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FOCAL SPASTICITY THERAPY: EFFECTS ON MOTOR FUNCTION, HEALTH RELATED QUALITY OF LIFE, AND CENTRAL NERVOUS SYSTEM PLASTICITY

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Like a grain on the beach,
A stone on the mountain.
Like a rose in the garden,
A tree in the woods.
Like a drop in the ocean,
A fish in the pond.
Like a leaf in the tree,
A straw on the fields.
I am alone, still among friends
Like friendship, like love,
it embraces us all.

Erik Bergfeldt

To Lennart
and my family

ABSTRACT

The overall aim of the thesis was to obtain knowledge about the effects of a comprehensive spasticity management from several perspectives. To achieve this goal, we investigated the effects on motor functions, health-related quality of life and the central nervous system correlates to a motor task. Already from the beginning in 1999 we adhered to a strict strategy for focal spasticity therapy with careful patient selection and additional therapeutic interventions. In all 141 patients (study I, II, IV) we found an overall improvement in motor functions in 88-90 % of patients' therapeutic targets. Spasticty improved 1.1-1.2 on the Ashworth Scale. Quality of life (study II, n=41) improved in three of the eight SF-36 health scales, of which two were related to daily physical activities. However, the most significant improvement was found in the dimension of social functioning, which has a strong correlation to a mental dimension and a moderate correlation to a physical. Study III performed in healthy individuals, showed the CNS correlate to a right hand motor task within the primary and secondary motor cortices, supplementary motor cortex, and cerebellum. The regional extent and magnitude of BOLD activities varied moderately between sessions. In Study IV we observed that the patients had recruited larger areas within the right (healthy) hemisphere. Compared to the healthy subjects the brain activity remained more intense (higher BOLD activity) and extensive (more voxels), suggesting increased neuronal activation, increased energy consumption and blood flow during motor performance even after treatment.

However, following the comprehensive focal spasticity management there was brain reorganization in a "normalising" direction in addition to improved motor function.

Key words: adults, cerebral palsy, stroke, traumatic injury, spasticity, botulinum toxin - type A , physical therapy, health-related quality of life, functional MRI, reproducibility, healthy subjects, motor task, data-glove

LIST OF PUBLICATIONS

I. Bergfeldt U, Borg K, Kullander K, Julin P. Focal spasticity therapy with botulinum toxin: effects on functions, ADL, and pain in 100 adult patients. J Rehabil Med 2006;38:166-171.

II. Bergfeldt U, Sköld C, Julin P. Short form 36 assessed health-related quality of life after focal spasticity therapy. J Rehabil Med 2009;41:279-81.

III. Bergfeldt U, Jonsson T, Bergfeldt L, Julin P. Atlas-based analysis of single-subject fMRI central nervous system activity during a hand motor task – a validity and reliability study in healthy individuals. In manuscript.

IV. Bergfeldt U, Jonsson T, Sköld C, Julin P. Central nervous system plasticity and functional effects in stroke patients receiving comprehensive focal spasticity management – an fMRI study. In manuscript.

These publications will be referred to in the text by their Roman numerals.

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily living
AS	Ashworth Scale
BA	Brodmann area
BL Scale	Birgitta Lindmark Motor Assessment Scale
BOLD	Blood oxygen level dependent
BoNT-A	Botulinum toxin type-A
CI	Confidence interval
CP	Cerebral Palsy
CNS	Central nervous system
CV	Coefficient of variation
EMG	Electromyography
FEAT	fMRI Expert Analysis Tool
FILM	FMRIB´s Improved Linear Modeling
fMRI	Functional magnetic resonance imaging
FSL	FMRIB Software Library
FWHM	Full width at half maximum
GLM	General Linear Model
HRQL	Health related quality of life
ICF	International Classification of Functioning, Disability and Health
MATLAB	The Mathworks, Natick, MA
MCFLIRT	Motion Correction using FMRIB's Linear Image Registration Tool
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PRM	European Federation of Physical and Rehabilitation Medicine
PT	Physical therapist
ROM	Range of motion
SPECT	Single photon emission computed tomography
SD	Standard deviation
SF-36	Short form-36
TBI	Traumatic brain injury
U	Units
UMNS	Upper motor neuron syndrome
VR-glove	Virtual reality data glove
WHO	World Health Organisation
Hz	Herz, periods per second
R	Right
L	Left
X plane	Frontal plane
Y plane	Sagittal plane
Z plane	Vertical plane
2-PD	Two-point discrimination
9HPT	Nine-Hole-Peg Test

1 INTRODUCTION

1.1 REHABILITATION MEDICINE

Rehabilitation has been defined by the World Health Organisation (WHO) as ”The use of all means aimed at reducing the impact of disabling and handicapping conditions and at enabling people with disabilities to achieve optimal social integration” (Martin 1988). This definition incorporates clinical rehabilitation but also the important concept of social participation: to remove social and vocational barriers to participation in people with disabilities. Within a health context, rehabilitation specifically has been defined as “a process of active change by which a person who has become disabled acquires the knowledge and skills needed for optimal physical, psychological and social function” (Bax 1988). This definition provides a more explicit indication of the process that is undertaken by individuals with disabilities in developing their own capacities, which is the area most effectively promoted by medical rehabilitation.

Rehabilitation medicine is the medical discipline that, on a scientific basis, covers interventions aimed at improving physiological and mental functioning. It uses physiological mechanisms (e.g. functional adaptation and neuroplasticity), as well as physical and mental training. It focuses not only on physical functioning but also on enabling people to participate actively in society (Gutenbrunner 2007). The principal aims in rehabilitation medicine are to optimise social participation and quality of life. This involves reducing the impairment and/or disability and to support an individual’s requirement to reach a level of autonomy and independence, including participation in vocational, social and recreational activity, consistent with their human rights (André 1999). When motor impairment due to spasticity occurs it can result in a patient experiencing difficulty in performing activities of daily living (ADL), attempting to use fine-motor skills or when ambulating. Environmental factors may therefore be an important influence as movements occur in interaction between the individual, the task, and the environment where the task is being performed.

To guide and aid the health care professional there is the Rehab-CYCLE developed by Stucki and Sangha (Stucki 1998). The endpoints of the rehabilitation management system are successful problem solving or the achievement of individual goals. The Rehab-CYCLE involves identifying the patient's problems and needs, relating the problems to relevant factors about the person and the environment, defining therapy goals, planning and implementing the interventions and assessing the effects **(**Fig.1).

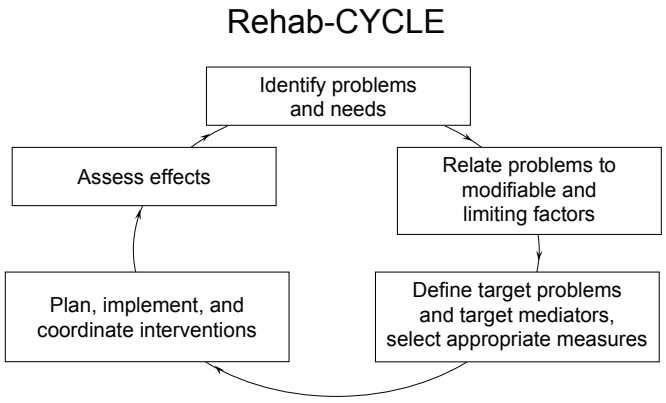


Figure 1. The Rehab-CYCLE

According to the European Federation of Physical and Rehabilitation Medicine (PRM), the prevalence of disability in most European countries is approximately 10% (Gutenbrunner 2007). Populations are ageing, and this is also creating increasing levels of disability. The PRM has adopted the WHO's International Classification of Functioning Disability and Health (ICF), and is also guided by the ICF biopsychosocial model. This model changed the concept of health towards a more holistic version, and was developed in cooperation with user organisations after criticism of the somatic focus of the biomedical model in the late 1970s. Today, the generally accepted definition of health is that given by the WHO: "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO 2002). The ambition is thus to achieve an overall state of health through a combination of physical, mental, emotional and social well-being. In general, modern definitions of the concept of rehabilitation are based on the ICF, which was approved for international use in May 2001 (resolution WHA54.21) (WHO 2001), after a revision of the 1980 International Classification of Impairments, Disabilities and Handicaps (ICIDH) (WHO 1980). Additionally, the biopsychosocial model is also the basis for current physiotherapy, defined by the World Confederation for Physical Therapy (WCPT).

The ICF is based on two parts, each with two components. Part one (functioning and disability) consists of body functions and structures, as well as activities and participation. Part two (contextual factors) comprises environmental and personal factors. The ICF, in relation to each of its components, chapters, categories and levels placed into a theoretical framework, provides a comprehensive description of a patient's physical health, psychological state, social and environmental relationship (Fig. 2). The ICF has been applied in study I (retrospectively), and in study II and IV (prospectively).

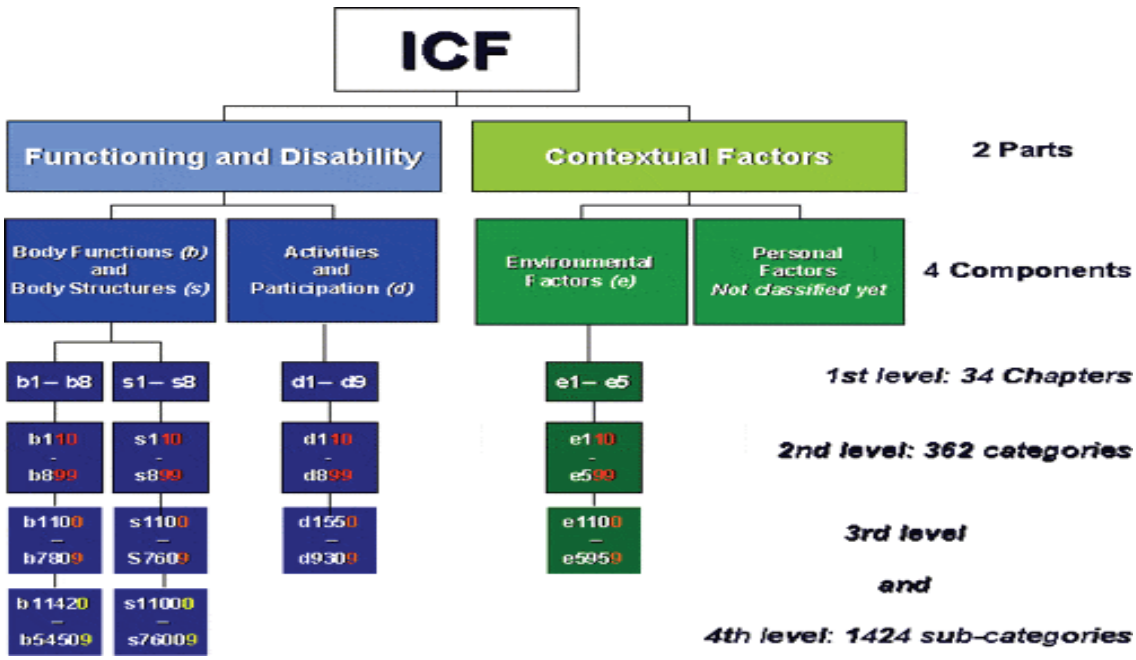


Figure. 2. The ICF classification is organized in a hierarchical scheme according to the following structure of the taxonomy and terminology: components, chapters (1st level), categories (2nd level) and 3-4th level. Source: www.unescap.org.

Multidiciplinary teamwork in rehabilitation medicine

Teamwork is a coordinated and continuous process of professional activity in order to achieve optimal outcomes, and is thus a fundamental factor in rehabilitation medicine (Korner 2004). The multidisciplinary team is the preferred model, through the joint sharing of knowledge it produces more than each profession could accomplish alone and leads to a mutual reinforcement and synergistic effort (Heruti 1995, Suddick 2006). Different professions, assessments and evaluations are brought together to obtain a holistic view of the patient's problems. This allows realistic rehabilitation measurements to be taken and realistic objectives to be set in order to obtain the best possible outcome (Norrefalk 2003). The term "multidisciplinary team" has been defined as "activities that involve the efforts of individuals from a number of disciplines. The efforts are disciplinary-orientated and, although they may impinge upon clients or activities dealt with by other disciplines; they approach them primarily through each discipline relating to its own activities" (Melvin 1980). The team usually includes a physician specialized in rehabilitation medicine and representatives for paramedic disciplines, e.g. physical therapists, occupational therapists, psychologists, social counsellors (social workers), nurses, speech therapists, orthopaedic technicians or engineers and medical secretaries.

Neurorehabilitation-organisation

Within the discipline of rehabilitation medicine there are subspecialties. The Stockholm Rehabilitation Clinic at Danderyd and Huddinge Hospital, comprises units for neuro-rehabilitation, traumatic brain injuries (TBI) and pain. In the neuro-rehabilitation unit, the overall aim is to aid recovery and to minimize and/or compensate for functional alterations from a nervous system injury or disease. Since 1999, the Danderyd/Huddinge unit includes an outpatient clinic for adult patients with spasticity due to upper motor neuron damage or disease, mainly depending on cerebral palsy, stroke, multiple sclerosis (MS) or other miscellaneous diagnoses.

1.2 SPASTICITY

Definition

The word spasm originates from the Greek word "spasmos" meaning to pull or drag, which is consistent with the definition of spasticity today as an involuntary, velocity-dependent, increased resistance to stretch.

The most used definition of spasticity is that given by Lance: "spasticity is a motor disorder characterised by a velocity-dependent increase in the tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motor neuron syndrome"(Lance 1980).

The velocity-dependent increase in muscle resistance to movement is essential and differentiates spasticity from other forms of increased muscular tone such as rigidity or dystonia. Muscle tone or the elastic tension of muscles, refers to the force with which a muscle resists being lengthened. Components of the muscle tone are the intrinsic elasticity or stiffness, but also a neuronal component related to the stretch reflex feedback loop that resists lengthening (Pearson 2000). In healthy subjects, this reflex is important in coordinating movements in which muscles are contracted and relaxed and in keeping the muscle from stretching too far.

Pathophysiology

The main factors affecting mobility in patients with injury to the central nervous system (CNS) are muscle overactivity (spasticity, rigidity, tremor, spastic co-contraction and spastic dystonia), motor weakness and soft tissue contractures (Gracies 2002a). In addition, somato-sensory and cognitive impairments affect control of simple and complex voluntary movements (Carey 1995). The most common disorders that may lead to upper motor neuron damage are diagnoses such as cerebral palsy (CP), stroke (ischemic or hemorrhagic), TBI, spinal cord injury (SCI), multiple sclerosis (MS), neurodegenerative diseases or infection of the brain (encephalitis or meningitis).

Although the pathophysiology of spasticity is not completely understood, the general opinion of the mechanism is that spasticity may develop when an imbalance occurs in the excitatory and inhibitory input to alpha motor neurons, leading to increased activity or excitability in the muscles (Mayer 1997, Thompson 2001). Shortening of motor neuron dendrites and collateral sprouting of dorsal root afferents may also play a role in the hyperexitability of the alpha motor neurons (Burke 1988, Katz 1989). In humans, a lesion of the upper motor neuron is generally believed not only to disrupt the pyramidal tract, but also nearby motor pathways such as the cortico-reticulospinal tract that is involved in voluntary movements (Pearson 2000). Damage to these tracts cause changes in activity of the alpha motor neurons and inter- neurons at the segmental level, which is considered essential for the development of spasticity (Mayer 2002).In the initial state, some muscles will be immobilised in a shortening position, which can be the first cause of muscle shortening. Muscle shortening, by itself, may also be the first generator of spasticity (Maier 1972), spasticity and muscle shortening may then continue to aggravate contracture (Fig. 3).

The upper motor neuron syndrome (UMNS)

Spasticity is one component of the UMNS together with released flexor reflexes, loss of dexterity and weakness (Meyer 2002) (Table 1). It is usually unequally distributed in the muscle groups of an extremity, which causes imbalance between agonists and antagonists and contributes to functional impairment. Spasticity is an important “positive” diagnostic sign of the UMNS and when functional shortening of muscles occur it restricts motion, and may cause disability. The “negative signs” are those features that have been lost following brain damage, e.g. loss of strength and dexterity (Burke 1988, Lance 1990, Meyer 2002). “Negative symptoms” due to structural shortening of muscles in changes in the rheologic (plasticity, visco-elasticity) properties of the involved muscles, tendons and joints causing stiffness and contractures, are among the most significant consequences of spasticity. Also, weakness may be more important to the function than spasticity itself and may be the primary contributor to impairment (Mayer 2002). The independence of the positive and negative features has been recognised (e.g. Burke 1988), and will importantly affect assessment and management procedures when viewing positive and negative signs as separate features. In the clinic, it is thus crucial to distinguish whether the muscle resistance is due to rheologic changes and/or spasticity, since the distinction has therapeutic implications (Mayer 2002).

Table 1. Clinical features in the UMNS

Positive symptoms

Spasticity
- increased muscle tone
- exaggerated tendon jerks
- stretch reflex spread to extensors
- repetitive stretch reflex discharges (clonus)

Released flexor reflexes
- Babinski response
- mass synergy patterns

Negative symptoms

Loss of dexterity
Weakness
- inadequate force generation
- slow movements

Additional: Loss of selective control of muscles and limb segments and rheologic changes in spastic muscles: stiffness, contracture, fibrosis, atrophy.

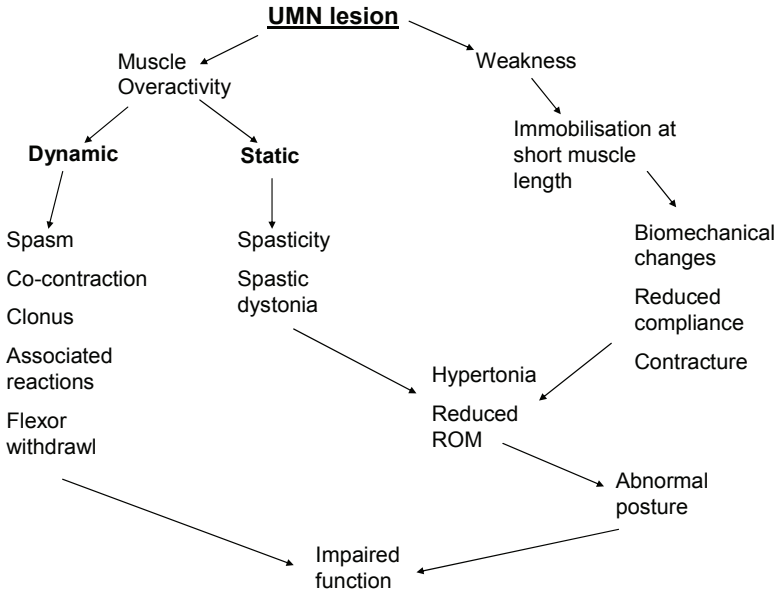


Figure 3. Consequences of an upper motor neuron (UMN) lesion. A model of the interaction between neural and biomechanical components of hypertonia in the UMNS (Sheean 2005)(ROM = range of motion)

Pain in spasticity

Spasticity is not recognized to be extremely painful. However, when spasms occur they may contribute to pain in causing joint deformities, macerated skin, muscle tightness or stiffness which subsequently may disturb sleep and cause fatigue (Dunne 1995, Wissel 2000). Pain may also be a spasticity trigger together with conditions such as pressure sores, constipation, emotional stress, fear, infections, and other external stimuli (Mayer 2002, Reichel 2005).

Frequency of spasticity

Studies of disorders in which spasticity is a common finding, have shown that spasticity affects between 37% and 78% of individuals with MS (Goodin 1999, Barnes 2003), 40% of those with SCI, more than 90% with CP (Wichers 2005), and approximately 50% of patients with TBI. Higher rates are found in those with midbrain and pons lesions (Wedekind 2005). Approximately 20-35% of stroke patients suffer from spasticity (Watkins 2002, Sommerfeld 2004, Welmer 2006).

Spasticity management

Spasticity therapy has emerged as an important approach to alleviate symptoms and is usually combined with physical interventions such as physical and occupational therapy and orthoses (Dengler 1992, Yablon 1996, Simpson 1996, Burbaud 1996, Turner-Stokes 2002, Bergfeldt 2006, Wissel 2008). However, not all spasticity can or even should be treated. Inappropriate treatment of spasticity may lead to loss of function, particularly when it is counterbalancing the effects of a paresis. Tone reduction is indicated only if spasticity interferes with function, positioning, care or comfort (Meyer 2002).

The primary treatment aim is to improve the quality of life for the patient and their family, in coordination with their caregivers. The development of treatment goals should, therefore, be realistic and clearly defined together with members of the spasticity management team The patient's age, preferences and ability to comply with treatment need to be taken into consideration prior to commencing therapy (Richardson 1999, 2002). Throughout the course of treatment, alterations in the treatment plan should be based on the response to therapy and adverse reactions, with expectations redefined during the therapy sessions.

Common treatment goals in general *and* in focal spasticity are:

- Functional improvements in mobility, transfers, seating and positioning, balance, wheelchair management and sexuality.
- Ease of care in dressing, feeding, positioning, hygiene and bathing.
- Increased comfort from the reduction of pain, improvement of sleep and improved orthosis fit.
- Prevention or treatment of musculoskeletal complications such as contracture, spasm and subluxation, reduction of pressure sores and increased efficacy of / reduced need for casting.
- Improved body image.
- Enhanced efficiency of physical and occupational therapy programmes.

The management of muscle overactivity in adults can be divided into *pharmacological therapies, physical management* and *surgical interventions*. A combination of these treatments is common (Fig.4).

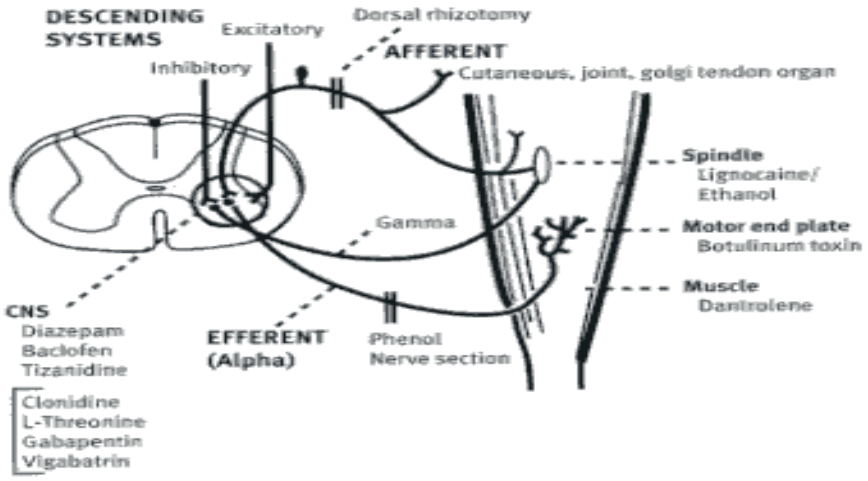


Figure 4. Management of spasticity: pharmacological and surgical intervention

Pharmacological therapies

A variety of medications are available for the treatment of spasticity. Pharmacological therapies can be systemic (general), using oral or intrathecal administration of "antispastic" drugs and/or local, with intramuscular or perineural injections. However, antispasmodic drugs are nonselective and may cause side effects such as generalised muscle weakness, fatigue and sedation. In severe and/or more generalised spasticity, oral agents and/or intrathecal baclofen may however provide relief (Gracies 2002a,b).

Intrathecal administration

A relatively recent neurosurgical procedure to effectively reduce spasticity is intrathecal placement of a baclofen pump - a surgically implanted programmable pump for the intrathecal delivery of baclofen medication directly to its site of action. This non-permanent method increases afferent inhibition at the spinal level. Many reports have attested efficacy and relief in those patients with severe spasticity not tolerating oral baclofen because of its adverse effects (Penn 1988).

Focal therapy with Botulinum toxin type-A (BoNT-A)

Clostridium botulinum is an anaerobic bacterium that produces the most potent and acute toxins known to man. It is a naturally occurring protein where ingestion of the bacterium or its toxins causes a syndrome called botulism with limb paralysis, facial weakness, ophtal-moplegia, dysarthria, dysphagia, dyspnea, constipation and urinary retention (Jankovic 2002). There are different forms of botulism, where foodborne botulism occurs following ingestion of contaminated food, or from wound infection with the toxin itself. Botulism is a life threatening condition for which there is access to an antidote but it is, however, today a rare disorder (Davis 1993).

There are 7 different serotypes of BoNT: A-G where Botulinum toxin type A (BoNT-A), is a purified form used worldwide for the treatment of abnormal muscle contractions. The ability to block acetylcholine release in a relatively long-lasting but reversible fashion with few side effects has made it an important tool in a wide variety of neuromuscular disorders, including spasticity, the dystonias, tremor, tics etc. (Jankovic 2002). BoNT-A has been in clinical use in the US since 1989, and was approved for use in Sweden in 1992.

BoNT - type A is quantified in units (U), where one unit is equivalent to the amount of toxin needed to kill 50% (LD 50) of a group of Swiss Webster mice (Aioki

2001). The adult recommended maximal dose is 400U. Dosing recommendations and their relation modifiers (patient weight, Ashworth score, duration of therapy, etc) are available in the literature (The WE MOVE spasticity study group 2002).

There are two commercially available BoNT-A products on the market: Botox® (Allergan, Irvine, CA, USA) and Dysport® (Ipsen Limited, Slough, Berkshire, UK), showing significant differences in potency (Heinen 2006).

BoNT - A affects the neuromuscular junction through binding and inhibition of acetylcholine release. It should enter the nerve endings to exert its chemodenervating effect. Once inside the cholinergic nerve terminal, BoNT-A inhibits the docking and fusion of acetylcholine vesicles at the presynaptic membrane (Fig.5). The drug may be given alone or in a combination with other spasticity treatments (Dressler 2005).

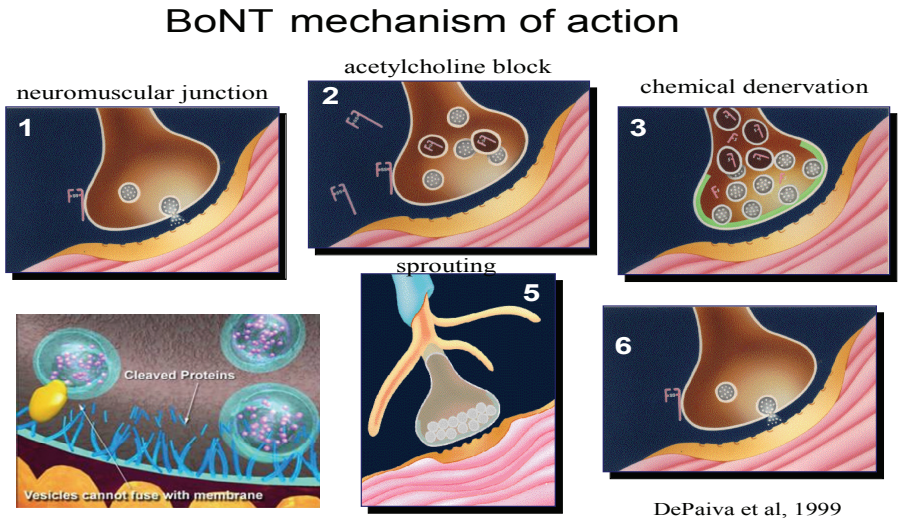


Figure 5. Showing the BoNT action mechanism

BoNT -A does not have regulatory approval for the treatment of spasticity in lower extremities, but is in Sweden approved of in upper extremities in stroke patients. However, it has been well studied in the treatment of spasticity in all forms and from all causes, particularly in CP and post-stroke spasticity (Verrotti 2006, Truong 2006, Sheean 2006, Satila 2006, Scholtes 2007, Kong 2007). Clinical effects are usually seen within 24 to 72 hours. The maximum weakening effect is almost always seen two weeks after injection. Duration of effect is usually 12 weeks. Gradually, spasticity returns which occurs when the effect of the toxin decreases. BoNT-A is dose dependent and reversible secondary to the regeneration process. Follow-up is crucial to measure the response to BoNT therapy and to fine tune muscle selection and the dosage prior to a possible re-injection (Sheean 2006).

The principal adverse effect is excessive muscle weakness in the injected muscles (overdosage), but also pain at the injection site and “flu-like” symptoms. Spread beyond the injected muscle does occur, although care in placing the injection in the muscle belly minimises this possibility. Although antibody formation appears to be rare with the use of BoNT-A it is recommended, when possible, to wait at least three months between injections and to use the minimum effective dose.

BoNT-B or Myobloc® has not been adequately evaluated in the treatment of spasticity to recommend its use in this patient population (Sheean 2006). The only randomised controlled trial that has assessed the use of intramuscular injections of

BoNT-B found that 10 000 units did not reduce muscle tone. Dry mouth was a common adverse event in the patients treated with BoNT-B (Sheean 2006).

Focal therapy with phenol perineural injections

Phenol nerve blockade is a very effective and cheap therapeutic option, and typically used when treating large muscles such as those of the anterior thigh (n. Obturator). The duration of the effect of phenol can be quite variable, from less than one month to more than two years (Pinder 2007). There are, however, several potential adverse effects attributed to the use of phenol, such as dysaesthesias and tissue necrosis. Nonselective tissue destruction to muscles or nerves may cause temporary or permanent pain near the injection site.

Before the advent of BoNT, treatment of spasticity with alcohol or phenol blockade was often used (Koman 1996). Today, however, alcohol is rarely used, and phenol is typically reserved for use in those cases that require the injection of large muscles or a large number of muscles. Phenol and BoNT may be combined to achieve maximum effect in specifically targeted muscles (Tilton 2003).

1.3 PHYSICAL INTERVENTIONS

The physical therapies are targeted at reducing muscle tone: improving range of motion, mobility, comfort and strength, and enhancing independence and the performance of activities of daily living (Albany 1997, Lockley 2004). Physical therapy, occupational therapy or both are included in most patient treatment regimens, with the level of the patient's and caregivers' motivation strongly associated with outcome.

Physiotherapy

Physiotherapy in spasticity management is aimed at promoting optimal movement patterns, enabling an individual patient to function as effectively as possible, minimising contracture and the development of deformity and reducing pain in order to reduce the burden of care and improve the quality of life (Richardson 2002). Accurate assessment, clear identification and appropriate measurement of the patient’s problem and therapy goals are of the highest importance for therapy outcome. In addition, implementation of the chosen intervention and reassessment and follow-up of the intervention provided has to follow the therapy plan (Johnson 2002).

In order to attain the identified goals there are various physical treatment approaches. Currently, a combination of different approaches is used. Physiotherapy for spasticity refers to a range of physical treatments (Fig.6). These therapy methods of spastic muscles are designed to reduce muscle tone, maintain or improve range of motion and mobility, increase strength and coordination and improve care and comfort. The choice of treatments is individualised to meet the needs of the person with spasticity.

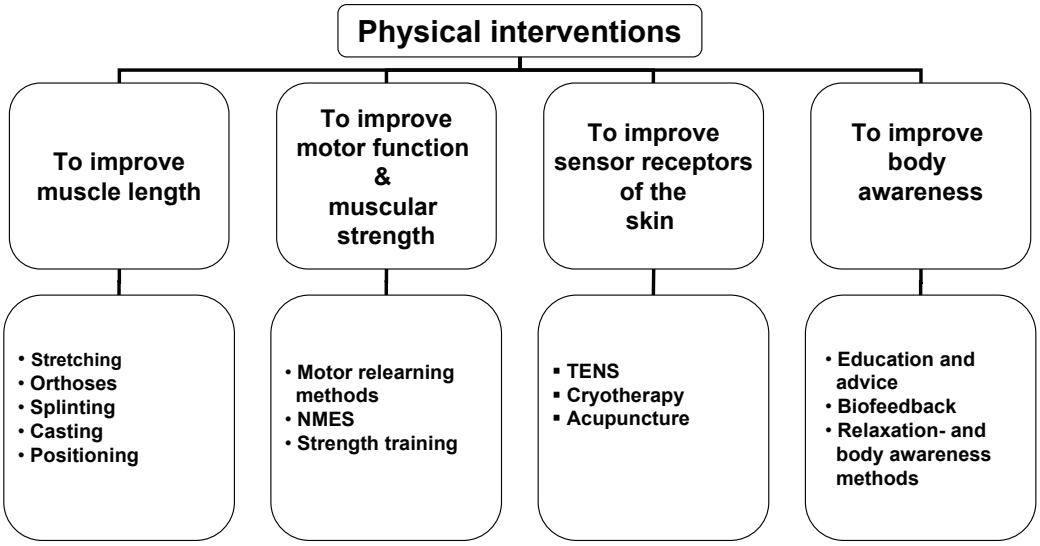


Figure 6. Physical management in spasticity therapy. NEMS = neuroelectromuscular - stimulation, TENS=transcutaneous electroneurostimulation

An important consideration before starting therapy is to determine the muscles involved in spasticity and the complex effect of these spastic muscles on joint movement and positioning, which may lead to the development of many different motor patterns (Meyer 1997). Because of the complex nature of spastic motor patterns, the physical therapist and the team need to have a good knowledge of these patterns. The appropriate means of their assessment will improve the skill in managing the spastic patient (Gormely 2002).

A variety of techniques may be used to better control or decrease spasticity before the therapist moves on to management for proper positioning, strengthening exercises or functional therapies.

Occupational therapy

The occupational therapist specialises in adaptation of the physical environment to meet the patient's needs and to teach modifications for dressing, feeding and grooming to the patient and caregiver. Educating the patient to understand and avoid compensations and positions that may reinforce spasticity is essential to carry over of the therapeutic programme. Such patient education may include ideal positions for ADL, sitting, transfers and sleeping. Additionally, the therapist offers expertise on adaptive devices such as wheelchairs and bath equipment and may advise on home and workplace modifications to increase accessibility and ease of use (Albany 1997).

Orthotic devices

Orthoses include any device that is used to support, align, prevent or correct deformities or to improve the function of movable parts of the body (Brunstrom 2001, Woo 2001). The primary goals in treating spasticity with orthoses include reducing tone, increasing or maintaining range of motion and preventing the breakdown of skin, e.g. the breakdown that can develop on the palm of the hand when the fist is continuously clenched.

Outcome measurements in the management of spasticity

Obtaining information on the response of spasticity to treatment is often difficult because the degree of spasticity may change throughout the day, - the course of the disease that causes the spasticity, or in response to various stimuli. Therefore, it is important when measuring response to treatment to have the assessment take place at the same time of day, in the same environment, and using the same measuring techniques and devices.

There are a number of commonly applied outcome measures to evaluate response to therapy (Table 2). A combination of rating instruments is often necessary because no individual instrument covers all areas of relevance. The choice of evaluation tools is dependent upon expected change.

Table 2. Example of measures used in spasticity management

	Outcome measures
Modality (ICF)	**Measure**
Body function and body structure (impairment)	Ashworth Scale (AS)/spasticity
	Goniometer/range of motion
	Visual Analogue Scale (VAS)/pain
	Dynamometer/hand strength
	Medical Research Council (MRC)/muscular strength
Activity (limitation)	The Birgitta Lindmark Motor Assessment Scale (BL-scale)
	Walking speed, stride length
	Nine Hole Peg test (NHP)/finger speed and dexterity
	Timed wheelchair mobility transfers
Participation (restriction)	Short Form-36 (SF-36)/health-related quality of life
	Sickness Impact Profile (SIP)/health related quality of life
Patient satisfaction	Visual Analogue Scale (VAS)
	Canadian Occupational performance (COPM)
	Verbal scale

Assessing muscle tone

Assessment of tone is central in neurorehabilitation. However, the lack of a precise definition of spasticity may account for the problem of developing a valid, reliable and sensitive method of measurement. Current clinical measurements are difficult and inaccurate (Kumar 2006). Thus, a prerequisite for using any scale is knowledge of its characteristics and limitations. The primary clinical measures of spasticity are the Ashworth Scale (AS) (Ashworth 1964) and the modified Ashworth Scale (MAS) (Bohannon and Smith 1987) (Table 3). However, assessing spasticity by measuring changes in resistance to passive movements only may not be sufficient, as the latter is influenced by many factors of which spasticity may only be one. Confusion exists about the AS and the MAS in their characteristics and limitations as measures of spasticity (Pandyan 1999).

The AS can be used as an ordinal level measure of resistance to passive movement, but not of spasticity. The MAS is considered fairly reliable (Gregson 2000) and not a valid ordinal level measure of resistance to passive movement or spasticity (Kumar 2006), and needs therefore to be treated as a nominal level measure of resistance to passive movement until the ambiguity between the 1 and 1+ grade is resolved. The AS may be more reliable than the MAS (Pandyan 1999). Thus, additional measurements of muscle activity (electromyography) will be required to quantify spasticity (Kumar 2006). The AS has been used in studies, I, II and IV.

Table 3. The Ashworth Scale

Ashworth 1964

0	No increase in muscle tone
1	Slight increase in tone manifested by catch-and-release or minimal resistance at end of the range of motion (ROM)
2	Marked increase in tone through most of ROM; the part of the body is still easily moved
3	Considerable increase in tone; passive movement is difficult
4	Affected part is rigid

The modified Ashworth Scale (Bohannon and Smith 1987)

1+	Slight increase in tone manifested by catch followed by minimal resistance in less than half of ROM

Additionally, there is the Tardieu Scale (Tardieu 1954) for assessing spasticity, which has been suggested to be a more appropriate clinical measure of spasticity than the Ashworth or modified Ashworth Scales. In theory, the Tardieu Scale does adhere more closely to Lance's definition of Spasticity since it involves assessment of resistance to passive movement at both slow and fast speeds. Some studies have identified the Tardieu Scale to be more sensitive than other measures, and to change following treatment with botulinum toxin. Validity and reliability tests of the scale for a variety of muscle groups in adult neurological patients have, however, not yet been undertaken (Haugh 2006).

While scales remain the most common method of measuring spasticity, there is considerable potential in instrumented techniques that can provide greater reliability and precision of measurement (Johnson 2002). There is a need for the development of new methods as well as techniques for spasticity measurement in the clinical setting.

The Birgitta Lindmark motor assessment scale.

For patients with cerebrovascular disease the Birgitta Lindmark Motor Assessment Scale (BL Scale) was developed (Lindmark 1988a).The chart for motor capacity assessment was modified after the Fugl-Meyer Sensorimotor Assessment Scale (Fugl-Meyer 1975). The chart comprises assessment of the ability to perform active movements and rapid movement changes, mobility, balance, sensation, joint pain and passive range of motion in the upper and lower extremity. There are seven parts (A-G), and each item within these parts is evaluated on a 4-point scale (0-3), with a higher score representing better function. A total score is then calculated. The paretic and the non-paretic sides can be evaluated parallel or separately, as well as other parts of the test might be used separately. In study IV, we choose to assess arm and hand

mobility and function with the BL Scale, A: I, II, III and B: velocity. The BL scale is considered reliable, valid and sensitive (Lindmark 1988b, c).

Surgical interventions

The goals of the surgical treatment of spasticity may include improving access for hygiene, the ability to tolerate braces and function such as walking, as well as reducing pain and the risk of deformities.

With *orthopedic surgery* muscles can be denervated and tendons and muscles can be released, lengthened or transferred. Most of the surgery takes place at the end of the organ: the muscle or the tendon. In tendon transfers, spastic muscles may be used to advantage by transferring them across the joint, relieving the deforming action of the muscle on the joint and simultaneously aiding the antagonist muscle. In some cases, a split transfer is desirable, for instance in the treatment of varus feet. In some situations, the transfer allows improved function. In others, the joint retains a passive but not an active function (Woo 2001).

In contracture release, the surgeon partially or completely severs the contracted tendon and then repositions the joint at a more normal angle. By altering the tension in the intrafusal muscle spindle, the stimulus for further contraction is diminished, which could lead to less Spasticity (Chambers 2002).

Neurosurgical procedures such as selective dorsal rhizotomy are also available, but mostly performed for the treatment of spasticity in children with CP. It may also be used on post-stroke spasticity to treat spasticity of the legs that interferes with movement or positioning. The method permanently reduces spasticity in cutting afferent excitatory nerve fibres emerging from the proprioceptors in the muscle spindles. The best result with this method can be achieved in a patient with good strength and balance, spasticity in either or both legs with minimal or no fixed contractures, no spasticity in the arms and strong motivation and support (Boop 2001).

Diagnoses common in rehabilitation medicine at our clinic and in our study

Stroke is defined as “a condition characterised by rapidly developing symptoms and signs of a focal brain lesion, with symptoms lasting for more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” (WHO, 1989). A stroke can be classified as ischemic (85%) (emboli, thrombosis) or hemorrhagic (15%). In Sweden, approximately 30 000 persons suffer acute stroke every year and about 100 000 have disabilities following stroke. The median age for stroke onset in Sweden is 76 years and 20% are younger than 65. Women and men are almost equally affected. Women are five years older at onset, and nearly twice as many men are afflicted before the age of 65 (Riks.stroke 2006).

Stroke causes death in approximately 20% of patients within six months. It is also a leading cause of morbidity, with motor deficits being the most common acute impairment after stroke and persisting in nearly half of all patients. Although much focus is on hemiparesis, injury to the motor system does not produce a homogenous clinical syndrome. Instead, weakness may be accompanied by other negative findings, such as slowness and fatigue, and by positive findings such as spasticity. Motor and sensory pathways are damaged due to lesion in the motor cortex, resulting in a contra lateral hemiparesis. Approximately two thirds of stroke patients suffer from impaired function in the upper extremities (69%) (Jorgensen 1995, 2000), and almost the same proportion (65%) in the lower extremities at admission (Jorgensen 2000).

CP is referred to a as an “umbrella term” encompassing a group of non-progressive, non- contagious conditions that cause physical disability in human

development. CP is caused by damage to the motor control centers of the developing brain. The complex syndrome of CP was already recognised and named in 1889 by William Osler. The current definition and classification of CP by Rosenbaum is from 2007. CP describes a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, behavior, and in severe cases, also by epilepsy and secondary musculoskeletal problems (Rosenbaum 2007).

The diverse symptomatology of CP is divided into three major classifications to describe different movement impairments: the spastic forms (83%), dyskinetic forms (12%) and ataxic forms (4%) (Hagberg 2001). In the different forms, the degree of motor and non-motor neurological involvement varies from mild to severe. Spasticity, however, with subsequent motor deficits, is the most dominating neurological symptom in the majority of the cerebral palsied. Additional long term effects of CP on patients and their families often include pain and reduced participation in society (Schwartz 1999, Majnemer 2008).

In ambulating patients with spastic diplegia, one of the most prevalent forms comprising spasticity in the lower extremities is scissor walking (where the knees cross) together with toe walking. In patients with more severe impairments, coordinated and isolated movements are almost impossible to perform. Joint and bone deformities and contractures are also common.

TBI is a lesion to the CNS cortex or spinal cord caused by an external force, and together with stroke, the most common reason for rehabilitation. Symptoms of TBI can be mild, moderate or severe depending on the extent of the damage to the brain.

1.4 HEALTH-RELATED QUALITY OF LIFE (HRQL)

Quality of life (QOL) is a personal assessment of the good and satisfactory characteristics of life (Finch 2002a). A global concept of an individual's own estimation of his/her life situation can include elements as diverse as perceptions of health, satisfaction with work environment, quality of family and social relationships, as well as financial well-being (Domholt 2000). In addition to a personal assessment of their own life situation, the individual's life expectations, and to what extent these are fulfilled are important components (Stensman 1985). Since quality of life as a global concept is a broad term, its use in health care research is limited. Therefore, a variety of measures of health-related quality of life (HRQL) have been developed, where HRQL is one dimension of the wider QOL (Domholt 2000). The construct of HRQL is broad and encompasses domains related to physical, mental (emotional and cognitive), social and role functioning, as well as an individual's perception of health and well-being (Fitzpatrick 1992). Within this construct, it is common to distinguish between generic and specific HRQL, the latter referring to, for example a specific disease, condition or patient group.

The generic HRQL instrument incorporates aspects that are relevant to all health states, including potentially healthy individuals. It can be applied to a wide range of populations and interventions and is often included in national population surveys. Generic measures allow the comparison of health across a wide variety of conditions and populations. They may be one-dimensional, e.g. addressing physical function such as the Bartel Index (gait, speed) or multidimensional, e.g. addressing social and

community life in conjunction with physical function like the Short Form Health Survey (SF-36) and the Sickness Impact Profile. Their comprehensiveness may be the most important attribute for their use in potentially healthy populations or when comparing groups with different conditions. A potential disadvantage of generic measures is that they may be less sensitive to change than specific measures (Maciejewski 1997). They may also have "ceiling and floor effects", limiting their ability to detect change at either the high or low end of the construct they are measuring. For example, the SF-36 includes several items reflecting a relatively high demanding physical function as walking a mile. An item such as this is unlikely to change in patients with chronic stroke, who after intervention, may have progressed only as far as to be able to dress and use the bathroom independently (Macijewski 1997). In addition, generic measures also tend to have less face validity (making sense to the person taking or administering the test) in that the patient or health professional may consider them too general to detect effects of intervention (Finch 2002b).

Specific measures may be specific to a disease, condition or patient.They are designed for a specific population with a condition or those with a disability in a part of the body. Therefore, specific measures tend to have greater face validity than generic measures (Atherly 1997). They may also be more sensitive in a patient group: most of the item scores are likely to change if problems are alleviated by an intervention, translating into a greater change in summary scores (Guyatt 1993). Because of their narrower focus, however, they may miss an anticipated effect of a treatment, such as a change in overall mental well-being or self-esteem (Atherly 1997). A patient-specific measure is the Canadian Occupational Performance Measure (COPM), tailored to suit those domains and constructs important to an individual patient (Law 1998).

Constructs such as HRQL cannot be rated using performance measures (e.g. walking, strength, range of motion). In this case, a self-report (questionnaires or interviews given by the patient or a caregiver) is particularly important to measure items that are most relevant to the individual patient. Different patients will provide different items, and it is generally agreed that these patient-specific measures should not be used to make comparisons among patients, or between groups of patients Measures that are specific to the patient, administrated as a self-report, can of course be used in conjunction with performance measures to explore the relationship between the patient's perception of his/her performance in a customary setting from his/her capacity in an ideal environment (Finch 2002b).

1.5 MAGNETIC RESONANCE IMAGING (MRI) AND FUNCTIONAL MAGNETIC IMAGING (FMRI)

Magnetic resonance imaging (MRI), or nuclear magnetic resonance imaging (NMRI), is primarily a medical imaging technique most commonly used in radiology to visualise the internal structure and function of the body. MRI is a relatively new technology, and has been in use for little more than 30 years (compared with over 110 years for X-ray radiography). It was first developed by Lauterbur (Lauterbur 1973).

MRI uses a powerful magnetic field to align the nuclear magnetization of hydrogen atoms in water in the body. Radiofrequency fields are used to systematically alter the alignment of this magnetisation, causing the hydrogen nuclei to produce a rotating

magnetic field detectable by the scanner. This signal can be manipulated by additional magnetic fields to build up enough information to construct an image of the body (Riederer 2004).

Using MRI, it is possible to create images of both surface and subsurface structures with a high degree of anatomical detail. MRI scans can produce cross sectional images in any direction. The MRI technology can provide a detailed assessment of the physical appearance, water content, inflammation or bleeding, and can also provide information about physiological and functional variables such as diffusion or blood flow at the time of imaging. A distinction is often made between "MRI imaging" and "functional MRI imaging" (fMRI), where MRI provides only structural information on the brain while fMRI gives both structural and functional data.

In 2003, the Karolinska Institutet Nobel Prize in Physiology or Medicine was awarded to Paul Lauterbur and Peter Mansfield for their developing of modern MRI (Fig.7).

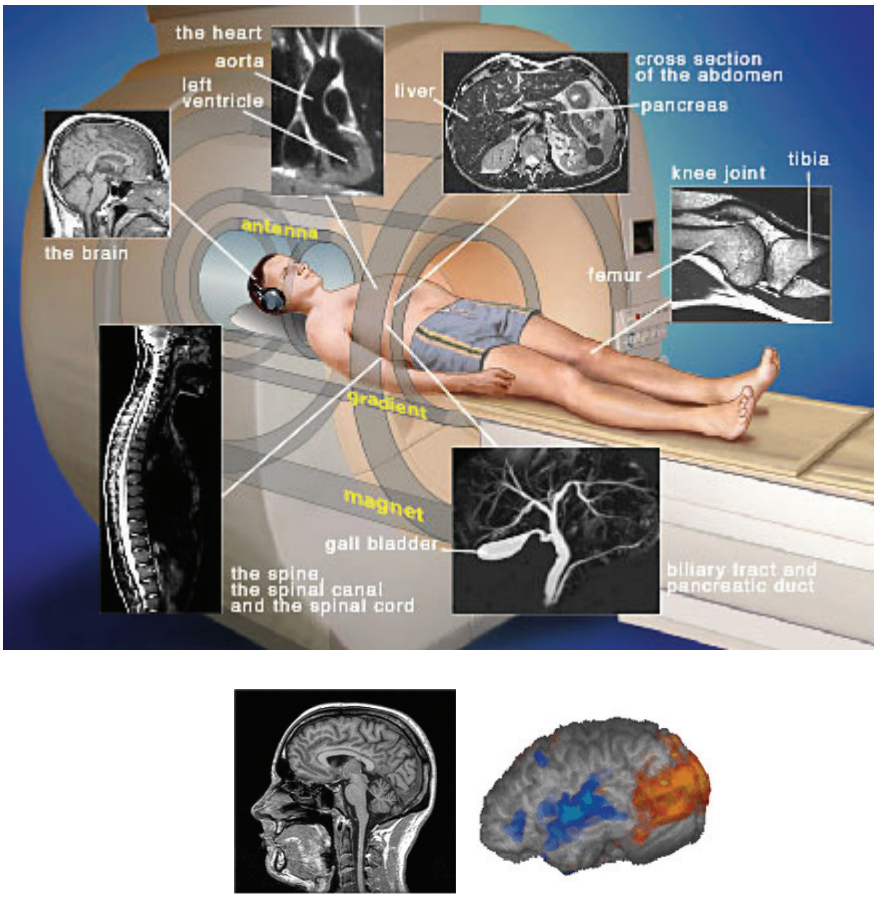


Figure 7. MRI is used for imaging of all organs in the body. Source: www.nobel.se, www.fmrib.ox.ac.uk/fsl

fMRI

fMRI is a specialised MRI scan, a technique for measuring brain activity. It measures the haemodynamic response, that is, changes in blood flow and blood oxygenation related to neural activity in the brain or spinal cord. When a brain area is more active it consumes more oxygen to meet the increased demand, thus blood flow increases to the active area. fMRI can be used to produce activation maps showing which parts of the brain are involved in a specific mental or functional process (Logothetis 2008).

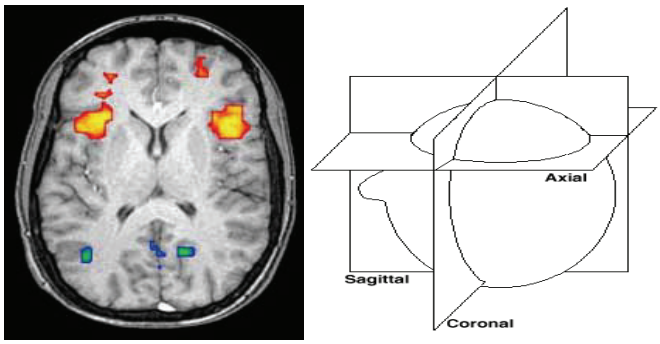
Since the early 1990s, fMRI has come to dominate the brain mapping field because it is non-invasive, provides no radiation exposure, has excellent spatial and good temporal resolution and is widely available. This has probably contributed to the common use for research in healthy subjects, neurophysiology, and increased application in clinical neuroimaging for the medical diagnosis of disease, in pre-surgical planning, studies of pre-symptomatic diagnosis, new therapies, functional brain disorders and in drug development.

Measuring changes in blood flow is however not new. The fist experiment was performed by the Italian scientist Angelo Mosso and can be found in William James's The Principles of Psychology, published in 1890 (James 1890). The suggestion that blood flow is coupled to neural activity was insightful, but the reported success can only have been wishful thinking on the part of the investigators.

"The subject to be observed lay on a delicately balanced table which could tip downwards either at the head or the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system…"

Figure 8. Photo of Angelo Mosso – the National Library of Medicine, USA

Another publication in the 1890s by Roy and Sherrington, showed that changes in blood flow and blood oxygenation in the brain are closely linked to neural activity (Roy and Sherrington 1890). In an experiment measuring oxygen metabolism and blood flow in 1948, Kety and Schmidt were the first to confirm that blood flow in the brain is regionally regulated by the brain itself (Kety 1948). They demonstrated that when neurons use more oxygen, chemical signals cause nearby blood vessels to dilate. The increase in vascular volume leads to a local increase in blood flow. The ability to measure cerebral blood flow (CBF), a correlate of brain metabolism, opened up the possibility of studying brain function in humans. The development of fMRI in the 1990s was generally undertaken by Ogawa and Kwong (Ogawa 1990, Kwong 1992), and is the latest in a long line of innovations, including positron emission tomography (PET) and near infrared spectroscopy (NIRS), which also use blood flow and oxygen metabolism to investigate brain activity (FMRIB Centre, Department of Clinical Neurology, University of Oxford).



a) b)

Figure 9a). Axial MRI slice at the level of the basal ganglia, showing fMRI BOLD signal changes overlaid in red (increase) and blue (decrease) tones. Functional imaging enables the processing of information by centers in the brain to be visualised directly. Such processing causes the involved area of the brain to increase metabolism and "light up" on the scan.
b). Axial, coronal and sagittal planes.

Blood oxygenation level dependent (BOLD) in fMRI - what does fMRI measure?

BOLD is the MRI contrast of blood deoxyhemoglobin discovered by Ogawa in 1990, who also recognized the importance of BOLD for functional brain imaging with MRI (Ogawa 1990). Figure 9a shows the fMRI BOLD signal visualised, and b) the reference planes.

Oxygen is delivered to neurons by haemoglobin in capillary red blood cells. When neuronal activity increases there is an increased demand for oxygen and the local response is an increase in blood flow to regions of increased neural activity. Fig.10.

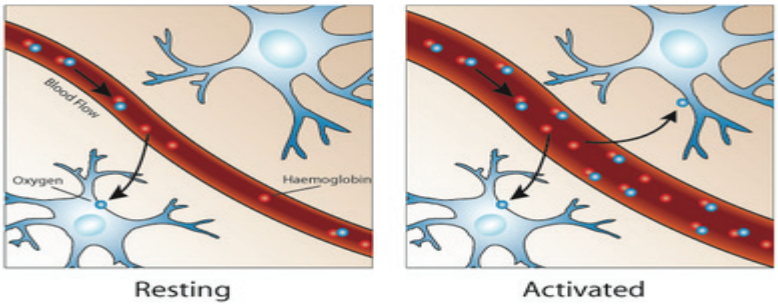


Figure 10. Diagram of the BOLD effect. Sourse: Stuart Clare, FMRIB Centre Oxford (www.fmrib.ox.ac.uk/fsl)

Haemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated. This difference in magnetic properties leads to small differences in the MR signal of blood depending on the degree of oxygenation. Since blood oxygenation varies according to the levels of neural activity these differences can be used to detect brain activity. This form of MRI is known as blood oxygenation level dependent (BOLD) imaging. Higher BOLD signal intensities arise from increases in the concentration of oxygenated hemoglobin since the blood magnetic susceptibility now more closely matches the tissue magnetic susceptibility. By collecting data in an MRI scanner with parameters sensitive to changes in magnetic susceptibility one can

assess changes in BOLD contrast. These changes can be either positive or negative depending upon the relative changes in both cerebral blood flow (CBF) and oxygen consumption compared to baseline. Increases in CBF that exceed changes in oxygen consumption will lead to increased BOLD signal. Conversely, decreases in CBF that outstrip changes in oxygen consumption will cause decreased BOLD signal intensity (Logothetis).

Critics of the technique argue that fMRI only measures the secondary physiological correlates of neural activity; that it is not a direct measure. This means that it is not a truly quantitative measure of activity - when comparing the fMRI response between individuals it is impossible to say whether the differences are neural or physiological in origin. Additionally, the temporal resolution of fMRI is limited by the slow blood flow response it depends upon; it cannot uncover the dynamics of brain activity on the sub-millisecond timescale on which neurons operate. There is also a complaint that FMRI overlooks the networking manner in which the brain operates, emphasising localised activity when it is the communication among regions that is most critical to brain function.

Technique

BOLD effects are measured using rapid volumetric acquisition of images with contrast weighted to be sensitive for signal changes caused by changing blood oxygenation level. Images are usually taken every 1–4 seconds, and the voxels in the resulting image typically represent cubes of tissue about 2–4 millimeters on each side.

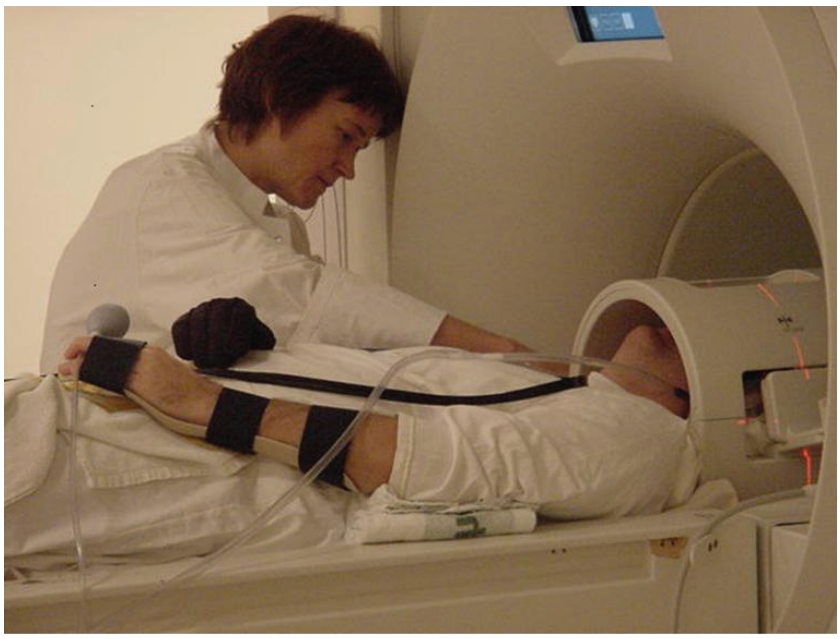


Figure 11. In our studies, MRI-data was acquired with a Siemens Magnetom Vision 1.5 T, and functional imaging was performed using a T2* - weighted gradient echo EPI mosaic sequence. The subjects were blindfolded and recorded instructions were delivered via a headset. A data glove was used to register the extension-flexion cycle frequency and to monitor compliance with the CD instructions. The one size data glove made from Lycra stretch fabric contained one embedded fiber optic sensor per finger. The optic sensors were linked to the computer via an optoelectronic unit, a ribbon cable and an interface box. In order to minimise flexor synergies and additional movements in the right wrist, a plastic orthosis was positioned over the wrist under the data glove. Another orthosis was used over the entire left hand and wrist to prevent co-contractions.

Subjects participating in an fMRI experiment are asked to lie still and are usually restrained with soft pads to prevent small motions from disturbing measurements. It is possible to correct for some amount of head movement with post-processing of the data, but large transient motion can render these attempts futile. An fMRI experiment usually lasts between 15 minutes and 2 hours, depending on the purpose of the study. Detailed instructions and descriptions of the experiment plan are given to each subject. Due to the nature of the MRI scanner there is an extremely strong magnetic field surrounding it, thus subjects must be examined for any ferromagnetic objects (e.g. watches, glasses, hair pins, pacemakers, bone plates and screws, etc.) before entering the scanning environment (Fig.11).

For analysis of the fMRI data there are several neuroimaging software applications available, e.g. FSL, SPM, AFNI, BrainVoyager, FreeSurfer and others.

The FMRIB Software Library (FSL)

In our studies, pre-processing and analysis were performed using the fMRI Expert Analysis Tool (FEAT) which is part of the Analysis Group at the Oxford Centre for Functional MRI of the Brain FMRIB Software Library (FSL) (see also: www.fmrib.ox.ac.uk/fsl). Within FEAT, the tool for pre-statistics includes using FMRIB's Linear Image Registration Tool (MCFLIRT) for Motion Correction (Jenkinson 2002), and the non-brain removal using the Brain Extraction Tool (BET) (Smith 2002). The fMRI statistical analysis of fMRI time series was carried out using the FMRIB´s Improved Linear Modeling (FILM), and local auto-correction correlation to fit the GLM voxelwise (Woolrich 2001). FLIRT was used for the registration to high resolution structural and/or standard space images (Jenkinson 2001).

The Jülich probability atlas was applied to analyse motor cortex-specific Brodmann areas (Eickhoff 2007, Toga 2006). fMRI, as described above, was used in studies III and IV.

1.6 TEST-RETEST RELIABILITY

A basic requirement of a measurement is that it is repeatable, i.e. if the same measurement is made on a subsequent occasion and nothing has changed then it would be expected to give the same result, within experimental errors (Campbell 2007). Studies of test–retest reliability are based on sequential assessments of subjects on different occasion's providng information about the stability of subjects' responses over time (Finch 2002c, Campbell 2007). Repetition of measurement is made on the same group of subjects and under similar testing conditions to ensure duplication. This approach provides evidence that a score measured at one occasion will be the same or very similar if the same instrument is used to measure the quality or quantity at another occasion. For a continuous observation which is measured more than once, one measure of repeatability is the coefficient of variation (CV) which is the within subject standard deviation divided by the mean of observations.

$$\text{CV (\%)} = \frac{100\text{x(within subject SD)}}{\text{Mean}} = \frac{100s\ \text{within}}{\text{x}},$$

X is the mean of all paired observations from n subjects, swithin = s = [(d12+….dn2)/2n]½, where d is the difference between the paired observations in each subject. CV is a measure of variation which is independent of the units in which the observation is measured. Commonly, a CV of <5% is considered acceptable (Campbell 2007), but in clinical practice a CV of < 10% is acceptable.

In the context of a study, if an individual is in a stable condition, an instrument should yield repeatable results if it is used repeatedly. This is usually assessed using a test-retest study with patients who are thought to have stable conditions and who are not expected to experience changes due to treatment effects. The level of agreement between the occasions is a measure of the reliability of the instrument. It is important to select patients whose condition is stable and to carefully choose a relevant between-assessment time-gap that is neither too short nor too long (Campbell 2007).

Test-retest and reproducibility in fMRI

The topic of reliability or reproducibility is not only of academic concern; the reliability of activations is of utmost importance in clinical settings, for example when imaging data are used for planning neurosurgical interventions (Beisteiner 2000, Roux 2003). In clinical research, the aim is often to follow the disease course and/or to detect effects of interventions (therapies). For the specific clinical question or test paradigm, the method validity and time-dependent variability are crucial factors (Havel 2006). Reproducibility or test-retest reliability of data cannot be inferred from the data collected in a single session experiment, but has to be tested empirically by repeated measurements (Carver 1978).

However, most fMRI data are collected in single session experiments and little is known about the reproducibility or test-retest reliability of the activation patterns found in these experiments (Havel 2006). Some authors claim a very good reproducibility of fMRI activation signals within one session (Yetkin 1996, Noll 1997, Rombouts 1998), or between sessions (DeYoe 1994, Gozal 1994, Robinson 1995, Noll 1997, Rombouts 1998). While others showed time dependent changes during a single fMRI experiment (Karni 1995, Condon 1997, Silva 1999). Compared with the total number of publications on the use of functional magnetic resonance imaging, the topic of reproducibility of functional imaging data has received little attention (Havel 2006).

Time-dependent changes in fMRI

The stability of cerebral activation associated with a particular behaviour or intervention over time is an important issue in functional imaging (Lobinoux 2001). Time-dependent changes may arise from either random or systematic processes. Random processes may be non-physiological, e.g. changes in the position of the subject in the high field strength (B_o) and in the radiofrequency head coil, field in-homogeneities, shimming differences, instability of the scanner fMRI signal, image noise, data processing and analysis, statistical [type I or II] errors. The latter may arise from small changes in performance, differences in strategies, or functional organisation constantly reshaped by behavioural demands for the learning of new motor skills. All these factors can change from one session to another and from one subject to another at random. Systematic processes are related to the repeated performance of a specified task such as attention, habituation and learning (Lobinoux 2001). It is known that responses in the sensory systems show habituation over time, leading to a reduction in functional activation or, conversely, to an enlargement of activation when learning occurs (Karni 1995). Unless time-dependent effects are assessed, time-dependent changes in brain activity may be erroneously attributed to

task-dependent effects (Lobinoux 2001). Thus, methodological aspects such as reproducibility and time-dependent changes appear to be a major issue.

1.7 BRAIN PLASTICITY

In contrast to what was previously believed, the adult brain retains a capacity for self-repair and functional reorganisation, which is part of the wider concept of brain plasticity (Pascual-Leone 2005). The mechanisms are complex and believed to operate on different levels, including sub cellular, cell-to-cell and macro-anatomical processes. Experimental animal as well as human studies have shown both strengthening contacts between individual neurons and continuous modulation of the cortical representation of areas of body parts, "cortical maps", in response to activity, behaviour and skill acquisition. According to one author, synaptic plasticity in cortical horizontal connections is likely to underlie cortical map reorganisation (Johansson 2004). Furthermore, activity-dependent modification of synaptic connections and reorganisation of adult cortical areas are thought to involve long-term potentiation and depression, mechanisms by which the information is stored in the central nervous system (CNS) (Johansson 2004). These processes in the brain may persist for months and even years after the injury.

Animal studies of rehabilitative and pharmacological interventions in post-stroke recovery applying modern imaging techniques suggest that beneficial interventions are related to "modulating neuroplastic mechanisms". Motor function recovery has thus been associated with adjacent areas taking over the function of the damaged areas or the utilisation of alternative pathways (Rossini 2007). Nudo and co-workers studied the CNS correlates of rehabilitative training on motor recovery after ischaemic infarct in primates (Nudo 1996a). A subtotal lesion of the cortical representation of one hand resulted in a further loss of hand territory in the adjacent, undamaged contra-lateral cortex, if no rehabilitation was applied. In contrast, repetitive training of the affected extremity prevented this loss of territory and sometimes even expanded the cortical representation, suggesting a cortical reorganisation. These authors suggested that potential mechanisms of brain plasticity could be the modulation of existing pathways, growth of new axonal processes and suppression of diaschisis (Nudo 1996b), where diaschisis refers to reduced function of non-injured brain areas due to damaged connections from the injured area (von Monakow 1914).

In human patients with stroke, longitudinal fMRI studies have shown increased activation of ipsilateral hemisphere compared to controls at baseline and a "normalization" of motor related brain activations (increased contralateral/ipsilateral activation ratio) related to clinical improvement (Ward 2004, Calautti 2007, Kwon 2007).

In parallel with the improvements of imaging techniques for the study of CNS organisation and reorganisation, new approaches for the rehabilitation of stroke patients have developed.

Despite technical and methodological differences there are consistent observations of training-induced reorganisation of the motor system.Thus, in one controlled clinical study on a relatively new physical rehabilitation approach, so called Constraint-induced movement therapy (CIMT) which is a concept of "learned non-use" of the unaffected arm, fMRI was used for assessing motor cortical reorganisation associated with motor function recovery. Gains in motor function were associated

with a shift of motor cortical activation toward the undamaged (ipsilateral) hemisphere (Schaechter 2002). Further support for this notion was obtained in severely affected stroke patients receiving therapy according to another principle idea: so-called bilateral practice. This method aims at facilitating the movement of the paretic extremity by using the facilitator drive of the unaffected extremity onto the affected one via intercallosal fibres. fMRI showed a significant shift in activity towards the ipsilateral hemisphere associated with motor recovery (Staines 2002). The animal experiments and clinical studies together point to the possibility of alterations involving both hemispheres.

Methods integrating structural and physiological aspects are thus fundamental for understanding the CNS function and its role in the initiation and control of motor and cognitive activities. With the rapid development in neuroimaging techniques available for human investigations it is now possible to test hypotheses based on basic neurobiological research in clinical practice.

1.8 AIMS

The overall aim of this thesis was to evaluate the effects on motor functions, health-related quality of life and central nervous system plasticity following spasticity management with intramuscular blockade and physical therapy in patients with spasticity as part of an upper motor neuron syndrome.

Specific aims of the studies were:

- To define the therapeutic targets and to assess the effects of focal spasticity therapy including botulinum toxin and physical therapy on functions, ADL and pain in patients with CP, stroke and TBI (Study I).
- To evaluate patient-perceived health status after focal spasticity management by applying the generic instrument Short Form 36 (SF-36) (Study II).
- To define the CNS correlates to a simple self-paced right hand finger extension-flexion motor task in healthy subjects using fMRI and a virtual reality data glove, and to study the time-dependent variability of this experimental model prior to a patient study (Study III).
- In stroke patients, to compare the therapeutic effects on motor function with the CNS correlates to a simple standardised right hand motor task monitored by a data glove and fMRI application (Study IV).

2 MATERIALS AND METHODS

2.1 STUDY OUTLINES

Study I

In this retrospective, descriptive study of four years of out-patient clinical work, one hundred consecutive patients (46 women, 54 men), mean age 41±14years, with spasticity due to CP, stroke and TBI, were studied to increase the knowledge of the effects of focal spasticity management in adult spastic patients. Analysis was made of the therapeutic targets and effects on functions, ADL and pain after focal spasticity therapy including botulinum toxin intramuscular injections together with physical therapy and orthoses. In addition to the categorisation of patient-chosen therapy targets, a verbal scale for patient self-reporting was applied and the AS scale in a subset.

Study II

In this prospective observational, interventional study 41 consecutive adult patients with CP, stroke and TBI (18 women, 23 men), mean age 52±13 years, received spasticity management as in study I. HRQL was assessed at baseline and at three months follow-up with the generic Short Form 36 (SF-36) Questionnaire. Spasticity was assessed with the AS scale and a verbal scale for patient self-reporting of therapy effect was used.

Study III

As part of the methodological development, and prior to our study in stroke patients (Study IV), a standardised finger motor task was performed twice in 10 healthy volunteers with right hand dominance (five women, five men). Mean age 51± 8years. Validity and reproducibility were analysed by investigating fMRI-derived CNS correlates to the standardised right hand motor task. The relation between movement frequency and BOLD activity was also studied.

Study IV

In this prospective explorative study, six first-time, right hand dominant stroke patients (four women, two men), mean age 66 ±10years, with right-sided hand paresis and spasticity were analysed by investigating the CNS correlates to a standardised right hand motor task after comprehensive focal spasticity management. Treatment effects were assessed before and 12 weeks after the injections applying the AS, BL, Jamar dynamometer and a verbal scale. In addition, the fMRI BOLD technique was used to evaluate CNS correlates to the standardised motor task. Finger movements were monitored with a data glove and fMRI data were analysed with the FMRIB Software Library (FSL), including the Jülich histological atlas for structure-function relation analysis.

2.2 STUDY POPULATIONS

The total study populations comprised 141 adult patients with spasticity due to an UMNS receiving their first focal spasticity treatment (Fig.12)**.** Ten healthy individuals, mostly from the Department of Rehabilitation Medicine, volunteered as a reference group. All patients were recruited from the Department of Rehabilitation Medicine out-patient spasticity clinic at Karolinska University Hospital Huddinge.

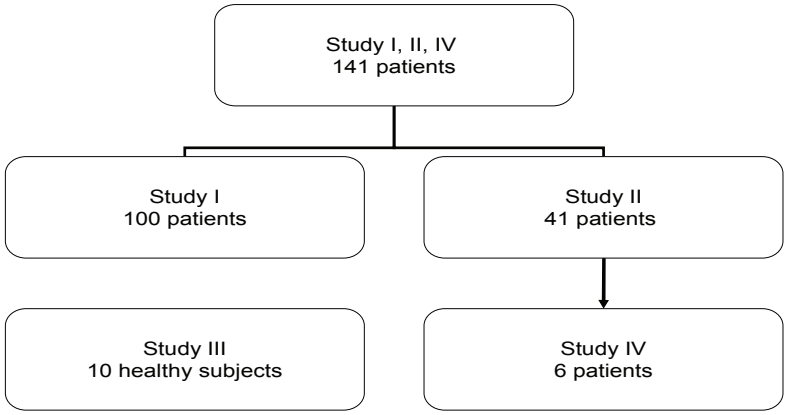


Figure 12. Study populations

The study populations fulfilled the following inclusion criteria:

Study I, II, IV. Selection criteria for focal spasticity management: at least one principal therapeutic target chosen by the patient or caregiver, identification of a well-defined clinical problem for which spasticity was judged to be a crucial component and remediable provocative factors could be excluded, access to additional therapy such as physical and occupational training, splinting, orthosis and assisted home training.

Additional criteria for study II and IV as listed below.

Study II. No noticeable cognitive impairment and an ability to communicate independently.

Study III. Healthy volunteers without claustrophobia or implanted metal objects

Study IV. Left-sided stroke >6 months, right hand dominance, spasticity in the finger flexors of the right hand < 4 on the AS, partial ability to extend the finger extensors, muscular strength ≥ 2 on the MRC, ability to understand and follow instructions and to communicate (no cognitive impairment or aphasia), no claustrophobia, no pacemaker or other metal object located inside the body and weight < 110 kg in order to fit into the MRI.

In Study I, 124 consecutive first referrals were included. Fifteen referrals were judged unsuitable for focal spasticity therapy, seven received injections but did not pursue the treatment plan (additional therapy and splinting), one was referred for treatment with baclofen and one had incomplete documentation.

Figure 13 describes the enrolment of the patients in Study II.

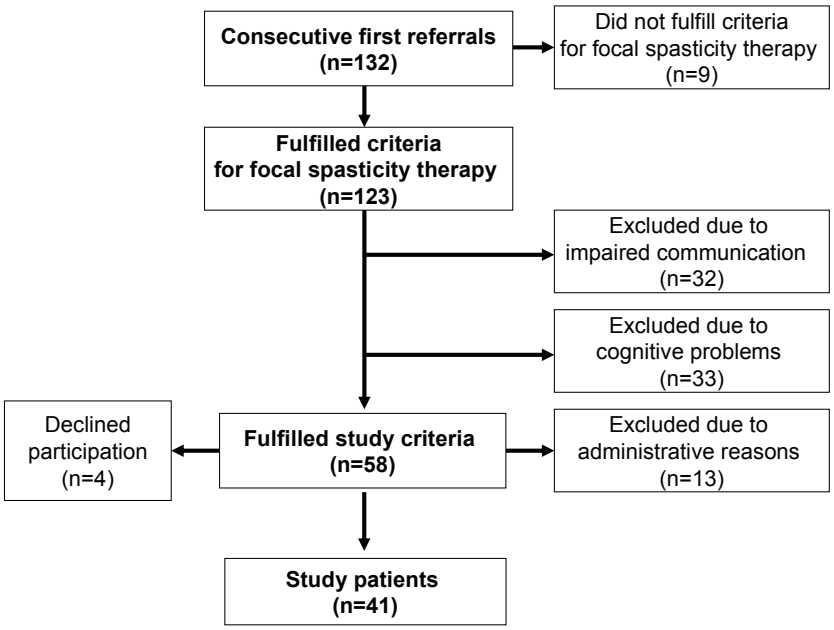


Figure 13. Patient recruitment scheme, study II

Ten healthy volunteers participated in Study III. The subjects were mainly personnel from the Department of Rehabilitation Medicine at the Karolinska University Hospital, Huddinge. Selection was based upon three criteria: 1) right-handed dominance, 2) no known acute or chronic diseases including CNS afflictions and 3) no contraindications to MRI (implanted metal device, pacemaker, former operations, claustrophobia or pregnancy).

In Study IV, six first-time stroke patients with right-sided hand paresis and spasticity following left-sided injury were investigated. Two patients were referred from other hospitals and four were enrolled through advertising in the Swedish Stroke Association newsletter.

Patient clinical characteristics are presented in Table 4. Identified and chosen principal therapy target-/s were categorised by the ICF in all patients, retrospectively in Study I and prospectively in Study II and IV (Table 5).

Table 4. Patient characteristics and spasticity management (n=141), 6* stroke patients in Study IV participated in Study II. Demographic data from the healthy subjects in Study III.

	Study I				Study II			Study III	Study IV
	CP	Str.	TBI	Misc.	CP	Str.	Misc.	Hsubj	Str.
n	41	39	15	5	7	27	7	10	6*
Women/Men	15/26	24/15	4/11	3/2	3/4	13/14	2/5	5/5	4/2
Age, mean	33	50	41	36	37	57	57	51	66
min-max	21-70	22-73	21-60	18-59	24-44	21-79	52-67	42-64	55-79
BoNT-A, units-on average	245	210	247	220	244	225	250		273U
Re-treatment < 6 months	25	24	8	4	5	17	5		5
Re-treatment >6 months	7	4	1	0	2	5	0		1
Positive side-effects, n	18	10	3	1	1	8	1		4
Negative side-effects, n	6	3	0	0	0	2	2		2
Physical Rx, n	21	31	13	5	5	22	5		6
Occupational Rx, n	0	12	5	1	1	4	0		1
Home training, w and/or wo assistance	35	29	15	5	2	19	5		
Spasticity treatment UE/LE	19/26	28/20	10/8	1/4	4/5	21/10	7/0		6/0
Spasticity treatment UE+LE	4	9	3	0	2	4	0		0
Orthosis UE/LE, n	11/15	13/18	3/5	1/2	0/4	11/7	2/2		5/0
Other orthotic devices, n	10	6	3	1	4	5	1		0

Miscellaneous diagnoses: MS, Rhett syndrome, anoxic brain injury, tumour, paraplegia of unknown aetiology. UE= upper extremity, LE= lower extremity. Positive side effects, e.g. reduced back pain, improved sleep and speech. Negative side effects, i.e. neuralgia, weakness.

Table 5. Principal therapeutic targets according to the International Classification of Functioning, Disability and Health (ICF) (for ICF codes see beneath).

ICF components	ICF code ¶, §	Study I CP	Str.	TBI	Misc.	Study II CP	Str.	Misc.	Study IV Str.	All pts
Body Functions (b)	b280	14	10	5	2	3	6	0	0	40
	b750	5	0	0	0	5	1	1	0	12
Body Structures (s)	s730	5	8	4	0	2	3	0	0	22
	s750	6	5	3	0	4	0	0	0	18
	s810	4	2	2	0	0	0	0	0	8
Activities and participation (d)	d360	2	0	0	0	2	0	0	0	4
	d415	8	1	1	1	1	0	1	0	13
	d420	5	8	3	1	2	0	0	0	19
	d440	10	14	3	1	2	15	0	(6*)	45
	d450	15	19	8	2	4	9	5	0	62
	d510	2	0	0	0	0	0	1	0	3
	d530	2	3	2	1	0	0	1	0	9
	d540	4	2	1	0	0	0	2	0	9
	d550	2	0	1	0	0	1	0	0	4
	d560	1	0	0	0	0	1	0	0	2
	d999	0	2	0	0	0	0	0	0	2
Environmental Factors (e)	e120	5	4	5	0	1	3	1	0	19

Str. = Stroke. Misc. = Miscellaneous diagnoses.
ICF code: components b, s, d and e, chapters 100, 200 etc., and second level 10, 20, 30 etc. The 3rd and 4th levels were not specified. §≥ per case.
* 6 stroke patients participated both in study II and IV are included in d440 stroke study II
Study III is excluded – due to only healthy individuals

ICF codes and the terminology used in Study I within brackets:

b280 Pain; sensation of pain (pain reduction)
b750 Movement functions; motor reflex functions (prevention of involuntary movements)
s730 Structures related to movement; structure of upper extremity (facilitation of physical and/or occupational therapy)
s750 Structures related to movement; structure of lower extremity (facilitation of physical and/or occupational therapy)
s810 Skin and related structures; structure of areas of skin (pressure sore reduction)
d360 Communication; using communication devices and techniques (facilitation of speech therapy)
d440 Mobility; fine hand use (improvement of ADL)
d450 Mobility; walking (improvement of mobility and/or gait pattern)
d415 Mobility; maintaining a body position (improvement of sitting and standing)
d420 Mobility; transferring oneself (improvement of transfer)
d510 Self care; washing oneself (improvement of ADL)
d530 Self care; toileting (improvement of ADL)
d540 Self care; dressing (improvement of ADL)
d550 Self care; eating (improvement of ADL)
d560 Self care; drinking (improvement of ADL)
d999 Community, social and civic life; unspecified (cosmetic issues)
e120 Products and technology; products and technology for personal indoor and outdoor mobility and transportation (improved wheelchair management and mobility, facilitation of orthosis wear)

2.3 METHODS

Table 6. Overview of outcome measures and methodology.

	Study I	Study II	Study III	Study IV
Body function and structure				
Ashworth Scale	**X**	**X**		**X**
Jamar-dynamometer				**X**
Sensory function 2-PD				**X**
Activity				
Birgitta Lindmark Motor Assessment Scale				**X**
Health-related quality of life / participation				
Short Form 36		**X**		
Patient satisfaction				
Verbal Scale	**X**	**X**		**X**
Brain activity				
Functional magnetic resonance imaging (fMRI)			**X**	**X**
Movement frequency and compliance				
Data glove			**X**	**X**

Assessment of body function and structure

The Ashworth Scale for assessing muscle tone (Ashworth 1964). The degree of resistance to passive movement of the target muscle group was estimated according to the Ashworth Scale (0-4). Special attention was paid to an optimal testing position, control of the speed of passive stretching and range of movement (See also Table 3).

The Jamar dynamometer (Asimow Engineering Co, Los Angeles, CA, USA) (Mathiowetz 1984) was used to measure isometric hand grip strength. A mean value of three contractions was calculated. A high instrument validity and reliability has been reported.

Sensory function was assessed by the two-point discrimination (2-PD) test (Bell-Krotoski 1993). This tests the discernment of two sharp, nearby objects touching the skin. Separate points on the finger pads should be discernable when their distance is at least 2-4 mm apart.

Assessments at the activity level

The Birgitta Lindmark Motor Assessment Scale (BL Scale) (Lindmark 1988a) was used to assess arm and hand mobility and function. The BL scale, a modified version of the Fugl-Meyer Sensorimotor Assessment (Fugl-Meyer 1975), utilises subscales for upper and lower extremity function. Of the total seven parts of the scale (A-G), two were used for the upper extremity, where A I, II, and III define the ability to perform active movements and B velocity of motion. In part B, the two issues for UE, out of four, were applied. Each item within these parts was evaluated on a 4-point scale (0-3), with a higher score representing better function. A total score was also calculated. The BL scale is considered reliable, valid and sensitive. (See also page 18; The Birgitta Lindmark Motor Assessment Scale). All BL tests were video recorded and then analysed by a physical therapist well acquainted with the method, but not involved in the study.

Assessment of health-related quality of life

The SF-36 questionnaire is considered a reliable and valid measure of perceived physical and mental health. It includes a reference population consisting of a sample of 8930 individuals from the general Swedish population (Sullivan 2002). SF-36 is grouped into eight multi-item health scales measuring physical functioning (PF, 10 items); role limitations due to physical health problems (RP, 4 items); bodily pain (BP, 2 items); general health perceptions (GH, 5 items); vitality (VT, 4 items); social functioning (SF, 2 items); role limitations due to emotional problems (RE, 3 items) and mental health (MH, 5 items). There is also a transition item (questions 1 and 2) on overall evaluation of health that provides a summary indicator and captures the impact of health problems not directly included in the other questions. For each item, the response ranges from two to six. The scores for items on each health scale are added and then linearly transformed to obtain a mean value ranging from 0 to 100. "0" indicates extreme problems and "100" no problems at all; the higher score the better the perceived health. PF, RP, BP and GH scales are aggregated to a physical health index, while RE, MH, SF, SF and VT provide a mental health index (Sullivan 2002). A physiotherapist not involved in the therapy distributed and collected the questionnaires at baseline and follow-up.

Assessment of patient satisfaction

In all cases, a verbal scale for the patient and/or caregiver to self-report the effect of therapy was used. The scale is comparative ("worse – the same – better") and regards an average effect (Pierson 1997, Wade 1995, Turner-Stokes 2002).

Assessment of brain activity

To study brain activity we applied the fMRI technique, which measures the haemodynamic response to increased demands. fMRI can be used to produce activation maps showing which parts of the brain are involved in a specific mental or functional process (See also page 22; fMRI).

Movement frequency and compliance

A data glove (5DT, Fifth Dimension Technologies, Cal., USA) was used to register the extension-flexion cycle frequency and to monitor compliance with the CD instructions. The one size data glove made from Lycra stretch fabric contained one embedded fibre optic sensor per finger. The optic sensors were linked to the computer via an optoelectronic unit a ribbon cable and an interface box (See also Figure 11).

All methods are summarised in Table 6.

2.3.1 Procedures

Studies I, II and IV. All patients received a comprehensive team-based spasticity management, which followed a time plan outlined in Figure 14.

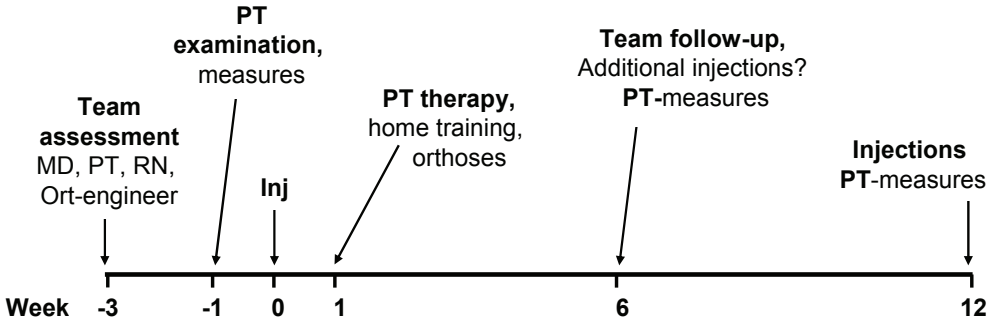


Figure 14. Time flow and therapeutic interventions at the outpatient clinic for focal spasticity management at the Karolinska University Hospital, Huddinge.

At the first visit the patient was assessed by a multidisciplinary clinical team, who decided whether to offer focal spasticity therapy by injecting botulinum toxin. The team consisted of a physician, a nurse, a physical therapist and, occasionally, an occupational therapist and an orthopedic engineer or technician. The selection criteria for focal therapy were: 1) at least one principal therapeutic target chosen by the patient or caregiver, 2) identification of a well-defined clinical problem for which spasticity was judged to be a crucial component and remediable provocative factors could be excluded, 3) no manifest contractures and 4) access to additional therapy such as physical and occupational training, splinting, orthoses and assisted home training.

As part of the decision process on focal spasticity therapy, muscles for BoNT-A injections were selected and based on the clinical examination and the patient's choice of target. In addition, clinical outcome measures were selected. Plans were also made for the additional subsequent interventions (training, orthoses etc.). The team Physical Therapist discussed physical interventions (e.g. passive stretching, activation of antagonists, electrical stimulation, forced use training) with the external therapist in charge of the subsequent therapy. For orthoses, orthopaedic shoes and footwear corrections patients were referred to the orthopaedic technician at the hospital.

At the *second visit*, intramuscular BoNT-A injections were given in muscles exhibiting muscle overactivity. Dosing was based on the guidelines for "Dosing and administration, and a treatment algorithm for use of BoNT-A for adult-onset spasticity" (Mayer 2002b). The injections were guided by electromyographic recording technique to define the presence of abnormal muscle activity (O´Brien).

The follow-up visit was scheduled for six weeks after the injections, at which time patient status, treatment effects, functional gains, patient satisfaction and compliance as well as any adverse events were evaluated by the referring therapist or the patient's physician (see baseline assessment). At this visit it was also decided whether to plan for a repeated set of injections, based on the response to the first set. In cases of re-injection another follow-up visit was scheduled 12 weeks after the injection, according to the recommended injection intervals of no less than three months (Brin 1997).

Additional procedures to the spasticity management described above were made separately in the following studies:

Study II. To evaluate the patient-perceived health status before and after focal spasticity therapy we applied the SF-36 questionnaire in a second series of patients receiving the same therapeutic strategy as those of our previous study. For the administration of the questionnaire the study protocol included four visits with a second follow-up three months post-injection.

Study III and IV. Functional magnetic resonance imaging was done during the motor task, consisting of 30 s active finger extension-flexion of the right hand in the full range of motion at a frequency chosen by each individual. It was repeated five times with resting intervals of 60 s in a block design in order to enhance the signal-to-noise ratio. Prior to the experiment, a presentation and explanation of the task procedure was given, followed by a training session. Inside the MR scanner, the subjects listened to verbal instructions pre-recorded on a CD ("activity - rest") via a headset. The same command was used in the monitoring room to synchronise the fMRI recording and data glove registration. The data glove was used to register the extension-flexion cycle frequency and to monitor compliance with the CD instructions. In order to minimise flexor synergies and additional movements in the right wrist, a plastic orthosis was positioned over the wrist under the data glove. Another orthosis was used over the entire left hand and wrist to prevent co-contractions. Head motion was minimised by using a head support system consisting of a deflatable vacuum pillow. During scanning, subjects were blindfolded to reduce eye movements. Headphones dampened scanner noise while a microphone allowed communication between staff and subjects. An E-vitamin was positioned on the right forehead to distinguish right and left in the subsequent analysis.

The experiment was performed on two occasions with a time interval of ≥ six weeks in Study III and 12 weeks in Study IV.

All measurements were acquired with a Siemens Magnetom Vision 1.5 T whole body MRI system with a standard head coil (Siemens, Erlangen, Germany). Functional imaging was performed using a T2*-weighted gradient-echo EPI mosaic sequence (TE = 60ms, TR = 2000 ms, FA = 90°, 23 slices covering the whole brain, slice thickness = 5mm, interslice distance = 1mm). According to a block design, data were collected in a total of 106 volumes in the functional experiment. The first four volumes were excluded from further analysis to avoid signal saturation effects. Each scanning session included the acquisition of a high resolution TI-weighted 3D scan with a voxel size of 3.75 x 3.75 x 5 mm^3 (≈ 0.07ml) and a field of view (FOV) of 256 x 256 mm. A magnetisation-prepared rapid acquisition gradient-echo (MP-RAGE) technique was employed. The scan covering the whole brain lasted for 10 minutes and 52 seconds. Furthermore, a T2-weighted and a proton density scan were acquired for clinical routine evaluation.

For the analysis of fMRI data pre-processing and analysis were performed using the fMRI Expert Analysis Tool (FEAT) Version 5.91 which is part of the Analysis Group at the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL). The following *pre-statistics* were applied: 1) Motion Correction using FMRIB's Linear Image Registration Tool (MCFLIRT) (Jenkinson 2002); 2) non-brain removal using the Brain Extraction Tool (BET) (Smith 2002); 3) spatial smoothing using a Gaussian-shaped kernel with a full width at half maximum (FWHM) of 5 mm, specifying neighbourhood size and weighting; 4) grand mean intensity normalisation of the entire 4D dataset by a single multiplicative factor, causing all single-session data sets to have the same overall mean intensity and 5) high-pass

temporal filtering (Gaussian-weighted least-squares straight line fitting with sigma=40.0s) to remove slow unwanted signals (i.e. heartbeat, breathing, scanner-related drifts) in each voxel's time series.

Study IV. A training concept was added including physical therapy once a week and a daily home training programme of 45 minutes. The protocol was standardised but had to be modified and individualized depending on the patient specific impairment.

The training programme for upper limb emphasised hand function in the hemiparetic hand although motor tasks involving both arms were included. A modified Carr and Shepard motor relearning programme for stroke was applied, comprising exercises for shoulder abduction, forward flexion, extension and elbow flexion and extension to elicit muscle activity and to train motor control (Carr and Shepard 1987). For the wrist function exercises were mainly aimed at extension, supination and radial deviation. In the hand, training was performed to enhance the major hand functions: to grasp, release and manipulate objects. The programme also included exercises with therapeutic dough of varying resistance for dexterity, coordination and strength. Stretching to improve or maintain length of muscles and to prevent contractures ended the programme. Patients were also encouraged to involve both hands in everyday tasks.

2.3.2 Statistical methods

For descriptive purposes, mean and standard deviation or median and range were used in all studies. Exact 95 % confidence intervals (95% CI) were applied as appropriate and obtained from the Geigy Scientific Tables, 1982.

The comparisons of scores on the Ashworth Scale at baseline and after intervention were analysed with the Wilcoxon matched pairs signed-rank test in Studies I and II.

In Study II, SF-36 was expressed on an ordinal scale and we used the Wilcoxon matched pairs signed-rank test for the comparison of baseline and follow-up scores. However, by convention, the SF-36 is usually treated as a nominal scale. In order to allow comparisons with other studies we therefore also used parametric statistics with mean values (Student's paired t-test).

The non-parametric Wilcoxon test was also used for other analyses because of mostly skewed data and/or a limited number of subjects.

Spearman's correlation analysis was employed in Study III regarding the relation between the movement frequency and BOLD activity.

STATISTICA versions 6.1-8.0 (StatSoft, Inc, Tulsa, OK, USA) were used for the analysis

A p-value < 0.05 was considered significant.

Ethical aspects/considerations

All studies were conducted according to the principles of the Declaration of Helsinki and had the approval of the local ethics committee. Informed consent was obtained from each participant.

When recruiting patients for Study IV, left-handed and hemiplegic patients expressed disappointment at not being accepted for participation. This was explained to be due to strictly methodological considerations.

Gender perspective

In Study three equal proportions of men and women were recruited. In the patient studies other aspects decided the enrolment as defined by the inclusion and exclusion criteria. There was a slight overweight for men vs. women, 77 vs. 64.

3 RESULTS

3.1 STUDY I

There were 227 principal therapeutic targets/indications for treatment: on average ~2.3 per patient. There was one indication in 50% of the patients, while the maximum was five in any one patient. Treatment effects in relation to the 227 principal therapy targets were improvement (“better”) in 211 (93%), no change (“the same”) in 15 (7%) and impairment (“worse”) in one patient. This corresponds to an overall improvement in 90 patients (90%), nine unchanged (9%) and worsening in one (1%). The efficacy was the same for upper and lower extremities, 52 of 58 for each (90%).

In the 30 patients where assessment of spasticity according to the AS was documented, the median score before intervention was three (mean 3.2; range: 4-1). After intervention the median was two (mean 2.0; range: 3-0), with an average improvement of 1.2 ($p < 0.001$).

In addition to the improvements related to a patient’s chosen targets and treatment goals, in 31 cases there were reports of other and unexpected improvements (≥1 per case) which might be related to the therapy (“positive side-effects”). These included passive-ADL, speech, balance and increased social participation, a decrease in clonic cramps and improvements in sleep, stamina, cosmetics, pain relief and reduction in seizures.

3.2 STUDY II

According to SF-36, a statistically significant improvement was found in the health scales physical functioning, role physical and social functioning. In the subgroup of 27 stroke patients statistically significant improvements were found in the same health scales.

Assessment of spasticity according to the AS gave a median score of two (mean 2.5; range: 2-4) before intervention. After intervention, the median was one (mean 1.4; range: 0-3) with an average improvement of 1.1 ($p < 0.001$). Spasticity improved in 38 patients (93%) and remained unchanged in three (7%).

Improvement according to the verbal scale ('better') was observed in 57 (86 %) therapeutic targets and remained unchanged ('the same') in nine (14 %), which corresponds to an overall improvement in 36 patients (88%), with five unchanged (12%).

In addition to improvements related to a patient’s chosen therapy targets and treatment goals, in 24 cases there were reports of other improvements (≥1 per patient), which might be related to the therapy. These positive side-effects after treatment in the upper extremities were: improved balance and increased walking distance in six patients reduced falling tendency in two, increased hand sensibility in four, reduced distal oedema in two, and decreased shoulder dislocation in two and relief of back pain and headache in three. After treatment of the lower extremities, distal upper motor activity increased in three patients and improved sleep was reported in two.

3.3 STUDY III

In the whole brain, maximum BOLD values in a single voxel, expressed as Z-values, varied between 4.7 and 15.5. As expected, this voxel was always in the left pre- and primary motor cortices. There was no significant difference in peak BOLD activities between recording session #1 and #2 and the variation was moderate with a CV of 29%.The distance between the two voxels with peak BOLD activities at the two sessions was short (3-8 mm) in five individuals, whereas the remaining five subjects showed larger variations. The median distance in space was 9.9 mm (3.0-58.7), but significantly less in each of the three orthogonal planes (1.3-6.5 mm). The mean BOLD activity during the motor task at the first and second session showed in all controls, a clear activation in primary and secondary motor cortices, supplementary motor cortex and cerebellum.

In BA4a, BA4p and BA6 the mean and maximum BOLD activities in the left hemisphere increased, respectively, approximately 1 and 9% compared to baseline. The corresponding figures in the right hemisphere were around 0.5 and 5%, respectively. This means that there was a clear lateralisation to the left hemisphere. The variability of the mean, median and the 90% of maximum values of BOLD activity was similar in these three areas. This pattern was consistent for the comparisons L1 versus L2 and R1 versus R2. For the L/R ratio, however, there was a difference in the CVs for BOLD mean and BOLD 90% between the three BAs with the following relation: BA6:BA4a:BA4p ≈ 1:2:2.5-3, with the least variability in BA6.

At the second session, the number of voxels reaching the threshold for a significant change in BOLD activity compared to the background decreased numerically, especially in the right hemisphere and in BA4a and BA4p. As a consequence, the left-to right ratios became accentuated.

There was no correlation between the extent or magnitude of BOLD activity on the one hand and the extension-flexion cycle frequency on the other in the group performing self-paced flexion-extension (range 0.19 -0.71 Hz). However, in the single subject performing paced extension-flexion at 0.25, 0.5 and 1 Hz, there was an increase in fMRI activity with increasing frequency, both in the number of activated voxels and in the BOLD activity in primary and secondary motor cortices using the automated regional analysis.

3.4 STUDY IV

According to the B.L total score, improvement was observed in five patients and deterioration in one. The median score before intervention was 21 (5–41). After intervention, the median was 27.5 (14-44), with an average increase of 7.2 ($p = 0.12$). Specifically, hand function improved in five patients, arm function in four and wrist function in two. One patient deteriorated in each function (#6). Three patients improved their ability to perform a movement at a certain speed, no change was observed in two and deterioration was observed in one patient (#6).

Applying the AS, there was a spasticity reduction in all individuals. The median score before intervention was 1.85 (1.3-2.7) and after 0.85 (mean 0.8, range 0-1.7), with an average improvement of 1.0 ($p = 0.03$). The largest decrease was observed in patient #6 but had adverse functional consequences.

Regarding fMRI, the main findings were at baseline, a ~1.5-3% increase in mean BOLD activity in the motor and pre-motor cortices (BA4a, BA4p and BA6) in response to the motor task, which was larger in the right than in the left hemisphere in two of these areas (BA4a and B4p). Furthermore, after intervention, there was a minor decrease in the left-sided and a larger decrease in the right-sided response, leading to a clear lateralisation (left/right >1) in a "normalising" direction in all three areas. This response pattern was also apparent from the numbers of activated voxels within the same areas in both hemispheres. Compared with our previous study on healthy individuals, the increase in mean BOLD activity was 2-4.5 times larger in the patient group and less clearly directed towards the left hemisphere. The mean finger flexion frequency during the fMRI sessions did not significantly differ between baseline and follow up.

4 GENERAL DISCUSSION

The overall aim of this thesis was to study the effects of a comprehensive spasticity management from several perspectives. To achieve this, we investigated the effects on motor functions, health-related quality of life and the central nervous system correlates to a motor task. Already from the beginning in 1999, we adhered to a strict strategy for focal spasticity therapy with careful patient selection and additional therapeutic interventions according to the 1997 and subsequent 2002 guidelines (Brin 1997, Turner-Stokes 2002). In all 141 patients (Studies I, II and IV) we found an overall improvement in motor functions in 88-90% of patient therapeutic targets. Spasticity improved 1.1-1.2 on the Ashworth scale. Quality of life (Study II, n=41) improved in three of the eight health scales, of which two were related to daily physical activities. The most significant improvement, however, was found in the dimension of social functioning, which has a strong correlation to a mental dimension and a moderate correlation to a physical. Study III showed the CNS correlate to the right hand motor task within the expected part of the brain. The regional extent and magnitude of BOLD activities varied moderately between sessions. In Study IV we observed that the patients had recruited larger areas within the right (healthy) hemisphere. However, following the comprehensive focal spasticity management there was brain reorganisation in a "normalising" direction in addition to improved motor function. Compared to the healthy subjects, the brain activity remained more intense (higher BOLD activity) and extensive (more voxels), suggesting increased energy consumption.

In a landmark randomised placebo-controlled study, Bashear et al. showed a significant improvement in 40 of 64 patients (62%; 95% CI: 50-74) after focal spasticity therapy with intramuscular botulinum toxin injections in upper extremity muscles compared with 17 of 62 (27%; 17-40) in the control group (Bashear 2002). There was, however, no report of adjunctive therapy, as subsequently commented upon (Landau 2003). Bashear's results might be compared with the improvement in 126 out of 141 patients in Studies I and II, (89%; 95% CI: 84-94). Assuming they used similar criteria for patient selection, which is not clearly stated in the publication, the difference in results might be related to the differences in therapy. The management strategy applied at our clinic included adjunctive therapy with, on average, 2.6 interventions per patient, which probably played an important role in achieving the treatment benefits as reported in Studies I and II. The concept of a multidisciplinary approach, which provides the opportunity for a comprehensive spasticity management, is thus in line with reports published before as well as during the conduction of this project (Brin 1997, Richardsson 1999, 2002, Turner-Stokes 2002, Ward 2008, Wissel 2008).

In our141 patients the proportion of therapy targets was equally distributed in the upper and lower extremities. BoNT is in Sweden, as in most European countries apart from France, approved for spasticity treatment in upper extremity (hand and wrist post-stroke) in adults. BoNT therapy in the lower extremities was therefore performed off-label (compassionate use) in agreement between the physician and the patient. We did, however, not observe any difference in the therapeutic effects between the upper and lower extremities, which was in line with two other studies (Wissel 2001, Opara 2007).

4.1 METHODOLOGICAL ASPECTS AND LIMITATIONS

The International Classification of Functioning, Disability and Health was published in 2001, but is still under development and implementation (ICF, Who 2001). It was conceived with the aim of changing the concept of health towards a more holistic version (Gutenbrunner 2007). Modern definitions of rehabilitation are based on the ICF. Because it was not part of clinical everyday work at the start of our spasticity clinic in 1999, it was implemented retrospectively for the categorisation of a patient's identified and chosen principal therapy target-/s in Study I (see Methods and Materials), but fully implemented in Study II.

Study I was a retrospective study with the inherent limitations of that particular design, although with prospective criteria for patient selection and management strategy. The overall aim was to systematically describe the results of such a strategy as a basis for subsequent studies. Although it would have been interesting to proceed with a randomised cross-over study comparing the effects of BoNT injections versus physical interventions in a cross-over design, we chose another direction for Study II. We were interested in pursuing the patient perspective with HRQL assessment. Thus, we focused on discovering whether the motor improvements corresponded to changes in HRQL. In addition to the main results discussed elsewhere in this thesis, a post hoc comparison was made of the results on the individual level between the changes within the three SF-36 subscales showing significant improvement on the group level, and the results on the verbal and Ashworth scales. The general impression was a moderate concordance, i.e. the generic SF-36 did not seem to provide results consistent with the specific instruments applied. However, most of the patients who improved in at least two of the three SF-36 subscales (n=18) also improved according to the Ashworth and verbal scales (Table 7). In contrast, there was concordance between the Ashworth and verbal Scales in 35 out of 41 patients (85%).

In the motor hand training programme in Study IV, we expected an improvement of around 90% on the basis of the results from Studies I and II. The result on the BL Scale with improvement in five out of six chronic stroke patients was in line with this expectation. Admittedly, this is a small sample. We applied to the local ethics committee for inclusion of 10 patients and received their approval. Unfortunately, for technical and administrative reasons, it was not possible to include more than six patients. The fMRI results therefore need confirmation, although the results seemed concordant and included patient #6, in whom there were also signs of brain reorganisation in a "normalising" direction despite a decrease in functional performance with ~30% in the BL total score.

The compliance with the training programme was in Study IV assessed via a diary, but unfortunately not in study I and II (apart from those included in study IV). The six stroke patients had 54-96% compliance to the 84 training sessions. The reason for not performing the training was mostly ascribed to fatigue, which was not systematically assessed although there are, instruments available (Glader 2002, Michielsen 2003). Compliance with the instructions for the motor task was in study III and IV confirmed with the data glove.

Table 7. Comparison on the individual level of outcome measures according to Short Form-36 (three subscales), the verbal and Ashworth scales denoted as better (1), unchanged (0) and worse (-1). Patient numbers in bold font in the left column are those showing improvement in two to three of the three SF-36 subscales (n=18).

Patient #	SF-36			Verbal scale	Ashworth scale	Better/unchanged/ /worse
	SF	PF	RP			
1	0	-1	0	1	1	2/2/1
2	1	1	0	1	1	4/1/0
3	1	1	-1	1	1	4/0/1
4	1	-1	1	1	1	4/0/1
5	1	0	1	1	1	4/1/0
6	0	-1	1	1	1	3/1/1
7	1	-1	1	1	1	4/0/1
8	1	1	0	1	1	4/1/0
9	-1	0	-1	0	1	1/2/2
10	0	0	0	1	0	1/4/0
11	1	0	-1	0	0	1/3/1
12	-1	0	1	1	1	3/1/1
13	0	0	1	1	1	3/2/0
14	1	-1	1	1	1	4/0/1
15	-1	1	0	1	1	3/1/1
16	-1	1	0	1	1	3/1/1
17	1	-1	1	1	1	4/0/1
18	-1	0	-1	1	1	2/1/2
19	0	-1	1	1	1	3/1/1
20	0	1	0	1	1	3/2/0
21	0	1	-1	1	1	3/1/1
22	1	1	0	0	1	3/2/0
23	0	0	0	1	1	2/3/0
24	1	0	0	1	1	3/2/0
25	0	-1	1	1	1	3/1/1
26	1	1	1	0	1	4/1/0
27	1	1	0	1	1	4/1/0
28	-1	0	0	1	1	2/2/1
29	1	1	1	1	1	5/0/0
30	-1	0	0	1	1	2/2/1
31	0	1	-1	1	1	3/1/1
32	1	-1	0	1	1	3/1/1
33	1	1	1	1	1	5/0/0
34	0	1	1	1	1	4/1/0
35	1	1	1	1	1	5/0/0
36	1	1	0	0	1	3/2/0
37	1	1	1	1	1	5/0/0
38	1	1	0	1	1	4/1/0
39	0	0	-1	1	1	2/2/1
40	-1	0	-1	1	0	1/2/2
41	0	0	-1	1	1	2/2/1
Better/un-changed/ worse	**20/13/8**	**18/14/9**	**16/16/9**	**36/5/0**	**38/3/0**	**128/51/26**

SF = social functioning, PF= physical functioning, RP = role physical

4.2 THOUGHTS AND POSSIBLE IMPLICATIONS

As an attempt to bring together important observations of the present thesis, a tentative model has been created as outlined in figure 15. It is naturally simplified as it is based on the present sub-studies, partly also because of limited insights into the structural-functional interactions in spasticity. It is also mainly based on what we have learned from stroke patients, which is the category included in all three patient studies.

At baseline, when patients were performing a motor task, there was more intense and extensive activity especially in the right hemisphere compared to healthy subjects.

According to a previous study in healthy subjects performing self-paced bilateral finger tapping, there is a relation between motor activation on the one hand and cerebral blood flow, BOLD activity and the cerebral metabolic rate of oxygen (CMRO2) on the other (Kastrup 2002). A linear relation between increased cerebral blood flow and CMRO2 with a ratio of 3:1 was reported (i.e. an increased CBF of 100% represents an increased energy consumption of 33%), but the relation between BOLD activity and CMRO2 was not presented. The results of our study imply that patients utilised more energy than healthy individuals when performing the same motor task. Spasticity management seemed to decrease task related BOLD activity (or regional blood flow), reflecting neuronal activation and thus energy consumption, especially on the right side. The intriguing issue is whether there is a relation between the reduction of motor related neuronal activation and cerebral energy consumption after therapy and the patients' functional improvement. In Study II, of 41 patients receiving BoNT in combination with physical interventions, we found the most significant improvement in the subscale social functioning, which has a strong correlation ($r \geq 0.70$) to the mental dimension (Sullivan 2002). In addition, there were 55 reports of "other and unexpected improvements" (positive side-effects) among 141 patients, supposedly related to therapy. Patients and relatives also frequently reported on increased socialisation with family and friends and participation in social activities. This might be a consequence of the reduction of the intensity and extension of BOLD activity after therapy, but could also be related to the lateralization, i.e. less of the right hemisphere was involved in a motor task usually governed from the left side. These observations might be one element of the important fatigue problem, which is well recognised in stroke patients. The implication would be that spasticity therapy might also reduce fatigue.

The results from these studies might also have implications for customising therapy to a patient's disabilities and point to the importance of evaluating the efficacy of different therapeutic methods or strategies by neuroimaging techniques. In our studies for example, when focusing on one problem at a time, improvement could be obtained in ~ 90% of a patient's principal therapeutic targets after comprehensive focal spasticity therapy. It remains though, that some patients had problems with adhering to the home training programme because of fatigue. There are different approaches on how to perform optimal physical therapy (Taub 2002). Comparisons including fMRI might shed light on this important issue.

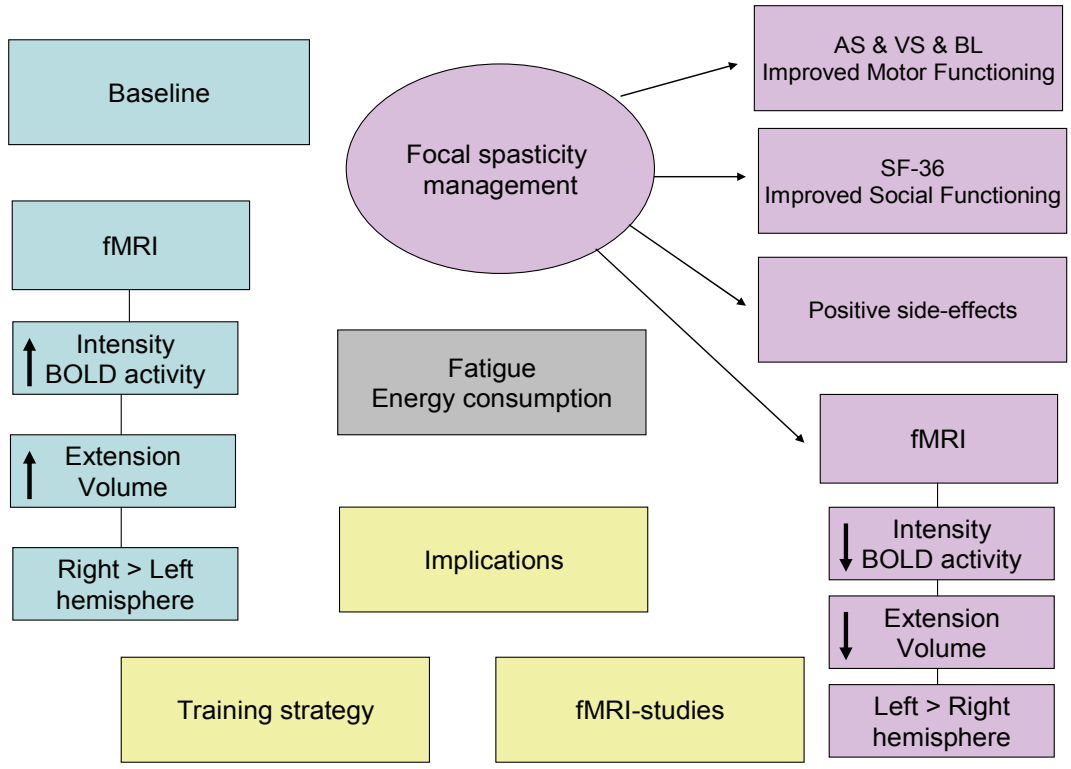


Figure 15. In an attempt to bring together important observations of the present thesis, a tentative model has been created as outlined.

4.3 CONCLUSIONS

- Improvement can be observed in ≥ 90% of patients and in their principal therapeutic targets in a cohort receiving their first focal spasticity treatment with botulinum toxin A and additional therapy. A strict strategy for patient selection and comprehensive management has to be followed.

- A comprehensive focal spasticity therapy with BTX-A intramuscular injections and physical interventions can improve patients perceived health-related quality of life in addition to improvements in objectively and subjectively measured motor functions.

- Automated regional analysis of fMRI activity during finger extension-flexion showed moderate method errors and standard deviations. These results constitute a reference for comparison with patients performing the same task.

- Comprehensive focal spasticity management can be associated with brain reorganisation in a "normalising" direction in addition to an improved motor function.

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