Biomechanical and Neural Aspects of Eccentric and Concentric Muscle Performance in Stroke Subjects

Implications for resistance training

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The picture on the cover page shows one of the Swedish physician Gustav Zander's (1835-1920) famous gymnastic machines. The picture is reproduced from Meyers Großes Konversations-Lexikon 6. Auflage 1905–1909, with permission from Zenodot Verlagsgesellschaft mbH. Source: http://www.zeno.org - Zenodot Verlagsgesellschaft mbH. (Public domain.)

To Ulrika Viktor and Aron!

*"One's first step in wisdom is to question everything
—and one's last is to come to terms with everything."*

George Christoph Lichtenberg, German physicist and astronomer

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Abstract

Muscle weakness is one of the major causes of post-stroke disability. Stroke rehabilitation programs now often incorporate the same type of resistance training that is used for healthy subjects; however, the training effects induced from these training strategies are often limited for stroke patients. An important resistance training principle is that an optimal level of stress is exerted on the neuromuscular system, both during concentric (shortening) and eccentric (lengthening) contractions. One potential problem for post-stroke patients might be difficulties achieving sufficient levels of stress on the neuromuscular system. This problem may be associated with altered muscular function after stroke. In healthy subjects, maximum strength during eccentric contractions is higher than during concentric contractions. In individuals with stroke, this difference in strength is often increased. Moreover, it has also been shown that individuals with stroke exhibit alteration with respect to how the strength varies throughout the range of motion. For example, healthy subjects exhibit a joint specific torque-angle relationship that normally is the same irrespective of contraction mode and contraction velocity. In contrast, individuals with stroke exhibit an overall change of the torque-angle relationship. This change, as described in the literature, consists of a more pronounced strength loss at short muscle length. In individuals with stroke, torque-angle relationships are only partially investigated and so far these relationships have not been analysed using testing protocols that include eccentric, isometric, and concentric modes of contraction.

This thesis investigates the torque-angle relationship of elbow flexors in subjects with stroke during all three modes of contractions – isometric, concentric, and eccentric – and the relative loading throughout the range of movement during a resistance exercise. In addition, this thesis studies possible central nervous system mechanisms involved in the control of muscle activation during eccentric and concentric contractions.

The torque-angle relationship during maximum voluntary elbow flexion was examined in stroke subjects (n=11), age-matched healthy subjects (n=11), and young subjects (n=11) during different contraction modes and velocities. In stroke subjects, maximum torque as well as the torque angle relationship was better preserved during eccentric contractions compared to concentric contractions. Furthermore, the relative loading during a resistance exercise at an intensity of 10RM (repetition maximum) was examined. Relative loading throughout the concentric phase of the resistance exercise, expressed as percentage of concentric torque, was found to be similar in all groups. However, relative loading during the eccentric contraction phase, expressed as the percentage of eccentric isokinetic torque, was significantly lower for the stroke group. In addition, when related to isometric maximum voluntary contraction, the loading for the stroke group was significantly lower than for the control groups during both the concentric and eccentric contraction phases.

Functional magnetic resonance imaging was used to examine differences between recruited brain regions during the concentric and the eccentric phase of imagined maximum resistance exercise of the elbow flexors (motor imagery) in young healthy subjects (n=18) and in a selected sample of individuals with stroke (n=4). The motor and premotor cortex was less activated during imagined maximum eccentric contractions compared to imagined maximum concentric contraction of elbow flexors. Moreover, BA44 in the ventrolateral prefrontal cortex, a brain area that has been shown to be involved in inhibitory control of motor activity, was additionally recruited during eccentric compared to concentric conditions. This pattern was evident only on the contralesional (the intact hemisphere) in some of the stroke subjects. On the ipsilesional hemisphere, the recruitment in ventrolateral prefrontal cortex was similar for both modes of contractions.

Compared to healthy subjects, the stroke subjects exhibited altered muscular function comprising a specific reduction of torque producing capacity and deviant torque-angle relationship during concentric contractions. Therefore, the relative training load during the resistance exercise at a training intensity of 10RM was lower for subjects with stroke. Furthermore, neuroimaging data indicates that the ventrolateral prefrontal cortex may be involved in a mechanism that modulates cortical motor drive differently depending on mode of the contractions. This might partly be responsible for why it is impossible to fully activate a muscle during eccentric contractions. Moreover, among individuals with stroke, a disturbance of this system could also lie behind the lack of contraction mode-specific modulation of muscle activation that has been found in this population. The altered neuromuscular function evident after a stroke means that stroke victims may find it difficult to supply a sufficient level of stress during traditional resistance exercises to promote adaptation by the neuromuscular system. This insufficiency may partially explain why the increase in strength, in response to conventional resistance training, often has been found to be low among subjects with stroke.

Svensk sammanfattning

Muskelsvaghet är en av orsakerna till funktionshinder efter stroke. I rehabiliteringsprogram för personer som drabbats av stroke förekommer det numera att styrketräning används i syfte att öka muskelstyrkan. Effekten av styrketräning har dock ofta visat sig vara begränsad. En viktig styrketräningsprincip är att muskulaturen belastas tillräckligt nära maximal styrka under både koncentriska kontraktioner (när man lyfter en vikt) och excentriska kontraktioner (när man kontrollerat sänker en vikt). Ett potentiellt problem skulle kunna vara att personer med stroke inte belastas optimalt under träning på grund av förändrad muskelfunktion. Efter stroke är muskelfunktionen ofta förändrad såtillvida att styrkenedsättningen är mer uttalad under koncentriska kontraktioner. Därutöver har man funnit att styrkenedsättningen är mest uttalad när muskeln är i sitt mest förkortade läge. Detta fenomen har dock inte studerats för alla tre kontraktionstyper, det vill säga excentriska, koncentriska och isometriska kontraktioner, hos personer med stroke.

Denna avhandling undersöker sambandet mellan styrka och ledvinkel över armbågsleden hos personer med stroke under alla tre kontraktionstyper – excentrisk, koncentrisk och isometrisk, samt relativ belastning genom rörelsebanan under en styrketräningsövning. Därutöver undersöker denna avhandling också hjärnans aktiveringsmönster under excentriska och koncentriska kontraktioner.

Sambandet mellan styrka och ledvinkel undersöktes hos personer med stroke (n = 11), åldersmatchade (n = 11) och unga försökspersoner (n = 11). Jämfört med kontrollgrupperna var maximal styrka för personer med stroke mest nedsatt, samt även den oproportionerligt stora styrkenedsättningen vid kort muskelängd som mest uttalad, under koncentriska kontraktioner. Denna avvikelse var minst uttalad vid excentriska kontraktioner. Vidare studerades hur hög belastningen på muskulaturen var i jämförelse med muskelns maximala styrka under en styrketräningsliknande övning för armbågsflexorer vid en träningsintensitet på 10RM. Den uppmätta belastningen under den koncentriska fasen av styrketräningsövningen, uttryckt som procent av den genomsnittliga koncentriska styrkan, var densamma för alla grupperna. Under den excentriska fasen av övningen var dock belastningen, uttryckt som procent av den maximala excentriska styrkan, signifikant lägre för personer med stroke. Träningsbelastningen utgjorde också en lägre andel av den maximala isometriska styrkan för personer med stroke, både under den koncentriska och under den excentriska fasen.

Funktionell magnetresonanstomografi (fMRI) användes för att undersöka hjärnans aktiveringsmönster hos unga försökspersoner (n = 18) och hos individer med stroke (n = 4) när de föreställde sig att de utförde maximal styrketräning för armbågsflexorer (motor imagery). Resultatet visade att

primära motorbarken och premotoriska barken var mindre aktiverade när unga friska försökspersonerna föreställde sig utföra maximala excentriska, jämfört med maximala koncentriska kontraktioner. Dessutom var en region i ventrolaterala prefrontala barken, som i tidigare studier visat sig vara inblandat i reglering och hämning av muskelaktivering, mer aktiverade under föreställda excentriska kontraktioner. Detta aktiveringsmönster i den prefrontala barken återfanns dock endast i den icke skadade hjärnhalvan hos personer med stroke.

Jämfört med kontrollgrupperna uppvisade försökspersonerna med stroke en förändrad muskelfunktion som bestod av en specifik nedsättning av styrkan under koncentriska kontraktioner samt också ett mer avvikande samband mellan styrka och ledvinkel under koncentriska kontraktioner. Den relativa belastningen under utförandet av en styrketräningsövning med en intensitet på 10RM var på grund av dessa avvikelser lägre för försökspersoner med stroke. Hjärnavbildnings-studierna indikerade att ventrolaterala prefrontala barken verkar vara involverat i ett kortikalt moduleringssystem som reglerar muskel-aktivering olika beroende på kontraktionstyp under maximala kontraktioner. Detta skulle kunna vara en underliggande mekanism bakom den hittills obesvarade frågan varför det är omöjligt att aktivera muskulaturen maximalt under excentriska kontraktioner. En störning av detta moduleringssystem hos personer med stroke verkar också kunna ligga bakom den förändrade regleringen av muskelaktivering som visat sig förekomma hos personer med stroke. Neuromuskulär funktion efter stroke är förändrad i flera avseenden vilket verkar medföra att muskulaturen inte belastas optimalt under konventionell styrketräning. Detta kan vara en delförklaring till varför styrkeökningen som svar på träning ofta är liten hos personer med stroke.

Abbreviations

ACSA	Anatomical cross sectional area
ACSM	American College of Sports Medicine
ANOVA	Analysis of Variance
AST	Angle Specific Torque
BA 44	Brodmann area 44, part of VLPFC
BOLD	Blood Oxygen Level Dependent
CON	Concentric
ECC	Eccentric
E/C ratio	Eccentric to concentric torque ratio
EEG	Electroencephalogram
EMG	Electromyography
EMG_{RMS}	Root-mean-square value of the electromyographic signal
fMRI	Functional magnetic resonance imaging
MC	Primary motor cortex
MRCP	Motor related cortical potential
MVC	Maximal voluntary contraction
PMC	Premotor cortex
PSCA	Physiological cross sectional area
RM	Repeated Maximum
TRAT	Truncated Range Average Torque
VLPFC	Ventrolateral prefrontal cortex

Original papers

Paper I   Hedlund M, Sojka P, Lundström R, Lindström B. *Better preserved torque-angle relationship during eccentric compared to concentric contractions in patients with stroke.* Isokinetics and Exercise Science, June 2012, Vol. 20, No. 2 . (In press)

Paper II   Hedlund M, Sojka P, Lundström, R, Lindström B. *Insufficient loading in stroke subjects during conventional resistance training.* Advances in Physiotherapy, March 2012, Vol. 14, No. 1, Pages 18-28.

Paper III   Olsson C-J, Hedlund M, Sojka P, Lundström R, Lindström B. *Increased prefrontal activity and reduced motor cortex activity during imagined eccentric compared to concentric muscle action.* (Pending acceptance)

Paper IV   Hedund M, Lindström B, Sojka P, Lundström R, Olsson C-J. *Is better preservation of eccentric strength after stroke due to a disturbed pre-frontal function?* (Manuscript)

Preface

My interest in the field of muscle function after a stroke arose from my clinical experiences. I started to work as a physiotherapist at a neuro-rehabilitation unit in 1996. In 1995, a Swedish study presented promising results with a special type of resistance training for stroke subjects. This study concluded that maximum eccentric (lengthening contraction) training was more effective than maximum concentric (shortening contraction) training with respect to increasing concentric strength for stroke subjects. At this time, the use of resistance training was still controversial in neurological rehabilitation and the training in the above-mentioned study was performed with special equipment only found in laboratories, a situation that made it difficult to transfer this knowledge to clinical practice. However, armed with this knowledge, knowledge about principles of resistance training, and knowledge about stroke rehabilitation, I began to explore using resistance training for my patients. A successful approach was to apply a greater load during the eccentric contractions than during the concentric contractions during resistance exercises. The training load was determined by trying to find the load that the patient could resist in a controlled manner throughout the whole range of motion for about 10 repetitions. After this load was determined, the patients, by themselves or with the help of an assistant, had to unload the weight during the lifting phase. I used this approach also for patients who had adequate concentric strength to use conventional training principles. This method was successful, but had limitations. For example, judging what is a controlled vs. uncontrolled eccentric contraction is difficult. In addition, it is often unclear what amount of unloading is obtained during the concentric contraction (lifting phase) and the need for unloading may also encumber adequate lifting performance. The method, however, was simple to use and often provided good and sometimes remarkable results.

Nevertheless, many questions arose from these experiences: What mechanisms underlie the increased differences in strength between eccentric and concentric contractions for individuals with stroke? Is the strength capacity throughout the ROM altered for subjects with stroke? How high is the intensity during the eccentric and concentric phase during resistance exercises when individuals with stroke use conventional resistance training principles? What is the highest intensity possible during eccentric contractions considering the potential risk for muscle damage? As there were no direct answers in the literature to these questions, the idea for this project was born. With the great help of my supervisors and colleagues, for several years now, I have had the opportunity to discuss and learn about these issues, quite literally, inside and out.

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1 Introduction

This thesis focuses on how muscular function – particularly eccentric and concentric force production – alters after an upper motor neuron lesion due to stroke. In addition, this thesis explores whether these alterations affect how musculature is loaded during resistance training exercises. One of the underlying questions is whether individuals with stroke are under-loaded during conventional resistance exercises, and if so, why. The introduction starts with a brief rationale behind the thesis. This rationale is followed by a conceptual overview of relevant neuromuscular terms, measuring methods, and a description of resistance training principles. Based on these biomechanical principles of resistance training, this introduction also highlights changes of neuromuscular function after stroke that theoretically might influence how musculature is loaded during conventional resistance exercises.

1.1 Rationale behind the thesis

Conventional resistance training, previously considered contraindicated in stroke rehabilitation (1), has become a common method to improve motor function and strength (2, 3). However, studies that have explored the effects of conventional resistance training after stroke have revealed that strength gains often are surprisingly small and result in small or no measurable improvements of the ability to perform activities in daily living (4). Similarly, partly disappointing results have been reported from resistance training studies with subjects who have lesions in the central nervous system due to causes other than stroke, i.e., children and adults with cerebral palsy (5). Conventional progressive resistance training –e.g., as outlined by American College of Sports Medicine (ACSM) (6)– has been adapted and developed to achieve optimal load on the neuromuscular system for individuals with normal muscle function.

After suffering a stroke, however, significant alteration in the central nervous system control of the muscles and secondary structural and functional changes in muscles lead to altered muscle function. It could be asked whether these alterations mean that resistance training should be modified to address these changes. There are indeed some indications that the training load is not optimal for subjects with stroke when they are subjected to conventional resistance training. For stroke subjects, strength increases has been found to level off unexpectedly early (within about six to eight weeks) during a progressive resistance training period (7). Furthermore, to date, only one study (8) has considered whether resistance training in stroke patients increases muscle cross-sectional area. This may indicate that subjects with stroke do not respond to resistance training in the same way as healthy subjects or that the stimuli provided by conventional resistance exercises is not optimal for long-term strength increases.

1.2 Conceptual overview

1.2.1 Muscular strength and function

Muscle strength can be defined as the ability of a muscle or muscle group to exert maximal force or torque at a specific velocity during a muscle contraction. Muscle power is characterized by the product of force and the velocity at which the force is produced during a movement (9). Although those definitions are quite straightforward, muscular strength can be measured and quantified in many different ways and with many different methods. In the context of resistance training, muscle strength does, in many respects, deal with the ability to develop torque across a single joint or across a joint system (10).

1.2.1.1 Muscle contractions

When muscles undergo activation and generate force, the resulting action depends on the applied and produced forces. When the force produced by the muscle exceeds the force applied to the muscle, the muscle will shorten. This is known as a shortening or concentric contraction. When the force applied to a muscle exceeds that produced by the muscle, it will lengthen. This is known as a lengthening or eccentric contraction. Eccentric and concentric contractions are so called dynamic contractions in which joint movement takes place. When the applied and produced forces are equal, no movement takes place and the whole muscle-tendinous complex remains the same length, even if the activated muscle fibres undergo a change in length (11). This is known as an isometric contraction (12). Isokinetic and isotonic contractions are forms of dynamic contractions that are present in testing and training contexts. During an isokinetic contraction, the velocity is held constant by a dynamometer throughout the range of motion. The force produced against or along the dynamometers lever arm can be measured to calculate the eccentric and concentric torque, respectively. Isotonic contractions is defined as a dynamic contraction where muscular tension is held at a constant level, but a true isotonic dynamic contraction does not really exist in vivo although the term is commonly used to describe a dynamic muscle contraction where the external load is fixed. Although the load is constant, the muscular tension during an isotonic dynamic contraction varies substantially due to alterations of external and internal moment arms during the movement and due to the influence of inertia. Since the movement velocity is free, the force requirement to lift a load varies according to acceleration and deceleration patterns. Alternative terms (e.g., isoinertial resistance) have also been suggested (13) to describe the physical properties of the resistance. In this thesis, the term isotonic will be used as it still is the most widely used term in the literature (14).

1.2.1.2 Muscle morphology and architecture

The ability for a contracting muscle to develop joint torque depends on a number of factors that can be classified as muscular, neural, and biomechanical. To understand the significance of altered muscle function after a stroke, some important muscular and biomechanical factors and the affects of age and mechanical loading will be addressed.

Skeletal muscle cells (muscle fibres) are composed of myofibrils, which are composed of a chain of contractile units called sarcomeres. The sarcomere is the basic contractile unit of a muscle and consists of thick (comprising mainly myosin) and thin (comprising mainly actin) filaments. Muscle fibrils generate force during activation of actin and myosin cross-bridge cycling. Ultimately, the more cross-bridges activated (i.e., in contact at a given moment), the more force is developed. The differences in force and velocity characteristics of a muscle can, to a great extent, be explained by i) the number of myofibrils in each muscle fibre, ii) the number of sarcomeres in series, and iii) the arrangement of muscle fibres relative the axis of force generation, i.e., the muscle architecture (10).

The intrinsic force producing capacity of a skeletal muscle is proportional to a muscle's cross sectional area. The anatomical cross sectional area (ACSA) is defined as the cross sectional area perpendicular to the muscles long axis. In most human muscles, the muscle fibres are oriented at an angle relative to the muscle's line of action. The physiological cross sectional area (PCSA) is defined as the cross sectional area perpendicular to the muscle fibres. The maximum force a muscle can produce is directly related to the PCSA (10). The PCSA and the ACSA partly depend on the number of fibrils packed in each fibre. Whole muscle hypertrophy is believed to be due to an increase or decrease in the size of the muscle fibres with no change in the number of fibres. Provided that the availability of substrate is not limited, the number of fibrils in each fibre increases with resistance training, but is reduced both as a result of detraining and aging (15). The increased synthesis of muscle proteins begins immediately after exercise (16), but myofibrillar hypertrophy is often not noticeable for several weeks or months (17). The potential effect for hypertrophy seems to be attenuated with age (18, 19).

The intrinsic force generating capacity may also vary per unit of PSCA and can be calculated and expressed as specific tension. Specific tension seems to increase following resistance training (20) and decrease with increased age. Measured specific tension has been found to be about 30% lower in older than in younger men (21). To some extent, this difference may be due to a selective atrophy and/or loss of the somewhat stronger fast muscle fibres (Type IIa and IIx fibres) compared to slow muscle fibres (Type I fibres) as well as to co-contraction in older subjects being higher

than in younger subjects (22). Lexell et al. (23) found Type II fibre cross sectional area of 80-year-old subjects to be 26% smaller than that of 20-year-old controls, whereas no difference existed in Type I fibre CSA with increased age.

Another important factor for muscle function is the number of sarcomeres in series, a factor that influences a muscle's intrinsic ability to perform fast contractions and to manage stress during heavy eccentric contractions (24). The number of sarcomeres in series also affects the muscle's length-tension relationship. Alterations in number of sarcomeres in series (e.g., fewer sarcomeres in series) results in a change of the optimum muscle length (25) while also resulting in a narrower length-tension relationship, which means that a muscle's force-producing capacity varies more throughout the range of motion (ROM) due to greater sarcomere length change for a given muscle excursion (26). The number of sarcomeres in series shows adaption in response to mechanical loading and aging. High tension during heavy resistance exercises, especially during eccentric contractions, seems to result in adaption composed of an increase in the number of sarcomeres in series (27), whereas immobilization in a shorten position (28) and aging (29) results in a corresponding reduction. However, immobilization per se does not seem to result in a reduction of sarcomeres in series, since immobilization in a lengthened position seems to increase the number of sarcomeres in series (28).

The PCSA is also influenced by the pennation angle of the muscle fibres. A greater pennation angle enables an increase in PCSA without the same increase in ACSA. There is, however, a trade off in the sense that the oblique fibre arrangement results in a lower resultant force along the muscle's line of action (30). Another disadvantage with a pennate fibre orientation is that it results in a shorter displacement for the muscle for a given displacement of the involved muscle fibres thereby lowering the maximum contraction velocity. This is counteracted by the fact that when pennate muscles shorten, they also rotate to a greater angle of pennation (31).

Over the past decade, several studies have demonstrated that force not only is transduced through myotendinous pathway (32), but also may be transduced through inter- and extra-muscular connective tissues (33, 34). Other studies have found that the importance of this phenomenon may be small in normal muscles (35), but it has been proposed to have an important role in muscle function changes after stroke.

1.2.2 Muscle force modulation

1.2.2.1 Muscle fibre recruitment

A muscle is composed of muscle fibres with different biochemical and physiological characteristics, e.g., shortening velocity and fatigability (36). Rather than controlling each fibre, the nervous system controls motor units. A motor unit consists of the alpha motor neuron with its axon, and all the muscle fibres it innervates share the same characteristics. Small motor units have small diameter axons and typically innervate rather few slow-contracting muscle fibres that are fatigue resistant. Small motor units also tend to have a low threshold for activation. Large motor units have large diameter axons and typically innervate many fast-contracting muscle fibres that are more fatigable. Large motor units also tend to have a higher threshold for activation. On the motor unit level, the production of force is modulated by the number of recruited motor units and the discharge rate of activated motor units. Motor units seem to be recruited and derecruited in a fixed order of their sizes (37, 38), known as Henneman's size principle. This principle has been found to be true in isometric and concentric conditions (39-41). However, the literature regarding recruitment order during eccentric conditions is somewhat controversial. Several studies show that the size principle is valid also during eccentric contractions (42-46), but some studies have suggested a selective recruitment of fast motor units during eccentric conditions in special conditions (47, 48).

Despite extensive research on the topic, the exact mechanisms underlying the improved recruitment of motor units in response to resistance training is not fully understood (49). Direct evidence for a neural response to resistance training is lacking and most of the evidence is based on indirect indications. It is known that when someone starts a resistance training program, there is often a fairly large increase in strength over the first training sessions in the absence of muscular hypertrophy (50). This early increase in strength is considered to be attributable to learning of the specific movements, but also to an increase in cortical excitability (51). Other indirect evidence of neural training effects is the so-called cross-over effect where a non-trained limb actually increases its strength without being subject to exercise, a phenomenon that can be seen in unilateral resistance training (52). This cross-over effect seems to be more pronounced in eccentric training than in concentric training (53). Furthermore, increased strength after mental practice of a specific task (motor imagery) is another indication that resistance training seems to increase the cortical output signal after training (54). Motor unit firing rates have been found to increase after resistance training in small (55) and large (56) muscle groups although these changes may be transient and moderated as other adaptations are manifested (55). A possible spinal mechanism underlying enhanced

motor unit activation is increased motor neuron excitability (57); however, recently it has been demonstrated that increased strength due to resistance training does not seem to be explained by increased motor neuron excitability of high threshold motor units, but rather by supraspinal adaptations resulting in an increased central drive (58).

1.2.2.2 Force velocity relationship

A muscle's capacity to generate force differs between contraction modes and velocities. The capacity of force production is greatest during eccentric contractions, followed by isometric contractions, and concentric contractions. For concentric isotonic muscle contractions, there is an inverse relationship between maximum shortening velocity and the load applied on the muscle. This phenomenon is also evident during maximum isokinetic contractions with decreased force production with increased contraction velocity. However, during isokinetic eccentric contractions, the force production does not seem to be affected by contraction velocity in the same way. The difference between maximum eccentric and concentric force producing capacity (59, 60) has its origin in the properties of the cross-bridges (61). Thus, an isolated muscle fibre has a superior intrinsic capacity for high force development during eccentric contractions. During electrical stimulation of isolated fibres in vitro, the measured force during eccentric contractions has been shown to be almost twice as high compared to the force developed during isometric or slow concentric contractions (59, 60). This large difference is obtained only during in vitro experiments when muscle fibres are electrically stimulated. In vivo, activation during the eccentric phase appears to be inhibited and eccentric strength is the same or up to about 40% higher than isometric strength (62). It appears that normal subjects are almost capable of full activation of their muscles during concentric and isometric conditions (63), but this is not the case during eccentric conditions (62, 64). Electrically induced maximum activation of muscle fibres during forced eccentric contractions is associated with severe muscle damage (65). For this reason, the inability to fully activate the muscle during maximum eccentric contractions are often regarded as protection mechanisms (66).

Hence, the modulation of the muscle activation depends on the contraction mode (concentric, eccentric, or isometric) (67). Although, it is well established that there are fewer motor units recruited during maximal eccentric contractions compared to maximal concentric contractions (68) as well as a lower discharge rate of these units (69, 70), it is still unclear where and how this contraction-mode specific modulation (inhibition and augmentation of muscle activation) is accomplished. Furthermore, for concentric contraction mode, the ability to generate muscle force decreases as a function of contraction velocity in vitro and to compensate for this in vivo the degree of activation of a

muscle increases with the increase in contraction velocity (62, 71). Therefore, the modulation of the muscle activation also depends on the speed of the contraction (67). The ratio between concentric and eccentric strength is referred to as the eccentric to concentric ratio (E/C ratio). The E/C ratio is speed dependent and in healthy subjects the ratio is usually found to be about 1.4-1.7. However, in subjects with upper motor neuron lesions, considerably higher E/C ratios have been reported.

1.2.2.3 Mode-specific modulation of force

The modulation of muscle activation seems to be contraction mode-specific (62, 66, 67, 72). The overall inhibition during eccentric contractions appears to be a very potent mechanism. For example, Webber and Kriellaars (73) found that the produced eccentric moment during voluntary maximum contractions was found to be around 50% of predicted eccentric moment capacity. The literature frequently suggests this system helps inhibit eccentric contraction via afferent input, e.g. from tension sensitive Golgi-tendon organs (62, 66). However, there is a lack of compelling objective data that shows that this system has this function in this context (74). Nevertheless, contraction-mode specific modulation of muscle activation seems to involve both the spinal level (62, 75, 76) and supraspinal levels (77). Several resistance training studies in which the effect of pure eccentric training protocols have been studied reveal a contraction-mode specific increase in descending drive during maximum eccentric contractions as a result of training (77). Thus, there are indications that cortical output may be mode-specific modulated and that this system is adaptable, but there are no established models so far that explain how such a system might work. A general hypothesis of a supraspinal regulatory system has been proposed to up/down regulate cortical motor drive during different conditions, e.g., during an on-going fatiguing task, in order to maintain adequate force without comprising homeostasis and/or tissue (78). As it seems necessary to avoid a complete activation of a muscle during eccentric contraction, a mode-specific modulation of muscle activation in these situations also accords with these, however controversial, theories that address supraspinal regulatory mechanisms, the so called central governor model (78).

Another indication of supraspinal involvement in contraction mode-specific modulation of muscular force is that the excitability of the motor cortex is lower during on-going eccentric compared to concentric contractions (79). In addition, apparently there is a paradoxical relationship between brain electroencephalographic (EEG) activity and muscle electromyographic (EMG) activity during the eccentric compared to concentric contractions (80). The paradox is that a lower EMG activity during maximum eccentric contractions (compared to concentric) is associated with a higher EEG activity. During isometric contractions, there exists an almost linear relationship between EEG activity and EMG

activity and force (81). Furthermore, Fang et al. (80) describes a temporal shift, where the movement-related cortical potential (MRCP) (especially within the pre-frontal cortex) occurs slightly earlier for an eccentric contraction. What this EEG-EMG paradox is caused by is not clear, but Fang et al. suggests that perhaps it is more difficult for the central nervous system to prepare, plan, and perform eccentric contractions. Another suggestion from Fang et al. (80) is that the elevated EEG activity may reflect that parts of the pre-frontal cortex, before and during maximum eccentric contractions, is involved in a mechanism that achieves adequate inhibition of muscle activation, a strategy that prevents muscle damage.

1.2.3 Measuring muscle strength

The measurement of strength deals with the ability of muscles to produce torque across a single joint (single joint movement) or across a joint system (multiple joint movement) (82). In clinical and experimental settings, three methods are commonly used to measure strength: maximal force produced during an isometric contraction; the torque produced during an isokinetic contraction; and the maximal load that can be lifted a specified number of repetitions. In clinical practice, manual methods using ordinal scales are used to quantify muscle strength, but these methods have several limitations (83).

Isokinetic dynamometers are often used to measure torque production during dynamic as well as isometric contractions. The dynamometer measures the force perpendicular to the lever arm and calculates the torque based on the measured force and the length of the moment arm. Maximum isometric strength testing is usually referred to as a maximal voluntary contraction (MVC) and measurement of isomeric strength can be performed at any point throughout the range of motion (ROM) against a fixed lever arm. Isokinetic measurements are performed at a fixed velocity to avoid the effect of acceleration. Some isokinetic dynamometers (e.g., Kin Com®) can also measure force during isotonic contractions. In this isotonic mode, the average resistance provided by the dynamometer throughout the ROM is constant, but the velocity of the movement is free as the system also takes into account acceleration. If the subject produces higher force and acceleration at the beginning of the movement, this will result in a corresponding reduction of the force requirement to move the lever arm during the latter part of the movement. In many respects, strength measurements in the isotonic mode are very similar to strength measurements or exercises that use mass loads, i.e., lifting free weights or using resistance exercise machines. One common method to measure strength using a load with mass is to determine the load that can be lifted once throughout the entire ROM, also known as the one repeated maximum (1RM).

1.2.4 Measuring muscle activity

When a muscle fibre is activated, an action potential is generated and propagates along the muscle fibre. The action potential propagates in both directions away from the motor point, located in the middle of the muscle fibre. These action potentials can be picked up by electrodes, making it possible to measure the degree of muscle activity. The record of muscle activation is the electromyogram (EMG).

EMG electrodes used to pick up action potentials are usually either intramuscular electrodes or surface electrodes. Surface electromyography has become a commonly used method to assess muscle activity and muscle fatigue. When a healthy muscle is at rest, a resting activity is always generated. When the muscle is activated, the number of activated fibres increases and the frequency of generated action potentials increases. The raw EMG is the signal that is actually generated by the muscle.
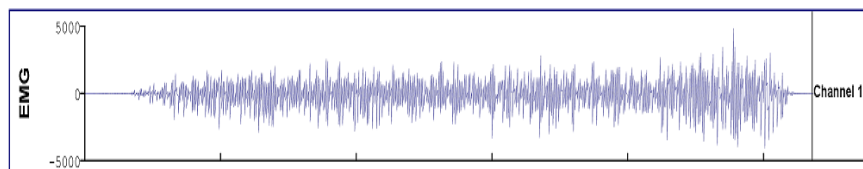
Figure 1: Raw surface EMG signal.

Figure 1 shows a raw surface EMG signal. In the raw graph, the X-axis displays time and the Y-axis displays amplitude in μV (micro-Volts). The raw EMG signal has both positive and negative values. Signal amplitude can range from 0 to 10 μV (peak-to-peak). As the muscle force increases, the number and amplitude of the spikes increases. When the muscle force decreases, the raw EMG signal decreases. To enable further analysis, the raw EMG signal is rectified by calculating the root-mean-square (EMG_{RMS}) value. The EMG_{RMS} represents the square root of the average power of the EMG signal for a given period. The power density spectrum of the EMG signal ranges from 0 to 400 Hz for most muscles. Two parameters of interest according to the power density spectrum are the mean frequency and the median frequency. The EMG_{RMS} value and the mean or median frequency are used to evaluate different aspects of muscle activation and muscular fatigue. To determine the degree of activation, the EMG_{RMS} value is used. To evaluate and monitor muscular fatigue, the mean or median frequency is often used (84).

1.2.5 Measuring cortical activity during motor events

Cortical activity associated with muscle contractions of the kind present in conventional resistance exercises has not been investigated to a great extent. One of the reasons for this might be the lack of adequate methods appropriate for high load muscle activities. Two methods used in this context are electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).

1.2.5.1 Electroencephalography (EEG)

EEG measures the brain's electrical activity using electrodes placed on the scalp. EEG can be used to examine movement-related cortical activity with high temporal resolution (85). The disadvantage of this method is its poor spatial resolution. The method is particularly suited for studying the time sequence for brain preparations before the execution of, e.g., a motor task. In the final seconds before voluntary movement production, there is an increase in electrical activity in the motor areas of the brain, known as the movement-related cortical potential (MRCP) (85).

1.2.5.2 Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging, is a non-invasive method that has increasingly been used to study brain activity in relation to, e.g., motor or cognitive activities. In fact, the neural activity is not measured directly, but indirectly. When neuronal activity increases, neuronal metabolism increases, which leads to a series of hemodynamic responses. Oxygenated haemoglobin has different magnetic properties than de-oxygenated haemoglobin and it is these differences that are the basic background on which the method is based. The signal recorded is called BOLD (Blood Oxygen Level Dependent) and forms the basis for most fMRI studies (86). During an fMRI session, several low-resolution functional volumes are recorded over time. Before the statistical analysis of the data, pre-processing of the data takes place. The pre-processing consist of a collection of techniques to assure the quality of the data; slice acquisition time correction to adjust for that different slices of the brain volume scanned at different times; correction of head movements; and spatial smoothing of the data using a Gaussian filter. The pre-processing is followed by the statistical analysis of the data. The statistical analysis can be divided into two levels. The first level analysis consists of a general linear model procedure for each subject. In the analysis, differences in BOLD signal strength are contrasted between two conditions (regressors). The number of tested contrasts depends on the research question. The second level analysis consists of that the single subject's statistics is fed into a multi-subject analysis.

When it comes to motor performance and fMRI, there are several limitations. Compared with EEG, fMRI has some advantages and some disadvantages. Although fMRI has a much better spatial resolution than EEG, fMRI has rather poor temporal resolution. Another limitation with fMRI is that all motions must be made in the supine position. Furthermore, the space in the fMRI scanner is very small, which reduces the degrees of freedom. The subject also has to keep his/her head perfectly still during the measurement, which makes it difficult to perform maximum contractions. In addition, metal measuring equipment or weights cannot be used in fMRI scanners.

A well-proven method for studying brain activity during more complex motor tasks is *motor imagery.* It is well described in the literature that execution and imagery of motor activities share many cortical areas and motor programs. Over the years, motor imagery has been successfully used to study motor representations because of the similarities between imagined and executed motor tasks (87). There are indeed differences between motor imagery and execution, and it has been shown that there may be partially different activation patterns within the motor system (88). Nevertheless, motor imagery is a method that easily can be performed in a scanner, so it can be used to study the underlying neural mechanisms of submaximal and maximal muscle contractions.

1.2.6 Upper motor neuron lesion and strength

An upper motor neuron lesion due to stroke produces neuromuscular impairments such as strength loss and spasticity (89). In the context of neurological rehabilitation, regular measurements of muscle strength have been considered insufficient and invalid ways to describe the complex motor function after stroke (1). Therefore, evaluation of motor function has primarily been based on assessment of the performance of specific movements (90-92). However, the increased interest in and use of resistance training in the stroke rehabilitation programs (4, 93, 94) and an increased understanding of the significance of muscular strength for post-stroke disability may have contributed to a renewed interest in muscular force function (95-100). One issue that has been debated in the literature is if reduced muscular strength in post stroke individuals mainly is caused by a reduced ability to produce agonist muscle force (71, 101-103) or, as earlier theories suggest, if reduced muscular strength mainly is caused by antagonist restraints due to an inappropriate reflex mediated co-activation of antagonists (e.g., spasticity) (1, 104). Most factors indicate that agonist muscle weakness and activation failure is the main problem (105).

Therefore, muscle weakness following stroke is to a great extent associated with a decreased ability to recruit individual motor units, a loss of functional motor units (106), and reduced firing rates for recruited

motor units (107). Furthermore, the paretic muscles may also undergo atrophy and an increase in non-contractile tissue content (108). Normal aging leads to larger slow-twitch and smaller fast-twitch motor units, resulting in an overall change in muscle fibre-type composition with relatively larger volume of type I fibres. In contrast, suffering a stroke seems to result in a shift to fast myosin heavy chain (type IIx fibres) (109, 110) possibly as a response to disuse and immobilization. In addition, muscle atrophy degeneration of the lower motor neurons also seems to occur as a result of the lesion of upper motor neurons due to stroke (111). The loss of motor neurons seems to start very early after stroke onset (112) and may therefore not only be due to disuse and immobilization.

1.2.7 Upper motor neuron lesion and muscle tone

In addition to reduced muscle strength, spasticity is another key-component of the upper motor neuron syndrome. The most used definition of spasticity is the Lance definition: "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex" (113). Spasticity is usually assessed during passive conditions during rapid elongation of a muscle when the patient tries to relax (114). There are numerous mechanisms that potentially might contribute to increased resistance to passive stretch at high velocities. One main factor is neural mediated reflex stiffness suggested to be caused by an altered balance between segmental monosynaptic reflex and descending inhibition. Another mechanism is passive muscle stiffness due to alterations in non-contractile elements. This increased resistance could also be due to active or elastic muscle stiffness resulting from the state of cross-bridge attachment (115, 116). Altered viscous properties of the muscle alter the velocity-dependent increase in muscle tone and can therefore mimic spasticity. An upper motor neuron lesion due to stroke is typically associated with reduction in loading on the musculotendinous complex and altered positioning of the limb, especially in the upper extremity. Immobilization in combination with spasticity seems to result in unique histological and biomechanical alterations (117, 118), which in various ways differ from changes due to immobilization or aging.

The term spasticity is used in the context of upper motor neuron lesions of both cerebral and spinal lesions. However, the pathophysiology behind stretch reflex mediated increase in muscle tone may differ depending on lesion locus (119, 120). In subjects with spinal cord injuries, the increased reflex response to a rapid muscle stretch appears to a great extent to be associated with denervation hypersensitivity (121). In subjects with stroke, on the other hand, the stretch reflex mediated muscle activity seems to be more associated with an increase in background activity, bringing the alpha-motor neuron closer to the threshold for activation

(122). As there may be no "true" stretch reflex gain or abnormal co-contraction during voluntary motions, it has been proposed that spasticity as the result of a stroke should be considered a disorder limited to resting limbs (123). There is no generally accepted and established method to differentiate between the various underlying components behind an increased velocity dependent stiffness of spastic muscles, but there are some promising attempts (124). A general problem in the quantification of spasticity, however, is that what is measured during resting conditions is not necessarily valid during activity.

1.3 Principles of resistance training

1.3.1 Relative loading

Progressive resistance training uses movements performed against some form of resistance and increases the resistance as strength increases so as to provide an adaptive stimulus (125). The strength gains that occur during the first weeks of a resistance training period is considered to be mainly due to neuronal effects (126), while further strength increase is considered to be due to an increase in muscle fibre cross-sectional area. Resistance exercises is associated with loading-induced mechanical deformation and muscular fatigue which in turn is linked to a number of physiological and biochemical processes that can initiate signalling pathways leading to hypertrophy (127). To induce a net increase in protein synthesis, there appears to be a more or less critical limit for the relative degree of mechanical tension on the muscle (128, 129). If the relative load is below this critical limit, the training will primarily result in metabolic adaptations of the muscles, leading to increased muscular endurance but not to an increased ability to generate force. On the other hand, if the relative load during exercise is very high, the total training volume will be low, which seems to reduce the stimulus that signals for hypertrophy (125). Strength increases associated with very heavy resistance exercise programs seem to be mainly related to neural adaption. An important determining factor for whether the training will result in a hypertrophy seems to be that the mechanical loading is sufficiently high even during the eccentric phase (130).

1.3.2 Determining training load

There are various methods to determine the training load. A commonly used procedure is to express the training load in relation to the load that can be lifted once but not twice, the one repetition maximum (1RM). Depending on the purpose (e.g., maximum strength, explosive strength, muscle growth, or endurance muscle strength), an external load is selected that represents a certain fraction of the 1RM. Training load can also be expressed as the load one can lift 10 repetitions but not 11

repetitions and so on (131). A commonly used procedure is to equate a certain repetition maximum (e.g., 10RM) to a certain percentage of 1RM. For an average individual, it has been demonstrated that a given repetition maximum corresponds reasonably well to a given fraction of the 1RM. To induce strength gains, it is commonly suggested that the load should be at least 60% of 1RM, which in a healthy average individual is equivalent to about 12-15RM.

1.3.3 Biomechanical principles for resistance training

Dynamic strength training is often carried out with free weights such as dumbbells, barbells, pulleys, or weight-cuffs. With this type of training, the external resistance is constant, but the torque load varies throughout the ROM since the external moment arm varies and due to the effects of inertia. In many established resistance exercises, the torque load matches the torque producing capacity throughout the ROM quite well. This type of training with a fixed load is sometimes known as isotonic exercise. For resistance exercise machines with a so-called accommodated resistance, the resistance varies throughout the ROM in a smaller degree compared with training with free weights (132). When exercising with free weights, training machines, or pulleys, one must also consider inertia according to Newton's second law (force = mass x acceleration). At the start of a motion during a resistance exercise, a change of the velocity must be achieved. Acceleration is the quantity that measures a change in velocity over a particular time. To produce acceleration, a force must be applied to the body and the size of the acceleration is directly proportional to the applied force and inversely proportional to the mass. In concrete terms, the force must be doubled to double the acceleration (133).

In conventional resistance training exercises, a contraction phase of about 1-2 seconds is common (125). This is relatively slow compared to movements in, for example, sport activities. However, the importance of acceleration even during these conditions should not be underestimated, since the beginning of even rather slow movements requires an acceleration, which then affects force requirement during the rest of the movement (134). If a lift has a specific start and stop, the average force required to perform the lift throughout the ROM is always the same since the mean acceleration is the same, i.e., zero (133). By using a lifting strategy with high initial acceleration, the resulting kinetic energy can be used to move the weight through parts of the ROM where muscle force cannot develop sufficient torque to overcome the torque produced by the weight. Such a point in the ROM is called a sticking point (135).

1.4 Neuromuscular changes after stroke with potential significance for resistance training

Several physiological, psychological, emotional, and social sequelae (136) as well as various movement-related impairments after stroke (89) may influence one's ability to perform resistance exercises and maintain participation in a resistance training program. Based on the above biomechanical principles for resistance training, some of the motor impairments that might influence how the musculature is loaded during resistance exercises will be addressed. However, not all subjects with stroke exhibit those changes.

1.4.1 Muscular and neural fatigue

Muscular fatigue (inability to maintain an expected force) during intensive work, such as a resistance exercise, is a difficult area to study and there is no single factor that alone underlies the development of muscular fatigue (137). Generally, it can be said that local muscular fatigue during a resistance exercise occurs due to an accumulation of metabolic by-products within and outside the muscle cell, which in various ways reduce the ability to generate force. The recovery after this type of muscular fatigue takes a few minutes (137). Moreover, it is also suggested that neural mechanisms play a role in the development of fatigue (138).

The knowledge of the mechanisms behind muscular fatigue in subjects with stroke is fairly limited. Most of the studies have used isometric protocols. It has been suggested that individuals with stroke may exhibit pronounced neural fatigue during sustained maximal and submaximal isometric contractions. During an isometric endurance test for elbow flexors, where the task was to generate as much force as possible as long as possible, subjects with stroke demonstrated a significantly faster force reduction down to 50% of the initial value. However, when maximum isometric strength was tested again within 2-3 seconds after failure (i.e., developed force was reduced to <50% of initial value), stroke subjects were able to develop almost the same force value as the pre-test value, which is not normally the case as local muscular fatigue overwhelms the effort (139). A similar result has recently been presented by Hyngstrom et al. (140). They found that neural fatigue played a more dominant role (compared to peripheral muscular fatigue) in the inability to maintain a submaximal contraction with the paretic leg when subjects with stroke followed a protocol of sustained submaximal isometric contractions at 20% of MVC. Recently, Knorr et al. (141) used twitch interpolation technique and transcranial magnetic stimulation (TMS) in healthy volunteers and post-stroke patients following a fatiguing protocol for knee extensors at 30% of MVC. They found that central neural fatigue, possibly

due to increased intracortical inhibition, was more frequently observed in the paretic limb in participants after stroke in comparison with their non-paretic side and in comparison with healthy controls. If this phenomenon also exists during sustained dynamic contractions such as in conventional resistance exercise, it would mean that 10RM, for subjects with stroke, would represent a lower percentage of 1RM, compared to subjects with an intact nervous system. In concrete terms, the load that they can lift 10RM would be lower in relation to their maximum strength and that failure does not have to be associated with muscular fatigue.

1.4.2 Rate of force development

People with stroke have been shown to have impaired ability to produce high rate of force development, especially during dynamic conditions (142). Hence, it can be assumed that persons with stroke during a resistance exercise have greater difficulties achieving high initial acceleration and greater difficulty adapting the acceleration pattern throughout the ROM to overcome an eventual sticking point (143). Intrinsic muscular factors that might underlie reduced rate of force development are, e.g., alterations in the ability to recruit fast muscle fibres and alterations in the number of sarcomeres in series. A neural factor responsible for increased rate of force development as a result of resistance training is an increased synchronization of motor units (144). This neural mechanism is not completely understood but is likely to occur through supraspinal sources (145). The phenomenon of motor unit synchronization, however, seems to be lacking after stroke (146, 147).

1.4.3 Eccentric to concentric ratio

The difference between eccentric and concentric strength in healthy subjects means that the eccentric phase always is somewhat under-loaded during a conventional resistance exercise; however, the relative loading given during eccentric phase, when lifting and lowering the same load, is usually considered to be sufficient in individuals with an intact nervous system (148). A meta-analysis (149) has noted, however, that if the load during the eccentric phase is selectively increased, a higher mechanical stress on the muscles is obtained, which seems to result in specific muscular adaptations and neuronal effects that cannot be achieved with concentric exercise only. It has also been shown that eccentric overload training in healthy individuals results in a selective increase in central drive during the eccentric phase (66).

It has been demonstrated that upper motor neuron lesions due to stroke and cerebral palsy are associated with an increased strength difference between eccentric and concentric muscle contractions (150, 151), but the underlying mechanisms are far from understood (104,152-156). Clark et

al. (71) have demonstrated that this might be associated with impaired modulation of maximum force production during eccentric and concentric muscle contractions. (62, 66, 157, 158). Clark et al. demonstrated that for healthy subjects the magnitude of the EMG activity of the agonists increased as a linear function of contraction velocity across eccentric and concentric contractions of knee extensors. In contrast, for stroke subjects, the magnitude of agonist EMG activity was unaffected by contraction velocity. Due to the absence of increased agonist co-contraction and passive stiffness, they excluded the possibility that this could be caused by a recurrent reciprocal inhibition, as suggested by, e.g., Knutson (159) or caused by passive antagonist restraint. The origin of this dysfunction is though unknown. Clark and colleagues although suggested that this phenomenon could be taken advantage of by selectively increasing the load during the eccentric phase. In fact, by 1995, Engardt (160) showed that training with maximal eccentric loading seems to give better effect on concentric strength compared to training with maximal concentric loading using isokinetic equipment, which provides accommodated resistance (161), irrespective of a possible abnormal E/C ratio or torque-angle relationship.

1.4.4 Torque angle relationship

In addition to an increased E/C ratio in individuals with stroke, it has been demonstrated that there also seems to exist an altered torque-angle relationship. The torque producing capacity varies throughout the ROM due to biomechanical and muscle-physiological reasons. However, in single-joint movements, there exists a joint specific torque angle relationship, sometimes called a strength curve. In healthy subjects, the strength curve is the same regardless of contraction type and contraction velocity; i.e., eccentric, concentric, and isometric strength curves are essentially similar (162). The overall change of the strength curve in people with stroke, as described in the literature, is a lower strength at short muscle length, demonstrated in both the upper and lower extremities (163, 164). This phenomenon might be attributable to altered neural and muscle-physiological properties. Li et al. (165) studied architectural parameters of the Brachialis muscle in subjects with stroke and found that the pennation angle in the affected side was somewhat increased during rest, but the pennation angle and fascicle length changes were smaller in the affected side during submaximal and maximal isometric contractions. The authors suggested that immobilization and contracture might cause a shortening of the fascicle and an increase in resting pennation angle in the affected side. Similar findings were also reported by Gao and Zhang (166).

Studies that have examined torque angle relationship in subjects with stroke have almost exclusively examined isometric strength profiles. Contraction velocity affects this relationship in that the strength curve appears to deviate more with increased concentric contraction velocity (167). However, to my knowledge, no studies exist in which strength curves during all contraction modes – eccentric, concentric, and isometric – in subjects with stroke are studied. An altered torque angle relationship may adversely affect the loading patterns during a resistance exercise when using resistance exercises designed for a normal strength curve. If there is a pronounced weakness in the inner part of the ROM, it might consequently lead to that a load that can be lifted throughout the entire ROM is low relative to the strength in the relatively stronger part of the ROM.

Aims of the thesis

This thesis investigates alterations of muscle function in stroke subjects (more than one year post-stroke) during isometric, concentric, and eccentric contraction and muscular loading during a conventional resistance exercise. For comparison, a group of healthy young subjects and a group of healthy age-matched subjects were also included. In addition, this thesis investigates how the central nervous system controls maximum eccentric and concentric contractions during a resistance exercise in normal and stroke subjects.

Specific aims

1) To investigate the effect of contraction mode and contraction velocity on torque-angle relationship in subjects with stroke and in healthy subjects. (Paper I)

2) To study muscular load and muscular activity during a conventional resistance exercise in subjects with stroke and in healthy subjects. (Paper II)

3) To examine cortical activity during a resistance exercise of elbow flexors, i.e., examine whether different brain regions are recruited during concentric contractions compared to the eccentric contractions during motor imagery of a maximum resistance exercise of the elbow flexors in healthy young subjects. (Paper III)

4) To examine prefrontal cortical activation patterns during maximum eccentric and concentric contractions in subjects who exhibit better preservation of eccentric strength. Hence, another specific aim is to test the hypothesis that a contraction mode-specific motor control system, with involvement of the prefrontal cortex, modulates the activation of motor cortex during maximum contractions and to test whether there is a disturbance of this system in stroke subjects who exhibit better preservation of eccentric strength. (Paper IV)

2 Methods

2.1 Design and overview of the studies

This thesis is based on four papers. Paper I and II describe results of an experimental laboratory study where isokinetic dynamometry and electromyography (EMG) was used in order to primary evaluate torque-angle relationships (Paper I) and relative loading during a resistance exercise (Paper II) among subjects with stroke and healthy control subjects. Data collection for these two papers was performed during a single experimental trial. Paper III and IV describe result from two experimental laboratory studies where functional magnetic resonance imaging (fMRI) was used in order to evaluate differences in activated brain regions between imagined maximum concentric and eccentric contractions of elbow flexors (motor imagery) in young healthy subjects (Paper III) and subjects with stroke (Paper IV).

2.2 Subjects

Subjects with stroke were recruited in collaboration with two rehabilitation centers at Umeå University Hospital. After an examination performed by a specialist in rehabilitation medicine, 11 subjects with stroke were recruited as volunteers to the study (Table 1). All stroke subjects were between 50-75 years of age, with at least 12 months since stroke onset and with clinical signs of an upper motor neuron lesion, i.e. strength loss and increased muscle tone. However, to be included, they also had to be able to perform active flexion and extension of the elbow joint against some resistance throughout the whole range of motion (ROM).

Table 1. Patient information (Paper I, II, IV)

Subj	Sex	Age	Time Years	Hemi	Lesion site	Etiology
1	M	64	8	Right		Infarct
2	M	64	3	Left	Occipital lobe	Infarct
3	M	72	2	Right	Mesensephalon	Infarct
4	M	64	6	Left	Pons	Infarct
5* (2)	F	54	9	Right	Basal ganglia; capsula interna; corona radiata	Hemorraghe
6* (4)	F	50	2	Right	Basal ganglia; corona radiata	Infarct
7* (1)	M	66	4	Right	MCA area	Hemorraghe
8	F	64	1	Left	MCA area	Infarct
9* (3)	M	61	1	Right	Basal ganglia; corona radiata; insula	Hemorraghe
10	M	68	4	Right	Basal ganglia	Hemorraghe
11	M	51	1	Left	Pons	Infarct

Note. Hemi = Hemisphere; Time = Time postinjury; * = Subject included in paper IV; Subject number in Paper IV within brackets.

Since a stroke in one brain hemisphere in various ways affects the motor performance on both sides of the body, we chose to use healthy controls as comparators, instead of using the "unaffected" arm as control. We

chose to use the non-dominant arm of the control subjects to minimize the effect of dextricity on the result. One control group is called the age-matched control group and was matched with respect to age and height. Since age itself is associated with changes in neuromuscular ability, partly similar to those seen after a stroke (168), we also recruited an additional control group, denominated the young control group, consisting of 11 moderately active students from Umeå University.

The subjects in Paper III were all between 20-30 years of age. Actually, the studied sample consisted of two different groups of subjects. One sample were recruited among subjects with long (> 2 year) experience of systematic heavy resistance training, including eccentric training, and one sample were recruited among resistance training novices, with none or negligible experience of resistance training. However, since we did not detect any differences between groups regarding our main research question, the two groups were pooled before analysis.

The subjects of Paper IV (Table 1) were a subset of subjects with stroke that also were participants in Paper I and II. Subjects were recruited among subjects with a single stroke which also demonstrated an increased eccentric to concentric torque ratio (>2.0), calculated from measurements of isokinetic strength, at a contraction velocity of 90° per/sec.

2.3 Measurements

Number of subjects, main assessments and main statistical analysis are listed in Table 2.

Table 2. Subjects, main assessments and main statistical analysis in presented papers

Paper	Subjects	Main assessment	Main statistical analysis
Paper I	11 subjects with stroke (50-75 years of age) 11 age matched controls 11 young controls	Maximum elbow flexor torque throughout the ROM using isokinetic and isometric measurements and EMG recording.	Repeated measures ANOVA in order to analyze normalized torque angle relationship.
Paper II	11 subjects with stroke (50-75 years of age) 11 age matched controls 11 young controls	Relative loading during an isotonic resistance exercise involving elbow flexors, using isotonic, isokinetic and isometric measurements and EMG recording.	Repeated measures ANOVA in order to analyze relative loading throughout ROM and development of fatigue during a resistance training task.
Paper III	18 healthy subjects with and without experience of heavy resistance training	Brain activity during an imagined motor task consisting of imagined maximum concentric and eccentric contractions of elbow flexors using fMRI.	General linear model (t-statistics) in order to analyze differences in recruited brain regions between concentric and eccentric phases of the task. First and second level analysis.
Paper IV	4 subjects with stroke	Brain activity during an imagined motor task consisting of imagined maximum concentric and eccentric contractions of elbow flexors using fMRI.	General linear model (t-statistics) in order to analyze differences in recruited brain regions between concentric and eccentric phases of the task. First level analysis.

2.3.1 Apparatus and measurements

2.3.1.1 Isokinetic dynamometry

In Paper I and II we used an isokinetic dynamometer (Kin Com®, Chattanooga Group Inc.; Hixon, TN, USA) for measurements of strength and load of muscles at elbow joint. The subjects were placed in the dynamometer in a seated position with the arm placed in a position to eliminate the effect of gravity on the forearm (Figure 2). In order to measure muscle tone, the resistive torque during passive motion was measured for four movement velocities (5, 60, 90 and 180 deg/s) for both directions of movement. Thereafter, for the purpose of EMG normalization, maximum voluntary contraction was performed at 90 degrees of elbow flexion. To evaluate torque-angle relationship, all subjects performed maximum contractions at three different contraction modes; isometric (zero velocity, concentric (positive velocity) followed by eccentric (negative velocity). Eccentric and concentric contractions were performed at two different velocities, slow (30 deg/s) and fast (90 deg/s). The torque-angle relationship were however analysed and presented along a contraction velocity continuum:

Fast eccentric	-90 deg/s
Slow eccentric	-30 deg/s
Isometric	0 deg/s
Slow concentric	30 deg/s
Fast concentric	90 deg/s

Figure 2. Photograph of subject positioned in experimental setup for testing of elbow flexor strength. The plane of movement was in horizontal plane. The elbow joint was aligned with the movement axis of the dynamometer. Fixation of EMG electrodes is not complete for clarity.

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Dynamic contractions were performed throughout the whole ROM (from 5-125) (Figure 3A). A truncated range of motion of 100 degrees (from 15-115) was then derived to determine a Truncated Range Average Torque (TRAT) (Figure 3C). For zero velocity (0 deg/s) the subjects performed isometric contractions at five different angles of elbow flexion to determine the Angle Specific Torque (AST) for 25, 45, 65, 85 and 105 degrees of elbow flexion (Figure (3B). The above defined TRAT was also divided into 5 parts of equal size, in order to determine dynamic AST-values (Figure 3D), corresponding to isometric AST-values.
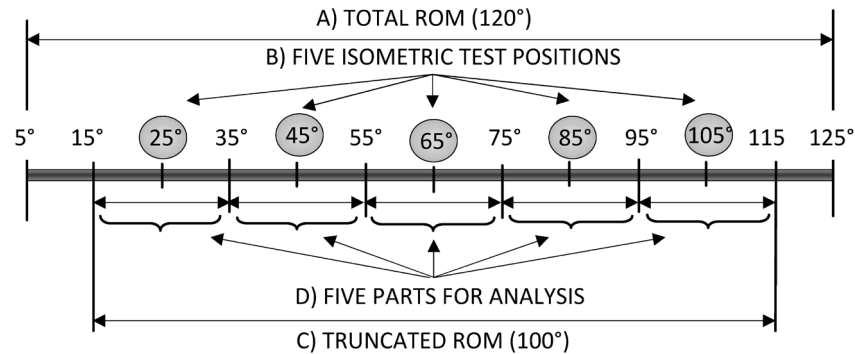
Figure 3. Illustration of the processed data throughout the range of motion (ROM) at the elbow joint, from 5°- 125° (0° corresponding to straight arm). The five analyzed elbow joint angles from the isometric and dynamic measurements are indicated.

2.3.1.2 Electromyography

During all test, EMG was monitored by means of pairs of silver–silver chloride surface electrodes from Biceps Brachii, Triceps Brachii (short head), Brachioradialis, and Pectoralis major. Electrode placement recommendations and standard procedures as described in detail in the SENIAM report (169) were followed. A reference electrode was attached to the neck on the spinous process of C7. For data acquisition of the EMG signals, a bipolar isolated EMG amplifier, type Braintronics ISO-2104 (EMGAmp, Braintronics BV, Almere, the Netherlands), was used. EMG signals were amplified (500-2000 times), band-pass filtered between 15-759 Hz, sampled at 2000 Hz and digitally stored (12 bits, Mysas, Dept. of Biomedical Engineering & Informatics, University Hospital, Umeå, Sweden).

In order to monitor fatigue development during the trial, isometric control contractions at a joint angle of 90 degrees of elbow flexion were performed at four time points during the test session. The first test was performed just before the maximum isometric trial, the second and third

test was performed two minutes after the isometric and isokinetic trials respectively. The forth and last test was performed within 30 seconds after the resistance exercise. The dynamometer's isotonic mode was used and the load was set to 50% of the isometric MVC. The subject was instructed to hold the arm stable against the load for 4 seconds at a joint angle of 90 degrees of elbow flexion. From the EMG measurements, the mean frequency of the surface EMG over the middle two seconds of the contraction was used for the fatigue analysis.

2.3.1.3 FMRI and Motor imagery

In Paper III and IV we used fMRI and motor imagery to compare patterns of cortical activation between the concentric and eccentric phases of an imagined maximum elbow flexion (i.e. a so called biceps curl). The participants imagined that they performed a series of maximum concentric and eccentric contractions within the scanner. As eccentric strength is superior to concentric strength, the participants were instructed that the load was different during the imagined contraction phases and that they should imagine that they had to put in maximum effort during both the concentric and eccentric phase during all contractions. The participants used internal imagery, or so called first person perspective. That means that they, there and then, imagined that they really performed the task, but without allowing any movement to occur. One week prior to the measurement, all stroke subjects were instructed how to perform the task and they were also requested to practice the task daily before the measurement took place.

In Paper III, the trial was composed of a continuous series of 18 repetitive cycles, composed of four phases. The four phases were; 1) the concentric phase; 2) a pause with elbow flexed and the weight unloaded; 3) the eccentric phase; and 4) a pause with elbows extended and the weight unloaded. Each phase lasted five seconds. In Figure 4, one cycle of the imagined task is illustrated. Exactly when and for how long they should carry out the different phases of the task was guided by an arrow shown on a computer screen which the subject watched via a tilted
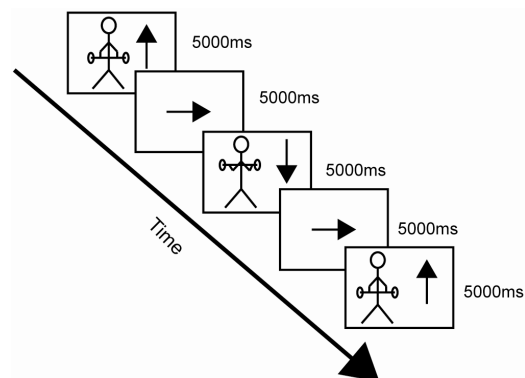

Figure 4. A schematic drawing of one cycle of the imagined concentric and eccentric contractions

mirror. In Paper IV, the trial was divided in two sets of series of 10 repetitive cycles, separated by a rest period, in where the cycles were identical to the cycles in paper III. Between the two sets a rest period of 30 seconds was inserted to allow for contrasting the BOLD signal during contractions to BOLD signal during rest.

2.4 Data analysis and statistical analysis

For data analysis in Paper I and II, an in-house program (MRD-Viewer, Dept. of Biomedical Engineering & Informatics, University Hospital, Umeå, Sweden) was used. The primary analysis in Paper I was to compare normalized torque-angle relationship among groups. Absolute torque values was individually normalized to the highest of the five torque values throughout the ROM for each contraction mode and velocity (164). This method was used to enable comparisons between groups irrespective of torque differences in torque amplitude among subjects. The primary statistical analysis in Paper I and Paper II was a two-way repeated measure ANOVA of the absolute and normalized torque angle relationships. A two-way repeated measures ANOVA was also used to analyze fatigue development during the trial and after the resistance exercise.

In Paper III we were interested in investigating differences in neural regions recruited for concentric and eccentric contractions. Three separate conditions; concentric (CON), eccentric (ECC) and pause (PAUSE) were set up as separate regressors. Then single subject analyses were made using the general linear model and SPMs (statistical parametric maps) were generated through t-statistics. The main contrasts to reveal differences between concentric and eccentric contractions was [CON > ÉCC] and [ECC > CON]. The threshold level was set to p=0.001 uncorrected. The second step included extracting BOLD-values for each local maxima identified by the contrasts in order to more clearly understand how the recruited brain regions behaves for the different conditions (concentric or eccentric). The BOLD values were calculated as the signal percentage change relative the mean of session (beta values). This was done for concentric and eccentric contractions respectively. For visualization of brain activity a mean anatomical image was used from MRIcro (www.sph.sc.edu/comd/rorden/mricro.html). For BOLD-plots an in house program (DataZ) was used. Anatomical localizations were determined using the Talairach and Tournoux atlas.

In paper IV we wanted to explore if the subjects with stroke would exhibit an altered cortical activation pattern than previously have been demonstrated with young healthy subjects. Four separate conditions; concentric (CON), eccentric (ECC), pause (PAUSE) between the contractions phases, and the 30s resting phase (REST) were set up as regressors. Single subject analyses were made using the general linear

model and SPMs (statistical parameters maps) were generated through t-statistics. We were particularly interested in observing eventual differences in activation patterns in ventrolateral prefrontal cortex (VLPFC), pre motor cortex (PMC) and motor cortex (MC), regarding differences between concentric and eccentric contraction phases. Therefore we performed functional regions of interest analysis (fROI) in two steps including a total number of six contrasts. In the first step, the involvement of VLPFC and MC/PMC was investigated by analyzing differences in activation pattern between the eccentric phase and the concentric phase. This was done by calculating the following contrasts; 1) [ECC > CON]; 2) [CON > ECC]. The next step was to analyzing differences between the both contraction phases and the rest phase. This was done by calculating the following contrasts; 3) [ECC > REST]; 4) [CON > REST]; 5) [REST > CON]; 6) [CON > ECC]. The analysis and presentation of the results was done subject by subject. Functional brain maps were superimposed on T1 weighted high resolution MR images. Anatomical localization of activated brain regions was determined using the Talairach and Tournoux atlas. Different threshold level was used for each subject and contrast to enable well-defined comparisons. The procedure for the choice of threshold level was to find the lowest possible threshold for which the number of activated clusters did not exceed 20. Threshold-level is presented for each subject and contrast in figures. The BOLD values were calculated as absolute signal change relative to baseline, i.e. 30 s resting phase (beta values). The statistical analysis was performed uncorrected for multiple comparisons. Activated regions outside ROI was localized and presented in an appendix. In Paper III, both first and second level analysis was conducted but in Paper IV only first level analysis was conducted.

3 Results

3.1 Biomechanical aspects

3.1.1 Absolute torque during strength measurements

The produced elbow flexor torque (Nm) during strength measurements was lower for the stroke group compared to the control groups (Figure 5A). Isometric and eccentric strength was generally better preserved than concentric strength. Average eccentric torque (i.e. the TRAT) at 90 deg/s was about 60% of the values for both control groups. The average torque for eccentric contractions at 30 deg/s was about 63% of both control groups values. For average isometric (0 deg/s) flexor torque, the stroke group value was 66 and 59% of the age-matched and young control group values respectively. For concentric contraction at 30 deg/s the stroke group average torque value was 59 and 53 % of the age-matched and young control group values respectively. The corresponding value for concentric contraction at 90 deg/s was 51 and 45 % of the age-matched and young control group values. The two- way repeated measures ANOVA revealed that the torque-angle relationship was rather similar among groups for eccentric and isometric contractions, but, as also can be seen in Figure 5A, the torque angle relationship deviated somewhat during the concentric contractions at the fastest velocity, which was also revealed by the repeated measures ANOVA.

3.1.2 Normalized torque angle relationship

When each AST value was normalized to the maximum AST value throughout the ROM, the differences between groups became more evident with respect to how torque angle relationship changed with a change in contractile velocity. The torque-angle relationships were essentially the same for the control groups, irrespective of contraction mode or velocity. However, for the stroke group the torque-angle relationship became more divergent from normal with increasing velocity, i.e. the more "positive" the velocity. In Figure 5B, this becomes evident when considering that the curvature of the surface are unchanged over all contraction velocities for the two control groups, whereas stroke group exhibits a reduction in force during concentric contractions. From the colour coding of the surface, it may also be seen that the stroke group shows a tendency toward a more pronounced curvature of the torque-angle relationship even for isometric and eccentric contractions compared to the control groups.
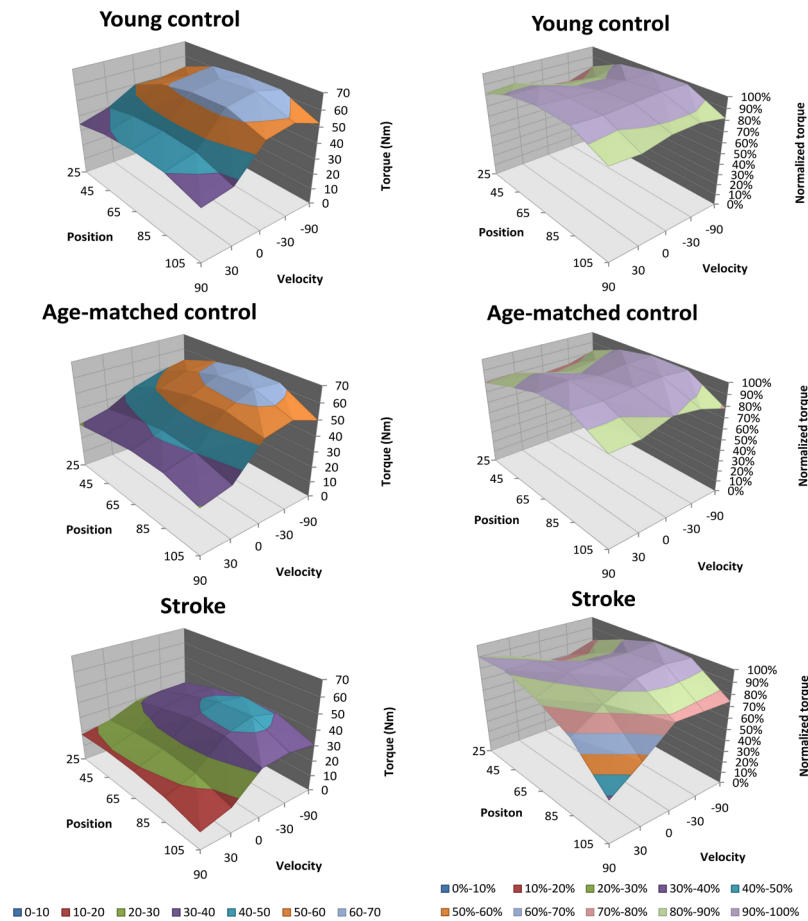
Figure 5A. Absolute torque-angle relation-ships for the young control group, the age-matched control group and the stroke group at the elbow joint. The z-axis is arranged in order of a velocity continuum. From the back of the z-axis; -90 deg/s, followed by -30 deg/s negative (eccentric) velocity, via isometric (0 deg/s) to +30 deg/s and +90 deg/s positive (concentric) contraction velocity. Along the x-axis absolute AST (Nm) are plotted for five joint angles (25, 45, 65, 85 and 105 deg). Colour coding of the surface curvature represents absolute torque values (Nm), in steps of 10 units. The stroke group produced significantly lower absolute torque values compared to the both control groups at all contraction modes and velocities.

Figure 5B. Normalized torque-angle relation-ship for young control group, age-matched control group and the stroke group at the elbow joint. The z-axis is arranged in the same order as figure 5A. Along the x-axis groups mean torque values for normalized AST are plotted for five joint angles. Normalization was conducted by dividing each AST to maximum AST obtained for each contraction velocity. Colour coding of the surface represents normalized value (percent of maximum velocity specific torque) in steps of 10 percent units. Both control groups demonstrated almost identical normalized torque-angle relationship irrespective of contraction mode and velocity. For the stroke group, the torque-angle relationship became more evident the more positive the velocity. The weakness was most pronounced during concentric contraction at 90 deg/s in the most flexed position (105 deg)

The two-way repeated measures ANOVA revealed that the normalized torque-angle relationship was rather similar among groups for eccentric and isometric contractions, but, that there was a significant interaction for both slow (p=0.006) and fast (p<0.001) concentric contractions. In Figure 3 B, this is reflected by the marked deviation of the normalized torque-angle relationship for concentric contractions.

3.1.3 Muscle tone

Resistive torque from elbow flexors and resistive torque from elbow extensors at 5 deg/s was low for all groups. However, with increased movement speed, the stroke group demonstrated a pronounced increase in resistive torque towards the end of the ROM for both directions of movement.

3.1.4 EMG patterns during strength measurements

Muscular activation and coactivation were found to be rather similar among groups. Mean agonist activation in Biceps Brachii, expressed relative to MVC, averaged over all contraction velocities was 0.75±0.14, 0.75±0.13 and 0.69±0.14 for the stroke group, age-matched control group and young control group respectively. For Brachioradialis, mean agonist activation was 0.73±0.26, 0.75±0.16 and 0.73±0.13 for the stroke group, age-matched control group and young control group respectively. Corresponding values for antagonist coactivation in Triceps Brachii was 0.43±0.31, 0.43±0.26 and 0.23±0.13. A one-way ANOVA showed that there were no significant differences among groups in levels of agonist activation in the Biceps Brachii or Brachioradialis or for antagonist coactivation in Triceps Brachii for any of the contraction velocities tested.

3.1.5 Loading patterns during the resistance exercise

Figure 6 shows the absolute torque produced during isokinetic strength measurements at 30 deg/s and during the resistance exercise plotted group by group for eccentric and concentric contraction phase respectively. The absolute training load differed among groups and stroke group performed the training task with a significantly lower training load (all p values <0.001). However, when comparing the relative load, it was revealed that for the concentric phase the truncated range average torque (TRAT) during the resistance exercise, expressed as percentage of TRAT during maximum concentric contractions at 30 deg/s was 65% for all groups. The relative load torque throughout the ROM was also very similar among groups. The TRAT during the concentric phase of the resistance exercise was 31±6% of isometric MVC torque obtained at 90 degrees of elbow flexion for the stroke group which was significantly lower compared to the age-matched, 40±4% (p=0.002) and young control group, 39±4% (p=0.002).

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For the eccentric contraction phase, the TRAT during the resistance exercise, expressed as percentage of TRAT during maximum eccentric contractions at 30 deg/s was 30±8% for the stroke which was significantly lower compared to the age-matched, 38±6% (p=0.04), and young 40±4% (p<0.001) control group. For the stroke group the isotonic TRAT during the eccentric contraction phase was 26±8% of the isometric MVC torque obtained at 90 degrees of elbow flexion, which was significantly lower compared to the age-matched, 36±4% (p<0.001) and young control group, 37±4% (p<0.001).
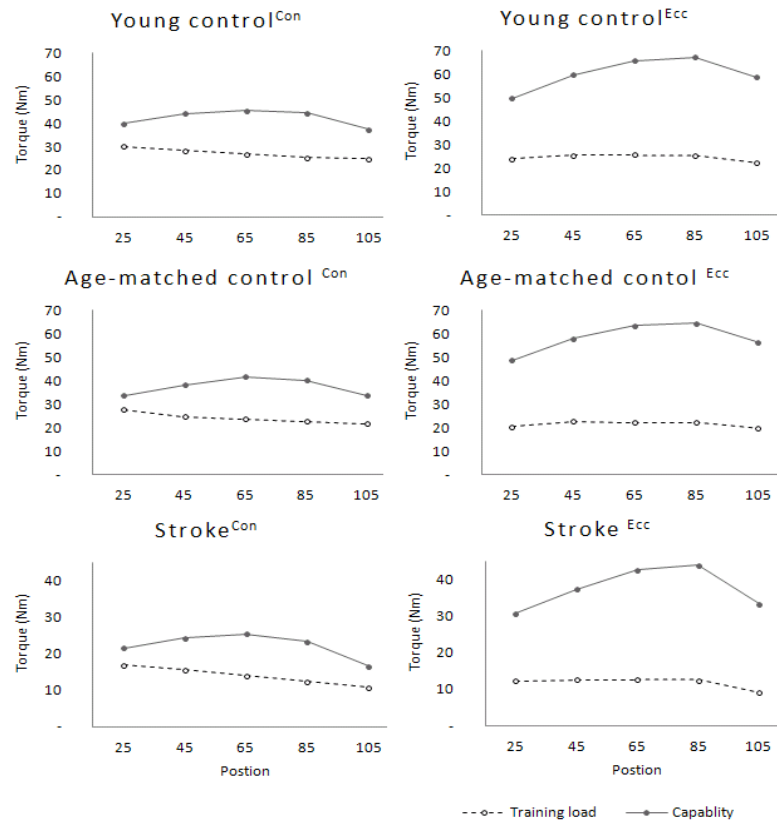
Figure 6. Angle specific torque values obtained during isokinetic strength measurements (filled circles) and the resistance exercise (open circles). The left column shows data from the concentric phase and the right column shows data from the eccentric contraction phase. The x-axis represents joint position (deg) (0 deg= straight arm) Note that the y-axis of stroke group has a different scaling than the control groups. The rationale behind this is to visualize the relative loading during exercise. The distance between plots in the y-direction is intended to illustrate the relative load. Error bars are excluded for clarity.

3.1.6 Muscle activation during the resistance exercise

Muscular activation during the resistance exercise was found to be somewhat lower for the stroke group compared to the control groups. Mean agonist activation in Biceps Brachii during the concentric contraction phase, expressed relative to MVC, was 0.78±0.19, 0.95±0.22 and 0.85±0.32 for the stroke group, age-matched control group and young control group respectively. For Brachioradialis, mean agonist activation for the concentric contraction phase was 0.72±0.24, 0.89±0.16 and 0.84±0.23 for the stroke group, age-matched control group and young control group respectively. During the eccentric contraction phase, agonist mean activation in Biceps Brachii was found to be 0.36±0.10, 0.39±0.05 and 0.44±0.15 for the stroke group, age-matched control group and young control group respectively. For Brachioradialis, mean activation during the eccentric contraction phase was 0.35±0.09, 0.48±0.13 and 0.42±0.12 for the stroke group, age-matched control group and young control group respectively. A one way ANOVA with a subsequent post hoc test revealed that the normalized EMG_{RMS} value was significantly (p=0.04) lower for the stroke group compared with age-matched control group only in Brachioradialis during the eccentric contraction phase.

3.1.7 Movement patterns during the resistance exercise

The average time to complete the concentric contractions was very similar between groups. The peak velocity was, however, somewhat higher and the angle of peak velocity was reached somewhat earlier in the ROM for the stroke group than the control groups. The stroke groups reached peak velocity at a joint angle of 63±11 degrees, which was somewhat earlier than the age-matched control group, 70±18 degrees, and the young control group, 79±12 degrees. The difference was significant between the stroke group and the young control group (p=0.04).
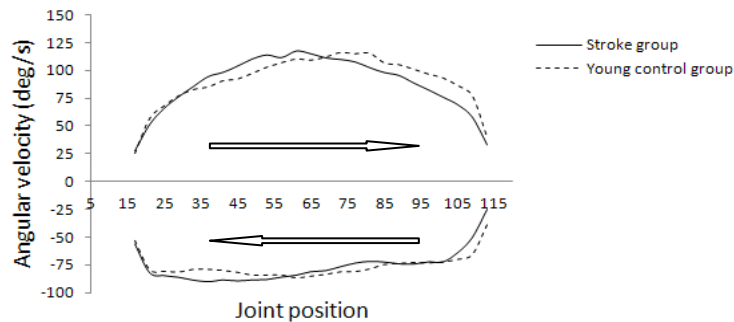

Figure 7. Angular velocity during the resistance exercise for the stroke group and the young control group. Positive angular velocity represents values obtained during the concentric contraction phase (movement direction goes from 15 deg to 155 deg). Negative velocity represents values obtained during the eccentric contraction phase (movement direction goes from 115 deg to 15 deg). Arrows indicates direction of movement.

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The average time it took to complete the eccentric contraction phase did not differ significantly among the groups, although, the stroke group exhibited a larger interindividual difference. The somewhat altered movement pattern between groups is illustrated in Figure 7.

3.1.8 Fatigue after the resistance exercise

Prior to the resistance exercise there were no signs of muscular fatigue since there were no reductions in the mean frequency of the EMG signal among groups during isometric control contractions. Immediately after the resistance exercise, there was however a lower percentage reduction of the mean frequency, expressed as percentage of first contraction, for the stroke group for both the analyzed elbow flexor muscles. The reduction for the stroke group for Brachioradialis was 3±16% and for the Biceps Brachii it was found to be 12±6%. A one-way ANOVA followed by a post hoc test revealed that the difference was significant for Brachioradialis for both the age-matched control and the young control group, 21±15% (p=0.03) and 28±15% (p=0.001) respectively, but not for the Biceps Brachii = 19±10% (p=0.15) and 20±9% (p=0.11) respectively.

3.2 Neural aspects

3.2.1 Cortical activation pattern in young subjects

The pattern of recruited brain regions differed between the concentric and eccentric phase of the task in the young healthy subjects. During the concentric phase, additional regions were recruited within the motor system. Peaks of activation were in the pre motor cortex (PMC) (Figure 8A) and motor cortex/premotor cortex (MC/PMC) (Figure 8B), the PMC (Figure 8C) and cerebellum bilaterally (Figure 8D). Interestingly the BOLD-plots revealed that for the eccentric phase these regions within the motor cortex were reduced (i.e., lower), when compared to the mean activity of the session. When brain activation during the eccentric phase was compared to the concentric phase, additionally recruited regions were found in the ventrolateral prefrontal cortex (VLPFC), BA 44, bilaterally (Figure 8E).

Figure 8. Cortical activation during simulated maximum concentric and eccentric contractions. Motor cortex, BA 6/4 (A, B) as well as Premotor cortex, BA 6 (C), was additionally recruited during the simulated concentric contractions in comparison with the simulated eccentric contractions. During the eccentric contractions these regions were instead reduced possibly reflecting a suppressing mechanism involving the cortex. Additional motor recruitment was also seen in the cerebellum for the concentric contractions (D). Pre-frontal cortex, BA 44 (E) was additionally recruited during the simulated eccentric contractions in comparison with the simulated concentric contractions, possibly reflecting the additional control that is required during eccentric movements and its importance in regulating force. Bars indicate the percentage signal change relative mean of session, error bars are standard error, and coordinates are in MNI-space.
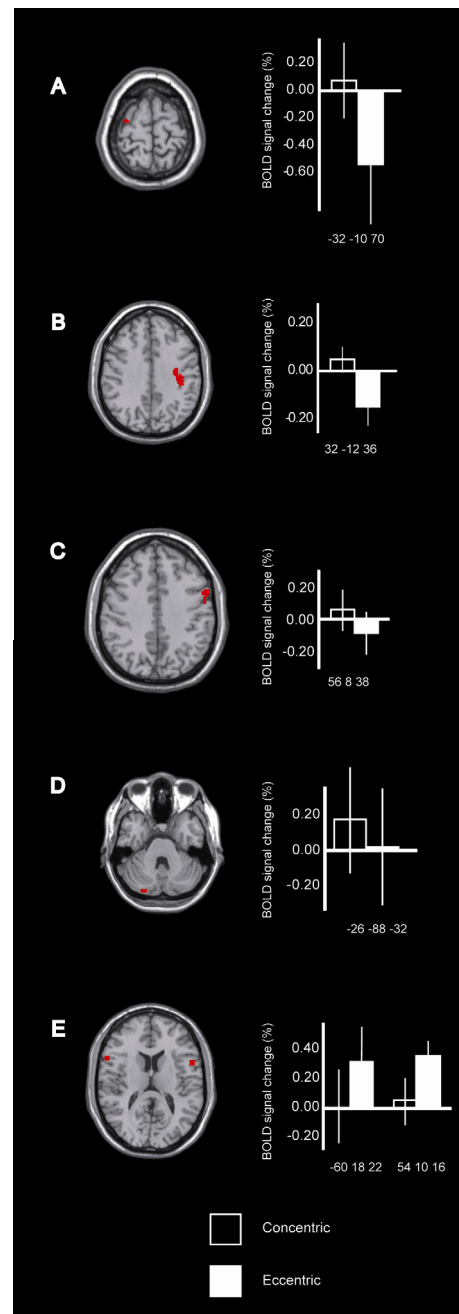
3.2.2 Cortical activation pattern in subjects with stroke

Three out of four subjects with stroke exhibited a general decrease in the BOLD signal within the VLPFC on the contralesional hemisphere especially during the concentric contraction phase, a pattern that was not evident on the ipsilesional hemisphere. For two of those subjects (subject 1 and 2), the BOLD signal within VLPFC was found to be stronger during the eccentric compared to the concentric contraction phase (Figure 9). In contrast, on the ipsilesional hemisphere the general pattern was a general increase in the BOLD signal within VLPFC, with no difference in the BOLD response between the two contraction phases (Figure 9 and 10). For one of the subjects (subject 4), there was a bilateral increase in the BOLD signal also in the contralesional hemisphere (Figure 10).

The BOLD response in MC and PMC regions was found to be rather diverse among subjects. A different BOLD signal response between concentric and eccentric contractions was evident only for one subject (subject 4) bilaterally (Figure 10). For subject 1 and 2, a BOLD signal response within the MC was identified only in the ipsilesional hemisphere for the contrast [ECC > REST] and [CON > REST] (Figure 9).
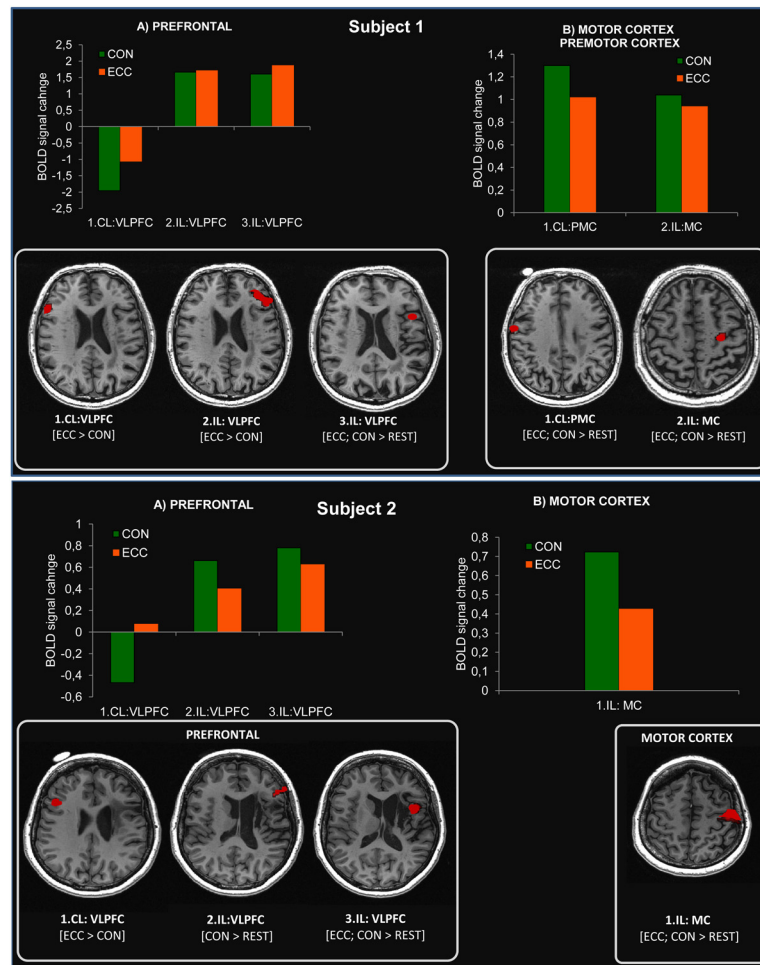
Figure 9. Recruited brain regions during imagined maximum concentric and eccentric contractions for subject 1 and 2. ***Subject 1:*** Within VLPFC, subject 1 demonstrated a stronger BOLD signal during ECC compared to CON in the CL hemisphere. In the IL hemisphere, two different clusters with increased BOLD signal compared to REST during ECC and CON were identified, but there were no differences between contraction phases. Within MC/PMC, no differences in BOLD response were found between concentric and eccentric phase in MC/PMC. For subject 1, a threshold level of 0.005 was used for contrast [ECC > CON]. For all other contrasts a threshold level of p=0.00001 was used, i.e. the lowest possible threshold for which the number of activated clusters did not exceed 20.

Subject 2: Within VLPFC, subject 2 demonstrated a stronger BOLD signal during ECC compared to CON in the CL hemisphere. In the IL hemisphere, two different clusters with increased BOLD signal compared to REST during ECC and CON were identified, but there were no differences between contraction phases. Within MC/PMC, no differences in BOLD response were found between concentric and eccentric phase in MC/PMC. For subject 2, a threshold level of 0.005 was used for all contrasts. For subject 2, a threshold level of p=0.005 was used for all contrasts.

Abbreviations: CL; Contralesional; IL; Ipsilesional; VLPFC; Ventrolateral prefrontal cortex; MC; Motor cortex; PMC; Pre motor cortex; CON; concentric phase; ECC; eccentric phase; REST; 30s. resting phase (baseline).

Note: Recruited regions are superimposed on individuals T1-weighted MR images. Negative or positive BOLD-signal change indicates task-related decrease or increase in the BOLD signal compared to baseline (30s resting phase).
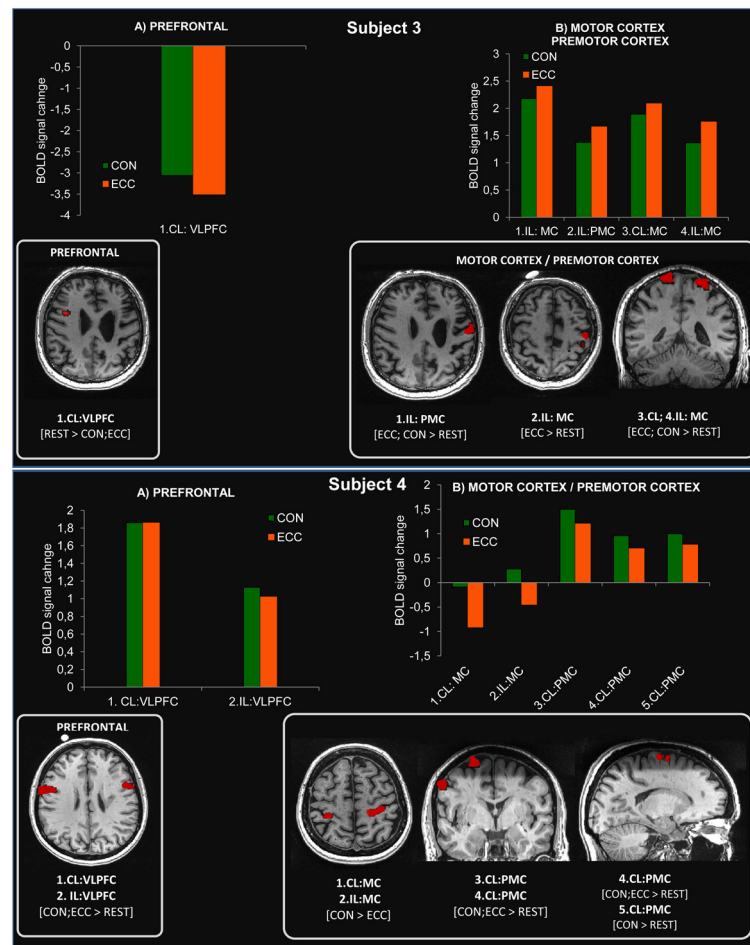
Figure 10. Recruited brain regions during imagined maximum concentric and eccentric contractions for subject 3 and 4. **Subject 3:** Within VLPFC, subject 3 demonstrated a decreased BOLD signal from REST during ECC and CON in the CL hemisphere. No significant difference in BOLD response was found between CON and ECC. Within MC/PMC, no significant differences in BOLD response were found between CON and ECC. For subject 3, the following threshold levels were used [ECC;CON > REST]; $p=0.0005$, [ECC;CON > REST]; $p=0.000000001$, i.e. the lowest possible threshold for which the number of activated clusters did not exceed 20.

Subject 4: Within VLPFC, subject 4 demonstrated an increased BOLD signal from REST during ECC and CON bilaterally. Within MC/PMC, cluster with stronger BOLD signal during CON compared to ECC were identified in the CL MC and the IL MC. For subject 4, the following threshold levels were used [CON>ECC]:$p=0.0000005$,[ECC;CON > REST] $p=0.0001$, i.e. the lowest possible threshold for which the number of activated clusters did not exceed 20.

Abbreviations: CL; Contralesional; IL; Ipsilesional; VLPFC; Ventrolateral prefrontal cortex; MC; Motor cortex; PMC; Pre motor cortex; CON; concentric phase; ECC; eccentric phase; REST; 30s. resting phase (baseline).

Note: Recruited regions are superimposed on individuals T1-weighted MR images. Negative or positive BOLD-signal change indicates task-related decrease or increase in the BOLD signal compared to baseline (30s resting phase).

4 Discussion

Stroke subjects exhibited a strength reduction that was more pronounced and a torque-angle relationship that was more deviated during concentric contractions compared to eccentric and isometric contractions. This altered neuromuscular function resulted ultimately to that the relative load torque during a resistance exercise represented a lower percentage of maximum torque producing capacity. The data also imply that the altered muscle function in stroke subjects might be influenced by impaired central motor drive due to an impaired contraction mode-specific modulation of muscular force through a mechanism involving the prefrontal cortex.

4.1 General discussion

4.1.1 Alteration of the torque-angle relationship

For the stroke group, the deviation of the normalized torque-angle relationship increased with increased contraction velocity during concentric contraction, whereas the opposite trend was found during eccentric contractions. For the age-matched control group and the young control group, the normalized torque angle relationship was about the same irrespective of contraction mode or contraction velocity, a finding that was also expected. The abnormal torque angle relationship during concentric contractions, which also increased with increasing contraction velocity, is compatible with antagonist restraint mediated by excessive co-contraction and or stiffness (passive mediated and stretch reflex mediated). In what way and to what extent these variables contribute to the altered torque-angle relationship cannot be specified from the data in this thesis. A completely accurate quantification of antagonist restraint, however, is difficult to achieve for several reasons. For example, the stretch reflex mediated stiffness during resting conditions is not directly transferable to active conditions. However, the absence of increased resistive torque during slow passive movements, absence of abnormal co-contraction (at least compared to the age-matched control group), and the fact that increased viscoelastic stiffness primarily is of importance at the beginning of a stretch during higher movement velocities (124) the impairment likely to be attributed also to neural mechanisms such as agonist activation deficit (71). However, clear-cut evidence of activation deficit was not provided by the electromyographic data.

The normalized torque-angle relationship for the stroke group during eccentric contraction was rather close to those of the control groups. There was, however, a trend toward a slightly more pronounced parabolic shape of the strength curve also during isometric and eccentric contractions compared to the control groups, a finding that might reflect

altered muscle architecture. We collected no data on muscle architecture, but the exhibited deviation of the strength curve during eccentric contractions is compatible with a number of described architectural changes after stroke. Reduced sarcomeres in series (26), increased pennation angle at rest (30), and a lower increase of the pennation angle during contraction (31), would result in changes in this direction. The absolute torque producing capacity was also affected by contraction mode and contraction velocity; i.e., there was an increased E/C ratio for the stroke group, a finding consistent with previous studies that examined subjects with cerebral lesions (150, 151, 170).

4.1.2 Reduced neuromuscular stress during resistance exercise

The relative loading during the resistance exercise was lower for the stroke group than the control groups. For all groups, the training load (10RM) for the resistance exercise seemed to have been determined by the average torque producing capacity (TRAT) during concentric contractions at the contraction velocity of 30 deg/s. Therefore, since the TRAT was reduced during concentric contractions in relation to maximum strength (isometric, eccentric, and concentric), the load torque during the resistance exercise was significantly reduced compared to the maximum torque producing capacity. As judged by a somewhat lower EMG activity during the resistance exercise and a lower reduction in EMG frequency immediately after the resistance exercise (used to monitor muscle fatigue) it cannot be excluded that neural fatigue, rather than muscular fatigue, also influenced the establishment of the training load. The EMG data, however, should be interpreted with some caution since it has been reported that subjects with stroke may exhibit differences in EMG patterns compared with healthy subjects (171-173). In any case, the training load indeed represented a lower percentage of maximum isometric strength for the stroke group, which may indicate that relative load and stress on the neuromuscular system during the resistance exercise was not sufficient to induce local muscular fatigue. An absence of signs of muscular fatigue after an isometric resistance exercise, as revealed by MRI analysis, was also reported by Ploutz-Snyder et al. (174). They suggested that lower signs of muscular fatigue in the paretic muscles, compared to the non-paretic side and to healthy controls, might be explained by activation failure during the maximum test, since they performed the resistance exercise at a given percentage of a subject's maximum isometric strength. In our trial, we determined the training load by trying out 10RM, which ensured that the load represented the load that the subjects would have had if they carried out a resistance exercise in clinical praxis.

Hence, the stress on the neuromuscular system that the stroke subjects were exposed to during the resistance exercise was lower and might therefore be insufficient to induce optimal strength gains. Several factors determine the initiation of a hypertrophic response and muscle architectural changes in response to resistance training: mechanical tension, muscle damage, and the metabolic stress associated with muscular fatigue (175-177). As the torque load during the resistance exercise represented a lower percentage of maximum torque producing capacity and as there were indications of a lower level of fatigue after the resistance exercise, it may be concluded that the resistance exercise was not optimal for the stroke subjects despite a seemingly adequate training intensity (10RM). Lee et al. (7) performed a 12-week resistance training program with stroke subjects using a training intensity of 80% of 1RM. They found that the increase in strength levelled off within about six to eight weeks. Until that point, strength increases are usually considered attributed to neural factors (50, 126, 178) and to achieve further increase in strength, local changes in muscle seem to be required (10, 50). This implies that the stimuli provided by the resistance exercises in Lee's study might have been insufficient, despite the seemingly high intensity. In Paper II, it was demonstrated that stroke subjects were significantly under-loaded, especially during the eccentric phase. To induce optimal strength gains in healthy subjects (50) as well as stroke subjects (160), it seems to be of important to adequately load also the eccentric phase.

4.1.3 Efficient lifting strategy

Stroke subjects used an efficient lifting strategy at the beginning of the concentric phase of the resistance exercise, which partially might have compensated for their relative weakness in the latter part of the ROM. The monitored movement pattern during the resistance exercise revealed that the stroke subjects took advantage of their "overcapacity" at the beginning of the movement, contrary to what might be expected due to a reduced rapid force capacity (142). This was expressed as a somewhat higher peak velocity, which was achieved somewhat earlier for the stroke group than the control groups. By applying a higher force and high acceleration in the beginning of the movement, the force requirement was somewhat reduced in the latter part of the movement (133). The instruction to the subjects did not encourage any particular lifting strategy, so this adjustment was entirely self-selected. Nevertheless, without this seemingly efficient lifting strategy, 10RM had probably represented an even lower percentage of their maximum strength.

4.1.4 A contraction mode-specific modulation system?

The fMRI study of healthy young subjects indicates that the ventrolateral prefrontal cortex (VLPFC) may be involved in contraction mode-specific modulation of muscular force during maximum contractions. The subjects demonstrated different cortical activation patterns during imagined maximum eccentric compared to imagined maximum concentric elbow contractions. The reduced BOLD amplitude in the primary motor cortex and premotor cortex during eccentric contractions is a finding that agrees with the established differences in muscle activation pattern between concentric and eccentric contractions, i.e., lower levels of muscle activation during eccentric compared to concentric contractions (179). This is also in line with findings that indicate a lower excitability of the motor cortex during eccentric contraction (79). The higher BOLD amplitude in VLPFC during eccentric contractions confirmed our hypothesis of a more pronounced prefrontal involvement during maximum eccentric contraction, as was demonstrated by Fang et al. (80).

The activation in VLPFC (BA 44) was at first somewhat surprising. The VLPFC, particularly Broca's area, is classically associated with speech production. However, a growing body of data suggests that this area in the prefrontal cortex also is associated with motor functions. In addition to the established role in oro-laryngeal movements and speech production, it has been suggested that this brain region also constitutes a high-level sensorimotor interface integrating sensory stimuli and cognitive tasks with related motor representations (180, 181). For example, it has been demonstrated that this brain area plays an important role during anticipatory modulation of grip force (182) and during precise modulation of force increment/decrement (183). Furthermore, Chambers et al. (184) found that a temporary deactivation of VLPFC, induced by transcranial magnetic stimulation (TMC), reduced inhibitory control during hand movements as it weakened the ability to stop an on-going movement. Rollnik et al. (185) used an inverse technique and activated the same prefrontal area and found that this resulted in reduced excitability of the motor cortex. This mechanism of enhanced inhibition of the motor cortex has successfully been used as a treatment for dyskinesia in patients with Parkinson's disease (186). VLPFC seems to have a heterogeneous role and has been proposed to act as a supramodal hierarchical processor with involvement in inhibitory processes in more general terms as well (187-189). Aron et al. (190) have presented a possible model for how VLPFC via a frontal-basal ganglia network may exert inhibitory control over MC during motor reprogramming. Furthermore, the influence on motor cortex may not be limited to inhibition. Schmidt and colleagues found that manipulation of the emotional status of the subjects altered force output during maximum strength testing. The emotional status (i.e., arousal) was associated with

increased bilateral activation of VLPFC, which in turn was directly related to an increased excitation of primary motor cortex (191). The authors suggest that this region, by driving the motor cortex, facilitates physical effort.

An alternative explanation for an increased activation of VLPFC is related to the fact that the task was to imagine performing maximal contractions. If assuming that the activation of VLPFC might reflect inhibitory processes, these processes could possibly also be associated with avoiding motor cortex activation to the level of motor execution during the imaginary task. Such a function, for example, has been attributed to the supplementary motor area (192). However, in the experiments in this thesis, two very similar motor imagery tasks were compared against each other (imagined eccentric vs. imagined concentric contraction), so such an effect would most likely have been cancelled out.

A reduction in neuronal drive to the muscle during maximum eccentric contractions has usually been suggested to be accomplished by inhibitory responses to afferent feedback (66, 157). However, in this study we used motor imagery that excludes the influence from afferent input associated with maximum contractions. If we assume that there exists a contraction mode-specific modulation system, involving the VLPFC, it appears that this system consists of a preplanned mechanism, independent of afferent input. However, this does not exclude the involvement of this system in integration and processing of afferent input from the periphery. Fang et al. (80) found that the event related cortical potential within the prefrontal cortex was stronger and occurred significantly earlier prior to maximum eccentric compared to maximum concentric contractions. Since the activation pattern that was detected during executed maximum contractions by Fang et al. (80), also was present during imagined maximum contractions in this thesis, the data further supports the assumption of a preplanned feedforward inhibition. This possible interpretation was also suggested by Fang et al. (80).

Hence, this brain region actually appears to be a key-player in a network involved in the regulation of cortical motor drive. Whether, and if so how, VLPFC plays a role regarding contraction mode-specific modulation of force during eccentric and concentric contractions is a novel hypothesis that needs to be investigated further. However, from the data in this thesis (Paper III), it can be stated that the activation pattern in VLPFC and in the MC/PMC differs between contraction modes when healthy young people imagine performing maximal concentric and eccentric contractions. Hence, this finding, with some support in the literature, might reflect the possibility that the inferior prefrontal cortex is involved in a regulatory system that modulates motor output differently during eccentric vs. concentric contractions. Such a regulatory system might be a

contributing factor to why it is impossible to maximally activate muscles during eccentric contractions, despite maximal voluntary effort (179).

4.1.5 Disturbed prefrontal function and the E/C ratio

Is better preservation of eccentric strength after stroke due to a disturbed pre-frontal function? As a first step to test the validity of the hypothesis of contraction mode-specific force modulation, we investigated cortical activation patterns in VLPFC and MC/PMC in four subjects with a verified disturbance in contraction mode-specific force modulation, evident by an increased E/C ratio. The fMRI data indicate that the pre-frontal function in VLPFC might be disturbed. For the healthy young subjects, there was a bilateral activation of VLPFC during bilateral elbow contractions. Conversely, among the selected sample of stroke subjects, different patterns were found. Significantly different BOLD signal amplitudes between imagined eccentric compared to imagined concentric contractions, as was evident in young healthy controls, were found only on the intact contralesional hemisphere in two of the subjects with stroke (subject 1 and 2). However, a significant difference in BOLD signal amplitude between concentric and eccentric contraction, as was found in young subjects, was found only in one of the stroke subjects bilaterally (subject 4). This subject demonstrated a bilateral BOLD signal increase during both concentric and eccentric contractions in VLPFC compared to rest.

Yet, it was not that VLPFC was not at all involved in the ipsilateral hemisphere in the stroke subjects. In fact, quite the opposite trend was found. For three subjects there was a significant increase in the BOLD amplitude in VLPFC in the ipsilesional hemisphere compared to the BOLD amplitude during rest. There was also a common characteristic: there was no difference in BOLD amplitude between contraction modes on the ipsilesional hemisphere. If assumed that VLPFC is a key player in contraction mode-specific modulation of muscular force, the lack of differentiated activation between eccentric and concentric contractions within the VLPFC on the ipsilesional hemisphere might reflect a lack of such modulation among tested stroke subjects. A complete comparison between data in Paper III and IV regarding activation pattern in relation to rest can unfortunately not be accomplished since the trial in Paper III did not include a resting phase.

A lack of mode-specific modulation may consist of either a lack of an expected inhibition during eccentric contractions or an abnormal inhibition/lack of excitation during concentric contractions. The common finding of an increased E/C ratio among some stroke subjects might be attributable to that the motor cortex may be equally modulated during concentric and eccentric contractions, which then would result in a shift in the EMG pattern (i.e., more similar activation during eccentric and

concentric contractions) as was reported by Clark et al (71). This observation was also evident in the selected sample of stroke subjects (Paper IV). A lack of mode-specific modulation may consist of either a reduced inhibition during eccentric contractions or the same degree of inhibition regardless of contraction mode. In any of these cases, the differences in torque producing capacity between the two contraction modes would be determined by the muscle fibres' inherent capacity to generate force, which is superior during eccentric contractions. In concrete terms, a lack of modulation might result in activating the motor inhibiting "brake" during contractions irrespective of contraction mode or an absence of the expected "inhibiting brake" during eccentric contractions. Most of the literature assumes that altered motor cortex modulation after stroke involves an abnormal and enhanced motor cortex inhibition. In fact, strength reduction after stroke seems to a greater extent be caused by hyperactivity of intracortical inhibitory mechanisms rather than direct lesions of descending motor tracts (193). Hummel et al. (194) found a twofold abnormality with respect to intracortical inhibition in stroke subjects. During rest, stroke subjects demonstrated a lack of intracortical inhibition of the motor cortex, but they demonstrated an enhanced intracortical inhibition of the motor cortex during movement preparation. Interestingly, short-term training induced changes seemed to be mediated to a great extent by the reduction of the inhibitory control of the motor cortex (195). In Paper IV, the enhanced BOLD signal in VLPFC in the ipsilateral hemisphere was expressed as a contrast to the BOLD signal at rest, an observation that might indicate a reduced inhibition of motor cortex excitability during rest. Liepert et al. (196) found evidence for motor cortex disinhibition during rest in subjects with cortical and subcortical stroke. They also reported that the level of cortical disinhibition during rest was significantly and positively correlated with the level of spasticity. Furthermore, resting EMG activity is often elevated in subjects with stroke (122, 123). A tempting speculation is that a disturbance of the prefrontal function also may be involved in an elevated EMG activity at rest and therefore, by extension, also to spasticity.

Traditionally, very little attention has been given to the role of the prefrontal cortex in stroke patients (197). An increased interest can be seen in the literature, but knowledge is still sparse regarding an involvement of the prefrontal cortex in the disturbed motor function after stroke. However, several recent studies have highlighted that this brain area, i.e., the VLPFC, seems to be associated with disturbed motor function in subjects with cerebral lesions due to e.g. stroke or multiple sclerosis. For example, Meehan et al. (198) found that this brain region seems to be of great importance for motor learning in subjects with subcortical stroke. In addition, Tomasova et al. (199) recently found that spasticity treatment with botulinum toxin significantly reduced the activation in this brain region during active movements. Furthermore, Steens et al. (200) reported a significant difference between subjects with

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multiple sclerosis and healthy controls regarding the activation pattern in this brain region during a fatiguing task. Interestingly, Lindberg et al. (201) found a significantly increased activation within the VLPFC in subjects with spasticity due to stroke during high velocity muscle stretch. Thus, the knowledge on the role of the prefrontal cortex in motor impairments after stroke is rudimentary but growing. This thesis adds to the growing body of evidence that highlights that this brain region, by any means, is involved in the disturbed motor function in this population.

4.6 Methodological considerations

4.6.1 Paper I and II

The aim of these papers was primarily exploratory, descriptive, and hypothesis generating. The subjects were also selected on the basis of clinical examination and not on stroke location, which, together with the small sample size, precludes sub-group analysis. The intention, however, was to provide a basis for understanding how and why the torque-producing capacity in stroke subjects alters throughout the ROM for different contraction modes and to analyse how an applied load actually stresses the neuromuscular system during a conventional resistance exercise. Rather large inter-individual variations were recognized, especially in the stroke group, but the experimental setup was standardized in such a way that we can assume the validity of the results. However, to differentiate between different factors contributing to the altered muscle function (e.g., the influence of altered intrinsic factors and spinal reflex-mechanisms), a more multimodal setup (e.g., including data on muscle architecture and spinal reflex analysis) is probably needed.

4.6.2 Paper III and IV

Motor imagery has been extensively studied for decades in healthy subjects as well as stroke subjects. Although there is a large body of data that support that motor imagery and motor execution share similar neural substrates (87, 202, 203), it is still debated whether this method can be implemented to indicate how the brain works in executed movements (204). Obviously, to confirm or reject the hypothesis that the prefrontal cortex is involved in mode-specific force modulation, it is required that the findings be repeated during execution of similar tasks. The experiments conducted and the data provided in this thesis can be seen as an initial step towards a better understanding of mode-specific force modulation.

4.7 Clinical implications and further research

A clinical implication of this thesis is that a conventional resistance exercise provided rather similar torque load patterns for the stroke subjects and the healthy controls. However, since the relative torque load was significantly lower in stroke subjects due to the altered neuromuscular function, it can be recommended that neuromuscular alterations, if present, should be taken into account when designing resistance exercises for stroke patients in order to provide an optimal stress on the neuromuscular system. The literature consistently states that the deviation in the torque-angle relationship in stroke patients mainly consists of a selective reduction of the force at short muscle length. This thesis indicates that this deviation mainly applies to concentric and to a lesser extent to isometric contractions and even less to eccentric contractions. Since the concentric torque producing capacity determines the training load, the overall stress on the neuromuscular system leads to an under-loading for un-adapted conventional resistance exercise for a single joint movement. Considering well-established principles for resistance training found in the literature, we conclude that resistance exercises should be modified to optimize muscular activation, relative load torque, and muscular fatigue. Local muscular adaptations in combination with neural adaptation is probably essential for long-term improvements of functional ability and, as important, to prevent degenerative muscular changes associated with increased age (23, 205). Another very important aspect is that local muscular adaptations also might have a value from a health perspective. For example, the prevalence of insulin resistance is greatly elevated in individuals with chronic stroke (206). Resistance training has been found to be a potent treatment to improve glycaemic control in older adults with type 2 diabetes (207, 208). Whether this positive effect also applies to stroke subjects remains to be determined.

It must though be remembered that the reason to why individuals with stroke often do not respond optimally to resistance training not solely have to be explained by suboptimal stress during conventional resistance training. A lack of response to traditional resistance training might also be related to the possibility that stroke patients might not obtain the same adaption in response to a given stimuli. This issue could be ruled out only after it has been clearly demonstrated that the performed exercises in an evaluated program were chosen and/or modified in order to ensure an optimal level of stress on the neuromuscular system. This thesis shows that the relative load obtained at an intensity of 10RM for stroke subjects does not necessarily correspond to the relative load as normally is provided at that intensity. Modifications that in different ways provide increased stimuli for strength gains (mechanical deformation and muscular fatigue) and have proved to be effective in other populations are of special interest for clinical application and for research. Below are

some conceivable potential modifications that could help individuals with stroke achieve optimal stress adaptations as the result of resistance training.

- Limit the execution of the movement to restricted parts of the ROM, i.e., restrict the movement to a selected part of the ROM (209) as was also suggested by Ada and colleagues (163). They suggested that the movement may be restricted to the weaker part of the ROM. An inverse approach is also conceivable, i.e., to limit the movement of the stronger portion of the ROM and thereby obtain higher mechanical tension (209). A third and more comprehensive strategy is to use different loads in the relatively stronger part vs. the relatively weaker part of the ROM to provide optimal relative loading and muscle activation throughout the whole ROM, a training strategy that is effective in healthy subjects (210).

- Use a lifting strategy with high acceleration in the early part of the movement to counteract the limitation of a relative weakness in the latter part of the ROM (211). Traditionally, explosive resistance training has not been used or studied in stroke rehabilitation. This might be found to be inadequate. Interestingly, recently published findings revealed that an explosive resistance training exercise where high speed (explosive) lifts were emphasized provided positive short-term neural adaptations including a persistent, but maybe temporary, increase in muscle activation (212). Furthermore, it was also just recently demonstrated that individuals with hemiparesis due to stroke performed a reach-grasp-lift task with better quality and accuracy when movements were performed faster than at their self selected speed (213).

- Strive to achieve adequate relative loading during the eccentric phase since the eccentric phase may be significantly under-loaded otherwise. It is, however, somewhat complicated to accomplish this in a straightforward way in clinical context. Different strategies could be tested. This could be done, for example, by providing accentuated eccentric load during coupled eccentric and concentric resistance training using special equipment (214, 215) or simply assist the load during the concentric phase by any means. Another strategy is to perform pure eccentric resistance exercises (216, 217), which was recently demonstrated effective in subjects with cerebral palsy (218). The best way to accomplish this with a straightforward feasible method in clinical practice is however yet to be found.

- Take advantage of the fact that the load torque in some exercises, due to biomechanical conditions, increases with increased muscle length, e.g., the squat exercise (219), which therefore might provide a better match to the altered torque-angle relationship found among subjects with stroke. Such a biomechanical condition may lie behind the common perception in

clinical practice that such exercises are preferable exercises in neurological rehabilitation (220).

- A potential experimental approach may be to incorporate low-intensity resistance training with restricted blood flow, a training strategy that has received much attention as of late. One problem with conventional resistance training for individuals with stroke may be associated with a lack of optimal stimuli for strength adaptation. The advantage with this method is that similar signalling pathways for muscle hypertrophy is initiated after resistance exercises at low relative loads (usually around 20% of 1RM), as normally are found only as a result of high intensity training (221).This approach has been proved to be efficient in young (222) and old (223) individuals. This method has not been tested in subjects with stroke and has to be evaluated regarding benefits, feasibility, and long-term safety before introduced in a high-risk population such as stroke patients.

This thesis primarily focuses on resistance exercises for stroke patients from a biomechanical perspective although a stroke may result in a variety of other impairments with respect to abnormal movement patterns, psychological function, and cardiovascular functions. In addition, status of the patient often varies substantially over time. This complexity implies that a successful rehabilitation program after stroke requires close guidance of a therapist over time (224). A strongly perceived need for such support also seems to exist among stroke survivors (225). Swedish stroke rehabilitation, however, goes the other way as most patients are referred at a very early stage to home-based self-exercise programs that lack the supervision that may be needed. Moreover, when rehabilitation is located in the home environment, the methods, e.g. resistance exercises, tends to become oversimplified. Furthermore, current guidelines for stroke rehabilitation in Sweden for motor training focus solely on task-oriented practice. For optimal results, this approach should probably be combined with adequately modified resistance training. Recently, it was demonstrated that high intensity resistance exercises provided superior results according to normalization of abnormal movement patterns and functional outcomes compared to a program consisting of functional task-oriented practice (226).

Over the last century, the focus of neurological physical therapy has shifted. In the 1950s, a major conceptual shift was evident when the focus shifted from peripheral consequences, to-non muscle elements in the central nervous system. The methods used were directed primarily at the nervous system (1, 227). Over the last decades, the focus has however changed to a more general approach that includes general principles of motor control mechanisms, muscle biology, biomechanics, motor learning and exercise science (228). This broader perspective has been important and of great value as a lesion in the central nervous system, due to e.g.

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stroke, leads to impairments on many levels. With this change in focus, however, motor impairments due to stroke has to a great extent been sought in secondary structural changes and a reduced muscular strength (165, 229-231). Indeed, peripheral changes need to be considered, but the findings in this thesis show that we must not forget that we have to deal with a damaged central nervous system. Muscle weakness is not merely a reduction of muscular force, but may also be associated with alterations in CNS pathways "upstream" of the motor cortex which, for instance, may alter the ability to modulate muscular force. For example, just recently, a report by Lindberg and colleagues showed that precision and adaptation of grip force tracking remained intact among stroke subjects, within there limited force range (232). In contrast, the modulation of force relaxation was found to be disturbed since the release duration was significantly prolonged in both the paretic and non-paretic hand compared to healthy subjects. Interestingly, it has been demonstrated that the VLPFC seems to be particularly involved in modulation of force relaxation during performance of a force-ramp task (183). The subjects in this thesis (Paper IV) exhibited various examples of disturbed activation within VLPFC during imagined maximum contractions. Future studies ought to address if those disturbances also are evident during submaximal force modulation tasks among subjects with stroke.

The findings from the fMRI studies in this thesis are a first indication that VLPFC may play a crucial role in a supraspinal contraction mode-specific modulation system for eccentric and concentric muscle force. However, this role is doubtless complex since the VLPFC is part of a complex network including many different brain regions, e.g. the basal ganglia (190). In this thesis, motor imagery was used as a method to study cortical activation patterns associated with maximum contractions. It is to be determined whether the cortical activation patterns found with this method also apply to the execution of maximal contractions although this is suggested by the findings in this study, complementary behavioural data, and previous findings in the literature. The assumption that the VLPFC may be involved in mode-specific modulation of eccentric and concentric contractions and that this modulation is deficient in stroke subjects is a novel hypothesis that provides a new starting point for further studies. It remains to be seen whether, how, and in what way this presumptive modulation system operates during executed contractions and how it may be altered in individuals who sustain injuries to their central nervous system. Furthermore, and not least important, future studies may consider whether this suggestive system is responsive to interventions.

5 Conclusions

In conclusion, stroke subjects exhibited altered muscular function comprising a specific reduction of torque producing capacity and, compared to healthy subjects, exhibited a deviant torque-angle relationship during concentric contractions. As a result, the stroke subjects' relative training load during a resistance exercise at a training intensity of 10RM was lower than for the controls. Furthermore, neuroimaging data indicates that the ventrolateral prefrontal cortex, a brain area that has been shown to play a key role in the inhibitory control of motor cortex, may be involved in a mechanism that modulates cortical motor drive differently depending on mode of contractions. This might partly explain why it is impossible to fully activate a muscle during eccentric contractions. Moreover, in stroke subjects, a disturbance of this system could also lie behind the lack of contraction mode-specific modulation of muscle activation, which has been found in stroke subjects. Altogether, neuromuscular function after stroke is altered in several respects, resulting in an insufficient level of stress being applied to the neuromuscular system during conventional resistance exercises. This finding may partially explain why the increase in strength in response to conventional resistance training often has been found to be low among stroke subjects. However, there are several potential ways to modify resistance exercise to compensate for this problem.

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