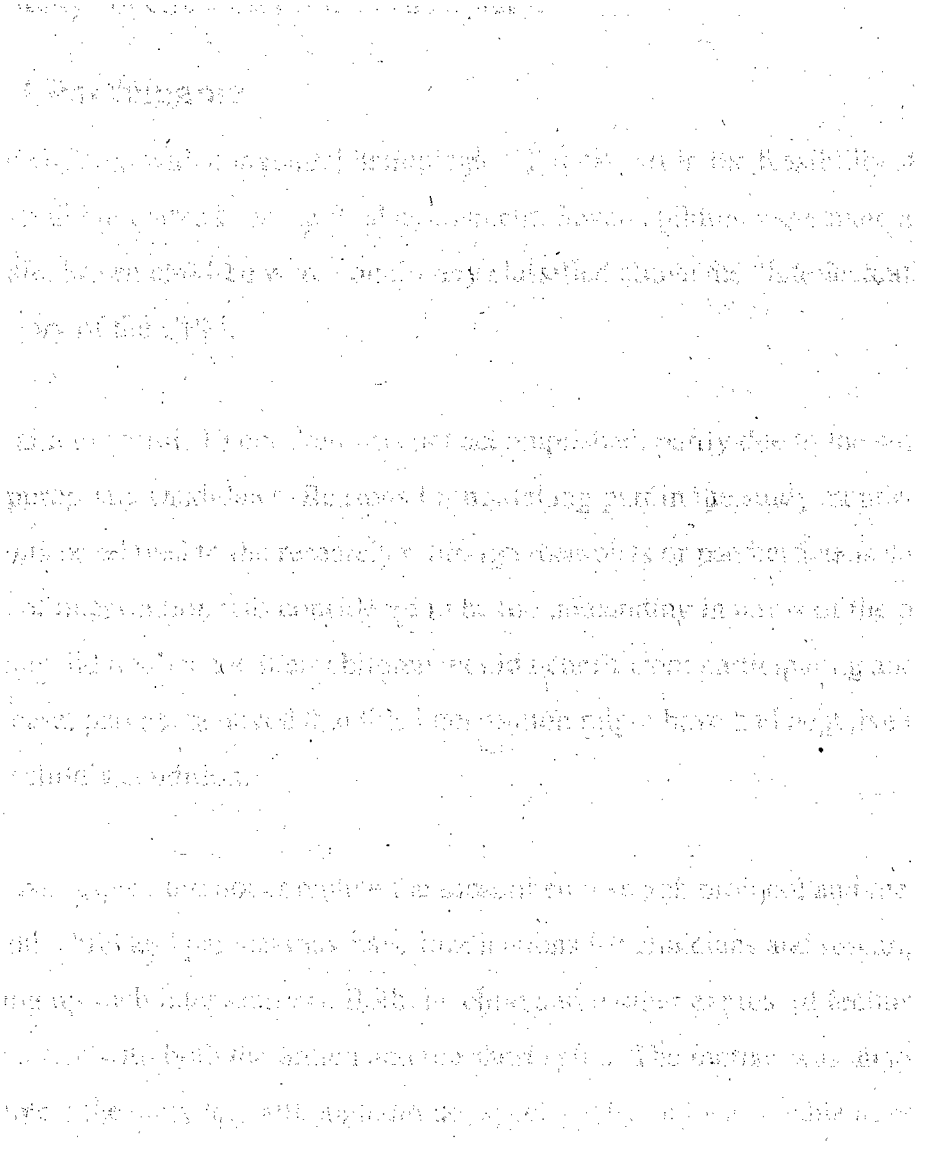
Figure 13. Mean affected hand use with the long splint



4.2.7. Summary of results

The questionnaire showed that although the children continued to be frustrated during the whole intervention period by all the splints, the long splint was the least accepted by both children and parents. Adherence problems were often reported with the mitten as it was easily removed by children. Results from the daily log also favoured the short splint. Despite the variability between participants in the time of splint-wearing, the median values were close to 1 hour in most cases. Children were unwilling to engage in activities while wearing the long splint, which was in contrast to the short splint with which parents reported good acceptance. Actometer readings were higher

with all the splints than without them but the highest values were observed with the short splint. Analysis of the videotapes revealed that especially the long but also the short splint was the most restraining device. In conclusion, the short splint was considered to be the most appropriate constraint, in terms of effectiveness, comfort, safety and adherence.



4.3. DISCUSSION

Results obtained from this feasibility study are discussed in terms of their impact on the effectiveness study.

No study has been found to date investigating the appropriateness of different constraints for a specific population or exploring the participants' attitude towards the constraint during the intervention period. The aim of this study was to identify the most appropriate splint in terms of effectiveness and adherence from children's and parents' perspective and to provide guidance in the design of a practical protocol that was tested for effectiveness in the next study.

4.3.1 Participants

Nine children with congenital hemiplegic CP took part in the feasibility study, one of whom did not attend for the final assessment. Seven children were male and two were female. Seven children were cognitively classified above the "intellectually average" category of the CPM.

The aim to recruit 15 children was not accomplished, partly due to the small number of appropriate candidates. Reasons for not taking part in the study mentioned by parents or relayed to the researcher through therapists or paediatricians were that this type of intervention was considered to be too demanding in terms of the parents' time, parents did not believe their children would benefit from participating and in at least one case, parents believed that this intervention might have had negative effect on their child's condition.

One participant did not complete the prescribed research protocol and the experience of both child and parents may have implications for clinicians and researchers when setting up such interventions. Both the child and mother expressed feelings of discontent with both the mitten and the short splint. The mother was unable to complete the daily log, although did not specify why and was unable to persuade the child to wear the splints - the long splint was probably not worn at all. Although other participants and their families expressed some feelings of frustration this did not affect their ability to to comply with the protocol.

4.3.2 Questionnaire

Some of the questions comprising the questionnaire could have been omitted as they provided the same information with the daily log.

The most restraining splint was the long splint. The mitten was reported to be the least demanding in terms of parents' time; the reason for this is probably that children could easily cope on their own as the mitten was not very restraining. The long splint was very demanding from parents' perspective. This could be interpreted in combination to the fact that the majority of parents felt that their child was at risk while wearing the long splint, due to affected balance; thus, the long splint required constant supervision. Parents would consent to their child's participation in a trial if the short splint was to be worn for a longer period. None of the parents considered the long splint to be appropriate for their child, while 6 out of the 8 parents would not consent if the long splint was to be used, mostly because it was too frustrating and children would not be persuaded to wear it for a longer period. Overall, the short splint was suggested by most parents as being the most appropriate in terms of effectiveness, comfort, safety and adherence.

4.3.3 Daily log

The daily logs provided information on the children's attitude towards each constraint but also the parents' perspective and concerns. Despite the variability between participants each splint was worn for approximately 1 hour and 20 minutes per day on average. The most frequent reason that the splints were removed was children's frustration. Completion of the minimum requirement of 1 hour-wearing was also a common reason, indicating that the children would hardly accept any splint for many hours per day. This is an important finding that should be taken into consideration when trying to design a child-friendly protocol of CIMT/ FUT. However, in this study splints were tested during a home based intervention, where a therapist was not present and thus, adherence was more difficult to achieve.

A large proportion of the participants were unwilling to engage in functional activities with the long splint. The main difference between FUT and CIMT is that the first does not include any structured exercise; however, functional use of the affected limb is necessary for therapy to be effective. When children are involved it might be useful to

provide a list of activities, in some of which children should engage daily. In this case, parents are the ones responsible for accomplishing the intervention on a daily basis. A similar protocol has been followed by Eliasson et al (2005) who found positive results after 2 months of intervention with 2 hours of daily restriction.

Children attempted to take the mitten off more often than the other splints, probably because it was the easiest to take off. This and the fact that it was not very restraining might be the reasons that children generally accepted it well. Interestingly though, the most well accepted splint was reported to be the short splint. This may be because the short splint was not uncomfortable compared to the very restraining long splint and to the mitten that was getting hot and sweaty after some time. However, since the daily logs were only completed by the parents, some of the responses might reflect their own point of view and not necessarily represent the child's opinion.

Few parents reported diminished protective reactions and sweaty hands, as a result of wearing the mitten or the short splint. In contrast, there were many reports regarding balance problems and diminished protective reactions due to the long splint. This, in addition to children's frustration was the reason for the negative parental comments for the long splint. The mitten was considered to not be restraining enough, while it was easy for children to take off. Comments on the short splint were mostly regarding refinements including straps that do not come undone easily and padding on the inside of the splint to prevent it from getting sweaty.

4.3.4 Actometer

Variability existed between participants in the actometer readings and with each constraint. However, the use of the affected hand was more extensive with all the splints than without them. In half of the participants, the increased use of the hand was almost equal with every splint. Overall, the short splint resulted in the most extensive use of the hemiplegic limb. The long splint despite being the most restraining resulted in less increase of the use of the hand compared to the short splint. This could be attributed to the fact that children might have been more willing to participate in activities with the short splint on, as was also reflected in the daily logs. However, many activities required bimanual manipulation, thus limiting children in the variety

of activities they could perform when the less affected hand was so effectively constrained with the long splint.

4.3.5 Reliability coefficient

The category 'Affected hand used as main hand' of the videotape report form was not very reliable as indicated by the reliability coefficient of 0.45. The other two categories showed a good level of reliability. However, this measure will not be used in the next study as functionality will be tested through standardised measures (QUEST and Melbourne Assessment of Unilateral Upper Limb Function).

4.3.6 Videotapes

To date, there is no established way of quantifying a qualitative measurement, such as a video. The videotape report form was used in this study to analyze the children's use of their hands in such a way that would reveal whether the splints were effectively restraining. Scoring the videotapes, using the present form proved to be difficult, as mentioned by all the assessors; two more assessors were initially involved but withdrew before completing the analysis. The analysis of the results was also very confusing. Several ways of scoring the forms were tried but were eventually abandoned because they could not reliably demonstrate the effectiveness of the constraints. Using normalised values and examining each category of the form separately was thought to be the most appropriate method for the analysis.

The use of the hemiplegic hand as an only and as a main hand was considered to reflect an effective restraining device. The findings showed that the affected hand was used more when the splints were worn than without them. The video recordings showed that the long splint was the most restraining device, while the actometer readings showed that the short splint resulted in the greatest increase in use of the affected hand. This discrepancy could be explained if we consider that large, gross motor movements produce a greater reading on the actometer than smaller, fine motor movements. If the participants were using their hands for smaller movements when wearing the long splint, this would have affected the actometer readings. Careful observation of the videotapes reveals that this was the case with many participants, who preferred to turn pages from a book or push buttons when wearing the long splint instead of engaging in activities that required large movements. There is also a chance

that the videotape results have been biased by the therapists' expectations, since there was no way for them to be blinded during the scoring procedure. The reason the affected hand was used as the only hand considerably more with the long and short splint compared to the mitt was almost certainly because, being rigid and restricting movement at the wrist (short splint) and wrist and elbow (long splint), they restricted movement more than the mitt. It was anticipated that the long splint would be least acceptable, but more surprisingly it was less effective than the short splint. The short splint was found most acceptable for a home-based intervention but might not be the best option if FUT was applied in the clinic, where the children would have constant supervision.

FUT is a demanding intervention and difficult for children and parents to adhere to. Most of the parents whose child participated in the study found it to be a useful experience, as indicated by a mother's comments: "It made us more aware of the need to pay attention to the exercise of the hemiplegic hand", while many were eager to participate in a forced use intervention, as shown by the words of another participant's mother: "I would be tempted to keep putting the splint on after the completion of the study". However, there were parents who found this intervention to be too frustrating for the children and themselves, while others believed that it was too demanding time-wise. CIMT, which includes structured exercise might have an advantage over FUT, as it may result in increased attention to and motivation of the child. Reorganisation studies have shown that functional use of the affected limb is necessary for therapy to be effective (Classen et al., 1998, Nudo et al., 1996a). However, CIMT is even more demanding intervention, which is the reason that many adult patients would not be willing to participate (Page et al., 2002a). Suggesting a modified version of CIMT that includes less hours of daily therapy distributed over a longer period in the home environment is challenging.

Variability was found to exist between participants despite the fact that they all shared similar characteristics. That points out the importance of identifying the most appropriate type of constraint to be used in CIMT/ FUT with a specific population, in terms of age, degree of disability etc. The small sample number does not allow for a definite conclusion to be made. The age range of the sample was wide, which could also be a reason for the variability observed. However, given the difficulty in

identifying appropriate numbers of participants, the options were limited. Another shortcoming of this study is that the participants were not classified according to the severity of the motor impairment. Although severe cases were excluded, variability existed in the degree of functional ability of the upper limbs. This study gives an indication of the potential appropriate constraint to be used with populations similar to the one used here. Further studies are needed though before we can conclude on this.

4.3.7 Conclusion

- The mitten was the least restraining device and easy for the children to take off, which resulted in adherence problems in many cases. The long splint despite being the most restraining device, did not seem to be more effective than the short splint, due to the fact that it was uncomfortable and frustrating for the children, who were unwilling to cooperate and participate in functional activities, while wearing it. Parents often believed their children were at risk while wearing the long splint, as it significantly affected their balance and protective reactions. Overall, the short splint was found to be the most effectively restraining device but also acceptable by parents and children.

- Limitations existed in the measures used. In the next study, the actometer will be used again, as well as the daily log. The latter though will be simplified to ensure adherence from the parents' perspective but also gathering of the necessary information. Videotape recordings will not be used in the next study, as the functional effects will be assessed via standardised functional tests. A combination of measures (Gross Motor Function Classification System-GMFCS and measures of upper limb function) will be used to provide a classification system that takes into account the upper limb function, in addition to the gross motor function.

- The same participants and others with similar characteristics will be recruited for the effectiveness study. However, due to the small number of appropriate candidates, the age range will be extended to include children from the age of 4 years old rather than 5, while one more research site will be added.

- The intervention that will be used in the next study will include a list of functional activities in which children should participate while wearing the constraint, whereas the parents/ caregiver will be the ones responsible for the accomplishment of the intervention.

CHAPTER 5

THE EFFECTIVENESS STUDY

This study formed the second half of the main project, which aimed to identify a CIMT protocol that would be practical and effective for children with CP. The protocol was designed based on findings from the feasibility study, which provided information to ensure practicality. The present study aimed to explore the functional effects of two versions of a modified paediatric CIMT protocol.

5.1 METHOD

5.1.1 Ethics approval

The study commenced after a favourable ethical opinion was obtained by the Southampton & South West Hampshire Research Ethics Committee and the community R&Ds of Southampton, Portsmouth and Poole (Appendix 3). The study was sponsored by the University of Southampton and received full R&G approval. Recruitment and consent was conducted under the guidelines set out in the MRC Clinical Trials Tool kit.

5.1.2 Objectives

The objectives of this part of the study were:

1) To explore the functional effects of a modified protocol of CIMT designed according to the findings of the feasibility study
2) To examine whether there is an additional benefit when the constraint is combined with functional activities and feedback compared to the use of the constraint only

5.1.3 Participants

Experience from the feasibility study and discussions with therapists and paediatricians showed that the number of children living in the Southampton area who would satisfy the selection criteria was small. This pilot study was conducted with a convenience sample and we aimed to recruit between 13 and 15 children. Data from the study will allow a power calculation to be made in preparation for a definitive

randomised controlled trial. Because of the small number of suitable children we anticipate that an adequately powered trial will need to be multi-centre.

Selection criteria

The same selection criteria were used as in the feasibility study except for age limit that was reduced from 5 to 4 years. Experience from the feasibility study did not identify any problems with younger children and both clinicians and parents suggested that younger children were sometimes more willing than older ones to participate in new interventions. Extending the age range had the potential to increase recruitment. The following criteria were applied:

Inclusion criteria

1. Children aged 4-11 years
2. Congenital hemiplegic CP
3. Children performing above the 10^{th} percentile on the Raven's Coloured Progressive Matrices
4. Normally using the affected upper extremity as a gross function in bilateral tasks, as determined by observation and from discussion with the child's occupational therapist and paediatrician
5. Willingness of parents/ caregiver and child to cooperate
6. Informed consent (parents/ caregiver) and assent by the child available

Exclusion criteria

1. Fixed contractures limiting the movement of the affected upper extremity more than one quarter of the normal range
2. Cognitive, behavioural or physical problems (as determined by GMFCS level IV and V) that would seriously interfere with the child's ability to comply with the protocol

Recruitment process

Participants were recruited from three research sites. The main collaborators were three consultant paediatricians and three occupational therapists in each of the sites

and the Child Health Information & Performance Manager in the main site. An advertisement was also published in the HemiHelp journal to widen access to the study (Appendix 9). The process followed was the same as in the feasibility study. Following ethical and Research Governance approval the collaborators, in cooperation with their colleagues, produced a list with all the children eligible for the study. The numbers of children identified were 45 overall (13, 19 & 13 from each site). A pack including the invitation letters (Appendix 4), parents' and children's information sheets (Appendix 5) were forwarded to the families by the collaborators. After the initial contact was made, children had their assessment of eligibility for inclusion in the study followed by enrolment if they satisfied all the inclusion and none of the exclusion criteria and following consent from parents and assent from children (Appendix 6). Six positive responses were initially received. All of these children met the selection criteria and were included in the study. A reminder letter was sent to families who had not responded, which resulted in the recruitment of three additional participants.

Screening process

A screening process, similar to the one described in the feasibility study ensured that potential participants satisfied all selection criteria. Children were classified according to the severity of CP, using the Gross Motor Function Classification System (GMFCS). GMFCS is a reliable and valid system that classifies children with CP by their age-specific gross motor activity. Motor function is described in terms of self-initiated movements with emphasis on function in sitting and walking (Palisano et al., 2006, Wood and Rosenbaum, 2000). Function is divided into five levels; children in Level I have the most independent motor function and children in Level V have the least. Each level provides functional descriptions for four age bands: 1-2, 2-4, 4-6 and 6-12 years (Palisano et al., 1997). GMFCS was chosen to be used in this study along with observation to exclude any potential participants that were severely affected. GMFCS has been widely adopted but a similar classification of hand function was not available at the time of initiation of the study. The Manual Ability Classification System (MACS) that has been developed recently (Eliasson et al., 2006) reports the collaboration of both hands together and classifies how children use their hands when handling objects in daily activities. MACS would be a valuable classification measure to be used in a future study.

5.1.4 Setting

Participants were receiving treatment from community-based services in three PCTs in Southern England serving children in both mainstream and special needs schools. The screening process and all the assessments took place in the School of Health Professions & Rehabilitation Sciences, at the University of Southampton. The intervention was based at children's homes.

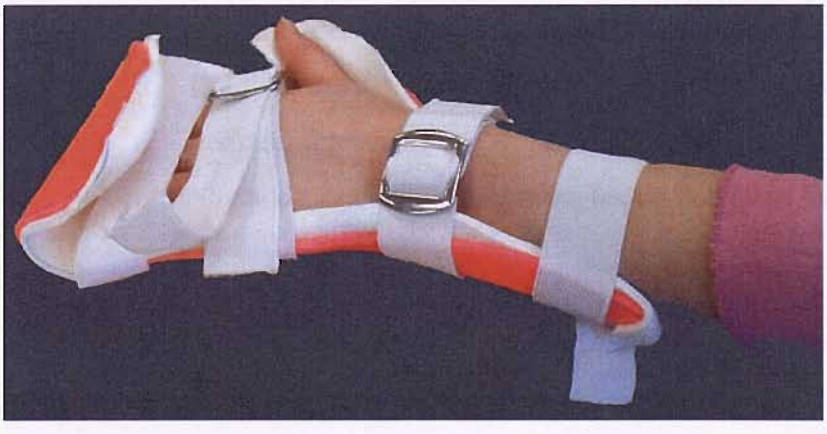
5.1.5 Design

An experimental design was used, in which each child acted as their own control, thus avoiding the difficulties of matching groups of children. This design was appropriate for a small sample (Bailey, 1997, Hicks, 1988) from a population in which wide variations between individuals were expected. Both qualitative and quantitative research methods were used. An A – B – C – A design was used where A was a non-intervention phase, and B and C were comparable intervention phases. This design enabled any additional benefit from the second intervention to be measured.

5.1.6 The constraint

The short splint was refined according to parents' suggestions in the previous study; padding was added to prevent the splint from getting sweaty and elastic suspenders were used instead of Velcro straps to ensure it would not be easily removed by the children (Figure 14). The splint was tested with the first two participants, who reported no problems. The splint was constructed by the researcher, who has received training on splint construction as an occupational therapist and also by another therapist specializing in splint making.

Figure 14. The splint



5.1.7 Outcome measures

5.1.7.1 Tests of upper limb function (Melbourne Assessment of Unilateral Upper Limb Function and QUEST)

The Melbourne Assessment and the QUEST were used to test the effects of the interventions on the functional use of both upper limbs and especially the affected one. Both tests were applied twice in the baseline period, after each of the two intervention phases and at the one-month follow-up. Administration time was approximately 15- 20 minutes. Tests were administered by the researcher and recorded on video for subsequent scoring by an assistant pediatric occupational therapist.

5.1.7.2 Actometer

An actometer was applied at the children's wrist by their parents to record the level of activity of the affected upper limb during the intervention periods. Parents were instructed to apply the device at the end of each of the 8 weeks for as long as the child was comfortable. They then had to record in the daily log the time the device was worn and the readings when it was placed at the child's wrist and when it was removed.

5.1.7.3 Daily log

The daily log was completed by parents/ caregiver (depending on who supervised the child while wearing the constraint) and consisted of open questions to provide information on:

a. The total daily amount of time the constraint was worn
b. The activities the child engaged in
c. The score the child achieved at the pc-feedback game (this was relevant only to the second intervention phase-mCIMT^{+})
d. The time the actometer was worn and readings (once at the end of each week of intervention)
e. Any additional concerns/ thoughts on behalf of the parent/ caregiver

5.1.8 Experimental procedure

The effectiveness study took place between August 2006 and August 2007. Following screening and informed consent by parents and assent by children, the splint was constructed. A letter and an information sheet were sent to children's GP to inform them of their participation in the study. At entry into the study, the demographic characteristics of the child were recorded, as well as the type and intensity of the treatment they were normally receiving (children carried on receiving their regular treatment). The study consisted of four phases (A – B – C – A), each of which lasted for one month (Table 15). There was no interval between each phase.

Forced use (mCIMT)

During mCIMT, children were required to wear the constraint for 2 hours/day. Parents were asked to gradually increase the time the constraint was worn to reach 3 hours after the first week and maintain it for the subsequent three. No additional intervention was given.

Motivating activities (mCIMT$^+$)

The second intervention, mCIMT$^+$ included the same intensity and duration of treatment as mCIMT but children were encouraged to participate in functional activities, which were decided upon after consulting individually with the parents of each child. This was done to ensure that the activities would be interesting and appropriate for each child. Parents were asked to actively participate in these activities, as much as possible to increase children's motivation. Children were given a PC game, which they were asked to play before taking off the splint at the end of each day. This was a simple game requiring unilateral manipulation. A joystick was attached to the computer, the amount of movement of which was recorded during the game. The game lasted 10 minutes and at the end a coloured bar was displayed on the screen showing to the children how much they had moved their affected hand. Motivational cues appeared as additional feedback to inform children of how well they did and to encourage them to keep trying.

Table 15. The procedure of the effectiveness study

Screening	Constraint build	Week 0		Week 4		Week 8		Week 12		Week 16
		Assessment 1	A No Intervention	Assessment 2	B mCIMT	Assessment 3	C mCIMT^{+}	Assessment 4	A No Intervention	Assessment 5
					Daily log & Actometer		Daily log & Actometer			

All the children participated in the two interventions in the same order as mCIMT^{+}was expected to be at least as effective as mCIMT. Parents were instructed to apply the constraint to children only when they were being supervised. During both interventions, the daily amount of time wearing the constraint could be split into sessions to increase adherence and practicality. Assessments identified the immediate effect of each intervention. Baseline assessments were added to ensure that the children's functional status was stable and thus, any improvements could be attributed to therapy; the post-treatment assessment examined whether any functional effects were maintained after one month. Actometer readings were taken at the end of each week of the intervention periods. Functional assessments were taking place at the beginning and the end of each phase at the University of Southampton. The researcher and parents had telephone communication every week to discuss the child's progress and any arising problems or concerns.

5.1.9 Data analysis plan

A DVD was produced with the video recordings after data collection was completed. Recordings were entered in a random order to ensure the assessor was blind as to the intervention phase each child was in. Descriptive statistics were used to present the demographic characteristics of the participants and the results from the pc game, the actometer and the two functional measures (Melbourne Assessment and QUEST).

A P-P plot was produced to test for normality of the data. The result showed an approximate normal distribution. Repeated measures ANOVA was therefore used to test for significance between changes of the Melbourne Assessment and QUEST over the 5 assessment points. To ensure significant changes would not be falsely implied, Friedman and Wilcoxon's tests were also performed in addition to the parametric test.

Graphical displays were used to illustrate the range of scores for Melbourne and QUEST at each assessment point, as well as the game score progress for each participant over the second intervention period (mCIMT^{+}). All the syntaxes and results of the study are included in CD1.

Content analysis was used to analyze the data from the daily logs.

5.2 RESULTS

5.2.1 Participants

Nine children responded positively, all of whom satisfied the selection criteria and were included in the study. The mean age of the participants' group was approximately 6.5 years (SD=25 months). Their main characteristics are presented in Table 16.

Table 16. Baseline characteristics of the participants of the effectiveness study showing their sex, age, gross functional and cognitive level and the amount of therapy normally received

Child ID	Sex	Age (years/ months)	GMFCS level	Regular treatment	Grade according to CPM *
1	Male	(7/ 10)	2	Once/ 3 months	II^+
2	Male	(11/ 0)	2	Once/ term	II^+
3	Male	(7/ 3)	1	Once/ 3 months	III^+
4	Male	(3/ 10)	3	Once/ 2 months	I
5	Male	(7/ 0)	2	Once/ term	III^-
6	Female	(4/ 7)	1	Once/ year	I
7	Female	(6/ 8)	1	Once/ 2 months	III^+
8	Male	(5/ 9)	1	Once/ 3 months	III^+
9	Female	(6/ 1)	1	Once/ year	II^+

GMFCS: Gross Motor Function Classification System

CPM: Coloured Progressive Matrices

CPM Grades: *I: "Intellectually superior"*

II: "Definitely above the average in intellectual capacity"

III: "Intellectually average"

IV: "Definitely below average in intellectual capacity"

V: "Intellectually impaired"

5.2.2 Functional measures

Assessment points 1-2 represent the baseline assessments, 3 is after mCIMT, 4 after mCIMT^{+} and 5 is the final assessment (follow-up). Scatterplots (Figures 15, 16) were designed to describe the distribution of values of the two functional measures over the baseline assessments. The values of Melbourne Assessment and QUEST at each assessment point are presented in Table 17.

Figure 15. Distribution of the Melbourne Assessment values over the baseline assessments

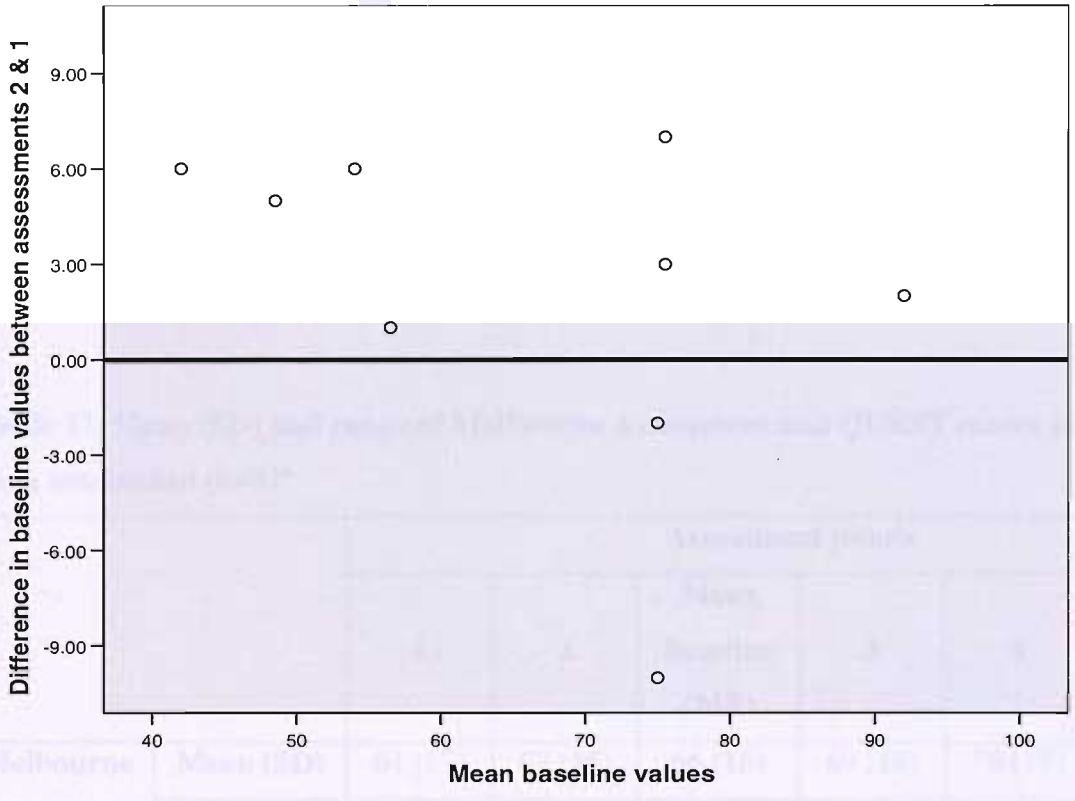


Figure 16. Distribution of the QUEST values over the baseline assessments

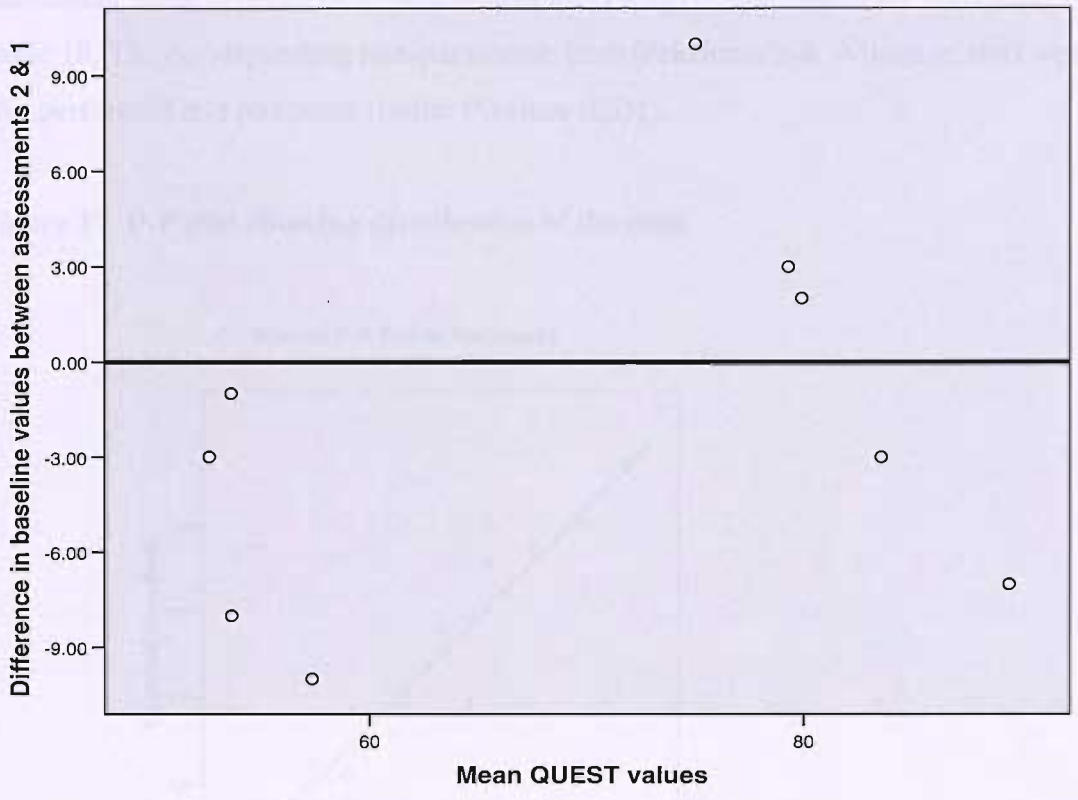


Table 17. Mean (SD) and range of Melbourne Assessment and QUEST scores at each assessment (n=8)*

		Assessment points					
		1	2	Mean baseline (MB)	3	4	5
Melbourne Assessment	Mean (SD)	64 (17)	67 (16)	66 (16)	69 (18)	76 (17)	75 (17)
	Range (min-max)	52 (39-91)	48 (45-93)	50 (42-92)	52 (43-95)	54 (44-98)	45 (48-93)
QUEST	Mean (SD)	70 (14)	68 (16)	69 (15)	77 (14)	78 (15)	78 (17)
	Range (min-max)	39 (54-93)	36 (50-86)	37 (53-89)	41 (53-94)	41 (56-97)	54 (45-99)

*One case is missing in assessment 5 for QUEST due to inability of child 4 to cooperate

A P-P plot showed an approximate normal distribution for the data (Figure 17). Repeated measures ANOVA was applied to examine the changes between each assessment point in Melbourne Assessment and QUEST. The results are shown in Table 18. The corresponding non-parametric tests (Friedman's & Wilcoxon test) were also performed and produced similar P values (CD1).

Figure 17. P-P plot showing distribution of the data

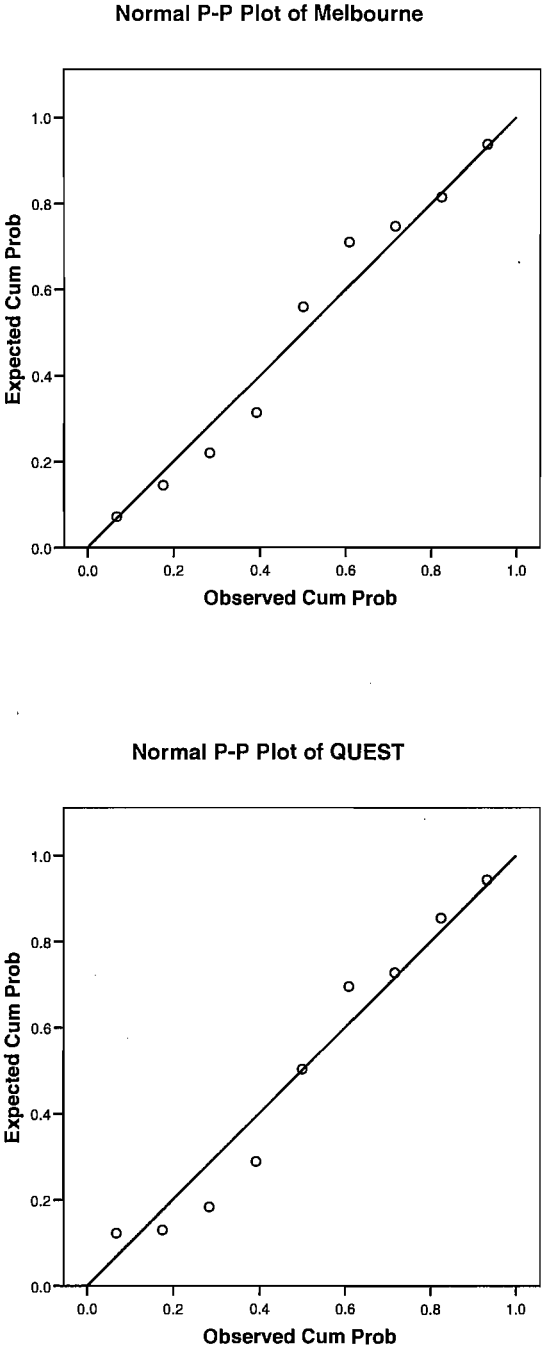


Table 18. Score differences (95% CI) and P-value (repeated measures ANOVA) of Melbourne Assessment and QUEST at each assessment (n=8)*

		Comparison between assessments			
		2-1	**3-MB**	**4-MB**	**5-MB**
Melbourne Assessment	**Difference (95% CI)**	3.11 (8.66/ -2.44)	3.44 (6.61/ .27)	10.33 (14.94/ 5.72)	9.33 (13.75/ 4.92)
	P-value	.232	.037	.001	.001
QUEST	**Difference (95% CI)**	1.96 (2.75/ -6.67)	8.09 (13.09/ 3.09)	9.16 (12.76/ 5.56)	6.49 (13.72/ -.75)
	P-value	.365	.006	.000	.072

MB: Mean baseline

* One case is missing in assessment 5 for QUEST

The range of scores for Melbourne and QUEST at each assessment point is shown graphically in Figure 18 and Figure 19, respectively.

Figure 18. Boxplot showing the median, spread and inter-quartile range of scores for Melbourne Assessment at each assessment

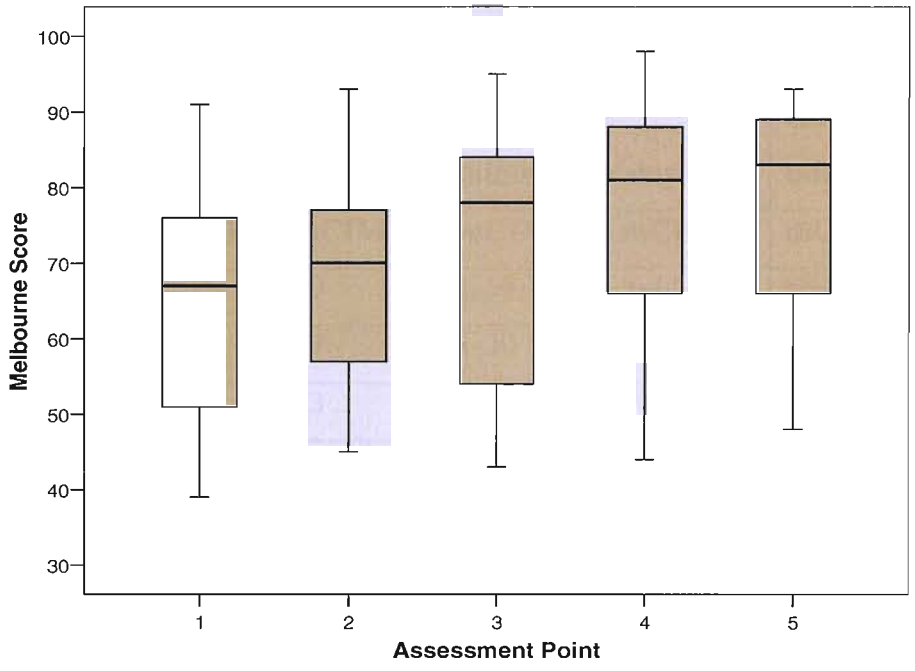
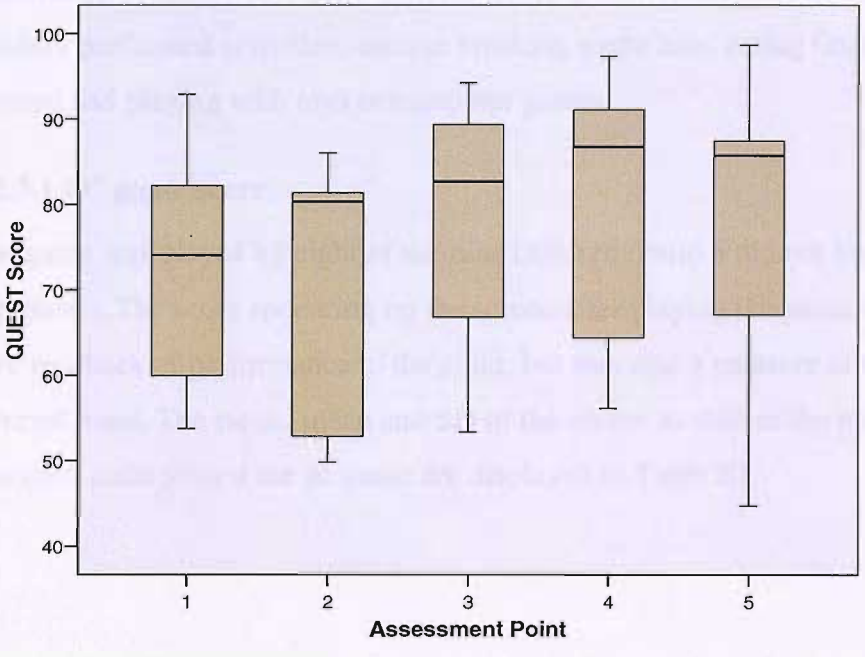


Figure 19. Boxplot showing the median, spread and inter-quartile range of scores for QUEST at each assessment point



5.2.3 Daily log

Analysis of the logs revealed that the splint was worn for 39 hours and 32 minutes on average over the mCIMT month, while during mCIMT^{+} the time increased slightly to

reach 40 hours and 28 minutes. The number of days and the amount of time that each child wore the splint during mCIMT and mCIMT$^+$ are shown in Table 19.

Table 19. Children's adherence during mCIMT and mCIMT$^+$

	Days		Hours – minutes per day		Hours – minutes overall	
	mCIMT	**mCIMT$^+$**	**mCIMT**	**mCIMT$^+$**	**mCIMT**	**mCIMT$^+$**
Child 1	27	29	1-59	2-44	53-44	79-30
Child 2	8	17	1-30	0-20	12-0	5-40
Child 3	27	23	1-39	2-42	44-33	62-0
Child 4	7	8	0-21	1-1	2-30	8-10
Child 5	22	21	0-30	0-40	10-55	14-5
Child 6	28	26	1-46	1-32	49-36	39-57
Child 7	26	17	2-36	1-48	67-36	30-45
Child 8	30	30	2-56	2-55	87-48	87-40
Child 9	20	23	1-21	1-35	27-7	36-30

Children participated in similar activities during both interventions. Most commonly, children performed activities, such as brushing teeth/ hair, eating finger food, getting dressed and playing with toys or computer games.

5.2.3.1 PC game score

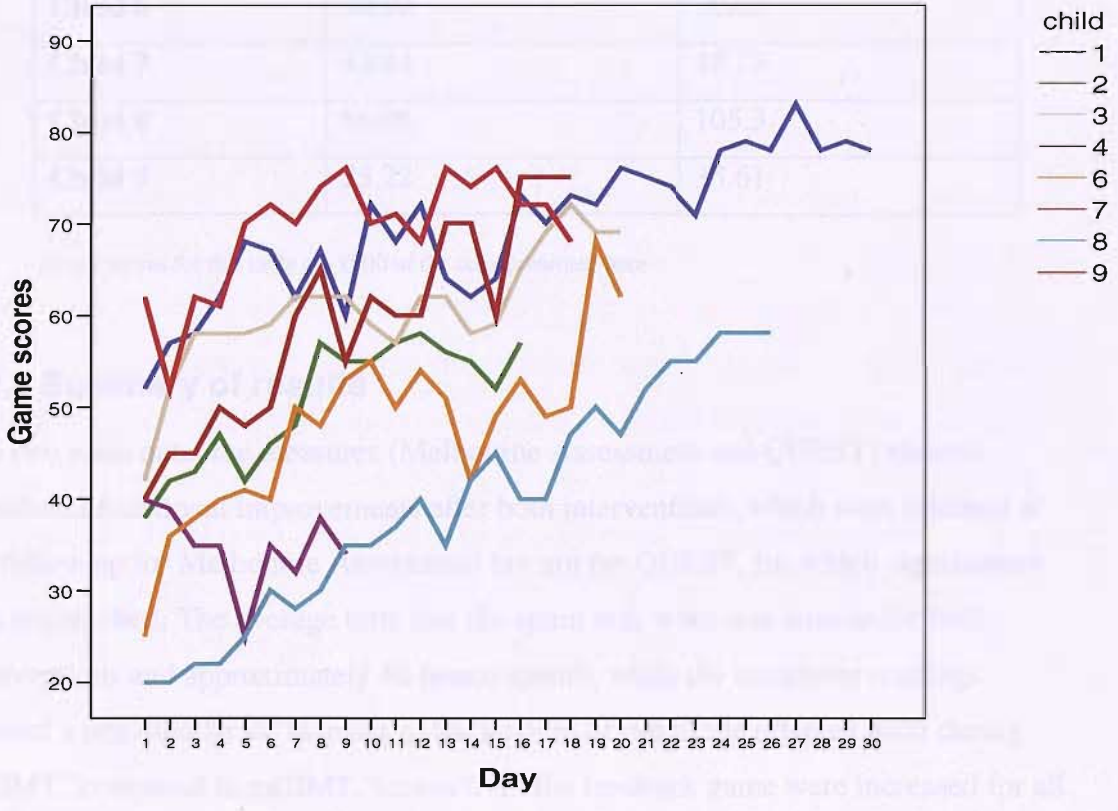
The game was played by eight of the nine children (child 5 did not have access to a computer). The score appearing on the screen after playing the game was primarily to give feedback of performance to the child, but was also a measure of the use of the affected hand. The range, mean and SD of the scores as well as the number of days that each child played the pc game are displayed in Table 20.

Table 20. Range and Mean (SD) of the scores of the pc game and the number of days that each participant played with it during mCIMT+

	Range (min-max)	Mean (SD)	No of days
Child 1	31 (52-83)	69.7 (7.7)	30
Child 2	20 (38-58)	50.5 (6.7)	16
Child 3	30 (42-72)	60.7 (6.6)	20
Child 4	15 (25-40)	34.8 (4.5)	9
Child 6	43 (25-68)	47.7 (9.6)	20
Child 7	24 (52-76)	69.2 (6.3)	18
Child 8	38 (20-58)	39.5 (12.5)	26
Child 9	35 (40-75)	59.2 (11.1)	18

All the children increased their scores at the game except for child 4, who used the game the fewest days compared to all other participants. Figure 20 shows a line graph presenting the score progress for each child during mCIMT+.

Figure 20. Game score progress for each participant



5.2.3.2 Actometer

There were several occasions when parents did not record activity four times during the intervention month, as they had been instructed. Normalised values were therefore calculated for each child during each intervention period. The mean value of the actometer readings for all participants during mCIMT was 3998 and a bit higher for mCIMT$^+$ (4308), a difference that was not statistically significant. The mean values for each child during the two interventions are shown in Table 21.

Table 21. Mean values of the actometer readings for each child during the two intervention periods

	mCIMT	mCIMT$^+$
Child 1	29.4	27.08
Child 2	2.21	3
Child 3	42.22	49.01
Child 4	36.66	58
Child 5	65.74	41.51
Child 6	30.92	20.13
Child 7	43.44	48.13
Child 8	86.06	105.3
Child 9	23.22	35.61

Actual scores for this table are x100 of the ones presented here

5.2.4 Summary of results

The two main outcome measures (Melbourne Assessment and QUEST) showed significant functional improvements after both interventions, which were retained at the follow up for Melbourne Assessment but not for QUEST, for which significance was not reached. The average time that the splint was worn was similar for both interventions and approximately 40 hours/ month, while the actometer readings showed a non-significant increase in the amount of use of the affected hand during mCIMT$^+$ compared to mCIMT. Scores from the feedback game were increased for all but one child at the end of mCIMT$^+$.

5.3 DISCUSSION

The aim of this project was to explore the idea of a 'child-friendly', practical and effective protocol based on forced-use principles. The results of the feasibility study identified the most appropriate splint in terms of effectiveness and adherence from children's and parents' perspective. The first study also provided guidance in the development of the modified protocol of paediatric CIMT. The effectiveness study examined and compared two protocols; mCIMT and mCIMT^{+}.

In the effectiveness study, the aim was to recruit 15 participants. Unfortunately, despite the efforts made the target was not reached. Nine children took part, all of whom completed both interventions and attended all of the assessment sessions. To explore the reasons for poor recruitment a survey was conducted and is reported in chapter 6.

5.3.1 Functional measures

Both the Melbourne Assessment and QUEST showed statistically significant differences after mCIMT and mCIMT^{+} compared with mean baseline values. The differences remained significant for the Melbourne Assessment at follow-up but for QUEST even though the values remained higher than mean baseline the difference was no longer statistically significant. The reason for this could be the fact that one child did not cooperate for the last QUEST measurement thus, leaving 8 cases and lowering the power of the data. As shown in Table 18, the confidence interval is very large for this measurement, which might also be a reason for the lack of significance. Functional changes were considered more reliable to be compared against the mean baseline values, instead of the second baseline assessment which could also be an option. This decision was based on the variability observed in the distribution of the values of the two measures over the baseline. However, for the Melbourne Assessment the second assessment produced a higher value in most cases, while for QUEST the reversed pattern was observed but the reason for this is unknown. Score differences of both functional measures were not significant over the baseline suggesting that the improvements shown were probably a result of treatment and not spontaneous recovery. The Melbourne Assessment was also used by Gordon et al (2007) to assess the results of 2-hour daily therapy (over the weekdays) for 4 weeks.

The lack of improvements could be due to the light regimen, the small sample number (n=6) or the low functional status of the participants, as evident from the mean Melbourne score of 52. The degree of improvements reported in QUEST by DeLuca et al (2006) were similar to the ones in this study despite the intensive therapy of 6 hours daily for 21 days and the use of a cast. This points out that a distributed form of CIMT like the one used in this study is not less effective than an intensive intervention, confirming the findings of other studies (Dettmers et al., 2005, Eliasson et al., 2005, Page and Levine, 2007b). Distributed practice has been shown (Donovan and Radosevich, 1999, Moulton et al., 2006) to enhance motor learning but most studies have been done with healthy adult subjects and their findings cannot be directly translated to children with CP. In addition, the type of distributed practice that has been shown to be beneficial involves intensive practice for a short period of time and then a long interval of rest, during which the brain uses the information gained to advance learning. Having a gap only for a few hours, as was the case in the present study may not be comparable.

Similarly to other paediatric studies (Bonnier et al., 2006, Eliasson et al., 2005, Nadeau and Wu, 2006) variability was observed between participants in the functional outcome. An age effect has not been supported, so far (Gordon et al., 2006) but the functional differences observed between participants at the baseline might account for the difference in improvements. Children 2 and 4 were the most severely affected and Child 3 the most highly functioning as determined by observation but also by the baseline scores of Melbourne (42, 49 and 92 respectively) and QUEST (57, 53 and 89 respectively). These three children made small or moderate improvements confirming other studies in both adults (Siebers et al., 2006, Teasell et al., 2006, Wolf et al., 2008, Mark and Taub, 2004) and children (Gordon et al., 2005, Gordon et al., 2006, Taub et al., 2007) reporting that low or very high functioning patients do not benefit from CIMT as much as moderate ones. An interesting finding is that the largest improvements were observed after mCIMT^{+} for the Melbourne Assessment and after mCIMT for the QUEST. The QUEST assesses the whole arm and range of movement, while the Melbourne Assessment is mostly about hand function. An explanation could be that gross arm function may improve more quickly than fine motor movement, as suggested by neuromaturational theories of development (Burke, 2007). Score difference for the main outcome measure, the Melbourne Assessment did not reach

what is considered to be a clinically significant change although it was relatively close after mCIMT$^+$, i.e. 10.33. Significance of the findings cannot be assumed due to this lack of clinically significant changes and the fact that no power calculation was performed to determine the necessary sample size. In an RCT, using a larger sample, it is possible that the treatment effect might be even more limited.

5.3.2 Daily log

Parental reports on the daily log revealed that the children wore the splint for approximately 80 minutes daily and this time remained almost stable between the two interventions. None of the children, except one wore the splint for all 30 days during either mCIMT or mCIMT$^+$ highlighting the increased difficulties in adherence that a home-based intervention might have. Parents engaged their children in functional activities during both interventions despite the instructions to follow a forced-use regimen (only splint-wearing without additional exercise) for the first month. The reason was that they found the use of activities to be the only way to keep the children motivated and away from attempts to take the splint off. The two low functioning children (Children 2 & 4) were the less compliant, wearing the splint as rarely as 7 days over 1 month and only for 20 minutes on some days. This raises the question of whether the limited improvements in these two cases were because of the small amount of therapy received rather than their physiological inability to improve. In this study, this assumption was not tested as it was considered inappropriate because of the small sample number. However, Eliasson et al (2005) reported that a correlation between amount spent in therapy and degree of improvements was not found in their participants. Similar findings have been reported in adults from the EXCITE trial (Kaplon et al., 2007). Either way it seems that in severe cases, frustration is so high that affects motivation and limits the benefit from CIMT.

5.3.3 Actometer

In accordance with parental reports in the daily log regarding splint-wearing time, actometer readings showed that children used their affected hand almost equally during the two interventions and there was only a slight increase during mCIMT$^+$. That seems reasonable considering that parents engaged children in functional activities in both interventions, leaving the pc game the only additional exercise during mCIMT$^+$. Great variability was observed in this measure also with some

children increasing their affected hand use in the second intervention and some others following the reversed pattern. The reliability of the actometer as an outcome measure is questionable especially when used to measure children's amount of UL use at home. Parents' informal reports revealed that different behaviours were observed in children when the actometer was on; some were overactive and others refused to participate in activities, which was not really reflecting their normal activity during intervention. Some parents were puzzled about proper reporting of the recordings despite careful demonstration by the researcher. Although the actometer had been tested to ensure it gives the same estimates for same movements, its overall recording does not really describe amount of movement effectively as for example a fine, manipulating movement would result in a small recording compared to a fast gross movement of the arm. Overall, the actometer should probably be used as a secondary measure in the lab, while the recordings should be taken by the researcher or someone familiar with this instrument.

5.3.4 PC Game

The PC game proved to be a valuable tool in the study, as it not only increased children's motivation and provided feedback but parents actually reported having difficulties in restricting the children from playing more than the requested daily time. A programme installed in the computer recorded joystick movement (and thus, the affected hand). All participants with the exception of Child 4, who played the game for only 9 days showed increase in the scores obtained at the end of each game session. Without a control group, it is impossible to know whether improvement in games scores would have occurred irrespective of the intervention.

5.3.5 Forced use (mCIMT) vs. Motivating activities (mCIMT$^+$)

One of the aims of the effectiveness study was to examine whether there would be an additional benefit when the constraint is combined with functional activities and feedback (mCIMT$^+$) compared to the use of the constraint only (mCIMT). Improvements after mCIMT, as measured by the functional tests became even larger after mCIMT$^+$ but the reason for this is unknown. Children were engaged in functional activities in both interventions but there were several other factors, such as the feedback given, the extended period of intervention and the increased adherence, as shown by the small increase of splint-wearing time that may have been the reason for

the additional improvements. Adherence may well be a consequence of the motivation but unless each of these factors is tested separately, we cannot conclude on their relative importance.

5.3.6 Conclusion, limitations and future work

A home based intervention would be helpful and practical to use either on its own or supplementary to therapy received in the clinic. Our observations suggest that some of the protocols that have been proposed for use in children may be insufficiently 'child-friendly' and not appropriate for therapy at home, while a distributed form of CIMT has been shown to be equally effective with other more intensive regimens.

Parents mentioned that in some cases children attempted to use their fingers through the suspenders. Future studies should test the use of a mesh covering the whole hand instead of the suspenders; this would ensure full restriction of the hand and would not cause problems that the mitt did in the feasibility study, i.e. being too hot or easy to remove by children.

A shortcoming of the design used in this study is that applying a measure repeatedly can be expected to have a learning effect and thus, some of the differences shown might be due to this effect rather than the intervention tested. In addition, all participants in this study took part in the two interventions with the same order, i.e. in mCIMT first and mCIMT$^+$ afterwards, as the latter was considered to be at least as effective as the former. This design poses a barrier in distinguishing between order effect and intervention effect; unfortunately the small sample number did not allow for randomization to be done among participants to receive either mCIMT or mCIMT$^+$ first. Another limitation of the present study is the lack of multiple baseline measurements. The two baseline assessments showed a large variability between participants, which stresses the need for repeated measurements until plateau in order to be able to reliably assume that the functional changes are an intervention effect. For these reasons this small pilot study cannot reach any definite conclusions. A large randomized trial would be an appropriate next step to test the observations made here.

One of the biggest issues that arose during the course of the project and which limited the ability to make robust conclusions was the one of poor recruitment both to the

feasibility and the effectiveness study. It was therefore, considered appropriate in order to design a practical protocol of paediatric CIMT to explore parents and therapist' views on the practicality and effectiveness of both the classic paediatric protocol and the one suggested by the present study. To address these issues a survey was designed that included questionnaires to parents of children that had been invited to take part in the study and paediatric physiotherapists and occupational therapists registered with the Association of Paediatric Physiotherapists (APCP) and the College of Occupational Therapists Specialist Section, respectively. The survey is presented in detail in the following chapter.

CHAPTER 6

THE SURVEY

6.1 INTRODUCTION

This study was undertaken to address the issue of poor recruitment to the main study with the objective of exploring therapists and parents' views on CIMT.

A survey conducted by Page et al (2002a) showed that 68% of the adult stroke patients who took part in the study would not be interested in participating in CIMT due to the intensity of the practice schedule and the duration of the restraint schedule. In accordance, over 68% of therapists cited concerns with CIMT practicality, speculating that it would be 'very difficult' or 'difficult' to administer. Such a survey has not been done for the paediatric population, so far. Therapists' opinion of and knowledge about paediatric CIMT was thought to be an interesting and potentially useful aspect to explore, especially since their advice to parents may have influenced recruitment. The concerns that parents might have for allowing their children to take part in CIMT were also investigated in an attempt to gather information that would help towards developing the most appropriate CIMT protocol.

6.2 METHOD

6.2.1 Ethics approval

The study was approved by the Southampton & South West Hampshire Research Ethics Committee for the parents' survey and the Ethics Committee of the School of Health Professions & Rehabilitation Sciences for the therapists' survey (Appendix 3). The study was sponsored by the University of Southampton and received full R&G approval. Recruitment and consent was conducted under the guidelines set out in the MRC Clinical Trials Tool kit.

6.2.2 Objectives

The objectives of the survey were:

1) To explore the views of parents of children invited to take part in the CIMT study

2) To explore the opinion of paediatric physiotherapists and occupational therapists on the effectiveness and practicality of the classic paediatric CIMT protocol and the protocol suggested in the present study in accordance with their knowledge and experience of CIMT

6.2.3 Questionnaires

The design of the questionnaires for this study was informed by experience gained during the previous phases of the study and in response to interaction with therapists, children and their parents. The questionnaires were reviewed by five professional colleagues, the researcher's supervisor and one other senior academic with an occupational therapy training. In response to their feedback, modifications were made that included changes to the design and question format, rewording of questions and instruction amendments to make them clearer. Following these changes, the questionnaires were re-reviewed. Both questionnaires were kept as brief as possible, requiring less than 15 minutes to be completed. The response choices were of nominal and ordinal level.

Parents' questionnaire

This questionnaire (Appendix 1) aimed to explore parents' views on CIMT and the reasons for poor recruitment. The questionnaire consisted of eight statements that, on the basis of the literature and the researcher's experience, were thought to represent the main reasons that parents hesitate to have their children involved in CIMT. Parents were asked to circle the appropriate point in a 5-point Likert scale, indicating how much they agree/ disagree with each statement. Extra space was given for parents to report any other reasons (apart from the ones provided as statements) that they might have had for not allowing their children to participate in CIMT. A screening question was added on top of this questionnaire to ensure that only parents who decided not to take part in the main study would respond.

Therapists' questionnaire

The therapists' questionnaire (Appendix 1) was designed to gather information about the extent of knowledge and experience that paediatric therapists have about CIMT and to explore their opinions about the effectiveness and practicality of the classic paediatric protocol and the protocol suggested in the main study. The questionnaire consisted of 5-point Likert scales ranging from 'I strongly agree' to 'I strongly disagree' and closed questions in some of which an explanation or clarification of the answer was required. A screening question was added on top of the questionnaire to ensure that only those therapists that have at least heard of CIMT before would respond.

6.2.4 Participants

All the parents that were invited into the main study were sent a questionnaire. As there was no data on which to base a power calculation, a convenience sample was recruited for the therapists' survey. The aim was to include approximately 100 respondents, which would allow a power calculation to be made for a future larger study.

Recruitment process

When recruitment for the main study had ended and following ethical permission, questionnaires were sent to therapists, who had been the main collaborators for the study. Although the aim was to explore the views of those parents who did not take

part in the mCIMT study, for confidentiality reasons therapists were asked to pass the questionnaire to all the parents who had been invited into the study. Due to unsuccessful attempts to contact some parents, the actual number of questionnaires that were finally sent out were 32,of the 45 families that were invited into the main study.

For the therapists' survey, questionnaires were sent to all paediatric physiotherapists (n=50), registered with the Association of Paediatric Physiotherapists (APCP) and a random sample of 150 paediatric occupational therapists registered with the College of Occupational Therapists (COT) Specialist Section. All therapists had already given permission to their professional bodies to be contacted for research purposes. Limited funds did not allow the inclusion of all 800 paediatric occupational therapists registered with the COT Specialist Section.

Selection criteria

The following inclusion criteria were applied for each of the two surveys:

(Parents)

-Parents whose children were invited in the effectiveness study

(Therapists)

-Paediatric physiotherapists or occupational therapists

-Registered with the COT Specialist Section or the Association of Paediatric Physiotherapists (APCP)

-Having given permission to their professional bodies to be contacted for research purposes

6.2.5 Experimental procedure

This survey took place between April 2007 and August 2007.

The parents' questionnaire was sent to therapists who had helped during recruitment of the main study, with a request to either hand or post the questionnaire (together with a pre-paid envelope addressed to the researcher) to all the parents that had been invited in the main study.

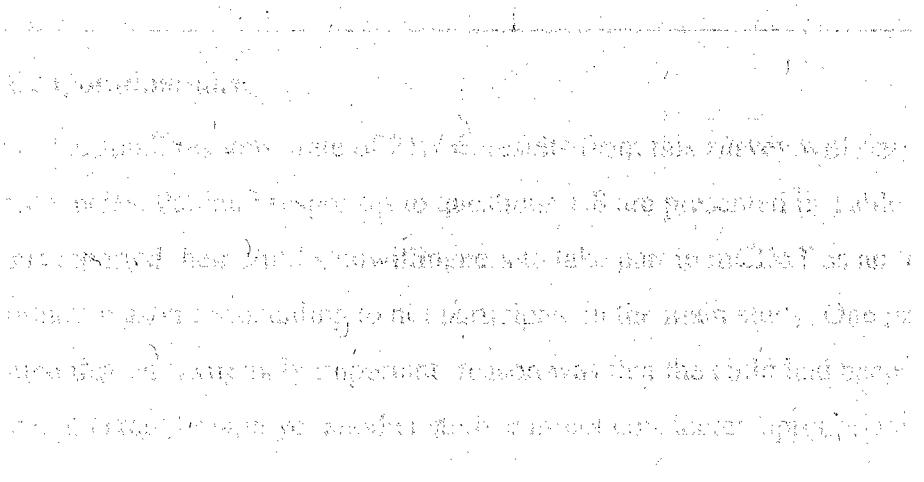
The therapists' questionnaire was sent to the professional bodies of paediatric physiotherapists and occupational therapists (APCP and the COT Specialist Section, respectively) on April 2007. Thus, therapists were sent the questionnaire by the administrative staff of their professional body and were asked to return it directly to the researcher using the pre-paid envelope that was enclosed.

Confidentiality

Both therapists and parents were informed that their responses would be anonymous. Therapists' names or addresses were not revealed to the researcher.

6.2.6 Data analysis plan

Frequencies and percentages of the responses were computed the closed items of both questionnaires. Content analysis was used to analyse questions, where explanation or clarification of the answer was required by the respondent. Crosstabulations and Chi-squared test or Fisher's Exact Test were used to correlate between nominal data. All the syntaxes and results of the study are included in CD1.



6.3 RESULTS

6.3.1 Parents' survey

6.3.1.1 Respondents

Out of the 32 questionnaires that were sent out, 5 completed questionnaires were sent back to the researcher. Nine children had participated in the main study, thus their parents were not required to respond. The response rate for the remaining 23 questionnaires was 21.7%. Biographical data of respondents is summarised in Table 22.

Table 22. Biographical data of respondents

	Parents' ID
Employment	
Full-time	1
Part-time	2
Unemployed	2
Living	
Alone	2
With partner	3
Other children	
Only 1	0
At least one more dependent	5

6.3.1.2 Questionnaire

Due to the small response rate of 21.7%, results from this survey will only be reported as frequencies. Parental responses to questions 1-8 are presented in Table 23. Four parents reported their child's unwillingness to take part in mCIMT as an 'extremely important' reason for deciding to not participate in the main study. One parent reported that an 'extremely important' reason was that the child had been studied a lot and being taken through yet another study was not considered appropriate. Another reason, added as 'important' by one parent was that they were concerned that mCIMT might be disruptive for schooling.

Table 23. Frequency of responses to questions 1-8 of the questionnaire, stating potential reasons that parents might have had for not taking part in mCIMT

	PARENTAL RESPONSES				
	1 Strongly agree	**2**	**3**	**4**	**5 Strongly disagree**
1. Time required for child supervision		1		3	1
2. Time required to travel to the university	1		2		2
3. Splint would interfere with child' s normal activities	1	1		2	1
4. Child would not have the time to wear the splint as much as required			1	3	1
5. Advice from health professionals made me reluctant				3	2
6. Child would not benefit from the treatment			1	2	2
7. Splint might be dangerous in case of falling	1			2	2
8. Splint might compromise child's normal development				3	2

6.3.2 Therapists' survey

6.3.2.1 Respondents

Responses were received from 145 therapists (response rate: 72.5%), 114 of which were occupational therapists and 31 physiotherapists. Their grades and years of experience are presented in Table 24.

Table 24. Therapists' distribution according to grades and years of experience

	Therapists number (%)
Grade	
Band 5	1 (1%)
Band 6	28 (19%)
Band 7	75 (52%)
Head	21 (15%)
Clinical Specialist	8 (6%)
Manager	11 (8%)
Years of experience	
2 or less	2 (1%)
3-5	11 (8%)
6-10	34 (24%)
11-15	18 (13%)
16 or more	79 (55%)

6.3.2.2 Questionnaire

Eighty five therapists (59%) replied that they have heard of CIMT, while 60 (41%) have never heard of it. Most of the therapists that have never heard of CIMT were occupational therapists (51 out of the 114, i.e. 45% compared to 9 out of the 31 physiotherapists, i.e. 29%). The degree of therapists' knowledge and experience of CIMT, as reflected in their responses to question 2 is shown in Table 25.

Table 25. Therapists' knowledge and experience of CIMT according to their responses to item 2 of the questionnaire

		Frequency of responses
Read a few papers		54
Read a lot/ been involved in discussions		10
Attended CIMT study days		11
Have used CIMT		8
Other	**Discussed it briefly**	5
	Had children participating in other people's research trials	4
	Just heard of it	11
	Attended one presentation	6

A cross-tabulation between therapists who have heard of CIMT and those who have not with the years of their professional experience revealed a trend showing that therapists who have never heard of CIMT are mostly the ones with many years of experience, as shown in Table 26.

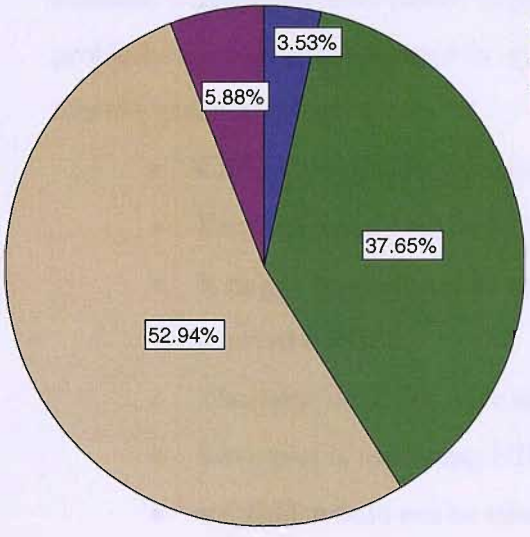
Table 26. Cross-tabulation between therapists who have heard of CIMT and those who have not with years of professional experience

		Years of experience (% of the overall number of therapists in each category)				
		2 or less	**3-5**	**6-10**	**11-15**	**16 or more**
Heard of CIMT	**YES**	2 (100)	5 (45)	20 (59)	8 (44)	49 (62)
	NO	0 (0)	6 (55)	14 (41)	10 (56)	30 (38)

Therapists rated on a 5-point Likert scale the degree to which they agree that the classic paediatric CIMT protocol and the protocol suggested in the main study would be very likely to improve children's upper limb function. Therapists also expressed their opinion as to whether the classic paediatric protocol and the one suggested here would be considered practical. The results are shown graphically in Figures 21 and 22.

Figure 21. Therapists' opinions on whether (a) the classic paediatric protocol or (b) the protocol suggested in this study would be very likely to improve children's upper limb function

(a)



(b)

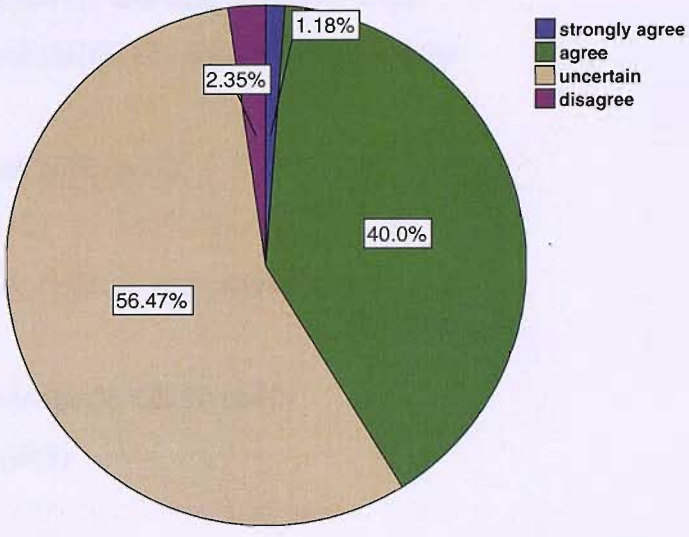
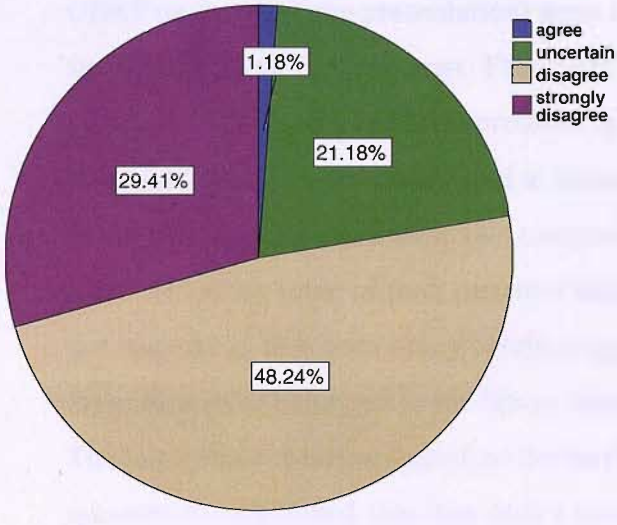
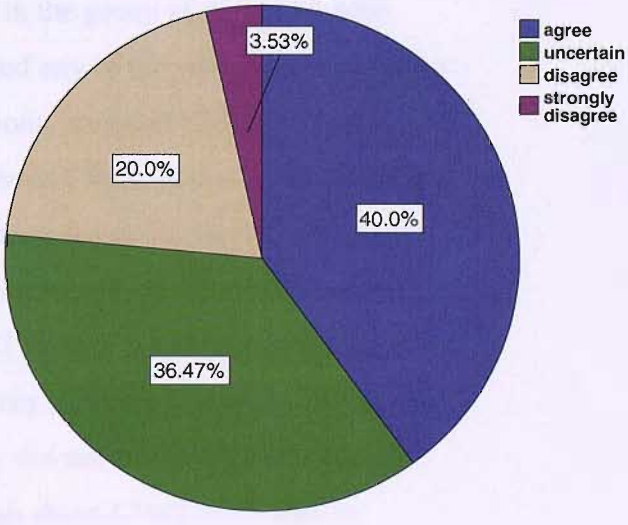


Figure 22. Therapists' opinions on whether (a) the classic paediatric protocol or (b) the protocol suggested in this study would be practical

(a)



(b)



Fourteen therapists replied that they would suggest participation in the newly suggested mCIMT to all of their patients if a trial was available. These therapists believe that mCIMT would be an intervention worth trying that seems to be effective. Fifty two therapists would suggest mCIMT to some of their patients depending on certain characteristics, such as compliance of both children and parents (n=41), children's cognitive level (n=9), degree of severity (n=17) and lack of behavioural problems (n=6). Fifteen therapists would not suggest mCIMT to their patients and the reasons given are that:

- Children would not be able to tolerate mCIMT (n=1)
- Families would not want to take part (n=2)
- It might be unethical to use mCIMT with children who cannot give consent (n=2)
- Therapist does not have sufficient knowledge on CIMT (n=7)
- Therapist is following NDT principles (n=3)
- mCIMT would not be effective (n=2)

To identify whether those therapists that would not suggest mCIMT have a sufficient knowledge of this treatment or not, therapists were divided into two categories according to their responses to questionnaire item 2. Those therapists that replied that they have only read a few papers and/ or ticked the 'Other' category (i.e. discussed CIMT briefly, had children participating in other people's research trials, just heard of CIMT or attended one presentation) were included in the group of therapists who know little about the treatment. Therapists that ticked any of the other responses from question 2 (i.e. read a lot/ been involved in discussions, attended CIMT study days, have used CIMT) were considered to know more about CIMT. A cross-tabulation was then performed between these two categories and those therapists that would suggest CIMT (to all or some of their patients) and those who would not. Four therapists did not respond as to whether they would suggest CIMT to their patients or not. One of these therapists belonged to the 'know more' category and three to the 'know less'. The latter three therapists justified the fact that they did not respond to the specific question by explaining that they didn't know enough about CIMT to be able to encourage a patient to participate or not. Out of the remaining 81 therapists who have heard of CIMT, 60 know only a little about this treatment. 23.3 % (n=14) of these

therapists that know a little would not suggest mCIMT. In contrast, from those therapists that know more only 4.7% (n=1) would not suggest it because 'it might be unethical to administer this treatment to children who cannot consent themselves'. Fisher's Exact Test was also calculated but statistical significance was not found (p= .1). The results of the cross-tabulation are presented in (Table 27).

Table 27. Cross-tabulation showing the correlation between those therapists that know little about CIMT and those that know more with therapists that would suggest mCIMT to their patients and those that would not

	Would suggest mCIMT	**Would not suggest mCIMT**
Know little about CIMT	46	14
Know more about CIMT	20	1

6.4. DISCUSSION

6.4.1 Parents' survey

Due to the low response rate (21.7%), parents' views on CIMT and the reasons for poor recruitment could not be adequately explored. Apart from the limited responses, a significant shortcoming in the parents' survey (in contrast to the therapists' survey) was the lack of consultation with parents for the development of the questionnaire. Potentially, this might have helped towards a higher response rate and a more thorough investigation of parental views. Investigating the opinions of parents on various aspects of CIMT would provide valuable guidance for the design of a practical protocol. A study aiming at exploring parents' views has already been initiated at the School of Health Sciences as an MSc project, being supervised by the researcher and Professor Jane Burridge.

6.4.2 Therapists' survey

An interesting finding of this survey was that a large number of paediatric therapists (41%) have never heard of CIMT. The percentage of occupational therapists who have never heard of it is much larger (45%) than the one of physiotherapists (29%) despite the fact that CIMT is mainly an upper limb rehabilitative technique, which would traditionally be of more interest to occupational therapists. Therapists with many years of professional experience were found to be more likely to not have heard of CIMT than the less experienced ones.

Most of the therapists (74%) who have heard of CIMT know very little about this treatment, i.e. have read a few papers, have discussed it briefly or have literally just heard of it. Only 8 out of the 145 respondents have used CIMT clinically with their patients. The reason for this could perhaps be the fact that 78% of therapists believe that the classic paediatric CIMT protocol is impractical. In contrast, only 24% of therapists consider the newly suggested mCIMT protocol to be impractical. In addition, therapists replied that the two protocols would most likely equally improve children's upper limb function.

Most therapists would suggest mCIMT to patients with specific characteristics, such as those with high likelihood of being compliant, those with no cognitive deficits and no serious behavioural problems. Fifteen therapists responded that they would not suggest mCIMT to their patients. Out of those, 14 belonged to the category that only knew a little about this treatment, while the one therapist that knew more on CIMT expressed concerns about the ethical issue of administering this treatment to children who cannot consent themselves. This clearly shows that especially therapists who have a good knowledge and/ or experience on CIMT would consider an intervention involving 2-3 hours of daily restriction of the non-affected limb for 2 months, accompanied by exercise worth of participation for children with CP.

Taken together, the findings of this study challenge the practicality of the classic paediatric CIMT. Therapists' responses suggest that a shorter daily restriction over a longer period of intervention might be a more practical option but perhaps equally effective. The findings of the main study come in support of this suggestion.

One could argue the relatively small sample number, which could be larger for occupational therapists, is a limitation of this study. The response rate of 72.5% is, nevertheless, considered satisfactory. Perhaps the biggest limitation of this survey is revealed by the important finding that the opinions expressed are these of therapists most of whom had limited knowledge and experience of CIMT. A larger scale study could perhaps add to the present findings by including more therapists with deeper knowledge on CIMT. What would be even more informative in such a study, is the inclusion of a more qualitative element, such as the use of focus groups and interviews. Two focus groups comprising of therapists who have a good knowledge on CIMT and therapists whose knowledge is limited would provide the opportunity for a more in-depth investigation and comparison between different clinicians' point of view.

Clinicians' thoughts are very important in order to identify a practical intervention. To fully examine the effectiveness of such a protocol though, it would be ideal to test the possibility of any cortical changes occurring as a result of the treatment in addition to functional effects. In adults, studies (Liepert et al., 2004, Liepert et al., 2001, Szaflarski et al., 2006, Wittenberg et al., 2003) have examined this possibility after

application of CIMT and the findings are supportive of a treatment-induced reorganization, which is usually characterized by an enlargement of the cortical area responsible for the affected limb. In children, brain imaging studies after CIMT are at an early stage. Since the objective of this study was to design a practical and effective protocol of paediatric CIMT, it was considered appropriate to examine the physiological effects of the suggested intervention. Functional MRI (fMRI) was available at the time of initiation of the study but due to the limited budget, this option was not feasible. Electroencephalogram (EEG) on the other hand, offers a low-cost option, simple to use, while being much more child-friendly compared to MRI. A specialist in the area of EEG and event-related potentials (ERP), Dr. Alexandra Hogan was based at the School of Psychology, in the University of Southampton. Dr Hogan is an expert in exploring a specific component of the ERP, called the lateralized readiness potential (LRP), which reflects the differential involvement of left and right motor cortices in preparing to execute unimanual motor acts. Because of the relevance of this potential to motor acting, it was thought to be an interesting aspect to explore in trying to identify any potential physiological changes following CIMT. Since LRP has never been tested in such a concept before, the aim of this small, supplementary study was to develop a test that would elicit lateralised waveform differentiation across healthy children and that would be feasibile to use with children with hemiplegic CP. This first step towards developing a simple, child-friendly method of recording brain changes in response to movement treatment is presented in detail in the following chapter.

CHAPTER 7

THE LATERALISED READINESS POTENTIAL STUDY

This study was conducted under the guidance and supervision of Dr. Alexandra Hogan. Dr. Hogan introduced the researcher to the concept of ERPs. The procedure of using the LRP equipment and collecting data was demonstrated initially by Dr. Hogan and the researcher then performed several pilot trials with colleagues to ensure correct use of the equipment, recording of data and careful consideration of all the safety issues. Data collection with the first eight healthy children was done under the supervision of Dr. Hogan and throughout the study, she was available if needed during the sessions. The technical staff of the School of Psychology was also available to provide support if required. The statistical analysis was done under the guidance of Dr. Hogan and some parts, such as the figures were exclusively produced by her. Review of the background literature and discussion of the findings was done primarily by the researcher but in accordance with Dr. Hogan's advice.

7.1 INTRODUCTION

When electrodes are attached to the human scalp and connected to an amplifier, the output reveals a pattern of variation in voltage over time. This voltage variation is known as the electroencephalogram (EEG). The EEG represents the residual electrical activity of post-synaptic potentials of populations of neurons, typically pyramidal cells. In other words, electrical fields from individual neurons summate to yield a dipolar field. This, results in positive/ negative waveforms recorded from electrodes at the scalp. If a stimulus is presented to the subject whilst recording the EEG, voltage changes can be observed that are specifically related to the brain's response to the stimulus. These voltage changes constitute the event-related potential or ERP (Coles and Rugg, 1995).

Based on variations in the task and stimulus, a variety of ERP components have been documented. ERP components usually derive their names from the polarity and latency of the waveform and may be 'locked' to stimulus presentation or response. The P300 component, for example indicates that it is a positive-going deflection that occurs 300ms following the stimulus onset (Nelson and Monk, 2001). The potential

associated with voluntary movements is known as the motor potential (MP). One of the basic components of the MP is the Bereitschaftspotential, which will be reviewed in detail below. A similar negative-going potential, known as the contingent negative variation (CNV) is thought to index expectation or motor preparation. The CNV is elicited by establishing a contingency between the presentation of two stimuli across time. The experiments usually involve the first stimulus, which is a click and then a flickering light which is the second and alerts the subject to press a button. The negative wave appearing between click and flicker is maximal at fronto-central regions and reaches its maximum negativity at around the time of the second stimulus. It has been suggested that the CNV may contain the Bereitschaftspotential as one of its components (De Jong et al., 1988, Shibasaki, 1993). Indeed, the CNV waveform has been segmented into two components: the O-wave and the E-wave. The O-wave is thought to be a correlate of the subject's orienting to the initial stimulus, while the E-wave reflects the subject's motor or sensory processing preparation for the subsequent stimulus and it is the one mostly related to the Bereitschaftspotential (Coles and Rugg, 1995, Nelson and Monk, 2001). Another potential that has been recorded in some subjects is the pre-motion positivity, occurring 80-90ms before the movement onset. Some researchers have managed to record it at the ipsilateral hemisphere during unilateral hand movement only, while others reported recording of this potential with bilateral simultaneous movement. This component has been thought to correspond to the initial activity in the cortico-cerebellar-motor cortex loop however its significance remains unclear. A large post-motor positive complex starts 30-90 ms after the movement onset. This has been suggested to be related to kinesthetic feedback (reafferente Potentiale).

When individuals anticipate making a response with a particular hand, an increase in negativity occurs that is larger at scalp sites contralateral to the responding hand. This negative ramp-like potential appearing over the human scalp, 1-2sec prior to movement onset has been termed as the Bereitschaftspotential or Readiness Potential (RP) (Coles et al., 1988, Gratton et al., 1988). This slow pre-movement negativity is initially of equal amplitude over both hemispheres with its earliest onset over the frontocentral midline, probably including the supplementary motor area (SMA). It begins to increase asymmetrically 400ms or more before movement onset with larger amplitudes over the hemisphere contralateral to the responding side and at scalp

electrodes placed above lateral central areas (C3 and C4) or over adjacent sites, frequently described as C3′and C4′. These sites are in close proximity to the areas of the brain assumed to control movement (De Jong et al., 1990, Rinkenauer et al., 2004). The RP has been assumed to reflect cortical processes associated with preparatory mechanisms related to the execution of specific motor acts. However, SMA or primary motor cortex (M1) cannot be assumed to be the only generators for the RP. Rather, such a preparatory activity shows a widespread distribution over both hemispheres. The lateralised part of the RP (LRP) reflects the differential involvement of left and right motor cortices in preparing to execute unimanual motor acts (De Jong et al., 1988, Deecke, 1987, De Jong et al., 1990, Kutas and Donchin, 1980). It is derived by subtracting the potential recorded above the site contralateral to the signaled effector from the ipsilateral site. When these difference waves are averaged across hands, they yield the LRP, reflecting pure hand-related ERP asymmetry (Masaki et al., 2004, Shibasaki and Hallett, 2006). LRP can be either stimulus-locked or response-locked. Stimulus-locked means that each point in the LRP is based on points from individual trials that follow the response signal by the same amount of time (t=0 at response signal onset). Response-locked LRP is based on points that precede the overt response by the same amount of time (Rinkenauer et al., 2004). The latency of LRP onset is dependent on response selection, so that the interval between the stimulus and the onset of the stimulus-locked LRP provides a relative measure of the duration of the processes involved in stimulus evaluation and response selection. Similarly, the interval between the onset of the response-locked LRP and the response provides a measure of the duration of motor processes, i.e. motor planning and execution (Prime and Ward, 2004). LRP's amplitude has been found to be insensitive to movement parameters other than movement side (De Jong et al., 1990). Thus, LRP seems to be a suitable real-time index of central activation processes involved in the generation of motor commands specific to unimanual movements.

The majority of research in this area is with adults. Some researchers have reported children's RP to exhibit a positive deflection, while others have failed to find positivity (Muller et al., 2002). LRP has been shown to be larger at frontal, central or parietal leads (Muller et al., 2002, Steger et al., 2000). Studies testing different ERP components have indicated that pronounced development occurs between middle

childhood and adulthood and that further investigations are needed to reveal the ways in which the CNS organises itself across development (Nelson and Monk, 2001).

Thus, there is limited evidence for the nature of lateralised motor preparation potentials in children. The potential importance of such information for our understanding of underlying brain organisation and function in children with hemiparesis is, however, considerable; for example for the development of rehabilitation techniques such as CIMT. ERP correlates of brain activity associated with motor activity in each hand may change before and after treatment. In addition, the timing and location of brain activity may indicate whether the abnormality lies in stimulus processing, response selection, motor preparation and/or movement initiation. The aims of this pilot study were two-fold. Firstly to develop a simplistic motor task that may be administered to children as young as 5 years, and to demonstrate differential (lateralised) ERP activity according to whether the left or right hand was used to respond. Secondly, to apply this task to children with hemiplegic CP to investigate the appropriateness, feasibilty, and validity of the ERP approach.

More specifically, it was hypothesised that left and right frontal cortex (incorporating the SMA and premotor cortices) would show a different pattern of activation according to whether a right hand or left hand response was required in a simple choice-response task ('FISH' task). On the basis of these normative data, 'FISH' waveforms obtained from four patients with hemiplegic CP were examined. It was predicted that these patients would show an abnormal pattern of waveform differentiation over the frontal cortex.

7.2 METHOD

7.2.1 Ethics approval

The study was approved by the Ethics Committee of the School of Psychology for the control group and by the Southampton & South West Hampshire Research Ethics Committee for the patient group (Appendix 3). The study was sponsored by the University of Southampton and received full R&G approval. Recruitment and consent was conducted under the guidelines set out in the MRC Clinical Trials Tool kit.

7.2.2 Objectives

-To develop a test that elicits lateralised waveform differentiation across a wide age-range of healthy children, i.e. a test that is simplistic enough that it would not be too attentionally demanding for very young children or too simple for older children.
-To explore the feasibility of using this test with children with hemiplegic CP.

7.2.3 Participants

This study was conducted with a convenience sample.

Recruitment process

The control group for this study consisted of 13 children, who were recruited from Southampton via friends and from members of staff and postgraduate students. A poster (Appendix 10), containing the researcher's contact details was placed in different Schools' board to inform parents that might be interested in their child's participation in the study. An information sheet (Appendix 5) was given to parents before they made the decision to take part in the study. Following this, formal consent from the parents and assent from the child was obtained (Appendix 6). A mutually convenient date and time was then arranged for an appointment at the ERP Laboratory at the School of Psychology.

A subgroup of children with CP was recruited from the main study cohort. An information sheet was given to parents and children (Appendix 5) if they satisfied the inclusion criteria, during the first assessment of the main study. They were asked to inform the researcher if they would like to take part in this additional study or not

before the CIMT intervention began so that the EEG recording could be obtained prior to any therapy. If they expressed their interest in participation a consent form was completed by the parents and assent by the child, similar to the ones used for the main study.

Selection criteria

The study was initiated with recruitment of the control group, while patients' participation followed a few months later. In the control group study, the age range was chosen to match the one of children with CP that could potentially take part in the ERP study. Attempts were made to explore the practicalities of the ERP measure with a wide age range (5-11 years old) of healthy children, so that an age-matched control could subsequently be selected for each of children with CP. The following inclusion criteria were therefore applied:

(Control group)

1) Healthy, unimpaired children who were between 5-11 years old
2) Children who attended mainstream schools (without a statement of educational needs)
3) Children with no medical history of epilepsy

(Patient group- in addition to the selection criteria of the main study)

1) Children aged between 5-11 years old
2) Children with no medical history of epilepsy

7.2.4 ERP test of premotor/motor brain activity: 'FISH'

During the ERP paradigm, the child was requested to sit, on their parent's lap if necessary, in front of a computer monitor while leads were placed on the scalp at specified positions. The leads were held in place with a watery gel, and with plasters where there was no hair (forehead, behind the ears). The EEG was recorded on a SynAmps^{TM} NeuroScan system, and digitized at a rate of 500Hz (band-pass 0.05-70Hz). In this study we used an EEG montage of 18 leads over lateral and midline sites of the conventional 10/20 EEG system (Jasper, 1958). Brain activity from 11 sites was analysed – left hemisphere (F3, FC3, C3), right hemisphere (F4, FC4, C4),

and midline (Fz, FCz, Cz, CPz, Pz). While EEG has limited spatial resolution (Sato et al., 2007), it is possible to infer that three leads predominantly represented prefrontal cortex activity (F3, Fz, F4), three leads predominantly reflected premotor cortex activity (FC3, FCz, FC4), and three leads predominantly reflected motor cortex activity (C3, Cz, C4). Leads were also placed above and below the right eye, as well as at the side of both eyes in order to record and exclude blink activity. Blinks result in a larger component than those elicited by brain activity, and can obscure brain activity as far back as the vertex (Cz). It is possible to extract blinks from the EEG trace using an automatic procedure based on a study by Semlitsch et al (1986). A lead on the forehead over the left eyebrow (FP1) served as the ground lead, and two leads placed on the bone behind each ear (mastoid) served as the reference electrodes. Reference electrodes are necessary so that electrical activity associated with activity other than that of the brain (e.g. skin conductance) may be subtracted from the brain activity of interest. Impedance values indicate the quality of the EEG recording and in line with convention, were kept below 15kΩ.

In order to facilitate the lead placement, a teddy bear was given to younger children with some spare leads and sticky tape. The child was told that everything will be done to teddy first so that they can see how the leads will be put on their head. The child was invited to put a lead on teddy's head for every lead that goes on their head. Parents and children were told that the leads are sensitive to the normal electrical activity of the brain and that this electrical activity is fed through an amplifier to a computer. They were further informed that it is not possible to send signals or electrical activity back to the brain. Once the leads were in place, the child was asked to sit as still as possible and watch some pictures on the computer. Children were asked to participate in a game called 'FISH'. In this game, the child saw a fish swimming to the left or to the right. They were asked to press the big button by their left hand when the fish was swimming towards the left, and the big button by their right hand when the fish was swimming towards the right. Fish stimuli were preceded by a cross that indicated to the child that they should 'get ready' to see a fish. One second later a left or right swimming fish appeared and remained on screen until the child had responded. The child was instructed to respond as quickly as possible. There was then a break (inter-stimulus interval) of 2000ms until the next cross stimuli. This task took approximately 12

minutes, while the whole procedure, including lead placement and removal lasted for approximately 45 minutes.

7.2.5 ERP Processing

ERP components were extracted from the EEG trace and processed offline, using NeuroScan 'Edit' Software. This was facilitated by codes in the EEG trace that were linked to either stimulus presentation or the child's response. Every time a stimulus occurred and a response was made a code appeared at the bottom of the EEG screen. There was a different code for left and right fish, and for left and right hand correct and error responses; all ERP averages were formed from correct responses only, as errors elicit other potentially over-riding ERPs (Hogan et al., 2006). Once blinks and muscle artifact had been removed the EEG was divided into chunks centred on the stimulus (fish presentation) codes (-200 to 1200ms: 0 = stimulus appearance). These EEG 'epochs' were then aligned across all sites (baseline corrected: -200 to 0ms) and any epochs contaminated by persisting muscle or movement artifact (+/- 100μV) removed following manual inspection of all epochs. The remaining epochs were then averaged together according to stimulus type[2] (Left pointing fish, Right pointing fish: as only those fish associated with correct responses were used it may be assumed that left fish equate to initiation of a left hand response and right fish equate to initiation of a right hand response). ERP averages obtained from individual children were averaged again into groups, and this ERP is called the 'Grand Average'. On the basis of the left and right fish grand averages (Figures 23, 24), it was decided to measure the negative area in the interval 250ms to 850ms. Area scores were considered more appropriate than a peak amplitude score as the latter requires a clear (sharp) peak to be present in all individual ERPs. Area scores were automatically calculated from individual left and right fish averages at each lead, and entered into SPSS for analysis. The more negative the area score, the deeper and longer the curve within 250 to 850ms.

[2] The response-locked potentials were also explored but did not yield any waveform differentiation, perhaps due to the wide age-range of the children. The few studies conducted with children have had a mixed approach, utilising stimulus and/ or response-locked data. For the purpose of the present, exploratory study, data analysis reflected the most sensitive waveforms, i.e. stimulus-locked.

Figure 23. Right Fish Grand Averages obtained from one child. The vertical line represents time 0, when the fish appeared. The waveform between time 0 is the baseline. The waveform after time 0 is of interest to the analysis [3]

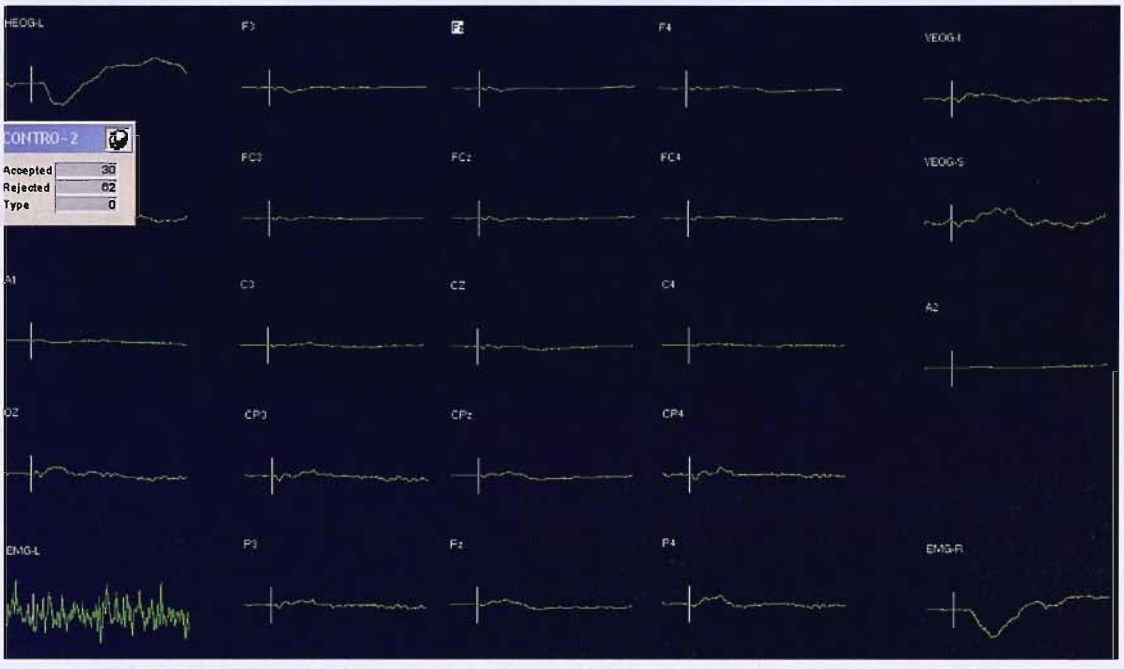
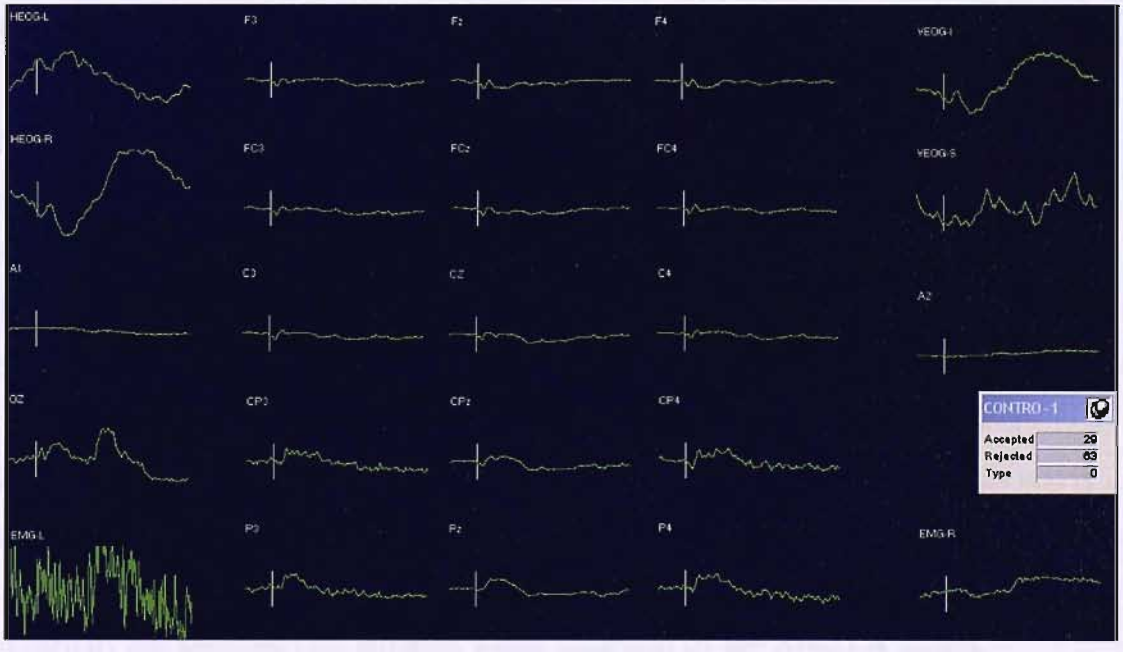


Figure 24. Left Fish Grand Averages obtained from the same child



[3] Attempts were made to record EMG response from the biceps. However, a clean EMG trace was not obtained from all children due to technical issues. This is reflected in Figures 23, 24, EMG-L/ EMG-R.

7.2.6 Experimental procedure

The ERP study took place between October 2005 and May 2007. Following informed consent, children were asked to participate only in one session, as described above. A skin test was performed for all children in order to test for allergy to gels. Itching or redness would not be conducive with the participant continuing. If a child found the leads intolerable, the leads were removed. Only one child did not want to cooperate and, despite his parents consent, the child was excluded from the study. The assessments were conducted in the ERP Laboratory of the School of Psychology, at the University of Southampton.

A debrief form (Appendix 11) describing the experiment and what we were hoping to find was given to parents after their appointment. This form also described our reasons for not providing individual feedback: individual ERP waveforms are not meaningful and this study was exploratory in nature.

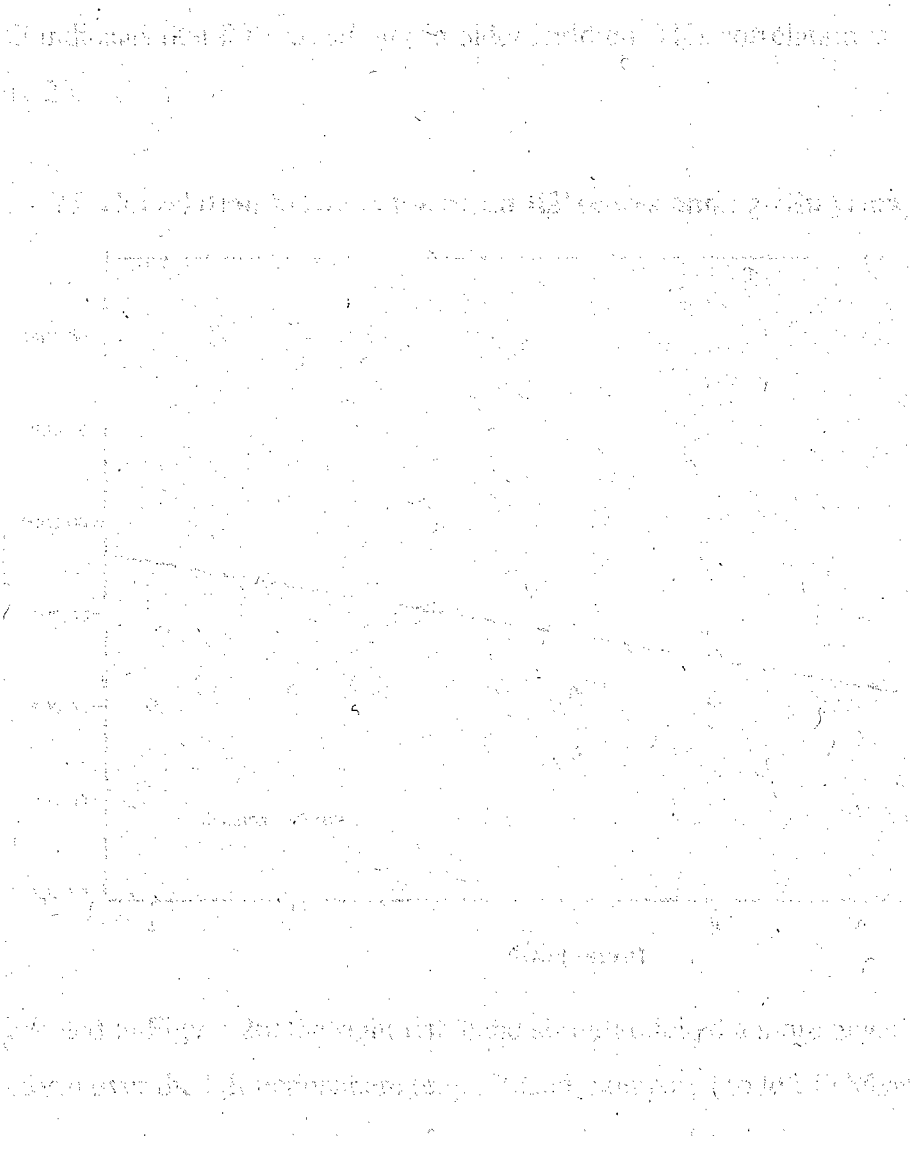
7.2.7 Data analysis plan

Behavioural and ERP (area score) data were obtained for each child, entered into SPSS and analysed.

1. Behavioural Data: The percentage of correct and error trials, as well as the mean reaction times (RT) were calculated for each child. The non-parametric Spearman's Rho (R_s) test was used to correlate age with percentage of correct trials and mean RT. The Mann-Whitney U test was used to compare behavioural measures between controls and CP children, due to the uneven group sizes.

2. ERP Data. The Shapiro-Wilk test was used to explore area score data as this test is appropriate for small samples (<50). The majority of leads (area scores) met the criterion for parametric analysis, but Greenhouse-Geisser corrected values ($F_{GG;}$ sphericity not assumed) are reported where indicated by the ANOVA model. Repeated measures ANOVA (rANOVA) was used for a simultaneous analysis of all data with within-subjects factors: condition (x2: left fish/hand stimuli, right fish/hand stimuli), location (x3: prefrontal cortex, premotor cortex {FC3, FC4}, motor cortex {C3, C4}), and side (x2: left hemisphere {F3, FC3, C3}, right hemisphere {F4, FC4, C4}. Significant effects ($p<.05$) and trends approaching significance ($p<.09$) are

reported. The rANOVA model was run for control data only in respect of the first hypothesis, namely that waveforms (area scores) would differentiate according to the responding hand. All the syntaxes and results of the study are included in CD1.

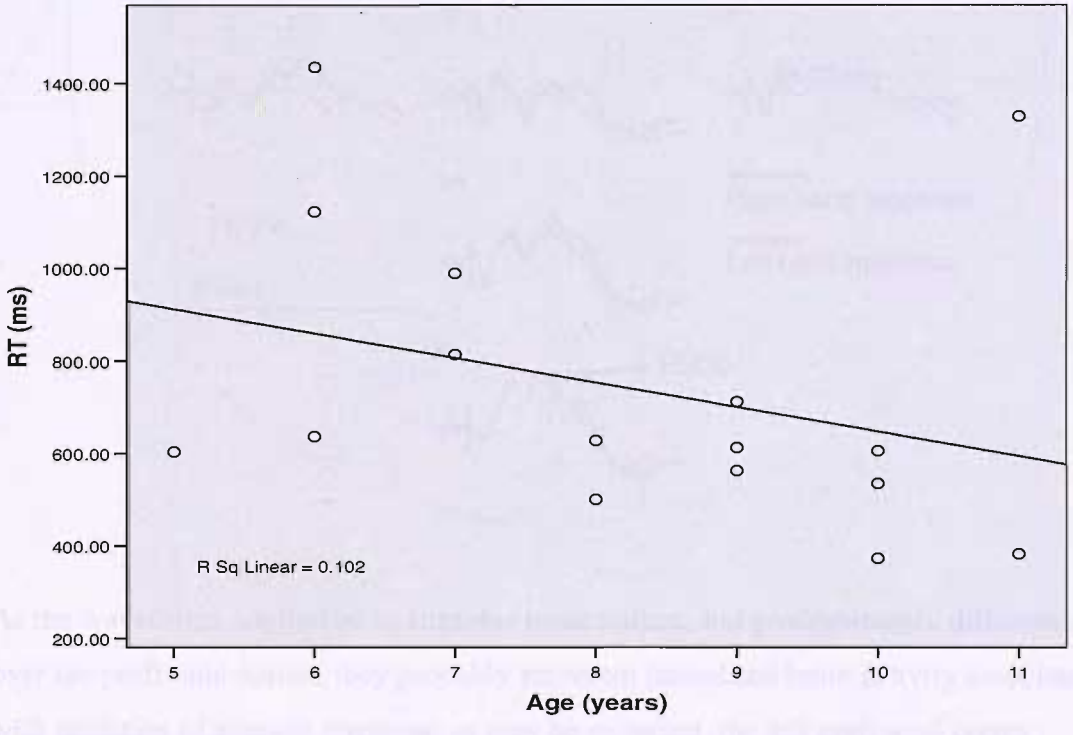


7.3 RESULTS

7.3.1. Normative Data from Control Children

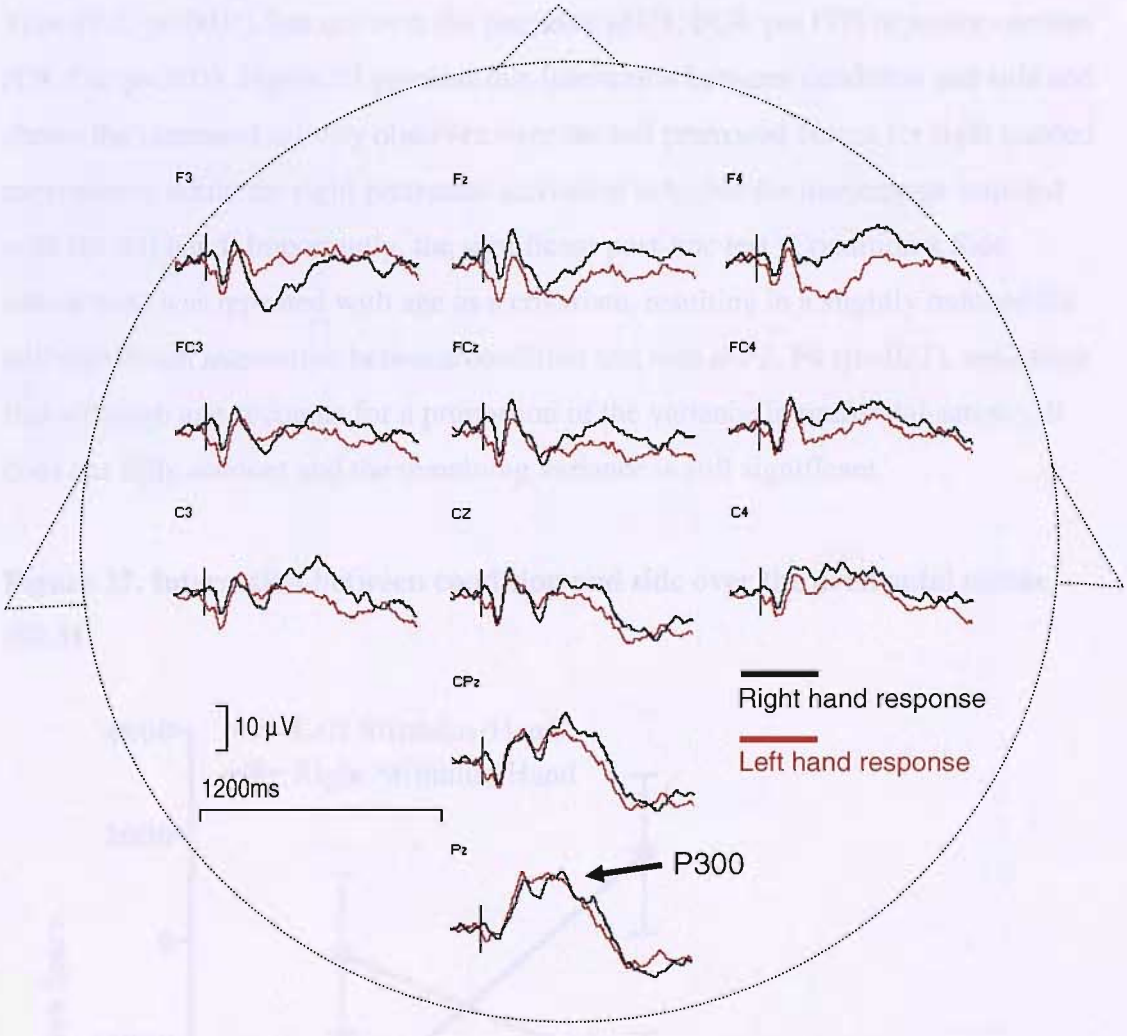
Out of the 13 controls, one child's data were corrupted, leaving 12 children in the control group. The median % of correct trials was 100 (range 92-100%); and the median RT for correct trials was 608.1ms (range 372.3-1434.3). A Spearman's test showed that there was no correlation between the percentage of correct trials and age (n=12, R_s= .246, two-tailed, p= .441), suggesting that younger children did not find the test more difficult than older children. However, the RT for correct trials was found to be negatively correlated with age (n=12, R_s= -.714, two-tailed, p= .009), which indicates that RT was shorter in older children. This correlation is shown in Figure 25.

Figure 25. Correlation between the mean RT scores and age (in years)



As revealed in Figure 26, the right fish/hand stimuli elicited a more negative waveform over the left hemisphere (e.g. F3 lead) compared to left fish/hand stimuli. The opposite pattern of activity was found over the right hemisphere.

Figure 26. Average waveforms obtained from 12 control children. The black line represents a response by the right hand (right pointing fish stimulus) and the red line represents a response by the left hand (left pointing fish stimulus). The waveforms are locked to stimulus presentation; the vertical bar represents the time at which the fish appeared on the screen. Negative is down.

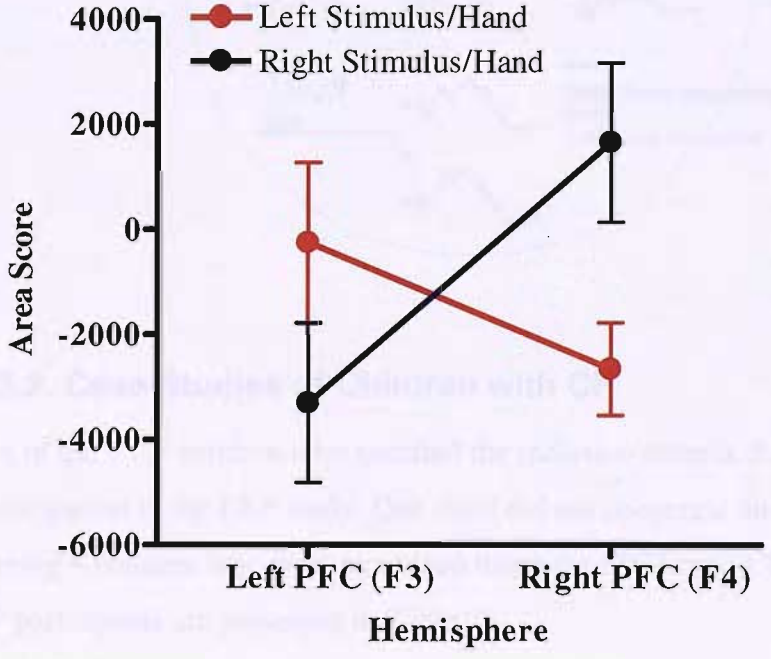


As the waveforms are locked to stimulus presentation, and predominantly differentiate over the prefrontal cortex, they probably represent lateralised brain activity associated with initiation of a motor response; as may be expected, the left prefrontal cortex showed greater activity associated with initiation of right hand responses and the right prefrontal cortex showed greater activity associated with initiation of left hand responses (Figure 27, 28). A P300 component is apparent over the midline (of greatest magnitude at CPz and Pz). This component was not formally assessed, but a lack of

apparent P300 differentiation indicates comparable sensory and cognitive processing of stimuli, irrespective of stimulus-type (left / right pointing fish).

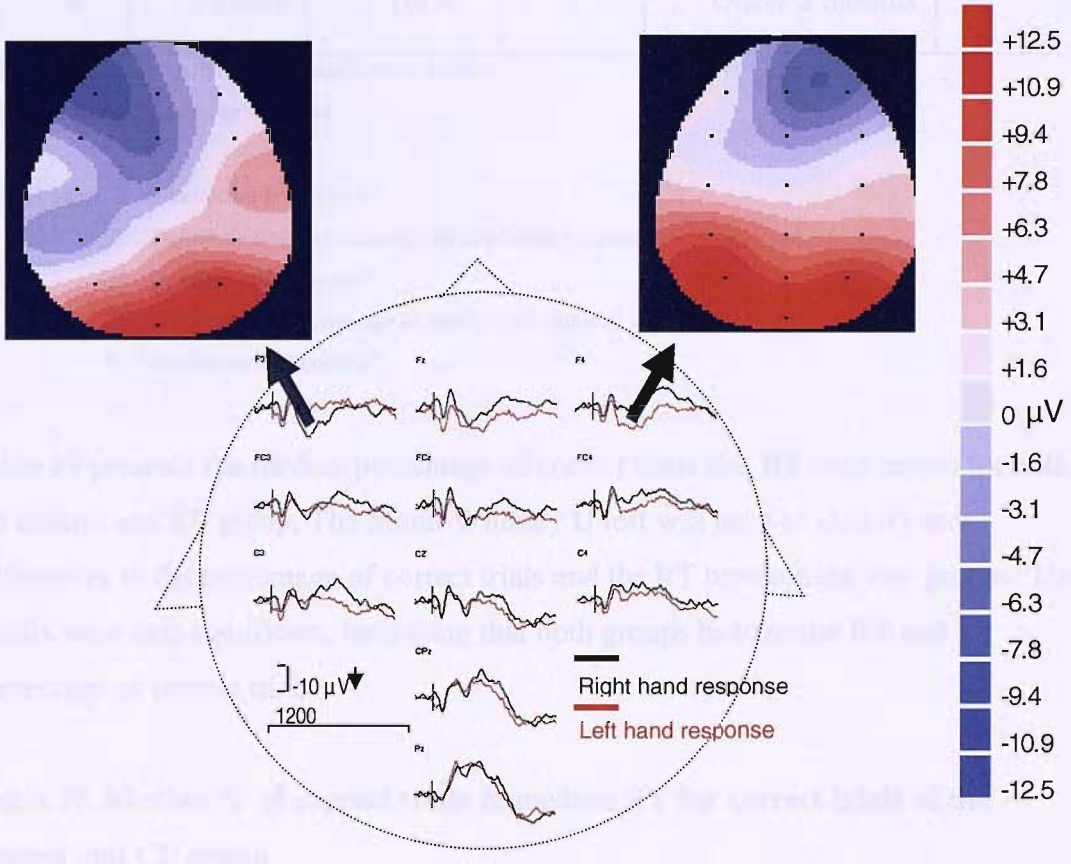
An interaction was revealed between condition, location and side ($F(2, 22) = 28.0$, $p < .001$). Post-hoc tests revealed that the waveform-differentiation according to condition was significant over the prefrontal cortex (F3, F4) (Condition x Side: $F(1, 11) = 19.2$, $p = .001$:), but not over the premotor (FC3, FC4: $p = .177$) or motor cortices (C3, C4: $p = .703$). Figure 27 presents this interaction between condition and side and shows the increased activity observed over the left prefrontal cortex for right handed movements, while the right prefrontal activation is higher for movements initiated with the left hand. Importantly, the significant post-hoc test (Condition x Side interaction) was repeated with age as a covariate, resulting in a slightly reduced but still significant interaction between condition and side at F3, F4 ($p = .021$), indicating that although age accounts for a proportion of the variance in prefrontal activity, it does not fully account and the remaining variance is still significant.

Figure 27. Interaction between condition and side over the prefrontal cortex (SEM)



The topographical maps in Figure 28 support the statistical analyses, demonstrating greater negative activity over the left prefrontal cortex for right fish/hand responses, and greater negative activity over the right prefrontal cortex for left fish/hand responses.

Figure 28. Topographic maps indicating focus of brain activity over the left lateral prefrontal cortex for right fish/hand responses, and over the right prefrontal cortex for left fish/hand responses



7.3.2. Case Studies of Children with CP

Out of the 7 CP children who satisfied the inclusion criteria, 5 expressed interest in participation in the ERP study. One child did not cooperate during the assessment, leaving 4 children who were examined using the FISH task. Characteristics of the 4 CP participants are presented in Table 28.

Table 28. Characteristics of the CP participants

Child ID	Sex	Age (years/ months)	GMFCS level	Regular treatment	Grade according to CPM *
1	Male	(7/ 10)	2	Once/ 3 months	II^+
2	Male	(11/ 0)	2	Once/ term	II^+
3	Male	(7/ 3)	1	Once/ 3 months	III^+
4	Female	(6/ 8)	1	Once/ 2 months	III^+

GMFCS: Gross Motor Function Classification System

CPM: Coloured Progressive Matrices

CPM Grades: *I: "Intellectually superior"*

II: "Definitely above the average in intellectual capacity"

III: "Intellectually average"

IV: "Definitely below average in intellectual capacity"

V: "Intellectually impaired"

Table 29 presents the median percentage of correct trials and RT (and range) for both the control and CP group. The Mann-Whitney U test was used to identify any differences in the percentage of correct trials and the RT between the two groups. The results were non-significant, indicating that both groups had similar RT and percentage of correct trials.

Table 29. Median % of correct trials & median RT for correct trials of the control and CP group

	Control group (n=12)	CP group (n=4)	Mann-Whitney
% correct trials (min-max)	100 (92-100)	100 (99-100)	P= .442
RT correct trials (min-max)	608.1 (372.3-1434.3)	879.06 (499.6-1328.4)	P= .332

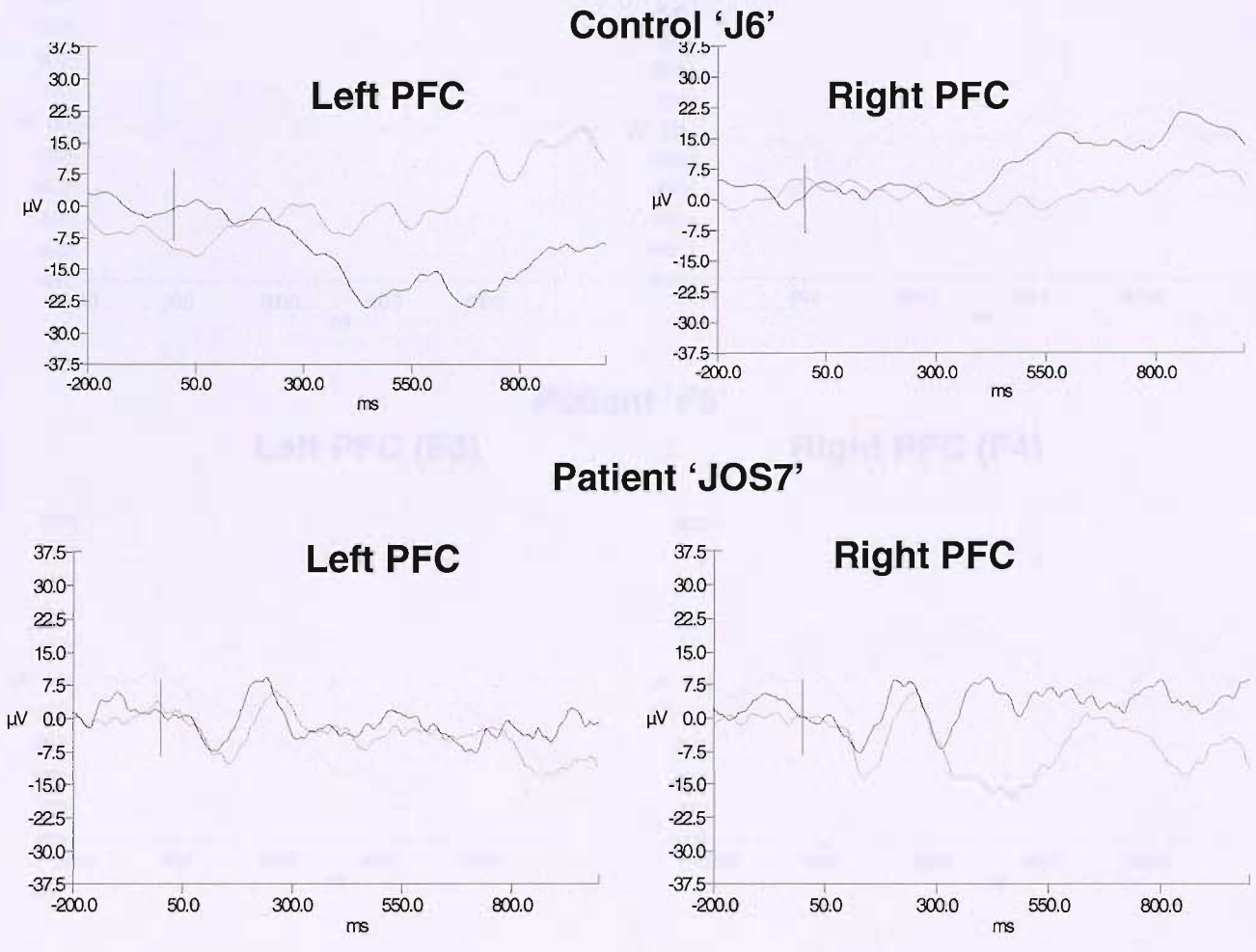
Due to the small number of CP children studied, and a difficulty in obtaining a sufficient number of trials (particularly from stimuli associated with the hemiparetic

hand), it was not possible to directly compare control and patient groups ERP data statistically. In addition, data obtained from one child with CP were insufficient to produce a reasonable figure. However, it was possible to assign the remaining three CP children a control of similar age in order to produce three case dyad study figures.

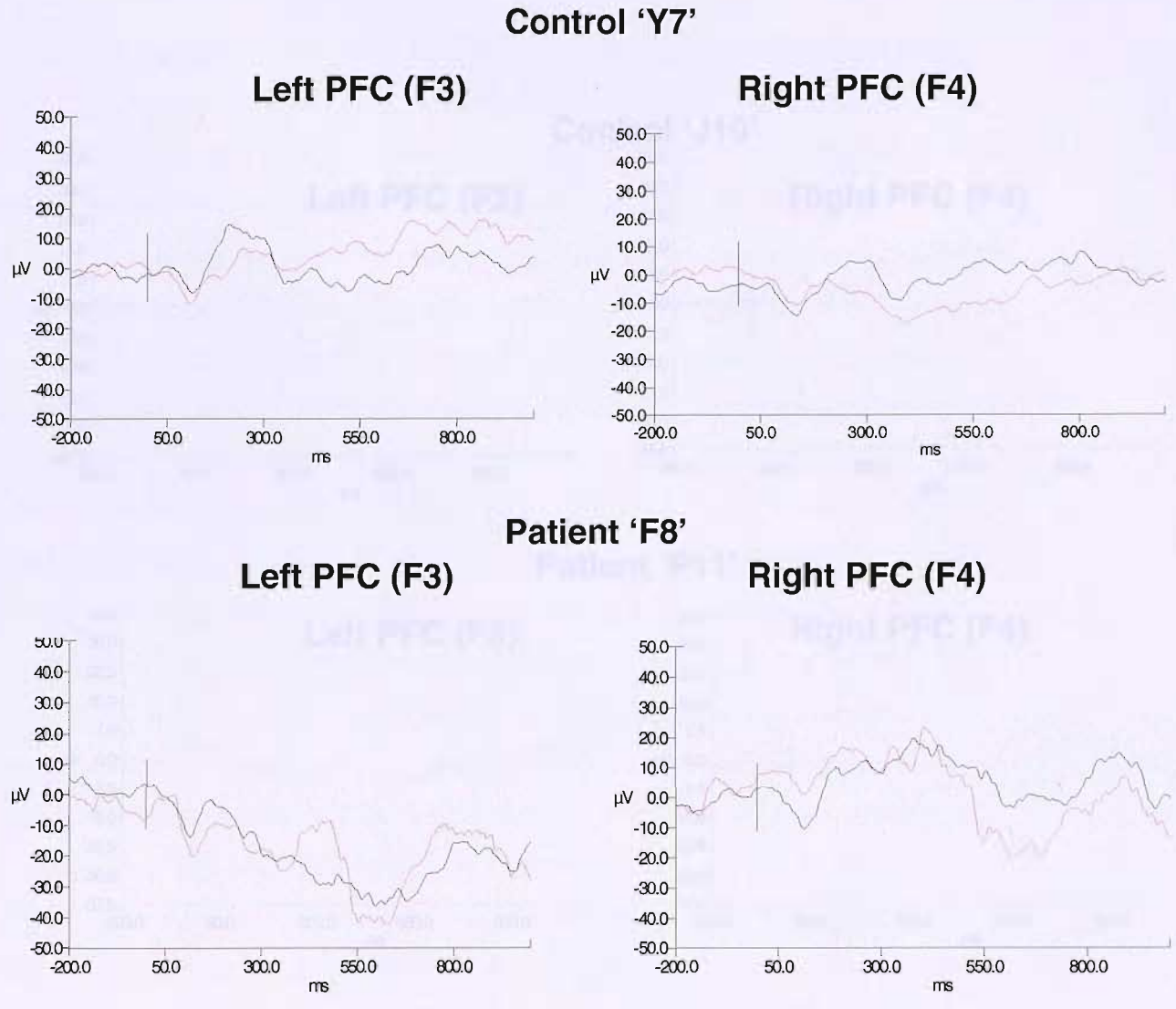
A lack of differentiation between waveforms in CP children can be observed in 2 of the 3 examples given below (Figure 29). Patient 'JOS7' and 'F8' had a left hemiplegia consistent with right hemisphere brain damage. Interestingly though, a degree of waveform-differentiation is evident over their right prefrontal cortex, but not over the left prefrontal cortex (Figure 29a & 29b). Patient 'P11', who was the most severely affected child included in the study did not show waveform differentiation on either side, despite paresis confined to the right hand (Figure 29c). While these three cases appear contrary to what may have been expected based on the normative data, it is important to acknowledge that individual ERP waveforms are rarely analysed, and it is only by averaging together the waveforms from a number of children with the same type of hemiparesis (left vs. right) that true effects may emerge. In this respect, further study is required to confirm the importance of the FISH ERP paradigm in the investigation of children with CP.

Figure 29. Individual waveforms of 3 children with CP and their age-matched controls

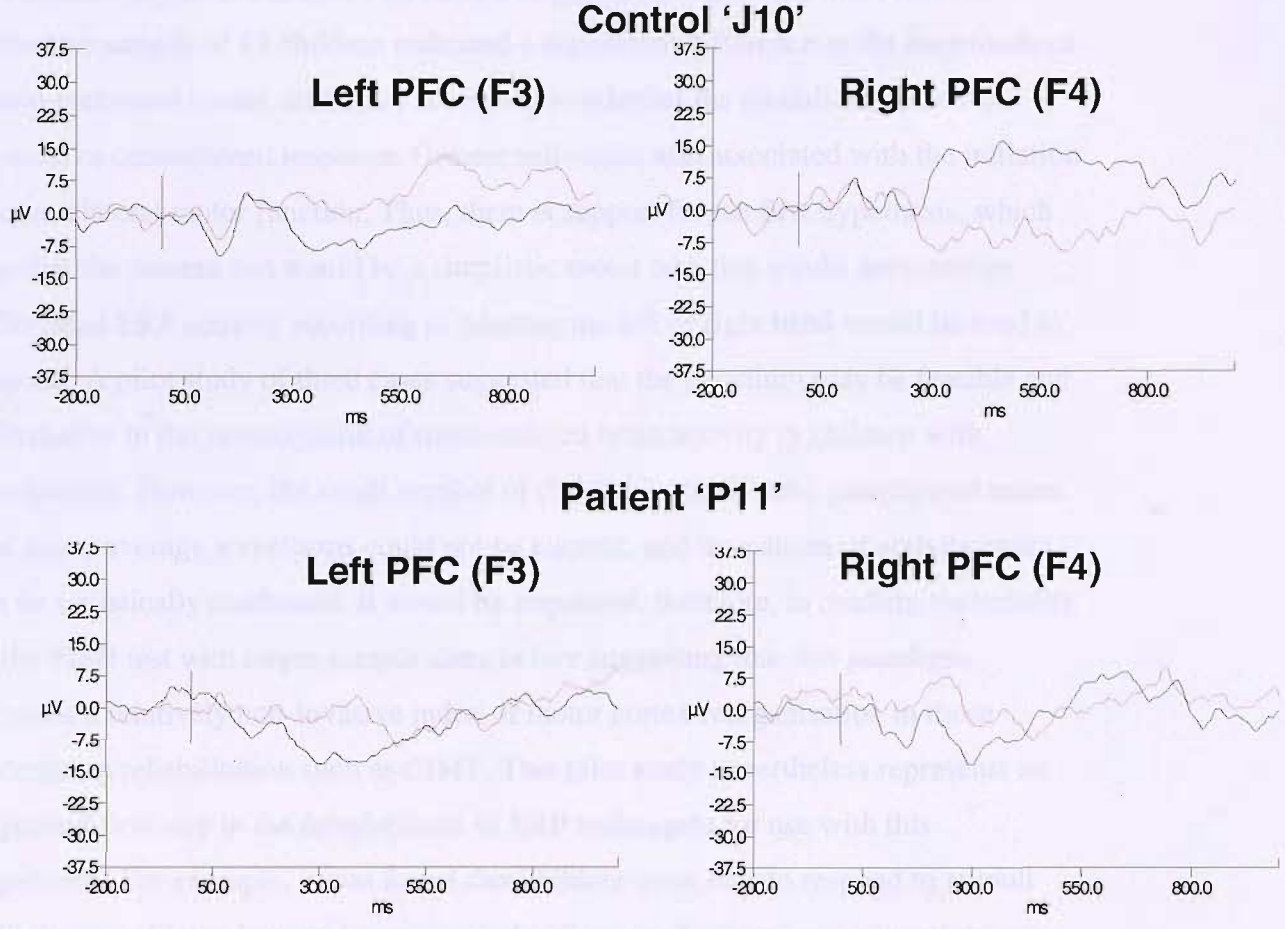
(a) 7 year-old boy with left hemiplegia (Jos7) and control (J6)



(b) 8 year-old boy with left hemiplegia (F8) and control (Y7)



(c) 11 year-old boy with right hemiplegia (P11) and control (J10)



7.4 DISCUSSION

A task was designed to elicit brain activity associated with premotor / motor initiation of a hand response in a simple two-choice response task. Data obtained from a normative sample of 12 children indicated a significant difference in the magnitude of lateral prefrontal cortex activation according to whether the stimuli instructed an ipsiteral or contralateral response. Greater activation was associated with the initiation of contralateral motor function. Thus, there is support for the first hypothesis, which was that the present test would be a simplistic motor task that would demonstrate differential ERP activity according to whether the left or right hand would be used to respond. A pilot study of three cases suggested that the paradigm may be feasible and informative in the investigation of motor-related brain activity in children with hemiparesis. However, the small number of children with CP who participated meant that grand average waveforms could not be elicited, and the pattern of activity could not be statistically confirmed. It would be important, therefore, to confirm the validity of the FISH test with larger sample sizes before suggesting that this paradigm provides a relatively non-invasive index of motor cortex reorganisation in those undergoing rehabilitation such as CIMT. This pilot study nevertheless represents an important first step in the development of ERP techniques for use with this population. For example, it was found that children were able to respond to stimuli with the use of large buttons (approximately 10 cm in diameter) and when there was no constraint of time, i.e. the fish remained on screen until the child had responded. This methodology allowed children with CP to demonstrate statistically equivalent error rates and response times to controls, suggesting that any brain wave differences elicited by the task are not due to physical disability per se.

In general, when examining ERP waveforms in wide age-ranges of children it is important to ensure that all children understand the task. The normative sample indicated that the task was appropriate for all ages assessed, indicating that the child's age and cognitive level did not influence ERP activity. Older children showed shorter RT, which could be expected as it is known that white matter, which facilitates speed of response, continues to develop until approximately the age of 20 (Casey et al., 2000, Mabbott et al., 2006). It would be important in future studies to investigate the response-locked ERP waveforms as well as the stimulus-locked waveforms, as this

will take into account RT variability. Indeed the lateralised readiness potential in adults is typically derived from the response-locked waveform, but less is known about the same motor potential in children, and other researchers have focused on stimulus-locked activity (Brandeis and Lehmann, 1986). Response-locked waveforms were examined in children in the present study, but found to be generally unclear and not particularly informative. In any case, the median response time was about 600ms in the normative sample and this was after the main component of interest had begun to deviate negatively. Thus, what is represented at these sites (prefrontal cortex) is likely to be brain activity associated with the initiation of a motor command. This may reflect lateralised readiness potential activity which, while normally associated with more posterior C3 and C4 activity in adults, may rely on a slightly different topography in children in whom selective brain circuits are still developing. The administration of this FISH task to adults would be important to confirm that possibility. In the meantime, it is safest to conclude that this task simply reflects differentiation of waveforms according to lateralization of function, without directly associating such activity with adult ERP nomenclature.

Importantly, as the P300 (associated with more cognitive/ memory updating) waveform at the midline was present and appeared normal for both types of response, it may be considered that the waveform differentiation over the prefrontal cortex represented brain processes associated with initiating a motor response, not dealing with the cognitive aspects of the task per se. This is also supported by the fact that RT and understanding of the task were similar between controls and CP children.

In summary, this FISH ERP test can be considered to show motor circuit differentiation according to lateralization of response in normally developing children. This is reflective of the way the brain initiates a motor response. Waveform differentiation in the CP children would be expected to appear reversed, i.e. lack of differentiation in the affected hemisphere. Although our observations do not support this hypothesis, the small number of children described herein and the pilot nature of this study does not allow for any conclusions to be made. Suffice to suggest that this task is feasible in children with CP, and that there may be some benefit in its further development and administration to larger groups of children with CP. However, to reach a point where LRP recordings could be used to test the physiological effects of

CIMT or other therapeutic treatment in children with CP requires a lot of further development and testing of the paradigm suggested in this study. Moreover, investigation using a controlled design is needed to examine what kind of LPR changes, if any could be translated as cortical reorganization.

CHAPTER 8

DISCUSSION

8.1 SUMMARY OF FINDINGS

This project was designed to investigate CIMT in children with hemiplegic CP. The effectiveness of CIMT, mainly in adults after stroke has been supported by several experimental, observational and brain imaging studies. However, this treatment method remains difficult to be incorporated into clinical practice due to practical issues. Page et al (2002a) revealed that many adult stroke patients and therapists would not be keen in participating in CIMT because of the intensity of the practice and restraint schedule. This is the reason that different modified protocols have been suggested with the modified version by Page et al (2002c) being the most well researched. In children, who are usually less motivated than adults, adherence to such an intensive regimen as the adult CIMT protocol is even more difficult. DeLuca et al (2006), who developed the paediatric CIMT protocol encouraged researchers to investigate whether reduced treatment hours and a more 'child-friendly' protocol could be effective. Thus, the aim of this study was to identify a practical, yet effective protocol to be used with children with hemiplegic CP.

8.1.1 The feasibility study

The literature shows a variety of restraints used with children. Although the type of restraint is recognised to be extremely important as it affects comfort, adherence and consequently treatment intensity (Gordon et al., 2005), in most cases researchers have failed to justify their choice of a specific restraint. The feasibility study was conducted in order to explore different constraints that have been used so far and identify the most appropriate from children and parents' perspective as reflected by effectiveness and adherence to home-based FUT. This study also provided guidance for the development of a practical home-based protocol that was later tested for effectiveness in the subsequent study. Nine children wore three restraining devices for a minimum of 1 hour/ day and as long as they could cooperate and feel comfortable with it. Each device was tested for 4 days. The amount of time that children would wear each splint

as well as the degree of involvement in functional activities with each restraint was considered indicative of the appropriateness of each device. The results showed that the short splint was more effectively restraining and more acceptable by children and their parents compared to the mitten that was getting too warm after some time and created adherence problems as it was easily removed by children. Children found the long splint uncomfortable, while parents expressed concerns about their children's safety and protective reactions while wearing it. None of the parents considered the long splint to be appropriate for their child, while 6 out of the 8 parents would not consent to their child's participation in CIMT if the long splint was to be used. As this study investigated the appropriateness of different splints in the home environment, the most appropriate constraint might be different in another setting, i.e. in the clinic where children would have constant supervision and receive more attention and might be more motivated.

Despite the fact that the intervention included only 1 hour daily wearing of the splints for 12 days, some parents found it to be too demanding in terms of their time, raising questions as to how practical could the classic paediatric CIMT protocol be considered, requiring 6 hours of daily exercise for 3 weeks. Completion of the minimum requirement of 1 hour-wearing was a common reason that the splints were removed, indicating that the children would hardly accept any splint for many hours per day. A modified CIMT protocol was considered more appropriate compared to FUT, as the functional activities were expected to result in increased attention to and motivation of the child but also because functional use of the affected limb has been shown to be necessary for therapy to be effective (Classen et al., 1998, Nudo et al., 1996a).

8.1.2 The effectiveness study

The feasibility study identified the need for an intervention that would include few hours of daily restriction. Studies (Donovan and Radosevich, 1999, Moulton et al., 2006) have shown that the same amount of practice distributed over a longer training period results in significantly better skill acquisition. A similar concept has been followed in the development of modified versions of CIMT either for adults (Page et al., 2004) or children (Eliasson et al., 2005, Gordon et al., 2007).

The effectiveness study aimed to explore the functional effects of a modified protocol of CIMT and examine whether there would be an additional benefit when the constraint was combined with functional activities and feedback compared to the use of the constraint only. Two interventions were therefore tested; mCIMT and mCIMT^{+}, each of which lasted for one month. During both interventions, children were required to wear the constraint for 2 hours/day and gradually increase the time the constraint was worn to reach 3 hours after the first week and maintain it for the subsequent three. In mCIMT functional practice was not required in contrast to the second intervention, mCIMT^{+}, in which children were encouraged to participate in specific functional activities that were appropriate and interesting for each child. In mCIMT^{+} a PC game was also included that required unilateral manipulation of a joystick. At the end of the game a coloured bar and motivational cues were displayed on the screen showing to children how much they moved their affected hand and encouraging them to keep trying. All the children participated in the two interventions in the same order as mCIMT^{+} was expected to be at least as effective as mCIMT. Despite the instructions to follow a forced-use regimen during mCIMT, parents engaged their children in functional activities, such as brushing teeth/ hair, eating finger food, getting dressed and playing with toys or computer games during both interventions. The use of activities was reported to be the only way to keep the children motivated and away from attempts to take the splint off.

Although the average splint-wearing time was approximately 80 minutes daily, both functional measures showed significant improvements, which were retained at the 1-month follow-up for the Melbourne Assessment. This confirms the findings of Eliasson et al (2005) and Naylor and Bower (2005), who showed improvements after modified interventions that included few hours of daily restriction and exercise distributed over a period of 2 and 1 month, respectively. What is most supportive of the effectiveness of this distributed form of CIMT though, is the fact that the degree of improvements in QUEST in the present study was found to be similar to the one shown by DeLuca et al (2006) after testing the classic paediatric CIMT protocol. With regard to the second objective of this study, improvements after mCIMT, as measured by the two functional tests became even larger after mCIMT^{+} (Mean Melbourne score

after mCIMT/ after mCIMT^{+}: 69/ 76, Mean QUEST score after mCIMT/ mCIMT^{+}: 77/ 78) but the reason for this is unknown. Children were engaged in functional activities in both interventions but several other factors, like the feedback given, the extended period of intervention and the increased adherence may have been the reason for the additional improvements.

Poor recruitment was one of the biggest problems throughout the study. Therapists had expressed concerns about the time required by families and children to take part in a CIMT intervention. Some parents expressed their doubts regarding the effectiveness of this treatment, while others believed that this intervention might have had negative effect on their child's condition. Examining the reasons for poor recruitment from both parents and therapists' point of view and their opinions on CIMT was considered important in the development of a practical paediatric CIMT protocol.

8.1.3 The survey

The survey was designed to address the issue of poor recruitment that was obvious in both studies of this project. The aim was to explore parents and paediatric therapists' views on various aspects of CIMT, which would provide guidance in the development of a more practical protocol. The low response rate from the parents' survey does not allow any conclusions but the fact that 4 out of the 5 parents explained that the main reason for not taking part in the CIMT study was that their children were unwilling to is indicative of the need to explore different aspects in order to develop a child-friendly regimen.

Out of the 81 therapists who had heard about CIMT, 66 replied that they would recommend CIMT to their patients. However, 78% of therapists considered the classic paediatric protocol to be impractical in contrast to the distributed form suggested in the present study. Confirming the findings of the main study, therapists replied that the two protocols would be equally likely to improve children's upper limb function.

8.1.4 The LRP study

Brain imaging studies have provided support for the effectiveness of CIMT in adults by presenting evidence of cortical reorganisation (Johansen-Berg et al., 2002, Liepert et al., 1998, Szaflarski et al., 2006). In children, this research area is yet at an early stage (Juenger et al., 2007, Sutcliffe et al., 2007), perhaps due to lack of 'child-friendly' techniques. The aim of this study was to develop an ERP test that elicits lateralised waveform differentiation across a wide age-range of healthy children and to explore the feasibility of using this test with children with hemiplegic CP.

In cooperation with an ERP specialist, a paradigm measuring the LRP component of the EEG was developed and tested with 13 unimpaired children and 4 children with hemiplegic CP that were recruited from the main study cohort. Children were asked to participate in a game in which they saw a fish swimming to the left or to the right and were asked to press the big button by their left hand when the fish was swimming towards the left, and the big button by their right hand when the fish was swimming towards the right.

In support of the first objective of the study, the simple motor task used demonstrated differential ERP activity according to lateralisation of response in healthy children, thus reflecting the way the brain initiates a motor response. The small number of children with CP that participated did not allow for a pattern of activity to be confirmed. However, the test was found to be feasible in children with hemiplegia, who were able to respond to stimuli with the use of large buttons and when there was no constraint of time. Children with CP demonstrated equivalent error rates and response times to unimpaired children, suggesting that any brain wave differences elicited by the task should not be considered to be due to physical disability per se.

8.2 CLINICAL RELEVANCE

CIMT might be a valuable intervention in the management of children with CP, bearing in mind that the most commonly used movement therapy for this population is NDT. NDT is centred on specific handling techniques aimed at decreasing abnormal muscle tone and facilitating normal movement pattern and reflexes. NDT focuses more on practicing isolated movements than functional skills. It was assumed that

NDT would lead to functional gains but the lack of scientific support is recognised for more than a decade now (Barry, 2001). Recent findings suggest a more functional approach in the field of rehabilitation (Dromerick et al., 2006, Krigger, 2006) and CIMT follows this notion.

Brain imaging studies (Liu and Rouiller, 1999, Nudo et al., 1996a) have shown that practice is a critical factor that influences skill acquisition. The present study cannot provide any support for the importance of exercise in the degree of functional improvements, as children were engaged in activities during both interventions. However, parental reports that activities were found to be the only way to keep the children away from attempts to take the splint off, confirms the importance of using interesting and age-appropriate activities in order to increase children's motivation. For this reason, FUT that includes only the constraint without additional practice might not be an appropriate option for young children. The distributed form of intervention tested here showed improvements similar to intensive protocols but this study also revealed that this form of therapy is preferable by parents, children and therapists. A home-based intervention offers a more practical option but also easier transfer of gained skills to everyday life (Pickett et al., 2007, Sterr and Saunders, 2006). Weekly supervisions by the therapist might help to eliminate any problems and provide support to children and families. In both studies it was evident that children and parents needed some encouragement to go on with the intervention; this points out the importance of a multidisciplinary team, at least when CIMT is applied in the clinic.

Despite the significantly reduced intensity of the intervention tested here compared to the classic paediatric protocol, poor recruitment may be indicative of the practical issues related with CIMT. This treatment is time-consuming for parents and children, requires a high level of motivation and the use of the constraint might cause great frustration to children and families. Further research is required to explore ways to make this intervention more acceptable by parents and children before it becomes clinically available. However, with some parents the reasons for not taking part in CIMT might be related to the lack of knowledge regarding this treatment technique. This is the case of at least one parent who was reluctant for her child to participate in CIMT as she was concerned that this intervention might have had negative effect on

the child's normal development. What is more critical though is therapists' lack of knowledge on CIMT. Findings from the survey revealed that a large proportion (41%) of therapists has never heard of CIMT, while from those that have, 74% know only little about this treatment. The percentage of occupational therapists who have never heard of it is much larger (45%) than the one of physiotherapists (29%) despite the fact that upper limb interventions would traditionally be of more interest to occupational therapists. Due to this lack of knowledge on CIMT, therapists are unable to inform and guide their patients on the advantages and disadvantages of this treatment technique. Thus, it is not surprising that 7 out of the 15 therapists, who would not recommend CIMT to their patients explained that the reason is the insufficient knowledge they have regarding this intervention. Educating therapists on CIMT through seminars, study days and practice sessions is crucial in order to create a bridge between research and clinical application of this treatment.

8.3 LIMITATIONS

The most important weakness of this project is the small sample number in both the main studies and the parents' survey. Despite the efforts, participants were fewer than what we aimed for and thus, robust conclusions cannot be reached. The parents' survey was conducted in order to investigate the reasons for poor recruitment but due to the low response rate, this could not be adequately explored. In both the parents and therapists' survey a more in-depth investigation, perhaps including focus groups would provide a more thorough picture of the different views and thus, would offer a better guidance in the development of a more practical protocol. The present project can only be considered to give an indication of the potential feasibility and effectiveness of this home-based, modified CIMT protocol but a larger study would be required before the findings can be considered to be generalisable to the population of children with hemiplegic CP. Suggestions for such a study are given in the following subsection.

One could argue that the 4 days used to test each splint in the feasibility study might have not been enough to properly explore the appropriateness of each constraint. However, keeping in mind the adherence issue, it was considered to be indicative of children's response and parental views. The wide age range of the sample and the difference in functional level between participants might have affected the results, as

it is possible that the appropriate constraint for younger or higher functioning children might be different compared to older or lower functioning ones. It was shown though that in general the long splint would create safety problems if used at home, which is probably the reason why none of the researchers have used it during the home-restraint hours. The mitten might not have created adherence problems to older and more motivated children but it does become warm and sweaty after some time.

Despite the advantages of the repeated measures design, the repeated application of a measure might be expected to have a learning effect. In the effectiveness study all the participants took part first in mCIMT and then in mCIMT$^+$ as the second intervention was considered to be at least as effective as the first one but the addition of feedback, increased adherence and the extra time of intervention were also factors that could account for the additional functional improvements that were observed. A control group would be needed to clarify these issues, while randomization of the participants to receive either mCIMT or mCIMT$^+$ first would be helpful in distinguishing between order and intervention effects. The addition of multiple baseline measurements at equal intervals until plateau would increase reliability as to whether the improvements observed were clearly due to treatment. Although most of the improvements in this study were retained at the follow-up, one month cannot imply long-lasting effects.

The measures used in this study provided a thorough picture of the effects of each intervention. However, the questionnaire used to explore the family's experience and opinion on the different splints was only completed by the parents and it may be possible that children's views were not reflected. Thus, in a future study it might be more informative if a specially designed questionnaire was included to investigate children's opinions. This would probably be feasible and reliable for children over 7 years old. Analysis of the video recordings and the actometers were found to have some limitations. The report form used to analyse the videotape recordings was shown to have low inter-rater reliability for one of the categories and thus, further development would be required if this measure was to be used again. Actometers were used to provide an indication of the actual amount of use of the affected hand. Other activity monitors are available (i.e gyroscopes) but their use is mainly restricted to gross motor function, such as walking (Luinge and Veltink, 2005, Tong and Granat, 1999, Uswatte et al., 2000). The reliability and validity of the actometer though is

questionable especially when used to measure children's amount of UL use at home. Despite the fact that actometers were chosen over accelerometers because they are usually well accepted by young children and easier to use by parents at home, all children did not accept the actometer well, while some parents were puzzled about proper reporting of the recordings.

8.4 FURTHER RESEARCH

Refinements of the splint could improve adherence; in particular a mesh covering the top of the hand and arm might be an important modification that would prevent children from 'cheating', using their fingers through the Velcros or elastic suspenders.

Further investigation in the parental views on CIMT is considered appropriate and has been initiated at the School of Health Sciences of the University of Southampton to provide insight as to what should be considered a 'child-friendly' protocol that is feasible for children and parents to participate in. Exploration of therapists' views could be taken further by including a deeper investigation (perhaps with the use of focus groups) into the views of those therapists that have a good level of knowledge on CIMT.

8.4.1 Randomised controlled trial

The effectiveness of the modified CIMT protocol designed in this study should be further explored in a randomised controlled trial (RCT). Experience from the present project indicates that a multi-centre study would probably be required in order to get a sufficient number of participants. Engagement of a large 'working group' of paediatricians and therapists in the recruitment, design and administration of the intervention would help to ensure feasibility of the protocol. In the survey, 8 therapists were found to have used CIMT in the past. The 'working group' of clinicians could be formed by such clinicians that already have some knowledge and experience in the technique. It would be expected that these therapists would probably be more interested in participating in a CIMT trial, which would give them the opportunity to work out problems that they have identified themselves while using CIMT with their patients.

To estimate the approximate sample size that would be required in an RCT for the results to be reliable and generalisable, a power calculation was performed. The test that was used is available at the following web page: www.stat.ubc.ca/~rollin/stats/ssize/n2.html. To perform the 2-sided test, the desired power was set at 90% and the alpha (p) at 0.01. The scores of the Melbourne Assessment were used as this was the primary outcome measure. The two values that were compared were the Mean baseline score and the Mean follow-up score because these were considered to be indicative of the average functional change shown by the participants. The standard deviation (sigma) for this score difference was 5.7. The result of the test showed that 12 participants would be required in each group. Accepting a drop-out rate of 10%, a future RCT should aim to recruit approximately 30 participants. Judging from the nine participants that were recruited from 3 research sites in the present study, it would be estimated that 3 or 4 main research centres should be required in a future trial, while recruitment should include surrounding areas, too. The results of this small study in which participants were carefull selected and given a great deal of attention and support may have resulted in better outcome that might be expected in a large RCT. Therefore a power calculation was also performed assuming a less favourable effect size taking a mean change of 6 points in the Melbourne Assessment and a SD of 8 (mean change and SD in the present study were 9 and 5.7, respectively). With the power set at 80% and p=.05, the required sample size for each group was found to be 28.

The QUEST and especially the Melbourne Assessment were found to be appropriate and indicative measures of the effects of the intervention in each child. However, the AHA has been especially designed to test the hemiplegic upper limb's input in bilateral activities, which is the aim of CIMT and thus, this measure would be suggested to be used in a future study, if appropriate for the specific age group of the participants. The Manual Ability Classification System (MACS) would also be a valuable tool in a future research since it has been especially developed to report the collaboration of both hands together and classifies how children use their hands when handling objects in daily activities. MACS might provide valuable information regarding potential appropriate CIMT candidates. In order to understand the mechanisms through which CIMT affects the functional status of patients, it would be

useful to include supplementary measures in addition to the functional ones. Future studies should examine the feasibility and validity of the LRP paradigm with a larger sample of children with hemiplegic CP, as this test could potentially prove to be a 'child-friendly' measure that would provide physiological support for the effects of CIMT. Further research into the suggested paradigm is required to examine whether differential ERP activity is present in CP children just as in the healthy developing ones according to whether the left or right hand is used to respond. If this hypothesis is confirmed, research should then focus on identifying patterns of cortical reorganization associated with the LRP. Kinematic analysis, which has only recently been applied, could also prove useful by providing insights into the spatiotemporal control of movement and the way this is affected by CIMT.

The use of a control group would be necessary to investigate which factors may be the ones that make the intervention more effective and which ones played a role in the additional functional improvements that were observed after mCIMT^{+}. A controlled study would also be informative as to the variability in responses observed in the present and other studies (Bonnier et al., 2006, Eliasson et al., 2005, Nadeau and Wu, 2006) and the appropriate CIMT candidate. To be able to distinguish between order and intervention effects, randomization of the participants to receive either mCIMT or mCIMT^{+} first would be necessary. A multiple baseline period at equal intervals between all measurements is needed since variability between participants has been observed to be large in the present and other paediatric CIMT studies conducted to date.A multiple follow-up period would also be advisable in order to examine the long-lasting effects, if any, of the intervention protocols suggested by this study.

8.5 CONCLUSIONS

- A short splint extending from fingertips to the elbow was found to be the most effectively restraining, safe to be used in the home environment and preferable by children and parents.
- Findings from the feasibility study pointed to a distributed form of CIMT as the most practical option for a home-based intervention. A modified protocol was designed, comprising 2 hours of daily restriction for 2 months. Feedback was also added to increase motivation in the second half of the intervention.

- Although children were wearing the splint for approximately 80 minutes, significant functional improvementswere revealed comparable to intensive CIMT regimens that were retained at the 1-month follow-up.
- Poor recruitment was obvious in both parts of the main study. To understand the reasons for this, parents and therapists' views on CIMT were surveyed. Due to the small response rate, the parents' survey did not provide sufficient information. Therapists' views supported the findings of the main study by suggesting that the classic paediatric CIMT protocol could not be considered practical in contrast to the distributed version suggested in this study, which was also thought to be equally effective.
- To provide insight into the physiological effects of CIMT, a test using the LRP component of the EEG was developed and evaluated with a small sample of unimpaired children and children with CP. The paradigm tested was shown to elicit lateralised waveform differentiation in healthy children and to be feasible for use with children with hemiplegia. The potential usability of this paradigm as an index of cortical reorganisation has to be further explored.

APPENDICES

APPENDIX 1

QUESTIONNAIRES

UNIVERSITY OF
Southampton
School of Health Professions
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FEASIBILITY STUDY

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Date:
Questionnaire version no 1
R&D reference number: WHC 548

QUESTIONNAIRE

Thank you for taking part in this study and for completing this questionnaire.

This questionnaire has been designed to provide information about the different types of constraint that may be used in "forced use" therapy. Your answers will help us to identify if the restraining device (splint or glove-like mitt) was beneficial and whether it caused discomfort to your child or yourself. In this way we will be able to choose a device that is appropriate for children with hemiplegia (weakness or paralysis of one lateral half of the body).

Please take some time to answer the questions following the instructions carefully.

Please answer each question according to what you observed while your child was wearing the splint.

There are no right or wrong answers.

Please answer the following questions by ticking the box that most closely represents your opinion.

Please tick only one box for each question.

1. Did your child engage in play activities or functional tasks while wearing the constraint (splint or glove-like restraining mitt)?
   - ❑ More than usual
   - ❑ Just as much as usual
   - ❑ Less than usual
   - ❑ Not at all

2. To what extent did you have to encourage him/ her to do so?
   - ❑ Great encouragement
   - ❑ Some encouragement
   - ❑ Little encouragement
   - ❑ No encouragement

3. Did your child accept this type of constraint easily?
   - ❑ Very easily
   - ❑ Fairly easily
   - ❑ Reluctantly
   - ❑ Unable to accept it

4. Did your child become used to wearing the splint?
   - ❑ Yes, after the first day
   - ❑ Yes, after 2 days
   - ❑ No, they continued to be frustrated by the splint
   - ❑ No, they became more frustrated as the days passed by

5. How demanding was the constraint period in terms of your time?
   - ❑ Very demanding
   - ❑ Quite demanding
   - ❑ Not very demanding
   - ❑ Not demanding at all

In the following questions please add your comments as well as ticking the boxes.

6. Was the constraint easily removed by your child?
   - ❑ Yes
   - ❑ No

   o If yes, did this create adherence problems (for example, did your child keep taking it off)?
   - ❑ Yes (please explain)

   .....

   .....
   - ❑ No

7. Were there instances that you felt your child was at risk while wearing the constraint?
   - ❑ Yes
   - ❑ No

   o If yes, why did you feel this way?

.....

.....

8. Were there any complications (e.g. irritated skin) that you believe were due to the constraint?
   - ❑ Yes (please state what).....
   - ❑ No

9. Would you consent to your child's participation in a similar trial in which this type of constraint would be applied for a longer period?
   - ❑ Yes
   - ❑ No

   o If not, would you please explain why?

   .....

   .....

10. Which splint would you consider as the most appropriate if your child was to wear it for a longer period of time? Would you please explain why?

- ❑ Mitten
- ❑ Short splint
- ❑ Long splint

.....

.....

.....

Thank you for completing this questionnaire

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

SURVEY (PARENTS)

Date:
Parents' Questionnaire Version No 3

Modified constraint-induced movement therapy in children with congenital cerebral palsy: A survey.

(Parents' Information Sheet)

During the last year we have been conducting a study investigating a new treatment for children with hemiplegia called constraint-induced movement therapy (CIMT). Recruitment of participants for this study has now ended. During the study we became aware that some parents were reluctant for their children to take part and we would like to understand why this was.

We are asking you and other parents, who were invited to take part in the study, to answer a few questions about the study and constraint-induced movement therapy (CIMT). Your answers will help us understand why people are reluctant to use CIMT and may help us to find ways of making it more acceptable.

Please take your time and answer each question according to your personal view.

There are no 'right' or 'wrong' answers.

We would like to confirm that it is up to you to decide whether you want to participate in this survey. If you decide not to return the questionnaire, you will not be asked again. If you decide to take part, please complete the attached questionnaire and send it directly back to the researcher, using the pre-paid envelope that is enclosed. All data gathered from this study will be stored for 15 years either in a computer with a password (for electronic data) or in a locked filing cabinet (for paper records). Data will be accessible only to the researcher and her supervisors. Your name and contact details have not been revealed to the researcher by your therapist who has agreed to pass this questionnaire to you on our behalf.

All results will be coded, i.e. they will not include any identifying information. It is hoped that the results of this study will be published within 18 months of its completion in a relevant scientific journal. However, you will not be identified in any such publication. This research is part of a PhD project funded by the Greek State Scholarships Foundation.

This study has been reviewed and approved by the Southampton & South West Hampshire Research Ethics Committee.

The following is a screening question. Please tick as appropriate.

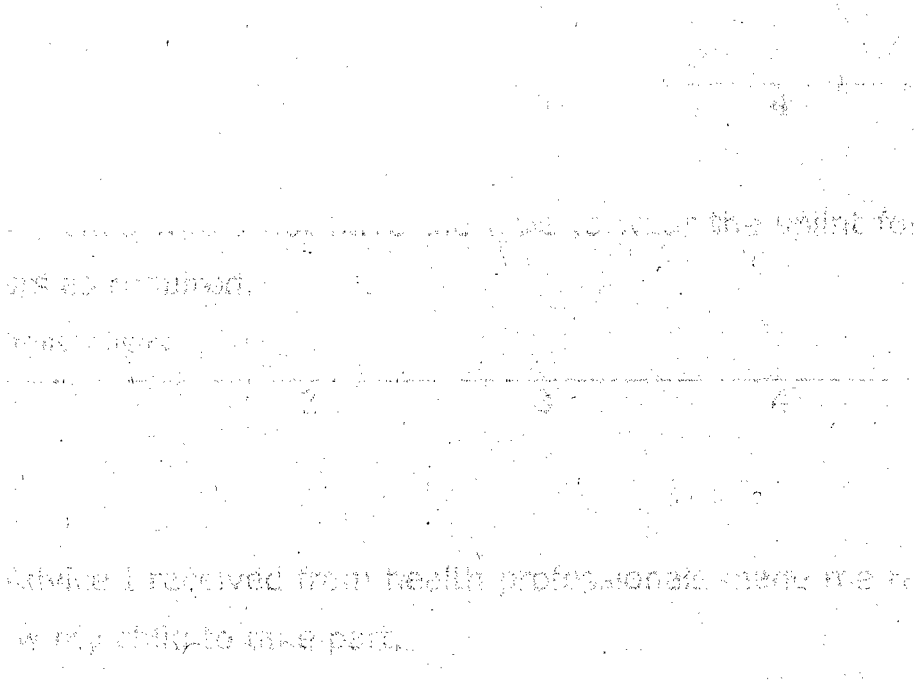
- Did you take part in the CIMT study with Ethics Number 06/ Q1702/ 74?

YES ☐

NO ☐

If you answered YES, please return the questionnaire using the pre-paid envelope. Thank you for your time.

If you answered NO, please read on.



The following eight questions ask about why you decided against your child taking part in the CIMT study. Please tell us to what extent you agree or disagree with the following statements.

1. The time required to supervise my child while wearing the splint was too much for me.

I strongly agree				I strongly disagree
1	2	3	4	5

2. The time required to travel to the University for the Assessments was too much for me.

I strongly agree				I strongly disagree
1	2	3	4	5

3. Wearing the splint would interfere with my child's normal activities.

I strongly agree				I strongly disagree
1	2	3	4	5

4. My child would not have the time to wear the splint for as many hours as required.

I strongly agree				I strongly disagree
1	2	3	4	5

5. Advice I received from health professionals made me reluctant to allow my child to take part.

I strongly agree				I strongly disagree
1	2	3	4	5

6. I did not think my child would benefit from the treatment.

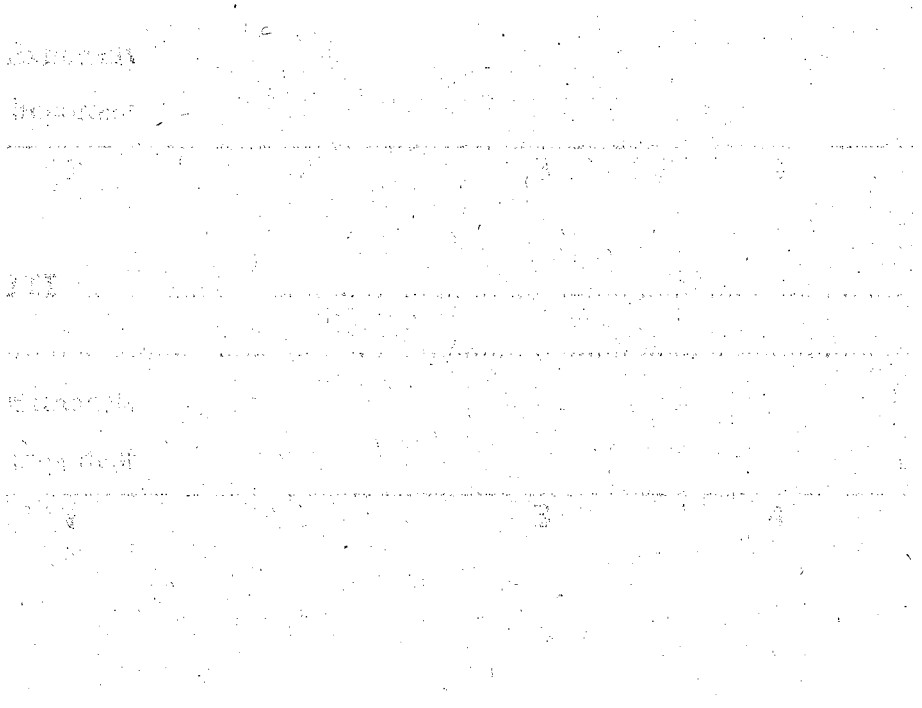
I strongly agree				I strongly disagree
1	2	3	4	5

7. I thought wearing the splint might be dangerous for my child in case of falling.

I strongly agree				I strongly disagree
1	2	3	4	5

8. I thought wearing the splint might compromise my child's normal development.

I strongly agree				I strongly disagree
1	2	3	4	5



You may have other reasons for not taking part in the study. If you do please could you explain them below? It would be helpful if you could also rate each one on how important it was by circling the appropriate number - as you did on the previous questions.

We have given space for up to three reasons, so please choose the most important three.

I.....

.....

Extremely important — Not important at all

1 2 3 4 5

II.....

.....

Extremely important — Not important at all

1 2 3 4 5

III.....

.....

Extremely important — Not important at all

1 2 3 4 5

The following questions will help us to interpret the answers you have given. Please tick the appropriate box in each case

About your employment

	Full-time
	Part-time

(Please specify your occupation).....

Please tick the box that applies to you

	I live alone
	I live with my partner or spouse

Please tick the box that applies to you

	I have only 1 child
	I have at least one other dependent child

Thank you for completing this questionnaire. Please return to:

Pavlina Psychouli

School of Health Professions and Rehabilitation Sciences

University of Southampton

Highfield Campus, Bldg. 45

Southampton, SO17 1BJ

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

SURVEY (THERAPISTS)

Ethics Reference Number: P07/02-01

Modified constraint-induced movement therapy in children with congenital cerebral palsy: A survey.

(Therapists' questionnaire)

Thank you for taking part in this study and for completing this questionnaire.

This questionnaire has been designed to provide information on what therapists know about constraint-induced movement therapy (CIMT) and what their opinion is about this new therapeutic approach. Your answers might help us develop a better way to administer CIMT to children with cerebral palsy.

Please take some time to answer the questions following the instructions carefully.

Please answer each question according to your personal view.

There are no 'right' or 'wrong' answers.

Please answer the following question by ticking each of the boxes below that apply to you.

1. What is your knowledge and experience of constraint-induced movement therapy (CIMT)?

1A.	**YES**	**NO**
I have heard of 'Constraint Induced Movement Therapy' (CIMT)	☐	☐

If you answered NO, please go to question 5. If YES please go to 1B.

1B.

- ☐ **I have read a few papers about it**
- ☐ **I have read a lot and been involved in discussions about it**
- ☐ **I have attended CIMT study days**
- ☐ **I have used CIMT with one or more of my patients**
- ☐ **Other (please explain)**

.....

.....

.....

.....

.....

- **Please indicate below to what extent you agree with the following statements.**
- **These statements refer to children with hemiplegic cerebral palsy between 4 and 11 years old.**

2. A CIMT regimen of 6 hours of daily restriction of the non-affected limb for 10 days, accompanied by exercise would:

A. Be very likely to improve the child's upper limb function

I strongly agree	I agree	Uncertain	I disagree	I strongly disagree
1	2	3	4	5

B. Be practical

I strongly agree	I agree	Uncertain	I disagree	I strongly disagree
1	2	3	4	5

3. A CIMT regimen of 2-3 hours of daily restriction of the non-affected limb for 2 months, accompanied by exercise would:

A. Be very likely to improve the child's upper limb function

I strongly agree	I agree	Uncertain	I disagree	I strongly disagree
1	2	3	4	5

B. Be practical

I strongly agree	I agree	Uncertain	I disagree	I strongly disagree
1	2	3	4	5

- **In the following statement please tick one of the options below.**
- **This statement also refers to children with hemiplegic cerebral palsy who are between 4 and 11 years old.**

4. If a trial of CIMT was available, which included 2-3 hours of daily constraint in a splint or sling, accompanied by exercise for 2 months, I would advise:

☐ **All of my patients who satisfied the selection criteria to take part.**

☐ **Some of my patients who satisfied the selection criteria to take part.**

☐ **None of my patients who satisfied the selection criteria to take part.**

(Please explain your reasons)

.....

.....

.....

.....

.....

- **The following questions will help us to interpret the answers you gave.**

5. Occupation (please tick the appropriate box)

	Occupational Therapist
	Physical Therapist

6. Grade (please tick the appropriate box)

	Band 5
	Band 6
	Band 7
	Head
	Clinical Specialist
	Manager

7. Years of practice (please tick the appropriate box)

	2 or less
	3-5
	6-10
	11-15
	16 or more

Thank you for completing this questionnaire. Please return to:

Pavlina Psychouli

School of Health Professions and Rehabilitation Sciences,

Postgraduate Office

University of Southampton

Highfield Campus

Southampton

SO17 1BJ

APPENDIX 2

DAILY LOGS

FEASIBILITY STUDY

DAILY LOG

This log has been designed to give us information about the advantages and disadvantages of each splint. It should be completed every day and ONLY by the person who was supervising the child during the restraint hours. Please answer the following questions, according to your observations and your personal opinion. Your answers will help us identify the most appropriate type of splint for children with cerebral palsy.

Name:.....

Date:.....

Type of constraint:

1. mitten
2. short splint
3. long splint

- Please record here about how long your child wore the constraint. It would be helpful to say how many sessions there were and the time it was worn in each session.

.....

.....

.....

.....

- Please record here the reasons for removing the constraint from the child's arm today. If the constraint has been removed more than once today, please explain the reasons that it was removed on each occasion.

.....
.....
.....
.....
.....

- Please comment here on your child's response to wearing the splint. For example did they accept it? Were they trying to take it off? How did they feel while wearing it? Did they engage in activities? What kind of activities? How did they adapt to activities that were difficult to be completed?

.....
.....
.....

- Please record here whether the constraint affected your child's balance or particularly made it difficult for them to use their arm to protect themselves if they tripped. Also please record here if they had any skin reaction to the constraint.

.....
.....
.....
.....

- Do you have any other thoughts, concerns or comments about the constraint or the whole experience? If so, please record them here.

.....
.....

EFFECTIVENESS STUDY

Version number: 2

DAILY LOG

This log has been designed to give us information about the performance and activities of children while wearing the splint. It should be completed every day and ONLY by the person who was supervising the child while the splint was being worn. Please answer the following questions, according to your observations. Your answers will help us create a clear picture about the use of the splint.

Name:.....

Date:.....

- Please record here about how long your child wore the constraint today. If the splint was worn in many sessions and the child had breaks in between please record here the overall time the splint was worn.

- Please record here the activities your child participated in, while wearing the splint. Also, please record the approximate amount of time your child participated in each activity.

.....

.....

.....

.....

- (If appropriate) Please record here the score your child achieved today on the feedback bar of the pc game.

- (If appropriate) Please record here the time the actometer was worn today and the readings when you initially placed it on your child's wrist and when you took it off.

- Do you have any other thoughts, concerns or comments about the constraint or the whole experience? If so, please record them here.

.....

.....

.....

.....

APPENDIX 3

ETHICS AND R&D APPROVAL FORMS

FEASIBILITY STUDY-MAIN ETHICAL APPROVAL

SL14 Favourable opinion following consideration of further information
Version 2, October 2004

Isle of Wight, Portsmouth & South East Hampshire
Local Research Ethics Committee
Finchdean House
St Mary's Hospital
Milton Road
Portsmouth
Hampshire
PO3 6DP

Telephone: 023 9283 5049
Facsimile: 023 9285 5312

Email: robin.ford@ports.nhs.uk

03 February 2005

Miss Pavlina Psychouli

PhD student
University of Southampton
School of Health Professions and Rehabilitation Sciences
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ

Dear Miss Psychouli

Full title of study: *Forced use therapy in children with congenital cerebral palsy: A feasibility study*
REC reference number: *04/Q1701/129*
Protocol number:

Thank you for your letter of 20 January 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Sub-Committee of the REC held on 03 February 2005. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

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

The favourable opinion applies to the research sites listed on the attached form. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed that they have no objection.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

FEASIBILITY STUDY-ETHICAL APPROVAL FOR AMENDMENT

NHS
Isle of Wight, Portsmouth &
South East Hampshire
Local Research Ethics Committee
Finchdean House
St Mary's Hospital
Milton Road
Portsmouth
Hampshire
PO3 6DP

Tel: 023 9283 5049
Fax: 023 9285 5312

Our Ref: 04/Q1701/129

PRIVATE AND CONFIDENTIAL
Miss Pavlina Psychouli
PhD student
University of Southampton
School of Health Professions and Rehabilitation Sciences
Highfield Campus,
Bldg. 45
Southampton
SO17 1BJ

5 May 2005

Dear Miss Psychouli

Full title of study: *Forced use therapy in children with congenital cerebral palsy: A feasibility study*
REC reference number: *04/Q1701/129*

Amendment date: 28 April 2005

The Chair at the meeting held on 3 May 2005 reviewed the above amendment.

Ethical opinion

The Chair gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Participant Information Sheet Version 3
Research Protocol Version 2

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Management approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects local management approval of the research.

Statement of compliance

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research

FEASIBILITY STUDY-ETHICAL APPROVAL BY R&D OF SOUTHAMPTON

Southampton City NHS
Primary Care Trust

Research and Development
1st Floor, Department of Psychiatry
Royal South Hants Hospital
Brintons Terrace
Southampton
SO14 0YG

Tel: 023 8082 5054
Fax. 023 8023 4243

Dr Martina Dorward, R&D Manager, (HPT and SCPCT)
e-mail: Martina.Dorward@wht.nhs.uk

7 December 2004

Ms Pavlina Psychouli
132A Avenue Road
SOUTHAMPTON
S014 6UA

Dear Pavlina

Research Project – Forced use therapy in children with congenital cerebral palsy Local Ethics No (LREC):04/Q1701/129

Thank you very much for returning the R&D database registration forms. Your project is now registered on the R&D database with identification number WHC 548.

This letter provides **CONDITIONAL** Southampton City PCT approval required for your project to commence.

This letter also confirms that The University of Southampton will act as Research Sponsor and will provide indemnity under the usual arrangements for student projects.

The conditions of this approval and indemnity require you as Principal Investigator to ensure the following:

- **You should not approach NHS patients or staff regarding this study until LREC approval has been granted.**
- **If this is a commercially sponsored trial of a pharmaceutical product that the Chief Pharmacist for your Trust has performed all the necessary checks regarding labelling, dispensing and storage of the medications**
- **There should be a 12 week interval between studies for patients/volunteers unless exemption from this policy has been obtained from the Director of R&D**
- **All staff involved in the project are familiar with the WHC R&D policies and Procedures and the Research Governance Framework for Health and Social Care**
- **All staff that will be involved with NHS patients and/or have access to identifiable patient data have a current or honorary contract of employment with the appropriate Trust.**
- **All data must be collected and stored in accordance with ICH GCP and/or MRC Guidelines for GCP in clinical trials.**
- **All essential documents are to be stored according to the respective Trust data protection policy.**

FEASIBILITY STUDY-ETHICAL APPROVAL BY R&D OF PORTSMOUTH

Portsmouth Hospitals NHS
NHS Trust

Miss P Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus
Building 45
Southampton
SO17 1BJ

Portsmouth NHS R&D Consortium
R&D Office
1st Floor Gloucester House
Queen Alexandra Hospital
Southwick Hill Road
Cosham, PO6 3LY
Tel: 023 9228 6236
Fax: 023 9228 6037
www.port.ac.uk/research/nhs

9th February 2005

Dear Miss Psychouli

Re: Forced Use Therapy in Children with Congenital Cerebral Palsy: A Feasibility Study.

MREC No: N/A LREC No: 04/Q1701/129 R&D No: PHT/2004/57ST

I have received confirmation that the above study has been processed through the Portsmouth NHS R&D Office. The Office has checked that the study has been subject to a peer review, a cost and funding review, and has received full ethical approval. On behalf of Portsmouth Hospitals NHS Trust I have therefore signed off the study and the above named project may now commence, in accordance with the agreed protocol, [however, please note the following conditions of this approval:]

As local lead researcher within the Trust, you should ensure that you and your team are fully aware of your responsibilities under the National Research Governance Framework for Health & Social Care (Dept Health, March 2001) and other professional codes of good conduct. You can access the Framework from the following web address, http://www.doh.gov.uk/research, but should you find yourself unsure of its requirements please do not hesitate to contact the R&D Office for support.

As this study is ongoing after April 2004, the University of Southampton will act as your official Research Sponsor.

Please ensure that the R&D Consortium Office receives details of any publications or conference presentations resulting from this research, and that all Serious Adverse Events are reported through normal Trust mechanisms to the Risk department and to the R&D Office immediately, but within at least 48 hours of their occurrence. An auditable log of Adverse Events should be kept on file in your department along side other study data and informed consent forms. Your files may be monitored in accordance with local research governance policy.

I wish you well with your project

Yours sincerely

[redacted]

Professor Ken Shaw,
R&D Director
Portsmouth Hospitals NHS Trust

EFFECTIVENESS STUDY-MAIN ETHICAL APPROVAL

SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEES (A)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Tel: 023 8036 2466
023 8036 3462
Fax: 023 8036 4110

Email: GM.E.hio-au.SWHRECA@nhs.net

EJC/STA/hph
04 July 2006

Ms Pavlina Psychouli
PhD student
University of Southampton
School of Health Professions and Rehabilitation Sciences
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ

Dear Ms Psychouli,

Full title of study: **Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study**

REC reference number: **06/Q1702/74**

Thank you for your letter of 29 June 2006, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

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

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). The favourable opinion for the study applies to all sites involved in the research. There is no requirement for other Research Ethics Committees to be informed or SSA to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

EFFECTIVENESS STUDY-ETHICAL APPROVAL BY R&D OF SOUTHAMPTON

Southampton City NHS
Primary Care Trust

Research and Development
1st Floor, Department of Psychiatry
Royal South Hants Hospital
Brintons Terrace
Southampton
SO14 0YG

Tel: 023 8082 5054
Fax: 023 8023 4243

05 June 2006

Pavlina Psychoulie
C/o School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield
SOUTHAMPTON
S017 1BJ

Dear Pavlina

Research Project – WHC 665 Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study

This letter provides the formal Southampton City PCT approval required for your project to commence. ***NB: You should not approach NHS patients or staff regarding this study until you have received full permission for the study from LREC***

This letter also confirms that The University of Southampton will act as Research Sponsor and will provide indemnity under the usual arrangements for student projects.

Please note that this trust approval (and your ethics approval) only applies to the current protocol. Any changes to the protocol can only be initiated following further approval from the ethics committee via a protocol amendment; the R&D office should be informed of these changes. Overleaf are a list are details of information that the R & D Office will require during the period of your research.

The conditions of this approval require you as Principal Investigator to ensure that the study is conducted within the Research Governance framework (RGF) and I encourage you to become fully conversant with the RGF in Health and Social Care document, which is available from the following link: www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ Any breaches of the RGF constitute non-compliance with the RGF and as a result Trust approval may be withdrawn and the project suspended until such issues are resolved.

Your project is registered on the R&D database with identification number **WHC 665.** It would be helpful if you could use this number on all correspondence with the R & D Office Please do not hesitate to contact us should you require any additional information or support. May I also take this opportunity to wish you every success with your research.

With best wishes

Yours sincerely

[redacted]

Helen Raphael (Mrs)
Research &Development Manager
Southampton City PCT (and Hampshire Partnership Trust)

EFFECTIVENESS STUDY-ETHICAL APPROVAL BY R&D OF PORTSMOUTH

Portsmouth City NHS
Primary Care Trust

Portsmouth NHS R&D Consortium
R&D Office
1st Floor Gloucester House
Queen Alexandra Hospital
Southwick Hill Road
Cosham, PO6 3LY
Tel: 023 9228 6236
Fax: 023 9228 6037

WWW.port.ac.uk/research/nhs

Ms P Psychouli
PhD Student
University of Southampton
School of Health Professions and Rehabilitation Sciences
Highfield Campus, Building 45
Southampton
SO17 1BJ

23rd August 2005

Dear Miss Psychouli

Re: Modified constraint-induced movement therapy in children with congenital Cerebral palsy: An effectiveness study.

MREC No: N/A LREC No: 06/Q1702/74

I have received confirmation that the above study has been processed through the Portsmouth NHS R&D Office. The Office has checked that the study has been subject to a peer review, a cost and funding review, and has received full ethical approval. On behalf of Portsmouth City Primary Care Trust and the Portsmouth NHS R&D Consortium I have therefore signed off the study and the above named project may now commence, in accordance with the agreed protocol.

As Local lead for this study you should ensure that you and your team are fully aware of your responsibilities under the National Research Governance Framework for Health & Social Care (Dept Health, March 2005) and other professional codes of good conduct. You can access the Framework from the following web address, http://www.doh.gov.uk/research, but should you find yourself unsure of its requirements please do not hesitate to contact the R&D Office for support.

As this study is ongoing after April 2004, the University of Southampton will act as the official Research Sponsor.

Please ensure that the R&D Consortium Office receives details of any publications or conference presentations resulting from this research, and that all Serious Adverse Events are reported through normal PCT mechanisms to the Risk department and to the R&D Office immediately, but within at least 48 hours of their occurrence. An auditable log of Adverse Events should be kept on file in your department along side other study data and informed consent forms.

Your files may be monitored in accordance with local research governance policy.
I wish you well with your project

Yours sincerely

[redacted]
Dr Paul Edmondson-Jones,
Director Improving Health & Quality/Lead Research & Development Officer, PCPCT

EFFECTIVENESS STUDY-ETHICAL APPROVAL BY R&D OF POOLE

Poole Hospital NHS
NHS Trust

12 July 2006

Ms Pavlina Psychouli
PhD Student
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus, Bldg 45
Southampton
SO17 1BJ

Dear Pavlina

Re: Modified constraint-induced movement therapy in children with congenital cerebral palsy: an effectiveness study
REC Ref. No.: 06/Q1702/74

The above named research project has been reviewed by the Research Governance Department, and I am pleased to advise you that permission to undertake the proposed project at Poole Hospital NHS Trust has been granted.

It is noted that the study has received a favourable opinion from the Southampton and South West Hampshire Research Ethics Committees (A) letter dated 04 July 2006, and is SSA exempt.

Conditions under which this approval is granted are:

- The invitation letters are written on Poole Hospital NHS Trust headed paper:
- The Research Governance Department are notified of:
  - Any amendments to the proposal and documents approved by Southampton and South West Hampshire Research Ethics Committees (A) on 04 July 2006:
  - Serious adverse events affecting patients recruited from Poole Hospital NHS Trust:
- One copy of the consent form for children recruited from Poole Hospital NHS Trust is returned to the Trust to be placed in the patient's medical records. These consent forms are to be sent to:

  Mrs P A Jarvis
  Associate Director of Operations (Women's and Children's CCG)
  Poole Hospital NHS Trust
  Longfleet Road
  Poole,
  Dorset
  BH15 2JB

In addition please send a copy of the research findings to the Research Governance Department on completion of the study.

National Research Ethics Service
SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEE (A)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Tel: 023 8036 2466
023 8036 2870
Fax: 023 8036 4110

Email: scsha.SWHRECA@nhs.net

STA

16 May 2007

Ms Pavlina Psychouli
PhD student
School of Health Professions and Rehabilitation Sciences
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ

Dear Ms Psychouli

Study title: **Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study**
REC reference: **06/Q1702/74**
Amendment number: **3**
Amendment date: **27 April 2007**

Thank you for submitting the above amendment, which was received on 02 May 2007. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 20 March 2007 refers).

The modified amendment was considered at the meeting of the Sub-Committee of the REC held on 08 May 2007. A list of the members who were present at the meeting is attached.

Ethical opinion

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

The committee requested that in the information sheet the sentences 'Thank you for taking time to complete this questionnaire' and 'Because only a small number of people are being surveyed, your response is very important to us' should be removed as these were felt to be coercive. A revised copy should be sent for information.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
Questionnaire	Parent Questionnaire 2	27 April 2007
Protocol	5	27 April 2007
Participant Information Sheet	2	27 April 2007
Modified Amendment	3	27 April 2007

University of Southampton

School of Health Professions and Rehabilitation Sciences

Professor Roger Briggs, Head of School

University of Southampton
Highfield
Southampton
SO17 1BJ
United Kingdom

Tel +44 (0)23 8059 2142
Fax +44 (0)23 8059 5301
Web www.sohp.soton.ac.uk/shprs/

3 May 2007

Pavlina Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton

Dear Pavlina

Submission No: PO7/02-01

Title: Constraint-induced therapy in cerebral palsy

I am pleased to confirm **full approval** for your study has now been given. The approval has been granted by the School of Health Professions and Rehabilitation Sciences Ethics Committee.

You are required to complete a University Research Governance Form (enclosed) in order to receive insurance clearance before you begin data collection. You need to submit the following documentation in a plastic wallet to Dr Martina Dorward in the Research Support Office (RSO, University of Southampton, Highfield Campus, Bldg. 37, Southampton SO17 1BJ):

- Completed Research Governance form (**signed by both student and supervisor**)
- Copy of your research protocol (final and approved version)
- Copy of participant information sheet
- Copy of SoHPRS Risk Assessment form, **signed by yourself and supervisor** (original should be with Zena Galbraith)
- Copy of your information sheet and consent form
- Copy of this SoHPRS Ethical approval letter

Your project will be registered at the RSO, and then automatically transferred to the Finance Department for insurance cover. **You can not commence data collection until you have received a letter stating that you have received insurance clearance.**

Please note that you have ethics approval only for the project described in your submission. If you want to change any aspect of your project (e.g., recruitment or data collection) you must discuss this with your supervisor and you may need to request permission from the Ethics Committee.

Yours sincerely

[redacted]

Dr Emma Stack
Chair, SHPRS Ethics Committee

Enc.

University of Southampton

School of Psychology

University of Southampton
Highfield Southampton
SO17 1BJ United Kingdom

Tel +44 (0)23 8059 5000
Fax +44 (0)23 8059 4597

7 October 2005

Pavlina Psychouli
School of Psychology
University of Southampton
Highfield
Southampton SO17 1BJ

Dear Pavlina,

Re: Intensive therapy in children with congenital cerebral palsy (CP): An effectiveness study

I am writing to confirm that the above titled ethics application was approved by the School of Psychology Ethics Committee on 19 September 2005.

Should you require any further information, please do not hesitate in contacting me on 023 8059 3995.

Please quote approval reference number PG/03/71.

Yours sincerely,

[redacted]

Kathryn Smith
Secretary to the Ethics Committee

SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEE (A)
1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Tel: 023 8036 2466
023 8036 3462
Fax: 023 8036 4110

Email: GM.E.hio-au.SWHRECA@nhs.net

STA/hph

02 October 2006

Ms Pavlina Psychouli
PhD student
School of Health Professions and Rehabilitation Sciences
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ

Dear Ms Psychouli

Study title: **Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study**
REC reference: **06/Q1702/74**

Amendment number:
Amendment date: **20 September 2006**

Thank you for submitting the above amendment, which was received on 21 September 2006. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 15 August 2006 refers).

The modified amendment was considered at the meeting of the Sub-Committee of the REC held on 27 September 2006. A list of the members who were present at the meeting is attached.

Ethical opinion

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved are:

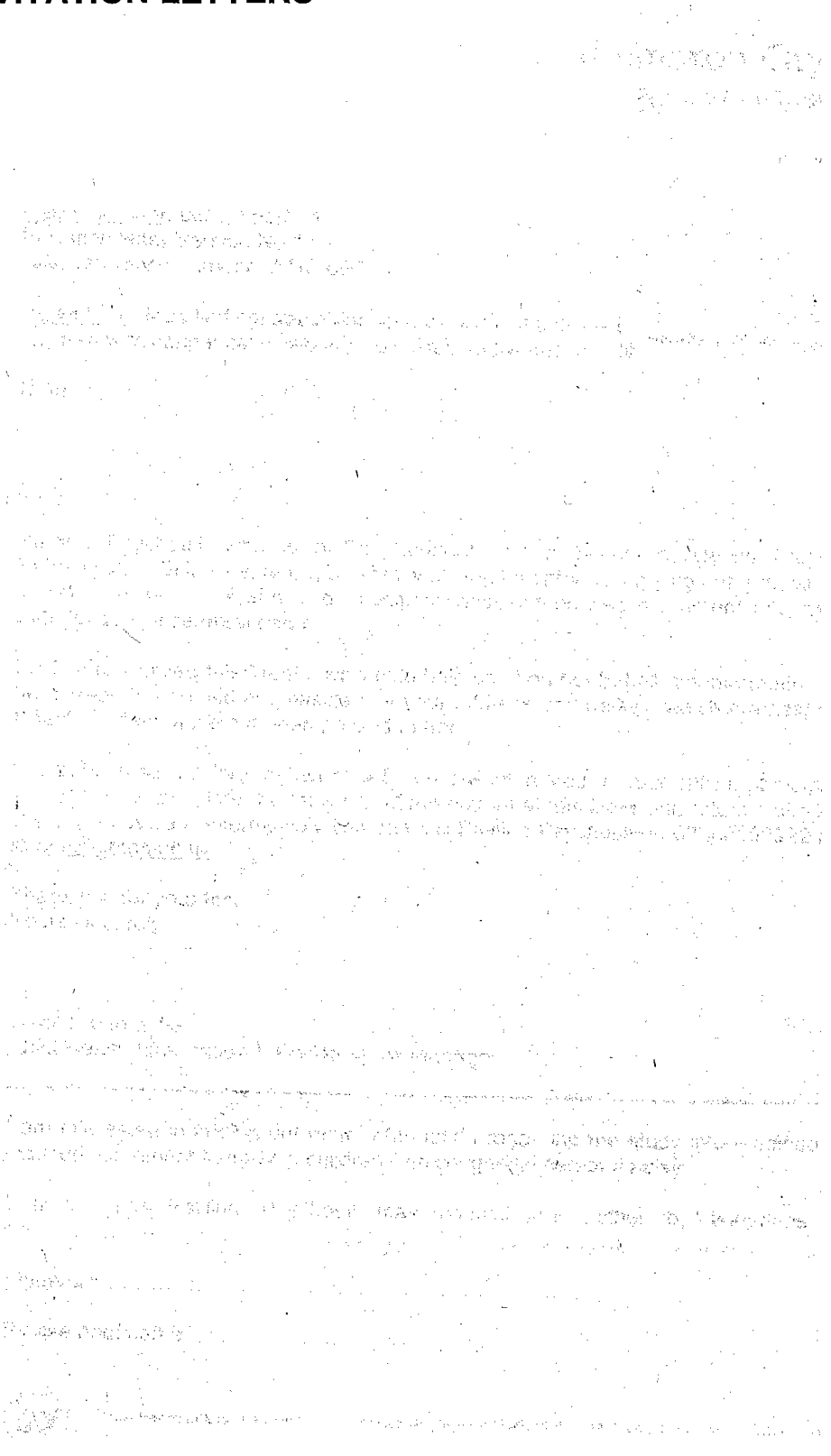
Document	Version	Date
Protocol	2	20 September 2006
Participant Information Sheet	2	20 September 2006
Participant Consent Form	1	20 September 2006
Debrief Form	1	20 September 2006
Modified Amendment		20 September 2006

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

APPENDIX 4

INVITATION LETTERS



FEASIBILITY AND EFFECTIVENESS STUDY

INVITATION LETTER FOR SOUTHAMPTON

Southampton City NHS
Primary Care Trust

Child & Family Services
4th Floor
Central Health Clinic
East Park Terrace
Southampton
SO14 0YL

Tel: 023 8090 2524
Fax: 023 8090 2603
Website: www.southamptonhealth.nhs.uk

Ethics number: 06/ Q1702/ 74
Invitation letter Version No 1
R&D reference number: WHC 665

Project title: Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study.

Date:

Dear .....

Pavlina Psychouli, who is a PhD student at the School of Health Professions and Rehabilitation Sciences, at the University of Southampton is carrying out a research project to identify the functional effects of modified constraint-induced movement therapy in children with congenital cerebral palsy.

Pavlina has asked this Trust if we would help send on her behalf, an information sheet about her research. I should emphasize that your address and details, which are held on our Child Health System, have not been passed to her.

If, having read the information sheet, you are interested in your child's participation in this study, please complete the reply slip at the bottom of this letter and return it directly to her, in the SAE provided. Alternatively you can call Pavlina Psychouli on 02380598922 or email her at pp8@soton.ac.uk

Thank you for your time
Yours sincerely

Janet Freemantle
Child Health Information & Performance Manager

I am interested in finding out more information regarding the study into modified constraint-induced movement therapy in children with congenital cerebral palsy.

I agree that Pavlina Psychouli may contact me (either by telephone or email) on.....

Signature.....

Please print name.....

INVITATION LETTER FOR PORTSMOUTH AND POOLE

Portsmouth City NHS
Teaching Primary Care Trust

Childrens Services
Dunsbury Way Clinic
Dunsbury Way
Leigh Park
Havant
Hants
PO9 5BG

Tel: 023 9248 2154
Fax: 023 9247 1892

Ethics number: 06/Q2201/81
Invitation letter Version No 1
R&D reference number: WHC 665

Project title: Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study.

Date:

Dear.....

I am writing on behalf of Pavlina Psychouli, who is a PhD student at the School of Health Professions and Rehabilitation Sciences, at the University of Southampton. Ms Psychouli is carrying out a research project to identify the functional effects of modified constraint-induced movement therapy in children with congenital cerebral palsy.

You have been sent this letter because you have a child with hemiplegia due to cerebral palsy, who is one of my patients. To find out more about this study please read the enclosed information sheet.

If, having read the information sheet, you are interested in your child's participation in this study, please complete the reply slip at the bottom of this letter and return in the SAE provided. Alternatively you can call Pavlina Psychouli on 02380598922 or email her at pp8@soton.ac.uk .

Thank you for your time.

Yours sincerely,

Consultant Paediatrician or Physical/ Occupational Therapist (*only the relevant clinician will sign the letter)*

I am interested in finding out more information regarding the study into modified constraint-induced movement therapy in children with congenital cerebral palsy.

I agree that Pavlina Psychouli may contact me (either by telephone or email) on

.....

Signature.....

Please print name.....

APPENDIX 5

INFORMATION SHEETS

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

FEASIBILITY STUDY-PARENTS' INFORMATION SHEET

Date:

Patient Information Sheet Version no 3

Ethics Number: 04/ Q1701/ 129

R&D reference number: WHC 548

Study title

Forced use therapy in children with congenital cerebral palsy: A feasibility study.

Invitation paragraph

Your child is being invited to take part in a research study. Before you decide on his/ her behalf it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please contact Pavlina Psychouli (Tel: 02380598922/ email: pp8@soton.ac.uk) if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part.

Thank you for reading this.

What is the purpose of the study?

Constraint-induced movement therapy (CIMT) includes restraining (using a splint or a glove-like mitt) the non-affected arm and providing intensive exercise to the affected one and has been shown to be effective mainly in adults with stroke. This intervention although effective, is very demanding and many patients and therapists believe it is not practicable. An intervention that may be more practical is called 'forced-use', comprising only the restraint element of CIMT without any additional exercise. Forced-use has been only sparsely investigated. Even less research has been done on

the effects of forced use on children with cerebral palsy (CP). Different restraining types might be suitable for different groups of children. In addition, a specific protocol is not really followed in practice and selection of a protocol that is effective and also practicable is challenging. Thus, the aim of this study is to identify the most appropriate way to provide forced use therapy in a group of children with congenital, hemiplegic CP. The duration of this study will be approximately 1,5 months.

Why has my child been chosen?

You have been sent this letter and information sheet because your child is between 5 and 11 years old and has hemiplegia (weakness or paralysis of one lateral half of the body) due to congenital CP. A total of 15 children will be included in this study.

Does my child have to take part?

It is up to you to decide whether your child should participate in the study. If you do decide that your child should take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide that your child should take part, they are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time or to not take part, will not affect the standard of care your child receives.

What will happen to my child if he/ she takes part?

If you give your consent for your child's participation in this study you will be contacted by telephone or email and a meeting will be arranged with you and your child. During this meeting your child will be assessed by the researcher using simple toys and a commonly used test to measure how well your child is able to understand instructions to make sure they are suitable to take part in the study This procedure will last approximately 45 minutes and will ensure that your child fulfills the selection criteria for this study. If following this session, we decide that your child can be included in the study, another meeting will be arranged during which measures of your child's hand and arm will be taken so that the 3 splints under study can be constructed. This meeting will last approximately 1 hour. After this, you will be given the splints for your child to wear. Each splint should be worn for 4 days, for a minimum of 1h/ day and only when your child is supervised by you, another member of the family or a caregiver. You should apply the splint for as long as the child can

cooperate and feel comfortable with it. The person who supervises the child during the constraint hours is the one who should complete the daily log given to you by the researcher. In this log you are asked to record how long the splint was worn, the reason it was removed, the child's behavior and any problems that might have arisen.
After each splint has been tried, you will be asked to fill in a questionnaire. This questionnaire will help us identify whether the splint was beneficial and if it caused discomfort to your child or yourself. This questionnaire requires a maximum of 15 minutes to be completed. At the same time, your child will be recorded on videotape during a 15-min free play. This videotape will provide detailed information about how the splint has affected the child's behavior, during this period. During this video recording, a small device at the size of a watch will be attached to your child's forearm to measure how much their arm moves. The same device will be applied at the beginning of the study, as well. The videotapes and all other data gathered from this study will be securely stored either with a password (for electronic data) or in a locked filing cabinet (for non-electronic data). Primary data will be stored for 15 years and will be accessible only to the researcher.
All the sessions will take place either at the Southampton General Hospital, the Child Development Centre in Portsmouth or at your home, whichever is more convenient to you. All traveling expenses will be reimbursed. The overall duration of this study is expected to be about 6 weeks.
This study does not require any changes in your child's normal therapy routine.

What are the alternative treatments?

Forced use therapy is not a replacement for other treatment methods and should always be provided in conjunction with conventional physical and occupational therapy.

What are the possible disadvantages and risks of my child taking part in this study?

Your child may experience some discomfort while wearing the splints and there is a slight risk of irritation of the skin. There are no major physical or psychological risks reported in the literature related to forced use therapy. Nevertheless, there is a possibility that your child might not be able to protect themselves if they fall while

wearing a splint. This is one of the reasons that the splints should be applied only when children are under your or the caregiver's supervision.

What are the possible benefits of my child taking part?

This is not a treatment and there is no direct benefit to your child. We are asking that your child tries the splints to enable us to understand more about how this treatment could be given to young children with hemiplegic CP. However, findings from previous studies have shown that forced use therapy has an effect on the quantity and quality of use of the hemiplegic hand in adults with stroke and children with CP.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, you will be informed and asked whether you want your child to continue in the study. If you decide that your child should continue in the study you will be asked to sign an updated consent form.

What happens when the research study stops?

When the research has been completed your child will go on with their routine therapy without participating in any forced use therapy interventions. However, you will be sent a summary of what we have found out by doing the study.

What if something goes wrong?

If your child is harmed by taking part in this research project, there are no special compensation arrangements. If your child is harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain or have any concerns about any aspect of the way your child has been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my child's participation in this study be kept confidential?

All information, which is collected about your child during the course of the research will be kept strictly confidential. Any information about your child, which leaves the University of Southampton will have his/ her name and address removed so that they

cannot be recognized from it. Consent will be sought for your child's GP and therapists to be notified of your child's participation in the study.

What will happen to the results of the research study?

It is hoped that the results of this study will be published within 18 months of its completion in a relevant scientific journal. However, your child will not be identified in any such publication.

Who is organizing and funding the research?

This research is part of a PhD project funded by the Greek State Scholarships Foundation.

Who has reviewed this study?

This study has been reviewed and approved by the Isle of Wight, Portsmouth and South East Hampshire Local Research Ethics Committee.

Contact for further information

If you have any questions or require any further information please contact:

Pavlina Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ

Tel: 02380598922
Email: pp8@soton.ac.uk

Thank you very much for taking the time to read this information sheet. If you decide for your child to take part in this study you will be given a copy of this information sheet and a signed consent form to keep.

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

FEASIBILITY STUDY-CHILDREN'S INFORMATION SHEET

Date:

Patient Information Sheet for children Version no 1

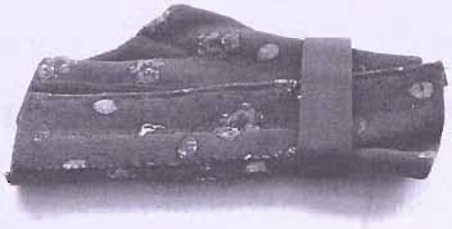
Ethics Number: 04/ Q1701/ 129

R&D reference number: WHC 548

Study title: Forced use therapy in children with congenital cerebral palsy: A feasibility study.

FINDING A WAY TO MAKE YOUR HAND WORK BETTER

- Have you noticed that one of your hands does not work as well as the other one? Sometimes it is hard for you to do things with this hand and so you prefer to use your strong hand.
- We would like to see if we can help your weak hand to work better. To do this, we want you to wear 3 different splints (a bit like the one in the picture) on your strong hand for part of each day. The splint will make it easier to do some things with your weak hand. This way your weak hand will get more practice and so become stronger.



- We will make a video of you with the splint on while you are playing and we would like you to wear a watch on your weak hand to count how many times you used it when you were playing (look at the picture below).

- Tell us or your parents if you do not want to take part.
- Even if you say you want to take part now, you can always change your mind later and it will be OK; nobody will mind.

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

EFFECTIVENESS STUDY-PARENTS' INFORMATION SHEET

Date:

Ethics Number: 06/ Q1702/ 74

R&D reference number: WHC 665

Where the word 'parent' is used, please read parent/ guardian i.e. those who have parental responsibility, which may include a legal representative e.g. grandparent.

1. Study title

Modified constraint-induced movement therapy (mCIMT) in children with congenital cerebral palsy (CP): An effectiveness study.

2. Invitation paragraph

You and your child are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you and your child if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. What is the purpose of the study?

Constraint-induced movement therapy (CIMT) includes restraining (using a splint) the non-affected arm and providing intensive exercise to the affected one and has been shown to be effective mainly in adults with stroke. This intervention although effective, is very demanding and many patients and therapists believe it is not

practical. An intervention that may be more practical comprises only the restraint element of CIMT without any additional exercise. Little research has been done on this type of intervention and therefore, it is not known to what extent it could be effective. In addition, a specific protocol is not really followed in practice and selection of a protocol that is effective and also practical is challenging. The aim of this study is to investigate the functional effects of a modified protocol of CIMT in children with congenital, hemiplegic CP when only the splint is applied and when functional practice at home is added. The duration of this study is estimated to be between 9-18 months.

4. Why has my child been chosen?

You have been sent this letter and information sheet because your child is between 4 and 11 years old and has hemiplegia (weakness or paralysis of one lateral half of the body) due to congenital CP. A total of 15 children will be included in this study.

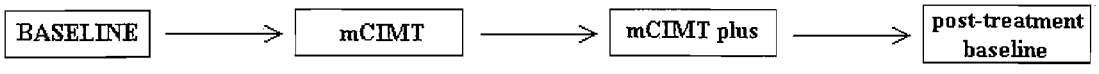
5. Does my child have to take part?

No. It is up to your child to decide whether or not to take part. You are both free to withdraw from the research at any time and without giving a reason. Your decisions about this will not affect the standard of care your child will receive.

6. What will happen to my child if we agree to take part?

If you are happy to take part and are satisfied with the explanations from our research team, you will be asked to sign a consent form. If your child is able to understand the research and is happy to take part and can write their name, they will be asked to sign a separate form, if they want to. You will be given a copy of the signed information sheet and consent forms to keep for your records.

This study is an observational study during which all children will take part in two interventions in turn. We have named the one intervention "modified constraint-induced movement therapy" (mCIMT) and the other one "$mCIMT_{plus}$". The following procedure will take place:



During our first meeting your child will be assessed by the researcher using simple toys and a commonly used test to measure how well your child is able to understand instructions to make sure they are suitable to take part in the study. This procedure will ensure that your child fulfills the selection criteria for this study. If we decide that your child can be included in the study, two functional tests will be applied. These tests will provide detailed information about how your child uses their hands. A research assistant will score the functional performance of your child using simple toys, while a videotape will also be recorded to provide information for the second test. This will later be scored by an assessor, other than the researcher. The assessor, the researcher and her supervisors will be the only people having access to your child's videotapes. These two functional assessments will take place again at the end of each phase (baseline, mCIMT, $mCIMT_{plus}$ and post-treatment baseline) and before the beginning of the next one.

Each phase will last for 1 month. During the baseline periods, no intervention will be given to your child. After the end of the baseline, a splint will be constructed and given to you for your child to wear. During "mCIMT" your child will be required to wear the splint for a minimum of 2 hours/day during weekdays and 2-3 hours/day during weekends. The time of daily restriction should be gradually increased so that after the 2^{nd} week of the intervention the splint is worn for 3 hours during weekdays and 3-4 hours during weekends. No additional intervention will be given. During "$mCIMT_{plus}$", your child will be required to wear the splint as much as during mCIMT but they will also have to participate in functional activities while wearing the splint. These activities will be decided upon after a discussion between you and the researcher takes place. This will be done in order to make sure that the activities are interesting and appropriate for your child. In addition, during "$mCIMT_{plus}$" you will be given a pc game for your child to play before taking off the splint at the end of each day. This is a simple, interesting game that your child will be able to play with the hemiplegic hand. A joystick will be provided if you don't have one, the movement of which will be recorded during the game. When the game finishes, 10 minutes later, a coloured bar will be displayed on the screen showing to you and your child how much they moved their hemiplegic hand. A small device at the size of a watch (actometer) will be given to you to attach it to your child's forearm once at the end of each week of the intervention periods to measure how much your child's arm moves.

This device should be worn for as much as your child can cooperate. The researcher will have telephone communication with you on a weekly basis, while home visits may also take place, if needed.

All the assessments will take place at the University of Southampton, at a mutually convenient time and will last approximately 1.5-2 hours. All traveling expenses will be reimbursed. The overall duration of this study is expected to be between 9-18 months.

This study does not require any changes in your child's normal therapy routine.

7. What does my child have to do if we agree to take part?

Your child should wear the splint for at least as long as described in section 6. In addition, during the latter your child will have to take part in functional activities (including the pc game). During these activities, you or the caregiver should actively participate as much as possible to increase the child's motivation. **The splint should be applied to the child only when they are being supervised either by you, another member of the family or the caregiver.** The person who supervises the child while the splint is worn is the one who should complete a daily log, which will be given to you. In this log you are asked to record how long the splint was worn, the activities the child engaged in, the score they achieved on the pc game and (once every week) the time the actometer was worn for and its readings. You will be required to come at the University of Southampton on five occasions, where we will assess the functional performance of your child.

8. What are the alternative treatments?

Modified constraint-induced movement therapy is not a replacement for other treatment methods and should always be provided in conjunction with conventional physical and occupational therapy.

9. What are the possible disadvantages and risks of taking part?

Your child may experience some discomfort while wearing the splint and there is a slight risk of irritation of the skin. If your child feels very uncomfortable with the splint, you can remove it and put it back on later. There are no major physical or

psychological risks reported in the literature related to CIMT. Nevertheless, there is a possibility that your child might not be able to protect themselves if they fall while wearing the splint. This is one reason that **the splint should be applied only when children are under yours or the caregiver's supervision.**

10. What are the possible benefits of taking part?

This is not a treatment and there is no direct benefit to your child but the information we get might help improve the treatment of young children with hemiplegic CP. However, findings from previous studies have shown that CIMT has an effect on the quantity and quality of use of the hemiplegic hand in adults with stroke and children with CP but the effects of the modified version that is being tested in this study are unknown.

11. What happens when the research study stops?

When the research has been completed your child will go on with their routine therapy without participating in any CIMT interventions.

12. What if there is a problem?

Any complaint about the way you or your child have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2. The researcher though can always be contacted for complaints.

13. Will my child's taking part in the research project be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential. The details are included in Part 2.

14. Contact Details:

If you have any questions, concerns or require any further information please contact the researcher:

Pavlina Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus, Bldg. 45

Southampton
SO17 1BJ
Tel: 02380598922
Email: pp8@soton.ac.uk

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

15. What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the researcher will tell you about it and discuss whether you and your child want to or should continue in the study. If you decide that your child should not carry on, their care will continue as normal. If you decide that your child should continue in the study you will be asked to sign an updated consent form. If the study is stopped for any other reason, you will be told why and your child's care will be continued as normal.

16. What will happen if my child or I don't want to carry on with the research?

You and your child can withdraw from the research at any time, but we will need to use the data collected up to your withdrawal.

17. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do her best to answer your questions (02380598922). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your paediatrician.

In the event that something does go wrong and your child is harmed during the research study, there are no special compensation arrangements. If your child is harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the University of Southampton but you may

have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

18. Will my child's taking part in this study be kept confidential?

If you decide for your child to join this study, some parts of their medical records and the data collected for the study may be looked at by authorised persons, such as your paediatrician, therapist, the researcher and her supervisors. All will have a duty of confidentiality to you and your child as research participants and nothing that could reveal you identity will be disclosed outside the research site. All information, which is collected about your child during the course of the research will be kept strictly confidential. Any information about your child, which leaves the University of Southampton will have his/ her name and address removed so that they cannot be recognized from it. Electronic data will be kept on a computer at the Univeristy of Southampton and will be password protected and accessed only by the researcher. All non-electronic data will be stored in locked filing cabinets. All the primary data will be stored securely for 15 years. This data will not be used in future studies without further approval from the relevant research ethics committee. Consent will be sought for your child's GP to be notified of your child's participation in the study.

19. What will happen to the results of the research study?

It is hoped that the results of this study will be published within 18 months of its completion in a relevant scientific journal. However, your child will not be identified in any such publication. A summary of the results will be sent to you after completion of the study.

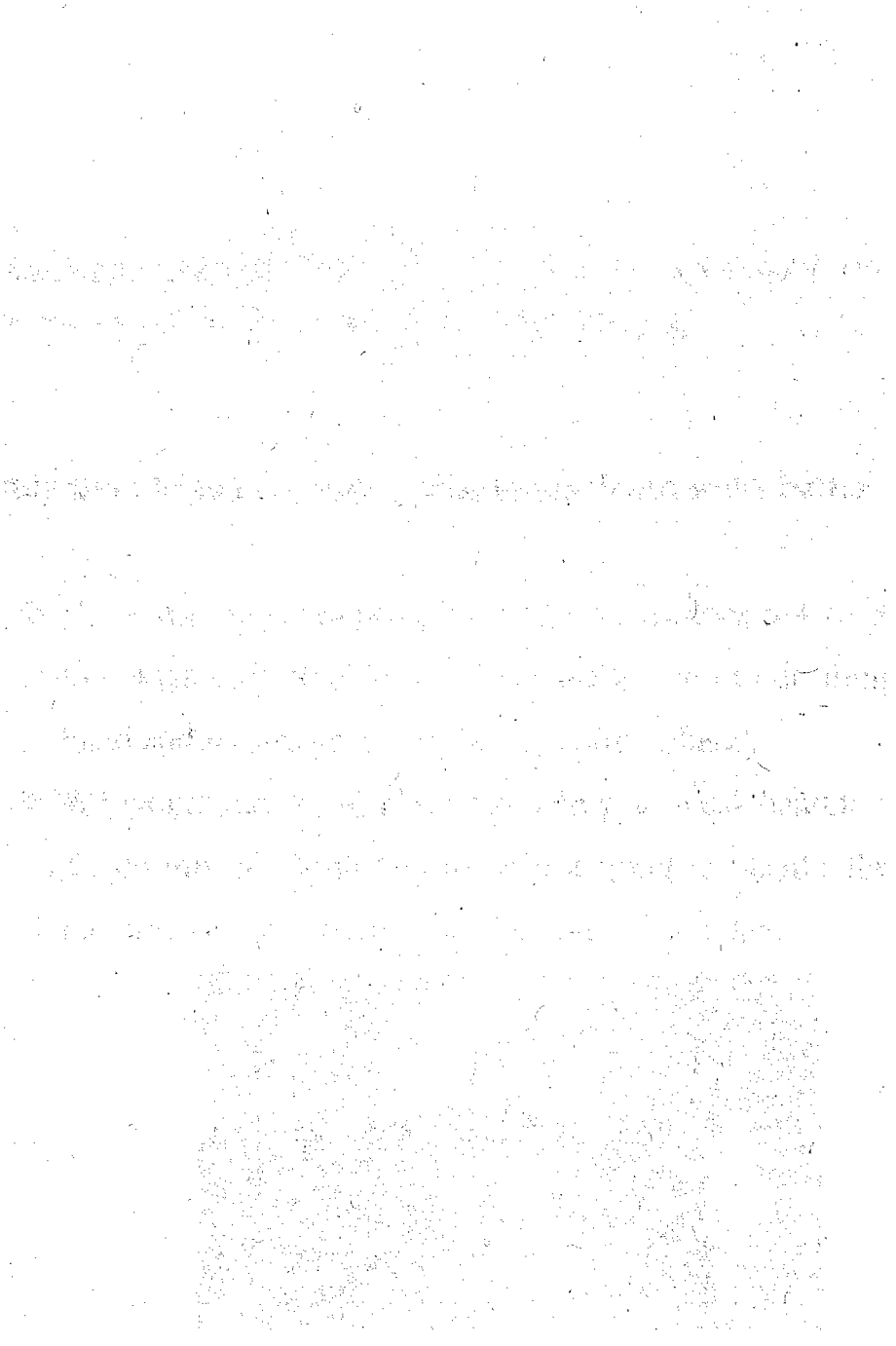
20. Who is organizing and funding the research?

This research is sponsored by the University of Southampton. The study is part of a PhD project, which is funded by the Greek State Scholarships Foundation. The researcher receives no payment for this study.

21. Who has reviewed this study?

This study has been reviewed and approved by the Southampton & South West Hampshire Research Ethics Committee.

Thank you very much for taking the time to read this information sheet. If you decide for your child to take part in this study you will be given a copy of this information sheet and a signed consent form to keep.



UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

EFFECTIVENESS STUDY-INFORMATION SHEET FOR CHILDREN UNDER 5 YEARS OLD

Date:

Ethics Number: 06/ Q1702/ 74

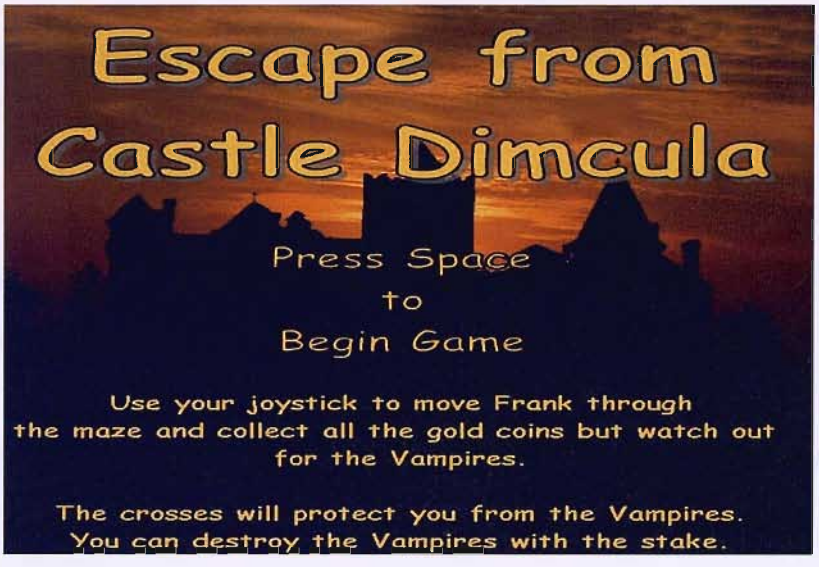
R&D reference number: WHC 665

Instructions for parents: Please read this information sheet and discuss the pictures with your child if they are unable to read it for themselves

Study title: Finding a way to make your hand work better

- Have you noticed that one of your hands does not work as well as the other one? Sometimes it is hard for you to do things with this hand and so you prefer to use your strong hand.
- We would like to see if we can help your weak hand to work better. To do this, we want you to wear a splint (a bit like the one in the picture) on your strong hand for part of each day.

- We also want you to do some things with your weak hand and play a game on your computer (look at the picture below) on some days. This way your weak hand will get more practice and may become stronger.



- We will make a video of you with the splint on while you are playing and we would like you to wear a watch on your weak hand to count how many times you used it when you were playing (look at the picture below).

- Tell us or your parents if you do not want to take part.
- Even if you say you want to take part now, you can always change your mind later and it will be OK; nobody will mind.

UNIVERSITY OF
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School of Health Professions
and Rehabilitation Sciences

EFFECTIVENESS STUDY-INFORMATION SHEET FOR CHILDREN 6-12 YEARS OLD

Date:

Ethics Number: 06/ Q1702/ 74

R&D reference number: WHC 665

Instructions for parents: Please read this information sheet to your child if they are unable to read it for themselves

Study title: Finding a way to make your hand work better

What is research? Why is this project being done?

Research is a careful experiment to find out the answer to an important question. This research will test if having your strong hand in a splint makes your other hand work better, especially if you use it more to do things.

Invitation to take part. Why have I been asked to take part?

You are being invited to take part in a research study. Read the following information carefully and discuss it with your parents before you decide if you want to take part or not. You have been asked to take part because you are between 4-11 years old and one of your hands is stronger than the other.

Did anyone else check the study is OK to do?

Before any research is allowed to happen, it has to be checked by a group of people called an Ethics Committee. They make sure that the research is OK to do. This study has been checked by the Southampton & South West Hampshire Research Ethics Committee.

Do I have to take part?

No. Taking part or not is entirely up to you and if you decide not to take part noone will mind.

What will happen to me if I take part in the research?

If you agree to take part your parents will have to sign a form, giving their permission for you to join the study and you can also sign a form, if you want.

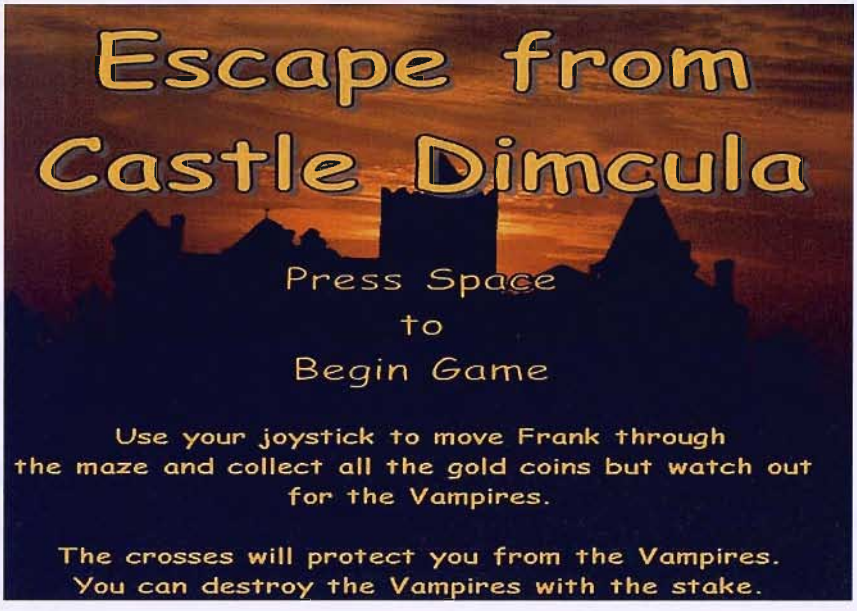
This study will last 4 months. During the first and fourth month you won't have to do anything. During the second and third month, we will give you a coloured splint (like the one in the picture below) to wear on your strong hand for a few hours each day. You will wear the splint at home but not at school and you can choose when to wear it. If you want to play sports or do anything else that the splint would not allow you to do, you can take it off and wear it again later. During one month, you will be asked to play games and do things at home while wearing the splint. One of these is a computer game (look at picture 2) that uses a joystick. You and your parents will have to come at the University of Southampton five times during the study, where we will test if your weak hand is working better and make a video of you while playing with toys. You will not have to lose any days off school.

Picture 1. SPLINT

Is there another sort of treatment I can have instead?

Some children have physical and occupational therapy.

Picture 2. COMPUTER GAME



Might anything about the research upset me?

You might feel a little uncomfortable with the splint, especially at the beginning. Your skin might also get a bit red or itchy. If this happens, you should tell your parents about it. While wearing the splint you might not be able to put your hand out to save yourself if you fall and this is why we ask your parents to be close to you when you are wearing the splint.

Will joining in help me?

We cannot promise the study will help you but the information we get might help treat young people like you with better treatments in the future.

What happens when the research stops?

When the research stops you will keep having your normal treatment without any therapy like the one you had during the study.

What if something goes wrong during the project?

In this case your parents will contact the researcher who will try to find a solution to the problem. If she is not able to do this, your parents will have other ways to complain.

Will my medical details be kept private if I take part? Will anyone else know I'm doing this?

The only people that might see your medical details or know that you joined the study will be your doctor and therapists, the researcher and her supervisors.

What happens if a better treatment comes along?

If better, proven treatment comes along, taking part in this study will not stop you getting it.

What if I don't want to do the research anymore?

If at any time you don't want to be in the study, just tell your parents. They will not be cross with you. You will go on with your usual treatment as normal.

Thank you very much for taking time to read this information sheet!

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School of Health Professions
and Rehabilitation Sciences

LRP STUDY-CONTROL GROUP
PARENTS' INFORMATION SHEET

Date:

Patient Information Sheet Version no 2

Study title

Brain waves and attention

Invitation paragraph

Your child is being invited to take part in a research study. Before you decide on their behalf it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please contact Pavlina Psychouli (Tel: 02380598922/ email: pp8@soton.ac.uk) if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part.

Thank you for reading this.

What is the purpose of the study?

We are currently investigating the effect of an intensive type of therapy on the manual skills of children with cerebral palsy who are between 4 and 11 years old. As well as finding out how this therapy affects the children's ability to use their hands, we also want to know more about how it affects their nervous system, especially their brain waves. To find this out we need to understand more about the brain waves of healthy children when they use their hands so that we can compare them with children who have cerebral palsy.

Why has my child been chosen?

You have been given this information sheet because your child is between 4 and 11 years old and is both physically and mentally healthy. A total of 15 children will be included in this study.

Does my child have to take part?

It is up to you to decide whether your child should participate in the study. If you do decide that your child should take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide that your child should take part, they, or you on their behalf, are still free to withdraw at any time and without giving a reason.

What will happen to my child if they take part?

If you give your consent for your child's participation in this study an appointment will be arranged with you and your child. This meeting will take place at the University of Southampton, School of Psychology and will last approximately 1 hour. During this time, we will measure your child's brain waves. This involves placing about 14 electrodes on the scalp, and keeping them in place with watery gel and sticky tape. The leads are sufficiently sensitive to pick-up electrical activity in the brain. Once the leads are in position, your child will be asked to play a computer game called 'Fish'. In this game they have to press one of two buttons according to the direction the fish is swimming. After the brain wave study, we will try to remove as much of the gel as possible. Your child may, however, wish to wash their hair when they get home. All data gathered from this study will be stored for 15 years either in a computer with a password (for electronic data) or in a locked filing cabinet (for paper records). Data will be accessible only to the researcher and her supervisors. All traveling expenses will be reimbursed.

What are the possible disadvantages and risks of my child taking part in this study?

The brain wave study is not unpleasant or uncomfortable, and Dr Hogan, who will supervise the session, is experienced in using this technique with children as young as 3 months. In the unlikely event that your child does find the experience unpleasant, the leads can be removed very quickly - in a couple of minutes. A skin test will be

performed for your child in order to test for allergy to gels. If itching or redness is present, your child will not further participate in the study.

What are the possible benefits of my child taking part?

There is no direct benefit to your child.

Will my child's participation in this study be kept confidential?

Personal information about you and your child will not be released to or viewed by anyone other than the researchers named at the end of this information sheet. All results will be coded so that they are anonymous, i.e. they will not include yours or you child's name or any other identifying information.

What will happen to the results of the research study?

It is hoped that the results of this study will be published within 18 months of its completion in a relevant scientific journal. However, your child will not be identified in any such publication.

Who is organizing and funding the research?

This research is part of a PhD project funded by the Greek State Scholarships Foundation.

Who has reviewed this study?

This study has been reviewed and approved by the Ethics Committee of the School of Psychology, University of Southampton.

Contact for further information

If you have any questions or require any further information please contact:

Pavlina Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ

Tel: 02380598922

Email: pp8@soton.ac.uk

Thank you very much for taking the time to read this information sheet. If you decide for your child to take part in this study you will be given a copy of this information sheet and a signed consent form to keep.

Project supervisor:

Dr Alexandra Hogan

Lecturer in Developmental Neurocience

[Dr Jane Burridge, Dr Colin Kennedy, Professor Ann Ashburn].

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

LRP STUDY-PATIENT GROUP
PARENTS' INFORMATION SHEET

Date:

Ethics Number: 06/ Q1702/ 74

R&D reference number: WHC 665

Where the word 'parent' is used, please read parent/ guardian i.e. those who have parental responsibility, which may include a legal representative e.g. grandparent.

1. Study title

Brain Wave Ancillary study.

2. Invitation paragraph

You and your child are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

This information sheet is supplementary to the one concerning the main study. All that applies in the main study (especially regarding Part 2) applies in this study, too. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

3. What is the purpose of the study?

The purpose of this study is to find out whether the nervous system of children with cerebral palsy (CP) and specifically their brain waves differ from those of healthy,

unimpaired children. The duration of this study is estimated to be between 9-18 months.

4. Why has my child been chosen?

You have been given this information sheet because your child is between 6 and 11 years old, they have hemiplegia (weakness or paralysis of one lateral half of the body) due to congenital CP and have no medical history of epilepsy. A total of 10-15 children will be included in this study.

5. Does my child have to take part?

No. It is up to your child to decide whether or not to take part. You are both free to withdraw from the research at any time and without giving a reason. If you decide to not take part in this ancillary study, you can still take part in the main study. Your decisions about this will not affect the standard of care your child will receive.

6. What will happen to my child if we agree to take part?

If you are happy to take part and are satisfied with the explanations from our research team, you will be asked to sign an additional consent form (except for the one you signed for the main study). If your child is able to understand the research and is happy to take part and can write their name, they will be asked to sign a form, if they want to. You will be given a copy of the signed information sheet and consent forms to keep for your records.

Recording of the brain waves will last approximately 45 minutes. During this time, 14 electrodes will be placed on your child's scalp and will be kept in place with watery gel and sticky tape. The leads are sensitive to pick-up electrical activity in the brain. Once the leads are in position, your child will be asked to play a computer game called 'Fish'. In this game they have to press one of two buttons according to the direction the fish is swimming. After the brain wave study, we will try to remove as much of the gel as possible. Your child may, however, wish to wash their hair when they get home. Recording of brain waves will take place in one occasion during the study, before the intervention period (mCIMT and $mCIMT_{plus}$).

All the assessments will take place at the University of Southampton, School of Psychology at a mutually convenient time. All traveling expenses will be reimbursed. The overall duration of this study is expected to be between 9-18 months.

This study does not require any changes in your child's normal therapy routine.

7. What are the possible disadvantages and risks of taking part?

The brain wave study is not unpleasant or uncomfortable, and Dr Alexandra Hogan, who will supervise the session has over 10 years experience in using this technique with children as young as 3 months. In the unlikely event that your child does find the experience unpleasant, the leads can be removed very quickly - in a couple of minutes. A skin test will be performed for your child in order to test for allergy to gels. If itching or redness is present, your child will not further participate in the study. It is very unlikely that this measure will detect any cases of previously undiagnosed epilepsy. However, in the event that the recordings show abnormal activity, this will be passed on to Professor Colin Kennedy, Paediatric Neurologist and co-supervisor of this study.

8. What are the possible benefits of taking part?

This is not a treatment and there is no direct benefit to your child but the information we get might help improve the treatment of young children with hemiplegic CP.

9. What if there is a problem?

Any complaint about the way you or your child have been dealt with during the study or any possible harm you might suffer will be addressed. The researcher though can always be contacted for complaints.

10. Will my child's taking part in the research project be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential.

11. Contact Details:

If you have any questions, concerns or require any further information please contact the researcher:

Pavlina Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus, Bldg. 45
Southampton
SO17 1BJ
Tel: 02380598922
Email: pp8@soton.ac.uk

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

LRP STUDY-CHILDREN'S INFORMATION SHEET

Date:

Ethics Number: 06/ Q1702/ 74

R&D reference number: WHC 665

Instructions for parents: Please read this information sheet to your child if they are unable to read it for themselves

Study title: Finding out how your brain works when you use your hands.

Why is this project being done?

This research will test how your brain works when you use each of your hands.

Invitation to take part. Why have I been asked to take part?

Read the following information carefully and discuss it with your parents before you decide if you want to take part or not. You have been asked to take part because you are between 6-11 years old and one of your hands is stronger than the other.

Did anyone else check the study is OK to do?

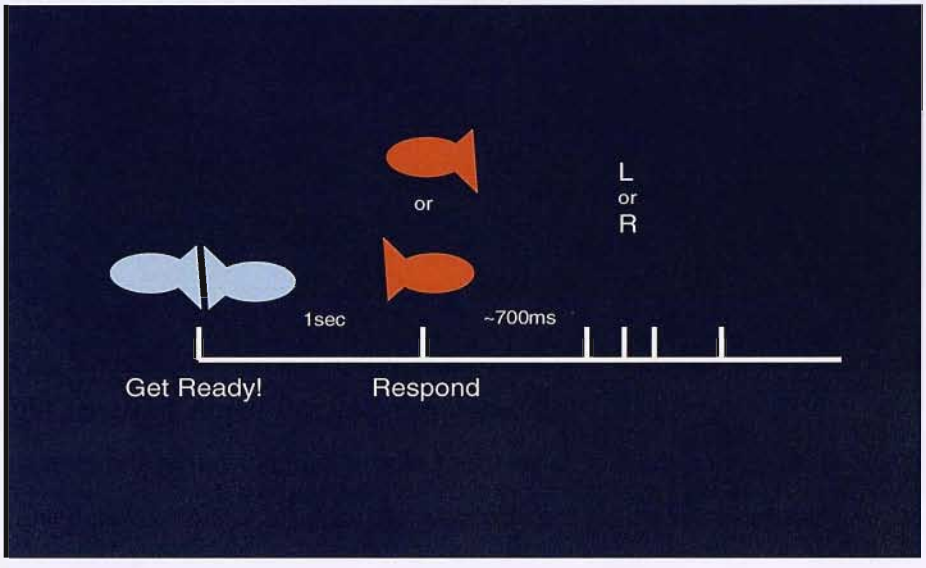
This study has been checked by the Southampton & South West Hampshire Research Ethics Committee.

Do I have to take part?

No. Taking part or not is entirely up to you and if you decide not to take part noone will mind.

What will happen to me if I take part in the research?

To see how your brain works we will have to meet you and your parents once. During this time, we will place 14 sticky pads on your head. We will then give you a computer game to play called 'Fish'. In this game you have to press one of two buttons according to the direction the fish is swimming (look at the picture below).



Might anything about the research upset me?

This research is not uncomfortable but if you do find it unpleasant the pads will be removed in less than 2 minutes and you will not have to do it again.

Will joining in help me?

The study will not help you but the information we get might help treat young people like you with better treatments in the future.

What if something goes wrong during the project?

In this case your parents will contact the researcher who will try to find a solution to the problem. If she is not able to do this, your parents will have other ways to complain.

Will my medical details be kept private if I take part? Will anyone else know I'm doing this?

The only people that might see your medical details or know that you joined the study will be your doctor and therapists, the researcher and her supervisors.

What if I don't want to do the research anymore?

If at any time you don't want to be in the study, just tell your parents. They will not be cross with you.

Thank you very much for taking time to read this information sheet!

APPENDIX 6

CONSENT/ ASSENT FORMS

UNIVERSITY OF
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and Rehabilitation Sciences

FEASIBILITY STUDY-PARENTS' CONSENT FORM

Pavlina Psychouli
School of Health Professions and Rehabilitation Sciences
University of Southampton
Highfield Campus, Bldg. 45
Southampton, SO17 1BJ
Tel: 02380598922
Email: pp8@soton.ac.uk

Date:
Consent Form version No 2
Ethics Number: 04/ Q1701/ 129
R&D reference number: WHC 548
Centre Number:
Study Number:
Patient Identification Number for this trial:

Title of project: Forced use therapy in children with congenital cerebral palsy: A feasibility study.

Name of researcher: Pavlina Psychouli

Please initial box

1. I confirm that I have read and understand the information sheet dated.....(version.....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐

3. I understand that sections of any of my child's medical notes may be looked at by the researcher and discussed with the consultant pediatrician and my child's therapists where it is relevant to my child's participation in the research. I give permission for these individuals to have access to my child's records. ☐

4. I understand that my child will be recorded on videotape to provide information about how the splint has affected their behaviour during the intervention period. ☐

5. I understand that my child's GP and therapists will be informed of my child's participation in this study. ☐

6. I agree for my child to take part in the above study. ☐

Name of Patient's parent	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

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and Rehabilitation Sciences

EFFECTIVENESS AND LRP STUDY (PATIENT GROUP)-PARENTS' CONSENT FORM

Date:

Ethics Number: 06/ Q1702/ 74

R&D reference number: WHC 665

Centre Number:

Study Number:

Patient Identification Number for this trial:

Title of project:

Name of researcher: Pavlina Psychouli

Please initial box

1. I confirm that I have read and understand the information sheet dated.....(version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. I also understand that if I decide for myself and my child to withdraw, data collected up to our withdrawal will be used. ☐

3. I understand that relevant sections of any of my child's medical notes may be looked at by the researcher and discussed with the consultant pediatrician and my child's therapists where it is relevant to my child's participation in this research. I give permission for these individuals to have access to my child's records. ☐

4. I understand that my child will be recorded on videotape to provide information about how each intervention period has affected their functional performance. ☐

5. I agree to our GP being informed of my child's participation in this study. ☐

6. I agree for my child to take part in the above study. ☐

Name of Patient's parent	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

When completed, 1 for parent/ guardian; 1for researcher site file; 1(original) to be kept in medical notes

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and Rehabilitation Sciences

EFFECTIVENESS AND LRP STUDY-CHILDREN'S ASSENT FORM

Date:

ASSENT FORM FOR CHILDREN

(to be completed by the child and their parent/ guardian)

Project title: Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study

Child (or if unable, parent on their behalf) /young person to circle all they agree with please:

Have you read (or had read to you) about this project?	Yes/No
Has somebody else explained this project to you?	Yes/No
Do you understand what this project is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Have you had your questions answered in a way you understand?	Yes/No
Do you understand it's OK to stop taking part at any time?	Yes/No
Are you happy to take part?	Yes/No

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your name _____

Date _____

Your parent or guardian must write their name here too if they are happy for you to do the project

Print Name _____

Sign _____

Date _____

The researcher who explained this project to you needs to sign too:

Print Name _____

Sign _____

Date _____

Thank you for your help.

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School of Health Professions
and Rehabilitation Sciences

LRP STUDY-PARENTS' CONSENT FORM (CONTROL GROUP)

Brain waves and attention

Consent Form (Date: .....)

Please bring this form to your child's appointment.

I _____ (full name in block capitals)

have read the information sheet dated ..... and consent to my child's participation in this study. I understand that I (and/or my child) may withdraw consent and discontinue participation at any time without penalty or loss of benefits to myself or my child. I understand that the data collected as part of this research study will be treated confidentially, and that published results of this project will maintain my and my child's confidentiality. In signing this consent letter, I am not waving my or my child's legal claims, rights, or remedies. A copy of this letter has been offered to me.

I give consent for my child to participate in this study (circle yes or no):

YES NO

(For children)

I give consent for my participation in this study (circle yes or no):

YES NO

Signature _____ Date _____

Name of Researcher taking consent:_____

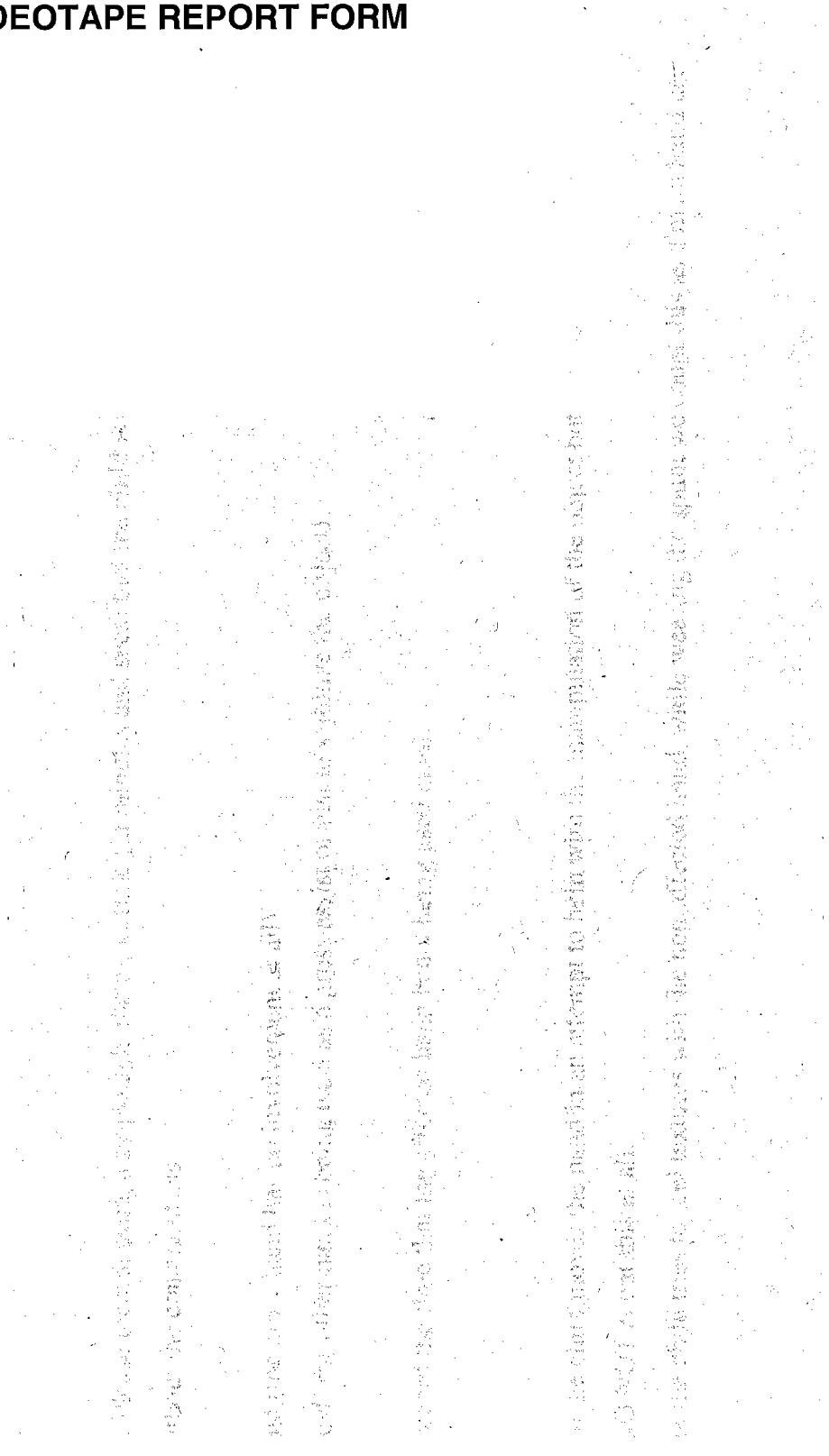
_____

The study has been described to my child by myself and/or the researchers, and I am satisfied that at this time my child appears enthusiastic about taking part. I understand, however, that I may withdraw them from the study at any time if I believe they are unhappy.

_____	_____	_____
Name of Parent	Date	Parent's Signature

APPENDIX 7

VIDEOTAPE REPORT FORM



VIDEOTAPE REPORT FORM

Instructions: Please record, using a stopwatch, the exact time (in minutes and secs) that the child is using their affected and non-affected hand (with and without the constraint) as:

-the only hand (the other hand has no involvement at all)
-the main hand (the other hand is being used as a gross assist or just to stabilize the object)

Please also record the time that the affected hand is not being used at all

- When the child moves the hand in an attempt to help with the manipulation of the object but does not use the hand eventually in any way, we DO NOT count this at all.
- When the child tries to feel textures with the non-affected hand, while wearing the splint we count this as a main hand use.

Rater's name:……..

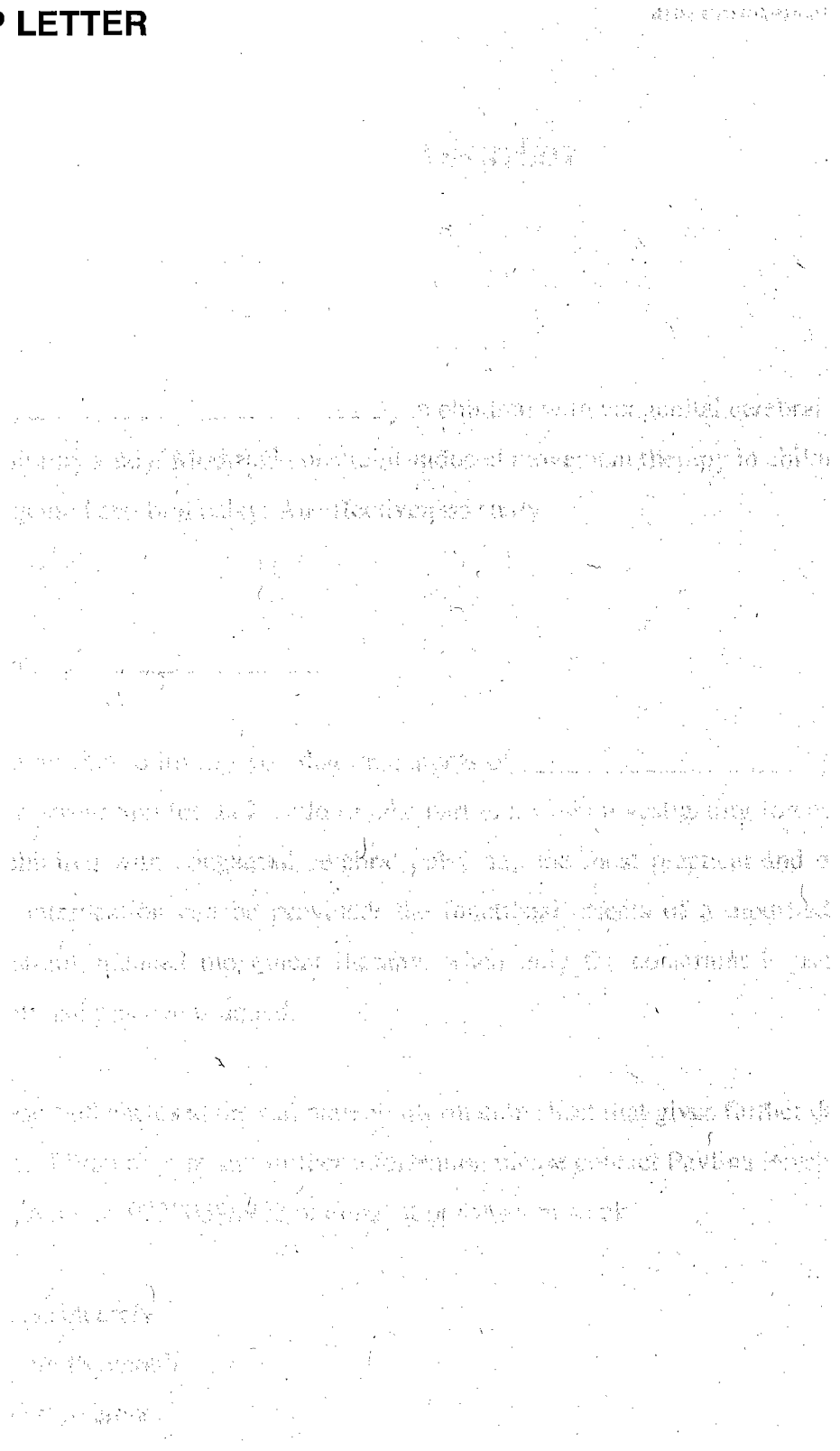
Child's id:……..

Splint type:……...

	WITH CONSTRAINT		WITHOUT CONSTRAINT	
	Affected hand	*Non-affected hand*	*Affected hand*	*Non-affected hand*
Used as only hand				
Used as main hand				
Hand not being used at all				

APPENDIX 8

GP LETTER



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and Rehabilitation Sciences

FEASIBILITY AND EFFECTIVENESS STUDY

Date:

Ethics Number: 06/Q1702/74

GP information letter version no 1

STUDY TITLE: Forced use therapy in children with congenital cerebral palsy: A feasibility study/ Modified constraint-induced movement therapy in children with congenital cerebral palsy: An effectiveness study.

Dear _____

I am writing to inform you that the parents of _____ have given their permission for their child to take part in a study investigating forced use therapy in children with congenital cerebral palsy and the most practical and effective way this intervention can be provided/ the functional effects of a modified protocol of constraint-induced movement therapy, when only the constraint is used and when additional practice is added.

Please find enclosed the full patient information sheet that gives further details of the study. If you require any further information please contact Pavlina Psychouli by telephone on 02380598922 or email at pp8@soton.ac.uk

Yours sincerely

Pavlina Psychouli

Lead Researcher

APPENDIX 9

HEMIHELP ADVERTISEMENT

Date:

RESEARCH STUDY

Title: ***Modified constraint-induced movement therapy (mCIMT) in children with congenital cerebral palsy: An effectiveness study***

Pavlina Psychouli is an occupational therapist and the chief investigator in the above mentioned research study, based at the University of Southampton. CIMT includes restraining (using a splint) the non-affected arm of children with hemiplegia and providing intensive exercise to the affected one. This intervention although effective, is very demanding and many patients and therapists believe it is not practical. An intervention that may be more practical comprises only the restraint element of CIMT without any additional exercise. In this study, the functional effects of two versions of a modified protocol of CIMT will be examined. One version will involve only the restraining part of CIMT, while the other will also include functional activities at home.

If you are a parent of a child with congenital cerebral palsy, aged 4-11 years, you are living in the cities or surrounding districts of Southampton, Portsmouth or Poole and you are interested in finding out more about this study, please contact Pavlina Psychouli on:

Tel. number: 02380598922 or via email at:

E-mail address: pp8@soton.ac.uk

APPENDIX 10

LRP STUDY POSTER

BRAIN WAVES AND ATTENTION

DOES YOUR CHILD'S BRAIN "LIGHT UP" WHEN THEY CONCENTRATE?

We are interested in finding out!

- **This simple test will be done in the Department of Psychology in the University of Southampton**
- **It will take 1 hour and involve recording brain waves using electrodes on the scalp**
- **It is fun to do!**
- **It will help us to understand how the brains of children with cerebral palsy work differently from those of healthy children, aged 5-11 years**

Would you and your child like to participate in this study?

For further information, please contact Pavlina Psychouli on 02380 598 922 or by email at pp8@soton.ac.uk

APPENDIX 11

LRP STUDY-DEBRIEF FORM

UNIVERSITY OF
Southampton
School of Health Professions
and Rehabilitation Sciences

Brain waves and attention

Post-participation description of study for parents and children (Date: .....).

As you know we are currently running a study to investigate the effects of an intensive type therapy in children with CP. In order for us to judge whether there are any physiological changes in these children' s brain after this therapy, it is necessary to compare their performance on the relevant measure to the performance of children who do not have any neurological problems. This is why we are grateful that you and your child agreed to participate in our study.

We were interested to see if we could record specific patterns of brain-wave activity in response to pictures. You may not have been familiar with this type of assessment and any comments about this part of the study are particularly appreciated.

Feedback about individual children is not given in this study. This is because individual brain waves do not show anything of interest. It is only when we average together brain waves from all children in each group that we can detect differences. Although our brain wave study is similar to a clinical EEG study (e.g. for epilepsy), it does not provide the level of information necessary for a clinical diagnosis. In other words, the information we obtained from your child is relevant only for the research questions of this study. If you are concerned about your child's health you should speak to your GP in the first instance.

We would like to thank you for your participation in our study, and remind you that you may withdraw consent for us to use your results even though you have already participated. If you have any further questions, please contact Pavlina Psychouli (pp8@soton.ac.uk).

If you have any concerns that the researchers could not address about your rights as a participant in this study, or if you feel that you have been placed at risk, you may contact the Chair of the School of Psychology Ethics Committee, School of Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: 023 8059 3995.

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